VISUfarma
the eye health company

Neuroprotection, Coenzyme Q10, and Glaucoma Management

ABSTRACTS OUTLINING THE ROLE OF COENZYME Q10 AND GLAUCOMA MANAGEMENT

VISU/EU/CQN/0026

Dear Professor, Doctor,

VISUfarma is a pan-European ophthalmic pharmaceutical company, created in 2016, with a clear mission: to bring global therapeutic innovation to European eye health. We are an ambitious and fast-growing ophthalmology player, commercialising a broad portfolio of pharmaceutical products and medical devices across Europe.

Glaucoma remains a leading cause of irreversible blindness worldwide.[1] While current treatment standards remain centered around controlling intraocular pressure, novel therapies targeting neuroprotection are coming to the forefront providing new and additional therapeutic options for your glaucoma patients.

Coenzyme Q10, also known as ubiquinone, is an endogenous molecule which is notably present in the mitochondria in every tissue where it serves as an electron transporter, an inhibitor of the apoptotic signal transduction, and an effective antioxidant.[2,3] Alongside its well documented clinical applications in a range of disease states,[4,5] broad experimental and clinical evidence document Coenzyme Q10 as having a specific retinal neuroprotective action.[6-10] Studies have shown Coenzyme Q10 to be an effective therapy preventing retinal ganglion cell apoptosis and loss in glaucoma-related models.[9-12]

The European Glaucoma Society recognises neuroprotection as an adjuvant therapy in the treatment of glaucoma.[13] The therapeutic approach towards glaucoma should remain unchanged as it relates to control of intraocular pressure as the critical risk factor. However, glaucoma is a neuropathy of the optic nerve and therapy may include Coenzyme Q10 to add its neuroprotective benefits.[1,14] Thus, in the spirit of innovation, VISUfarma is pleased to present you with a summary of the latest literature on neuroprotection, Coenzyme Q10, and insights in glaucoma management. The intent of this booklet is to provide clinical data for your information and we hope that you will appreciate the value.

Sincerely,

Tom van Haarlem, MD
Chief Executive Officer, VISUfarma

Contents

Neurodegeneration & Neuroprotection in Glaucoma

Bioenergetic-based neuroprotection and glaucoma

Schober MS[1], Chidlow G, Wood JP, Casson RJ
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Abstract

Primary open-angle glaucoma (POAG) is a pressure-sensitive optic neuropathy which results in the death of retinal ganglion cells and causes associated loss of vision. Presently, the only accepted treatment strategy is to lower the intraocular pressure; however, for some patients this is insufficient to prevent progressive disease. Although the pathogenesis of POAG remains unclear, there is considerable evidence that energy failure at the optic nerve head may be involved. Neuroprotection, a strategy which directly enhances the survival of neurons, is desirable, but remains clinically elusive. One particular form of neuroprotection involves the notion of enhancing the energy supply of neurons. These 'bioenergetic' methods of neuroprotection have proven successful in animal models of other neurodegenerative diseases and conditions, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and traumatic brain injury, but have been relatively unexplored in glaucoma models. This review focuses on some of the potential approaches for bioenergetic neuroprotection in the retina, including increasing the energy buffering capacity of damaged cells, decreasing the permeability of the mitochondrial membrane pore and free radical scavenging.

Clin Exp Ophthalmol. 2008 May;36(4):377-85.

Current perspective of neuroprotection and glaucoma.

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[1]Glaucoma and Retinal Neurodegeneration Research Group, UCL Institute of Ophthalmology, London, UK ; Eye Centre, Renmin Hospital of Wuhan University, Wuhan, People's Republic of China.

Abstract

Glaucoma is the second leading cause of blindness worldwide and is most notably characterized by progressive optic nerve atrophy and advancing loss of retinal ganglion cells (RGCs). The main concomitant factor is the elevated intraocular pressure (IOP). Existing treatments are focused generally on lowering IOP. However, both RGC loss and optic nerve atrophy can independently occur with IOP at normal levels. In recent years, there has been substantial progress in the development of neuroprotective therapies for glaucoma in order to restore vital visual function. The present review intends to offer a brief insight into conventional glaucoma treatments and discuss exciting current developments of mostly preclinical data in novel neuroprotective strategies for glaucoma that include recent advances in noninvasive diagnostics going beyond IOP maintenance for an enhanced global view. Such strategies now target RGC loss and optic nerve damage, opening a critical therapeutic window for preventative monitoring and treatment.

Clin Ophthalmol. 2015 Nov 11;9:2109-18.

Neuroprotective agents in the management of glaucoma

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Abstract

Glaucoma is an optic neuropathy, specifically a neurodegenerative disease characterized by loss of retinal ganglion cells (RGCs) and their axons. The pathogenesis of RGC loss in glaucoma remains incompletely understood and a broad range of possible mechanisms have been implicated. Clinical evidence indicates that lowering intraocular pressure (IOP) does not prevent progression in all patients; therefore, risk factors other than those related to IOP are involved in the disease. The need for alternative, non-IOP-lowering treatments focused at preventing progression, that is, neuroprotectants, has become of interest to both the patient and the physician. Experimental evidence accumulated during the past two decades lend a great deal of support to molecules endowed with neuroprotective features. However, translation to the clinic of the latter drugs results unsuccessful mostly because of the lack of reliable in vivo measure of retinal damage, thus hampering the good therapeutic potential of neuroprotective agents given alone or as adjuvant therapy to IOP-lowering agents. Further research effort is needed to better understand the mechanisms involved in glaucoma and the means to translate into clinic neuroprotective drugs.

Eye (2018) 32:938–945

Retinal Ganglion Cell Death & Mitochondrial Dysfunction: Their role in Glaucoma

Mitochondria: Their role in ganglion cell death and survival in primary open angle glaucoma.

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Abstract

Retinal ganglion cell axons within the globe are functionally specialised being richly provided with many mitochondria. Mitochondria produce the high energy that is required for nerve conduction in the unmylenated part of the ganglion cell axons and for the maintenance of optimum neuronal function. We proposed that in the initiation of glaucoma (POAG) an alteration in the quality of blood flow dynamics in the optic nerve head results in sustained or intermittent ischemia of a defined nature. This results in normal mitochondrial function being negatively affected and as a consequence retinal ganglion cell function is compromised. Ganglion cells in this state are now susceptible to secondary insults which they would normally tolerate. One secondary insult to ganglion cell mitochondria in such a state might be light entering the eye. Other insults to the ganglion cells might come from substances such as glutamate, prostaglandins and nitric oxide released from astrocytes and microglia in the optic nerve head region. Such cascades of events initiated by ischemia to the optic nerve head region ultimately cause ganglion cells to die at different rates.

Exp Eye Res. 2010 Jun;90(6):750-7.

The molecular basis of retinal ganglion cell death in glaucoma.

Almasieh M[1], Wilson AM, Morquette B, Cueva Vargas JL, Di Polo A.
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Abstract

Glaucoma is a group of diseases characterized by progressive optic nerve degeneration that results in visual field loss and irreversible blindness. A crucial element in the pathophysiology of all forms of glaucoma is the death of retinal ganglion cells (RGCs), a population of CNS neurons with their soma in the inner retina and axons in the optic nerve. Strategies that delay or halt RGC loss have been recognized as potentially beneficial to preserve vision in glaucoma; however, the success of these approaches depends on an in-depth understanding of the mechanisms that lead to RGC dysfunction and death. In recent years, there has been an exponential increase in valuable information regarding the molecular basis of RGC death stemming from animal models of acute and chronic optic nerve injury as well as experimental glaucoma. The emerging landscape is complex and points at a variety of molecular signals - acting alone or in cooperation - to promote RGC death. These include: axonal transport failure, neurotrophic factor deprivation, toxic pro-neurotrophins, activation of intrinsic and extrinsic apoptotic signals, mitochondrial dysfunction, excitotoxic damage, oxidative stress, misbehaving reactive glia and loss of synaptic connectivity. Collectively, this body of work has considerably updated and expanded our view of how RGCs might die in glaucoma and has revealed novel, potential targets for neuroprotection.

Prog Retin Eye Res. 2012 Mar;31(2):152-81.

Oxidative stress and mitochondrial dysfunction in glaucoma.

Chrysostomou V[1], Rezania F, Trounce IA, Crowston JG.
[1]Centre for Eye Research Australia, The University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, VIC 3002, Australia.

Abstract

Mitochondrial dysfunction increases reactive oxygen species (ROS) production and when this overwhelms the cellular antioxidant defences, oxidative stress ensues. Oxidative stress is recognized as a common pathologic pathway in many neurodegenerative diseases. Recent reports have also demonstrated oxidative stress in ocular tissues derived from experimental glaucoma models and clinical samples. There is also accumulating evidence pointing to mitochondrial dysfunction being present in some glaucoma patients. Thus oxidative stress from mitochondrial dysfunction may also play a causal role in glaucoma. The mechanisms by which oxidative stress may induce retinal ganglion cell loss in glaucoma are not fully understood but could include direct neurotoxic effects from ROS or indirect damage from oxidative stress-induced dysfunction of glial cells. This review will consider the evidence for the presence of oxidative stress in glaucoma; the mechanisms by which oxidative stress may contribute to disease pathogenesis; and also consider therapeutic approaches that target oxidative stress as a means of protecting against optic nerve degeneration.

Curr Opin Pharmacol. 2013 Feb;13(1):12-5.

Maintenance of retinal ganglion cell mitochondrial functions as a neuroprotective strategy in glaucoma.

Osborne NN[1], del Olmo-Aguado S.
[1]Fundación de Investigación Oftalmológica, Avda. Doctores Fernández-Vega 34, E-33012 Oviedo, Asturias, Spain.

Abstract

Loss of vision in glaucoma occurs because retinal ganglion cells (RGCs) die. RGCs have probably more mitochondria than any other neurone in the CNS. It is proposed that stress to mitochondria of individual RGCs is a major trigger of the disease and also provides an explanation why different RGCs die at different times. Pharmacological agents that can maintain mitochondrial functions, in particular to attenuate oxidative stress and to sustain energy production, might therefore provide a novel way of slowing down RGC death and help in the treatment of glaucoma.

Curr Opin Pharmacol. 2013 Feb;13(1):16-22.

Measurement of Systemic Mitochondrial Function in Advanced Primary Open-Angle Glaucoma and Leber Hereditary Optic Neuropathy.

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[1]Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Melbourne, Australia.

Abstract

Primary Open Angle Glaucoma (POAG) is a common neurodegenerative disease characterized by the selective and gradual loss of retinal ganglion cells (RGCs). Aging and increased intraocular pressure (IOP) are glaucoma risk factors; nevertheless patients deteriorate at all levels of IOP, implying other causative factors. Recent evidence presents mitochondrial oxidative phosphorylation (OXPHOS) complex-I impairments in POAG. Leber Hereditary Optic Neuropathy (LHON) patients suffer specific and rapid loss of RGCs, predominantly in young adult males, due to complex-I mutations in the mitochondrial genome. This study directly compares the degree of OXPHOS impairment in POAG and LHON patients, testing the hypothesis that the milder clinical disease in POAG is due to a milder complex-I impairment. To assess overall mitochondrial capacity, cells can be forced to produce ATP primarily from mitochondrial OXPHOS by switching the media carbon source to galactose. Under these conditions POAG lymphoblasts grew 1.47 times slower than controls, whilst LHON lymphoblasts demonstrated a greater degree of growth impairment (2.35 times slower). Complex-I enzyme specific activity was reduced by 18% in POAG lymphoblasts and by 29% in LHON lymphoblasts. We also assessed complex-I ATP synthesis, which was 19% decreased in POAG patients and 17% decreased in LHON patients. This study demonstrates both POAG and LHON lymphoblasts have impaired complex-I, and in the majority of aspects the functional defects in POAG were milder than LHON, which could reflect the milder disease development of POAG. This new evidence places POAG in the spectrum of mitochondrial optic neuropathies and raises the possibility for new therapeutic targets aimed at improving mitochondrial function.

PLoS One. 2015 Oct 23;10(10):doi:10.1371/journal.pone.014919.

Resistance to the most common optic neuropathy is associated with systemic mitochondrial efficiency.

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[1]NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK.

Abstract

Glaucomatous optic neuropathy, an important neurodegenerative condition and the commonest optic neuropathy in humans, is the leading cause of irreversible blindness worldwide. Its prevalence and incidence increase exponentially with ageing and raised intraocular pressure (IOP). Using glaucomatous optic neuropathy as an exemplar for neurodegeneration, this study investigates putative factors imparting resistance to neurodegeneration. Systemic mitochondrial function, oxidative stress and vascular parameters were compared from isolated lymphocytes, whole blood and urine samples between 30 patients who have not developed the neuropathy despite being exposed for many years to very high IOP ('resistant'), 30 fast deteriorating glaucoma patients despite having low IOP ('susceptible'), and 30 age-similar controls. We found that 'resistant' individuals showed significantly higher rates of ADP phosphorylation by mitochondrial respiratory complexes I, II and IV, hyperpolarised mitochondrial membrane potential, higher levels of mitochondrial DNA, and enhanced capacity to deal with cytosolic calcium overload and exogenous oxidative stress, as compared to both controls and glaucoma patients. While it has been known for some years that mitochondrial dysfunction is implicated in neurodegeneration, this study provides a fresh perspective to the field of neurodegeneration by providing, for the first time, evidence that systemic mitochondrial efficiency above normal healthy levels is associated with an enhanced ability to withstand optic nerve injury. These results demonstrate the importance of cellular bioenergetics in glaucomatous disease progression, with potential relevance for other neurodegenerative disorders, and raise the possibility for new therapeutic targets in the field of neurodegeneration.

Neurobiol Dis. 2015 Oct;82:78-85.

Emerging Mitochondrial Therapeutic Targets in Optic Neuropathies.

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[1]Centre for Eye Research Australia, 75 Commercial Road, Melbourne, 3004, Victoria, Australia; Ophthalmology, University of Melbourne, Department of Surgery, Australia.

Abstract

Optic neuropathies are an important cause of blindness worldwide. The study of the most common inherited mitochondrial optic neuropathies, Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) has highlighted a fundamental role for mitochondrial function in the survival of the affected neuron-the retinal ganglion cell. A picture is now emerging that links mitochondrial dysfunction to optic nerve disease and other neurodegenerative processes. Insights gained from the peculiar susceptibility of retinal ganglion cells to mitochondrial dysfunction are likely to inform therapeutic development for glaucoma and other common neurodegenerative diseases of aging. Despite it being a fast-evolving field of research, a lack of access to human ocular tissues and limited animal models of mitochondrial disease have prevented direct retinal ganglion cell experimentation and delayed the development of efficient therapeutic strategies to prevent vision loss. Currently, there are no approved treatments for mitochondrial disease, including optic neuropathies caused by primary or secondary mitochondrial dysfunction. Recent advances in eye research have provided important insights into the molecular mechanisms that mediate pathogenesis, and new therapeutic strategies including gene correction approaches are currently being investigated. Here, we review the general principles of mitochondrial biology relevant to retinal ganglion cell function and provide an overview of the major optic neuropathies with mitochondrial involvement, LHON and ADOA, whilst highlighting the emerging link between mitochondrial dysfunction and glaucoma. The pharmacological strategies currently being trialed to improve mitochondrial dysfunction in these optic neuropathies are discussed in addition to emerging therapeutic approaches to preserve retinal ganglion cell function.

Pharmacol Ther. 2016 Sep;165:132-52.

The Protective Role of Coenzyme Q10

Coenzyme Q10 ameliorates oxidative stress and prevents mitochondrial alteration in ischemic retinal injury.

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Abstract

Coenzyme Q10 (CoQ10) acts by scavenging reactive oxygen species for protecting neuronal cells against oxidative stress in neurodegenerative diseases. We tested whether a diet supplemented with CoQ10 ameliorates oxidative stress and mitochondrial alteration, as well as promotes retinal ganglion cell (RGC) survival in ischemic retina induced by intraocular pressure elevation. A CoQ10 significantly promoted RGC survival at 2 weeks after ischemia. Superoxide dismutase 2 (SOD2) and heme oxygenase-1 (HO-1) expression were significantly increased at 12 h after ischemic injury. In contrast, the CoQ10 significantly prevented the upregulation of SOD2 and HO-1 protein expression in ischemic retina. In addition, the CoQ10 significantly blocked activation of astroglial and microglial cells in ischemic retina. Interestingly, the CoQ10 blocked apoptosis by decreasing caspase-3 protein expression in ischemic retina. Bax and phosphorylated Bad (pBad) protein expression were significantly increased in ischemic retina at 12 h. Interestingly, while CoQ10 significantly decreased Bax protein expression in ischemic retina, CoQ10 showed greater increase of pBad protein expression. Of interest, ischemic injury significantly increased mitochondrial transcription factor A (Tfam) protein expression in the retina at 12 h, however, CoQ10 significantly preserved Tfam protein expression in ischemic retina. Interestingly, there were no differences in mitochondrial DNA content among control- or CoQ10-treated groups. Our findings demonstrate that CoQ10 protects RGCs against oxidative stress by modulating the Bax/Bad-mediated mitochondrial apoptotic pathway as well as prevents mitochondrial alteration by preserving Tfam protein expression in ischemic retina. Our results suggest that CoQ10 may provide neuroprotection against oxidative stress-mediated mitochondrial alterations in ischemic retinal injury.

Apoptosis. 2014 Apr;19(4):603-14.

Coenzyme Q10 inhibits glutamate excitotoxicity and oxidative stress-mediated mitochondrial alteration in a mouse model of glaucoma.

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[1]Laboratory for Optic Nerve Biology, Hamilton Glaucoma Center and Department of Ophthalmology, University of California, San Diego, La Jolla, California.

Abstract

PURPOSE: To test whether a diet supplemented with coenzyme Q10 (CoQ10) ameliorates glutamate excitotoxicity and oxidative stress-mediated retinal ganglion cell (RGC) degeneration by preventing mitochondrial alterations in the retina of glaucomatous DBA/2J mice.
METHODS: Preglaucomatous DBA/2J and age-matched control DBA/2J-Gpnmb(+) mice were fed with CoQ10 (1%) or a control diet daily for 6 months. The RGC survival and axon preservation were measured by Brn3a and neurofilament immunohistochemistry and by conventional transmission electron microscopy. Glial fibrillary acidic protein (GFAP), superoxide dismutase-2 (SOD2), heme oxygenase-1 (HO1), N-methyl-d-aspartate receptor (NR) 1 and 2A, and Bax and phosphorylated Bad (pBad) protein expression was measured by Western blot analysis. Apoptotic cell death was assessed by TUNEL staining. Mitochondrial DNA (mtDNA) content and mitochondrial transcription factor A (Tfam)/oxidative phosphorylation (OXPHOS) complex IV protein expression were measured by real-time PCR and Western blot analysis.
RESULTS: Coenzyme Q10 promoted RGC survival by approximately 29% and preserved the axons in the optic nerve head (ONH), as well as inhibited astroglial activation by decreasing GFAP expression in the retina and ONH of glaucomatous DBA/2J mice. Intriguingly, CoQ10 significantly blocked the upregulation of NR1 and NR2A, as well as of SOD2 and HO1 protein expression in the retina of glaucomatous DBA/2J mice. In addition, CoQ10 significantly prevented apoptotic cell death by decreasing Bax protein expression or by increasing pBad protein expression. More importantly, CoQ10 preserved mtDNA content and Tfam/OXPHOS complex IV protein expression in the retina of glaucomatous DBA/2J mice.
CONCLUSIONS: Our findings suggest that CoQ10 may be a promising therapeutic strategy for ameliorating glutamate excitotoxicity and oxidative stress in glaucomatous neurodegeneration.
Invest Ophthalmol Vis Sci. 2014 Feb 18;55(2):993-1005.

Mitochondrial Dysfunctions and Role of Coenzyme Q10 in Patients with Glaucoma

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Abstract

Mitochondrial function is closely linked to numerous aspects
of eye health. Imbalance between the creation of energy and the development of reactive oxygen species (ROS) seems to be the cause of the development of mitochondrial dysfunctions. As a result of this energy deficit, the level of oxidative stress in the eye tissues increases, leading to numerous ophthalmic impairments. It is important to distinguish between primary mitochondrial eye diseases and secondary mitochondrial changes. Primary mitochondrial eye diseases, for example Leber's hereditary optic atrophy (LHON), retinitis pigmentosa and chronic progressive external ophthalmoplegia are caused by direct damage to mitochondrial function induced by defective genes, either located on mitochondrial DNA (mtDNA) or the DNA of the nucleus (nDNA). In contrast, secondary mitochondrial dysfunctions are caused by environmental factors. In recent years, there has been growing evidence that mitochondrial dysfunctions play an important role in many common eye diseases, such as glaucoma, dry eye, diabetic retinopathy, cataract and age-related macular degeneration (AMD). This article summarises current knowledge of mitochondrial dysfunctions and the role of coenzyme Q10 (CoQ10) as a possible treatment option – with a special focus on glaucoma.

Klin Monatsbl Augenheilkd 2018; 235: 157–162

Evidence on neuroprotective properties of coenzyme Q10 in the treatment of glaucoma

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Abstract

Glaucoma, the leading cause of visual impairment and irreversible blindness worldwide, is a multifactorial, progressive optic neuropathy characterized by loss of retinal ganglion cells, alterations of the optic nerve head, and specific visual field defects. Clinical evidence shows that intraocular pressure is the major risk factor of the treatable disease. However, in some patients, glaucoma develops and continues to progress despite normal intraocular pressure values, suggesting that other risk factors are involved in the disease. Consequently, neuroprotective treatments, focused on preventing retinal ganglion cells death by acting on different therapeutic strategies but not focused on intraocular pressure reduction, has therefore become of great interest. In this contest, coenzyme Q10, showing evidence in slowing or reversing pathological changes typical of the disease, has been proposed as a potential neuroprotective agent in glaucoma. In this review, we describe the possible mechanisms of action of coenzyme Q10 and the recent evidence in literature regarding the neuroprotective activity of the molecule.

Neural Regen Res 2019; 14(2):197-200.

Therapeutic Potential of Co-enzyme Q10 in Retinal Diseases

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Abstract

Background: Coenzyme Q10 (CoQ10) plays a critical role in mitochondrial oxidative phosphorylation by serving as an electron carrier in the respiratory electron transport chain. CoQ10 also functions as a lipid-soluble antioxidant by protecting lipids, proteins and DNA damaged by oxidative stress. CoQ10 deficiency has been associated with a number of human diseases in which CoQ10 supplementation therapy has been effective in slowing or reversing pathological changes. Oxidative stress is a major contributory factor in the process of retinal degeneration.
Method: The related literature was reviewed through searching PubMed using keywords: CoQ10, CoQ10 and oxidative stress, CoQ10 and retinal degeneration. The functions of CoQ10 were summarized and its use in the treatment of age-related macular degeneration and glaucoma highlighted. The therapeutic potential of CoQ10 for other retinal diseases was also discussed.
Results: CoQ10 has been applied in different types of neurodegeneration. CoQ10 is detectable in retina and declines with ageing. Early studies showed treatment of CoQ10 improved visual function in patients with age-related macular degeneration. In glaucomatous models, CoQ10 exposure protected ganglion cell death from environmental stress; in glaucoma patients, CoQ10 treatment demonstrated beneficial effects on function of inner retina and enhancement of visual cortical response. Since oxidative stress also plays a critical role in the pathogenesis of diabetic retinopathy and retinitis pigmentosa, CoQ10 is a therapeutic target for both conditions.
Conclusion: A wide range of evidence supports a role of CoQ10 in retinal diseases through inhibiting production of reactive oxygen species and protecting neuroretinal cells from oxidative damage.
Current Medicinal Chemistry, 2017, Vol. 24(39):4329-4339.

Topical Coenzyme Q10 demonstrates mitochondrial-mediated neuroprotection in rodent model of ocular hypertension

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Abstract

Coenzyme Q10 (CoQ10) is a mitochondrial-targeted antioxidant with known neuroprotective activity. Its ocular effects when co-solubilised with α-tocopherol polyethylene glycol succinate (TPGS) were evaluated. In vitro studies confirmed that CoQ10 was significantly protective in different retinal ganglion cell (RGC) models. In vivo studies in Adult Dark Agouti (DA) rats with unilateral surgically-induced ocular hypertension (OHT) treated with either CoQ10/TPGS micelles or TPGS vehicle twice daily for three weeks were performed, following which retinal cell health was assessed in vivo using DARC (Detection of Apoptotic Retinal Cells) and post-mortem with Brn3a histological assessment on whole retinal mounts. CoQ10/TPGS showed a significant neuroprotective effect compared to control with DARC ($p<0.05$) and Brn3 ($p<0.01$). Topical CoQ10 appears an effective therapy preventing RGC apoptosis and loss in glaucoma-related models.

Mitochondrion. 2017 36: 114-123.

Coenzyme Q10 instilled as eye drops on the cornea reaches the retina and protects retinal layers from apoptosis in a mouse model of kainate-induced retinal damage.

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Abstract

PURPOSE: To evaluate if coenzyme Q10 (CoQ10) can protect retinal ganglion cells (RGCs) from apoptosis and, when instilled as eyedrops on the cornea, if it can reach the retina and exert its antiapoptotic activity in this area in a mouse model of kainate (KA)-induced retinal damage.
METHODS: Rat primary or cultured RGCs were subjected to glutamate (50 µM) or chemical hypoxia (Antimycin A, 200 µM) or serum withdrawal (FBS, 0.5%) in the presence or absence of CoQ10 (10 µM). Cell viability was evaluated by light microscopy and fluorescence-activated cell sorting analyses. Apoptosis was evaluated by caspase 3/7 activity and mitochondrion depolarization tetramethylrhodamine ethyl ester analysis. CoQ10 transfer to the retina following its instillation as eye drops on the cornea was quantified by HPLC. Retinal protection by CoQ10 (10 µM) eye drops instilled on the cornea was then evaluated in a mouse model of KA-induced excitotoxic retinal cell apoptosis by cleaved caspase 3 immunohistofluorescence, caspase 3/7 activity assays, and quantification of inhibition of RGC loss.
RESULTS: CoQ10 significantly increased viable cells by preventing RGC apoptosis. Furthermore, when topically applied as eye drops to the cornea, it reached the retina, thus substantially increasing local CoQ10 concentration and protecting retinal layers from apoptosis.
CONCLUSIONS: The ability of CoQ10 eye drops to protect retinal cells from apoptosis in the mouse model of KA-induced retinal damage suggests that topical CoQ10 may be evaluated in designing therapies for treating apoptosis-driven retinopathies.

Invest Ophthalmol Vis Sci. 2012 Dec 17;53(13):8295-302.

Effects of coenzyme Q10 in conjunction with vitamin E on retinal-evoked and cortical-evoked responses in patients with open-angle glaucoma.

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[1]Fondazione per l'Oftalmologia G. B. Bietti, IRCCS.

Abstract

PURPOSE: To evaluate pattern-evoked retinal and cortical responses [pattern electroretinogram (PERG) and visual-evoked potential (VEP), respectively] after treatment with coenzyme Q10 in conjunction with vitamin E in open-angle glaucoma (OAG) patients.
METHODS: Forty-three OAG patients (mean age, 52.5±5.29 y; intraocular pressure <18 mm Hg with β-blocker monoterapy only) were enrolled. At baseline and after 6 and 12 months, simultaneous recordings of PERG and VEPs were obtained from 22 OAG patients who underwent treatment consisting of coenzyme Q10 and vitamin E (Coqun, 2 drops/d) in addition to β-blocker monoterapy (GC group), and from 21 OAG patients who were only treated with β-blockers (GP group).
RESULTS: At baseline, intraocular pressure, PERG, and VEP parameters were similar in both GC and GP groups (analysis of variance, P>0.05). After 6 and 12 months, PERG and VEP response parameters of GP patients were unchanged when compared to baseline. In GC patients, PERG P50 and VEP P100 implicit times were decreased, whereas PERG P50-N95 and VEP N75-P100 amplitudes were increased (P<0.01) when compared to baseline. In the GC group, the differences in implicit times and amplitudes with respect to baseline were significantly larger (P<0.01) than those recorded in the GP group. The improvement (12 mo minus baseline) of VEP implicit time was significantly correlated with the changes of PERG P50-N95 amplitude (r=-0.66171, P=0.0008) and P50 implicit time (r=0.68364, P=0.00045) over a period of 12 months.
CONCLUSIONS: Coenzyme Q10 associated with vitamin E administration in OAG shows a beneficial effect on the inner retinal function (PERG improvement) with consequent enhancement of the visual cortical responses (VEP improvement).

J Glaucoma. 2014 Aug;23(6):391-404.

Systemic Benefits of Coenzyme Q10

Oxidative stress, aging, and diseases

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Abstract

Reactive oxygen and nitrogen species (RONS) are produced by several endogenous and exogenous processes, and their negative effects are neutralized by antioxidant defenses. Oxidative stress occurs from the imbalance between RONS production and these antioxidant defenses. Aging is a process characterized by the progressive loss of tissue and organ function. The oxidative stress theory of aging is based on the hypothesis that age-associated functional losses are due to the accumulation of RONS-induced damages. At the same time, oxidative stress is involved in several age-related conditions (ie, cardiovascular diseases [CVDs], chronic obstructive pulmonary disease, chronic kidney disease, neurodegenerative diseases, and cancer), including sarcopenia and frailty. Different types of oxidative stress biomarkers have been identified and may provide important information about the efficacy of the treatment, guiding the selection of the most effective drugs/dose regimens for patients and, if particularly relevant from a pathophysiological point of view, acting on a specific therapeutic target. Given the important role of oxidative stress in the pathogenesis of many clinical conditions and aging, antioxidant therapy could positively affect the natural history of several diseases, but further investigation is needed to evaluate the real efficacy of these therapeutic interventions. The purpose of this paper is to provide a review of literature on this complex topic of ever increasing interest.

Clinical Interventions in Aging 2018:13 757–772.

CoQ10 a super-vitamin: review on application and biosynthesis

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Abstract

Coenzyme Q10 (CoQ) or ubiquinone is found in the biological system which is synthesized by the conjugation of benzoquinone ring with isoprenoid chain of variable length. Coenzyme Q10 supplementation energizes the body and increases body energy production in the form of ATP and helps to treat various human diseases such as cardiomyopathy, muscular dystrophy, periodontal disease, etc. Reports of these potential therapeutic advantages of CoQ10 have resulted in its high market demand, which focus the researchers to work on this molecule and develop better bioprocess methods for commercial level production. At the moment, chemical synthesis, semi-synthetic method as well as bio-production utilizing microbes as biofactory are in use for the synthesis of CoQ10. Chemical synthesis involves use of cheap and easily available precursor molecules such as isoprenol, chloromethylquinone, vinylalane, and solanesol. Chemical synthesis methods due to the use of various solvents and chemicals are less feasible, which limits its application. The microbial production of CoQ10 has added advantages of being produced in optically pure form with high yield using inexpensive medium composition. Several bacteria, e.g., Agrobacterium, Paracoccus, Rhodobacterium, and yeast such as Candida, Rhodotorula are the potent ubiquinone producer. Some alternative biosynthetic pathway for designing of CoQ10 production coupled with metabolic engineering might help to increase CoQ10 production. The most common practiced strategy for strain development for commercial CoQ10 production is through natural isolation and chemical mutagenesis. Here, we have reviewed the chemical, semi-synthetic as well as microbial CoQ10 production in detail.

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Coenzyme Q10 for the treatment of heart failure: a review of the literature

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Abstract

Coenzyme Q10 (CoQ10) is an endogenously synthesised and diet-supplied lipid-soluble cofactor that functions in the mitochondrial inner membrane to transfer electrons from complexes I and II to complex III. In addition, its redox activity enables CoQ10 to act as a membrane antioxidant. In patients with congestive heart failure, myocardial CoQ10 content tends to decline as the degree of heart failure worsens. A number of controlled pilot trials with supplemental CoQ10 in heart failure found improvements in functional parameters such as ejection fraction, stroke volume and cardiac output, without side effects. Subsequent meta-analyses have confirmed these findings, although the magnitude of benefit tends to be less notable in patients with severe heart failure, or within the context of ACE inhibitor therapy. The multicentre randomised placebo-controlled Q-SYMBIO trial has assessed the impact of supplemental CoQ10 on hard endpoints in heart failure. A total of 420 patients received either CoQ10 (100 mg three times daily) or placebo and were followed for 2 years. Although short-term functional endpoints were not statistically different in the two groups, CoQ10 significantly reduced the primary long-term endpoint— a major adverse cardiovascular event—which was observed in 15% of the treated participants compared to 26% of those receiving placebo (HR=0.50, CI 0.32 to 0.80, p=0.003). Particularly in light of the excellent tolerance and affordability of this natural physiological compound, supplemental CoQ10 has emerged as an attractive option in the management of heart failure, and merits evaluation in additional large studies.

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The Effect of Coenzyme Q10 on Morbidity and Mortality in Chronic Heart Failure

Results From Q-SYMBIO: A Randomized Double-Blind Trial

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Abstract

OBJECTIVES: This randomized controlled multicenter trial evaluated coenzyme Q10 (CoQ10) as adjunctive treatment in chronic heart failure (HF).

BACKGROUND: CoQ10 is an essential cofactor for energy production and is also a powerful antioxidant. A low level of myocardial CoQ10 is related to the severity of HF. Previous randomized controlled trials of CoQ10 in HF were underpowered to address major clinical endpoints.

METHODS: Patients with moderate to severe HF were randomly assigned in a 2-year prospective trial to either CoQ10 100 mg 3 times daily or placebo, in addition to standard therapy. The primary short-term endpoints at 16 weeks were changes in New York Heart Association (NYHA) functional classification, 6-min walk test, and levels of N-terminal pro–B type natriuretic peptide. The primary long-term endpoint at 2 years was composite major adverse cardiovascular events as determined by a time to first event analysis.

RESULTS: A total of 420 patients were enrolled. There were no significant changes in short-term endpoints. The primary long-term endpoint was reached by 15% of the patients in the CoQ10 group versus 26% in the placebo group (hazard ratio: 0.50; 95% confidence interval: 0.32 to 0.80; p ¼ 0.003) by intention-to-treat analysis. The following secondary endpoints were significantly lower in the CoQ10 group compared with the placebo group: cardiovascular mortality (9% vs. 16%, p ¼ 0.026), all-cause mortality (10% vs. 18%, p ¼ 0.018), and incidence of hospital stays for HF (p ¼ 0.033). In addition, a significant improvement of NYHA class was found in the CoQ10 group after 2 years (p ¼ 0.028).

CONCLUSIONS: Long-term CoQ10 treatment of patients with chronic HF is safe, improves symptoms, and reduces major adverse cardiovascular events.

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Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Previous studies have demonstrated a possible association between the induction of coenzyme Q10 (CoQ10) after statin treatment and statin-induced myopathy. However, whether CoQ10 supplementation ameliorates statin-induced myopathy remains unclear.
Methods and Results: PubMed, EMBASE, and Cochrane Library were searched to identify randomized controlled trials investigating the effect of CoQ10 on statin-induced myopathy. We calculated the pooled weighted mean difference (WMD) using a fixed-effect model and a random-effect model to assess the effects of CoQ10 supplementation on statin-associated muscle symptoms and plasma creatine kinase. The methodological quality of the studies was determined, according to the Cochrane Handbook. Publication bias was evaluated by a funnel plot, Egger regression test, and the Begg-Mazumdar correlation test. Twelve randomized controlled trials with a total of 575 patients were enrolled; of them, 294 patients were in the CoQ10 supplementation group and 281 were in the placebo group. Compared with placebo, CoQ10 supplementation ameliorated statin-associated muscle symptoms, such as muscle pain (WMD, _1.60; 95% confidence interval [CI], _1.75 to _1.44; P<0.001), muscle weakness (WMD, _2.28; 95% CI, _2.79 to _1.77; P=0.006), muscle cramp (WMD, _1.78; 95% CI, _2.31 to _1.24; P<0.001), and muscle tiredness (WMD, _1.75; 95% CI, _2.31 to _1.19; P<0.001), whereas no reduction in the plasma creatine kinase level was observed after CoQ10 supplementation (WMD, 0.09; 95% CI, _0.06 to 0.24; P=0.23).
Conclusions: CoQ10 supplementation ameliorated statin-associated muscle symptoms, implying that CoQ10 supplementation may be a complementary approach to manage statin-induced myopathy.

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New insights
in
Glaucoma Management

Present and New Treatment Strategies in the Management of Glaucoma.

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Abstract

Glaucoma is a neurodegenerative disease characterized by retinal ganglion cell (RGC) death and axonal loss. It remains a major cause of blindness worldwide. All current modalities of treatment are focused on lowering intraocular pressure (IOP), and it is evident that increased IOP is an important risk factor for progression of the disease. However, it is clear that a significant number of glaucoma patients show disease progression despite of pressure lowering treatments. Much attention has been given to the development of neuroprotective treatment strategies, but the identification of such has been hampered by lack of understanding of the etiology of glaucoma. Hence, in spite of many attempts no neuroprotective drug has yet been clinically approved. Even though neuroprotection is without doubt an important treatment strategy, many glaucoma subjects are diagnosed after substantial loss of RGCs. In this matter, recent approaches aim to rescue RGCs and regenerate axons in order to restore visual function in glaucoma. The present review seeks to provide an overview of the present and new treatment strategies in the management of glaucoma. The treatment strategies are divided into current available glaucoma medications, new pressure lowering targets, prospective neuroprotective interventions, and finally possible neuroregenerative strategies.

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A Systematic Review of End-of-Life Visual Impairment in Open-Angle Glaucoma: An Epidemiological Autopsy

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Abstract

Purpose: Glaucoma patients are still at risk of becoming blind. It is of clinical significance to determine the risk of blindness and its causes to prevent its occurrence. This systematic review estimates the number of treated glaucoma patients with end-of-life visual impairment (VI) and blindness and the factors that are associated with this.
Methods: A systematic literature search in relevant databases was conducted in August 2014 on end-of-life VI. A total of 2574 articles were identified, of which 5 on end-of-life VI. Several data items were extracted from the reports and presented in tables.
Results: All studies had a retrospective design. A considerable number of glaucoma patients were found to be blind at the end of their life; with up to 24% unilateral and 10% bilateral blindness. The following factors were associated with blindness: (1) baseline severity of visual field loss: advanced stage of glaucoma or substantial visual field loss at the initial visit; (2) factors influencing progression: fluctuation of intraocular pressure (IOP) during treatment, presence of pseudoexfoliation, poor patient compliance, higher IOP; (3) longer time period: longer duration of disease and older age at death because of a longer life expectancy; and (4) coexistence of other ocular pathology.
Conclusions: Further prevention of blindness in glaucoma patients is needed. To reach this goal, it is important to address the risk factors for blindness identified in this review, especially those that can be modified, such as advanced disease at diagnosis, high and fluctuating IOP, and poor compliance.

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The impact of visual symptoms on the quality of life of patients with early to moderate glaucoma

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Abstract

Purpose: To investigate the visual symptoms and to determine the impact of visual symptoms on vision-related quality of life (QoL) in patients with early to moderate glaucoma.
Methods: A retrospective, hospital-based, cross-sectional study was conducted from July 1 to August 31, 2014, at a university referral center. A total of 176 patients with early to moderate glaucoma underwent a comprehensive ocular examination, including Humphrey visual field testing. The patients were divided into six groups based on visual symptoms that could be verified by forced-choice questions. Vision-related QoL was assessed by the Korean version of the National Eye Institute Visual Function Questionnaire 25 (K-NEI-VFQ-25). We compared the mean deviation (MD) and questionnaire scores among the groups.
Results: Of 352 eyes, 107 (30.4%) were symptomatic. The most common visual symptoms were partial blurring (15.91%), followed by a missing part (7.67%) and a black part (5.97%) of the image. The symptomatic groups (blurred part and missing part) had a significantly worse MD than the asymptomatic group. The symptomatic groups tended to have more visual field defects than the asymptomatic group. The overall NEI-VFQ-25 score in the symptomatic group (black part) was significantly lower than that in the asymptomatic group. Similar effects were observed for other subscale scores, including social functioning, mental health, role difficulties, dependency, and peripheral vision.
Conclusions: Vision-related QoL may be severely compromised in glaucoma patients with visual symptoms. Patients with visual disorders should be evaluated for glaucoma and QoL.

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Macular Damage, as Determined by Structure-Function Staging, Is Associated With Worse Vision-related Quality of Life in Early Glaucoma

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Abstract

Purpose: Macular damage is common early in glaucoma and has previously been identified as a significant factor affecting vision-related quality of life (VRQoL) across the spectrum of glaucomatous damage. This report uses structure-function correlation to identify early macular damage and assess its relationship with the National Eye Institute Visual Function Questionnaire (NEI VFQ-25).
Design: Cohort study.
Methods: Setting: Institutional. Study Population: Eighty-eight eyes of 44 participants with early open-angle glaucoma (24-2 mean deviation [MD] better than −6 dB). Observation Procedure: Focal and diffuse macular defects were identified based on corresponding abnormal regions on probability maps from spectral-domain optical coherence tomography (SD-OCT) optic disc and macular cube scans, and 10-2 and 24-2 visual fields (VF). Main Outcome Measure: VRQoL, as measured by the NEI VFQ-25.
Results: Twenty-five of 44 (57%) "worse" eyes (defined by 24-2 VF MD) and 13 of 44 (31%) "better" eyes had macular damage. Mean (±standard deviation) MD of worse and better eyes were −3.03 dB (±2.3) and −1.15 dB (±1.7), respectively. Compared to those without macular damage, lower NEI VFQ-25 scores were seen in patients with macular damage in the worse eye (85.4 [± 9.0] vs 94.6 [± 3.3]; P = .0001) and the better eye (84.8 [± 11.1] vs 91.3 [± 6.3]; P = .017). Arcuate damage outside the macula did not affect VRQoL (better eye, P = .40; worse eye, P = .87).
Conclusions: Early glaucomatous macular damage, as detected by abnormal topographic regions on measures of structure and function, is associated with decreased VRQoL. Arcuate damage outside the macula does not have an association with VRQoL in early glaucoma.

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