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Case Report

Exploratory Approaches for the Use of Coenzyme Q10 with Aloe Vera Gel for Leber's Hereditary Optic Neuropathy: Case Report

Megumi Hasegawa[1], Akira Yagi[2]* and Suzuka Ataka[3]

[1]*Pharmacist, Kampo Pharmacy Grace-Meg-Salon, Toshima-ku, Tokyo, Japan*

[2]*Special Adviser of Japan Aloe Science Association and Emeritus Professor, Fukuyama University, Hiroshima, Japan*

[3]*The Director of Med Cell Clinic, Osaka, Kita-ku, Umeda, Osaka, Japan*

***Corresponding Author:** Akira Yagi, Special Adviser of Japan Aloe Science Association and Emeritus Professor, Fukuyama University, Hiroshima, Japan.

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Abstract

There are currently no proven treatments for Leber's hereditary optic neuropathy (LHON; Designation criteria for LHON: Intractable disease 302). Symptomatic treatment and genetic counselling are important in the management of patients with LHON. Idebenone and CoQ10 may prove useful in the treatment of patients with LHON as free radical scavengers. CoQ10 deficiency leads to mitochondrial encephalomyopathy due to interruption of oxidative phosphorylation. Bioavailability treatment of CoQ10 by oral CoQ10/γ cyclodextrin is beneficial in LHON patients. Here we discuss the role of fat-soluble CoQ10 with aloe vera supplementation for LHON patient on the standard point of bioavailability and butyrate-induced modulation of gene expression and cellular function. Lastly, we exhibited a case report of LHON patient by using a lot of CoQ10 with aloe vera supplementation.

Keywords: *Coenzyme Q10; Aloe Vera Gel; Leber's Hereditary Optic Neuropathy*

Introduction

Coenzyme Q10 (CoQ10) is a ubiquitous cofactor in the body, in which the inner mitochondrial membrane plays a pivotal role in the generation of ATP-electron transfer chain. In addition, CoQ10 acts as an antioxidant protecting the cell from oxidant stress by reactive oxygen species. CoQ10 maintains a proton gradient across lysosome membranes to facilitate the breakdown of cellular waste products. During the ageing process, the body becomes deficient in CoQ10 and results in several systemic manifestations. The preliminary insight into using dietary supplementations, CoQ10 with aloe vera juice, to support and optimize quality of life in the people suffering from muscle performance was performed in the questionnaire including 10 points regarding their fatigue, a blood circulatory, headache, and muscle performance [1].

Diseases affecting the retina and brain, such as age-related macular degeneration, glaucoma, Alzheimer's disease and Parkinson's disease have exhibited faults in cellular biochemical reaction attributable to decreased levels of CoQ10 [2]. CoQ10 is originally and synthetically delivered as idebenone and has been evaluated in several studies of patients with Alzheimer's disease, cognitive decline, and dementia. Idebenone, which was evaluated in several studies of patients with Alzheimer's disease, and cognitive decline, has shown to improve visual acuity in Leber's Hereditary Optic Neuropathy (LHON). LHON is caused by primary mitochondrial DNA mutations affecting the mitochondrial respiratory chain complexes [3]. The molecular pathology is thought to be responsible for the dysfunction and eventual apoptotic loss of retinal ganglion cells in the eye, resulting in blindness ultimately. Designation criteria for LHON have been established by the Ministry of Health, Labor, and Welfare of Japan as an intractable disease: 302.

To obtain some specific biochemical markers of age-related macular degeneration (AMD), coenzyme Q10 (CoQ10) levels were determined in plasma and platelets from 19 exudative AMD patients and 19 age-related controls. The results supported the concept that free radicals play a pathogenic role on AMD and that CoQ10 may have a protective effect [4]. CoQ10 is a fat-soluble benzoquinone composition that functions originally as an antioxidant, a membrane stabilizer and a cofactor in the production of adenosine triphosphate by oxidative phosphorylation. The solubility of CoQ10 in digestive juices is extremely low, resulting in a low degree of bioavailability by oral administration. CoQ10/γ cyclodextrin complex revealed excellent pharmacokinetic properties, and significantly higher area under the CoQ10 concentration curve (AUC) in blood plasma from time 0-48 hr. Long-lasting high plasma concentration of CoQ10 provided various kind of health benefits [5].

Present review shows that the effects of CoQ10 and the deficiency can be counteracted through the high oral administration of CoQ10 with intestinal drug absorption enhancement by aloe vera gel supplementation in a high bioavailability in the case report of Leber's hereditary optic neuropathy patient.

Neuroprotective effects of histone deacetylase inhibitors in retina

Histone acetylation and deacetylation can regulate chromosome assembly, gene transcription, and posttranslational modification. They are regulated by histone acetyltransferases and histone deacetylases, respectively, and histone deacetylase inhibitors (HDACis) have the ability to cause hyper-acetylation of histone and non-histone proteins, resulting in a variety of effects on cell proliferation, differentiation, anti-inflammation, and anti-apoptosis. HDACis showed neuroprotective effects in nervous system damage [6]. Apoptosis of retinal photoreceptor cells is a main feature of retinal degenerative diseases. Therefore, HDACis pivotally expressed therapeutic potentials for retinal degenerative diseases.

Influence of aloe vera gel on immune modulation, gut microbiota status, calorie restriction and the role of short chain fatty acids including butyric acid

The health-promoting potential of a balanced microbiota status modulated by calorie restriction (CR) posits a possible close link between gut microbiota (GM) and healthy aging. CR without malnutrition is the most powerful intervention to increase lifespan in simple model organisms and rodents. Two years of CR had broadly favorable effects on both whole-body and regional adiposity that could facilitate health span in humans [7]. The dietary natural source of butyrate through a high fiber diet or butyrate produced by fermentation of non-digestive fiber, such as acemannan in aloe vera gel, is highly appealing approach to present a simple and selectively lower risk method to potentiate the improved outcomes in aged people with brain dysfunctions [8].

The therapeutic potential of a calorie-restricted diet to manage leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON) is a rare mitochondrial retinopathy, caused by mutations in subunits of complex I of the respiratory chain, which leads to elevated levels of oxidative stress and an insufficient energy supply. This molecular pathology seems to be responsible for the dysfunction and eventual apoptotic loss of retinal ganglion cells in the eye resulting in basic blindness [9]. Storoni., *et al*. [10] proposed that a calorie-restricted ketogenic diet has the therapeutic potential to activate mitochondrial bio-energetic power. In earlier reports we discussed that health- promoting potential of a balanced gut microbial state modulated by calorie restriction estimates to have a possible close link between gut microbiota and healthy aging, and that butyrate fermented effectively affects for insulin sensitivity and sirtuin activation through HDAC inhibitors on slowing aging processes [8,11].

Intestinal drug absorption enhancement by aloe vera gel

Absorption-enhancing aloe vera gel has shown a powerful potential to enhance drug permeation across the intestinal epithelial barrier. The transport system of insulin in the presence and absence of the aloe vera extract was fully investigated by Chen., *et al* [12]. Aloe

vera gel was able to significantly reduce the trans-epithelial electrical resistance (TER) of the Caco-2 cell monolayers at concentrations above 0.5% w/v and thereby showed the ability to open tight junctions between adjacent cells. It is important to note that TER value change is fully reversible in the intestinal epithelial barrier. The aloe vera gel extract solution significantly enhanced the transport of insulin across the Caco-2 cell monolayers compared with the control. Aloe vera gel exhibited a potential to be used as absorption enhancer in novel dosage form for drugs with poor bio-availabilities with administrated orally. The co-administration of absorption enhancing agents with macromolecular drugs (e.g., protein and peptide drugs) and high molecular dietary fibers has been identified as a means to improve the oral bioavailability of these natural high molecular origins [13,14].

Bioavailability of CoQ10 by the oral CoQ10/γ-cyclodextrin and CoQ10/ β-cyclodextrin

The solubility of CoQ10 in water is extremely low, resulting in a low bio-availability by oral administration. To improve the low dissolution and bio-availability of CoQ10 by means of complexation with various cyclodextrins (CD), Uekaji., *et al*. [15] investigated the use of the CoQ10-γ CD. The authors found that this long-lasting high CoQ10 concentration in plasma provides various health benefits. Rooney., *et al*. [16] investigated prolonged supplementation with oral CoQ10/β-cyclodextrin inclusion complex in nineteen Thoroughbreds. The prolonged oral CoQ10/ β-cyclodextrin supplementation diet of young, healthy untrained Thoroughbreds increased mean plasma CoQ10 concentration by 99% and mean skeletal muscle complex I+III activity by 65% with variability in absorbance among horses. Enhancement in bioavailability of oral ingestion of CoQ10 by using of cyclodextrins supplementation suggests a possible participation of aloe vera gel polysaccharide to improve visual recovery in LHON patient.

Therapeutic potential of idebenone to improve visual recovery in Leber's hereditary optic neuropathy (LHON) patients

Pemp., *et al*. [17] investigated the changes in visual function and the mutual relation with retinal structure in acute and chronic twenty-three LHON patients treated with idebenone. The strong correlations between optical tomography and visual function parameters were pointed out only after the treatment. The sustained visual recovery after the treatment may strongly suggest a reactivated signal transduction in dysfunctional retinal ganglion cells that survive the acute phase.

A protective action on mitochondrial disease models: miRNA-181a/b downregulation

MiRNAs-containing foods (plants, milk, and animal) are absorbed into the intestine and the miRNAs delivered into the bloodstream via gut membrane. Endocytosis of the exosome (extracellular vesicles that have the same topology as the cell and are rich in selected potential vehicle for bioactive compounds) results in delivery of miRNAs and regulation of the expression of their target genes. Use of miRNAs in foods may be an effective method of disease prevention by synergic combination of modulated miRNA and nutritionals. MiRNA-181 has preferential priority over the B-lymphoid cells of mouse bone marrow, retina, lung, and brain. MiRNA-181 has high-level indication to the thymus which supports the idea that it modulates T cell development in this organ. In humans this miRNA is involved in the mechanisms of immunity. The ectopic expression of miRNA181 in hematopoietic stem/progenitor cells directed to an increased fraction of B-lineage cells in both tissue-culture differentiation assays and adult mice [18]. MiRNAs (miR-181a and miR-181b) were found to specifically regulate the expression of genes involved in mitochondrial homeostasis in the retina by direct targeting of nuclear respiratory factor 1 (*Nrf 1*). Downregulation of these miRNAs in Ndufs4$^{-/-}$ mouse model with LHON-like feature resulted in preservation of functional retinal ganglion cells through a co-activation of mitochondrial biogenesis and mitophagy (the selective degradation of mitochondria by autophagy) and improving the visual phenotype. Indrieri., *et al*. [19] demonstrated that miR-181a/b is important for mitochondria homeostasis in the retina. MiRNA-181a/b inactivation in different animal models of mitochondrial diseases protects neuronal degeneration and ameliorates the disease phenotype in tested models. MiRNA-181a/b inhibition protects neurons from cell death and ameliorates the phenotype of different *in vivo* models of mitochondrial disease, i.e. such as LHON.

B cell-intrinsic epigenetic modulation of antibody responses by short chain fatty acids and butyrate- induced histone acetylation regulates miRNA expression

Short chain fatty acids such as butyric and propionic acid are metabolites from dietary fiber's fermentation by gut microbiota that can affect differentiation or functions of T cells, macrophages and dendritic cells. Sanchez., *et al*. [20] showed that short chain acids (SCFAs) directly impact B cell intrinsic functions at the low does to moderately enhance class-switch DNA recombination (CSR). On the other hand, SCFAs at high doses decrease in a broad physiological range over AID and Blimp-1 expression, CSR, somatic hyper-mutation and plasma cell differentiation. The activation of HDAC inhibitors; butyric and propionic acid impacts intestinal and systemic T-dependent and T-independent antibody responses. The epigenetic impact of SCFAs on B cells extends to inhibition of autoantibody production and autoimmunity in mouse lupus models.

Li., *et al*. [21] showed that butyrate induced histone acetylation regulates miRNA expression. MiRNA expression microarray profiling revealed that 35 miRNA transcripts are significantly ($P < 0.05$) differentially expressed after cells were treated with 10 mM butyrate. Among them, 11 transcripts are differentially expressed very significantly ($P < 0.01$). The functional and pathways analysis using MetaCore analytical suite shows differentially expressed miRNAs targeting some very important gene networks and differentially expressed miRNA may interfere with butyrate induced modulation of gene expression and cellular functions. The data indicate that the complicated interaction between miRNA and histone acetylation forms a highly integrated regulatory mechanism.

Case Report

A 70-years female had blurring and clouding of vision in right eye on March 2017 and her vision loss started in right eye on July 2017. Overtime, vision in right eye worsened with a severe loss of visual acuity. She was diagnosed Leber's hereditary optic neuropathy (LHON). Although central vision in LHON patient gradually improves in a small percentage of cases, in most cases the vision loss is very deep lasting. She got a second opinion of doctor in another hospital, and she was recommended to take a lot amount of CoQ10 to prevent LHON in left eye on May 2018. She started to take CoQ10 1000 mg/day with aloe vera juice 800 ml/day. After three months critical flicker fusion frequency in right eye changed from 15Hz into 33Hz (Standard value: > 35Hz), and visual acuity test in right eye changed 0.03 into 0.4, and left eye was 1.2 into 1.2. On December 2020 at 73-years old, her visual acuity has no trouble in vision and she can drive in night. She continues to take CoQ10 300 mg/day with aloe vera juice 400 ml/day without cataract.

Discussion

In the preliminary report possible prophylaxes of CoQ10 with aloe vera gel to enhancement muscle performance and prevention of headache [1] and to risk remission for congenital heart disease patient were exhibited [22]. Through the ageing process the body system becomes deficient in CoQ10, resulting in reverent manifestation situation. A case report of CoQ10 operative in the mitochondrial membrane successfully showed for Leber's hereditary optic neuropathy (LHON). The bioavailability of aloe vera gel supplementation for CoQ10 was successfully estimated for LHON patient.

Summary/Conclusion

There are currently no proven treatments for Leber's hereditary optic neuropathy (LHON) and symptomatic treatment and genetic counselling are important in the management with LHON. We discussed the role of CoQ10 with aloe vera gel supplementation for a LHON patient, based on the bioavailability standpoint of fat soluble CoQ10, and exhibited a case report of LHON patient. Antioxidant properties of CoQ10 with aloe vera gel supplementation improved visual acuity in LHON patient.

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