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Prooxidant State and Mitochondrial Dysfunction in Retinitis Pigmentosa (RP) Suggest the use of Mitochondrial Nutrients Aimed at Counteracting RP Progression

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REVIEW ARTICLE

INTRODUCTION

In our recent article [1], we summarized the available evidence linking retinitis pigmentosa (RP) to redox anomalies and melanogenesis *vs.* mitochondrial dysfunction, and suggested potential new strategies toward counteracting RP pathogenesis by means of mitochondrial cofactors or "mitochondrial nutrients" (MNs).

Based on that previous report, the present mini-review is aimed at scoring the long-established database about RP-related prooxidant state and mitochondrial dysfunction, as well as the updated reports on these subjects, and the present therapeutic prospects in RP management.

KEYWORDS

Retinitis pigmentosa, Mitochondrial dysfunction, Antioxidants, Flavonoids

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LONG ESTABLISHED DATABASE

As already reported by Luft (1994) [2] the concept of "mitochondrial medicine" was recognized for an extensive - and growing - number of diseases, providing prospect grounds for therapies aimed at counteracting mitochondrial dysfunction.

Early efforts to treat RP-associated prooxidant condition [3] and mitochondrial dysfunction [4,5] provided well-founded prospects for RP management.

USE OF ANTIOXIDANTS IN RP MODELS

The recognized occurrence of a prooxidant state in RP led to several studies testing the effects of antioxidants in RP models. A study by Sanz et al. (2007) [6] tested the effects of some antioxidants in the photoreceptors of the rd1 mouse, an animal model for RP, and to determine if antioxidants could delay the progress of photoreceptor cell death. Retinas of rd1 mice and congenic wild type controls were examined for DNA oxidation and fragmentation. Rd1 retinas were studied in *vitro* and in *vivo* using lutein, zeaxanthin, alpha lipoic acid and reduced l-glutathione. Individual antioxidants had no significant rescue effect but the combination slowed down the rd1 rod photoreceptor degeneration, indicating an additive or synergistic effect.

Fructus Lycii and *Salvia miltiorrhiza* Bunge extract (FSE) were tested *vs.* oxidative stress-induced photoreceptor ferroptosis in RP [7]. The protective effect of FSE on the retina function and structure of rd10 mice was evaluated using histopathological examination, fundus photographs, and

electroretinography. As a conclusion, FSE was suggested in clinical therapeutics to alleviating RP and the mechanism by which inhibits ferroptosis of photoreceptors following oxidative stress.

A mixture of antioxidants was selected to try to maximize protection against oxidative damage achievable by exogenous supplements [8]. Alpha-tocopherol, ascorbic acid, Mn (III) tetrakis (4-benzoic acid) porphyrin, and alpha-lipoic acid were tested in mice that were treated with daily injections of the mixture or each component alone, showing an increase in two biomarkers of oxidative damage, carbonyl adducts measured by ELISA and immunohistochemical staining for acrolein, in the retinas of rd1 mice. The staining for acrolein in remaining cones at P35 was eliminated in antioxidant-treated rd1 mice, confirming that the treatment markedly reduced oxidative damage in cones; this was accompanied by a 2-fold increase in cone cell density and a 50% increase in medium-wavelength cone opsin mRNA. Antioxidants also caused some preservation of cone function based upon photopic electroretinograms. The data supported the hypothesis that gradual cone cell death after rod cell death in RP is due to oxidative damage, and that antioxidant therapy may provide benefit.

A recent study reported on the protective effects of flavonoids in acute models of light-induced retinal degeneration [7]. The results showed that flavonoids modulate the cellular processes, such as oxidative stress, inflammatory responses and apoptosis, that are activated during retinal degeneration. flavonoids stimulate rhodopsin gene expression. The effects of two main dietary flavonoids, quercetin and myricetin were evaluated. Treatment with these flavonoids prior to light insult remarkably protected retina from deterioration and preserved its function. Altogether, flavonoids were found to have significant prophylactic value for retinal degenerative diseases.

RP-ASSOCIATED MITOCHONDRIAL DYSFUNCTION - EFFECTS OF MITOCHONDRIAL NUTRIENTS

A recent and growing database highlights the relevance of mitochondrial dysfunction in RP pathogenesis, along with the protective function of mitochondrial cofactors, or mitochondrial nutrients (MNs) [9-13].

It should be stressed that each MN is characterized by distinct roles in mitochondrial function. Thus, their therapeutic functions may be confined by their different roles in mitochondria, suggesting their combined use in clinical applications, as suggested by Tarnopolski [14] and confirmed by us.

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