Mitochondrion 36 (2017) 7–14

Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Targeting mitochondrial function to treat optic neuropathy

Nuri Gueven *, Monila Nadikudi, Abraham Daniel, Jamuna Chhetri

Pharmacy, School of Medicine, University of Tasmania, Hobart, TAS, Australia

ARTICLE INFO

Article history:
Received 31 May 2016
Received in revised form 25 July 2016
Accepted 26 July 2016
Available online 28 July 2016

Keywords:
Retinopathy
Optic neuropathy
Age-related macular degeneration
Diabetic retinopathy
Glaucoma
Leber's hereditary optic neuropathy (LHON)
Mitochondrial dysfunction
CoQ_{10}
Idebenone
EPI-743
MitoQ
SkQ1
Ocluvia
MTP-131

ABSTRACT

Many reports have illustrated a tight connection between vision and mitochondrial function. Not only are most mitochondrial diseases associated with some form of vision impairment, many ophthalmological disorders such as glaucoma, age-related macular degeneration and diabetic retinopathy also show signs of mitochondrial dysfunction. Despite a vast amount of evidence, vision loss is still only treated symptomatically, which is only partially a consequence of resistance to acknowledge that mitochondria could be the common denominator and hence a promising therapeutic target. More importantly, clinical support of this concept is only emerging. Moreover, only a few drug candidates and treatment strategies are in development or approved that selectively aim to restore mitochondrial function. This review rationalizes the currently developed therapeutic approaches that target mitochondrial function by discussing their proposed mode(s) of action and provides an overview on their development status with regards to optic neuropathies.

1. Introduction

Mitochondria are dynamic intracellular organelles that are involved in a multitude of cellular processes ranging from metabolic functions to calcium homeostasis and the regulation of cell death. Their most important function however is to supply cells with chemical energy in form of ATP. Mitochondrial numbers vary from hundreds to thousand depending on the specific energy demands of the host cell. Consequently, high mitochondrial content is found in tissues with a high energy demand such as the visual system. Therefore, not surprising, the visual system is highly susceptible to impaired energy supply as a consequence of mitochondrial dysfunction. This is supported by the observation that practically all patients with mitochondrial disorders typically show some form of visual impairment such as decreased contrast sensitivity, impaired colour vision, optic nerve dysfunction, pigmentary retinopathy, retinal dysfunction, loss of retinal ganglion cells (RGC) and blindness (Fraser et al., 2010; Chhetri and Gueven, 2016). In addition, the major ocular diseases including diabetic retinopathy, glaucoma and age-related macular degeneration are also associated with mitochondrial dysfunction and share clinical similarities with the hereditary mitochondrial diseases (Chhetri and Gueven, 2016; Jarrett et al., 2008). In addition to the production of chemical energy, mitochondria are also one of the major sites for the generation of reactive oxidative species (ROS), especially under conditions where normal mitochondrial function is disturbed (Nita and Grzybowski, 2016). The resulting oxidative stress is known to cause damage to mitochondrial membranes, proteins and mitochondrial DNA (mtDNA). This macromolecular damage further worsens bioenergetic failure by impairing normal electron flow through the mitochondrial respiratory chain (Guo et al., 2013). Ultimately, the sum of these events is thought to result in retinal cell death and loss of visual acuity (Jarrett et al., 2010).

Despite the evidence that mitochondrial dysfunction is a common denominator at the heart of many ophthalmological indications, at present there are hardly any approved treatment options that aim to protect vision by normalizing mitochondrial function. The most insight and useful data that support this specific type of pharmacological intervention is derived from trials in Leber's Hereditary Optic Neuropathy (LHON) patients. LHON, one of the most common mitochondrial disorders, is typically associated with acute or subacute vision loss in one eye, followed by loss of visual acuity in the second eye within a few weeks (Yu-Wai-Man et al., 2011). During the early course of the disease colour

* Corresponding author at: Pharmacy, School of Medicine, Faculty of Health, University of Tasmania, Australia.
E-mail address: nguven@utas.edu.au (N. Gueven).
URL: http://www.utas.edu.au/pharmacy (N. Gueven).

http://dx.doi.org/10.1016/j.mito.2016.07.013
1567-7249/

vision is frequently affected (Yu-Wai-Man et al., 2011). While LHON is mostly seen in young adults between 15 and 35 years of age, vision loss is observed in around 50% of male carriers but only 10% of female carriers (Yu-Wai-Man et al., 2011). LHON is caused by mutations in the mtDNA encoded subunits of NADPH-ubiquinone oxidoreductase (mitochondrial Complex I) in combination with so far mostly uncharacterized risk factors. Over 95% of all cases are associated with one of the three pathogenic 'primary LHON mutations' in complex I subunits: ND1 (3460G>A), ND4 (11778G>A) or ND6 (14484T>C). These mutations impair oxidative phosphorylation, reduce ATP production and give rise to oxidative stress that makes RGC more susceptible to apoptotic cell death (Yu-Wai-Man et al., 2011). Consequently, neuronal signal transmission from the retina to the brain is affected, which in the long term also affects neuronal viability in the innervated brain regions (Rizzo et al., 2012).

Among the disorders characterized by mitochondrial dysfunction-induced vision loss, LHON is remarkable. Although, in most LHON cases vision loss is permanent, cases of spontaneous visual recovery have been reported, often years after disease onset (Fraser et al., 2010). This spontaneous recovery of visual acuity suggests that in the initial stages of the disease, vision loss is not a direct consequence of retinal cell loss but might rather be a consequence of cellular dysfunction that impairs signal transmission between the retina and the brain (Howell, 1998; Gueven, 2014). In line with this hypothesis, the selective loss of RGCs in LHON, observed as thinning of the retinal nerve fibre layer (RNFL), occurs only at the late, atrophic stage of the disease, which makes visual recovery impossible at this time point (Carelli et al., 2002; Carelli et al., 2007). Therefore, the time period between cellular dysfunction and cell loss can be regarded as a window of opportunity where vision could be restored by normalizing mitochondrial function (Howell, 1998). Considering the mitochondrial origin of many ocular diseases, targeting mitochondria could be a potential disease modifying treatment for optic neuropathies where only symptomatic or no treatment options are currently available (Chhetri and Gueven, 2016).

2. Drugs and drug candidates

2.1. Coenzyme Q10

Coenzyme Q_{10} (CoQ_{10}) is a naturally occurring ubiquinone present in all cellular membranes of all tissues and is predominantly synthesized in the liver. It belongs to the class of benzoquinones that differ mainly in their tail length, which significantly affects their solubility (Fig. 1). A large proportion of CoQ_{10} is present in the mitochondrial inner membrane as an integral part of the mitochondrial electron transport chain, where it is mainly responsible for the shuttling of electrons from complexes I and II onto complex III. This redox activity is essential for mitochondrial ATP synthesis in a concentration-dependent manner. At the same time CoQ_{10}, fully reduced to the hydroquinone acts as an effective antioxidant that can scavenge free radicals within cellular membranes (Papucci et al., 2003; Chen et al., 2011). Several neurodegenerative and age-related disorders that are associated with visual impairment (Nunomura et al., 2007; Valero, 2014; Chhetri and Gueven, 2016) have been associated with low CoQ_{10} levels (Crane, 2001; Aguilaniu et al., 2005; Navas et al., 2007). Lowered CoQ_{10} levels by up to 40% have been reported for the retina (Qu et al., 2009) and the resulting oxidative stress has been implicated in many eye diseases like cataract formation, diabetic retinopathy, glaucoma and age-related macular degeneration (Williams, 2008; Kernt et al., 2010; Chhetri and Gueven, 2016). Consequently, dietary CoQ_{10} supplementation has been suggested as intervention for many retinopathies but only a limited number of clinical trials have included CoQ_{10}. At present, real evidence from properly controlled clinical trials for the effectiveness of CoQ_{10} to protect against vision loss is not available. This absence of measurable therapeutic effectiveness is also attributed to the extreme hydrophobic nature of CoQ_{10} and its poor bioavailability. Although, dietary CoQ_{10} was reported to increase CoQ_{10} plasma levels (Gueven et al., 2015), it remains unclear if CoQ_{10} can actually enter the eye. As a consequence, short-chain CoQ_{10} analogues with increased solubility, bioavailability and better pharmacokinetic properties have been widely investigated.

2.2. Short-chain Quinones

2.2.1. Idebenone

Idebenone is widely described as a synthetic analogue of CoQ_{10} due to its structural similarity to CoQ_{10} (Fig. 1). Similar to CoQ_{10}, in the reduced state idebenone can act as an electron carrier in the mitochondrial electron transfer chain (ETC) and as potent antioxidant, which has led to the assumption that idebenone is a functional CoQ_{10} analogue. However, idebenone has a much shorter and less lipophilic side chain that also includes a terminal hydroxyl group. Likely due to its changed structure and solubility, idebenone differs from CoQ_{10} in many respects (Gueven et al., 2015). In contrast to CoQ_{10}, idebenone was reported to participate in redox reactions outside the mitochondria (Haefeli et al., 2011). Many mitochondrial disorders, including optic neuropathies such as in LHON and glaucoma are associated with dysfunctional mitochondrial complex I (Chhetri and Gueven, 2016; Lee et al., 2012). In this context, idebenone promised to directly alleviate this defect, which was based on its reported electron carrier function that takes place in the presence of a dysfunctional complex 1 enzyme. Importantly, this function has not been associated with CoQ_{10}, which is a direct result of its much lower solubility (Haefeli et al., 2011; Erb et al., 2012; Giorgio

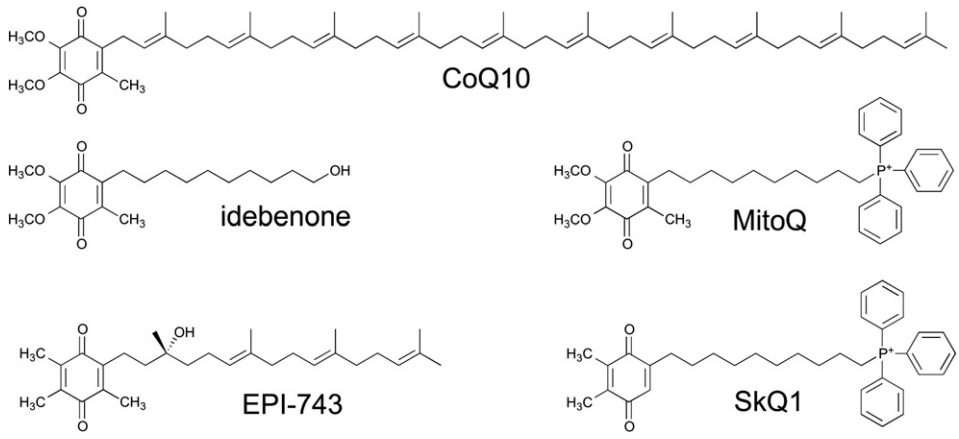

Fig. 1. Structural comparison of coenzyme Q10 (CoQ10) and the most advanced short-chain quinone compounds that are either marketed (Idebenone, SkQ1) or in clinical development for mitochondrial and/or ophthalmological indications.