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Visual light effects on mitochondria: The potential implications in relation to glaucoma☆

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ABSTRACT

Light of different wave-lengths have the potential to interact with four major mitochondrial protein complexes that are involved in the generation of ATP. Neurones of the central nervous system have an absolute dependence on mitochondrial generated ATP. Laboratory studies show that short-wave or blue light (400–480 nm) that impinges on the retina affect flavin and cytochrome constituents associated with mitochondria to decrease the rate of ATP formation, stimulate ROS and results in cell death. This suggests that blue light could potentially have a negative influence on retinal ganglion cell (RGC) mitochondria that are abundant and not shielded by macular pigments as occurs for photoreceptor mitochondria. This might be of significance in glaucoma where it is likely that RGC mitochondria are already affected and therefore be more susceptible to blue light. Thus simply filtering out some natural blue light from entering the eye might be beneficial for the treatment of glaucoma.

Long-wave or red light (650–800 nm) affects mitochondrial complex IV or cytochrome oxidase to increase the rate of formation of ATP and ROS causing the generation of a number of beneficial factors. Significantly, laboratory studies show that increasing the normal amount of natural red light reaching rat RGC mitochondria in situ, subjected to ischemia, proved to be beneficial. A challenge now is to test whether extra red light delivered to the human retina can slow-down RGC loss in glaucoma. Such a methodology has also the advantage of being non-invasive. One very exciting possibility might be in the production of a lens where solar UV light is convertes to add to the amount of natural red light entering the eye.

1. Introduction

A body of evidence exist to support the view that mitochondrial dysfunction accounts not only for the initiation of glaucoma (primary open-angle glaucoma) but also for the progressive loss of vision (Lee et al., 2012; Lee et al., 2011; Osborne, 2010; Osborne et al., 2006; Osborne et al., 2016). Similarities between glaucoma and mitochondrial optic neuropathies such as Leber's Hereditary Optic Neuropathy and Autosomal Dominant Optic Atrophy exist where a specific loss of retinal ganglion cells (RGCs) is a common feature. However, unlike mitochondrial optic neuropathies which have a genetic origin, glaucoma is generally viewed as a disease caused by impairment in the regulation of blood flow (Fig. 1) to the optic nerve head (ONH). In high tension glaucoma this may be primarily caused by, raised intraocular pressure (IOP) while in both normal and high tension glaucoma diurnal fluctuations in IOP, arterial hypertension, low systolic perfusion pressure, low diastolic perfusion pressure, a reduction of blood pressure in hypertensive patients, cardiovascular disease, migraines, vasospastic disorders, arteriosclerosis or cerebral spinal fluid pressure changes might be the causes (Caprioli and Coleman, 2010; Hayreh, 2001; Leske et al., 2008; Osborne, 2010; Osborne et al., 2006).

An inefficient delivery of blood supply to the ONH can induce ischemia, which is defined as a reduction in the supply of nutrients and oxygen. In the retina mitochondria are particularly concentrated in the unmyelinated portion of mammalian RGC ONH axons (Andrews et al., 1999; Bristow et al., 2002; Carelli et al., 2004). Mitochondria perform a number of tasks including maintaining homeostasis, and numerous metabolic functions that include oxidative energy metabolism, control of intracellular calcium levels and the regulation of neuronal excitability and synaptic transmission (Chan, 2006; Moreira et al., 2010; Schon and Manfredi, 2003). Neurons such as RGCs, contrast to most dividing cells e.g. fibroblasts, have an absolute requirement for optimal mitochondrial function to maintain survival (Osborne et al., 2008). Approximately 90% of generated ATP in neurones is used to maintain membrane dynamics and even a brief period of oxygen or glucose deprivation results in impaired mitochondrial function, loss of a neurone's action potential and eventual cell death (Albers and Beal, 2000; Moreira et al., 2007).

The present information therefore argues that glaucoma is initiated by impairment in the regulation of ONH blood flow to cause a compromise in

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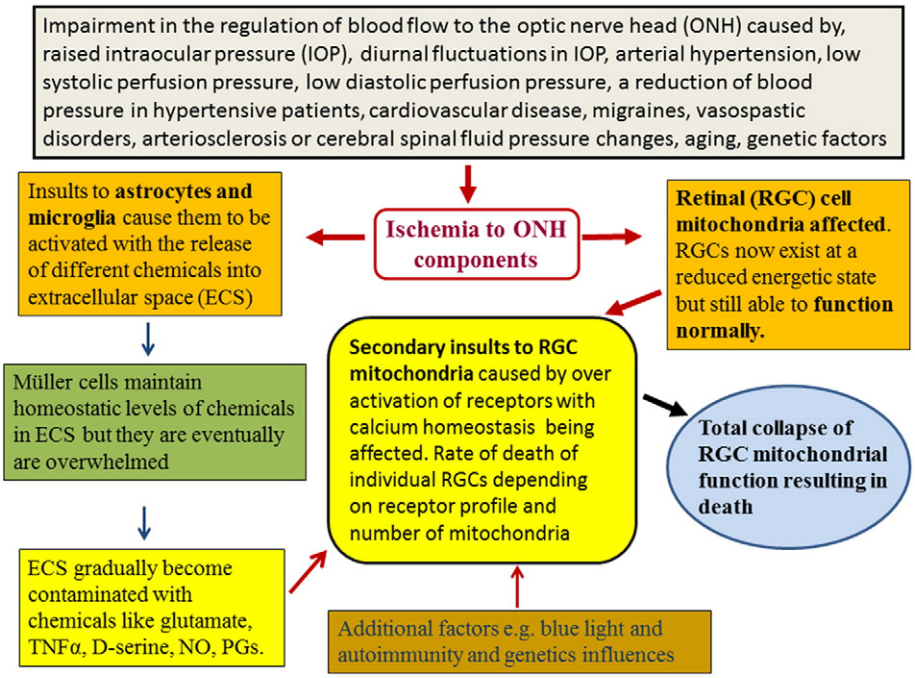

Fig. 1. Hypothesis summarising the proposed steps that might occur in glaucoma resulting in the death of RGCs at different times.

RGC mitochondrial homeostasis (Fig. 1). Over time, RGC mitochondrial susceptibility is then envisaged to gradually deteriorate because of various insults that include the influence of short wave light, eventually culminating in neuronal death (Fig. 1) (Almasieh et al., 2012; Calkins, 2012; Osborne, 2010; Osborne et al., 2014; Osborne et al., 2016; Vecino et al., 2016). Thus the use of barrier filters to reduce the amount of short wave length light reaching the retina might enhance the survival period of RGC mitochondria in glaucoma subjects.

The purpose of this overview is to summarise laboratory experiments that argue a case for the potential negative effects of blue light for glaucoma subjects. It is important to emphasise that it is not proposed that blue light can "induce" normal or high tension glaucoma but rather have the potential exacerbate the diseases through an action on RGC mitochondria. Moreover, the well-known beneficial properties of red to infra-red light in enhancing mitochondrial function will be highlighted and proposed as a non-invasive potential means for the treatment of glaucoma. Presently, only IOP lowering agents are used to treat glaucoma and it is thought that the mode of action is to either directly or indirectly enhances blood delivery to the ONH.

1.1. Visible light and mitochondria

Mitochondria contain a number of chromophores that can absorb light of various wavelengths. Flavin and cytochrome oxidases associated with the electron transport system of mitochondria are involved in the generation of ATP and absorb light. Indeed, (Chance and Hess, 1959) demonstrated that the absorption of light by tumour cells in the violet/green to red portion of the visual spectrum was qualitatively identical to that of isolated mitochondria. It is worth noting in this context that mitochondria associated with neurones in other parts of the central nervous tissue than those in the retina are not exposed to visible light. Also, in the eye the cornea has to be transparent and mitochondria located in this tissue as well as the lens will be more exposed to light than cells elsewhere, which are often shielded by skin pigments.

The cornea absorbs wavelengths below 290 nm while the lens in the adult human eye absorbs longer-wavelength UVB (295–310 nm), and the full range of UVA (310–340 nm). Both the cornea and the lens also absorb part of the infrared radiation - mainly the water bands at 980 nm, 1200 nm, and 1430 nm (Behar-Cohen et al., 2011; Said and Weale, 1959). The vitreous absorbs light of >1400 nm up to 10 μm (Boettner and Wolter, 1962). Thus, the non-ionizing radiation reaching the retina is the so-called 'visible component' of the electromagnetic spectrum (340–800 nm), and some of the near infrared (800–1400 nm). The average human retina absorbs approximately 10^{12} to 10^{15} photons at a time which can be greatly increased by workplace exposure (e.g. welders), activities in high light environments (such as sunshine during skiing) or medical imaging of the retina (Hunter et al., 2012; Porter et al., 2006).

The transmission of visible light to the retina decreases with increasing age, largely because of age-related changes in the composition of the lens, which accumulates chromophores that absorb short-wavelength visible light. On reaching biological systems, photons are transferred into chemical molecules. Depending on the wavelength and energy of the light, the type of molecule and the environment in which it is located, either a release of free radicals (photodynamic effect) or an emission of light (fluorescence) occurs. Photodynamic effects depend on the production of "singlet oxygen" and reactive oxygen species (ROS) (Wilson and Patterson, 2008). Excess ROS production can result in the modification of lipid, protein and DNA functions.

Haemoglobin and other proteins that contain porphyrin, such as the mitochondrial enzyme cytochrome oxidase (COX), are known to have absorption maxima around 400–410 nm (Mellerio, 1994). The porphyrin triplets formed by absorption of photons can result in the formation of singlet oxygen and ROS (Bonnett et al., 1980). It is also known that COX absorbs particularly in the blue and red parts of the spectrum in both its oxidised and reduced forms (Bell and Hall, 1981). Another mitochondrial enzyme, cytochrome P450, absorbs light of wavelengths around 450 nm when bound to carbon monoxide (Ortiz de Montellano, 1995). Flavins such as riboflavin (vitamin B_2) and flavoprotein nucleotides are essential components of numerous cytosolic and mitochondrial enzyme systems. The absorption spectra of flavins are around 450–520 nm and when activated, causes oxidation of several substances and the generation of hydrogen peroxide (García and Silva, 1997; Hockberger et al., 1999). Porphyrins are also targets of blue light and have been particularly studied in the context of photodynamic therapy (Dolmans et al., 2003; McCarron et al., 2003), but porphyrins also exist in the mitochondrial inner membrane and therefore are potentially affected by blue light (Gorgidze et al., 1998; Wataha et al., 2004).