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Review

The effect of visual blue light on mitochondrial function associated with retinal ganglions cells☆,☆☆

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ABSTRACT

The retina is the only part of the central nervous system that is exposed to light radiation between 400 and 780 nm. Short wavelength light (SWL) ranging between 400 and 480 nm are absorbed maximally by chromophores located in mitochondria. An abundance of mitochondria are located in retinal ganglion cell (RGC) intraocular axons and photoreceptor inner segments and as a consequence SWL will impact these organelles. The purpose of this article is to summarise the experimental evidence for the possible negative effects of SWL on RGC mitochondria, *in situ*. The threat of damage to photoreceptor mitochondria may be less than to RGCs, since macular carotenoid, located chiefly in Henle's layer of the photoreceptor inner segment absorbs SWL. The article underlines the hypothesis that SWL contributes to RGC death when these neurones are not in an optimum homoeostatic state as is likely to occur in conditions such as glaucoma and possibly other types of pathologies and even old age. A case therefore exists for the idea that shielding RGCs to slow down visual loss in certain circumstances. This can theoretically be achieved with lenses that reduce transmission of SWL but specifically allow for maximal transmission of 479 nm[1] light to stimulate melanopsin and maintain an optimum sleep/wake cycle.

1. Introduction

Mitochondria perform a number of tasks associated with a variety of functions in defined cell types (Chan, 2006; Schon and Manfredi, 2003). While certain cell types generate sufficient ATP to maintain function through mitochondrial-independent processes like glycolysis this is not the case for neurones (Osborne et al., 2008). Neurons require an abundance of ATP and dependent on optimum mitochondrial function. Approximately 90% of mitochondrial generated ATP is used to maintain membrane dynamics for neuronal survival and even a brief period of oxygen or glucose deprivation results in impaired function, loss of action potentials and subsequent death (Albers and Beal, 2000; Moreira et al., 2007). Significantly, retinal ganglion cell (RGC) intraocular axons are abundant in mitochondria to produce the energy required to propagate action potentials in this part of this neurone (Bristow et al., 2002; Wang et al., 2003). Thus efficient intraocular axon mitochondrial function is essential to maintain overall function of RGCs.

The aim of this article is provide evidence to suggest that short wavelength light (SWL) ranging between 400 and 450 nm falling on the retina will have a negative function of RGCs in certain situations because of maximum absorption by RGC intraocular axonal mitochondrial chromophores (Fig. 1). An abundance of mitochondria also exists in the inner segments of photoreceptors (Stone et al., 2008) revealing their importance and the possible influence of SWL on these organelles in photoreceptors. However, the intensity of SWL falling on photoreceptor mitochondria will be less than in RGCs because of absorption by retinal tissue and particularly by the macular carotenoids (Krinsky et al., 2003).

2. Light effects on mitochondria

Numerous studies have shown that light impinging on the retina (approximately 400–780 nm) is absorbed by enzyme complexes of the electron transport system of mitochondria. Significantly, SWL loosely defined as being between 400 and 450 nm in the blue/violet part of the spectrum (Chen et al., 1992a, 1992b, 2003; Egorov et al., 1999; Godley et al., 2005; Jung et al., 1990; King et al., 2004), as opposed to long wavelength (approximately

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[1] Although the peak wave length of melanopsin is around 479nm even filtering out SWL of up to 485nm will still allow for sufficient stimulation of melanopsin.

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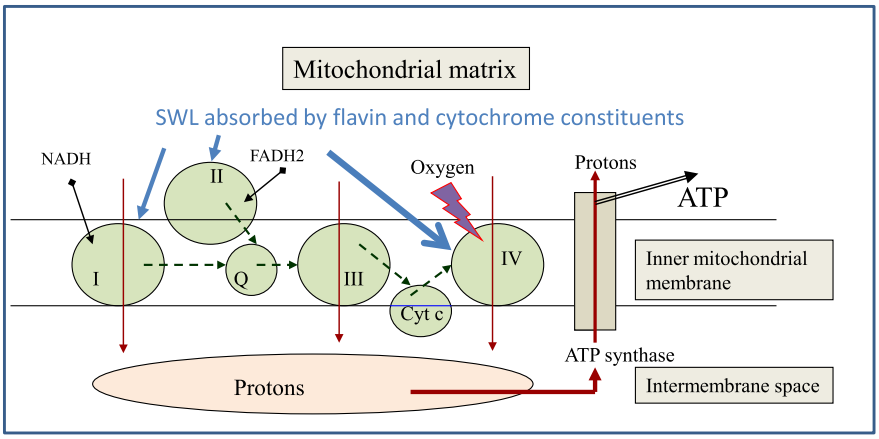

Fig. 1. Flavin and cytochrome constituents associated with complex I, II and IV of the electron transport chain are able to absorb short wavelength (SWL) in the range of 400–480 nm (blue arrows). Only retinal mitochondria are directly exposed to SWL light in the central nervous system. It is proposed therefore that when retinal ganglion cell mitochondria no longer function optimally (for one reason or another) SWL can stimulate this process. The electron transport chain generates optimum levels of ATP and free radicals like nitric oxide when sufficient oxygen is available to bind to complex IV or cytochrome c oxidase. This process requires the substrates NADH and $FADH_2$ to donate electrons (black arrows) to the electron transport chain at complexes I and II and transfer them along a chain of other carriers (ubiquinone or Q, complex III, cytochrome c or Cyt c and complex IV or cytochrome c oxidase) also situated in the inner mitochondrial membrane. At complexes I, III and IV the electrons are used to translocate protons from the mitochondrial matrix to the intermembrane space (red thin arrows). This process generates a proton-electrochemical potential gradient across the inner mitochondrial membrane, which is known as the proton-motive force. The proton-motive force (red thick arrow) is used to drive gradient-dissipating activities, including the generation of ATP by ATP synthase, which is the main pathway for the return of protons to the matrix.

750 nm or more) or red light (del Olmo-Aguado et al., 2012; Fitzgerald et al., 2013), negatively affects mitochondrial functions. The potential for a negative effect of SWL on retinal cell mitochondria *in situ* therefore exists and if this is the case then reducing the amount of SWL impinging on the retina might be beneficial in such situations (Osborne et al., 2006, 2008). This might relate to the ageing retina, where functional mitochondria are thought to no longer be in an optimum homoeostatic state. The mitochondrial theory of ageing argues that progressive accumulation of mutations in mitochondrial DNA (mtDNA) reduces ATP output and increases ROS production driving oxidative stress, inflammation and cell loss (Boveris and Navarro, 2008; Dietrich and Horvath, 2010; Harman, 1981; Osborne et al., 2014). It might also relate to metabolic diseases like type II diabetes where mitochondrial-associated abnormalities and changes in bioenergetics occur (Szendroedi et al., 2012) and where RGCs are particularly affected (Kern and Barber, 2008). It may relate to inherited optic neuropathies, like Leber's optic neuropathy, where genes associated with subunits of complex I of the mitochondrial respiratory chain are affected (Carelli et al., 2004). It might also relate to glaucoma, as it is proposed that once glaucoma is diagnosed, many functional RGCs exist in a reduced homoeostatic state and are then susceptible to SWL (Osborne, 2010; Osborne et al., 2006, 2001). As shown in Fig. 2, RGC mitochondria may therefore not exist in an optimum homoeostatic state in various retinal diseases (e.g. glaucoma, diabetes, inherited optic neuropathies) and in the aged retina. It is proposed that RGCs existing in such a state will benefit from a reduction in SWL impinging on their intraocular axons.

3. Light reaching the retina

The wavelength of light reaching the retina varies over the range between 400 and 780 nm. More reactive shorter wavelengths are prevented from reaching the retina by the cornea and lens (Hunter et al., 2012; Sliney, 2002). The cornea absorbs wavelengths below 295 nm while the lens strongly absorbs wavelengths of light between 300 and 400 nm (Behar-Cohen et al., 2011; Said and Weale, 1959). Both the cornea and lens also absorb some infrared radiation (980–1430 nm) and the vitreous absorbs light above 1400 nm (Boettner and Wolter, 1962). Absorption of the shorter wavelengths of visible radiation by the lens rises exponentially with age, due to yellowing caused by a gradual accumulation of chromophores in the lens (Behar-Cohen et al., 2011; Weale, 1988). Thus, the region of the electromagnetic spectrum termed "visible light" that reaches the retina is between 400 and 780 nm or even 800 nm and each day the average human retina absorbs approximately 10^{12} to 10^{15} photons that 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 negative effect of light generally on the retina was first demonstrated in the 1960s. Early laboratory studies revealed that when rodents are exposed to continuous or intense amounts of fluorescent or incandescent light sources, damage to their photoreceptors can occur (Gorn and Kuwabara, 1967; Grignolo et al., 1969; Kuwabara and Gorn, 1968; Noell et al., 1966; O'Steen, 1970; O'Steen and Anderson, 1972). Retinal photoreceptors, paradoxically, are uniquely adapted to function over a wide range of ambient conditions, but it is now clear that prolonged intense light exposure not only causes photoreceptor damage but also induces the generation of reactive oxygen species (ROS). Significantly, the light intensity experienced by nocturnal animals to cause visual cell damage needs only to be two or three times above room lighting for this to occur (Noell, 1965; Noell et al., 1966; Organisciak and Vaughan, 2010). Such findings have historically been related to the aetiology of debilitating ocular conditions where photoreceptor dysfunction takes place as occurs in age-related macular degeneration (AMD) (Andley and Chylack, 1990; Beatty et al., 2000; Feigl, 2009; Sliney, 1988).

4. Retinal chromophores potentially involved in photodamage

Light of defined wavelengths is capable of interacting with various eye tissues through different mechanisms. Some eye pigments absorb specific wavelengths of light and in the process help to maintain retinal homoeostasis. Other chromophores are affected by specific wavelengths of light to induce oxidative stress, defined