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MINIREVIEWS

# Blue light induced retinal oxidative stress: Implications for macular degeneration

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## Abstract

A number of studies have shown that oxidative stress can be harmful for the retina. The real causal circumstances that lead to degenerative diseases like age related macular degeneration remain obscure. Whether light induced radical stress is a direct interaction of light with photoreceptors or a secondary mechanism within the pigment epithelium or choroid is in discussion. Among the molecular mechanisms involved are production of reactive oxygen species (ROS), secondary lipid peroxidation, protein oxidation and DNA-damage. The initial trigger to write this review was first a recent finding of our group that the photoreceptor outer segments produce great amounts of ROS and second the detection of ectopic enzymes of the respiratory chain localized there - in addition to the hitherto known ROS sources like the visual pigments with their intermediates and the photoreceptor mitochondria harbouring the respiratory chain.



**Key words:** Blue light; Oxidative stress; Retina; Photoreceptor; Age related macular degeneration

**Core tip:** The role of blue light and oxidative stress in the pathogenesis of retinal degenerative diseases like age related macular degeneration is still under debate. Recent studies including ours have demonstrated that all molecules of the respiratory chain are present in the outer segment of the photoreceptors-also being the source of reactive oxygen species-even more than the reactive oxygen species production in inner segment mitochondria. These two new findings have also important implications for many degenerative diseases of the retina. In this respect we revisited the literature regarding the photoreceptor reactions after blue light and radical stress.

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## INTRODUCTION

Age related macular degeneration (AMD) has-like many neurodegenerative diseases-a multifaceted genesis with genetic, metabolic, immune and environmental factors[1,2]. Blue light damage and oxidative stress are prominent among the environmental factors, which are discussed recently[3,4]. Comprehensive and update reviews were

published about oxidative stress in retinal cells in general and the relation to AMD by Jarrett *et al*[2] as well as about the blue light impact in the retina[4]. So we focussed more on the localization of blue light induced oxidative stress in retinal cells, especially in photoreceptors.

Here we want to show that photoreceptors are direct sources of oxidative stress after blue light impingement-especially their outer segments, in addition to the commonly known sites of radical production (mitochondria, chromophores and photosensitizers like lipofuscin). This is due to complex metabolic machinery in the outer segments where ectopic enzymes of the respiratory chain are located - besides the commonly known sources like NADPH-oxidases (NOX) and the visual pigments and their metabolites.

## THE PHOTORECEPTORS AND THEIR SURROUNDINGS AS POSSIBLE SITES OF RADICAL PRODUCTION

Compared to other cell types of the retina, some features render the photoreceptors most vulnerable to oxidative damage. The photopigment rhodopsin is located within the outer segment discs. This rhodopsin undergoes photochemical processes, which lead to intermediates producing radicals a fact which is shown by the protein RPE65 (regeneration cycle protein of rhodopsin): without RPE65 blue light is much less dangerous for the retina[5]. Rhodopsin regeneration can also be halted by halothane, which renders the retina relatively insensitive to blue light[6].

Also secondary sources for radicals exist in the outer segments of the photoreceptors: high amounts of polyunsaturated fatty acids, which are especially prone to oxidation and carboxyethylpyrrol-modified proteins (CEP). These derivates of the non enzymatic oxidation of docosahexanoid acid originate during radical impact, molecules that are believed to be very harmful because these adducts can cause neovascularisation in tiny concentrations and independent from the VEGF pathway[7]. All these lipid and protein oxidation products deposit near Bruch's membrane and in Drusen below the RPE. Furthermore, these CEP proteins and other derivates of this kind are antigenic[8].

Normally, an over boarding accumulation of such waste products is prevented by constant renewal of the outer segment discs (around 10 of the many 100 discs per day)-means about 3 billion times disc shedding till an age of 70 years[9-11].

Oxidation of the disc membranes is also driven by the enormously high pO2 coming from the choroid-a region, which was previously thought to be "overperfused"[12-14]. However, in more pathologic states also zones of choroidal hypoxia can exist. Mostly, zones of wet-AMD-choroidal neovascularisation are located in areas of poor choroidal perfusion[13,14]. In non-exudative AMD, too the average choroidal flow is lower[15].

Even more important than the absolute oxygen partial pressure (pO2) in the choroid is the pO2 gradient also under physiological conditions. In their review, Stefánsson *et al*[14] report that under physiologic conditions "the pO2 decreases almost linearly with the distance from the choro capillaries to the inner portion of the photoreceptors". Interestingly, at the inner portion of the photoreceptors, the pO2 can reach 0 mmHg in the dark and is a little higher in the light. Hindrances in the diffusion through Bruch´s membrane (see above) will even lower this pO2 at the inner segment of the photoreceptor. At its outermost part (the ellipsoid), is the location of the photoreceptor mitochondria. This location, nearest possible to the pO2 source, is typical for the mitochondria that are moving actively to this location in many cell types[16].

## BLUE LIGHT STRESS IN THE RETINA

The term light (or blue light-) stress of the retina is a multifaceted one: One should discern between (1) high intensity short-term damage (till 10 s): this means that the energy which impinges the retina is higher than the thermal diffusion (burning of the retina and especially of the RPE); and (2) low-dosage long-term effects (10 s and longer - till decades in human eyes).

For AMD pathogenesis Lawwill *et al*[17] demonstrated in 1977 that also low irradiation intensities of short wave length light could induce significant quantities of radicals-here, a cumulative retinal damage takes place during this kind of irradiation. Such low threshold blue light (may also be fractionated) can lead to accumulation of dangerous oxidation products also with the previously mentioned secondary oxidative reactions[17-19].

Regarding the whole eye, the cornea absorbs the UV - fraction of the light, the lens absorbs also wavelengths above 380 nm till around 400 nm. In elderly persons, the lens can absorb even wavelengths higher than 450 nm. This means the lens has a yellow till brownish colour-filtering out parts of the blue spectrum[20-22].

Besides the regulation *via* the pupil, the sensitivity of the eye is adjusted by regulation of the amount photopigment within the photoreceptors. More sensitive photopigment is located in the disc membranes under low light than if it is adapted to bright light. In addition to this, a feedback control *via* the horizontal cells exists[23]. If the spectrum is not continuous and shows only a few peaks, *e.g.*, in strip lamp light the eye adjusts to the irradiation energy, which is integral to the peaks (which is less than in a continuous spectrum at the level of the peaks). Thus, the eye increases its sensitivity and gets more vulnerable light especially to the harmful wavelengths (blue peak). Many experimental studies prove the capability of the photoreceptors to adapt by the mechanisms mentioned above. Indeed, animals reared in dark have more photopigment than those reared under a normal day-night cycle [18,24-28].

## ROS DAMAGE IN THE MACULA

The photoreceptors of the macula are exposed directly

to the light-no other cell layers are covering the photoreceptors and are absorbing parts of the light spectrum *via* cytochromes or other cell pigments[29].

Within the photoreceptors of the macula, the antioxidative molecules lutein and zeaxanthin filter out blue light due to their yellow colour as natural "sunglasses". These (also antioxidative) molecules are concentrated here thousand fold compared to other regions of the retina. The presence of lutein in this domain is also consistent with the proposed role of carotenoids in energy dissipation: in post-mortem human macula and retinal pigment epithelium a significant singlet oxygen scavenging capacity was found, which was based on these carotenoids[30]. Furthermore, Woo *et al*[31] could show experimentally that lutein itself has a great neuroprotective potential.

## COMBINATION OF BLUE LIGHT STRESS AND ROS DAMAGE

A hint for the close connection of blue light stress and ROS production in the RPE comes from the observation that blue light toxicity is much higher under oxygenation levels near 100%-a situation found in vicinity to the choroid[32].

Another factor is the wavelength of light: In contrast to green light, blue light only hardly regenerates the rhodopsin molecule, thus intermediates accumulate and produce again ROS, superoxide radicals, hydrogen peroxide, hydroxyl radicals and other free radicals[12,33-40].

## MITOCHONDRIA AS SOURCES OF ROS

The photoreceptors need even more energy than neurons and under aerobic conditions this energy is delivered by mitochondria[41,42]. Blue light and oxidative stress can elicit extra radical production by the respiratory chain handling with free electrons[43]. As a consequence of the radical stress coming from the mitochondria also other cell organelles are under thread including the nucleus and the DNA[44].

In the photoreceptors the mitochondria are most numerous in the "ellipsoid" of the inner segment-directly beneath the cilium that connects the inner segment with the outer segment forming a very small channel where the membranes, proteins and also ATP, pyruvate and other energy sources have to pass to the outer segments. However, one should keep in mind that the outer segment discs membranes consume a lot of energy, too.

In addition to mitochondria, numerous other radical sources are present in the cell, *e.g.*, membrane bound NADH and NADPH oxidases, so the impact of oxidative stress can elicit enhanced ROS production from different sites.

## EFFECT OF BLUE LIGHT ON MITOCHONDRIA

Experimental studies show that blue light impact enhanced radical production especially in mitochondria. Enzymes of the respiratory chain absorb wavelengths between 440 and 450 nm producing radicals subsequently[45]. Inhibiting the respiratory chain by enzyme blockers or application of antioxidants reduces ROS formation and cell death[46].

The high amount mitochondria within the photoreceptors are sources of radical production and indeed, blue light elicits radical production there[47]. Also the radicals originating in the rhodopsin cycle in the outer segments produce di-retinoid-pyridinium-ethanolamine (A2E)-the most hazardous component of lipofuscin first found within the retinal pigment epithelium (RPE) and later within the Drusen[48-50]. Interestingly, A2E blocks cytochrome c oxidase within the mitochondria[51]. So the radical product A2E itself is blocking the respiratory chain and leads (as vicious cycle) to an increased deviation of electrons producing again new ROS.

## ECTOPIC ENZYMES OF THE RESPIRATORY CHAIN WITHIN THE OUTER SEGMENTS

Panfoli *et al*[52-54] were the first authors who published the discovery that the outer segments discs harbour ectopic enzymes of the respiratory chain. The activity of these enzymes was in a range comparable to that of the respiratory enzymes in mitochondria. Panfoli *et al*[52-54] could also confirm the high proton gradient between outer and inner compartment of the discs. This is an important analogy because, *e.g.*, rods possess a double space encircled by membranes like the mitochondria do. Regarding the highly energy consuming process of phototransduction and the rapid increase of energy demand in light and dark cycles. Calzia *et al*[55] argue that it would be doubtful that ATP and phosphocreatine can diffuse from the inner segment (mitochondria!) to the outer third of the outer segments (only these are active in the rhodopsin cycle) with a proper timing[56]. Overall the $O_2$ consumption of the outer segments is three-fold greater than the inner retina[57]. The above mentioned paper of the Panfoli group[55] show even evidences that parts of the respiratory complexes come from mitochondrial membranes fused with the newly formed membranes of the outer segment discs.

Interestingly, we could show in our recent paper using a mouse explant model[58] that dyes that mark double membranes separating high proton gradients (like it was thought to be exclusively the case in mitochondria) and thus stain exclusively mitochondria, mark the outer segment of photoreceptors, too[58].

In this paper, we have also studied the ROS production (localisation and amount) in photoreceptors of retinal explants after blue light. We were surprised that the same amounts or even more of ROS were produced in the outer segments compared to the inner segments. Possibly, this ROS production in the outer segments is due to the newly found respiratory complex activity (see

above) or alternatively also due to NOX[59]-this is still to determine.

In the light of the present results, the energy delivery for the process of constant disc renewal should be therefore the predominant function of the inner segment mitochondria because shedding of outer segment membrane discs is prone to interference by blue light and ROS and this function requires a vast amount of energy (see above). The results of our recent study also suggest that not only the respiratory complexes of the mitochondria in the inner segment but also of the outer segments should be responsible for this very high oxygen consumption seen in the outer retina[58]. Impairment of the metabolic machinery (*e.g.*, lower pH) means also an inefficient photo transduction, which could be demonstrated by Calzia *et al*[60].

On the other hand, the high vulnerability of the outer segments to ROS damage could also lead morphologically to disorganisation of the photoreceptor outer segments[61]. In this regard we could demonstrate in a previous paper[61] that, indeed, after blue light and enhanced ROS production the alignment of the outer segments and the disc arrangement is disturbed, long before the photoreceptors go into degeneration and apoptosis. This finding corroborates a hypothesis of Eckmiller[62] that explains why this disturbed alignment of photoreceptors and other retinal cells along the visual pathway are responsible for the distortions of the central visual field in early AMD[63] patients.

## CONCLUSION

The review of the literature and the new results of the Panfoli group and of our group show how complex the pathogenesis is during the early stages of AMD. This also suggests that clinicians should look especially to the macular photoreceptors, to the alignment of outer segments with more refined methods. What is also needed is the development of high resolution functional imaging of the metabolic state in the different retinal layers because only the very late stages of AMD can be monitored and treated till now. Such refined imaging methods would also allow monitoring of the impact of dietary[63] and life style changes on the progression of early AMD.

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