Retinal Light Damage
Retinale Licht-Schäden

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Summary:

Even moderate exposures of ambient light can impose a threat to human retina and the retinal pigment epithelium - under particular preconditions. Repetitive light-stress implicates reversible phototoxic damage thereby paving the way towards age related macular degeneration (AMD) via temporal summation. Aggravating and interacting prerequisites like genotype/complement factors, smoking, nanomaterials (NM) and obstructive sleep disorders (OSA) as well as other factors ‘reflective of nature and nurture’ (97, 98) eventually impact on the severity of retinal light damage linked to possible formation and progression of AMD.

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Zusammenfassung:

Unter gewissen Voraussetzungen können mäßige, scheinbar nicht überdosierte Licht - Belastungen Schäden der Netzhaut verursachen. Genotyp/Komplement-System, Rauchen, Stoffwechsel-Störungen, möglicherweise auch Schlaf-Apnoe und ‚Nano-Toxikologie’ können in der Summe die Entstehung einer ‚alters-bedingten’ Macula - Degeneration (AMD) auslösen und beschleunigen.

Key words: retinal light damage, age related macular degeneration (AMD), nanotoxicology, obstructive sleep apnoe (OSA)

Schlüsselwörter: Retinale Licht - Schäden, alters-abhängige Macula-Degeneration (AMD), Nano-Toxikologie, Schlaf - Apnoe

Background

Visible radiation and ultraviolet (UV) (118) has the potential to damage retina and pigment epithelium (75). Undesired adverse reactions comprise the generation of potentially damaging reactive oxygen species (ROS) within highly vulnerable retinal structures. 'Medium energy' (83) Photons striking the rhodopsin molecule causing a rotational change of visual pigment in the photoreceptor cells initiating a cascade of chemical events culminating in signals being transferrred to the visual cortex. Visual perception results from a response to visible radiation between 380 and ~780 nm reaching the retina (6). The more reactive shorter wavelengths of non-ionising radiation are prevented from reaching the retina by cornea and lens [68,8). The cornea absorbs wavelengths below 295 nm while the lens (age-related) absorbs strongly in the long UV-B (300–315 nm) and the full UV-A (315–400 nm). Both cornea and lens also absorb part of the infrared radiation - at water bands (at 980, 1200, and 1430 nm). The vitreous absorbs light above 1400 nm (1400–10000 nm). Thus the non-ionising radiation reaching the retina is the so-called 'visible component' of the electromagnetic spectrum.

Physiological responses to absorption of light in photoreceptors include phototransduction related events (7). Activation of rhodopsin initiates a cascade of events leading to closure of sodium channels, hyperpolarisation of photoreceptor membrane and a decrease in intracellular calcium (82, 76). The phototransduction system is modulated by several proteins such as S-modulin (recoverin), guanylate cyclase-activating protein, phosducin and calmodulin in a calcium-dependent manner, which induces light and dark adaptations (25). Light adaptation results in a decrease in oxygen consumption in photoreceptor inner segments (1, 64). The downstream cellular events associated with retinal light damage are fully discussed in the review of Remé et al. (89).

The visual pigments representing the most relevant chromophores in human retinae comprise 11-cis-retinal–protein complexes which collectively absorb across the whole of the visible spectrum. Selectivity is achieved by the different light absorption characteristics of rods and the three types of cones found in the human retina. In addition the retina contains a number of other categories of chromophores which readily absorb visible light. These include the broad band absorbers melanin and lipofuscin; haemoglobin and other proteins (e.g., mitochondrial enzymes) containing porphyrin with absorption maxima around 400 nm (Soret band) and less intense Q-bands at longer wavelengths (e.g., 600 nm) (70); flavins and flavoproteins, which absorb blue light with maximum at about 450 nm (23) and macular pigment, which strongly absorbs between 400 and 530 nm (5). Absorption increases with decreasing wavelength and thus melanin and lipofuscin have been implicated in blue light damage to the retina (9)

Mechanisms of Light damage

Evidence collected since the 1960s (75) suggests that light may damage the retina in a number of ways involving different chromophores and cellular events (58). Radiation-induced tissue damage can occur at least via one of three fundamental processes:

Mechanical (or ionisation), thermal photocoagulation (or photovaporisation) and photochemical. Mechanical damage results from extremely short exposures at high irradiance levels which cause sonic transients or shock waves that mechanically disrupt the tissue. However, while such energy may be applied via lasers for surgery to the front of the eye it does not normally reach the retina. Thermal damage can occur if incident energy, for example, short-intense exposures (100 ms–10 s), is trapped or absorbed in a substrate molecule resulting in a significant increase in temperature usually quoted as 10°C or more for retinal damage (66). Such damage tends to occur in the blue/green and green regions of the visible spectrum and is dependent on the absorption spectrum of the chromophore (70). As discussed earlier the retina contains a number of chromophores, in particular melanin and haemoglobin, which readily absorb visible or infrared light, and have the ability to undergo very efficient non-radiative decay from their electronically excited states to the ground state. Surgeons have targeted the absorption properties of these chromophores, photothermal sensitizers, to create ‘therapeutic’ tissue damage using laser sources. The depth of penetration is dependent on wavelength, e.g., optical radiation from argon lasers (457–524 nm) is primarily absorbed in the retinal pigment epithelium while that from krypton red (around 650 nm) and diode lasers (790–830 nm) is absorbed by the choroid as well as the RPE (68, 4). Although such exposures are used therapeutically to produce retinal photocoagulation, they are not encountered in the natural environment.

Longer exposures (typically quoted as being 10 s and longer) to much less-intense light sources may cause retinal damage by photochemical mechanisms - via temporal summation - most likely to be of relevance to the development of AMD.

Photochemical damage has been the most extensively studied form of light damage owing to its ability to cause damage under ambient conditions and its potential role in retinal damage. Photochemical reactions take place in normal ambient conditions and involve a reaction between energetic photons and an absorbing molecule. In the presence of oxygen this reaction leads, via a number of intermediary steps, to the production of reactive oxygen species (ROS) including singlet oxygen, superoxide, hydrogen peroxide and hydroxyl radicals. These ROS are highly toxic and can cause lipid peroxidation, protein oxidation and mutagenesis (7). ROS production is also a natural by-product of respiration and is believed to have a major role in ageing (3).

Photochemical damage is the most probable cause of hazards by ophthalmic instrumentation (61, 71, 44, 45) and may be responsible for solar retinitis. Sliney and Wolbarsht (100) measured the energy of the blue part of the solar spectrum, and found that gazing at the midday sun for about 1000 s could result in threshold retinal damage. Photochemical damage occurs when light is absorbed by a photosensitizer that is a chromophore, which upon photo-excitation to photo-excited singlet state undergoes intersystem crossing and forms a transient excited triplet state. The excited triplet state is long-lived, allowing for interaction with other molecules producing free radicals (via electron (hydrogen) transfer (type I of photosensitised damage)), or singlet oxygen (via

transfer of excitation energy from the photo-sensitizer in the triplet state to molecular oxygen (type II of photosensitized damage)) (27). Photo-sensitized damage mediated by oxygen has been employed in photodynamic therapy of tumours and retinal neovascularisation. The outer retina (retinal pigment epithelium and rod outer segments), being immediately adjacent to the choroid is highly oxygenated. However, there are a number of potential endogenous photo-sensitizers in the outer retina exposed continually to significant fluxes of incident light. Therefore, there are potentially favourable conditions for photodynamic damage to occur. Moreover, the dependence on oxygen concentration suggests that light-induced damage to the retina (45, 33) is indeed photodynamic in nature. Photochemical damage usually demonstrates delayed onset following light exposure, and in the retina, this delay may be several hours.

Retinal photochemical damage has been broadly subdivided into two types dependent on the action spectra, duration of exposure and the irradiance energy required to cause damage (70, 35). The first type of damage corresponds well with the absorption spectrum of the visual pigments. On the other hand, the action spectra of light damage to the retina under conditions where rhodopsin is completely bleached suggests that there is a shift in the site of damage from the rod outer segment at short wavelengths to the pigment epithelium at longer (>470 nm) wavelengths (29, 10), suggesting that there are at least two other mechanisms responsible for photodamage. The second type of damage is considered to originate in the RPE (36, 116), and appears to correlate with endogenous melanin and lipofuscin granules although as will be discussed below the vitamin A metabolites are also likely to be important. Since such damage occurs at the shorter wavelength end of the visible spectrum it is often referred to as ‘blue light damage’. Furthermore, this second type of damage appears to be an oxygen-dependent phenomenon since elevated blood oxygen has been reported to increase retinal photosensitivity, lower the damage threshold and increase the extent of damage at a given radiant exposure in primates (44, 93). Protective effects of antioxidants and lowering oxygen tension suggest that this type of light damage is related to initiation of oxidative reactions in the retina. Toxic effects of blue light have also been observed for RPE cells in culture (22, 80). The blue light toxicity was oxygen dependent, being 10 times more efficient at 95% oxygen compared to 20% oxygen. On the other hand, the irradiation of RPE cells under anaerobic conditions did not result in toxicity even when light intensity was increased 2-fold (13).

Most research on different types of retinal photodamage has been undertaken on rodent models with only few studies on primates. It is therefore questionable whether the results obtained on nocturnal rodents may approximate the photo-damage in primates, which are more susceptible to the second type of photo-damage, induced by near UV or blue light (69). In primates, it has been shown that the energy of irradiation with 533 nm wavelength has to be about 20 times higher than the energy of irradiation with 440 nm to induce threshold photo-damage (34) and about 400 times higher for 500 nm than for 380 nm (19). Also, the limited data on light damage in humans show prominent RPE damage (115, 30).

It should also be noted that there are several methods of assessment of light damage (89, 69, 33, 59, 42) including psychophysical (reduction in visual field, colour defects), electroretinographic (reduction in rod function), physiological (e.g., disruption of the blood–retina barrier), morphological (e.g., mitochondrial swelling, aggregation of melanosomes observed as hypopigmentation, disorganisation of the RPE layer, apoptosis of photoreceptors and RPE cells) and biochemical (e.g., loss of rhodopsin, decreased activity of several enzymes, oxidation of retinal proteins, lipid peroxidation, and loss of docosahexaenoic fatty acids).

To minimise the destructive potential of ROS, cells have developed a number of defence mechanisms, for example enzymic (e.g. superoxide dismutase, catalase, haeme oxygenase and phospholipases) and non-enzymic (e.g. vitamin E, A and C) antioxidants. The RPE is further protected from the ravages of ROS damage by melanin which is an ROS scavenger. In particular, it has the capacity to minimise the production of hydroxyl, one of the most potent oxidative moieties (7). However, it is the photoreceptors which have developed the ultimate solution to oxidative damage i.e. the continuous replacement of their cellular constituents (68). Cellular isoforms (PrP^{C}) - 'chameleonic attributes' - of the pathological prion protein seem to protect the photoreceptors from light damage (28, 104).

Ideally the cellular defence mechanisms, such as those described above, should be sufficient to combat the toxic effects of ROS damage. In reality, however, the defence mechanisms are imperfect systems and the resulting lifetime accumulation of ROS damage may contribute not just to age-related eye disease but to ageing itself (3). Indeed it has been suggested that ROS damage to mitochondrial DNA in the RPE is a primary mechanism in the pathogensis of AMD (63). The rate at which ROS damage accumulates is likely to accelerate over time because cellular defence mechanisms are known to decline with age (7). For reasons to be outlined later, we suggest that the RPE is particularly vulnerable to age-related ROS injury because the decline in its melanin content, associated with advancing years, is accompanied by an increase in its lipofuscin content. Lipofuscin is not just a potent generator of ROS but also has an inhibitory effect on antioxidant activity (98).

Acute light exposure studies

Animal studies suggest that there are two distinct types of photochemical damage, one associated with short exposures operating at the level of the RPE and the other associated with longer, relatively less-intense exposures, at the level of the photoreceptor outer segments.

Short exposures, up to about 12 h, to relatively intense short-wavelength light, sometimes referred to as the "blue light hazard", can produce damage at the level of the RPE in primates (35). The dependence of this type of light damage on oxygen concentration (33, 44, 93) and the ability of various antioxidants to reduce light damage (21, 78) confirm its oxidative origins. There are a number of candidate chromophores for this type of damage most notably, melanin and lipofuscin.

Although capable of producing reactive oxygen species at high irradiance levels, melanin seems an unlikely candidate for the mediation of light-induced damage in AMD. According to Mellerio (70) the action spectra for ‘blue-light-damage’ does not coincide with the absorption spectrum of melanin nor its action spectrum for the uptake of oxygen. Total melanin content of the retina reduces with age (95) and its spatial distribution does not coincide with AMD. Indeed, melanin is generally thought to be photo-protective and increased pigmentation is generally associated with a reduced risk of AMD (52).

Laboratory studies have shown lipofuscin to be a potent generator of ROS including singlet oxygen, superoxide anion and hydrogen peroxide (92). These products are cytotoxic and give rise, directly or indirectly, to lipid peroxidation, protein oxidation, loss of lysosomal integrity, cytoplasmic vacuolation and cell death (18). Most importantly the action spectra for photochemical damage to the RPE in primate retina (34,36) and the aerobic photoreactivity of lipofuscin (92) are coincident suggesting that lipofuscin is largely

responsible for this type of "blue light damage". A number of components are likely to contribute to lipofuscin's photoreactivity. One of these components, known as A2E, has been shown to produce ROS, trigger RPE cell apoptosis, damage DNA and lead to RPE cell death (106,107, 108, 109). However, A2E is only weakly photoreactive and is unlikely to explain the photoreactivity of lipofuscin (7).

Longer exposures (typically, 12–48 h) to lower intensities produce damage at the level of the photoreceptors. This type of damage was initially demonstrated in the rat where rod photoreceptor degeneration was noted after a period of constant illumination from fluorescent lamps (75). Similar findings were obtained in young primates with the notable exception that cones were more vulnerable than rods showing degeneration after a 12 h exposure when the retinal irradiance was between 195 and 361 μW/cm2 (110). However, the apparent susceptibility of cones is unlikely to reflect a difference in damage threshold but rather a difference in repair capacity i.e. rod outer segments are replaced more rapidly than cone outer segments (68). A number of mechanisms may contribute to light-induced photoreceptor damage. The photo pigments themselves have long been implicated in receptoral damage. Early studies have shown that the degree of light-induced damage positively correlated with pre-exposure rhodopsin content and that the action spectrum for photoreceptor damage was similar to that of rhodopsin (74,77). However, more recent evidence has shown that deep blue light is 50–80 times more efficient at causing receptor damage than green light despite the fact that it is absorbed less efficiently (86). This observation has been explained on the basis of rhodopsin photo-reversal (31). That is, blue light promotes the photo-isomerisation of all-trans-retinal which leads to the regeneration of rhodopsin and an increase in photo-transduction signalling this in turn leads to photoreceptor apoptosis. The exact sequence of events remains unclear but in relatively dim light photoreceptor apoptosis is mainly dependent on a transducin-dependent pathway (38). Receptoral damage may also result from the liberation of ROS by all-trans-retinal which is a well-known photo-sensitizer and capable of producing singlet oxygen and superoxide anions after photo-excitation with blue light (7).

On a cautionary note it should be remembered that the majority of the animal studies mentioned above have used nocturnal rodents and it has not been established that the same damage pathways have a significant role in diurnal species.

Furthermore, all of these investigations described above have used exposures that are shorter and more intense than might be encountered in the natural environment usually i.e. they comprise ‘acute’ light exposure studies where the damage inflicted by photochemical reactions has outstripped, at least in the short term, the capacity of the various defence and repair mechanisms. Consequently, they are only related indirectly to the effects of ‘chronic’ light exposure in elderly humans. What these studies do show, however, is that light and in particular blue light has the potential to cause retinal damage via photochemical mechanisms and that the nature of damage is dependent not just on the photo-reactivity of a variety of chromophores but on the capacity of the defence and repair systems in addition.

Chronic light exposure

Chronic exposure to ambient lighting produces ROS in the same way that acute exposures do because all photochemical reactions demonstrate reciprocity between irradiance and exposure duration (100). That is, both are capable of producing damage. The nature of that damage will reflect the capabilities of the various defence and repair mechanisms, and the time at which the damage is observed. For example, the acute light exposure studies described above typically obtain measures of threshold damage in young animals after defence systems have been overwhelmed and repair systems have had insufficient time to react. Damage from chronic light exposure in elderly humans whose defence and repair mechanisms are compromised is likely to be quite different. On the basis that ROS damage has a major role in ageing, it seems likely that the damage caused by chronic light exposure might manifest as accelerated ageing (3, 63).

The studies described above have shown that two distinct retinal layers are highly susceptible to photochemical injury i.e. the photoreceptor outer segments and the RPE, and that this damage is likely to be mediated by the visual pigments and lipofuscin, respectively. Although both may contribute to the development of AMD, and in particular geographic atrophy, there are several reasons for believing that lipofuscin is of particular importance. Firstly, RPE cells are retained throughout life, their repair systems operate at a molecular level and this type of "closed system" is more likely to accumulate ROS damage than cells of the "open system" type in which there is abundant component renewal e.g. photoreceptors (68). Secondly, the chronology of lipofuscin accumulation in the RPE is coincident with the development of AMD (26). Thirdly, longitudinal studies of in vivo autofluorescence (which has been ascribed to the presence of lipofuscin) have shown that it is areas of retina with the highest autofluorescence that are most susceptible to degeneration (56) In addition - it was suggested that the bis-retinoid pigments of lipofuscin, following photoactivation and cleavage, serve to activate complement. (Zhou); Superoxide seems to contribute to the oxidation of already-oxidized A2E, a bis-retinoid pyridinium compound that accumulates as lipofuscin pigment in retinal pigment epithelial (RPE) cells (51).

Phototoxicity contributed by lipofuscin increases substantially with age because the protective effects of lens senescence are offset by a substantial increase in the concentration of photo-reactive elements in the retina (20) and the effect of age on lipofuscin mediated photo-damage because of lipofuscin's inhibitory effect on antioxidant activity (98).

Although this phototoxicity increases steadily with age the potential for blue light damage is likely to be many times greater for those developing AMD where lipofuscin ‘hot spots’ may act as a focus for local oxidative damage (56). Indeed, massive quantities of lipofuscin have been demonstrated in the RPE of eyes with atrophic AMD (94). The hypothesis, that lipofuscin-mediated photochemical damage increases with age, and particularly so for those developing AMD, may explain why antioxidant therapy is beneficial in these groups (49).

If light were to have a role in the pathogenesis of AMD the evidence outlined above enables us to make several predictions. Firstly, increased exposure to short-wavelength radiation, both in terms of intensity and duration, should increase the risk of AMD. Secondly, exposure to short-wavelength radiation in old age will be a greater risk than exposure at other times of life. Thirdly, antioxidants should reduce the risk of AMD (122) and more specifically their protective effects should be greater for those with the highest concentration of lipofuscin (67).

Clinical evidence for the role of light in the pathogenesis of AMD

The phototoxic effects of light from ophthalmic instruments are well documented (17, 44, 71,72). Although these exposures are acute, the oxygen-dependent nature of the resulting damage suggests an oxidative mechanism.

Of more relevance to the pathogenesis of AMD, several studies have reported the effects of an increase in chronic short-wavelength light exposure. The use of intraocular lenses without UV filters seems to increase the incidence of retinal light damage following cataract surgery (57).Epidemiological evidence has shown that progression of AMD is approximately 2.7 times more likely following cataract extraction and intraocular lens implantation (53, 84). The increased risk of AMD progression has been directly attributed to an increase in blue light exposure (14, 53). Werner et al. (118) observed a reduction of blue colour vision in pseudoaphakic eyes without UV filtration.

It is also of interest to note that the optical density of macular pigment is significantly reduced in smokers (37). The reduction in optical density would increase blue light exposure and this would be consistent with a blue-light contribution to the heightened risk of AMD in smokers (102).

Due to the ‘habit to close one eye in sunlight’ (46) ‘asymmetrical’ UV- and light lesions like pinguecula, pterygium, cataract etc. of the leading eye can be observed. Subclinical retinal symptoms of incipient retinal light damage can be described as ‘discrete dyschromatopsia’. Colours appear somehow desaturated, ‘whashed out’, faded, black seems to be slightly greyish, white appears somehow 'dirty' when being compared with the image from the other eye. No fundus changes might be detectable in this early - pre-clinical stage. In amblyopic eyes the typical changes of a macular degeneration (AMD) scarcely will be diagnosed before they become manifest clinically in the dominant eye. The majority of amblyopic eyes seems to be spared from ‘AMD’ - another observation pointing at the potentially phototoxic role of visible light in the development of AMD.

The ’asymmetrical’ distribution of atrophic and degenerative areas in sectoral retinitis pigmentosa (113, 114) indicates the effect of light exposure evidentiary. Photoreceptor layer topography revealed a thinner outer nuclear layer inferior to the fovea (Jacobsen) corresponding to the preferred retinal locus of fixation above central retina (88). Light phototoxicity may play an expressive role manifesting itself in form of asymmetric distribution. (39) The health of the pigment epithelium (RPE) plays a critical role in the pathogenesis of retinal light damage (11) 'There is increased risk of apoptosis in the inferior retina (superior visual field) where environmental light dose is expected to be higher' (12). In theT4R RHO mutant dog retina immuno-cytochemistry showed that key proteins in the cascade of processes induced by exposure to light were localized in the inner nuclear layer. Three early biochemical events, activation of ERK1/2, c-Fos phosphorylation, and induction of AP-1 DNA - binding activity, occur in Müller cells after clinical exposure to light in the preapoptotic phases of photoreceptor degeneration. AP-1 activation seems to be a survival response in this peculiar model of AD retinitis pigmentosa.(Gu). These findings emphasize again the rife underestimated role of neuroglia, particularly Müller's fibers, a structure showing its dominating influence also in electroretinographic recordings (117, 40).

Epidemiological evidence for the role of light in the pathogenesis of AMD

There have been several population-based studies that have evaluated the role of ultraviolet and visible light on the development of AMD (14, 16 , 96, 111, 112, 119).

An extensive survey of the watermen in the Chesapeake Bay area concluded that chronic exposure to blue or visible light may be related to the development of AMD (111). Similarly, the authors of the Beaver Dam Eye Study also suggest that their measures indicate that visible light rather than UV might be associated with AMD (13). Conversely, Darzins et al. and the Eye Disease Case Control Study Group (1992) found no such relationship (16; 24). A positive correlation between facial skin-changes caused by chronic UV- and light exposure and AMD was suggested by Hirakawa (41).

Aggravating factors:

Apart from genetic predisposition (12, 43, 54, 103), complement system (97) in particular, smoking, metabolic - (50) and dietary 'imbalance' (81), obstructive sleep apnea (OSA) (48, 2) causing reduced oxygen partial pressure in retina and optic nerve, should not remain unregarded. Possible adverse effects of ultrafine dust particles or highly active nanomaterials (NM) (62, 87) on chorio-capillaris and vulnerable central retina (85) remain enigmatic until better monitoring (99) of NM will allow better insight into these open-end questions.

In Conclusion,

retinal function depends on photon-capture or light-trapping; however, excessive exposure to light may cause damage to higly vulnerable (85) retinal structures. Solar retinopathy is well documented in humans following gazing at the sun (42) without proper eye protection (65) and due to prolonged exposure to several common ophthalmic instruments (45, 55, 61, 71, 72) or prolonged exposure to artificial light (58). Accumulating damage induced by chronic phototoxic reactions occurring in the retina has been suggested to be involved in the aetiology of debilitating ocular conditions such as AMD. Light damage to the retina seems to be multi-factorial and several different mechanisms - partly unrecognized and unexplored (2,48, 120) - may be involved, depending on the chromophore responsible for initiation of photodamage.

One of the main chromophores responsible for the light-induced cascade of events leading eventually to impairment of cellular function and cytotoxicity are visual pigments. The mechanisms of photodamage by rhodopsin may occur via several different mechanisms including:

1) an intracellular calcium concentration decrease, due to prolonged rhodopsin activation in meta-rhodopsin II state, resulting in initiation of apoptotic response; or
2) release of (photo) toxic products of photobleaching, such as retinal.

Outer retina and retinal pigment epithelium are inherently at risk due to continual exposure to high fluxes of incident light, high concentrations of oxygen and the presence of a number of potential photosensitisers initializing photooxidative damage . Moreover, high concentrations of polyunsaturated fatty acids, including docosahexaenoic acid, seem to be extremely susceptible to peroxidation. It is believed that photosensitized oxidations are

involved in the phototoxic reactions occurring in retinal structures, but their exact mechanisms, like the chromophores that photosensitize the photooxidative damage to the retina, are still unknown.

The role in retinal photodamage of flavins and porphyrins, present as prosthetic groups of several important enzymes, is still poorly understood. Lipofuscin, which accumulates during ageing in RPE, is a potent photosensitiser, which photogenerates singlet oxygen, superoxide anion, hydrogen and lipid peroxides. However, it is still unknown, what is the molecular constituent of lipofuscin responsible for its photoreactivity. Melanin has been rejected as a potential candidate responsible for photochemical damage to the retina based on observations of similarity of end-points in photodamage in albino and pigmented animals; however, the same observations may raise the possibility that in pigmented animals photoprotective effects must balance the photodamaging effects of melanin in pigmented animals, as melanin absorbs a significant fraction of incident photons. Macular pigment is most likely to play a protective role as a blue light filter to a certain extent and possibly as an antioxidant, but more experimental evidence is needed to support this hypothesis.

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