Chapter 15
Retinal Photooxidative Stress and Its Modifiers

Masaki Tanito

Abstract Retinal damage is classified into three types based on the mechanisms of the damage, i.e., photothermal, photomechanical, and photochemical, with the last likely the most common form of light-induced damage, since the natural range of light energy sufficient causative. Photochemical damage is caused by reactive oxygen species and free radicals generated by light exposure, also called photooxidative stress. Although different types of photooxidative stress have been proposed, they sometimes cannot be differentiated clearly in various experimental settings. Epidemiologic studies have suggested a correlation between environmental light exposure and development/progression of human retinal degeneration such as age-related macular degeneration and retinitis pigmentosa. The double bonds in long-chain polyunsaturated fatty acids (PUFAs), which are highly enriched in the retinal membranes, could be target substrates to propagate photooxidative stress in the photoreceptors. Posttranslational modification of retinal proteins by PUFA-degraded molecules, such as 4-hydroxynonenal and 4-hydroxyhexenal, causes retinal degeneration and neuroprotection depending on the timing and level of formation.

Keywords 4-Hydroxynonenal (4-HNE) • Age-related macular degeneration (AMD) • Docosahexaenoic acid (DHA22:6*n*-3) • Nuclear-factor-E2-related factor 2 (Nrf2) • Polyunsaturated fatty acids (PUFAs) • Retinal photooxidative stress

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15.1 Types of Light-Induced Retinal Damage

Retinal damage is classified into three types based on the mechanisms [1]. Photothermal damage is induced by at least a 10 °C increase in ambient temperature in the retinal tissue originating from transfer of radiant energy from photons to the tissue during an exposure duration between 0.1 and 1.0 s [2–4]. Thermal damage results from a tissue temperature of 55–58 °C that causes cellular apoptosis, temperature of 60–68 °C that causes apoptosis and necrosis, and temperatures of 72 °C or higher that cause immediate cell death [1]. Laser photocoagulation, transpupillary thermotherapy, and micropulse diode laser are clinical applications that cause thermal damage. Photomechanical damage, as that caused by Nd:YAG laser, is induced by rapid introduction of compressive or tensile forces on retinal tissues by exposure to light with high irradiances (typically mega- or terawatts/cm^2) during a very short time (typically between nano- and picoseconds) [5, 6]. Photochemical damage is independent of either photothermal or photomechanical damage and is thought to be the most common mechanism of light-induced retinal damage, since the natural range of light causes this type of damage [7]. Theoretically, photochemical damage, as that caused by photodynamic therapy, is caused by reactive oxygen species and free radicals generated by light exposure; thus, this is also referred to as photooxidative stress.

15.2 Action Spectrum of Retinal Damage Induced by Photooxidative Stress

15.2.1 Light Properties

Among the electromagnetic waves, the wavelengths between 400 (380 nm) and 800 nm (760 nm) are called visible light because they reach the retina and are the source of visual information. Ultraviolet (UV) light is that with wavelengths shorter than visible light. Among the UV wavelengths, UVB (wavelengths between 290 and 320 nm) and UVA (wavelengths between 320 and 400 nm) are absorbed by the cornea and crystalline lens, respectively, do not reach the retina, and are not used for visual sensing in humans. Infrared light with a wavelength longer than visible light also is absorbed by the crystalline lens. In phakic human eyes, photooxidative stress is thought to result mainly from visible light wavelengths (Fig 15.1).

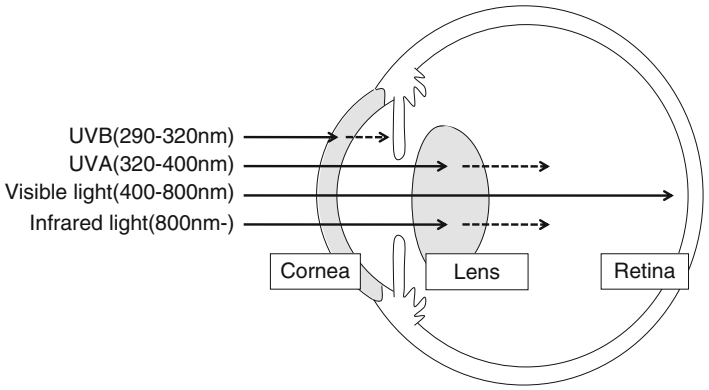

Fig. 15.1 Transmission of light through the cornea and crystalline lens. Light wavelengths that are shorter (ultraviolet) or longer (infrared) than visible light are absorbed by the cornea or lens and do not reach the retina

15.2.2 Types of Photooxidative Stress

Previous studies have suggested two possible mechanisms of retinal photooxidative stress [8, 9]. Noell et al. first reported retinal damage induced by constant green light (wavelengths, 490–580 nm) at relatively low retinal irradiance (<1 mW/cm^2) during a long exposure time (at least 1.5 h, typically >8 h) in rats [7]. The action spectrum of this damage is similar to the absorption spectrum of rhodopsin. This type of photooxidative stress is referred to as Noell's damage or class I damage. Noell's spectrum of retinal damage has been reported subsequently in mice [10], macaque monkeys [11], fish [12], and chickens [13]. Ham et al. first reported retinal damage induced by visible light [14] and later by UV radiation [14] at higher retinal irradiance and shorter (<5 h) exposure times than Noell's damage in monkeys. In Ham's experiments, the susceptibility of retinal damage decreased monotonically from short to long wavelengths (Fig 15.2). This type of photooxidative stress is referred to as Ham's damage, class II damage, or blue-light hazard. Ham et al. later reported the spectrum of retinal damage in rabbits [15], rats [16, 17], and squirrels [18]. Currently, Ham's action spectrum serves as the basis for international standards or guidelines for protection against retinal damage by lasers and other light sources [19, 20] (Fig 15.3); the spectrum of Noell et al. is not included because it is considered to be exclusive to rodents [8]. These guidelines are used mainly to protect eyes from acute light damage such as that induced by sunlight [21] or to determine the upper limits of light exposure in a work environment. Thus, no reliable standards yet have been established to protect eyes from chronic light exposure.

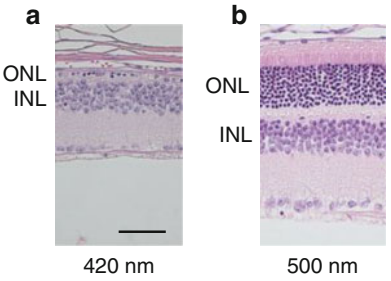

Fig. 15.2 Wavelength dependence of retinal light damage. Albino mice are exposed to light with a narrow bandwidth. The eyes are nucleated 1 week after light exposure. (**a**) A retinal section from a mouse exposed to 420-nm wavelength light at 500 J/cm^2. Most of the ONL has disappeared, suggesting severe retinal damage resulting from light exposure. (**b**) A retinal section from a mouse exposed to 500-nm wavelength light at 500 J/cm^2. Most of the ONL is preserved, suggesting mild retinal damage from light exposure. *INL* inner nuclear layer. Scale bar = 50 μm

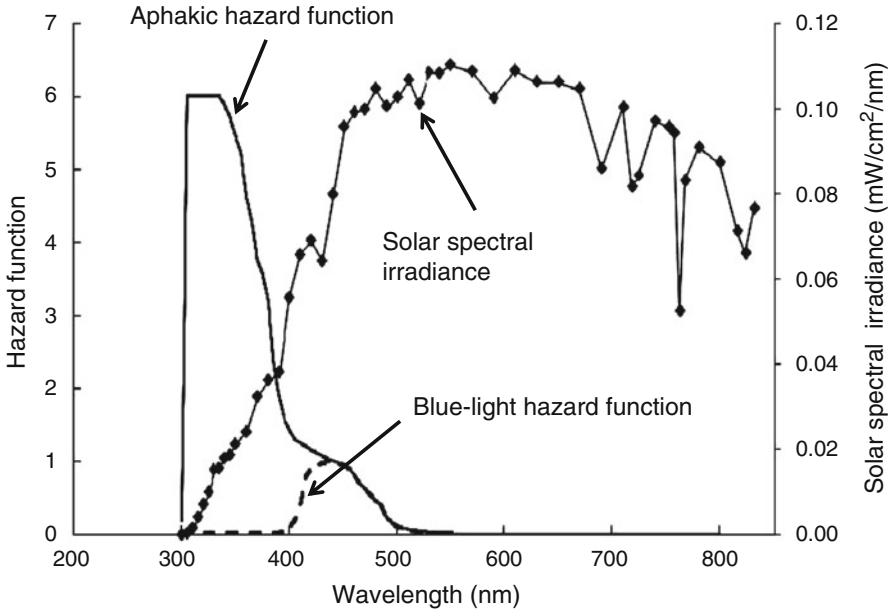

Fig. 15.3 Aphakic hazard function, blue-light hazard function, and solar spectral irradiance. The aphakic hazard function (*solid line*) and the blue-light function (*dashed line*) show the effectiveness of optical radiation in producing photochemical retinal damage as a function of wavelength (*left axis*). The solar spectral irradiance shows the distribution of the radiant power of sunlight over a 37° tilted hemispheric surface with an air mass coefficient of 1.5 (*right axis*). This figure was generated from the data reported in References 19, 20, and 21

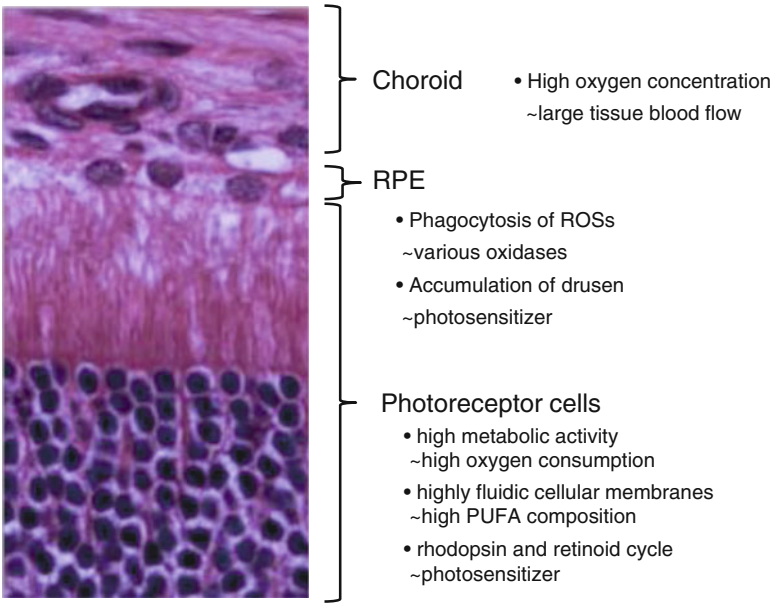

Fig. 15.4 Conditions around the outer retina. Various conditions around the outer retina are suitable for this location to be susceptible to photooxidation damage. *PUFA* polyunsaturated fatty acids

15.2.3 Target of Photooxidative Stress

Across species, photoreceptors are the primary target of retinal damage caused by UV light and the shortest visible violet light (Fig 15.4). With Noell's spectrum of damage, damage is observed in the photoreceptor cells with exposure to light for 1.5–48 h and in both photoreceptors and retinal pigment epithelium (RPE) cells with longer (8–50 days) durations [22], indicating that sustained visual cycle turnover and accumulation of rhodopsin-related molecules including retinoids and intermediate products of the visual cycle are the primary suspects in the initiation of damage [23]. With Ham's spectrum of damage by visible light, the rod and cone photoreceptors are not expected to be primary targets of damage since rhodopsin and cone opsin are breached during a relatively short exposure time. The damage occurs predominantly in the RPE [24], indicating that changes in molecules in the RPE, including lipofuscin, melanin, and intermediate products of the visual cycle, are primary suspects for damage initiation [9]. Photooxidation of visual cycle-related molecules (Fig 15.5), such as all-*trans*-retinal [25], all-*trans*-retinol [26], and all-*trans*-retinyl ester [27], are thought to be sensitizers of retinal damage. Accumulation of all-*trans*-retinal leads to light-induced retinal damage [28], which can be decreased by various types of antioxidants such as ascorbate [29],

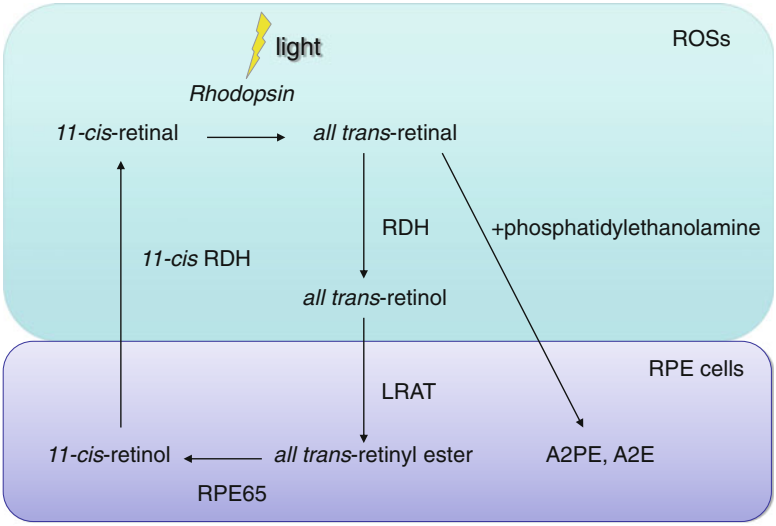

Fig. 15.5 Visual cycle. *RDH* all-*trans*-retinol dehydrogenase, *LRAT* lecithin retinol acyltransferase, *RPE65* retinal pigment epithelium-specific 65 kDa protein, *11-cis RDH* 11-*cis* retinol dehydrogenase, *A2PE* phosphatidyl-pyridinium bisretinoid, *A2E* pyridinium bisretinoid

dimethylthiourea [30], thioredoxin [31, 32], 4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPOL) derivatives [33, 34], and phenyl-*N*-*tert*-butylnitrone (PBN) [35, 36] (Fig 15.6). Inhibitors or modulators of the visual cycle prevent retinal light damage [37] and may be therapies for dry age-related macular degeneration (AMD) in humans [38].

15.2.4 Fate of Photoreceptor/RPE Cells in Photooxidative Stress

Although two different types of photooxidative mechanisms have been proposed, dataset analyses in previous studies have not clearly distinguished both types of mechanisms in various experimental settings [8]. In either pathway, the apoptosis is the main pathway of light-induced cell death [39] (Fig 15.7). Apoptosis of the photoreceptors also is thought to occur in retinitis pigmentosa (RP) and AMD. The susceptibility to retinal damage differs greatly among animal species. Generally, albino animals sustain light damage more easily than pigmented animals, and albino rats are more susceptible to retinal light damage than albino mice. Exposure to white fluorescent light at 2,700 lx for 6 h causes devastating apoptotic

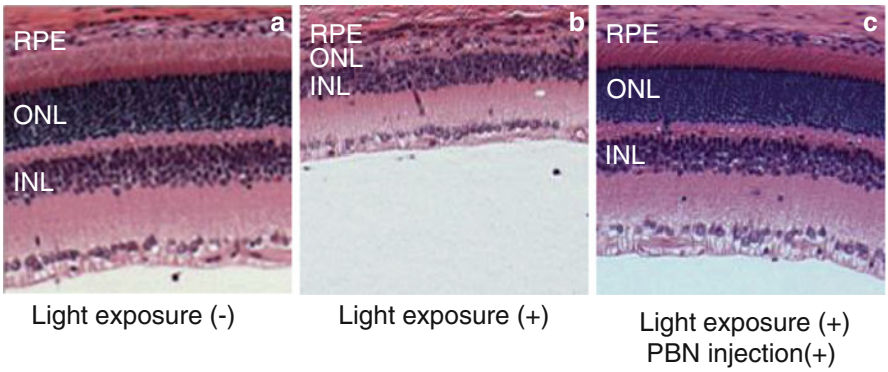

Fig. 15.6 Inhibition of retinal light damage by a free radical scavenger. (**a**) A retinal section from an albino rat not exposed to light. (**b**) A retinal section from a rat exposed to 5 k lx white fluorescent light for 6 h. The eye was enucleated 7 days after light exposure. (**c**) A retinal section from rat preinjected with PBN intraperitoneally 30 min before and then exposed to 5 k lx white fluorescent light for 6 h. The eye was enucleated 7 days after light exposure. *INL* inner nuclear layer

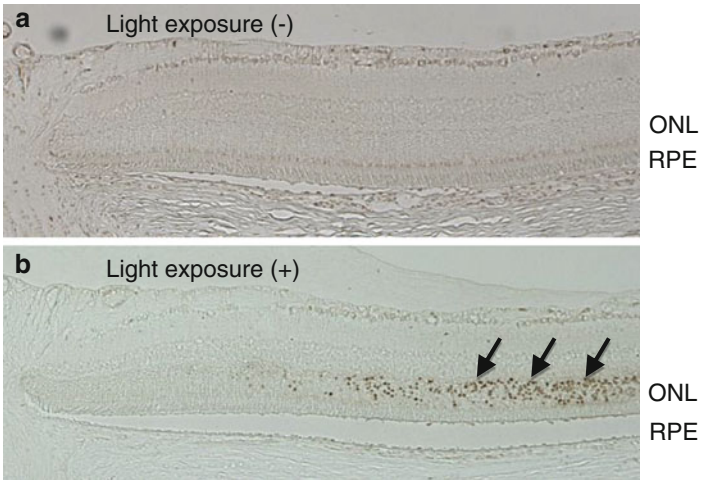

Fig. 15.7 Detection of apoptotic photoreceptor cells after light exposure by terminal deoxynucleotidyl transferase dUTP nick-end labeling (*TUNEL*) staining. (**a**) A retinal section from an albino rat not exposed to light. (**b**) A retinal section from a rat exposed to 5 k lx white fluorescent light for 3 h. The eye was enucleated 24 h after light exposure. TUNEL-positive photoreceptor cells are observed in the ONL (*arrows*)

photoreceptor cell loss in albino rats raised in a dim cyclic light environment [34], whereas exposure to white fluorescent light at 8,000 lx for 2 h only promotes oxidative stress in pigmented mice [40].

15.3 Role of Membrane Fatty Acids and Photooxidative Stress

15.3.1 Fatty Acids in the Retina

N-3 and *n*-6 polyunsaturated fatty acids (PUFAs), which contain two or more methylene interrupted *cis* double bonds, are major families of fatty acids in mammalian cells. Through a series of oxidation (desaturation) and chain elongation reactions, *n*-3 and *n*-6 fatty acids are synthesized from essential fatty acids 18:3*n*-3 and 18:2, respectively. Phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol comprise, respectively, 40–50 %, 30–35 %, 5–15 %, and 3–6 % of the PUFAs in the retinal photoreceptor phospholipids [41]. Thus, the highest levels of PUFAs in any tissues are in the phospholipids in the retinal membranes. The most abundant retinal fatty acid is docosahexaenoic acid (DHA, 22:6*n*-3); its levels in the rod outer segment (ROS) membrane phospholipids are 40–50 % of the total fatty acids [41]. *n*-3 PUFA deprivation resulting from *n*-3-deficient diets resulted in only modest changes in retinal DHA levels; thus, the retina retains DHA and other *n*-3 PUFAs [42]. More substantial changes were seen during the last trimester of pregnancy and throughout the nursing period when an *n*-3-deficient diet was fed to pregnant rats and when the same diet was given to weaning rats for 10–12 weeks [43]. Under these conditions, the DHA levels in the ROS decreased by 50 % and were replaced by nearly equal amounts of 22:5*n*-6. The electroretinography responses decreased in animals that were DHA deficient, especially the *a*-wave amplitudes in rats [44], guinea pigs [45], and monkeys [46]. *n*-3 deficiency reduces the activation of rhodopsin, reduces and delays rhodopsin-transducin coupling, and decreases cGMP-phosphodiesterase activity in biochemical assays [47].

15.3.2 Fatty Acids: A Molecular Target of Photooxidative Stress

With exposure to damaging light, mice with lower *n*6/*n*3 ratios and higher DHA levels in ROS had greater retinal damage [48], which suggested a positive correlation between the DHA level and retinal vulnerability to photooxidative stress (Fig 15.8). As already mentioned, both types of photooxidative stress are initiated by light absorption by the target molecules. Such chromophores, called

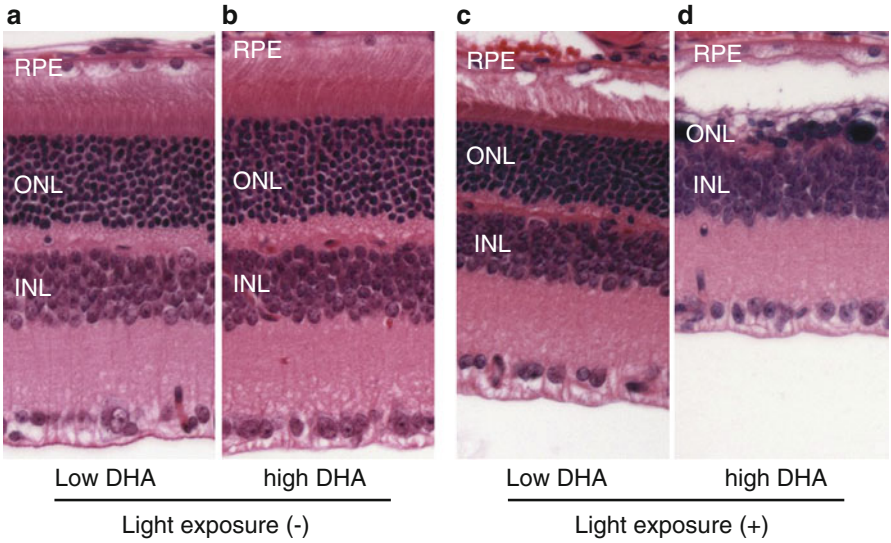

Fig. 15.8 Effect of retinal fatty acid composition on susceptibility to retinal light damage. Albino mice with low (**a**, **c**; *n*-6/*n*-3 PUFA ratio in ROSs, 1.6) or normal DHA (**b**, **d**; *n*-6/*n*-3 PUFA ratio in ROSs, 0.2) levels in the retina are exposed to white fluorescent light for 24 h. The eyes were enucleated 7 days after light exposure. (**a**, **b**) With no light exposure, the difference in the retinal DHA level does not result in marked morphologic changes. A retinal section from an albino rat not exposed to light. (**c**, **d**) After light exposure, more severe loss of the ONL is seen in retinas from mice with high DHA level than those with low DHA levels, suggesting that retinal DHA can be a molecular target of photooxidation. *INL* inner nuclear layer

photosensitizers, are photoexcited by light, undergo intersystem crossing, and produce free radicals. The free radicals then can directly attack the PUFAs and initiate free radical chain reactions that cause lipid peroxidation in cellular membranes and generation of lipid radical species that cause PUFA degradation into oxidized products, including aldehydes. Thus, PUFAs in ROS are target substrates to propagate oxidative stress. Some extremely reactive aldehydes potentially can damage intracellular and extracellular molecules that are a distance from the initial site of free radical attack; this occurs because aldehydes are relatively longer lived than free radicals [49, 50]. Damaging aldehydes include 4-hydroxyalkenals, i.e., 4-hydroxynonenal (4-HNE) and 4-hydroxyhexenal (4-HHE), α, β-unsaturated aldehydes that are end products of lipid peroxidation of PUFAs. 4-HNE forms from *n*-6 PUFAs, such as linoleic acid and AA [51], and 4-HHE forms from *n*-3 PUFAs such as DHA, eicosapentaenoic acid, and linolenic acid [52] via several nonenzymatic steps. These highly reactive aldehydes can react readily with histidine, cysteine, or lysine residues of proteins to form stable Michael adducts with a hemiacetal structure [53]. They exhibit cytopathologic effects, e.g., inhibition of enzyme activity and protein, RNA, and DNA synthesis; cell-cycle arrest; and apoptosis [49]. The aldehyde-modified proteins accumulate in the photoreceptor cells by 3 h after light exposure (Fig. 15.9). The retinal location of these proteins corresponds

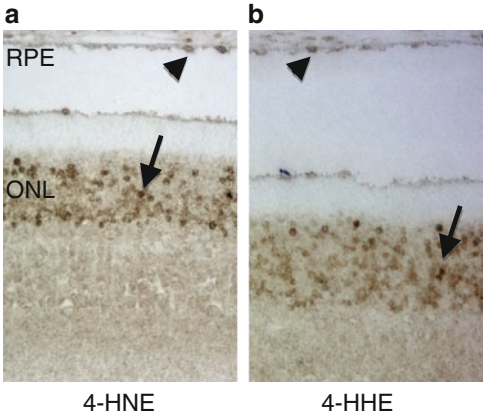

Fig. 15.9 Initiation of reactive aldehyde-modified proteins by damaging light exposure in the retina. The eyes are enucleated 3 h after the 5 k lx white fluorescent light exposure for 3 h. Positive immunoreactivity against 4-HNE- and 4-HHE-modifided proteins is seen in the ONL (*arrows*) and RPE (*arrowheads*) layers. 4-HNE, 4-hydroxynonenal; 4-HHE, 4-hydroxyhexenal

well with the locations with increased terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining at 24 h and severely decreases the outer nuclear layer (ONL) thickness 7 days after exposure. The posttranslational protein modifications caused by these aldehydes occur early before apoptosis and subsequent photoreceptor cellular loss [54].

15.4 Role of Environmental Light and Photooxidative Stress

15.4.1 Light-Adaptation Neuroprotective Phenomenon

Environmental light may regulate the cellular or tissue tolerance to photoreceptor cell damage induced by more intense light exposure. Albino mice and rats raised in bright (300–800 lx) cyclic light were resistant to light (1,700–3,000 lx for 24–72 h)-induced photoreceptor cell apoptosis compared with animals raised in dim (5 lx) cyclic light [55, 56] (Fig. 15.10). There is 6.5 times more DHA compared with palmitic acid in the ROS of rats raised in dim (<10 lx) light and only 0.6 in bright (400 lx) light. This is accompanied by shorter ROS, lower concentrations of rhodopsin, and altered rates of rhodopsin regeneration [56]. Albino rats exhibit a "photostasis phenomenon," by which they adapt to environmental light to capture a constant number of photons daily [57]. Therefore, retinal survival mechanisms against harmful bright light may include control of photon capture and the efficacy of visual transduction through control of the ROS DHA level [58].

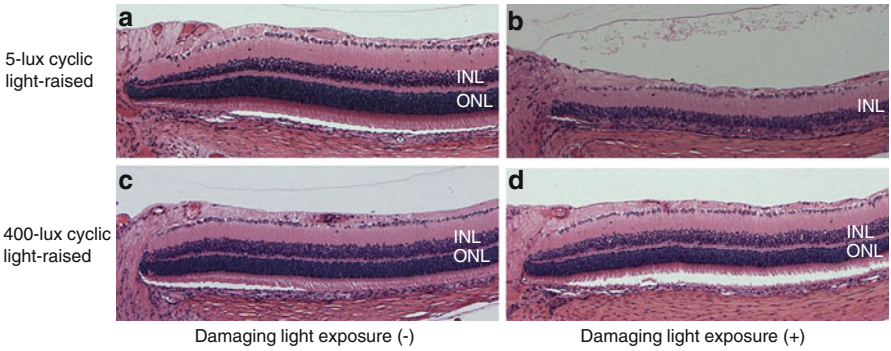

Fig. 15.10 Effect of environmental light on susceptibility to retinal light damage. Albino rats born and raised for 4 weeks in dim (5 lx; **a**, **b**) or bright (400 lx; **c**, **d**) cyclic light are exposed to damaging light (3,000 lx, 6 h; **b**, **d**). The eyes were enucleated 7 days after light exposure (**b**, **d**). (**a**, **c**) Without damaging light exposure, mild loss of the ONL is observed in rats raised in *bright light* (**c**) compared to rats raised in *dim light* (**a**). (**b**, **d**) After damaging light exposure, the ONL thickness is markedly reduced in rats raised in *dim light* (**b**) compared to those raised in *bright light* (**d**), indicating the presence of a light adaptation neuroprotective phenomenon. *INL* inner nuclear layer

15.4.2 Endogenous Defense Mechanisms Against Photooxidative Stress

Rats raised in bright cyclic light had higher retinal levels of endogenous antioxidant enzymes glutathione (GSH) peroxidase [59], GSH reductase [59], GSH S-transferase [59], thioredoxin (Trx) [60], Trx reductase [60], and proteins modified by 4-HNE compared with those raised in dim cyclic light [60]. Rats raised in bright cyclic light also had more DNA binding of transcription factor nuclear-factor-E2-related factor 2 (Nrf2) to the antioxidant-responsive element (ARE) [60]. A sublethal dose of 4-HNE in vitro upregulated the Trx system via the Nrf2-ARE pathway and protected cells from H_2O_2-induced damage. Thus, in the early stages of cellular stress, generation of 4-HNE at low concentrations plays an important role in cell signal transduction and gene expression, and Nrf2-ARE-driven gene regulation is involved in the molecular mechanism of the retinal neuroprotection phenomenon [60]. Trx inducers, e.g., geranylgeranylacetone, an antigastric ulcer drug, or sulforaphane, a component of broccoli sprout, effectively upregulate endogenous Trx in retinal tissues [61, 62]. These compounds mimic an adaptive response mediated by bright cyclic light. Accordingly, modulating the Trx system via activation of the Nrf2/ARE pathway may be a molecular target to prevent photooxidative stress-related retinal diseases such as AMD, RP, and photic maculopathy.

15.5 Light Stress and Retinal Degeneration in Humans

Epidemiologic studies have suggested that excessive light enhances the progression and severity of AMD and some forms of RP [63, 64]. Twelve of 14 publications in a recent meta-analysis reported that light exposure, including longer/intense outdoor activity and sunbathing, can be a risk factor for AMD; six of those articles reported a significant association [65]. Hirakawa et al. measured the extent facial wrinkles, which is associated with a history of sunlight exposure, in patients with age-related maculopathy (ARM) [66] and found that the wrinkles were more severe in patients with late ARM than in those with early ARM. This suggested that lifetime sunlight exposure is an important factor in the progression of late ARM. Subretinal accumulation of drusen is a major risk factor for development of AMD (Fig. 15.11). Drusen, which contains esterified cholesterol-rich, apolipoprotein B-containing lipoprotein particles, are constitutively produced by the RPE [67] and modified bisretinoid (A2E), which forms because of a reaction between all-*trans*-retinal and phosphatidylethanolamine [68]. Thus, drusen may be a waste product of RPE

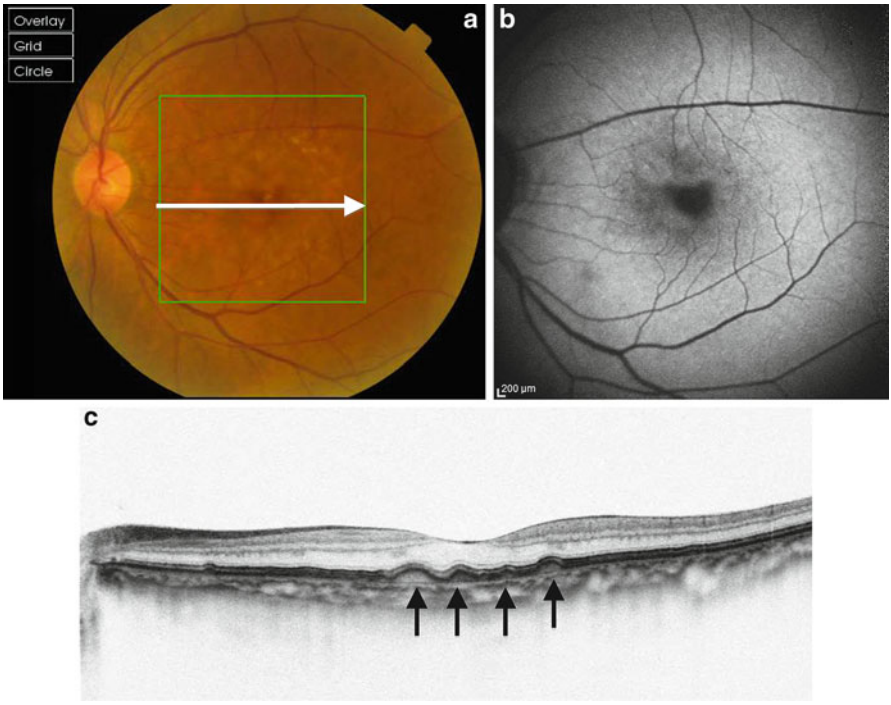

Fig. 15.11 Accumulation of drusen in AMD. Fundus photograph (**a**), fundus autofluorescence image (**b**), and optical coherence tomography (**c**) image of human macular degeneration show intense subretinal accumulations of yellowish-white autofluorescent-positive drusen under the RPE layer (**c**, *arrows*). The *arrow* in (**a**) indicates the scanning direction in (**c**)

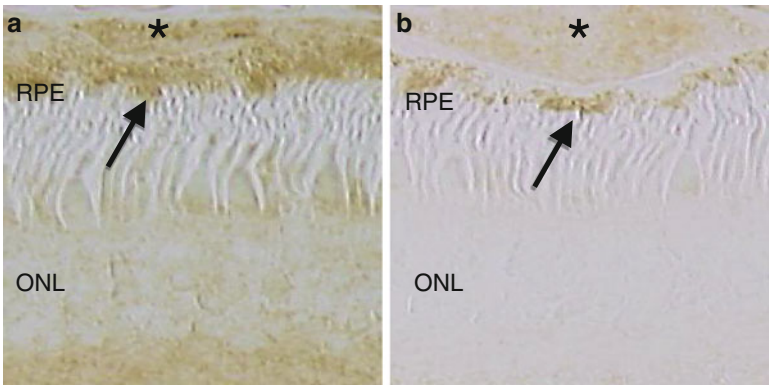

Fig. 15.12 Detection of reactive aldehyde-modified proteins in monkey drusen. Positive immunoreactivity against 4-HNE-modified (**a**) and 4-HHE-modified (**b**) proteins is seen in the RPE (*arrows*) and drusen (*asterisks*)

phagocytosis and retinoid cycle (Fig. 15.5). A proteomic approach to the study of damaging light-exposed rat retinal specimens found that intense light exposure increased 4-HNE-protein modifications in specific retinal proteins from several functional categories including energy metabolism, glycolysis, chaperone, phototransduction, and RNA processing [69]. Many of these proteins are common components among the accumulated proteins in drusen from monkey [70] (Fig. 15.12) and human [71] eyes. Accordingly, drusen form as a result of subretinal/RPE accumulation of degenerated macromolecules such as proteins and lipids, and photooxidation of fatty acids in photoreceptor cells triggers these pathological steps (Fig. 15.13).

15.6 Filtering of Short-Wavelength Visible Light

15.6.1 Presence of Macular Pigment and Supplemental Lutein/Zeaxanthin

The retinal defense mechanism against photooxidative stress includes superoxide dismutase, catalase, glutathione peroxidase, and vitamins E and C. The pigment concentrated in the macula lutea also is part of this defense system (Fig. 15.14). In the 1980s, the carotenoids lutein ((3R3′R,6′R)-lutein), zeaxanthin ((3R,3′R)-zeaxanthin), and meso-zeaxanthin ((3R,3′S;meso)-zeaxanthin) were identified as the primary components in macular pigment [72, 73]. Meso-zeaxanthin, a stereoisomer of zeaxanthin not in the natural diet, is synthesized enzymatically in the retina [74].

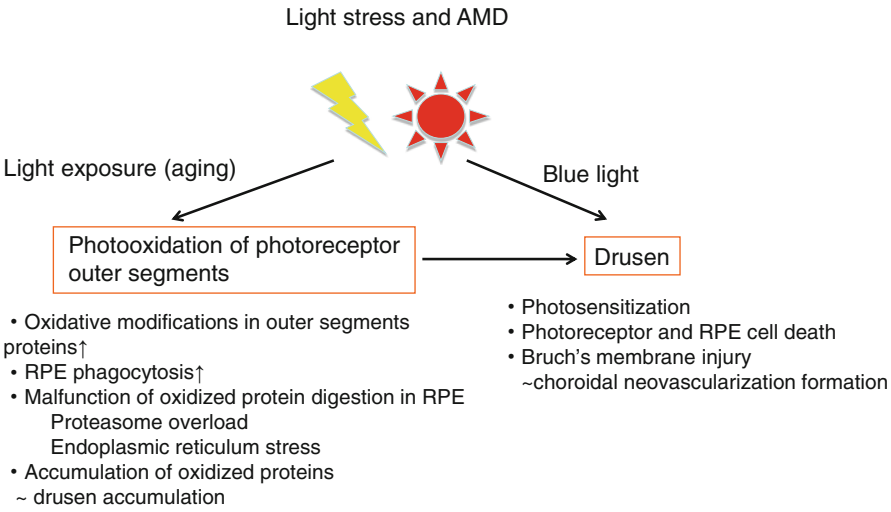

Fig. 15.13 Possible mechanisms between chronic light exposure and AMD. Lifelong exposure to environmental light causes malfunction of the RPE cell machinery of the photoreceptor outer segment waste, resulting in drusen accumulation. Accumulated drusen can act as a photosensitizer of *blue light*, which enhances photoreceptor and RPE cell damage via photooxidative stress

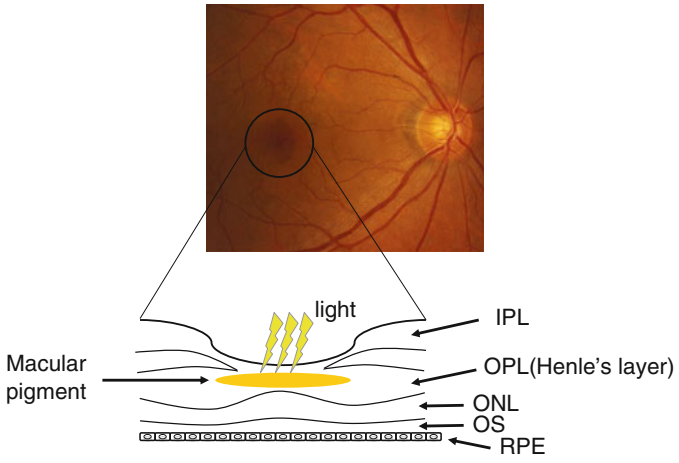

Fig. 15.14 Schematic distribution of macular pigments in a human macula. The highest concentration of macular pigments (*yellow oval*) accumulates in the light path to the foveal photoreceptor cells. *IPL* inner plexiform layer, *OPL* outer plexiform layer, *OS* outer segments

These three carotenoids absorb blue light and act as a filter that may attenuate photochemical damage from short-wavelength visible light, since yellow filters blue from white light (Fig. 15.15). These carotenoids also are antioxidants that may protect against light-induced oxidative retinal damage by quenching oxygen

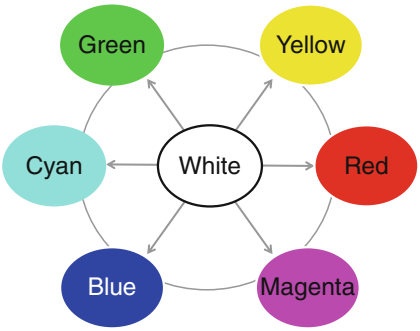

Fig. 15.15 Color circle. A pair of opposite ends of each diameters of the circle are complimentary colors. *Yellow* specifically filters *blue* from *white* light

radicals [75, 76]. A pathological study of autopsy eyes [77], measurements of macular pigment optical density (MPOD) by resonance Raman spectroscopy [78, 79], and other methods [80] have shown that the concentration of macular pigment in patients with AMD is significantly lower compared with normal, healthy eyes. The MPOD levels decrease in light irises and in association with tobacco smoking, low uptake of lutein and zeaxanthin, excessive light exposure [81–83], and aging [78, 79, 84]. Growing evidence has suggested that intake of these carotenoids protects against visual loss from AMD [85–88], although a large-scale randomized control study failed to find a positive effect of adding lutein/zeaxanthin to a nutrient formulation that included vitamins C and E, beta carotene, and zinc in reducing the risk of progression to advanced AMD [89].

15.6.2 Yellowing of Crystalline Lens with Aging and Implantation of Yellow-Tinted Intraocular Lens During Cataract Surgery

The absorption properties of the cornea and crystalline lens help protect the retina from light damage. Yellowing of the crystalline lens with aging causes a progressive increase in absorbance of visible light in the blue range (Fig. 15.16); thus, the aging human crystalline lens also blocks phototoxic blue light [90–92]. Removing the crystalline lens during cataract surgery increases the amount of optical radiation that reaches the retina, and implanting an intraocular lens (IOL) lowers the ocular defenses against photic retinopathy [93]. IOLs with UVR-blocking dye bonded to optic polymers were introduced in the early 1980s [93] and are commonly implanted during cataract surgery. The transmission properties of the colorless UVR-blocking IOLs may not be comparable to those of the aging crystalline lens in absorbance of blue light, which causes Ham's-type retinal phototoxicity [14]. Epidemiologic studies have suggested that the odds ratios of AMD prevalence are 1.7–3.8 in eyes after cataract surgery [94–96] (Fig. 15.17). In prospective studies that spanned 5–10 years, the Beaver Dam Eye Study and Blue Mountains

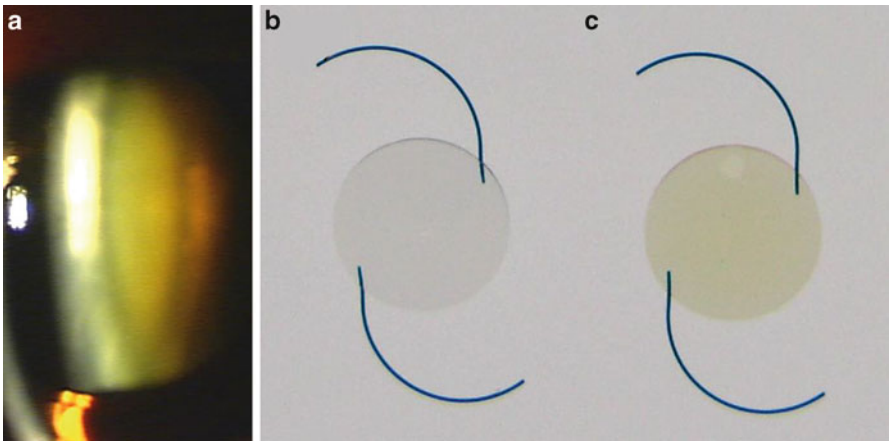

Fig. 15.16 Cataract and IOLs. (**a**) Yellowing of the crystalline lens with aging. (**b**) UVR-blocking clear IOL. (**c**) UVR- and blue-light-blocking yellow-tinted IOL

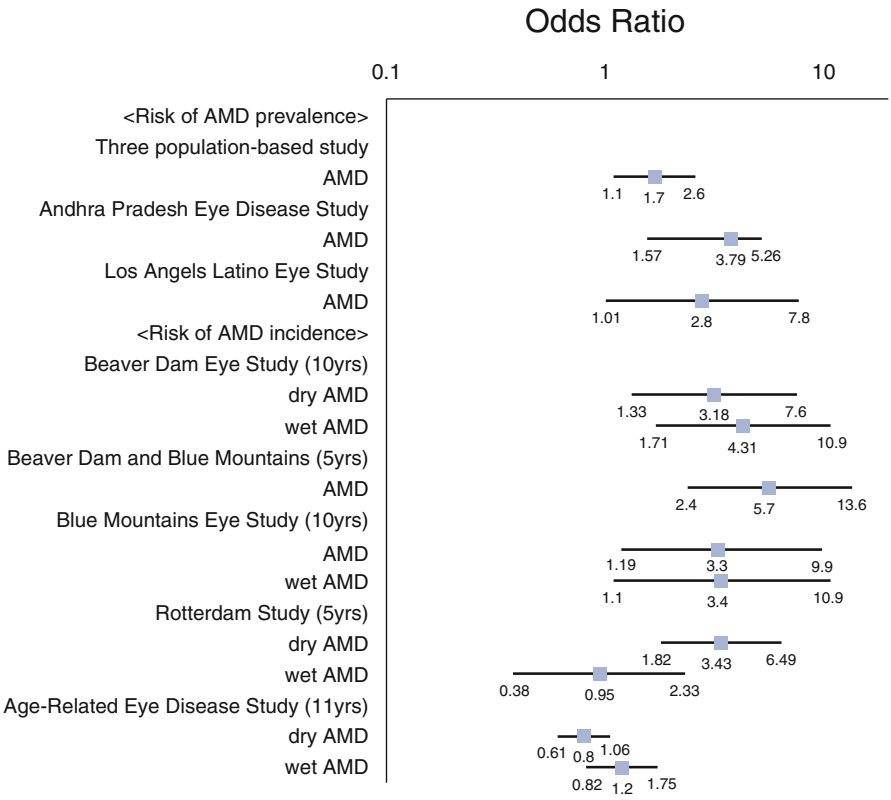

Fig. 15.17 Risk of cataract surgery in AMD prevalence and incidence. Each *bar* indicates the 95 % confidence interval of the odds ratio

Eye Study reported a significant relation between cataract surgery and increased risk of AMD [97–100]. However, the Age-Related Eye Disease Study did not find a significant association between cataract surgery and development of the dry- or wet-type of AMD [101] (Fig. 15.17). To compensate for reduced filtering of blue light by the colorless UVR-blocking IOLs, blue-light and UVR-absorbing yellow-tinted IOLs made of rigid polymethylmethacrylate were introduced in the 1990s [102]; later these were made of foldable silicone or soft acrylic material (Fig. 15.16). Yellow-tinted IOLs that were evaluated in experimental studies confer a protective effect against retinal photooxidative stress in photosensitizing A2E-laden RPE cells exposed to blue light [103] and artificial sunlight [104] in vitro and in rats [105], mice [106], and rabbits [107] exposed to blue or white light in vivo. Obana et al. reported higher levels of macular pigment in eyes implanted with yellow-tinted IOL than in eyes implanted with clear IOLs 1 year and longer after cataract surgery [108]. A large clinical trial should evaluate the effects of blue-blocking filters on AMD development and progression and identify the best balance of filtering spectra for visual function.

Disclosure Chapters 3, 4, and 5 include text extracts from Reference [109] that were used with permission of Future Medicine Ltd.

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