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REVIEW

Retinal light toxicity

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Abstract

The ability of light to enact damage on the neurosensory retina and underlying structures has been well understood for hundreds of years. While the eye has adapted several mechanisms to protect itself from such damage, certain exposures to light can still result in temporal or permanent damage. Both clinical observations and laboratory studies have enabled us to understand the various ways by which the eye can protect itself from such damage. Light or electromagnetic radiation can result in damage through photothermal, photomechanical, and photochemical mechanisms. The following review seeks to describe these various processes of injury and many of the variables, which can mitigate these modes of injury.
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Keywords: light-induced retinopathy light-induced retinal degeneration; phototoxic retinopathy; photochemical; photomechanical; photothermal

Introduction

The ability to translate photic stimulus into usable visual information relies on the complex interaction between the different structural and functional components of the eye and brain. Visual perception is initiated when light reaches the retina and is converted from radiant energy into visual transduction. Light has toxic potential and the eye has adapted several mechanisms to protect the retina from light-induced injury. Nonetheless, under certain conditions, light will cause injury to the eye, a feature that has been known and well documented both in the clinical and basic science literature.

As early as 360 BC, Socrates warned in Plato's *Phaedo*, 'people may injure their bodily eye by observing and gazing on the sun during an eclipse'. In more modern times, Galileo suffered visual loss from his studies of sun spots and Sir Isaac Newton described a retinal visual scotoma and visual afterimage that persisted for days as a consequence of observing the sun directly through a telescope.[1–3]

Numerous reports in the literature support the claim of light-induced retinal damage. Solar damage to the retina, the retina pigment epithelium (RPE), and the choroid were first studied clinically in 1916 by Duke-Elder and MacFaul. In 1966, Noell *et al*[4] suggested that damage to the retina was also possible with low-intensity light. Histological studies by Green and Robertson examined eyes exposed to various levels of light on patients scheduled to undergo enucleation secondary to choroidal melanoma. These studies further corroborated the potential toxic effect of light on the neurosensory retina and RPE.[5] Additional reports have added to our knowledge of phototoxicity by showing retinal damage secondary to the experimental application of light using slit lamp ophthalmoscopy or indirect ophthalmoscopy. Retinal damage secondary to the use of the operating microscope for cataract surgery[6–15] or endoillumination during vitreoretinal surgery[16–19] has served as further evidence of phototoxicity. The application of light in the form of lasers has been used therapeutically to induce injury to the retina for the treatment of such disease processes as diabetic retinopathy, choroidal neovascularization, and the treatment of various intraocular neoplasms.

In this review, we will discuss the following subjects: the basic properties of light that allow light to cause damage to the retina, the basic principles surrounding the three different types of photic damage, the variables affecting these mechanisms of injury, and the role of photic injury in disease pathogenesis and treatment.

Light properties

Light is a form of electromagnetic energy. Electromagnetic radiation has a dual wave-particle nature. When light is absorbed by a photoreceptor, its particle nature is important. The portion of the electromagnetic spectrum that interacts with the eye is referred to as

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optical radiation and includes wavelengths from ultraviolet (100–400 nm), visible light (400–760 nm) to infrared (760–10 000 + nm; Figure 1). The Commission Internationale de l'Eclairage further defined several subgroups in order to establish classes of wavelengths with similar photon energy. Accordingly, ultraviolet light has been further classified into three subgroups, UVA (315–400 nm), UVB (260–315 nm), and UVC (100–260 nm). Infrared light has also been subdivided into three groups consisting of IRA (700–1400 nm), IRB (1400–3000 nm), and IRC (3000–10 000 + nm). Visible light is referred to as short (blue), medium (green), and long wavelength (red) corresponding to the peak absorption spectra of the cone visual pigments.[20–24]

Tissue optics

Of particular pertinence to the effect of light on the retina is the manner in which light traverses a series of ocular tissue or media to reach the retina. Although the eye is designed to focus light specifically on the central retina, some of the light entering the eye is either absorbed or scattered by the tissue and media between the front of the eye and the retina. The relationship between the wavelength-dependent properties of absorption and scattering are referred to as tissue optics. Absorption of optical energy by a molecule refers to the manner by which a photon originating from the light source is taken up by tissues in the eye. Absorption has a fundamental function in determining the potential toxicity of light on the retina as the retina is not exposed to light absorbed by the other ocular structures. Light scattering refers to the deflection of a photon's trajectory secondary to change of refractive index or interaction with particles in the transmission media and is not significant with regard to retinal damage because the amount of light deflected from the retina is small in comparison with total irradiation. Other factors determining possible tissue damage include the direction of gaze, lens characteristics, duration of direct light transmission through the pupil, the presence of iris pigmentation, and pupil diameter.[24–30]

The two most important sources of tissue absorption through which electromagnetic radiation may be propagated are the cornea and the lens. The cornea absorbs almost all ultraviolet radiation below 295 nm. This includes all UVC and most UVB light. The natural crystalline lens absorbs most light near UVB (300–315 nm) and all UVA light. Owing to changes in the crystalline lens with age, the cataractous lens absorbs more of the shorter-wavelength light, which further limits the amount of short-wavelength light (300–400 nm) propagated to the retina.[31] As the vitreous gel is comprised of approximately 98% water, its absorption properties resemble those of water. Wavelengths in the visual spectrum (400–700 nm) and IRA (700–1400 nm) bands are readily propagated, while UV, IRB, and IRC bands are almost entirely absorbed. The remaining propagated radiation spectra ranging between 400 and 1400 nm in wavelength is referred to as the retinal hazard region.[6,24–29,31–41]

Macular pigments (zeaxanthin, lutein, and meso-zeaxanthin) are thought to confer additional protection to the retina through their ability to absorb relatively high-energy blue light. With an absorption spectrum peaking at 460 nm, these macular pigments are estimated to filter approximately 40% of visible blue light[42] (Figure 2).

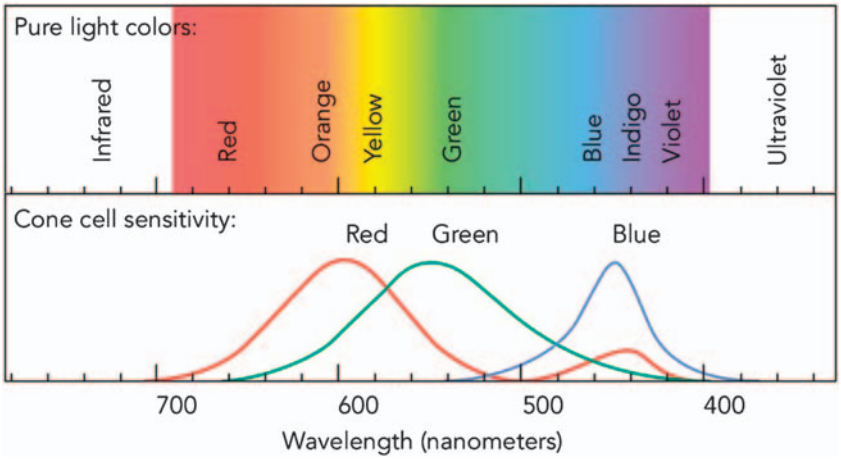

Figure 1 The portion of the electromagnetic spectrum that interacts with the eye is referred to as optical radiation and includes wavelengths from ultraviolet (100–400 nm), visible (400–760 nm), and infrared light (760–10 000 + nm). *How Things Work: The Physics of Everyday Life*, 3rd edn; Louis A Bloomfield; Copyright Wiley 2005. Reprinted with permission of John Wiley & Sons, Inc.

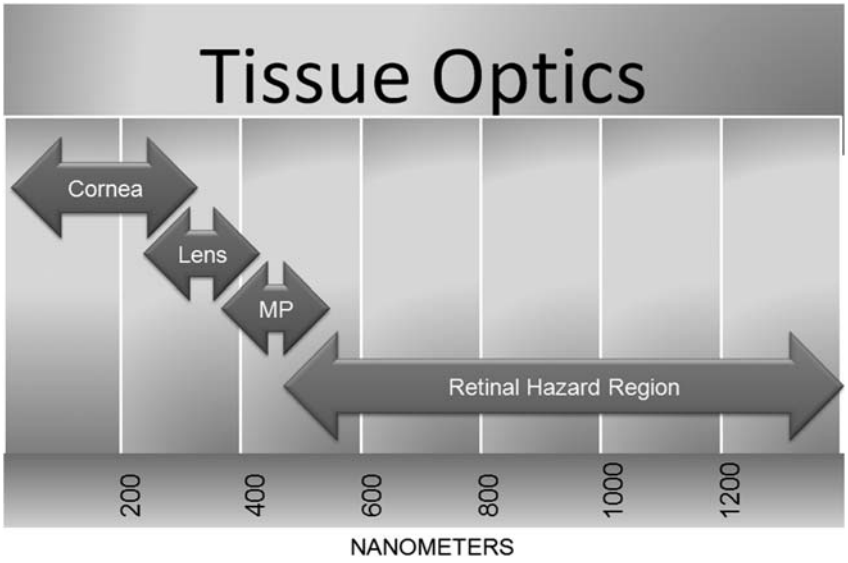

Figure 2 Schematic representation of the tissue optics of the human eye. The cornea, lens, and macular pigment (MP) absorb electromagnetic radiation preventing potential photic energy from high-energy, short-wavelength light. The retinal hazard region represents electromagnetic radiation not absorbed by the aforementioned ocular tissue.

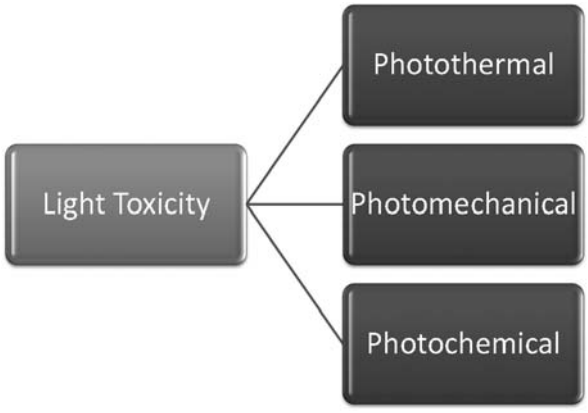

Figure 3 Schematic representation of the three major forms of photic injury.

Types of damage

The mechanisms by which light is thought to cause damage to the retina include the following: photothermal, photomechanical, and photochemical[43–46] (Figure 3). To better understand the different mechanisms, we will briefly review the wave-particle duality of light first described by Einstein in 1905. While we may often think of light as being comprised of a continuous spectrum of different radiant wavelengths, it is vital to also consider the more particulate properties of light, including the existence of light as quanta of energy referred to as photons.

Photothermal damage

Photothermal damage occurs by the transfer of radiant energy, a photon, from light to the retinal tissue. A photon can be absorbed by a molecule only if the photon energy is equivalent to the energy difference between the molecule's current energy state and an allowed higher-energy level known as the excitation state. For wavelengths of light at the upper end of the visible spectrum, as well as wavelengths of light near infrared (600–1400 nm), vibrational and rotational energy states predominate over the excitation states. Therefore, rather than attain their excitation states, molecules in the tissue tend to gain both rotational and vibrational energy. This increase in mean kinetic energy is dissipated as molecules collide with each other and their temperature increases. The ability of light to cause an increase in mean kinetic energy is inversely proportional to the wavelength of the light. This relationship between light and energy is described by the equation:

$$E = hc/\lambda$$

where energy (E) equals Planck's constant (h) multiplied by the speed of light (c) divided by the wavelength of light. The shorter the wavelength, the greater the potential increase in kinetic energy and the greater the rise in temperature for a given exposure time. In a closed system, there is a proportional relationship between exposure time and thermal effect; in an open system, the amount of energy required to produce a given thermal effect increases for longer exposure times as energy in

the form of heat dissipates to the surrounding environment during the exposure. The duration of thermal exposure is usually between 0.1 and 1.0 s.[47–49]

Irreversible thermal damage in the retina typically occurs only after the ambient temperature in the retina is raised by at least 10°C. Depending on the extent of damage induced by the rise in thermal energy, cells may undergo apoptosis secondary to lower-level thermal damage (55–58°C), apoptosis and necrosis for more severe levels of thermal damage (60–68°C), and immediate cell death secondary to more severe thermal exposure (72°C or greater). On a cellular and molecular level, increases in temperature cause the denaturing of proteins, loss of molecular tertiary structure, and fluidization of membranes.[50–52]

Absorption of photothermal energy is thought to occur by one of three pigments: melanin located primarily in the melanosomes of the RPE and melanocytes of the choroid, xanthophyll located primarily in Muller cells and neurosensory retina, and haemoglobin in the blood vessels of the neurosensory retina and choroid. Melanin, the most effective absorber is located primarily in the RPE. Therefore, an eye with an abundance of melanosomes, as in a heavily pigmented fundus, will more readily absorb photothermal energy. Following the application of laser to the retina and RPE, histological evidence of thermal damage is seen initially at the level of both the RPE and photoreceptors.[5,53–57]

Perhaps, the most common example of photothermal damage to the retina is in the form of the clinical usage of lasers for the treatment of various disease states of the retina including diabetic retinopathy, retinal oedema, retinopathy of prematurity, tumours of the choroid and retina, retinal tears, and retinal detachments (Figure 4). While the indication for treatment and the method of application may vary depending on the disease entity, the basic concept of causing injury to the retina or focal lesion via the application localized thermal energy and subsequent increase in temperature remains the same.

In the case of transpupillary thermotherapy (TTT), a red diode laser (810 nm) is used to apply electromagnetic energy to a tumour or focal vascular lesion and cause a temperature increase to 45–65°C leading to irreversible cytotoxic damage. Most commonly, TTT is used as an adjunct to radiation or chemotherapy in the treatment of choroidal melanoma and retinoblastoma, respectively.[58,59]

Experimental studies with animal models have allowed ophthalmologists to titrate laser settings to attain the desired temperature increase. TTT is generally applied to the surface of a lesion using a 1–3 mm spot size and 1 min spot duration. Tumours or lesions treated with TTT show cellular destruction and necrosis resulting from direct cytotoxic effects including cell nucleus and mitochondrial damage. The damage occurs because of the changes in the structure and function of various cellular proteins, which become denatured causing profound cellular dysfunction and eventually leading to cell death through apoptosis or necrosis.[58,59]

Tissue photocoagulation after laser photocoagulation results from an intermediate temperature increase above the damage threshold (65°C), but below the tissue water boiling point, resulting in immediate tissue destruction. The application of laser photocoagulation differs from thermotherapy in that laser photocoagulation generally uses either Krypton (647 nm) or Argon (514 nm) laser with shorter exposure times (<1.0 s), and smaller spot sizes (generally between 50 and 400 μm). Histological studies show that the retina undergoes two stages. The first stage directly follows the application of laser exhibiting immediate tissue destruction and oedema. The second stage, or reparative stage, is characterized by lessening oedema, pigmentary migration, and scar formation. Accordingly, laser photocoagulation can be used for its destructive properties as it is in panretinal phototherapy in which the goal of treatment is to destroy peripheral retina in a effort to lower the ischemic burden in the eye, or in order to create a strong tensile adherence or the retina to the underlying RPE through scar formation as it is when lasering around a retinal tear.[60]

Of recent interest is the use of micropulse diode lasers (810 nm) for the treatment of various retinal diseases. Theoretically, micropulse diode laser may spare damage to the neurosensory retina by raising temperature of

LASER TREATMENT	Type of Photic Damage
Transpupillary Thermotherapy (TTT)	Photothermal
Laser Photocoagulation	Photothermal
Micropulse Diode Laser	Photothermal
Nd:Yag laser	Photomechanical
Photodynamic Therapy (PDT)	Photochemical

Figure 4 The ability of light to cause photic damage to the retina is utilized in several different types of laser treatments. Through either photothermal, photomechanical, or photochemical mechanisms, laser can be used to treat various ocular pathology.

the RPE to just below the temperature at which protein denaturization occurs. In turn, this would limit the collateral photothermal effect on the neurosensory retina and fail to cause the effects normally seen with standard continuous wave laser photocoagulation. Micropulse diode laser is typically delivered with a train of short (0.1–0.3 ms) bursts, for a total exposure time of 0.1–0.5 s. As the laser is delivered in a series of rapid but distinct 'micropulses', the tissue is allowed to cool between bursts. While this treatment has shown some early success in the treatment of central serous chorioretinopathy, diabetic macular oedema, proliferative diabetic retinopathy, and macular oedema secondary to branch retinal vein occlusion, further evaluation is needed.[61–67]

Photomechanical damage

Photomechanical damage refers to tissue damage resulting from mechanical compressive or tensile forces generated by the rapid introduction of energy into the melanosomes of the RPE. Photomechanical damage is thought to be caused by high irradiances in the range of megawatts or terawatts per cm squared and exposure times in the range of nanoseconds to picoseconds. The introduction of energy occurs more rapidly than the relaxation time needed to relieve the mechanical stress produced in the tissue by thermoelastic expansion. This results in the formation of microcavitation bubbles, which are lethal to the RPE and other cells. These compressive and tensile forces are thought to generate sonic transients or shock waves that can also result in permanent damage to the RPE or photoreceptors. The amount of damage is related to the rate of delivery and amount of energy absorbed.[32,33,68–74]

The most common clinical application of photomechanical damage in ophthalmology is the use of radiation from the Nd:Yag laser, which is typically used to create an iridotomy in patients with closed-angle glaucoma or cause retraction of an opacified posterior lens capsule in patients after cataract surgery. Pulsed lasers are rarely used in vitreoretinal surgery because of the potential for collateral retinal damage, particularly full thickness retinal defects and haemorrhage.[68,72–74]

Photochemical damage

Photochemical damage is thought to be the most common mechanism by which light exposure causes retinal damage. By definition, photochemical damage is damage to the retina that is independent of either mechanical or thermal retinal damage. The hypothesis was first suggested by Noell *et al* in 1966 after discovering that the retina of albino rats were irreversibly damaged by continuous exposure to ambient light within the range of the natural light spectrum. This finding inspired extensive scientific investigation, further elucidating the mechanisms of this non-mechanical, non-thermal retinal damage.[4]

Photochemical damage is theorized to result from the exposure of retinal tissue to generated free radicals. While the retina possesses inherent mechanisms to protect against such insult, it is thought that damage may occur once these protective mechanisms have been overcome.[75–77] Photochemical damage is associated with both long-duration exposure times as well as lower-wavelength (higher-energy) light exposure.

Chromophores are theorized to mediate the light-induced damage to the retina.[43–46,78,79] Chromophores in the retina and RPE include, but are not limited to, the photoreceptors, flavoproteins, heme proteins, melanosomes, and lipofuscin. Light with wavelengths in the high-energy portion of the visible spectrum interacts with chromophore molecules contained within the retina and RPE. A chromophore is a region in a molecule in which the energy difference between two different molecular orbitals falls within the range of the visible spectrum. Visible light that hits the chromophore can thus be absorbed by exciting an electron from its ground state into an excited state.[43,46,79–81]

The exposure of radiant energy can cause the generation of free radicals in one of two ways. In the first mechanism of free radical generation, absorption of radiant energy causes excitation of electrons from the 'ground state' to the 'excitation state'. However, the excitation state is unstable and because of this volatility the raised level of energy in the excitation state can be dissipated in one of several ways. While some atoms will simply release the quanta of energy that they previously absorbed and return the excited electron to the ground state, other interactions may lead to the formation of free radicals or reactive oxygen species. Free radicals form after the higher energy level of the excitation state is used to split the bond in another molecule either by direct electron exchange or direct hydrogen exchange. In the second mechanism, the absorption of radiant energy leads to the direct transfer of energy from the excited chromophore to oxygen, creating a singlet oxygen species. Once generated, free radicals can attack many molecule types, thereby causing damage and rendering them inactive. Tissues in which there is a large concentration of cell membranes are particularly vulnerable to free radicals; the attack of free radicals on polyunsaturated fatty acids results in lipid peroxidation that breaks down membranous structures. Lipid peroxidation is propagated as a chain reaction and

can cause extensive damage. Retinal photoreceptors, particularly the outer segments, possess large amounts of membrane and are, therefore, thought to be especially susceptible to this type of free radical-induced damage. Free radicals are also thought to induce protein oxidation in much the same way as lipid oxidation, hence also causing injury to both the neurosensory retina and RPE.[46,78,81–84]

Work in rodent models has divided photochemical injury to the retina into two distinct classes.[46,85] The first class of injury is thought to be rhodopsin linked and mediated by the photoreceptors in the outer segments of the neurosensory retina. This follows from the observation that the action spectrum of Class I damage is identical to the absorption spectrum of visual pigment. Class I damage is characterized be relatively low level of irradiance (below 1 mW/cm^2) of white light, and the exposure may take place over hours to weeks. While there is some debate as to whether the initial site of damage from low-level exposure to visible light is the outer segment of the neurosensory retina or the RPE, most believe the damage from class I photochemical injury occurs at the outer segment of the neurosensory retina.[81,86–89] Class II injury is characterized by exposure to high irradiances (above 10 mW/cm^2) of white light with an action spectrum peaking at shorter wavelengths of white light. Class II injury is thought to occur initially at the level of the RPE. These two classes of retinal damage have been shown in both rodent and primate models.[46,85,87,88,90–93]

Ophthalmoscopic evidence of underlying photochemical retinal toxicity may not always be present on examination. More severe photochemical retinal toxicity will manifest within the first few days of exposure as outer retinal whitening. Within a few more days, mild pigmentary changes may become evident with coarse pigmentary changes developing in the subsequent 1 to 2 weeks. After a period of about 4 to 5 weeks, epiretinal membranes may develop over the lesion. At 3 to 6 months following photic insult, the only remaining evidence of photochemical injury may be a yellowish plaque-like lesion.[94–97]

More recently, high-resolution autofluorescence imaging using an adaptive optics scanning laser ophthalmoscope has been used to examine changes resulting from photochemical injury to the retina. Studies by Morgan *et al* on macaque retinas showed an immediate decrease in autofluorescence of RPE cells following a 15-min exposure of 568 nm light. Follow-up autofluorescence revealed long-term damage in RPE cells at the exposure site.[98] Further work by Morgan *et al*[99] validated the notion of reciprocity between exposure duration and power, by showing that varying exposure duration and power while maintaining a constant radiant exposure resulted in the same amount of autofluorescence reduction.

The biological response of both the neurosensory retina and RPE to light damage has been studied by Rattner *et al* who showed that there is evidence of a 'genomic' response to photochemical retinal toxicity. Using microarray RNA blot and *in situ* hybridization, they were able to show increases in transcription for RNA transcripts coding for protective proteins such as Mmp3, Serpin a3n, Serpin b1a, and Osmr, as well as decreases in transcription of genes coding for visual cycle components.[100]

Histologic and electron microscopic examinations in rat models have shown that evidence of photochemical retinal injury may be seen as early as 3 h after exposure. The first alterations were seen in the outer segments of the photoreceptor cells, which appear swollen and tortuous. Additionally, the lamellar structure of the outer segment discs becomes disrupted. Pyknosis (condensation of chromatin in the cell nuclei) and swelling of the mitochondria then occur in the inner segments. Subsequently, there is an increase in the number of phagosomes and myeloid bodies in the RPE, the damaged photoreceptors disappear, and the RPE ends up adhering to Mueller cells. Tso *et al* studied photochemical retinal injuries in the rhesus monkeys. They described the histologic response to photochemical injury as occurring in three stages: the acute stage occurs within 24 h of the photic insult and is characterized by retinal oedema, RPE pigment disorganization, irregularity of the photoreceptors, and the presence of abnormal pigmentary cells in the subretinal space; the second stage, or reparative stage, occurs approximately 1 week after the initial insult and is characterized by a macrophage response; the third stage, or chronic degenerative stage, can occur weeks to months after the photic injury and is characterized by the proliferation of RPE cells and the formation of a plaque between Bruch's membrane and the outer retina consisting of RPE cells and macrophages.[96,97,101–103] Additionally, work by Postel *et al*[104] showed the presence of cystoid macular oedema, subretinal nodules of hyperplastic RPE, and atrophy of the nerve fibre and ganglion cell layers. Recent work by Albert *et al*[105] has shown the development of progressive stages of retinal degeneration and choroidal neovascularization after long-term intense cyclic light exposure in albino rats (Figure 5).

Clinically, photochemical principles are utilized in photodynamic therapy (PDT) for the treatment of various posterior segment pathology including exudative macular degeneration, choroidal haemangioma, central serous chorioretinopathy, myopic choroidal neovascularization, and polypoidal choroidal vasculopathy. Unlike, TTT or photocoagulation,

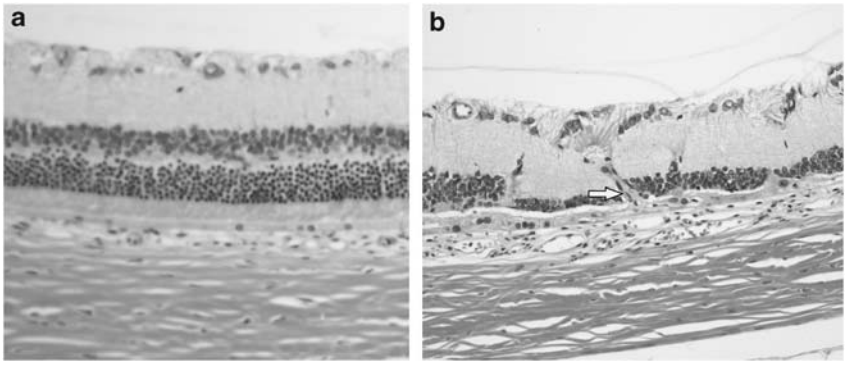

Figure 5 Normal histology of albino rat retina (a). Histopathology of abnormal rat retina exhibiting the development of atrophy and choroidal neovascularization (arrow) after several months of intense cyclic light exposure (b). Courtesy of Richard R Dubielzig, DVM, School of Veterinary Medicine, University of Wisconsin.

PDT does not rely on the thermal properties of electromagnetic radiation. PDT uses a photosensitizer (verteporfin) that is activated by light (689 nm). After verteporfin is administered intravenously to the patient and a delay allows for optimum biodistribution, the treatment site is irradiated with visible or near-infrared light (689 nm). Absorption of this light by the photosensitizer initiates photochemical reactions generating cytotoxic products that result in the desired therapeutic effect. Owing to the localization of verteporfin to the retinal and choroidal vasculature, the effects of the PDT are theoretically localized to these vessels as well as the immediate surrounding tissue.[106]

Variables in photochemical injury

Just as the extent of photomechanical injury and photothermal injury varies with the rate of energy delivery and the magnitude of thermal increase, the severity of photochemical injury also depends on a number of different variables.

Photochemical injury is both dose dependent and cumulative in nature. As retinal injury can be caused by exposure to otherwise innocuous visible light, there appears to be some critical dose or threshold at which exposure becomes injurious. The safe exposure times for common ophthalmic instruments has been reported in the literature and supports the concept of a critical threshold dose necessary for injury. This was suggested by Noell *et al*[4] in their studies of retinal light toxicity. Recent work by Eichenbaum *et al* supports these findings. They noted a graded histologic and electron microscopic response to a fibreoptic light source in which the retinas were continuously exposed for 2, 4, and 6 h.[107–110]

Noell showed that a single 5-min exposure to light did not induce any significant damage to the retina. However, three or four 5-min exposures, each followed by a 1-h dark recovery time, led to significant retinal damage. This work was further substantiated by the work of other investigators including Irvine *et al* in 1984 who found that sequential 4-min exposures in the eye of a rhesus monkey caused a lesion similar in appearance to the monkey's fellow eye treated with a continuous 8-min exposure.[4] However, the effect of cumulative light exposure is not purely additive, as the work of both Ham *et al*[111] and Sperling and Johnson[112] suggests a more complicated relationship between exposure time and resultant retinal damage. Histologic examination of rat retinas after exposure to narrow band light and up to 2 months of recovery time by Bush *et al*[113] revealed that despite damage, the retina possessed some ability to regenerate and repair itself. It is supposed that the inner segment of the photoreceptor is able to regenerate the outer segment discs, allowing the retina to recover from photic damage to the outer segments. However, if the damage from light exposure extends to the inner segment, there may be a more permanent insult to the retinal tissue.

While there is a great deal of concordance among the findings in different animal studies, it is apparent that the results from rodent models is not fully applicable to primate models or vice versa, as there is a great deal of both interspecies and intraspecies variation. Mice and rats have been shown to have lower thresholds for photic injury than do primates.[46,114–116] When comparing humans and monkeys, it has been found that much lower levels of retinal irradiance with similar durations of exposure are needed to cause photochemical injury in monkeys than in humans. For instance, exposure of an anesthetized rhesus monkey for 15 min to the retinal irradiance of 0.27 W/cm^2 from an indirect

ophthalmoscope (dose of 243 J/cm^2) resulted in severe damage to photoreceptors and RPE changes. Humans are routinely exposed to higher total doses of light during surgical procedures such as cataract surgery or vitrectomy surgery with only a few case reports of permanent retinal injury.[81,94,117,118] Additionally, intraspecies genetic differences have shown that alterations in specific genes such as the RPE 65 gene in mice can result in either higher sensitivity or high resistance to light-induced damage. Interestingly, while the presence of a wild-type genetic code for RPE 65 can be closely correlated to protection from light-induced damage in one species of mouse, it may not prove to have the same correlation in a specific species of rat.[46,119–121]

The presence of both rhodopsin and lipofuscin seems to have a function in the potential for photochemical damage to the retina. Independent studies by Noell *et al* and Organisciak *et al* suggest that rhodopsin may have a deleterious effect on photochemical damage to the retina. These experiments showed that rats reared in darkness had both more rhodopsin and were more susceptible to damage that rats raised in cyclic light conditions. Meanwhile, lipofuscin similarly can generate superoxide anions after exposure to light with the rate of free radical production directly related to the intensity of light exposure and inversely related to the wavelength of light exposure.[80,122–125] Generation of these free radicals can in turn cause RPE damage, induce lipid peroxidation, and lysosomal dysfunction. Studies on cultured cells by Davies *et al*[126] have shown these changes upon exposure to lipofuscin and low-wavelength light.

The extent of photochemical retinal damage also seems to vary according to the manner of exposure. Organisciak *et al*,[127] exposed rats to a single dose of high-intensity light at various times of the day and night and found that retinal damage was greatest at the beginning of the night cycle. Similarly, Duncan and O'Steen showed that susceptibility to light-induced cell death in rats also depended on which part of the light-dark cycle the animals received their light exposure. In this study, rats were exposed to 4 h of high-intensity fluorescent light during different portions of their normal 14 : 10 light-dark cycle for an 8-day period of time. Rats receiving light exposure at the end of their dark period or beginning of their light period showed greater retinal damage than those receiving light exposure at the end of their light cycle. The period of greatest potential damage correlate to the period of greatest outer segment phagocytosis.[128]

While the previously mentioned studies do suggest that some relationship exists between photochemical damage to the retina and the settings of light exposure, it is also clear that adaptation mechanisms can have a vital function in reducing the susceptibility to light damage. Penn and Williams[129] described one of these adaptive effects, termed photostasis, in which the concentration of rhodopsin is regulated so that the relative absorption of photons remains steady and independent of the intensity of environmental light. Evidence of photostasis was further supported by additional studies showing reduced levels of outer segment rhodopsin in rodents exposed to higher levels of light intensity.[130] Other forms of adaptation include the generation of endogenous antioxidants upon exposure to light. Several rodent experiments have shown that rats raised in lighted environments may produce protective antioxidative enzymes to guard against photic damage.[131–133]

As discussed earlier, photochemical damage seems to be heavily mediated by the generation of free radicals and excited state and reactive oxygen species, it stands to reason that both endogenous and exogenous antioxidants may have a protective function against photochemical damage. In fact, this presumption is supported by many studies showing the benefit of such mediators. A study by Mittag *et al*[134] showed that mice carrying a mutation in the gene coding for superoxide dismutase, a known enzymatic antioxidant, were more susceptible to light-induced damage than mice without the mutation. Further, studies have elucidated the potential benefit of vitamin and antioxidant supplementation to reduce light-induced damage.[77,131,135–139] Zeaxanthin, meso-zeaxanthin, and lutein are dietary carotenoids, which together form macular pigment and are thought to provide protection against oxidative damage. Owing to their molecular nature, the macular pigments are able to use their high number of double bonds to neutralize singlet oxygen, free radicals, and triple state photosensitizers, and thereby limit lipid membrane peroxidation.[42] Conclusive evidence that carotenoids behave as antioxidants was first provided by Khachik *et al*,[140] who showed the oxidation products of zeaxanthin and lutein in the retina. *In vitro* studies of human RPE cells have shown increased survival of RPE cells when they are subjected to oxidative stress in the presence of zeaxanthin and other antioxidants when compared with RPE cells exposed to the same conditions without antioxidant supplementation.[141] The protective role of lutein, zeaxanthin, and other antioxidants has also been shown in many other animal studies.[142,143]

Owing to the ability of macular pigments to serve as both effective absorbers of high-energy, short-wavelength light, as well as antioxidants, many investigators have started to measure macular pigment optical density. In fact, several groups of investigators have shown an increase in macular pigment density

resulting from dietary supplementation of carotenoids.[144–146] Additionally, the lutein antioxidant supplementation trial (LAST) and the LUNA study both support the association between dietary supplementation and macular pigment density.[147,148] Others have noted great variability in macular pigment optical density depending on factors such as gender, body fat composition, and smoking.[149,150] While the role of macular pigment optical density remains of limited clinical use at this time, studies such as the Carotenoids and co-antioxidants in age-related maculopathy are investigating the use of macular pigment optical density measurement in relating dietary carotenoid supplementation on the progression of ARMD.[151]

Sunlight exposure and age-related macular degeneration

The ability of light to cause damage resembling the changes seen in age-related macular degeneration, in animal studies, has led to the investigation of sunlight exposure as a risk factor for macular degeneration. Owing to the difficulties of collecting quantitative data surrounding lifetime light exposure, much of what we have learned comes from epidemiologic studies. Researchers have attempted to use proxies for assessing cumulative light exposure including iris colour, change in iris colour, skin colour, reported behaviour of sun avoidance, skin tone, skin sensitivity, history of skin cancer, history of severe sunburns, use of sunglasses and hats, facial hyperpigmentation, and length of facial wrinkles.

While several studies have correlated light iris pigmentation and lighter coloured hair with age-related macular degeneration, other studies have not confirmed this association.[152] In fact, the two largest studies to date, The Beaver Dam Eye Study and the Blue Mountains Eye Study, do not conclusively support the association of lightly pigmented irises and age-related macular degeneration. The Beaver Dam Eye Study followed 2764 patients over a 10-year period. After collecting data on iris colour, reported skin responsiveness to sunlight, and hair colour at age 15, colour stereoscopic photographs were compared. Multivariate analysis revealed an increased incidence of retinal pigment epithelial changes in patients with blue eyes *vs* those with brown eyes. Likewise, patients with blonde hair were more likely to undergo similar retinal pigmentary changes than individuals with brown hair. The study concluded, however, that iris colour was inconsistently related to the presence of early age-related macular degeneration lesions and the progression of age-related macular degeneration.[153] While initial data from The Blue Mountain Eye Study found an association between blue iris colour and both late and early age-related macular degeneration, 5-year longitudinal data did not corroborate this finding.[154,155]

A study from Japan by Hirakawa *et al* used computer-based image analysis to measure facial hyperpigmentation and facial wrinkle length as an indication of lifetime sun exposure. The computer-based measurements were compared in 67 patients without ocular disease, 75 patients with early age-related macular degeneration, and 73 patients with late age-related macular degeneration. The study results showed a statistically significant association between more facial wrinkling and late ARMD. However, the study conversely suggested that less facial hyperpigmentation was present in patients with ARMD. Again, the study results did not conclusively associate increased sun exposure with the development of ARMD.[156] While the collected data does not firmly support photochemical oxidative stress as a definitive cause or exacerbating factor of age-related macular degeneration, there still remains a fundamental belief among many clinicians and scientists that oxidative stress whether metabolic, inflammatory, or photic in nature contributes to many of the changes seen in age-related macular degeneration.

Many observational studies have tried to answer whether dietary supplementation of antioxidants is protective against ARMD. Recent data analysis from the original Age-Related Eye Disease Study (AREDS) found an independent association between higher levels of dietary lutein and zeaxanthin intake and a lower likelihood of having neovascular ARMD, geographic atrophy, and large or extensive intermediate drusen. Likewise, the Blue Mountains Eye Study found that those patients with the highest level of dietary lutein and zeaxanthin intake were less likely to have incident neovascular ARMD, and that those intermediate levels of lutein and zeaxanthin intake were less likely to have incident soft or indistinct drusen. The AREDS II trial, a placebo-controlled randomized control trial, has completed enrolment and is currently seeking to determine the role of lutein and zeaxanthin as well as omega 3-polunsaturated fatty acids on the progression to advanced ARMD.[42,157,158] While the results for AREDS II will not be known for several more years, many vitreoretinal specialists advocate the use of supplementary carotenoids in their high-risk patients.

Concern over the effects of photic damage on the retina and the possible role in the pathogenesis of macular degeneration has caused some ophthalmologist to recommend the use of sunglasses with UV protective coating as well as blue light filtering lenses. In addition, in an effort to provide protection against photic damage after cataract surgery, several companies have produced blue blocking lenses with yellow chromophores.

While the cataractous natural crystalline lens naturally filters wavelengths of light ranging from 300 to 400 nm, clear IOLs allow light in this range to be transmitted to the retina. In an effort to replicate the potentially protective effect of a cataractous natural crystalline lens, some surgeons have elected to implant these blue blocking lenses. While work by Sparrow *et al* showed the reduction of RPE cell death *in vitro* after exposure to blue, white and green light filtered through a blue blocking lens, it is uncertain whether this will translate to a protective effect against ARMD and other retinal diseases. Many investigators remain sceptical regarding the role of blue blocking lenses as most patients with macular degeneration are phakic at the time of diagnosis and have developed disease despite the protective tissue optics of the aged natural crystalline lens. There is also concern regarding the effect of blue blocking lenses on scotopic function and circadian rhthyms.[159–161]

Conclusion

The ability of light to cause injury to the retina has been shown both clinically and experimentally. While neurosensory retina and RPE are protected from light-induced exposure by the absorption profile of the surrounding ocular structures, including the cornea, crystalline lens, and macular pigments, as well as the ability of the retinal photoreceptors to regenerate its outer segments, photic injury is still possible. The principles of photomechanical, photothermal, and photochemical injury to the retina provide a framework for understanding and photic injury to the retina.

Our understanding of the mechanism of light damage has grown extensively in recent years, but much remains to be learned in the effort to reduce the effects of potentially toxic exposures. This knowledge is pertinent to reducing the morbidity of disease processes potentially related to light exposure, such as age-related macular degeneration. Additionally, as vitreoretinal surgeons continue to introduce the use of potentially photoactive vital dyes such as indocyanine green to enhance surgical techniques, it becomes increasingly important to be able to identify and minimize the potential harmful effects of these agents.

Already, advances in nutritional supplementation, intraocular lens composition and design, and the potential for reduced irradiance from surgical lighting equipment have helped us to reduce the potential for light-induced damage. The availability of new imaging technology, better surgical instrumentation, and new tools for genomic research should help us better understand the mechanism of light-induced injury, as well as identify methods of intervention for minimizing damage to the retina.

Conflict of interest

The authors declare no conflict of interest.

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