Photobiomodulation of the Visual System

Subjects: Pathology
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Humans express an expansive and detailed response to wavelength differences within the electromagnetic (EM) spectrum. This is most clearly manifest, and most studied, with respect to a relatively small range of electromagnetic radiation that includes the visible wavelengths with abutting ultraviolet and infrared, and mostly with respect to the visual system. Many aspects of our biology, however, respond to wavelength differences over a wide range of the EM spectrum. Further, humans are now exposed to a variety of modern lighting situations that has, effectively, increased our exposure to wavelengths that were once likely minimal (e.g., “blue” light from devices at night). This paper reviews some of those biological effects with a focus on visual function and to a lesser extent, other body systems.

Keywords: Electromagnetic radiation ; photobiomodulation ; action spectrum ; phototoxicity ; visual system

1. Introduction

James Maxwell, building on postulates from Gauss, Riemann, and Faraday, proposed in 1864 that an electromagnetic “disturbance” exists that travels in free space with the velocity of light [1]. His theory was later confirmed by Hertz around 1888 [1] and thus began our understanding of electromagnetic (EM) radiation. It is now accepted that EM radiation is the flow of photons that behave as both particles and waves, and is divided into bands depending on the propagating wavelength. To illustrate, gamma waves have wavelengths measured at the atomic level (<100 pm), while the wavelengths of radio waves are measured in miles. Despite a relatively long history of research, the effects of EM radiations on human biology are relatively understudied, and carries the oft-quoted paradox of being both necessary and antithetical to life. From this general aphorism, however, many specific questions can be posed: What are the common sources of EM? What wavelengths promote health, and which detract, and at what intensities? What and how are biological processes affected with acute and chronic EM exposure? These questions merit immediate comment.

The most commonly encountered source of EM radiation is the sun. Within the 48% of the sun’s radiation that actually reaches the earth’s surface [2], 49.4% is infrared (>700 nm), 42.3% is visible (400–700 nm), 6.3% is ultraviolet (UV) A (320–400 nm), 1.5% is UVB (290–320 nm), and 0.5% is UVC (<290 nm) [3]. The bulk of this paper will therefore concentrate on these wavelengths. However, the level of irradiance in the “visible” spectrum is much higher, owing to the evolutionary tuning of our visual system. That is, we see what is most energetic at the earth’s surface. The positive and negative effects of EM radiation on the eye will be discussed shortly.

Another commonly encountered source of EM radiation are radio frequency emitters. Radio frequency emitters have been around for some time (circa Heinrich Hertz, 1886) but not in such high numbers, nor have the detection devices for such emitters (cellular phones) been in such constant and close proximity to humans. As such, there has been concern that chronic exposure to this seemingly insignificant energy source (around 3 kHz–300 GHz) carries the potential for tissue damage. Reflecting such concerns [4], the National Toxicology Program published extensive results [5] on the effects aggregated over a lifespan of about 2 years, including in utero, of radiofrequency exposures on the brains and hearts of rats and mice. The study found significant pathological changes, such as DNA damage, using similar frequencies as those used by the telecommunications industry (900 and 1900 MHz), but the study used much higher energy exposures. Mice in the study, for instance, were exposed to intensities of up to 10 Watts/Kg (analogous to ~500 Watts for a 110-pound human) for around 9 h per day. Cell phone energy varies from about 2 Watts to around 0.2 Watts during a call. The relatively recent release of 5G cellular networks has its own health controversies [6][7], and of course, some individuals keep their cell phones within close proximity constantly.

Hence the conundrum when considering the interaction of EM radiation and biology: how are the relatively intense, acute, and easily quantifiable exposures used in animal models comparable to the relatively weak exposures that humans experience over a lifetime? Human behavior is complex. How does one link any complex outcome to any single (often weak) input with dozens of significant and confounding correlates? Not surprisingly, for example, epidemiological studies on the relation of cancer to cell phone usage are inconsistent at best [5].

Similar challenges are encountered when relating light damage to chronic ocular disease. Intense acute studies on animal models tend to show very clear results with easily described underlying mechanisms (for example, Barker et al. studied the protective effects of xanthophylls on short-wave light-induced retinal damage [8]). Long-term chronic studies tend to be inconsistent [9] and depend strongly on the nature of the disease. With respect to the latter, for instance, easily quantified (e.g., eyelid malignancies) or relatively acute conditions (e.g., photokeratitis) show a much more straightforward relation to actinic light than more difficult to quantify retinal diseases such as macular degeneration [10].

As a consequence, some researchers have decided to focus less on chronic degenerative diseases, which are characterized by long latencies and complex etiologies, and more on acute biological effects. If a stressor causes effect X, this is both meaningful in its own right and likely has implications for long-term disease. For example, cells phones (radio frequency detectors) are often carried around the waist and reproductive germ cells divide rapidly (spermatogenesis/oogenesis), which are easy to quantify in terms of cell counts and dynamics. There is good evidence that mobile phone exposure influences oxidative stress, sperm mobility, and fertilization [11]. Implantation of a UV-transmitting intraocular implant in one eye and a UV-blocking implant in the other causes loss of S-cone sensitivity in the UV-transmitting eye over a span of five years [12], not the same as AMD but S-cone loss is significant in its own right, a likely good indicator of approaching retinal disease [13].

Taking such a direct approach—light exposure vs biological response—allows a number of answerable questions to be posed. The first is methodological: How does one relate wavelengths, throughout the EM spectrum, to human biological response? This methodology was perhaps best worked out by plant photobiologists in the form of action spectra. Action spectroscopy is characterized by the measurement of biological effects that occur as a function of wavelength [14]. The Commission Internationale de l'Eclairage (CIE) defines the photobiologically active range from UVC (100 nm) to IRC (1,000,000 nm) [15]. The origin of this technology began with the obvious and differential light sensitivity of plants. It was used, for example, to originally identify chlorophyll as the pigment most likely involved in photosynthesis [16]. Photochemistry, in general, was based on the observation that reactants respond (react) to some wavelengths more strongly than others. It was natural to generalize these observations to the photobiology of organisms. At first, the emphasis was on damage: some wavelengths were more damaging than others [17]. After, studies shifted to the efficacy of certain wavelengths in mediating a variety of biological reactions. The effects were ubiquitous.

2. Phototoxicity, Dosimetry, and Action Spectrum of the Visual System

Light is the primary stimulus used by the visual system? What is less obvious is that different wavelengths of light influence literally every aspect of the visual process. The early philosophers, from the Greeks to the Chinese, focused mostly on how wavelength related to the perception of color. The first systematic/empirical study of wavelength and color has been attributed to Isaac Newton (Opticks, 1704), but, as art and science flourished hand in hand through the Renaissance, so did interest in the underlying optics of color. Prominent intellectuals like Goethe published treatises such as Zur Farbenlehre ('Theory of Color,' 1810). It was not until 1916 [18], however, that human spectral sensitivity curves were published and then codified by the CIE [19]. What followed, and is beyond the scope of this review, were extensive studies of how the optics of the eye are affected by wavelength [20], as well as characteristics as diverse as spatial [21] and temporal vision [22]. Along with this work came the realization that different wavelengths of light are more or less damaging to the visual system, and other surface tissues such as skin. Van Norren and Vos published a comprehensive review of the history of research on actinic action spectra [23]. This empirical work mostly began with animal models (the work of Noell and Ham in the 1960s) but the damaging effects of light were also being actively considered in the ophthalmic literature [17].

Light, in this case, with its potential to harm, refers mostly to the higher energy portions of the EM spectrum, although significant exposure to lower energy light (say infrared) can also predispose an individual to damage. For example, thermal lensing can defocus NIR at high intensities and increase susceptibility [24]. Historically, the primary source for high-energy light came from the sun. Even now, although many common devices (mobile phones, computers, etc.) emit light in the short-wave portions of the spectrum, the amount is likely not significant enough to initiate photo-oxidative damage [25].

Light that damages the eye is termed phototoxic. Phototoxicity can take different forms depending on the wavelength and intensity of the approaching EM radiation. Ocular phototoxicity is subdivided into photothermal (photocoagulation), photomechanical (photoacoustic), or photochemical damage. Photothermal damage typically occurs with the longer visible and NIR wavelengths of 600–1400 nm, where photons have enough energy to cause molecular vibration without splitting electrons from atoms within the molecule. This is inferred as heat and is particularly damaging to the crystalline lens (e.g., "glassblowers" cataract) [26] and intentionally applied to the retina for laser photocoagulation of certain disease states (e.g., diabetic retinopathy, retinal edema, etc.) [27]. Photomechanical damage generally refers to a very short pulse

(e.g., nanoseconds) of very high energy (e.g., megawatts/cm2) that results in a thermoelastic pressure wave [28]. This shock wave results in microcavitation bubbles and permanent tissue change. A common example is the neodymium-doped yttrium aluminum garnet (Nd:Yag) laser used to punch a hole in the peripheral iris (iridotomy) to help control glaucoma. The Nd:Yag laser is often set to 532 nm, 700–900 mW, for 0.1 s [29]. Photochemical damage is thought to occur when photons are absorbed by the molecules of a tissue, exciting the electrons from the ground to excited state (i.e., the formation of free radicals or reactive oxygen species). This is typically associated with long exposure times and higher energy light [27]. Photochemical ocular damage is associated with the pathogenesis of diseases such as macular degeneration and choroidal neovascularization. Photochemical exposures are additive according to the Bunsen-Roscoe law of photochemistry which basically states that damage can occur from an intense radiation source for a short time, or a less intense source for a longer period of time [30]. Paradoxically, the damaging photochemical process is also utilized in photodynamic therapy (PDT) where unwanted anomalies are treated with a photosensitizing drug then exposed to EM radiation (e.g., 689 nm) to induce the free radical process and reduce the anomaly [31].

There are many factors to consider when calculating the dose of when a particular wavelength can cause harm to a tissue. Apart from the numerous environmental factors [32][33], radiation that reaches the ocular surface is also dependent upon anatomical factors that might limit its entry into the eye [34][35] such as the size and shape of the nose, skin reflectance, protruding eye (exophthalmos), sunken eye (enophthalmos), eyelid droop (ptosis), eyelashes, eyebrow, and prominence of the supraorbital ridge. Once the radiation reaches the ocular surface, then factors such as wavelength (action spectra), aversion responses (looking away, pupil constriction), tissue repair, size of the light source, exposure intensity, exposure area, and exposure duration all play a role [30]. Nonetheless, general exposure guidelines are provided in Tables 1–5 where appropriate.

Several recent reviews are available that discuss the impact that electromagnetic radiation has on the eye [23][36], skin [37] [38], and other biological functions [39]. In brief, as noted, UV damage is photochemical, not photothermal. “Actinic ultraviolet” is most significant below 320 nm (UVC and UVB) but affects deeper structures of the eye based on penetration (e.g., UVA penetrates deeper and may be more significant for retina). More recent reports suggest that UVB [40] and near UVA (360–400 nm) [41] are important for myopia control. Furthermore, blue (464 nm) and red (634 nm) may be important for emmetropization when coupled with a multifocal lens [42].

Although, significant exposure to lower energy light (say infrared) can also predispose an individual to damage. For example, thermal lensing can defocus NIR at high intensities and increase susceptibility [24].

2.1 The Eyelids

Table 1 summarizes the effects of high-energy light on the eyelids. As shown in the table, most of the effects of light on the eyelids can be predicted by the general effects of light on skin, with the exception that the skin of eyelids is thin (as light filters go, they have an average optical density of around 2.1 ± 0.3 in the visible range, [43]). They are also somewhat protected by the supraorbital bone and eyebrows [36]. Lids, ridges, and brows combine to also provide some protection to the cornea, the other major ocular surface tissue. The action spectra for the cornea is summarized in Table 2.

Table 1. Electromagnetic radiation action spectra and dosimetry thresholds for the lids.

	EMR Phototoxicity and Dosimetry of the Lids	
Wavelength	**Effect**	**Reference**

	Average erythemal UV dose of Americans is about 25,000 J/m2/year.	[44]
	3X more carcinogenic than UVA (e.g., squamous cell carcinoma, SCC).	[44]
	Squamous cell carcinomas account for about 8%, and melanomas about 2%, of all-cause cancer in Croatia.	[45]
UVB	Basal cell carcinomas (BCC) account for 80–90% of all malignant tumors of the eyelid.	[46]
280 < 315 nm	Excess exposure increases risk of erythema, melanogeneisis, DNA damage, immune suppression, photo-aging.	[44]
	UVB is major cause of sunburn, which is leading risk factor for melanoma and non-melanoma skin cancers.	[44]
	BCC may be due to strong UVB exposure at a young age, whereas SCC appears due to chronic/cumulative exposure.	[10]
UVA	Photoaging: main effect on the lids is sagging skin.	[44]
315 < 400 nm		
Visible	Intense visible (e.g., 532 nm laser pointer) has been shown to cause ecchymosis of upper and lower eyelids.	[47]
380 < 760 nm		
	Photodynamic therapy (at 634 nm) is an effective treatment for basal cell carcinoma.	[48]
Infrared	Thermal radiation can cause burns ranging from mild to third degree and eventually skin death.	[49]
Exposure Limits	UVR	
(see text discussion)	3 mJ/cm^2 for 8 h daily to avoid redness (erythemal), and this is one-third to one-quarter of the minimal erythemal dose.	[50]

2.2 The Cornea

Table 2. Electromagnetic radiation action spectra and dosimetry thresholds for the cornea.

Wavelength	**EMR Phototoxicity and Dosimetry of the Cornea** **Effect**	**Reference**
	Momentary exposure to UVC can cause photokeratitis such as welders flash.	[51]
UVC		
100 < 280 nm	Susceptibility to photokeratitis may peak at 270 nm with exposure thresholds as low as 3 mJ/cm2.	[52]

	10 h of UVA or 23 min of UVB can cause photokeratitis.	[53]
	UVB absorption is 1.8 times higher in the anterior 100 nm of the human cornea than in the posterior layers. The absorption coefficients of the epithelium and Bowman's membrane are higher than the stroma, but the stroma absorbs more due to thickness. Tryptophan and ascorbic acid absorb UVB.	[54]
UVB 280 < 315 nm	300 nm causes apoptosis in all three layers of the cornea and induces keratitis. Apoptosis in all layers of the cornea occurs 5 h after exposure.	[55]
	UVB light can accelerate the physiological loss of corneal epithelium be two mechanisms, shedding and apoptosis.	[10]
	The biological damage potential at 295 nm is 375 times more than the biological damage potential at 320 nm.	[56]
	Climatic droplet keratopathy—chronic UVA and UVB.	[10]
	Corneal crosslinking: primary treatment for corneal ectatic disease, involves application of vitamin B2 (riboflavin) + 370 nm to stiffen the cornea.	[57]
UVA 315 < 400 nm	Epithelium: pseudo-keratinization, polyhedral intermediate cells, necrosis, lymphatic infiltration.	[58]
	Bowman's membrane: detachment from epithelium, thickened, micro-bleedings.	[58]
	Stroma: swelling and collagen disorganization, inflammatory cells, angiogenesis blood vessels.	[58]
	Endothelial detachment.	[58]
Visible 380 < 760 nm	Punctate keratitis caused by 532 nm laser pointer.	[47]
	Climatic droplet keratopathy with higher blue (400–500 nm) light exposures, in addition to UVA and UVB.	[59]
NIR 760 < 1400 nm	The cornea transmits 96% of incident infrared in the 700–1400 nm range, limiting sensitivity to IR harm, especially in the 750–990 nm range. Significant exposure results in causing protein coagulation which can cause irreversible damage especially on endothelium layer. High-dose IR damage to the cornea causes immediate pain and vascularization, with potential of loss of transparency and opacification in response to burns that causes ulcers.	[49]

Exposure Limits (see text discussion)	315–400 nm: 1 J/cm^2 for exposure time < 1000 s 1 mW/cm^2 for time ^{3} 1000 s 180–400 nm: 3 mJ/cm2 pulsed hazard 770–3000 nm 1.8t$^{-0.75}$ W/cm2 for time < 20 s 0.1 W/cm^2 for time > 20 s 1.8t$^{0.25}$ J/cm^2 for time < 45 s	[30]

As shown in Table 2, many of the significant effects to the cornea are highly wavelength-dependent and in the low UV range. As ocular structures go, the cornea represents the main interface between the eye and environment, and hence absorbs the largest amount of radiation [58]. This, perhaps, saves deeper structures to a large degree but creates great susceptibility of the cornea to very low wavelengths. This is a risk both indoors and out. With respect to the former, UV light is used in entertainment such as black lights at nightclubs, and mass presentations of photokeratitis have been reported [60]. UV used as a disinfectant has been reported in 41 cases of photokeratitis in poultry workers [61]. UV promotes inflammation (keratitis) though a number of interleukins, cytokines, and matrix metalloproteinases that, ultimately, mediate cell damage [58]. It should be noted that corneal crosslinking is a procedure used to stiffen an ectatic cornea by the combination of a photoinducer (vitamin B2) and 370 nm light [62]. The light used to conduct the corneal crosslinking procedure (365 or 370 nm) can also be used to effectively treat some cases of infectious keratitis [63].

2.3 The Conjunctiva

The other ocular surface tissue that is also an eye-environment interface is the membranous conjunctiva. Effects of EM radiation on the conjunctiva are outlined in Table 3. The most obvious clinical manifestations of light damage to the conjunctiva are pterygium and pinguecula (noncancerous growths, often nasal, visible on the sclera). Since the conjunctiva interfaces with the external environment, many factors can induce general inflammation of the conjunctiva (conjunctivitis). This has made recent news, for example, as a relatively unique symptom of COVID-19. Early in the natural and recent history of the novel coronavirus pandemic was the observation that the condition can cause changes (often irritation) to the conjunctiva (indeed, the first doctor who identified the new condition was an ophthalmologist, Li Wenliang). These changes manifest as dry eye, blurred vision, and mild follicular conjunctivitis [64]. Ocular changes, like conjunctivitis, do not typically accompany many other systemic infections (like influenza or even other coronaviruses like SARS or MERS). Almost 80% of conjunctivitis cases are specific to the adenovirus [65] and occur early in life (0-4 years of age). Reaction of the eye to systemic infection is relatively rare. This implies that CoV may be relatively unique in its ability to influence surface tissues of the eye. This may be why this strain of coronavirus (HCoV-NL63) caused alarm when identified initially in an infant displaying conjunctivitis. A subsequent study of 28 cases of children with confirmed HCoV-NL63 infections showed that 17% had conjunctivitis [66]. Although the disease could come in contact with the conjunctiva as an aerosol, the presence of CoV in the conjunctival sac [67] suggested it might also arise from within the patient and be expressing through lacrimal fluid. Viruses often absorb in the UVC range [68] which is why UV light is sometimes used as a germicidal (e.g., hospital rooms sometimes use upper room germicidal irradiation) and is being actively considered to help retard the spread of CoV, and UVC appears most effective [69].

Table 3. Electromagnetic radiation action spectra and dosimetry thresholds for the conjunctiva.

Wavelength	**EMR Phototoxicity and Dosimetry of the Conjunctiva** **Effect**	**Reference**
UVC 200–280 nm	Erythema: Although only 1% of 254 nm may penetrate the stratum corneum, mild erythema still results.	[52]

UVB 280–315 nm	Ocular surface squamous neoplasia (OSSN) declines by 49% for each 10 degree increase in latitude.	[70]
	Pterygium: hyperplasia of the bulbar conjunctiva that grows over the cornea.	[10]
	Pterygium: Associated with long-term exposure to UVA and UVB.	[10]
	Pterygium: High prevalence between latitudes ± 37 degrees.	[71]
	Pterygium may initiate by UV-induced changes in corneal epithelial stem cells.	[72]
	Pinguecula: fibro-fatty degenerative change in bulbar conjunctiva.	[10]
UVB, UVA and Visible	Pinguecula: Weak association with long-term UVA and UVB.	[10]
	Pinguecula: May be a histological link with sun-induced skin changes.	[73]
	448 nm at 0.8 mW/cm for 6 h resulted in lysosomal membrane permeabilization of the conjunctiva.	[74]
	Conjunctival UV autofluorescence can be used to accurately determine the time spent outdoors.	[75]
	Damage of conjunctiva caused by 532 nm laser pointer.	[47]
Exposure Limits (see text discussion)	270 nm: 3 mJ/cm2 within minutes can cause conjunctival injection, chemosis, damaged epithelial cells, and the presence of inflammatory cells.	[76]

Almost 80% of conjunctivitis cases are specific to the adenovirus [65] and occur early in life (0–4 years of age). The reaction of the eye to systemic infection is relatively rare. This implies that CoV may be relatively unique in its ability to influence surface tissues of the eye.

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