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Healthy Blue Light and the Eye

What Every Eye Care Professional Should Know About the Science of Chronobiology

New Evidence Identifies the Role of Blue Light in Circadian Function

The study of blue light's effects on the visual system is fascinating for ophthalmologists because our depth of knowledge on the subject was quite limited until very recently. New research is revealing that blue and other short-wavelength light has an important impact on circadian and other biorhythms upon which virtually every physiological and hormonal system in the body depends. There is much to learn. Researchers are excited about an important new understanding that links blue-light transmission to the retina, and to the science of chronobiology.

In ophthalmology, the expanding knowledge about blue light is generating fresh controversy over whether to block its transmission through IOLs with the addition of either violet or blue-light filters. As evidence mounts that blue light triggers hormones that control circadian rhythms, many ophthalmologists are starting to question the initial wisdom of IOLs' mimicking the crystalline lens' natural yellowing process, out of fear that inhibiting blue light may have unintended consequences. For example, it is well established that elderly people have disrupted sleep cycles and suffer from higher rates of depression compared with younger people. Additionally, most epidemiological studies have shown that environmental light exposure is not a risk factor for age-related macular degeneration. Thus, the implications of this research are far reaching, even within ophthalmology alone. These questions remind us that we need to proceed carefully and thoughtfully with new research and technological advances lest our efforts to mitigate certain problems cause others. The history of science is filled with examples of "the law of unintended consequence."

I am pleased to introduce this monograph, which presents the latest research in the area of blue light and human biorhythms. One of the most exciting developments has been the discovery of a new class of photosensitive retinal ganglion cells that contain melanopsin and respond directly to blue-light exposure. The participating authors, including researchers who are on the forefront of ganglion-cell research, discuss the new findings and their various aspects as well as how they are reshaping ophthalmologists' perspectives about appropriate light exposure for patients. As a practitioner and student of ophthalmology, I am constantly educating myself about new findings and relevant knowledge in disciplines that intersect with ophthalmology.

I am confident that you will find the material in this monograph to be stimulating, and perhaps even "illuminating."

—Roger F. Steinert, MD

Contributors

Martin A. Mainster, PhD, MD, FRCOphth, is the Luther L. Fry Professor of Ophthalmology at the University of Kansas Medical School in Prairie Village, Kansas. He is a consultant to Advanced Medical Optics, Inc., IRIDEX, and Ocular Instruments Corporations. Dr. Mainster may be reached at mmainste@kumc.edu.

Patricia L. Turner, MD, is a Clinical Assistant Professor of Ophthalmology at the University of Kansas Medical School in Prairie Village, Kansas. She has received travel expenses from Advanced Medical Optics, Inc., but acknowledged no other financial interest in the products or companies mentioned herein. Dr. Turner may be reached at mmainste@kumc.edu.

Debra J. Skene, PhD, is Head of the Neuroendocrinology Research Group (www.surrey.ac.uk/SBMS/neuroendocrinology) at the University of Surrey in Guildford, United Kingdom. She acknowledged no financial interest in Advanced Medical Optics, Inc. Professor Skene may be reached at +44 (0) 1483 689706; d.skene@surrey.ac.uk.

David M. Berson, PhD, is the Sidney A. Fox and Dorothea Doctors Fox Professor of Ophthalmology and Visual Sciences and Professor of Neuroscience at Brown University in Providence, Rhode Island. He acknowledged no financial interest in Advanced Medical Optics, Inc. Dr. Berson may be reached at (401) 863-2555; david_berson@brown.edu.

Christian Cajochen, PhD, is Professor in Neuroscience and Head of the Centre for Chronobiology, Psychiatric University Clinics in Basel, Switzerland. He acknowledged no financial interest in Advanced Medical Optics, Inc. Professor Cajochen may be reached at +41 (61) 3255318; christian.cajochen@unibas.ch.

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Cataract Surgery Should Improve Vision *and Health*

Blue light and the eye's important role in good health.

BY MARTIN A. MAINSTER, PHD, MD, FRCOPHTH, AND PATRICIA L. TURNER, MD

Speculation that environmental light exposure is a risk factor for age-related macular degeneration (AMD) remains unproven despite almost a century of study, but it has motivated some manufacturers to introduce IOLs that restrict visible light as well as UV radiation. Blue-blocking IOLs attenuate substantial amounts of violet (400-440 nm) and blue (440-500 nm) light.

It has been known for over 50 years that blue light is important for vision in dim environments.[1,2] A rapidly growing body of scientific evidence now documents that blue light is vital for optimal systemic and mental health.[2,3] Blue-blocking IOLs were designed almost a decade before the discovery of retinal ganglion photoreceptors and their important role in good health and quality of life. UV-blocking IOLs have provided pseudophakes with their best possible photoreception for over 3 decades. Blue blocking IOLs sacrifice rod and retinal ganglion photoreception for ineffective photoprotection against an unproven hazard. Here are the facts.

PHOTOTOXICITY AND AMD

AMD is a complex multifactorial process. Smoking and age are its only consistently documented risk factors. The phototoxicity-AMD hypothesis posits that photic retinopathy (retinal phototoxicity) from repeated environmental light exposure causes AMD.[2-4] Many mechanisms other than light have been postulated for AMD, including choroidal sclerosis, RPE dysfunction, genetic defects, retinoid deficiency, and inflammation.[4]

Acute retinal phototoxicity experiments and the phototoxicity-AMD hypothesis have been used to advocate blue-blocking IOLs, despite the fact that AMD is a chronic process whereas photic retinopathy occurs only when brilliant light exposures overwhelm retinal defenses acutely. The only common clinical examples of retinal phototoxicity are solar and welding arc maculopathies and operating microscope and endoilluminator injuries.[4,5] Acute phototoxicity can injure the retina but it cannot simulate AMD, just as scalding water can scar skin but it cannot simulate a lifetime of normal bathing.[2]

Figure 1 shows that the risk of UV-blue phototoxicity (the "blue light hazard") increases with decreasing wavelength.[2,6] Thus, UV radiation is more hazardous

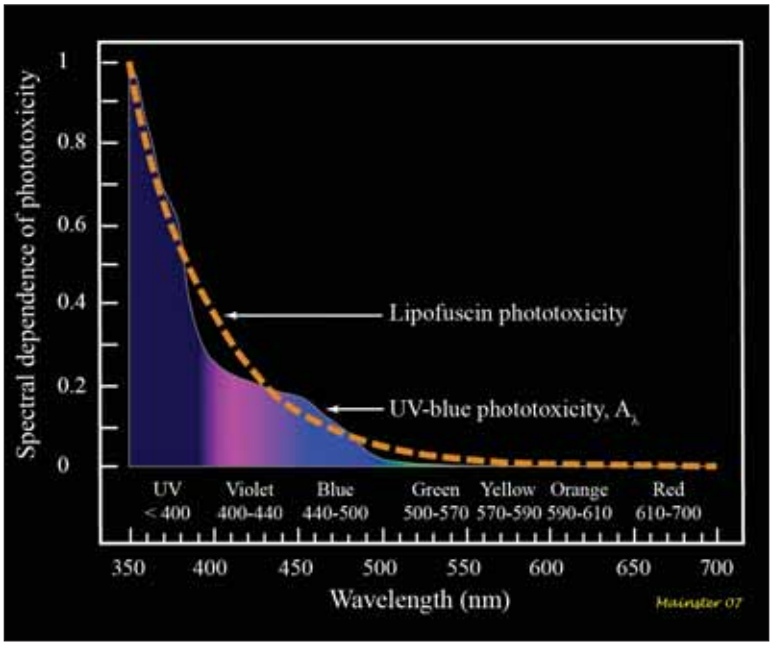

Figure 1. Acute UV-blue phototoxicity[6] (A_λ) and lipofuscin phototoxicity[64] increase rapidly with decreasing wavelength, so UV radiation is more hazardous than violet light, which is more hazardous than blue light.

than violet light, which is more hazardous than blue light. The international standard phototoxicity risk function[6] (A_λ in Figure 1) is based on experiments in which young, dilated, anesthetized monkeys were exposed to intense light from lasers or powerful xenon lamps.[7] Retinal damage from acute UV-blue photic retinopathy can damage the macula, but it requires very high retinal irradiances such as those causing solar and welding arc macular injuries.[8,9]

> "Blue-blocking IOLs have no proven efficacy, so they do not represent evidence-based medicine, and there is no medical justification for permanently limiting blue light that is vital for photoreception."

The Beaver Dam and Blue Mountain Eye Studies found that cataract surgery was correlated with late AMD,[10] but the Age-Related Eye Disease Study and recent Swiss and Chinese studies showed that pseudophakia is not a major risk factor in neovascular AMD.[11-13] If there is a correlation between cataract surgery and AMD, it is probably due to shared risk factors and/or the physiological effects of intraocular surgery.[2,10]

The phototoxicity-AMD hypothesis' greatest weakness is its lack of support by nine[14-22] of the eleven[14-24] major epidemiological studies that examined it.[2,3] These large studies should have confirmed the hypothesis if environmental light exposure were linked closely to AMD. Their failure to do so suggests that (1) lifelong light exposure is not a significant risk factor in AMD, (2) it is inherently difficult to estimate a subject's cumulative light exposure, or (3) factors such as variable genetic susceptibility obfuscate a weak correlation.[2,3] Additionally, "there is no existing evidence that AMD prevalence varies with latitude,"[25] and there should be a definite link if light were a significant risk factor for AMD.

Popularity of the phototoxicity-AMD hypothesis persists despite its failures because RPE lipofuscin accumulates with aging, hypothetically increasing an older adult's risk of retinal phototoxicity.[3,4] Conversely, pupil area and crystalline lens transmittance decrease progressively with age, substantially reducing retinal illuminance and phototoxic risks.[3] When phototoxic risks are compared for phakic and pseudophakic eyes, 65- and 75-year-old pseudophakes with a 20.00 D blue-blocking IOL have the equivalent ocular ages (EOAs) of 28- and 34-year-old phakic adults, respectively.[3] Most AMD occurs in phakic individuals over 60 years of age, so blue-blocking IOLs are less effective than young adult crystalline lenses that do not prevent AMD.[2,3]

The Centers for Medicare and Medicaid Services concluded that "the relationship between blue light and AMD is speculative and not proven by available evidence."[26] Blue-blocking IOLs have no proven efficacy, so they do not represent evidence-based medicine, and there is no medical justification for permanently limiting blue light that is vital for photoreception.

SUNLIGHT AND MELANOMA

Blue-blocking IOLs have also been advocated using data from one study showing that decreasing violet and blue light reduces proliferation in uveal melanoma cell culture stimulated by intense, 12-hour white-light exposures.[27] Conversely, several other reports show that blue light inhibits the growth of melanoma and leukemia cells in vitro.[3,28,29]

Regardless of the relative merits of these laboratory studies, "the literature does not support a significant role for sunlight—which includes blue light—in the oncogenesis of uveal melanoma."[30] Indeed, recent epidemiological evidence shows that the incidence of uveal melanoma actually increases with decreasing solar exposure,[31] consistent with the long reported inverse relationship between solar exposure and non-skin cancer mortality, which may be mediated by the beneficial effects of vitamin D.[32]

PHOTOPIC VISION

Standard D-15 and FM 100-hue tests do not detect differences between the color vision of pseudophakes with UV- or blue-blocking IOLs.[33] Nonetheless, tritan defects can be demonstrated in pseudophakes with blue-blocking filters using a Moreland anomaloscope,[34] and blue-blocking IOLs are not recommended for United States Air Force aircrew because of their need to perform operational color vision tasks.[34] Additionally, color disparity problems required explantation of a blue-blocking IOL in a patient with a UV-blocking IOL in her contralateral eye.[35,36] Blue-blocking IOLs also decrease photopic luminance contrast.[37]

Reduction of chromatic aberration has been mentioned as a possible benefit for blue-blocking IOLs.[38] In fact, the photopic performance of pseudophakic eyes at medium and high spatial frequencies is determined primarily by wavelengths between 500 and 600 nm that are focused better on the retina than shorter or longer wavelengths.[39] Thus, violet and blue wavelengths contribute little to modulation transfer at mid

or high spatial frequencies,[39] accounting for the failure of blue-blocking chromophores to improve pseudophakic contrast sensitivity.[33,39]

SCOTOPIC AND MESOPIC VISION

Blue light provides 7% of cone-mediated photopic vision and 35% of rod-mediated scotopic sensitivity.[2] Thus, blue light is much more important for vision in dim than bright environments. Cone photoreceptors image headlight-illuminated objects during night driving, but rods provide the remaining visual field.[40] Driving, mobility, and peripheral vision problems are all associated with rod- but not cone-mediated dark adaptation parameters.[41] When you get up at night and lighting is too dim to see color, you are using rod-mediated vision.

Scotopic vision and other rod-mediated visual functions decline progressively with age due to decreasing pupil area[42,43] and crystalline lens transmittance[44] that reduce the amount of blue light available for retinal photoreception. UV-blocking IOLs provide equivalent ocular ages for rod photoreception roughly 15 years more youthful than blue-blocking IOLs.[3] Diminishing neural sensitivity causes additional age-related loss in rod photoreception.[45] By 75 years of age, crystalline lens yellowing and pupillary miosis reduce phakic scotopic sensitivity to only 25% of that of a 10-year-old eye.[3] A recent study showed that pseudophakes with blue-blocking IOLs have reduced scotopic vision at violet and blue wavelengths,[46] a loss previously correlated with night driving difficulties.[47]

Blue-blocking IOLs offer 14% to 21% less scotopic sensitivity than UV blockers.[2,48] This reduction is small compared to the broad range of visual sensitivity,[48] but (1) it is a loss, (2) perimetric tests are poor surrogates for common visual tasks in dim illumination, (3) rod vision deficits are worse in people with AMD and diabetic retinopathy, (4) reduced night vision causes older adults to curtail nighttime activities,[49] and (5) impaired dark adaptation increases older adults' risk of falling, debilitating injury, long-term hospitalization, and death.[2,50]

CIRCADIAN PHOTORECEPTION

Circadian photoreception is unconscious. It adjusts (photoentrains) our internal biological time to match environmental day/night cycles, so it is essential for good physical and mental health.[2,3,51] Circadian photoreception is mediated by blue-light–sensitive retinal ganglion photoreceptors that were discovered in 2002.[52,53] Approximately 1% of all human retinal ganglion cells are photoreceptors.[54-56]

The axons of most retinal ganglion cells mediating conscious vision synapse in the lateral geniculate nuclei of the thalamus, but most axons from retinal ganglion photoreceptors synapse in nonvisual nuclei, including the paired suprachiasmatic nuclei of the hypothalamus and other diverse brain centers.[3] Suprachiasmatic nuclei are the human body's master biological clock. Circadian rhythmicity permits our body to anticipate and prepare for essential daily activities. For example, it takes time to upregulate protein synthesis and increase blood sugar, heart rate, and blood pressure before arising.[3,51] Suprachiasmatic nuclei have their own intrinsic periodicity, which usually differs from the 24-hour period of the geophysical day, so the advantages of circadian rhythmicity are lost without effective

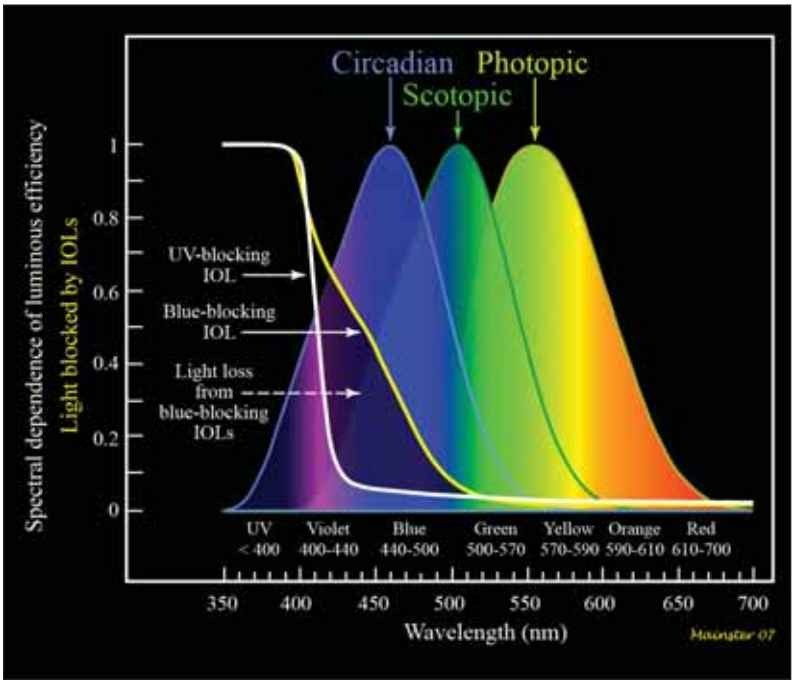

Figure 2. Circadian (λmax ≈ 460 nm),[54,55] scotopic (λmax ≈ 500 nm),[65] and photopic (λmax ≈ 555 nm)[66] spectral sensitivities. The fraction of light blocked at different wavelengths is also shown for 20.00 D UV-blocking (AMO ClariFlex) and blue-blocking (Alcon Natural) IOLs. The area between the two IOL curves is the violet, blue, and green light lost by blue-blocking in comparison to UV-blocking IOLs. Blue light accounts for 55% of circadian and 35% of scotopic photoreception.

photoentrainment to external environmental diurnal rhythms.

Melatonin conveys timing information from the suprachiasmatic nuclei to synchronize peripheral clocks throughout the human body. Melatonin itself has important antioxidant, anticancer, and antiaging functions. Bright light suppresses melatonin secretion and increases core body temperature, alertness, and cognition.[2,3,57] Effective blue-light exposure is crucial to synchronize melatonin secretion to environmental day/night cycles.

> "It has been shown, however, that cataract surgery with a UV-only blocking IOL can decrease insomnia and daytime sleepiness."

The spectral efficiency of melatonin suppression peaks at 460 nm in the blue part of the spectrum (Figure 2). This blue-light dependence arises because retinal ganglion photoreceptors express the blue-light sensitive photopigment melanopsin.[54,55] Blue light provides 55% of melatonin suppression[2] (Figure 2), which is a standard surrogate for retinal photic input to nonvisual brain centers, including the suprachiasmatic nuclei.

Circadian rhythmicity is often disturbed in aging and in people with insomnia, depression, and memory loss.[3,51] Circadian dysfunction occurs in coronary artery disease, hypertension, diabetes, Alzheimer's disease, and many forms of cancer.[3] Health risks are correlated with the degree and duration of circadian disruption. Numerous clinical studies have shown the risks of disturbed circadian photoentrainment and the benefits of optimal rhythmicity.[3]

Circadian photoreception declines progressively with age because of decreasing crystalline lens transmittance[44] and pupil area.[42,43] These optical factors reduce the effective circadian retinal illuminance of 65- and 75-year-old eyes to only 27% and 17% of that of 10-year-old eyes, respectively.[3] Diminishing neural sensitivity probably causes additional age-related loss in retinal ganglion photoreception. Blue-blocking IOLs decrease circadian photoreception by 27% to 38% as compared to UV-blocking IOLs.[2] Less blue light is the likely cause of decreased nocturnal melatonin secretion reported in many older adults, and some elderly sedentary lifestyles provide only half the total daily luminance of young adults.[58] If circadian photoreception is compared in phakic and pseudophakic eyes, UV-blocking IOLs provide equivalent ocular ages 15 to 20 years younger than blue-blocking IOLs.[3] For example, 75-year-old pseudophakes have equivalent phakic ocular ages of 50 and 33 with 20.00 D blue-blocking and UV-blocking IOLs, respectively.[3]

Older adults cannot appreciate the decline of retinal ganglion cell photoreception directly because it is not a conscious process. It has been shown, however, that cataract surgery with a UV-only blocking IOL can decrease insomnia and daytime sleepiness.[59] Therapy with light can also reduce insomnia and restore older adults' peak nocturnal melatonin levels to youthful levels.[58]

CONCLUSION

One third of all adults have sleep problems,[60] insomnia is well known to increase with aging,[61] and only 12% of people over 65 years old deny sleep complaints.[62] Many physicians are unaware of their patients' sleep problems because older and blind patients typically fail to inform even primary care physicians about their significant insomnia.[3,60,63] Most patients do not know about the eye's important role in insomnia, so they are even less likely to discuss sleep difficulties with their ophthalmologists. The medical literature documenting that blue light is important for good health grows rapidly. Withholding blue light has its dark side.

If light were a risk factor for AMD in some people, then pseudophakes should wear sunglasses in extremely bright environments because blue-blocking IOLs provide less photoprotection than young adult crystalline lenses that do not prevent AMD.[2,3,5] The big difference between sunglasses and blue-blocking IOLs, however, is that people have the freedom to remove their sunglasses for optimal photoreception whenever they choose to do so.

After 3.5 billion years of evolution, life on earth is well adapted to its blue sky. Blue light is essential for good vision and health. The use of blue-blocking IOLs is not evidence-based medicine. The purpose of cataract surgery is to improve vision and quality of life. Cataract surgery can provide older adults with better conscious vision in bright and dim environments. Increasing blue-light–dependent unconscious circadian photoreception extends the benefits of cataract surgery beyond image-based vision to improved health and longevity. ■

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Blue Light and Sleep

What research is revealing about sleep disorders in the elderly.

BY DEBRA J. SKENE, PHD

Science has established two widely accepted facts about the aging human body that relate to the discussion of light exposure and sleep. One is that the crystalline lens grows dense and yellows. The second is that our sleep efficiency and other parameters of sleep change as we age. This article reviews the current research regarding the possible link between the aging ocular lens and sleep problems.

> "We established that light-induced suppression of melatonin was maximally sensitive to short-wavelength blue light."

THE CONNECTION BETWEEN LIGHT AND SLEEP

Traditionally, older people have more trouble sleeping than younger individuals. The elderly awake more often during the night, achieve deep sleep less frequently and for shorter durations, sleep for shorter lengths of time, and are more likely to nap during the day.[1-4]

Scientists have long suspected that light influences the circadian rhythms of the human body. My colleagues and I at the Neuroendocrinology Research Group at the University of Surrey (Guildford, UK) conducted the first study to demonstrate that the blockage of blue light as occurs in the aging lens may reduce the circadian system's sensitivity to light. We exposed young (24 ± 3 years) and older women (57 ± 5 years) to short-wavelength blue light and compared the ability of this light to suppress the nocturnal production of melatonin as a marker of the integrity of the circadian system (Figure 1). The results confirmed our hypothesis that the older subjects would respond less to blue light if their crystalline lenses had changed.[5]

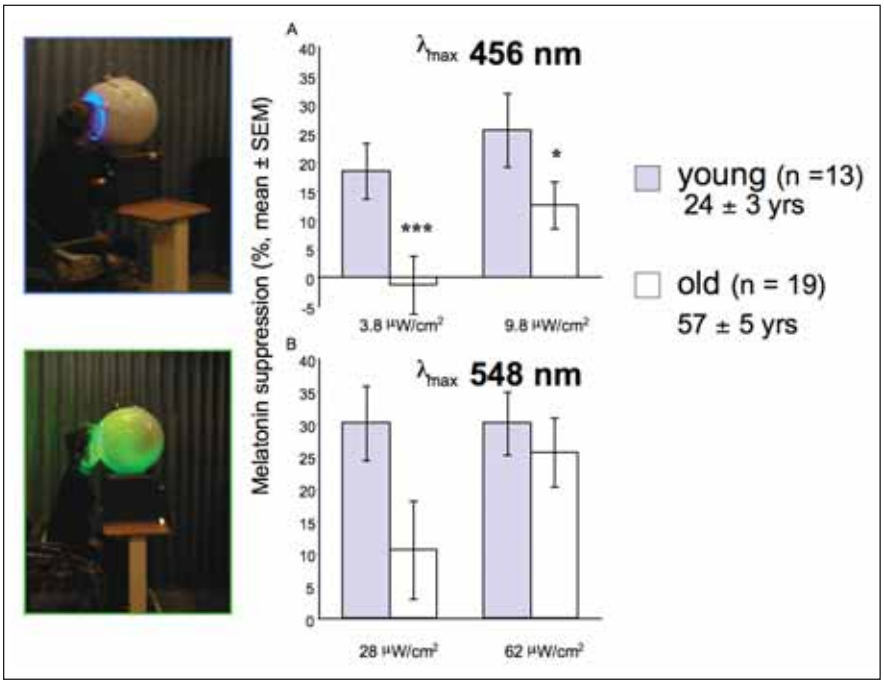

Figure 1. Melatonin suppression in young and older women following short-wavelength blue light (λmax 456 nm) and longer-wavelength green light (λmax 548 nm).

Previous work by other researchers had revealed further clues about the relationship between light, the visual system, and circadian rhythms. Provencio et al discovered the existence of the photopigment melanopsin (a photoreceptor) in human retinal ganglion cells.[6] In our laboratory, we established that light-induced suppression of melatonin was maximally sensitive to short-wavelength blue light (at wavelengths of around 440 to 480 nm).[7] Brainard et al[8] found similar results.

Later work from our laboratory and others showed that

other "nonvisual" effects of light (eg, phase shifting the circadian system; the alerting effect of light) were also short-wavelength sensitive.[9-14] Furthermore, studies have established the importance of light duration, intensity,[15] and now the spectral composition of light in triggering these biological responses.

LIGHT EXPOSURE AND AGING

Ophthalmologists know that as the crystalline lens increasingly ages, its transmission of short-wavelength light to the retina is reduced. The consequences of this interference are the subject of many current studies, particularly in the context of whether or not to include blue-light filters in IOLs.

> "Blue light is maximally effective at resetting the circadian system and promoting alertness, and therefore it should not be barred from reaching the retinal ganglion cells."

From a chronobiological point of view, as discussed previously, blue light is maximally effective at resetting the circadian system and promoting alertness, and therefore it should not be barred from reaching the retinal ganglion cells. We and other researchers are currently examining the optimal amount of daily light exposure older people need to maintain good sleep and synchronized circadian rhythms. One such study is taking place in elderly care homes, where we are measuring subjects' motor activity as an indication of quality of sleep and assessing the effect of room lighting on this. Previous studies have shown that increased lighting in elderly care homes helps reduce people's daytime napping and improves the duration of their night sleep.[16-19] We are presently conducting similar experiments using "blue-enriched" white light to assess its effect on residents' sleep.

Recently, my group also conducted clinical studies that demonstrate that men older than 60 years have a reduced response to the alerting effect of blue light compared with young men.[20] Both age groups responded similarly to longer-wavelength green light, which confirms that lenticular yellowing does not block this wavelength to the same extent as it blocks blue light. Based on these findings, and as a chronobiologist, I would recommend that people who have not had cataract operations should get as much exposure to outdoor light as they can, and that cataract surgery patients should receive IOLs that do not block out this wavelength, so that the body clock is better able to synchronize with its light/dark environment.

SUMMARY

The effects of blue light in humans have only been researched since approximately 2000, and there is much still to learn. It is worth noting that the intensities of blue light being studied are very low (below 30 $\mu W/cm^2$) and are well below the safety limit. The laboratory studies from both my laboratory and others have clearly shown the effectiveness of short-wavelength blue light in affecting the circadian system. The challenge now is to confirm these effects in real-life field studies. ■

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The Discovery and Role of Ganglion-Cell Photoreceptors

New findings on the connections between the eye and the brain.

BY DAVID M. BERSON, PHD

For many years, my colleagues and I have been interested in the structure and function of retinal ganglion cells. These are the sole output cells of the retina and thus the exclusive conduits of visual information from eye to brain. Our interest has been to try to integrate information about the inputs, outputs, and physiology of these cell types to understand what roles they play in visual function. Here, I discuss the recent research in my lab and others on one particularly strange type of ganglion cell and its role in the body's reflexive responses to daylight.

Most researchers now agree that there are roughly 20 different types of ganglion cells. These types differ from one another in their morphology, synaptic connections within the retina, physiological properties (such as their responses to various patterns of light) as well as their projections to the brain. The outlines of this story—the division of the retinal output into distinct "channels"—were glimpsed as early as the late 1800s, but the field is still groping for a broad and coherent functional understanding. Which ganglion cell types and visual targets are involved when we track down a fly ball, when we select the best mango in the supermarket, or when we read a poem or recognize a face?

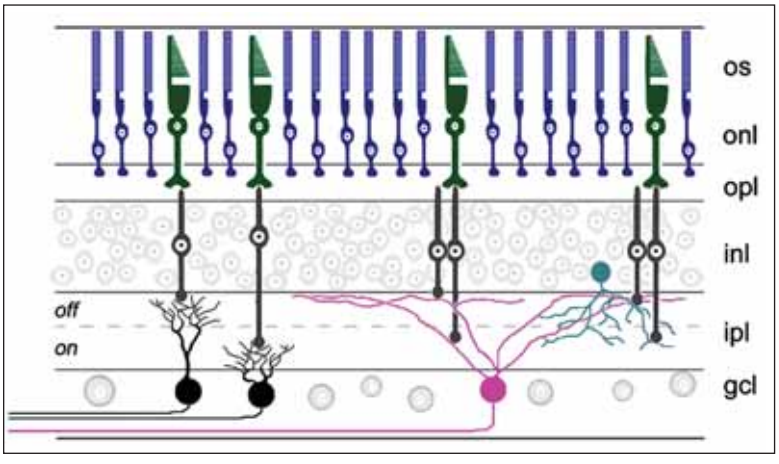

Figure 1. This schematic of a vertical section through the retina shows the ganglion-cell photoreceptor in purple. In addition to being intrinsically photosensitive, it receives excitatory synaptic inputs from bipolar cells (black) and inhibitory inputs from amacrine cells (blue-green). These provide a circuit by which conventional photoreceptors, that is the rods (blue) and cones (green), can influence the photosensitive ganglion cells. Examples of conventional ganglion cells, which lack the capacity for phototransduction, are shown at bottom left (black).

GANGLION-CELL PHOTORECEPTORS AND THE RETINOHYPOTHALAMIC TRACT

Our recent work has focused almost entirely on a single rare type of ganglion cell that is unique in being intrinsically photosensitive to light. Our discovery of these cells came from our efforts to understand the origin of a direct pathway from the retina to the suprachiasmatic nucleus in the hypothalamus, the central "pacemaker" for the circadian clock. The role of this pathway, known as the *retinohypothalamic tract*, is to synchronize the circadian system with the rising and setting of the sun. This is a prime example of a specialized retinal

output channel with a clearly defined function. We became interested in this pathway because animal behavioral studies in the 1990s, largely by Russell Foster and his colleagues,[1] had suggested something very peculiar about its retinal origins. They found that mice with severe degeneration of rod and cone photoreceptors, although effectively blind in most respects, showed robust circadian and pupillary responses to light. This was odd, because the dogma in the field was that ganglion cells are dependent on indirect inputs from rods and cones for their visual responsiveness. Might there be a previously unrecognized retinal photoreceptor, distinct from rods and cones, that feeds light information to the retinohypothalamic tract?

> "Melatonin plays an important role in many physiological processes, including sleep, and there are now suggestions that it may have some anticancer properties as well."

A key development in resolving this mystery arrived with the dawn of the new millennium, when a group led by Ignacio Provencio, PhD, now at the University of Virginia, discovered a novel opsin.[2] Opsins are the protein component of vitamin-A–based photopigments such as those in rods and cones. In mammals, Dr. Provencio found that this protein, which he called *melanopsin*, was expressed only in what appeared to be a rare subpopulation of ganglion cells. Although several years would pass before melanopsin was proven to be a functional photopigment, Dr. Provencio inferred (correctly, as it turned out) that it might in fact be the photopigment of the mysterious third class of photoreceptors.

Provencio's work prompted my research group to seek definitive physiological evidence for novel retinal photoreceptors linked to the retinohypothalamic tract. Luckily, we were well positioned technically to address this question. In the preceding several years, we had been correlating the structure, function, and central projections of ganglion cells through in vitro experiments. We began by injecting a fluorescent dye into a specific visual brain region and allowing the dye to be transported back to the retina along the optic axons. Then, we extracted the living retina, located the glowing cells, and targeted them for recording and intracellular dye filling, thus revealing the form and function of specific ganglion-cell types. It was easy for us to exploit this approach to study the ganglion cells supplying the suprachiasmatic nucleus. In striking violation of existing dogma, we found that these ganglion cells did indeed respond to light, even when we blocked all synaptic input from other retinal neurons with drugs or by isolating the cells from the retina. Thus, these ganglion cells, by any standard, were true photoreceptors—cells that could autonomously transduce light energy into bioelectric signals. These findings, which we published in 2002,[3] provided a plausible explanation for the biological clock's mysterious responsiveness to light in the absence of rods and cones.

PROPERTIES AND FUNCTIONAL ROLES

What are the properties of these novel photoreceptors, and how do they relate to the effects of light on human physiology? Almost everything about ganglion-cell photoreceptors is different from the classical rod and cone photoreceptors. For example, their electrical response has the opposite polarity. Also, they are less sensitive to light. They typically have very sluggish light responses, always much slower than those of rods and cones, and for weaker light stimuli their response may develop only after a full minute of exposure. Their responses are remarkably sustained, apparently lasting as long as the stimulus does, and are also very slow to decay away after the light is turned off. The firing rate of these cells is systematically related to light intensity, which is very unusual among ganglion cells. Also, their spectral tuning differs from that of rods and cones, with an optimal response to blue light of 480 nm. Interestingly, these properties mimic the circadian system's response to light. In general, it takes a lot of light to shift the circadian system, and the longer the exposure to light, the more the clock shifts. The spectral behavior of these cells also matches the spectral behavior of the circadian system in animals lacking rods and cones. These peculiarities in cellular function therefore seem to carry over to an animal's behavior.

The behavioral roles of these cells extend well beyond the circadian system. Another major output of this system is to the pupillary light reflex pathway. Along with a circadian response, retinally degenerate mice with no rods and cones adjust the size of their pupil to the intensity of light entering the eye. Another physiological output of this system seems to be to the pineal gland, which is the source of melatonin in the circulation. Melatonin plays an important role in many physiological processes, including sleep, and there are now suggestions that it may have some anticancer properties as well. Melatonin levels are highest at night, but light at night can dramatically reduce them. Evidence is growing that the pathway by which light exerts it effect arises largely from this class of retinal output cells. Ganglion cell photoreceptors thus seem to have a variety of functional roles that we are just beginning to identify.

CURRENT RESEARCH

My laboratory is presently following several lines of inquiry regarding the retinal circuits and functional roles of ganglion cell photoreceptors. We are trying to understand the sequence of biochemical events that link light absorption by melanopsin to the electrical response of the cells. By analogy to other photoreceptors, this is likely to be a complicated process involving many macromolecular players and modulation at many levels. We are also studying retinal circuits that permit interactions between the classical and ganglion-cell photoreceptors. The ganglion cells clearly are getting significant synaptic input from other retinal neurons, and there is also emerging evidence that these influences may be reciprocated. Recent unpublished work by Samer Hattar, PhD, and colleagues at Johns Hopkins University suggest that ganglion cells are conducting both melanopsin signals and rod or cone signals to the circadian and pupillary systems. We hope to learn more about where else these signals are being sent in the brain and their role in mediating other visual reflexes, as well as, perhaps, some aspects of conscious visual experience.

GANGLION-CELL PHOTORECEPTORS IN OPHTHALMOLOGY

Although these cells have been studied mainly in rodents, there is no doubt that they exist in humans and other primates. Dennis Dacey, PhD, and colleagues at the University of Washington, Seattle, have shown that nonhuman primates have ganglion-cell photoreceptors and that their photopigment and physiological properties (including their spectral tuning) are very similar to those in rodents.[4] Behavioral evidence in humans also parallels the animal studies. For example, Charles A. Czeisler, PhD, MD, of Harvard Medical School and Brigham and Women's Hospital in Boston, and his colleagues have shown that various reflexive responses to light persist in some humans with advanced retinitis pigmentosa. Although light evoked no conscious sensation in these patients, it could still evoke both hormonal responses and circadian entrainment.[5,6] These exciting findings imply that ganglion-cell photoreception persists in at least some cases of severe outer retinal disease, and this needs to be considered when weighing surgical treatment options in these patients. ■

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RESULTS OF AN INDEPENDENT THIRD-PARTY SURVEY

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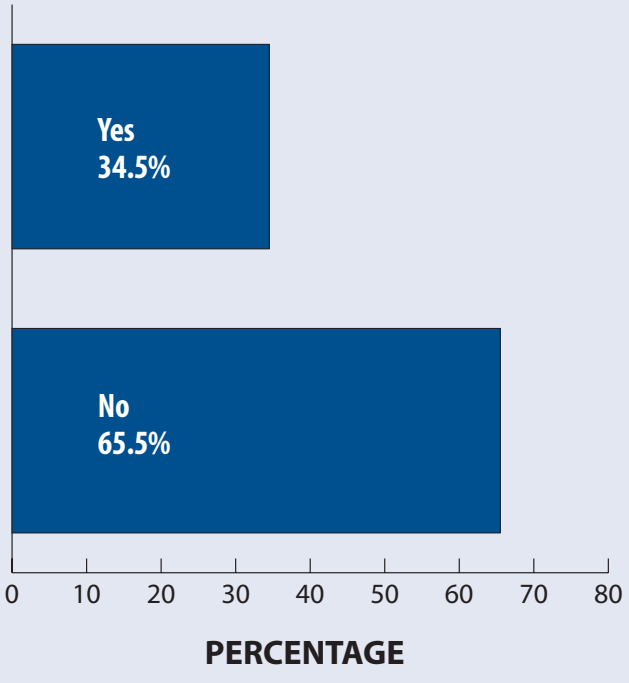


* Survey was produced by Step Ahead Knowledge Acquisition LLC

The Circadian System and Blue Light

The importance of natural light to human biological rhythms.

BY PROFESSOR CHRISTIAN CAJOCHEN, PHD

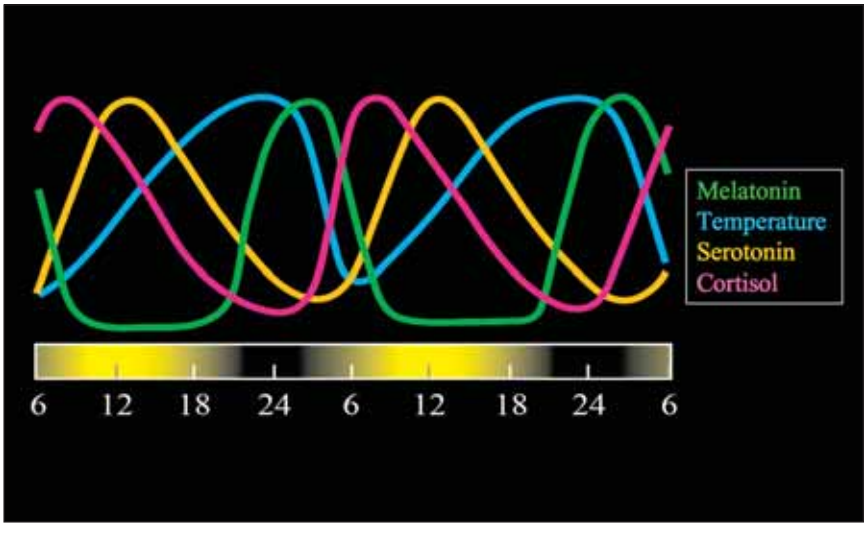
In the late 1970s and early 1980s, researchers began to realize that humans are more sensitive to natural light than they previously thought. In fact, chronobiologists now have evidence that light is the strongest and most important synchronizer for human circadian physiology.[1] This article reviews the basics of circadian function.

SYNCHRONICITY

In humans, circadian rhythms are generated in the suprachiasmatic nuclei (SCN), a specific part of the anterior hypothalamus located above the optic chiasm. Chronobiologists refer to this area as the *circadian pacemaker*, because it controls all circadian rhythms ranging from gene expression, to hormones, to cognitive functions (Figure 1). It runs on a schedule that is slightly longer than 24 hours for most people.

Humans are particularly sensitive to morning and evening light. Berson et al[2] detected a novel, third type of photoreceptor in the retina of mammals, including humans. This novel photoreceptor cell type, an intrinsic photosensitive retinal ganglion cell, is considered to play a crucial role in many of the nonvisual biological effects of light. The existence of such a photoreceptor can explain why pupil constriction, melatonin suppression, and circadian entrainment are still possible in transgenic mice without rod or cone photoreceptors.[3,4] Similarly, studies in humans have indicated that a partial or complete loss of the visual system still allows for normal melatonin suppression and circadian phase shifting.[5] The photosensitive ganglion cells in the retina have their own neural connections to the SCN. Moreover, they also have direct and indirect (via the SCN) projections to brain areas implicated in the regulation of sleep and arousal. The spectral sensitivity of melanopsin ganglion cells is different from that of the classical photoreceptors.[6] This allows researchers to design human study protocols to test the nonvisual effects of light at specific wavelengths (ie, monochromatic light) and derive conclusions about involvement of the new photoreceptors in the circadian response to light.

When we are not exposed to natural daylight, we lose our synchronicity with the external light/dark cycle and begin to freerun on our longer internal time schedule, thus disrupting our sleep/wake cycles. For example, many blind people suffer from sleep disorders due to their inability to synchronize with the external light/dark cycle. Thus, they are sleepy during the day and awake during



(Courtesy of Martin A. Mainster, PhD, MD, FRCOphth.)

Figure 1. Virtually every physiological and hormonal system in the human body exhibits and depends on circadian control.

the night. Blind people who still have melanopsin receptors in their eyes, however, maintain functioning circadian alignment and entrainment. Bilateral enucleation immediately eliminates any circadian synchronization.[7] It is unknown at this time whether or not a majority of blind people has functioning melanopsin.

> "Older people with lenticular yellowing are less sensitive and require more intense light."

LEVELS AND TIMING OF LIGHT

Classical vision can function with very low intensities of light and allows people to see some of their environment in nearly complete darkness. The circadian system responds to higher levels of polychromatic light (100 to 200 lux[8,9]), depending on age and time of day. Older people with lenticular yellowing are less sensitive and require more intense light. With blue-enriched light or monochromatic light between 460 and 480 nm, up to 10 times lower light intensities can be used to elicit the same circadian responses as with polychromatic light (however, this intensity is still higher than for classical vision).[10]

Duration of exposure to light also affects the function of the circadian system. In controlled laboratory settings, researchers can generate responses such as melatonin suppression and changes in heart rate by exposing people to 150 lux of light for 5 to 10 minutes. For light therapy, however, such as in patients suffering from seasonal affective disorder, we recommend exposure to more than 1,000 lux of polychromatic light for at least 1 hour.

CURRENT RESEARCH

For now, study in this area is focused on answering relatively simple questions, such as what type of light is best for people who have particular visual problems, and what kind of light therapy would benefit shift workers and people suffering from jet lag.

Currently, my colleagues and I are investigating light's effects on various physiological markers, such as core body temperature, levels of cortisol, heart rate, and even sleep. For example, we are studying brain wave activity during sleep following light exposure prior to sleep. Also, we are planning a large, multicenter clinical study to examine the effects of replacing cataractous crystalline lenses in elderly patients.

IMPLICATIONS

As we learn more about the intricacies of the visual and circadian systems, we find that there are no easy solutions to modern-day problems, such as nighttime shift work. Exposure to light during the wrong circadian phase can quickly throw the body's biological rhythms out of sync. Chronobiologically, it would be best to keep light levels low in the workplace at night to preserve workers' correct circadian rhythms. On the other hand, employers would probably prefer to keep lights bright to help workers stay alert and active. Shift workers who want to reset their circadian system so that they may sleep during the day should avoid exposure to morning light, which would return their body clock to its natural rhythms. Wearing orange-tinted glasses may be one way for these workers to keep blue light from affecting their body clock, although it could also make them sleepier, because blue light also has alerting properties.

SUMMARY

Historically, ophthalmologists and chronobiologists have not been interested in the same aspects of visual research. Chronobiologists are now realizing that light entering the eye could be affected by various ophthalmic conditions before it reaches the retina and ultimately influences the brain. In fact, because my colleagues and I at the Centre for Chronobiology, Psychiatric University Clinics in Basel, see a lot of patients with sleep/wake dysfunction, we now routinely send our patients to an ophthalmologist to determine if it could be caused by an ocular problem. Likewise, ophthalmologists are more interested in the chronobiology of the visual system. I am very excited to see what findings will come from current and future research collaborations. ■

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