

Article ▶ What Optometrists Need to Know About IpRGCs and Why

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ABSTRACT

Intrinsically photosensitive retinal ganglion cells (IpRGCs), a recently discovered third type of retinal photoreceptor, are located in the retinal ganglion cell layer of the retina and mediate the production of melatonin in the pineal gland. Their responses to light can alter the biological clock in the suprachiasmatic nucleus of the hypothalamus, affecting circadian rhythms. IpRGCs influence sleep, alertness, mood, headaches, reproduction, and immune function. This information has numerous implications for optometrists, including the use of tinted lenses to block blue light, counseling patients about intraocular lenses, the perils of computer and television use before bed, and special considerations for shift workers and patients with bipolar disorder.

Keywords: blue light, circadian rhythms, intrinsically photosensitive retinal ganglion cells, IpRGC, melatonin, retino-hypothalamic pathway, suprachiasmatic nucleus of hypothalamus

Introduction

As optometrists, we know that light is necessary for vision. However, in the past decade, another key function of retinal light has been discovered. To be true to the definition of light, which includes the creation of vision, this energy is technically termed optical radiations.¹ Optical radiations in the short wavelength spectrum, peaking around 484 nanometers, stimulate changes in the human circadian system.² The importance of these frequencies that impinge on the retina, travel on through the retino-hypothalamic tract to the circadian pacemaker in the suprachiasmatic nucleus of the hypothalamus, and terminate in the pineal gland to influence the production of the hormone melatonin has become increasingly apparent in the past few years.

The popular press has headlines such as: "Avoid Breast Cancer. Sleep in the Dark..."³ and "Gene Mutation May Cause Some Cases of Seasonal Affective Disorder."⁴ Medscape, the online journal, includes "Melatonin Analog May Have Role in Treating Major Depression."⁵ The New York Times is regularly covering this topic. In 1981 in their Science Times Section, they published "From Fertility to Mood, Sunlight Found to Affect Human Biology"⁶ and more recently: "Aging of Eyes is Blamed for Range of Health Woes."⁷

This is indeed a timely and complicated topic. What do we as eye care providers need to know, and why should we be informed about this newly discovered photoreceptor? Intrinsically photosensitive retinal ganglion cells (IpRGCs) are responsible for affecting human functions as

diverse as sleep, alertness, mood, metabolism, migraine headaches, and immune function.^{1,8-10} Watching television or using a computer or other lighted devices before bed can disrupt the production of melatonin. Electric light at night, coupled with the new lighted technologies, can affect sleep, weight, diabetes, and mood and is implicated in increasing the rates of some cancers.^{1,8-12}

Overview

The retina contains a third retinal photoreceptor. In addition to the rods and cones that we all learned about in elementary school, a new photoreceptor has been discovered in the past decade.¹³ It is not in the outer layer like rods and cones, but in the inner ganglion cell layer. Not all ganglion cells are photosensitive, just a small number of them.¹⁴ They are referred to as

the IpRGCs.¹⁴ These cells contain a vitamin A-based opsin called melanopsin.¹⁵ Melanopsin was originally identified in the skin of a frog.^{13,14} It was confirmed in fish, amphibians, reptiles, and birds (including chickens).¹⁶ In tadpoles, it is present in the following locations: dermal, magnocellular preoptic nucleus, several layers of the retina, and the suprachiasmatic nucleus of the tadpole brain.¹³ Melanopsin has been extensively studied in the retina in mice^{14,16,17} (especially knockout mice with no rods or cones but who still exhibit circadian responses).² In humans, melanopsin and the IpRGCs provide the link from the retina through the suprachiasmatic nucleus of the hypothalamus (our biological clock or circadian pacemaker) to the pineal gland, where their response to light mediates the production and suppression of the hormone melatonin.¹⁷ IpRGCs react with a depolarizing response to light, the opposite of the rods' and cones' hyperpolarization.¹⁴ In addition, although they do exhibit adaptation to ambient light and dark, it is at a much slower rate than the rods and cones.¹⁸

IpRGC compares to rods and cones

To summarize: humans have a small population of melanopsin-containing IpRGCs. They are located in the inner layer of the retina and collect and transmit information about ambient light intensity which:

1. Affects the pupillary light reflex through the LGN and travels to pretectum and superior colliculus (pathways shared with the visual portion of the optic nerve)^{19,20}
2. Synchronizes circadian rhythms in the suprachiasmatic nucleus of the hypothalamus.^{1,2}

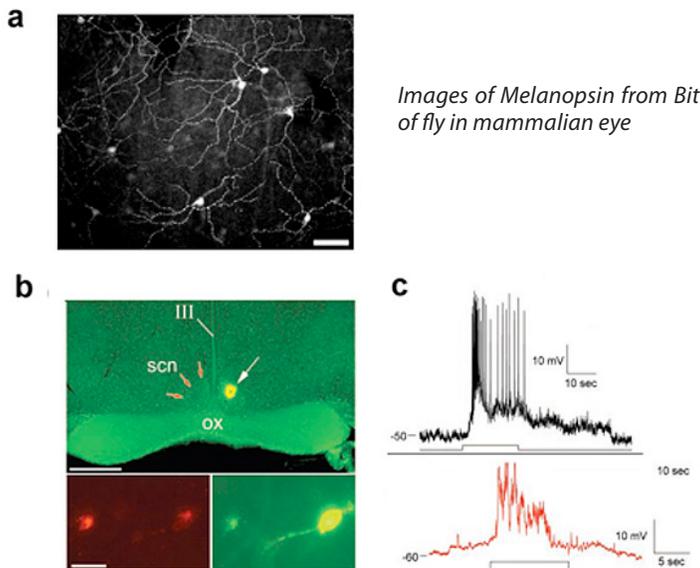


Figure 1. Discovery of IpRGCs. (a) Melanopsin immunostaining of ganglion cells in the whole-mount retina. (b) Injection of tracer into the SCN above the optic chiasm (ox) (top panel) and subsequent retrolabeling of IpRGCs (red image, lower left panel), which express melanopsin (green image, lower right panel). (c) Whole-cell patch clamp recordings of IpRGCs showing responses to light under synaptic blockade in the whole retina (black trace), and after mechanical isolation (red trace). Adapted from Provencio et al. 2002 and Berson et al. 2002.

3. Regulates the release of melatonin from the pineal gland.^{10,12,19-21}

Melatonin: Neuro-hormone with Many Roles in the Human Body

Melatonin is a neuro-hormone that has increasingly become a topic of interest and research. Melatonin is naturally synthesized from the amino acid tryptophan.²² Synthetic melatonin is sold as a supplement and is popular as an aid to induce or improve sleep. Yet, melatonin has numerous other actions that are being examined, both in popular press and in the scientific literature. A recent on-line post by Chris Kresser entitled “How artificial light is wrecking your sleep, and what to do about it” notes: “But melatonin suppression has far worse consequences than simply poor sleep outcomes; it has also been shown to increase the risk of cancer, impair immune system function, and possibly lead to cardiometabolic consequences such as type 2 diabetes, metabolic syndrome, obesity, and heart disease.”²³

Immune & Antioxidant Properties of Melatonin

Melatonin’s actions include effects on the immune system, particularly in the area of gonadotropic cancers such as breast and prostate cancer,^{21,23-25} and as an antioxidant²¹ and anti-aging hormone.²⁶

Outlining melatonin’s antioxidant activities, researchers stated: “Melatonin was discovered to be a direct free radical scavenger less than 10 years ago. Besides its ability to directly neutralize a number of free radicals and reactive oxygen and nitrogen species, it stimulates

several antioxidative enzymes which increase its efficiency as an antioxidant.”²⁷

In “A Review of the Multiple Actions of Melatonin on the Immune System” by Carrillo-Vico et al., the authors note: “Additionally, melatonin shows a remarkable functional versatility by exhibiting antioxidant, oncostatic, anti-aging, and immunomodulatory properties, among others.”²⁶ They go on to state: “Melatonin’s molecular mechanisms involve ... both direct radical scavenging and redox-modulated processes.”²⁶

Melatonin and Gonadotropic Cancers

Melatonin has been referred to as an anti-gonadotropic substance that decreases the incidence of hormone-dependent mammary tumors.²⁸ There have been a variety of studies linking breast cancer in night shift-working women, but there is not a consensus on the relative contribution of heredity, shift work, light-at-night, architectural lighting, and disrupted circadian rhythm to this reported higher incidence.^{11,19-25} The National Institute of Environmental Health Sciences is considering how best to study the connections between light, melatonin production, and health. A primary area of research planned is to study the relative rise in breast and prostate cancer with increased exposure to electric lighting.¹¹

Melatonin and the Sleep Wake/Dark Light Cycle

More and more individuals complain of sleep issues, but they are notably prevalent in those who have experienced traumatic brain injury. An article on Medpage Today notes: “Trouble

sleeping long after traumatic brain injury may be due to disruption of both melatonin production and sleep architecture, a study has found.”²⁹ It goes on to state that “more than one year after traumatic brain injury, patients had significantly reduced levels of melatonin in the evening compared to healthy controls.”²⁹ In addition, a May 31, 2013 article in Science Daily states: “Results show that six weeks of morning bright light therapy resulted in a marked decrease in subjective daytime sleepiness. This improvement was further associated with improvements in the propensity to fall asleep and nighttime sleep quality. Bright light therapy also affected depressive symptoms.”³⁰

Nobel Prize laureate Julius Alexrod performed experiments that made clear the role of melatonin in circadian rhythms and sleep-wake cycles.³¹ The production of melatonin in the pineal gland is inhibited by light (or more properly optical radiations of 460-480 nanometers) and stimulated by darkness. Artificial lighting has reduced the length of darkness in winter, which affects this process. The secretion of melatonin increases after the onset of darkness, peaks in the middle of the night, and can be interrupted by exposure to light.²⁸

Short bursts of light will not interrupt the production of melatonin, whereas long exposure to light at night does.^{1,10} The presence of light suppresses and the absence of light stimulates the production of melatonin in the pineal gland. The electromagnetic spectrum, which we call light, produces vision and also affects circadian function.

Visual Light Versus Circadian Optical Radiations

Optometrists use light and evaluate its visual effects on patients every day. In addition, behavioral and neuro-optometrists often speak of the “other fibers” that travel to the brainstem, cerebellum, and pre-tectum in addition to the retino-hypothalamic pathway. There are frequent discussions of the non-visual fibers and their role in blind sight, posture, ambient vision, and vision therapy. But perhaps we need to go a step further by exploring the effect of the optical radiations that stimulate circadian function when we consider our patient’s vocations and avocations and include this information as we evaluate and treat our patients.

As noted above, implications of light and circadian function are already being well covered in the popular press. The New York Times article mentioned above, “Aging of Eyes is Blamed for Range of Health Woes,” examines the effect of age and lens changes and the use of yellow versus clear intra-ocular lenses (IOLs) on circadian rhythms.⁷ Blue light, which is the key player in circadian rhythms, is also implicated in the initiation and exacerbation of age-related macular degeneration, causing many surgeons to implant blue-blocking IOLs. This article calls the practice into question, hypothesizing that blue-blocking IOLs may have an adverse effect on circadian function.⁷

ARMD Danger versus Circadian Function: Risks in General and through IOL Transmission

Age Related Macular Degeneration (ARMD) is a condition that every optometrist sees in the

office. We currently counsel our patients on the use of protective sun lenses as well as vitamin supplementation as ways to forestall, delay, or protect against the progression of retinal damage. An article in the May 2013 *Optometry Times* entitled “The Benefits and Dangers of Blue Light” by Christian Sotty addresses the issue of blocking light which leads to retinal pigment epithelium (RPE) cell death, yet preserving light which affects the biological clock. Studies using an ARMD porcine cell model demonstrated that RPE cell death peaks at 435 nanometers. The article concludes: “... we need to be able to distinguish good light from bad clearly so that we can then develop a sophisticated filtering system to address the harmful effects of one while retaining the positive effects of the other.”³²

As optometrists, we often spend time talking with our aging patients about cataracts, cataract extraction, and IOL options. Whereas counseling a patient on IOL considerations was formerly limited to bifocal or toric lenses versus the standard single focal type, now the frequency transmission of the IOL has become a new variable to consider. As noted above, it is important to ensure blocking frequencies that might cause macular degeneration, but within close limits to preserve circadian function.³³ Many surgeons, however, are unaware of the transmission properties of the IOLs they recommend and implant.

After reading “From Fertility to Mood, Sunlight Found to Affect Human Biology” in the *New York Times*,⁶ this author decided to see if there was any closure about what to recommend to patients concerned about IOL

light transmission and the yellow versus clear IOLs. This writer consulted an expert on circadian function, Dr. Mark Rea of the Light Research Center of Rensselaer Polytechnic Institute. Dr. Rea stated that it’s not so much the actual pre-retinal light filtering, but the contrast between day and night that is important. He cited an experiment using yellow contact lenses (which could be analogous to yellow IOLs) by Domien Beersma³⁴ which seems to indicate that the human eye, after a week or so, compensates to changes in pre-retinal illumination and readjusts to allow the individual to re-establish their circadian responses. In summary, he comments: “It would seem then that the phototransduction mechanisms of the circadian system adjust sensitivity based upon the history of light exposure. Computer Assisted Design workers would therefore be more sensitive to light at night than construction workers.”³⁵ So, perhaps IOLs’ specific light transmission characteristics are not the only consideration, but also the patient’s overall exposure to light and dark. The biological clock needs both: exposure to light and time in the dark to properly reset.

Does our Dependence Upon and Use of Artificial Lighting Both Day and Night Affect our Circadian Function?

Light Pollution and Light at Night (LAN) Effects on IpRGC and Melatonin

Light pollution is prevalent throughout most of the civilized world. Wired.com has photos comparing the United States at night since the late 1950s; the light at night steadily increases.³⁶ The most vocal groups protesting

light at night are astronomers, both professional and amateur, but it affects us all. Could light pollution produce a major effect on circadian rhythms? Could changes in relative darkness at night in our world be impacting human mood and metabolism? If melatonin synthesis can be adversely affected by exposure to light, we can control the light in our homes, but what about the ambient environmental light? Satellite photos literally highlight the lack of darkness in our world at night. In 2007, the National Institute of Environmental Health Sciences convened a meeting at which they acknowledged the changes in the health profile with increasing use of electric lighting, including the rise of certain cancers (e.g. breast and prostate) and the prevalence of obesity and early-onset diabetes.¹¹

However, before information about physical effects of light were acknowledged, there was another effect of light (or optical radiations) which was actually extensively studied back in the 70s—that of its effect on mood. The literature has long acknowledged seasonal affective disorder (SAD) and the usually salutary effect of using a light box for those who suffered from winter depression.³⁷ In the quarter of a century since then, the connection between circadian rhythms and bipolar disorder has been clarified: light having a positive effect on depression, but implicated in triggering mania.³⁸ Individuals with bipolar disorder appear to be exquisitely sensitive to light regulation. They are usually advised to keep regular hours of sleep, to sleep in total darkness with blackout curtains if necessary, to avoid shift work, to refrain from using lights

(especially computer or television) for at least two hours before bedtime, and that these measures are vital to their mood regulation.⁸ Computers and television are potentially the worst culprits since they transmit blue light, which maximally excites melanopsin. Eliminating television, light-emitting technological devices, and computers before bed would not be popular with many individuals, so blue-blocking lenses are an option.³⁸

Tints as a Solution to Blue Light at Night

Kaymov et al. studied the efficacy of blue-blocking lenses on simulated shift work with positive results: melatonin production was not disrupted, and the individual's work performance was not adversely affected.²⁴ James Phelps, a psychiatrist who hosts the website psycheducation.org, recommends amber lenses for bipolar patients.³⁸

Eye care professionals need to educate their patients about the activity of the IpRGCs and the efficacy of blue-blocking lenses to preserve melatonin production. These lenses would be especially important for night shift workers who suffer from insomnia, irritability, increased accidents, and higher cancer rates.¹¹ However, most of us, including children and especially students, use an iPad, smart phone, computer, or watch television at night, and many find their sleep adversely affected. Blue-blocking lenses at night can be offered as an option to a large proportion of our patients. Commercial “blue blockers” and amber lenses are both good options for patients who want to block the suppression of melatonin.

The Brain Power Incorporated (BPI) FL-41 tint, which blocks 550 nm and below, is one of two tints most often recommended by the author. However, some patients may find it too dark for computer use at its full density, and while it can be made lighter, this change affects transmission characteristics. The patient can be given the option of a tinted lens or a removable tinted clip.

The FL-41 lens, called the Comfort Lens, is touted to be beneficial for “photophobia, blepharospasm, and migraines by blocking blue and green wavelengths.”³⁹ Circadian darkness is achieved by the absence of blue light.³⁸ Recently, our patients have also voiced positive responses to the BPI Omega (lavender) tint, which, according to the manufacturer, blocks similar wavelengths as the FL-41.

BPI Spectrum of transmission of FL41tint IpRGCs and Melatonin in Ocular Disease

The use of lenses at night to protect melatonin production is important for optometrists and their patients, yet the topic of ocular disease processes and their effects on the circadian system is also an important consideration. Since melanopsin is a retinal photoreceptor located in the ganglion cell layer of the retina, it is affected by ocular disease.

Glaucoma: A 2005 study⁴⁰ which involved elevating intraocular pressure in rats concluded that the melanopsin-containing retinal ganglion cells were less likely to be affected by ocular hypertension than the rods and cones. This is thought to be due at least in part to the branching pattern of the dendrites. In contrast, another article cites glaucoma, with its diurnal

variations and damage to the ganglion cell layer, as “the main ocular disease that could directly compromise light input to the circadian system.”⁴¹

Uveitis is an ocular disease that appears to respond well to the administration of and/or presence of melatonin in the system. Scientific articles concerning uveitis and the effect of melatonin indicate that this is an active area of research. One study in which uveitis was induced in hamsters and a pellet of melatonin was implanted subcutaneously two hours before in some of the eyes showed that “melatonin prevents the clinical, biochemical, histological, ultrastructural, and functional consequences of experimental uveitis.”^{42,43} Another study focused on patients suffering from uveitis and found that “nocturnal peak of plasma melatonin was greatly decreased (45%) in patients with uveitis.” They postulate a pineal inflammation in these patients.⁴⁴

Ageing Changes Affecting Circadian Function

IOL transmission has been discussed previously, but for completeness, cataracts and IOL considerations are reiterated in this section. The effect of aging, pupillary miosis, lens transmission changes,⁴⁵ and IOLs all affect the pre-retinal light reaching the IpRGCs. Turner et al. state that “a 10-year-old child has circadian photoreception 10 fold greater than a 95-year-old phakic adult” and “a 45-year-old adult retains only half the circadian photoreception of early youth.”⁴⁵ Echoing the concerns noted above, the authors conclude, “Unconscious and conscious

photoreception should both be considered in IOL design and selection in order to maximise [sic] the non-visual as well as visual benefits of cataract surgery.”⁴⁶

Summary

What Optometrists Need to Know About Melanopsin, IpRGCs, Melatonin, and Circadian Rhythms.

- Melanopsin is the photopigment or intrinsically photoreceptive component: the “Ip” in the IpRGCs.¹⁵
- IpRGCs are a distinct class of photoreceptors that, unlike rods and cones (outer layer), are located in a small percentage of ganglion cells in the inner layer of the retina.¹⁵
- Melanopsin signals more like the photosensitive cells of invertebrate photoreceptors,^{13,19} so they may be older than the visual photoreceptors in an evolutionary sense.²³
- IpRGCs pull from a larger receptive field than rods and cones.¹⁴
- They transmit information about ambient light by “slow sluggish depolarizations” in contrast to the “faster hyperpolarizing of rods and cones”^{2,14}
- Melanopsin responds optimally to blue light of about 460-480 nanometers, and, like rods and cones, is capable of light and dark adaptation.^{1,47}
- The retinohypothalamic pathway begins with the IpRGC ganglion cells in the retina and travels to the suprachiasmatic nucleus of the hypothalamus, the location of the “master circadian clock which orchestrates

the timing of all daily biological functions.”² Ultimately, circadian light produces melatonin suppression in the pineal gland and “other non-visual responses including phase shifting and alertness.”¹

- Melatonin, produced in the pineal gland in the absence of light suppression, is a neuro-hormone with many biological actions including sleep induction, effects on reproduction and fertility, anti-oxidant immune properties, and participation in the suppression of gonadotropic cancers such as breast and prostate.^{21-26,28}

Advice Optometrists Can Give Patients Based on IpRGC Function

- We can share with our patients our knowledge about the effects of aging (pupillary miosis, media changes, and cataracts) and the diminished transmission of light that may be related to sleep issues in the elderly.
- We can acknowledge the prevalence of sleep issues after brain injury to our patients who have suffered a TBI and provide them with or encourage them to explore bright light therapy.
- We can discuss the importance of an IOL’s transmission and its effect on blue blocking to protect against ARMD while preserving the wavelengths for circadian function.
- We can explore the implications of wavelength cutoff of the IOLs being used with our local cataract surgeons.
- We can discuss the fact that using an iPad, smart phone, computer, or television

during the last two hours before bed will disrupt the production of melatonin and may adversely affect the ability to go to sleep or to stay asleep.

- We can provide blue blocking lenses for patients who still choose to use blue light emitting devices at night, especially those who work night shifts.
- We can mention the known sensitivity to light and dark to our patients who are bipolar, advising dark bedrooms and regular hours and suggesting that this information be discussed with their psychiatrist or psychologist.
- We can be on the lookout for more information in the literature on melatonin and its effects in uveitis and see if it will become a possible treatment for humans.
- We can be aware of the effects of retinal damage to the circadian system, especially in our glaucoma patients.
- We can discuss the deleterious effects of light at night with our patients, community, and local and national politicians.

These are a few ways we can begin to explore this fascinating new area of the IpRGCs, melatonin production, and their myriad and multi-faceted effects on human life, health, and longevity.

Conclusion

Optometrists who are already knowledgeable about the retino-geniculate pathway and its myriad connections within the cortex need to begin to learn about the retino-hypothalamic pathway and its effects on their

patients. Knowledge of the IpRGC, melanopsin, and the actions of melatonin in humans presents optometrists with more options and considerations when evaluating and counseling patients on lifestyle and eyewear.

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