The Importance of Melanopsin Activation in Perception, Health, and Lighting Design

Dingcai Cao*, Pablo A. Barrionuevo*
***Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, IL, 60612**

Abstract

We reviewed the role of melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) in light-dependent functions, including circadian rhythm that is important for health, pupil responses and visual perception. We then discussed the implications for lighting design. Finally we described a five-primary photostimulating method that can independently control melanopsin activation in humans.

Author Keywords

Melanopsin; ipRGC; Photoreceptors; Circadian; Pupil; Visual perception; Color; Contrast Sensitivity; Health; Lighting; Display; Five-primary photostimulating method.

1. Introduction

In addition to rod and cone photoreceptors, there exists a third class of photoreceptors in the mammalian retina, called intrinsically photosensitive retinal ganglion cells (ipRGCs) [1-3]. IpRGCs express melanopsin, a photopigment with a peak sensitivity at ~482nm (see Fig. 1 for human photoreceptor spectral sensitivity functions). IpRGCs also receive synaptic inputs from rods and cones. The combination of melanopsin activation, rod and cone inputs enable ipRGCs to signal a large dynamic range of light levels in the environment (by a factor of 10 billion from dim starlight to bright sunlight).

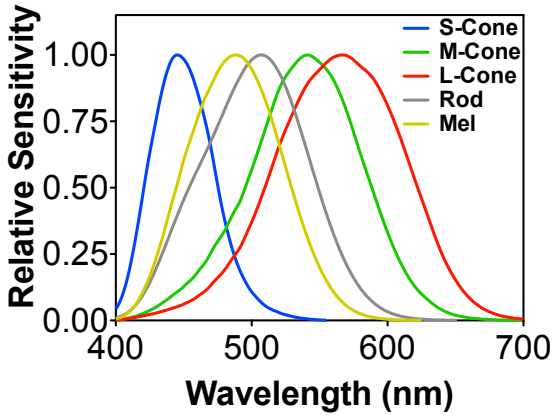

Figure 1: Human photoreceptor spectral sensitivity functions.

IpRGCs project to brain areas such as the suprachiasmatic nucleus (SCN) to mediate circadian photoentrainment [4] or the olivary pretectal nucleus (OPN) to control pupil light responses [5]. IpRGCs also provide light information to the pineal melatonin production system and sleep regulation system, and modulate cognitive function, attention and emotion [6]. Therefore, ipRGCs are considered to be the primary photoreceptors for sub-conscious non-image-forming (NIF) functions that are important for our normal biological activities and health. IpRGCs are also found to project to the lateral geniculate nucleus (LGN), the thalamic relay to the visual cortex, and therefore the melanopsin-based signal may also contribute to conscious image-forming (IF) vision [1]. Here we reviewed the importance of melanopsin activation on health and visual perception and the implications for lighting design.

2. Impact on Health

A normal ipRGC function is important for normal biological, physiological activities and health. IpRGCs are found to be important for several non-retinal diseases, such as sleep disorders, seasonal affective disorder, mood disorders, and migraines [6]. One of the critical mechanisms for ipRGCs affect health is their photic input to the circadian system.

In a simple configuration, the central circadian system can be conceptualized as having three components: (1) the central clock, which generates the rhythms, (2) input pathways that provide signals to synchronize the central clock, and (3) output pathways that convey the central clock signal to other regulatory systems in the brain and body (Fig. 2). The central circadian clock exists in the SCN, a tiny region located in the hypothalamus, sitting right above the optic chiasm. There are three major neural input pathways to the SCN: (1) retinal photoreceptors that transmit the light signal to the SCN via the retinohypothalamic tract, (2) neuronal projections from the raphe nuclei, which provide non-photic inputs, and (3) neuronal projections from the intergeniculate leaflet (IGL), which also receives inputs from the retina and raphe nuclei. The output pathways are implicated in the control of the endocrine system (such as melatonin release), and other brain and body regions controlling various behaviors such as sleep/wake.

The correct timing of the central circadian clock relative to the environment is essential for optimal sleep, waking functions and health. In humans, the central circadian clock has an average endogenous period slightly greater than 24 hours (~24.2 h) [7]. To prevent this, daily input signals are required to shift the clock earlier (*phase advance*) to synchronize the clock's timing to the external 24-hour solar day, and light is the strongest *zeitgeber* ("time giver") to the central circadian clock. In humans, light in the evening or first part of the night causes the clock to shift rhythms later (*phase delay*) and light in the morning shift the clock earlier (*phase advance*). Thus morning light is essential for producing corrective daily phase advances in humans, while evening light can produce phase delays, which exacerbate the human clock's endogenous tendency to drift later and promote circadian misalignment. Circadian misalignment can lead to difficulty in falling asleep, maintaining sleep, excessive daytime sleepiness lower quality of life, worsen mood and well-being, worsen depression, reduce cognitive performance and increase rates of myocardial infarction and cancer.

IpRGCs can not only influence health through their photic input to the circadian system, but also provide direct light information to brain areas that are important for sleep, cognition, and mood [6]. In addition, ipRGCs are found to be related to retinal diseases such as glaucoma and age-related macular degeneration [8]. Thus, melanopsin activation in ipRGCs exerts a major influence on circadian timing, which in turn impacts mental and physical health.

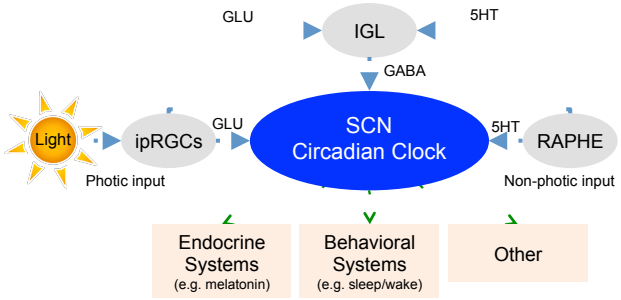

Figure 2: The three main components of the central circadian system: 1) central clock in the SCN; 2) input pathways, and 3) output pathways. IpRGCs provide photic inputs and RAPHE provides non-photic inputs to the SCN. IGL, which receives inputs from both ipRGCs and RAPHE, also send signals to the SCN. The neurotransmitter in each pathway is shown: GLU for glutamate; GABA for gamma-Aminobutyric acid; 5HT (serotonin). RAPHE: the raphe nuclei; IGL: the intergeniculate leaflet.

3. Impact on Pupil Responses

IpRGCs send photic signals to the OPN to control pupil light responses [5]. Pupil size variation produces a number of changes in retinal stimulation to affect visual functions, including retinal illuminance (the amount of light falling into the retina), the ratio of rod/cone stimulation, spectral sensitivity and spatial resolution [9]. In fact, the melanopsin spectral sensitivity function estimated from *in vivo* post-illumination pupil response (PIPR) in humans or macaques [10] is almost identical to that measured from *in vitro* ipRGC recording in macaques (peak at 482 nm) [1]. Therefore, pupil light reflex measurement can be used as a functional marker of ipRGC response. We now know that tonic pupil responses are driven preferentially by melanopsin activation, while rod and cones are combined to signal phasic pupil responses [11, 12]. Further, the melanopsin-mediated PIPR has long integration duration [13].

4. Impact on Visual Perception

Compared with rod or cone photopigment, melanopsin phototransduction is extremely sluggish [14]. In addition, ipRGCs are rare (~3,000, only ~0.2% of total number of RGCs in the primate or human retina) with large cell bodies, dendrite trees and large receptive fields (least 5-10 times more extensive than those for classical RGCs) [1]. It is proposed that ipRGCs sacrifice spatiotemporal resolution to reliably signal ambient illumination levels [14]. However, emerging evidences have shown that melanopsin activation in ipRGCs contributes to visual perception *directly* or *indirectly*.

IpRGCs act as a photon counter in the same way than a light meter in a camera. This unique capability, not shared by other photoreceptors, could serve as a reference for the visual system to optimize light adaptation. Indeed, melanopsin has been found to regulate cone electroretinograms (ERGs) in mice [15] or humans [16]. More recently, it is reported that melanopsin activation level can modulate the spatial/temporal tuning patterns of visual network [17].

Melanopsin activation can affect visual perception directly. It has been reported that humans lacking an outer retina [18] or animals with rods and cones ablated genetically [19] can preserve some light detection functions. In people with normal retinas, melanopsin activation could contribute to brightness discrimination [19], chromatic discrimination [20] and contrast sensitivity [21, 22]. However, the mechanisms for melanopsin activation affecting conscious visual perception are not well-understood.

Visual perception in primates and humans is mediated by three primary visual pathways that transfer visual information from the retina to different layers of the LGN and then subsequently to the visual cortex, including the magnocellular (MC-), parvocellular (PC-), and koniocellular (KC-) pathways [23, 24]. These pathways combine differential long (L-), middle (M-) and short (S-) wavelength sensitive cone signals. The MC-pathway processes summed L- and M-cone excitations to signal luminance information. The PC-pathway uses the difference in L- and M-cone excitations to mediate the "red-green" chromatic signal. The KC-pathway processes the responses of S-cones opposed to the sum of L- and M-cones to signal the "blue-yellow" chromatic information. However, we have no direct knowledge about how signals arising from melanopsin contribute to the three primary visual pathways to alter visual perception. Using principal component analyses based on the excitations of the melanopsin, rods, S-, M- and L-cones for 9 hyperspectral natural images under 21 natural illuminants, we analyzed the contribution of melanopsin activation to the three primary visual pathways, namely the MC-, PC- and KC-pathways. With only cone excitations considered, the principal components revealed were consistent with the patterns of cone combinations in the MC-, PC- and KC-pathways [25]. Further analysis indicated that melanopsin contributed strongly to the MC- and KC-pathways and weakly to the PC-pathway [26].

5. Implications in Lighting Design

Traditionally, lighting industry guidelines followed criteria for optimal visual perception/performance, aesthetics and energy efficiency. The discovery of ipRGCs introduces a new dimension of considerations for lighting or display designs: that is, how to minimize the adverse effect of artificial lights, via ipRGC phototransduction, on mental and physical health while maximize visual functions and energy efficiency.

Biological adaptation to the sun has evolved over billions of years, however, people in modern society spend a large portion of their time in environments illuminated by artificial lights, working in front of computer displays, watching TV, or interacting with smartphones/tablets for reading, internet surfing, social networking, or video gaming etc. Compared with natural sunlight, the artificial illuminants or display lights are substantially dimmer, have different spectral compositions (thus different melanopsin activation levels). Our computation indicated that the artificial illuminants (5 LEDs, 5 High Pressure Sodium lamps, and 27 fluorescents) have significantly lower melanopsin activation level than 25 CIE D natural daylights ([27], Fig. 3). Therefore, indoor workers would experience substantially lower melanopsin activation compared with outdoor daylight. On the other hand, the artificial lights can be turned on at any time, such as nighttime thus replacing the natural light-dark transition. These abrupt state-light changes

will potentially disrupt normal biological and physiological functions, causing various adverse health effects, such as circadian rhythm disruption, sleep disorders, mood disorders, and even cancer [28]. For example, a latest study demonstrated that evening use of light-emitting-eReaders impaired sleep, circadian timing and next-morning alertness [29]. Therefore, lighting (ambient and occupational lighting or display lighting) has become a public health issue [30]. To improve human quality of life and health, how to design artificial lights to optimize NIF functions (which are important for physical and mental health) as well as image-forming functions (which are important for normal daily function and life quality) has become an important issue.

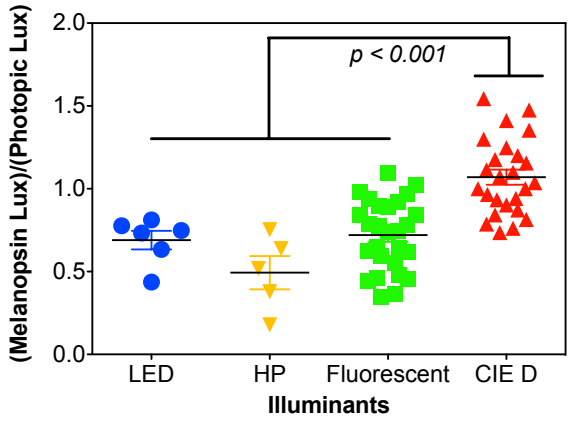

Figure 3: The relative melanopsin activation with different illuminants at the same photopic illuminance levels.

Additionally, primate ipRGCs responds excitatory to melanopsin activation, rod, L- and M-cone inputs but inhibitory to S-cone inputs [1]. This unique characteristic of its receptive field was shown to appear in pupillary recordings [22, 31]. This chromatic opponency of ipRGCs may also be evolved to signal the large spectral changes, from bluish to orangish, produced at dawn and dusk to set the biological clock more precisely [1]. Artificial lighting with unvaried chromaticities cannot trigger ipRGCs' responses as natural sunlight.

Finally, the discovery of ipRGCs will have great implication of light specification and regulation. Currently, regulations for lighting industry are based on photometry units (i.e. lux for illuminance or cd/m^2 for luminance). These units consider a particular visual function, the combination of L- and M-cone in the magnocellular pathway. Although many other visual functions could be considered, this function produces the additive photopic spectral-luminosity function V_λ, which is suitable for use in lighting industry [32]. However, melanopsin spectral sensitivity function is shifted to shorter wavelengths with respect to the overwhelmingly used V_λ. Therefore traditional photopic units cannot reflect the state of melanopsin activation that is important for health and perception. Recently, new approaches were proposed to cope with this issue by considering melanopsin activation [33, 34].

6. Advances in Human Melanopsin Research

Research on ipRGC functions in non-human species can employ modern molecular and transgenic techniques to understand melanopsin, rod or cone contributions. Studying the human melanopsin functions requires a *non-invasive* way to isolate melanopsin activation from rod and cone inputs. To address this, we developed a five-primary photostimulator [22], which can account for five types of photoreceptor excitations in human retina, including melanopsin-mediated ipRGCs, rods, L-, M- and S-cones (see Fig. 1 for spectral sensitivity functions).

The five-primary photostimulator [22] includes a bundle of five optic fibers to transmit the lights from the five bright LEDs through a homogenizer and diffuser to achieve a homogeneous field. A field lens and artificial pupil create a Maxwellian view. The lights from 5 LEDs are filtered by interference filters that produce dominant wavelengths of 456 nm (''B''), 488 nm ("C"), 540 nm (''G''), 592 nm (''A''), and 632 nm (''R''). A laboratory-created board (LED driver) controls LED light outputs. The board consists of a TLC5940 chip (Texas Instruments, 12-bit resolution) that can control up to 16 LEDs independently using Pulse Width Modulation dimming.

The theoretical basis for achieving independent control of the activities of the five types of photoreceptors (i.e., S-, M-, and L-cones, rods and melanopsin-containing ipRGCs) in the human retina is *silent substitution* [35]. The silent substitution method can be understood in a simple way. For example, consider a retina that has only two types of photoreceptors, say L-cones and M-cones. Using two LEDs with peak spectra at 540 nm (green) and 632 nm (red), respectively, the intensities of the two LEDs can be adjusted such that L-cones will have the same excitation based on the L-cone spectral sensitivity function. In this situation, if the two LEDs are switched on and off in an alternating fashion, L-cones cannot differentiate between the two LEDs because the L-cones have the same excitations from the two LEDs. However, since M-cones have a different spectral sensitivity function than L-cones, when the two LEDs are alternated to keep L-cone excitation constant, then M-cone excitations are not constant. In this sense, using two LEDs can silence one type of photoreceptor (L-cone in this example) while modulating the second type of photoreceptor (M-cones in this example). This approach can be expanded to silence two types of photoreceptors using three well-chosen LEDs, or three types of photoreceptors using four well-chosen LEDS, and finally four types of photoreceptors using five well-chosen LEDs. Five LEDs are necessary when separate measurements of S-, M-, L-cones, rods and melanopsin-containing ipRGCs responses are desired. Besides generating photoreceptor-isolating stimulation, this photostimulator can easily present stimulations to modulate combinations of photoreceptors, which are suitable to study how ipRGCs are combined with other photoreceptor inputs in visual and non-visual pathways. Other attempts [e. g. 21, 31] using a four-primary method can only study melanopsin function at photopic light levels.

7. Conclusions

Human biology has evolved in direct relation and dependence with natural sunlight. Since the intrusion of massive artificial light sources, such as computer monitors, TV, self-illuminated personal electronic devices, indoor and street lighting, this relationship has been altered. Melanopsin activation in ipRGCs is important for many aspects of human functions, such as perception, cognition, circadian rhythm, sleep, mood and has great impact on health. Therefore, it is necessary for lighting and display designers to consider the new discovery of this century to improve, or at least affect as little as possible, human quality of life and health.

8. References

1. Dacey, D.M., et al., *Melanopsin-expressing ganglion cells in primate retina signal color and irradiance and project to the LGN.* Nature, 2005. **433**: p. 749-754.
2. Berson, D.M., F.A. Dunn, and M. Takao, *Phototransduction by retinal ganglion cells that set the circadian clock.* Science, 2002. **295**(5557): p. 1070-1073.
3. Hattar, S., et al., *Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity.* Science, 2002. **295**: p. 1065-1070.
4. Hattar, S., et al., *Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice.* Nature, 2003. **424**: p. 76-81.
5. Lucas, R.J., et al., *Diminished pupillary light reflex at high irradiances in melanopsin-knockout mice.* Science, 2003. **299**: p. 245-247.
6. LeGates, T.A., D.C. Fernandez, and S. Hattar, *Light as a central modulator of circadian rhythms, sleep and affect.* Nature Reviews Neuroscience, 2014. **15**(7): p. 443-454.
7. Czeisler, C.A., et al., *Stability, precision, and near-24-hour period of the human circadian pacemaker.* Science, 1999. **284**: p. 2177-2181.
8. Feigl, B. and A.J. Zele, *Melanopsin-Expressing Intrinsically Photosensitive Retinal Ganglion Cells in Retinal Disease.* Optometry & Vision Science, 2014. **9**(18): p. 894-903.
9. Pokorny, J. and V.C. Smith, *How much light reaches the retina? In C.R. Cavonius (ed), Colour Vision Deficiencies XIII.* Documenta Ophthalmologica Proceedings Series, 1997. **59**: p. 491-511.
10. Gamlin, P.D., et al., *Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells.* Vision Research, 2007(47): p. 946-954.
11. Barrionuevo, P.A., et al., *Assessing Rod, Cone, and Melanopsin Contributions to Human Pupil Flicker Responses.* Investigative Ophthalmology & Visual Science, 2014. **55**(2): p. 719-727.
12. McDougal, D.H. and P.D. Gamlin, *The Influence of Intrinsically Photosensitive Retinal Ganglion Cells on the Spectral Sensitivity and Response Dynamics of the Human Pupillary Light Reflex.* Vision research, 2010. **50**(1): p. 72-87.
13. Joyce, D.S., et al., *Temporal characteristics of melanopsin inputs to the human pupil light reflex.* Vision Research, 2015. **107**: p. 58-66.
14. Berson, D.M., *Strange vision: ganglion cells as circadian photoreceptors.* TRENDS in Neurosciences, 2003. **26**(6): p. 314-320.
15. Barnard, A.R., et al., *Melanopsin regulates visual processing in the mouse retina.* Current biology, 2006. **16**(4): p. 389-395.
16. Hankins, M.W. and R.J. Lucas, *The primary visual pathway in humans is regulated according to long-term light exposure through the action of a nonclassical photopigment.* Current Biology, 2002. **12**: p. 191-198.
17. Allen, Annette E., et al., *Melanopsin-Driven Light Adaptation in Mouse Vision.* Current Biology, 2014. **24**(21): p. 2481-2490.
18. Zaidi, F.H., et al., *Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina.* Current Biology, 2007. **17**(24): p. 2122-2128.
19. Brown, T.M., et al., *Melanopsin-based brightness discrimination in mice and humans.* Current Biology, 2012. **22**(12): p. 1134-1141.
20. Horiguchi, H., et al., *Human trichromacy revisited.* Proceedings of the National Academy of Sciences, 2013. **110**(3): p. E260-E269.
21. Tsujimura, S., N. Hamazono, and K. Okajima, *Temporal contrast sensitivity function based on cones and melanopsin photoreceptors.* Journal of Vision, 2014. **14**(10): p. 593.
22. Cao, D., N. Nicandro, and P. Barrionuevo, *A five-primary photostimulator suitable for studying intrinsically photosensitive retinal ganglion cell functions in humans.* Journal of Vision, 2015. **15**(1): p. 27, 1-13.
23. Lee, B.B., *Visual pathways and psychophysical channels in the primate.* The Journal of Physiology, 2011. **589**: p. 41-47.
24. Dacey, D.M., *Parallel pathways for spectral coding in primate retina.* Annual Review of Neuroscience, 2000. **23**: p. 743-775.
25. Ruderman, D.L., T.W. Cronin, and C.C. Chiao, *Statistics of cone responses to natural images: Implications for visual coding.* JOSA A, 1998. **15**(8): p. 2036-2045.
26. Barrionuevo, P.A. and D. Cao, *Contributions of rhodopsin, cone opsins, and melanopsin to postreceptoral pathways inferred from natural image statistics.* J Opt Soc Am A Opt Image Sci Vis, 2014. **31**(4): p. A131-9.
27. Cao, D. and P. Barrionuevo, *Estimating photoreceptor excitations from spectral outputs of a personal light exposure measurement device.* Chronobiology International, 2014: p. In press (epub Oct. 7, 2014).
28. Blask, D., et al., *Council on Science and Public Health Report 4. Light Pollution: Adverse Health Effects of Nighttime Lighting.* 2012, American Medical Association House of Delegates Annual Meeting.
29. Chang, A.M., et al., *Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness.* Proceedings of the National Academy of Sciences, 2015. **112**: p. 1232-1237.
30. Pauley, S.M., *Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue.* Medical Hypotheses, 2004. **63**(4): p. 588-596.
31. Spitschan, M., et al., *Opponent melanopsin and S-cone signals in the human pupillary light response.* Proceeding of the National Academy of Sciences, 2014. **111**(43): p. 15568-15572.
32. Lennie, P., J. Pokorny, and V.C. Smith, *Luminance.* Journal of the Optical Society of America. A, Optics and image science, 1993. **10**(6): p. 1283-1293.
33. Lucas, R.J., et al., *Measuring and using light in the melanopsin age.* Trends in neurosciences, 2014. **37**(1): p. 1-9.
34. Rea, M., *The lumen seen in a new light: Making distinctions between light, lighting and neuroscience.* Lighting Research and Technology, 2014: p. in press (ePub March 31, 2014).
35. Estévez, O. and H. Spekreijse, *The "silent substitution" method in visual research.* Vision Research, 1982. **22**: p. 681-691.