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Light and Human Health: **An Overview of the Impact of Optical Radiation on Visual, Circadian, Neuroendocrine, and Neurobehavioral Responses**

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**Light and Human Health:
An Overview of the Impact of Optical Radiation
on Visual, Circadian, Neuroendocrine,
and Neurobehavioral Responses**

**Publication of this Technical
Memorandum has been approved
by the IES. Suggestions
for revisions should be directed
to the IES**

**Prepared by:
The IES Light and Human Health Committee**

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Approved by the IES Standards Committee, April 4, 2018, as a Transaction of the Illuminating Engineering Society.

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Published by the Illuminating Engineering Society, 120 Wall Street, New York, New York 10005.

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Printed in the United States of America.

ISBN # 978-0-87995-369-0

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Light and Human Health: An Overview of the Impact of Light on Visual, Circadian, Neuroendocrine, and Neurobehavioral Responses

1.0 INTRODUCTION

Light is currently defined as optical radiation entering the eye that provides visual sensation in humans.¹ Despite this specific vision-related definition, light has been increasingly related to a range of ocular circadian, neuroendocrine, neurobehavioral, and therapeutic responses in humans. Technically, the term *optical radiation* should be used to describe the portion of the electromagnetic spectrum spanning ultraviolet, visible, and infrared radiation that stimulates all these biological responses. Since the term *light* (or *lighting*) is so widely used to describe optical radiation in the lighting community as well as in the biological and medical research community, the reader is advised that these terms are often used interchangeably in these communities. In this document the term *optical radiation* is used when referring to biological responses other than the visual ones.

Most publications from the Illuminating Engineering Society (IES) to date have described light's impact on the human visual system. In some instances, such as in *The Lighting Handbook*, 10th ed., certain physiological and psychological effects of optical radiation are also discussed. The neurophysiology and neuroanatomy of the human visual system are well documented, and almost all lighting technologies, standards, measurement devices, and applications have (until now) been based solely on that understanding. In this Technical Memorandum, however, the Light and Human Health Committee summarizes the extant body of knowledge on a topic that is new to the architectural lighting community: the impact of optical radiation on circadian, neuroendocrine, and neurobehavioral systems. This document is not concerned with the impact of optical radiation on the skin or other tissues, only ocular exposures.

Much like the dual functions (audition and balance) long associated with the ear, the mammalian eye has dual roles in detecting optical radiation for image-formation (vision) as well as for circadian, neuroendocrine, and neurobehavioral responses. Although this is not a new area of scientific investigation, it is a relatively new topic for many IES members.

Most published scientific research in this area has come primarily from controlled laboratory and clinical experiments, although some studies have attempted to

integrate the results into practical situations where they would be beneficial. Therefore, readers will find that the information discussed in this Technical Memorandum is mostly research-based. Recommended practice and application advice are not included.

Since the effects of optical radiation can be profound for human health and well-being, it is increasingly important for the lighting community to understand the direct biological influences of light/dark cycles. It may be possible to develop new lighting technologies and applications that will have health benefits. It may also be possible to employ existing technologies in novel ways to positively influence human health. The counterpoint is also true: it may be possible to employ existing and new technologies in ways that are deleterious to human health.

In brief, this Technical Memorandum describes the retinal mechanisms involved when optical radiation signals are converted into neural signals (a phenomena called *phototransduction*) for vision and for other body functions. Optical radiation reaching the retina not only impacts on how humans see the world, it also regulates physiology and behavior, both directly and indirectly. This includes acute effects such as suppressing pineal melatonin production, elevating morning cortisol production, increasing subjective alertness, enhancing psychomotor performance, changing brain activation patterns to a more alert state, elevating heart rate, increasing core body temperature, activating pupil constriction, and even stimulating circadian clock gene expression.

Perhaps the most important and long-term effect of optical radiation is its ability to reset the internal circadian body clock and synchronize it to local time. Circadian rhythms are daily rhythms that repeat approximately every 24 hours and are driven by an endogenous clock. Nearly all behavioral and physiological parameters exhibit circadian rhythms, and thus circadian clock synchronization is paramount to the body's efficient and appropriate functioning. The neurobehavioral (e.g., sleep/wake cycle) and neuroendocrine (e.g., hormone production) axes are thus influenced by optical radiation both directly (acute effects) and indirectly, via circadian clocks that drive and coordinate the rhythmicity in these systems.

One of the most exciting discoveries in science during the past decade was the identification of a novel type of photoreceptor in the retina, called *intrinsically photosensitive retinal ganglion cells* (ipRGCs). This discovery led to a series of studies to better understand the characteristics, function, and role of the ipRGCs. Questions that have been studied thus far include how the ipRGCs respond to optical radiation, how they regenerate after an optical radiation stimulus, how they provide input to

the higher brain centers driving optical radiation-dependent responses, and how they interact with the classical photoreceptors (rods and cones) to provide such information. The findings of these studies are summarized in this Technical Memorandum, but it is important to note that new studies are being conducted and new knowledge is being added to the literature every month, if not every week. The reader is encouraged to continuously search for the most current information on this topic.

The reader will also find here a section discussing the circadian, neuroendocrine, and neurobehavioral systems and how they respond to optical radiation. The majority of the studies in the literature, and hence the majority of the discussion in this document, investigate the interaction and influence of the circadian system on the neurobehavioral and neuroendocrine responses. It is important, however, to keep in mind that the impact of optical radiation on the neurobehavioral and neuroendocrine responses is not exclusively via the circadian system.

In addition to summarizing the current knowledge in retinal photoreceptors and physiology associated with vision and other neural responses, this Technical Memorandum also discusses the impact of various lighting characteristics (quantity, spectrum, timing, duration, light history) on the visual, circadian, neuroendocrine, and neurobehavioral systems. Current knowledge suggests that the optimal light for vision differs from optical radiation for circadian, neuroendocrine, and neurobehavioral responses.

The Light and Human Health Committee decided that, as a first step to introduce this new topic to IES members and the lighting community, it was important to write a short and focused document summarizing the latest research in the phototransduction physiology of the circadian, neuroendocrine, and neurobehavioral systems, coupled with a discussion of the optical radiation characteristics that can be controlled by a lighting professional, which affect the visual and non-visual systems. Thus, this Technical Memorandum has a twofold mission:

- To explain the physiology by which the retina converts optical radiation signals into neural signals for vision and for circadian, neuroendocrine, and neurobehavioral responses.
- To discuss the responses of these systems to optical radiation stimuli.

The next challenge is to incorporate this new information into standard practice and applications, which will be discussed in the future reports from the Committee. It is felt that the information provided here will serve as the foundation for future IES publications that will be more application oriented.

2.0 OVERVIEW OF THE RETINA

The eye can be subdivided into two parts: *ocular* (lens and sclera) and *neural* (retina). The function of the ocular parts is to place a focused, clear image of the outside world on the retina with minimal absorption and scattering, and to filter out damaging optical radiation. The retina, which is an extension of the brain, absorbs optical radiation signals and converts them into electrical signals. The processing of visual, circadian, neuroendocrine, and neurobehavioral responses begins in the retina. Subsequently, photic information is sent to various parts of the brain for further processing.

Ganglion cell axons pass electrical signals to the brain (in brief spikes) via two main output pathways from the eye. For visual responses, electrical signals are transmitted from the retina along the primary optic tract to the visual cortex via the lateral geniculate nucleus (LGN) and along the secondary optic tract to the superior colliculus.² For non-visual responses, signals are transmitted to the suprachiasmatic nuclei (SCN), ventral preoptic areas (VPO), subparaventricular zones (sPVZ), intergeniculate leaflet (IGL), and the pretectal areas (PT) via the retinohypothalamic tract (RHT).³

2.1 Classical Visual Photoreceptors

The retina contains the photoreceptors that detect optical radiation for vision, circadian, neuroendocrine, and neurobehavioral responses. Photoreceptors contain *photopigments* (light-absorbing proteins) that are maximally sensitive to different electromagnetic radiation wavelengths and that have discrete absorbance spectra, which describe the probability of a photon being absorbed as a function of radiation wavelength.

The shapes of the absorbance spectra are very similar for all opsin-basedⁱ photopigments. These absorbance spectra can be graphically approximated with a Dartnall nomogram, a single-sensitivity function resembling a parabola but having different peak wavelength sensitivities, depending upon the opsin moiety (*moiety* is a part or portion of a molecule). The wavelength of maximal sensitivity (absorption maximum, $\lambda_{\max}$) is a consequence of the amino acid sequence of the opsin protein and its interaction with the chromophore (a part of the molecule responsible for absorbing photons).

All vertebrate retinas are composed of three layers of nerve cell bodies (the cell body is the largest part of the cell, where the nucleus and other unique struc-

ⁱ Opsins are light-sensitive protein-coupled receptors found in photoreceptor cells of the retina.

tures responsible for making energy and removing waste are located — see **Figure 1**):

- The outer nuclear layer, where cell bodies of rods and cones are located
- The inner nuclear layer, containing cell bodies of bipolar, horizontal, and amacrine cells
- The ganglion cell layer, where cell bodies of ganglion cells (and some displaced amacrine cells) connect to ganglion cells

Classical photoreceptors — rods and cones — send all photic information to the brain via cells in the outer plexiform layer (OPL) of the retina, which in turn send them to ganglion cells. The visual message leaves the retina as ganglion cell axon spike discharges that occur either when a spot of light stimulates the retina (ON discharge), or when the spot of light is extinguished (OFF discharge). In order to keep the ON and OFF channels separate through the ganglion cells to the brain, the inner plexiform layer (IPL) is divided into two functionally discrete sublaminae, called *a* (the OFF layer) and *b* (the ON layer).

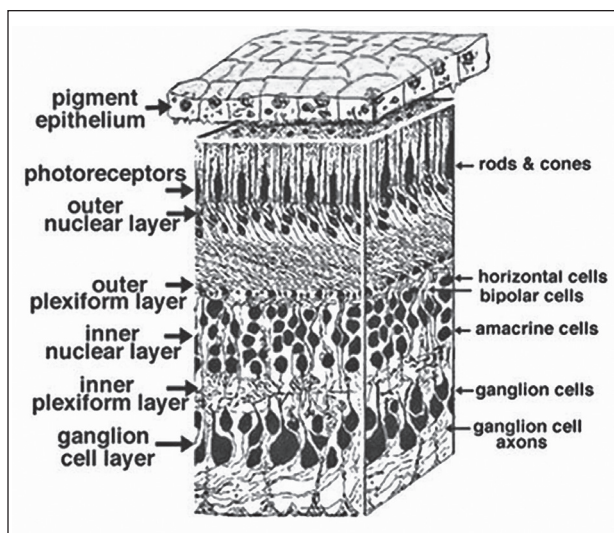


Figure 1. All vertebrate retinas contain layers of nerve cell bodies. Rods and cones are in the outer nuclear layer. (Image republished by permission from Webvision: <http://webvision.med.utah.edu/>)

Until recently, it was believed that there were only two classes of photoreceptors in the vertebrate retina: rods, which are responsible for vision under very low light levels (scotopic vision), and cones, which are responsible for vision at daylight (photopic) levels, color vision, and for discriminating fine details. Rods outnumber cones by a ratio of approximately 20:1.

Photopic vision is generally assumed to occur when the visual system operates at adaptation luminances

higher than approximately 3 cd/m². Scotopic vision is generally assumed to occur when the visual system operates at adaptation luminances below approximately 0.001 cd/m². Rods and cones both operate at light levels between these values (mesopic vision). Although these values for the boundaries between scotopic, mesopic and photopic vision are traditionally cited, the precise values between scotopic and mesopic vision and between mesopic and photopic vision are dependent upon the characteristics of the specific visual scene at any given time.

Rods contain the visual photopigment rhodopsin, with a peak sensitivity at about 507 nm in vivo.⁴ The human retina contains short (S-), medium (M-) and long (L-) wavelength cones. The S-cones contain the visual photopigment cyanolabe and are maximally sensitive to wavelengths at about 440 nm in vivo; the M-cones contain the visual photopigment chlorolabe and have a peak spectral sensitivity at about 535 nm in vivo; the L-cones contain the visual photopigment erythrolabe and are maximally sensitive to wavelengths at about 565 nm in vivo.⁴ Color vision is initiated in the distal retina by combining the outputs from these three cone types into two spectrally opponent mechanisms, red versus green and blue versus yellow.

Rods and cones are located in the outer nuclear layer of the retina. They respond to a light stimulus with sustained hyperpolarization (increase in the absolute value of the cell's membrane potential), rather than with depolarization (decrease in the absolute value of cell's membrane potential) spikes as exemplified by all other neurons.² When a rod or cone photoreceptor is in the dark, potential across photoreceptor membranes is low, the photoreceptor is depolarized, and a steady release of neurotransmitter occurs. When the photoreceptor is illuminated, the potential across the membranes increases and the membrane becomes hyperpolarized, reducing the rate of release of the neurotransmitter.²

2.2 Circadian, Neuroendocrine, and Neurobehavioral Photoreceptors

In addition to understanding how the retina converts light signals to neural signals for the visual system, it is necessary to determine the photic pathways involved in circadian, neuroendocrine, and neurobehavioral responses and to characterize which photopigments are involved in these responses.

2.2.1 Identifying Photopigments. The methodology to determine the spectral sensitivity of a biological response that depends on an optical radiation stimulus and then establish the underlying photopigments driving the response is called *action spectroscopy*. This technique compares the efficacy of different

electromagnetic radiation wavelengths at different irradiances to induce the response.

An action spectrum is one of the principal tools for identifying the photopigments that initiate optical radiation-induced responses. The spectral sensitivity of photopigments is dependent on the amino acid structure of the opsin and the interaction with the chromophore. By definition, an action spectrum is the relative response of an organism to different wavelengths of visible and near-visible electromagnetic radiation.⁵⁻⁷ Knockout rodent models,ⁱⁱ cellular transgenic experiments (transgenic animals are those that have been modified by placing in them, at the embryonic stage, genes of other animals or modified versions of their own genes), and other techniques have been used to try to identify the photopigments concerned with circadian, neuroendocrine, and neurobehavioral phototransduction.

2.2.2 Action Spectra. There are two basic types of action spectra: *polychromatic* and *analytic*. Polychromatic action spectra are developed using broader-bandwidth light source stimuli that have half-peak bandwidths greater than 15 to 20 nm, or that emphasize particular wavelengths against backgrounds of “white” light. These types of action spectra are useful for:

- Identifying interactions of biological responses to multiple electromagnetic radiation wavelengths
- Elucidating how organisms respond to optical radiation in more natural settings
- Guiding the development of the more sophisticated analytic action spectra

By themselves, however, polychromatic action spectra have limited utility for identifying the specific chromophores and/or photopigments that initiate photobiological responses⁸

Analytic action spectra, however, in the absence of any confounding factors, should match the absorption spectra of the photopigment driving the response. As in other fields of photobiology, the earliest action spectrum studies on neuroendocrine and circadian responses to light utilized polychromatic stimuli. Polychromatic action spectrum studies in both humans and rodents were reasonably consistent in suggesting that the region between 450 nm and 550 nm provides the strongest stimulation of circadian and neuroendocrine responses (for further review, see Brainard and Hanifin, 2005⁹).

ⁱⁱ A knockout is a genetically-manipulated animal (mutant) that may, for example, lack rods and/or cones.

Although diminished in its capacity to elicit neuroendocrine and circadian responses, long wavelength optical radiation at a sufficiently high irradiance can acutely suppress melatonin, as well as phase shift or entrain circadian rhythms in both rodents and humans.¹⁰⁻¹⁴ Similarly, both polychromatic and monochromatic ultraviolet (UV)-A radiation detected by the eyes, although not as strong as wavelengths in the middle of the visible spectrum, can suppress melatonin and regulate the circadian pacemaker, the photoperiodic reproductive response, and the immune response in rodents.¹⁵⁻¹⁷ This physiological regulation is possible because the ocular lens of rodents freely transmits UV radiation (down to 300 nm) back to the retina.

2.2.3 Studies Using Blind Animals. Consistent with the hypothesis that a novel photoreceptor participated in circadian phototransduction, some of the earlier polychromatic and analytic action spectra indicated peak wavelengths that suggested circadian responses might not be mediated by the classic rod and cone photoreceptors.⁹ Concurrent to the action spectra work, researchers initiated studies on blind animals and humans to examine whether the lack of classical photoreceptor input to the circadian system interfered with neuroendocrine or circadian regulation. The data emerging from those studies made it increasingly clear that neither the rods nor the cones used for vision were the primary transducers necessary for circadian, neuroendocrine, and neurobehavioral responses.¹⁸⁻²⁶

More-recent studies with rodless-coneless mice (*rd/rd cl*)ⁱⁱⁱ showed that these mice exhibit normal or even enhanced sensitivity for melatonin suppression and circadian phase shifting of locomotion.^{27,28} These results confirm that classical rods and cones are not required for circadian photoreception in mice. Removal of the eyes in both mice and humans, abolishes circadian phase shifting^{27,29,30} and melatonin suppression.^{19,28} Collectively, the studies suggest that the mammalian eye contains specific photoreceptors for the regulation of circadian, neuroendocrine and neurobehavioral optical radiation responses that are distinct from the classical visual photoreceptors.

2.2.4 The Discovery of Melanopsin. A question remained: what was the photopigment mediating these non-visual responses? In 1998, a seminal discovery was made in the cloning of melanopsin, the fifth opsin-based photopigment, from the mammalian eye. This discovery ultimately led to a paradigm shift in the understanding of mammalian phototransduction. Melanopsin, a molecule found originally

ⁱⁱⁱ Nomenclature used for animals that lack rods and cones (knockout animals).