Photoreception for Circadian, Neuroendocrine, and Neurobehavioral Regulation

John P. Hanifin and George C. Brainard

Department of Neurology, Thomas Jefferson University

Abstract In the art and science of lighting, four traditional objectives have been to provide light that: 1) is optimum for visual performance; 2) is visually comfortable; 3) permits aesthetic appreciation of the space; and 4) conserves energy. Over the past 25 years, it has been demonstrated that there are nonvisual, systemic effects of light in healthy humans. Furthermore, light has been used to successfully treat patients with selected affective and sleep disorders as well as healthy individuals who have circadian disruption due to shift work, transcontinental jet travel, or space flight. Recently, there has been an upheaval in the understanding of photoreceptive input to the circadian system of humans and other mammals. Analytical action spectra in rodents, primates, and humans have identified 446–484 nm (predominantly the blue part of the spectrum) as the most potent wavelength region for neuroendocrine, circadian, and neurobehavioral responses. Those studies suggested that a novel photosensory system, distinct from the visual rods and cones, is primarily responsible for this regulation. Studies have now shown that this new photosensory system is based on a small population of widely dispersed retinal ganglion cells that are intrinsically responsive to light, and project to the suprachiasmatic nuclei and other nonvisual centers in the brain. These light-sensitive retinal ganglion cells contain melanopsin, a vitamin A photopigment that mediates the cellular phototransduction cascade. Although light detection for circadian and neuroendocrine phototransduction seems to be mediated principally by a novel photosensory system in the eye, the classic rod and cone photoreceptors appear to play a role as well. These findings are important in understanding how humans adapt to lighting conditions in modern society and will provide the basis for major changes in future architectural lighting strategies. *J Physiol Anthropol 26(2): 87–94, 2007*
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Introduction

Light is a potent biological and therapeutic force which is fundamental to life on our planet. Living things vary in their capacity to use visible and near-visible radiant energy from the sun for survival but the vast majority of organisms owe their existence to using solar light as an energy source. Despite this incontroversial fact, what is known about light's effects on humankind is still in its infancy. Traditionally, the design of artificial lighting has adhered to providing illumination that gives the best possible input to the visual system while addressing aesthetic and ecological needs of the space being illuminated. Integrating the recent discovery of a new sensory system in the human eye that detects environmental light for neurobehavioral regulation is the challenge facing lighting engineers, architects, and scientists.

Phototransduction and Action Spectra for Circadian, Neuroendocrine, and Neurobehavioral Responses

There is a basic principle shared by all species in their ability to respond to light stimuli: all photobiological responses are mediated by organic molecules that absorb light quanta and then undergo physical-chemical changes. These light-induced changes subsequently evoke broader physiological responses within the organism. This process is termed phototransduction, and the specific molecular complexes that absorb light energy to initiate photobiological responses are called photopigments. As a rule, these photoactive molecules do not absorb energy equally across the electromagnetic spectrum. Photopigments have their own characteristic wavelength absorption spectrum that depends on their atomic structure (Grossweiner, 1989; Horspool and Song, 1994; Coohill, 1991; 1999). A photopigment's pattern of wavelength sensitivity, or its absorbance spectrum, is like a fingerprint—it is unique to that molecular complex.

In the field of photobiology, an action spectrum is one of the principal tools for identifying the photopigment that initiates a light-induced response. An action spectrum is the relative response of an organism to different wavelengths of visible and

near-visible electromagnetic radiation. Photobiologists have evolved a set of refined approaches for determining action spectra that are applicable to all light-responsive organisms (Grossweiner, 1989; Horspool and Song, 1994; Coohill, 1991; 1999). There are two types of action spectra: polychromatic and analytic (Coohill, 1999). In general, when researchers initially study light-sensitive biological reactions, they begin by determining polychromatic action spectra. Such action spectra are developed using broader bandwidth light stimuli that have half-peak bandwidths greater than 15–20 nm. Although these action spectra are valuable for identifying interactions of biological response to multiple wavelengths and guiding more sophisticated analytic action spectra, they have limited utility for identifying peak sensitivities of specific photopigments that initiate photobiological responses (Coohill, 1999).

Earlier action spectrum studies on neuroendocrine and circadian responses to light utilized polychromatic stimuli. Across this set of publications, both humans and rodents were studied in terms of pineal melatonin synthesis, circadian phase shifting, or photoperiodic responses (Brainard and Hanifin, 2005 for review). The polychromatic action spectra are consistent in suggesting that the general spectral region between 450 nm and 550 nm provides the strongest stimulation of circadian and neuroendocrine responses in mammals with little to no responsiveness to the longer wavelength end of the visible spectrum. Long wavelength light of sufficient high intensity, however, can acutely suppress melatonin, as well as phase shift or entrain circadian rhythms in both rodents and humans (Brainard and Hanifin, 2005; Hanifin et al., 2006).

Some of the earlier polychromatic action spectra indicated peak wavelengths that suggest circadian responses might not be mediated by the classic rod and cone photoreceptors. Similarly, early studies with blind animals with destruction of retinal photoreceptors due to prolonged light exposure raised the possibility that neither the rods nor the cones used for vision participate in regulating the circadian and neuroendocrine systems (Pevet et al., 1984; Webb et al., 1985). Despite profound loss of photoreceptors and vision, light detection for circadian and photoperiodic regulation was preserved. A decade of research in the 1990s on mice with hereditary retinal disorders (*rd/rd* and *rds/rds*) and on transgenic coneless (*cl*) mice have shown that these animals still exhibit normal light-induced melatonin suppression and circadian locomotor phase shifts despite a nearly total loss of classical visual photoreceptors (Foster et al., 1991; Lucas et al., 1999; Freedman et al., 1999). Similarly, studies performed on humans with no conscious perception of light demonstrated intact circadian responses to light (Czeisler et al., 1995; Klerman et al., 2002). A field study run on visually impaired individuals showed that those who had no visual light perception had abnormal circadian rhythms as measured by urinary 6-sulfatoxymelatonin (aMT6s), a metabolite of melatonin, compared to blind subjects who retained a degree of visual light perception (Lockley et al., 1997). Color vision

deficient subjects studied for light suppression of melatonin suggested that a normal three-cone system is not required for this response (Ruberg et al., 1996). The data emerging from those studies made it increasingly clear that there was a non-rod, non-cone photoreceptor at work in circadian phototransduction.

In the mid 1980s, circadian and neuroendocrine researchers began employing monochromatic wavelengths and increasingly sophisticated photobiological techniques for determining analytic action spectra. Analytical action spectra are determined comparing the effects of two or more monochromatic light stimuli with half-peak bandwidths of 15–20 nm or less. It is optimal to develop analytic action spectra by establishing a set of dose-response curves (fluence-response curves) at different wavelengths for a specific biological response. An action spectrum is then formed by plotting the reciprocal of incident photons required to produce the biological response versus wavelength (Grossweiner, 1989; Horspool and Song, 1994; Coohill, 1991; 1999). Recent analytical action spectra demonstrating the wavelength sensitivity of various physiological responses are summarized in Table 1. It is important to note that all of the action spectra in Table 1 fit the data to opsin nomograms with relatively high coefficients of correlation and indicate shorter wavelength peak sensitivities (λ_{max}) in the blue portion of the visible spectrum. Across those studies, the calculated λ_{max} indicates peak photosensitivity of 459 nm to 484 nm. Together, all of those studies suggested that a novel photoreceptor system was involved in circadian and neurobehavioral phototransduction mediated by the eye. While these analytical action spectra were being developed, other work was clarifying the biochemical and anatomical nature of this novel sensory system.

The Discovery of Melanopsin and Intrinsically Photosensitive Retinal Ganglion Cells

Melanopsin, a molecule found originally in frog skin light-sensitive melanophore cells was an early leading candidate for the mammalian circadian photopigment, since it is expressed in anatomical areas where a nonvisual photoreceptor is likely to be present (Rollag, 1996; Provencio et al., 1998). Melanopsin also shares predicted structural similarities with all known opsins, including seven transmembrane proteins. Provencio and colleagues (2000) identified melanopsin in the inner human retina, cloned both human and mouse melanopsin, and showed a large sequence homology to invertebrate opsins. This structural similarity to invertebrate opsins would makes sense in allowing the photopigment to regenerate distant from chromophore-regenerating tissues, such as the retinal pigment epithelium (RPE).

Melanopsin-containing ganglion cells with extended neural networks were identified in the rodent retina (Berson et al., 2002; Provencio et al., 2002; Hattar et al., 2002; Panda et al., 2002) as well as human (Provencio et al., 2000; Rollag et al., 2003; Hannibal et al., 2004) and primate inner retinas (Dacey

et al., 2005). In rodents, melanopsin has been found in a specific subtype of intrinsically photosensitive retinal ganglion cells (ipRGC) which project to a number of nonvisual nuclei, including the suprachiasmatic nuclei, intergeniculate leaflets, olivary pretectal nuclei, preoptic nuclei, and subparaventricular zones (Gooley et al., 2001, 2003; Hattar et al., 2002; Hannibal et al., 2002, 2004). These ipRGCs respond to light on their own when separated physically or blocked by drugs from receiving input from other neurons (Berson et al., 2002; Dacey et al., 2005).

In the past few years, studies have provided convincing evidence that melanopsin is a functional circadian photopigment in ipRGCs. In blind humans, melanopsin expression was maintained in the retinas of people with severe retinal diseases (Hannibal et al., 2004). Three recent studies have provided even more compelling evidence that melanopsin is the photopigment responsible for ipRGC phototransduction (Melyan et al., 2005; Qiu et al., 2005; Panda et al., 2005). When nonphotosensitive cells such as mouse paraneurons, human kidney cells, and *Xenopus* oocytes are transfected with the human or mouse melanopsin genes, each cell type becomes light-sensitive. The discovery of melanopsin and ipRGCs is a crowning scientific achievement, has led to a revolution in our understanding of circadian photoreception, and is beginning to guide scientists into new uses of light for circadian, sleep, and other disorders.

The Use of Light for Clinical and Nonclinical Applications

Seasonal Affective Disorder (SAD) is the most studied clinical condition that employs light as a therapeutic agent. SAD is a type of depression in which symptoms occur yearly during the shorter days of autumn and winter and remit during the longer days of spring and summer. Symptoms include low mood, reduced interest, decreased concentration, low energy and fatigue, increased need for sleep, increased appetite, and carbohydrate cravings with consequential weight gain (Lewy et al., 1982; Rosenthal et al., 1984; Lam and Levitt, 1999). Light therapy has proven to be an effective therapeutic intervention for patients of all ages with SAD (Terman et al., 1998; Eastman et al., 1998; Lam and Levitt, 1999; Terman et al., 2001). Patients vary in their responsiveness to light therapy and the current standard practice is a trial of 10,000 lux white fluorescent light for 30–60 minutes in the morning (Lam and Levitt, 1999; Terman et al., 2001). Recently, a preliminary Phase I study on SAD patients testing narrow bandwidth blue light was significantly better than dimmer red light in reversing symptoms of major depression with a seasonal pattern; however, the optimum blend of wavelengths for treating this disorder is still not known (Glickman et al., 2006). Although a majority of studies employing light therapy have focused on treatment of SAD, additional clinical applications of light treatment have been explored, including light for the treatment of non-seasonal depression, various sleep disorders, menstrual-

cycle related problems, bulimia nervosa, and senile dementia (Kripke, 1998; Terman et al., 1995; Parry et al., 1989; Kripke, 1993; Lam et al., 1994; Forbes et al., 2004; Tuunainen et al., 2005).

Light therapy for use in resolving problems associated with intercontinental travel and shift work are currently being evaluated. While the body readjusts its biological clock to a new time zone, many people experience symptoms such as daytime sleepiness, nighttime insomnia, gastrointestinal distress, irritability, mild depression, and confusion (Boulos et al., 1995; Revell and Eastman, 2005). The average period of readjustment may range from three to twelve days, depending on the direction of travel and the number of time zones that have been spanned. Similar to intercontinental travelers, shift workers are also forced to make changes to their usual sleep and wake times. It has been estimated that approximately 20% of workers in industrialized nations participate in some form of shift work (US Congress, 1991; Eastman et al., 1995). It has been observed that shift workers have a higher incidence of cardiovascular disease and gastrointestinal distress as well as cognitive and psychological problems. Many researchers hypothesize that these ailments are caused, in part, by difficulty adjusting to a night shift or rotating schedules. A number of studies have shown that properly timed exposure to light and darkness may enhance workers' circadian systems to adapt to shift schedules (Czeisler et al., 1986; Lewy et al., 1987; Eastman et al., 1995; Czeisler et al., 1990; Minors et al., 1991; Revell and Eastman, 2005). Recently, studies have specifically tested monochromatic and polychromatic short wavelength (blue) light for improved efficacy compared to longer wavelength monochromatic light for inducing circadian phase shifts in healthy humans under laboratory conditions (Lockley et al., 2003; Warman et al., 2003; Revell et al., 2005).

As with shift work applications, light is being tested as a countermeasure for disruption of circadian rhythms and sleep-wake patterns in astronauts during long duration space flight (Czeisler et al., 1991; Whitson et al., 1995; Stewart and Eastman, 1996; Dijk et al., 2001; Wright et al., 2001). Disturbed circadian rhythms and altered sleep-wake patterns are major risk factors for the health and safety of astronauts (NASA, 2004). Associated behavioral changes include decreased alertness, diminished concentration, and performance decrements, all of which can compromise the safety of personnel and the objectives of space missions. Preliminary studies of astronauts and ground control workers have shown light treatment to be an effective tool for supporting circadian entrainment (Czeisler et al., 1991; Whitson et al., 1995; Stewart and Eastman, 1996; Dijk et al., 2001; Wright et al., 2001). Ongoing research continues to investigate how to optimize light as a countermeasure for circadian and sleep disruption in space flight missions (Fucci et al., 2005).

Bright light exposure appears to have an acute stimulatory "alerting" effect on healthy humans. An early study showed that subjects working a continuous 30-hour shift demonstrated

Table 1 Analytical action spectra studies for circadian, neuroendocrine and ocular responses.

Species	Response	Peak (λ_{Max})	Citation
Mouse *rd/rd*	Circadian Phase-Shifting	480	Yoshimura and Ebihara, 1996
Human	Melatonin Suppression	464	Brainard et al., 2001
Human	Melatonin Suppression	459	Thapan et al., 2001
Mouse *rd/rd*	Pupillary Light Reflexes	479	Lucas et al., 2001
Human	Cone Cell ERG-wave	483	Hankins and Lucas, 2002
Rat	Ganglion Cell Depolarization	484	Berson et al., 2002
Mouse *rd/rd cl*	Circadian Phase-Shifting	481	Hattar et al., 2003
Monkey	Ganglion Cell Depolarization	482	Dacey et al., 2005

Table 2 Correlated color temperature (CCT) effects on circadian and neuroendocrine responses.

Citation	CCT Comparisons	Parameters Measured
Deguchi and Sato, 1992	7,500 K, 5,000 K, 3,000 K	Reaction Time
Mukae and Sato, 1992	6,700 K, 5,000 K, 3,000 K	Heart Rate Variability
Morita and Tokura, 1998	6,500 K, 3,000 K	Core Temperature, Melatonin
Noguchi and Sakaguchi, 1999	5,000 K, 3,000 K	Heart Rate Variability, EEG, Subjective Drowsiness
Yasukouchi et al., 2000	7,500 K, 5,000 K, 3,000 K	Skin Temperature, Rectal Temperature, Expired Gas
Kozaki et al., 2005	6,700 K, 5,000 K, 3,000 K	Polysomnography, EEG, EOG, EMG
Sato et al., 2005	6,480 K, 3,150 K	Rectal Temperature, Salivary Melatonin
Yasukouchi and Ishibashi, 2005	7,500 K, 6,700 K, 5,000 K, 3,000 K	Arousal Level, Heart Rate Variability, Blood Pressure, Body Temperature Reg., Sleep Architecture

enhanced behavioral and cognitive performance as well as significant differences in body temperature, melatonin and cortisol levels when working under 3,000 lux of white light as compared to a dimmer light exposure of 100 lux (French et al., 1990). Several other experiments have demonstrated the immediate alerting effects of bright light on humans (Badia et al., 1991; Campbell et al., 1995; Brainard et al., 1996; Boyce et al., 1997; Cajochen et al., 2000). Further testing of the alerting effects of short wavelength light has shown greater potency than longer wavelength light for alerting effects as measured by subjective and objective behavioral assessments, as well as polysomnography, heart rate, and thermoregulation in healthy human subjects (Lockley et al., 2006; Cajochen et al., 2005; Revell et al., 2006). These studies suggest that short wavelength light is more potent than long wavelength light for acutely enhancing alertness.

Over the last decade scientists have discovered many neurobehavioral changes based on the correlated color temperature of polychromatic, fluorescent lights. Specifically, it was found that lights with a higher color temperature evoke stronger melatonin suppression compared to lamps with a lower color temperature in healthy humans (Morita and Tokura, 1998; Sato et al., 2005). Additionally, higher color temperature fluorescent lamps have a more potent effect on core body temperature than low color temperature lamps

(Morita and Tokura, 1998; Yasukouchi et al., 2000). Further, blood pressure and EEG frequency have been shown to increase under a high color temperature as compared to lower color temperatures (Noguchi and Sakaguchi, 1999; Yasukouchi and Ishibashi, 2005). When examining the effects of illumination prior to sleep, deep sleep (S4) was reduced under a high color temperature compared to a low color temperature during the first half of sleep (Kozaki et al., 2005). Table 2 summarizes some of the published studies which have probed these effects of color temperature on human physiology. Together, this literature consistently demonstrates that higher correlated color temperature lamps induce stronger neurobehavioral effects than lower correlated color temperature lamps in healthy subjects. Such results are consistent with the recently completed analytical action spectra shown in Table 1.

Given the peak sensitivities observed in studies using monochromatic light (Table 1), it is logical to predict that polychromatic light sources will evoke stronger circadian, neuroendocrine, and neurobehavioral responses if they are enriched in the blue portion of the visible spectrum. The literature capsulated in Table 2 appears to support that concept.

Figure 1 shows two normalized spectral power distributions (SPDs) from two polychromatic light sources: atmospheric daylight and an incandescent light bulb. If these complex light
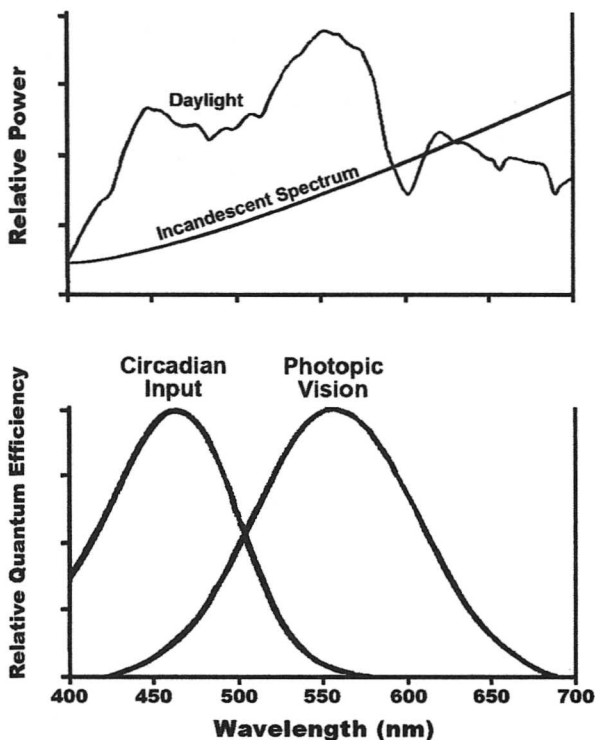
Fig. 1 The top graph provides a normalized spectral power distribution (SPD) for daylight and incandescent lamplight. It is important to note that typical incandescent lamplight is much weaker than daylight but normalizing the SPDs permits a comparison of wavelength distributions. The daylight SPD was measured on a clear day in Philadelphia at 3:00 PM in July, 2006. The incandescent SPD is derived from Figure 2–5 of the Handbook of the Illuminating Engineering Society of North America (IESNA, 2000). The bottom right graph illustrates the relative wavelength sensitivity of the three-cone photopic visual system with a peak sensitivity of 555 nm. The bottom left graph represents a model of wavelength sensitivity for mammalian circadian, neuroendocrine, and neurobehavioral responses that appear to be regulated by ipRGCs. This model is based on the published action spectra shown in Table 1, and may have a peak sensitivity between 446 and 484 nm (Brainard and Hanifin, 2005).

sources were compared on an equal photon density basis, it might be expected that daylight would be more powerful than the incandescent source in eliciting neurobehavioral responses. Ultimately, future studies are needed to compare a wide variety of natural and artificial polychromatic light sources to determine if this concept is generally true.

Conclusions

The seminal discovery of a new photosensory system in the human eye opens the door for further development of light therapy for clinical and non-clinical applications as well as potential use in general architecture. Much more work must be done, however, before there is any certainty about the optimum blend of wavelengths for these types of applications.

Careful characterization of the spectral power distribution of

the polychromatic stimuli that later permits calculation of the relevant spectrally weighted values needs to be employed in all future studies. Ultimately a new, dedicated metric for quantifying light for circadian, neuroendocrine, and neurobehavioral regulation will need to be determined. Such a metric must be based on a clear understanding of the ipRGC photoreceptors, their interactions with classical rod and cone photoreceptors, and their behavior in complex dynamically illuminated environments. Integrating this rapidly expanding branch of neuroscience with the fields of lighting engineering and architecture will be the next challenge facing photobiologists into the 21st century.

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Correspondence to: George C. Brainard, Ph.D., Department of Neurology, Thomas Jefferson University, 1025 Walnut Street, Suite 507, Philadelphia, PA 19107

Phone: 215–955–7644

Fax: 215–923–7588

e-mail: george.brainard@jefferson.edu