THE BIOLOGICAL POTENCY OF LIGHT IN HUMANS: SIGNIFICANCE TO HEALTH AND BEHAVIOR

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ABSTRACT

Light entering the eyes activates a specific neural pathway which regulates circadian and neuroendocrine physiology. That pathway is predominantly separate from the pathway which supports vision and visual reflexes. Disruption of the circadian and neuroendocrine systems, which can result from seasonal, daily and acute changes in usual light exposure, may contribute to a variety of clinical and non-clinical disorders. It has now been established that appropriately timed light exposures can be effective in the treatment and prevention of these disorders. Ultimately, such findings will enable the development of lighting strategies which are optimal for vision as well as physiological health and well being.

Key words: Architectural Lighting, Behavior, Circadian, Health, Melatonin, Neuroendocrine, Photobiology, Photometry, Pineal Gland, Radiometry

1. INTRODUCTION

Architectural lighting has traditionally been engineered with the purposes of maximizing visual performance, maintaining visual comfort, providing an aesthetically pleasing environment and conserving energy [1-3]. Scientific evidence of the past 20 years has led to a growing appreciation that, separate from vision and visual reflexes, light perceived by the eye can influence human physiology, mood and behavior [4-9]. These findings provide the basis for fundamental changes in future lighting strategies that can optimize human health and well being.

2. THE NEURAL REGULATION OF THE NONVISUAL EFFECTS OF LIGHT

Non-visual information about light is detected by the eyes and transmitted by the retinohypothalamic tract (RHT), a neural pathway which projects to the suprachiasmatic nuclei (SCN) in the hypothalamus [4,10]. The SCN serve as the primary central circadian oscillators which regulate daily rhythms such as the sleep wake cycle, body temperature rhythms and 24 hour secretory patterns of hormones. As illustrated in Figure 1, the SCN modulate these diverse circadian rhythms by connections to many regions of the central nervous system.

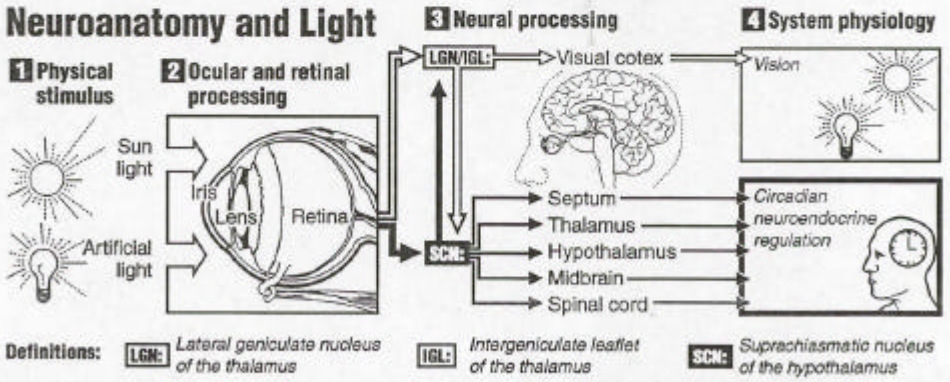

Figure 1. The diagram above provides a simplified explanation of the neuroanatomy that is responsible for mediating both the sensory capacity of the visual system and the non-visual regulation of circadian and neuroendocrine functions. (Unpublished illustration by Aaron Steckelberg, Philadelphia, 2003.)

Although the RHT is separate from the visual system, there is a functional connection between the primary visual pathway and the circadian neuroanatomy by way of a projection from the intergeniculate leaflet to the SCN [10,11]. One well-studied circadian pathway extends from the

hypothalamus, the upper thoracic intermediolateral cell column, and the superior cervical ganglion [10,11]. By this pathway, the ambient light-dark cycle entrains the rhythmic synthesis and secretion of pineal melatonin. High levels of melatonin are secreted during the night, and low levels are secreted during the day [12,13]. In addition to entraining circadian rhythms of melatonin, light at night can elicit an acute suppression of the high nocturnal levels of this hormone. This acute light-induced suppression of melatonin has been consistently observed in many species, including humans, and has been used as a tool in many studies to examine the ocular, neural and biochemical physiology of melatonin regulation and circadian rhythms [10,14,15].

The photoreceptor physiology of the circadian system has been a matter of continued debate. Earlier studies of mice lacking rod photoreceptors showed preservation of circadian responses and seemed to implicate a cone-like photoreceptor in the mediation of light input to the circadian pathway [16,17]. More recent evidence suggests that a novel photoreceptor may be primarily responsible for transduction of photic stimuli in circadian regulation. Animal studies supporting involvement of a novel photoreceptor include circadian phase-shifting and melatonin suppression by light in rodless-coneless transgenic mice [18,19]. Similarly, in human studies, melatonin can be suppressed by exposing the eyes to light in visually blind people or in people with color vision deficits [20,21]. Furthermore, in normally sighted humans, the action spectra for melatonin suppression appear to be independent of the three-cone visual system [22].

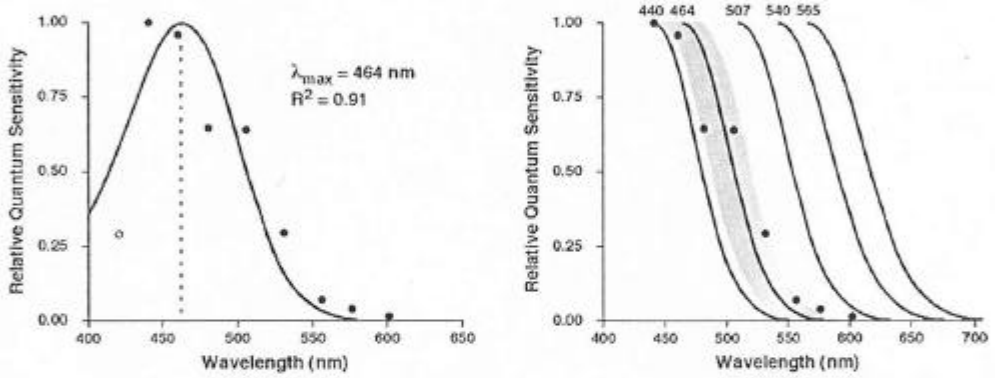

Figure 2. The above graphs demonstrate data from the recently published action spectrum for melatonin suppression in humans [23]. The graph on the left is the action spectrum for suppression of melatonin in humans. This action spectrum for percent control adjusted melatonin suppression was done with 72 healthy subjects. Solid circles represent the half-saturation constants of eight wavelengths (440, 460, 480, 505, 530, 555, 575, and 600 nm) plotted as log relative sensitivity. The open circle depicts an estimation of the half-saturation constant derived from limited 420 nm data of eight subjects exposed to a single intensity of 31.8 $\mu W/cm^2$. The solid curve portrays the best-fit template for vitamin A1 retinaldehyde photopigments, which predicts a maximal spectral absorbance range of 446-477 nm. The melatonin suppression data represented in this graph relative to the opsin nomogram has a high coefficient of correlation (R^2 = .91). The figure on the right represents a comparison of melatonin suppression and visual system action spectra. Maximal spectral response and the long wavelength limb of the melatonin suppression template is plotted alongside templates of wavelength sensitivity for human rods and cones which support vision. The shaded region surrounding the template represents ± SD from the data. This representation demonstrates the spectral sensitivity of melatonin suppression as distinct from those photoreceptors of the visual system, indicating probable involvement of a novel photoreceptor in circadian phototransduction. Both figures are reprinted with permission from [23, Copyright 2001 by the Society for Neuroscience].

Finally, five recent action spectra developed in separate animal and human studies found a common 446-484 nm region of peak sensitivity for: melatonin suppression in humans; electroretinogram B-waves in humans; pupillary constriction in rodless, coneless mice; and direct retinal ganglion cell response to light stimuli in rats [23-27]. When interpreting these studies in

4. NON-CLINICAL APPLICATIONS OF LIGHT THERAPY: JET LAG, SHIFT WORK, SPACE FLIGHT

In addition to the treatment of clinical disorders, the utility of light therapy for resolving problems associated with intercontinental travel, shift work and space flight are currently being evaluated. Traveling across time zones can interfere with social and business schedules, disrupt circadian rhythms, and consequently impair both physical and psychological health. 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 [6, 64]. 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 [64]. While the benefit of light in alleviating jet lag seems likely, the best way to use light for minimizing symptoms remains uncertain. If timed properly, bright light should accelerate re-entrainment of the circadian rhythm. Recently, a controlled field study tested light treatment of jet lag following a westward flight across 6 time zones (Zurich to New York). The data showed that a 3-hour exposure to a bright white light of 3000 lux during the first two evenings at the New York destination accelerated circadian re-entrainment [65]. Further studies, however, are still needed in order to determine how to best use light for this malady.

Similar to intercontinental travelers, shift workers are also forced to make changes to their usual sleep and wake times. However, circadian disruption in shift workers is generally longer lasting and therefore, the body also requires a longer period of time to readjust. Shift work is a term used to describe a job that involves any type of non-standard schedule and may include evening or night work, rotating shifts with constantly changing hours, split shifts and extended duty (usually over 12 hours). It has been estimated that approximately 20% of workers in industrialized nations participate in some form of shift work [6, 66]. Certain industries such as police, healthcare, military and telecommunications require 24 hours a day, seven days a week of constant operation. In addition, many companies have strong economic incentives for incorporating shift work into their schedule and progressing towards continuous operation. Despite the economic value of shift work, it can lead to problems of decreased productivity, increased accidents, and serious health consequences. It has been observed that shift workers have a higher incidence of cardiovascular disease and gastrointestinal distress as well as cognitive and psychological problems [6, 66]. Many researchers hypothesize that these ailments are caused, in part, by difficulty adjusting to a night shift or rotating schedules. In addition, there is a potential link to breast cancer in women who are exposed to light at night, as is often the case with shift workers [67, 68]. The potential relationship between exposure to light at night and cancer risk will be discussed below in further detail. A number of studies have shown that properly timed exposure to light and darkness may enhance workers' circadian systems to adapt to shift schedules [47, 48, 66, 69-71]. The use of light treatment and scheduled exposure to darkness for shift work problems, however, is complex and requires further investigation.

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 enhanced behavioral and cognitive performance (reaction time, mathematical skills and complex problem solving) when working under 3000 lux of white light as compared to a dimmer light exposure of 100 lux [72]. In addition to behavioral differences, physiological measures such as body temperature, melatonin and cortisol levels were significantly different with bright versus dim light exposure [72]. Although most experiments have demonstrated the immediate alerting effects of bright light on humans [71-76], it is important to note that the acute performance- enhancing effects of bright light exposure have not been seen in all studies [77].

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 [78-81]. Disturbed circadian rhythms and altered sleep-wake patterns are major risk factors for the health and safety of astronauts. 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 [78-81]. Ongoing research continues to investigate how to optimize light as a countermeasure for circadian and sleep disruption in space flight missions. Emphasis has been on illumination of general living quarters as well as design of space vehicle windows, habitat windows, and space

suit visors for manned missions [82]. Results from such studies also may be relevant to general architectural lighting design on earth for civilian problems of shift work and jet lag.

5. EXPOSURE TO LIGHT AT NIGHT AS A POTENTIAL RISK FACTOR FOR CANCER

While optimizing light exposure for treatment of the various clinical and non-clinical applications is important, minimizing light exposure during certain times may be equally critical. Exposure to light at night has been proposed as a potential cancer risk factor due to the disproportionately high prevalence of breast cancer in industrialized nations [83, 84]. This theory is supported by the suppressive effects of nocturnal light on pineal melatonin and the decrease in melatonin production that has been associated with increased risk of breast cancer [13, 83-86]. Numerous epidemiological studies support this hypothesis as well, with observations of decreased breast cancer in blind women and increased breast cancer in women who do shift-work [67, 68, 87-91]. Congruent with these findings, there is also a significantly decreased incidence of breast cancer in regions where people are exposed to lower levels of ambient light due to the daytime darkness of extended winter seasons, [92].

A range of human, animal and *in vitro* studies also indicate an apparent relationship between light, melatonin and cancer, although the dynamic is still not fully understood [93-100]. A decrease in melatonin coupled with an increase in tumor growth has been observed in pre-operation breast cancer patients and in rats with chemically induced and transplanted mammary tumors [97, 98]. Carefully controlled studies on rats found that light administered during a usual dark period served not only to inhibit melatonin secretion, but also increased the rate of tumor growth [99, 100]. Although it is premature to make definitive conclusions regarding the possibility that nighttime light exposure is a risk factor for cancer in humans, the impact of circadian disruption may extend beyond sleeping disorders and winter depression to include risk of breast cancer and possibly other hormone-sensitive cancers. Ultimately, it may become necessary to adjust standards for nighttime lighting as our understanding of the relationships between light, circadian disruption and melatonin regulation progresses.

6. MEASURING LIGHT FOR NEUROENDOCRINE AND CIRCADIAN REGULATION

In general, characterization of light exposures for photobiological responses should include radiometric quantification of intensity and spectrum [101-106]. Direct measurement is commonly determined as a function of wavelength in the form of irradiance or photon density. When describing a light source with a narrow spectral bandwidth, the total power per unit area or total photon flux per unit area is sufficient to quantify the light. As the spectral bandwidth of the light stimulus increases, however, this becomes a less than adequate measure because photobiological responses vary significantly in their sensitivity to different wavelengths. A numerical characterization of the light can be calculated by weighing the spectral values by an action spectrum appropriate to the effect under consideration. For example, there are standard, defined spectral weighting functions for rods (night or scotopic vision) and cones (day or photopic vision) when characterizing light for visual responses [1, 2, 106].

In addition to supporting vision and visual reflexes, the human eye serves as a detector for non-visual information about light. When the acute light-induced suppression of melatonin suppression was first observed, there were no defined action spectra for circadian regulation or melatonin suppression in humans [14]. Consequently, photopic measures of light were often used as a surrogate measure in human studies of circadian and neuroendocrine physiology. Practically, recommended doses of light for therapeutic purposes have often been provided in terms of a given illuminance (lux) at a specified distance from the eye [49, 50, 58, 63, 65]. A recent human study has specifically demonstrated that using photometry for characterizing light for melatonin regulation is inappropriate [22]. Further, the two action spectra for human melatonin suppression confirm that the three cone photopic visual system is <u>not</u> the primary transducer of light stimuli for melatonin suppression in humans [23, 24]. Figure 3 illustrates a small portion of the data from one of the action spectra which shows that, relative to photopic visual sensitivity, the peak spectral sensitivity for melatonin regulation is shifted into the blue portion of the visible spectrum [23].

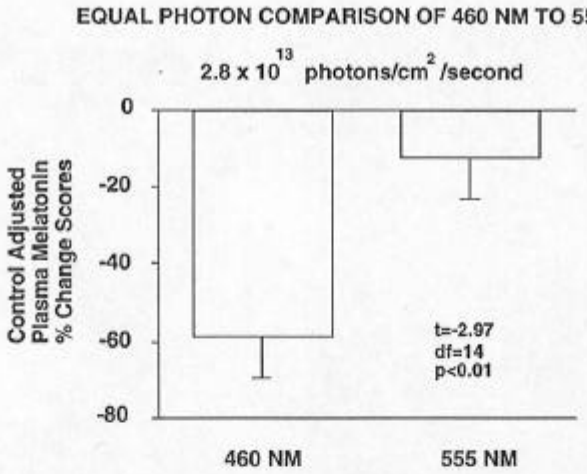

Figure 3. This graph provides a comparison of melatonin suppression in healthy male and female subjects following ninety minute exposures to 460 nm (n=8) and 555 nm (n=8) monochromatic light of equal photon densities (2.8 x 10^{13} photons/cm^2/second). The bars represent group mean + SEM control adjusted plasma melatonin percent change scores for 460 nm and 555 nm exposures. These data show that the 460 nm exposure elicits a significantly greater response, indicating that the peak wavelength sensitivity for the photopic visual system (555 nm) is not the most potent wavelength for light-induced melatonin suppression in humans [23].

These results suggest that the current standard practice of using photometric values (lux) to quantify light used therapeutically for affective disorders, sleep disorders, or circadian disruption due to shiftwork and jet travel may not be optimum. The need for a specific light measurement technique for human circadian regulation and light therapy has been known for a number of years [8, 22, 53] and is starting to be promoted within the lighting engineering community [107]. It should be noted, however, that the data presented here involve only the melatonin suppression response in healthy humans. It remains to be determined if there are similar wavelength sensitivities for circadian phase-shifting or light therapy for clinical disorders. Ultimately, the melatonin studies open the door for redefining how light should be measured relative to the circadian system.

7. CONCLUSION

Exploring the behavior of light and the physiology of vision has been a passion for philosophers and scientists for at least two millennia [108]. In contrast, the empirical study of the circadian, neuroendocrine and therapeutic effects of light is relatively recent - spanning only a few decades. Despite its relative youth, this field of study is critically important to understanding how to optimize lighting in places where people live and work. The rapid progress being made towards understanding photic input for circadian and neuroendocrine function in humans will help to clarify the connections between light, health and well being.

Visual performance, visual comfort and aesthetic enhancement of the built environment have traditionally been the primary focus of architectural lighting strategies. There is now enough information to warrant consideration of how to best utilize light in order to support, rather than disrupt, the natural environmental light-dark cycle and human biological rhythms. Consideration of light's impact on the human circadian and neuroendocrine systems when developing lighting standards may help reduce the occurrence of selected disorders such as winter depression, sleeping disorders, and breast cancer. It is now timely for the engineers, designers, manufacturers and architects to seize the opportunity to develop lighting strategies that optimize human health and well being.