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Ocular Input for Human Melatonin Regulation: Relevance to Breast Cancer

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Abstract

The impact of breast cancer on women across the world has been extensive and severe. As prevalence of breast cancer is greatest in industrialized regions, exposure to light at night has been proposed as a potential risk factor. This theory is supported by the epidemiological observations of decreased breast cancer in blind women and increased breast cancer in women who do shift-work. In addition, human, animal and in vitro studies which have investigated the melatonin-cancer dynamic indicate an apparent relationship between light, melatonin and cancer, albeit complex. Recent developments in understanding melatonin regulation by light in humans are examined, with particular attention to factors that contribute to the sensitivity of the light-induced melatonin suppression response. Specifically, the role of spectral characteristics of light is addressed, and recent relevant action spectrum studies in humans and other mammalian species are discussed. Across five action spectra for circadian and other non-visual responses, a peak sensitivity between 446–484 nm was identified. Under highly controlled exposure circumstances, less than 1 lux of monochromatic light elicited a significant suppression of nocturnal melatonin. In view of the possible link between light exposure, melatonin suppression and cancer risk, it is important to continue to identify the basic related ocular physiology. Visual performance, rather than circadian function, has been the primary focus of architectural lighting systems. It is now necessary to reevaluate lighting strategies, with consideration of circadian influences, in an effort to maximize physiological homeostasis and health.

Ocular Input for Human Melatonin Regulation: Relevance to Breast Cancer Risk

Breast cancer is the most common form of malignancy found in women and the second leading cause of cancer mortality. Based on epidemiological evidence collected from 1995 to 1997, the National Cancer Institute estimates that approximately 1 in 8 women in the United States will develop breast cancer during her lifetime. Identified risk factors for female breast cancer include: early age at onset of menarche, late age at onset of menopause, first full-term pregnancy after age 30, history of pre-menopausal breast cancer for mother and/or a sister, and a personal history of breast cancer or benign proliferative breast disease. Environmental conditions associated with technological advancements also appear to be indicative of an increased risk, with a much higher prevalence of breast cancer in industrialized regions as compared to that of developing nations. Consequently, theories about the potential role of exposure to light at night have been proposed [1, 2]. The theory that nighttime light exposure may be a risk factor for cancer is suggested by the suppressive effects of nocturnal light on pineal melatonin [3,4] and the decrease in melatonin production that has been associated with increased risk of breast cancer [5]. A wide range of human, animal and in vitro studies further support this theory [6].

Studies have repeatedly shown a simultaneous decline in melatonin and an increase in tumor growth in pre-operation breast cancer patients [7] and in rats with chemically induced and transplanted mammary tumors [8]. In addition, pinealectomy, which inhibits melatonin production, serves to promote growth of induced mammary cancers in rats [9,10]. Similarly, light administered during an otherwise normal dark phase also inhibits host melatonin secretion and increases the rate of tumor growth in rats [11, 12]. It is, therefore, not surprising that both physiological and pharmacological administration of melatonin demonstrate oncostatic properties [6]. Melatonin appears to inhibit mammary tumorgenesis in rats [13] and block estrogen-induced proliferation of human breast cancer cells [14]. One study found that large doses of melatonin did not inhibit estradiol-induced proliferation in vivo, and pinealectomy did not increase proliferation, suggesting that melatonin may not work directly to inhibit estradiol-induced proliferation [15]. While the mechanisms involved in the melatonin-cancer relationship remain uncertain, estradiol [15, 16,17], tumor fatty acid metabolism [18], and linoleic acid [12] appear to be important factors in the regulation of tumor progression. Taken together, recent studies indicate a complex dynamic between melatonin and breast cancer, although a relationship seems evident in certain experimental models [6].

Epidemiological evidence supports a correlation between light exposure and breast cancer, although the empirical demonstration of the melatonin link is absent from these studies. Women blind to light, for example, have a reduced risk of developing breast cancer [19, 20, 21, 22]. One study identified a dose-response relationship between visible light and breast cancer risk, with a progression in severity of visual impairment and thus, decreasing ability to perceive light, associated with a decreased risk of developing breast cancer in women [21]. In other studies, those exposed to light at night due to night and shiftwork showed a much higher incidence of breast cancer [23, 24, 25]. Another approach involved investigating the occurrence of breast cancer in regions where people are exposed to lower levels of ambient light due to the daytime darkness of extended winter seasons. As would be hypothesized, a significantly decreased prevalence of breast cancer was found within the Arctic population [26]. These epidemiological studies exploring light-cancer relationships, in conjunction with the previously described melatonin-cancer findings, offer enough information to warrant further investigation of the light-melatonin-cancer hypothesis. In that context, there is significant value to examining the regulation of melatonin by light in humans.

In almost all species, melatonin levels are high at night and low during the day [4, 27]. The natural light-dark cycle entrains neural activity via ocular input, serving to modulate the rhythmic synthesis and secretion of melatonin from the pineal gland. Input to this system follows the retinohypothalamic tract [RHT], a neural pathway distinct from that of the visual system [28]. The retina detects light information, and neural impulses are subsequently sent to the hypothalamic suprachiasmic nuclei [SCN], which serve as the primary circadian oscillators in the regulation of daily rhythms. Although predominantly anatomically separate, the visual and circadian pathways are functionally connected with a projection from the intergeniculate leaflet to the SCN [29]. Circadian information is ultimately transmitted from the SCN to the pineal gland via a multisynaptic pathway, with connections in the hypothalamus, spinal cord, superior cervical ganglion and post-ganglionic sympathetic fibers [28].

In addition to synchronizing the circadian melatonin rhythm, nighttime light exposure of the eye(s) can acutely disrupt activity of the pineal enzyme serotonin-N acetyltransferase and consequently, elicit a marked depression in circulating melatonin levels. The acute light-induced suppression of melatonin has served as a useful tool in studying many of the underlying mechanisms of circadian physiology [3, 4, 28, 30]. Early attempts, however, showed an inability of light to suppress melatonin in humans when light levels between 100 and 800 lux were utilized [31, 32, 33, 34]. In 1980, Lewy et al. evoked a strong suppression in human melatonin when employing sixty-minute exposures to 2500 lux of white light, but subjects exposed to 500 lux still did not demonstrate this effect [35]. While 500 lux is more than adequate for stimulating the human daytime (photopic) visual system, it was not enough to significantly suppress melatonin in that experiment.

It could be expected that different light levels would be required to elicit melatonin suppression as compared to visual stimulation since both an anatomical and functional dichotomy exist between the visual and circadian pathways [28, 29, 36, 37]. However, when later human studies controlled for factors not previously considered,

a suppressive response was observed with light levels as low as 100 lux of polychromatic white light [3, 39]. Some of the elements which have been shown to contribute to the effectiveness of photic stimuli in regulating melatonin include: the physical properties of the light stimulus, the geometrical relationship of the light stimulus to the eyes, consistency and direction of gaze, physical state of ocular tissues, pupil dilation, retinal field exposure, photoreceptor sensitivity, and potential spatial and/or temporal summation of light stimuli [3].

Currently, one of the best markers of the human circadian pacemaker is the plasma melatonin rhythm. Light exposure in the evening causes a phase-delay while light administered during late night/early morning hours results in a phase-advance [39]. Phase shifting by light exposure to the eyes, similar to acute melatonin suppression, demonstrates a characteristic intensity-dependent response [30, 40, 41]. Until recently, much higher levels of light have been required to evoke a phase shift of the circadian melatonin rhythm as compared to that needed to elicit an acute suppression of melatonin [42, 43, 44]. While the light required for phase-resetting once appeared to require very bright exposures of at least 2500 lux [46], more recent studies have found that as low as 100 to 180 lux of polychromatic white light can cause a phase shift of the human circadian clock [41, 47, 48].

When considering light-induced suppression of melatonin and its potential link to cancer risk, it may appear somewhat reassuring that higher illuminances of light are necessary to produce a circadian response as compared to that needed for visual stimulation. However, spectral characteristics of the light source further influence the amount of light needed to inhibit melatonin production [30, 49, 50]. Figure 1 illustrates the action spectrum for percent control-adjusted melatonin suppression in 72 healthy human subjects in the study completed by Brainard and colleagues [30]. This particular action spectrum is based on a set of fluence-response curves at eight monochromatic wavelengths between 440 nm and 600 nm. The fluence-response curve for any particular wavelength demonstrates a within-subjects comparison of eight subjects that each completed a series of seven or more nighttime melatonin suppression tests at varying irradiances. Data from each of the fluence-response curves was extracted, with the reciprocal of incident photons required for a half-saturation melatonin response plotted as a function of wavelength. The resulting spectral peak sensitivity at approximately 464 nm best fits a vitamin A_1 retinaldehyde opsin template, suggesting that a novel photoreceptor may be mediating circadian responses to light [30].

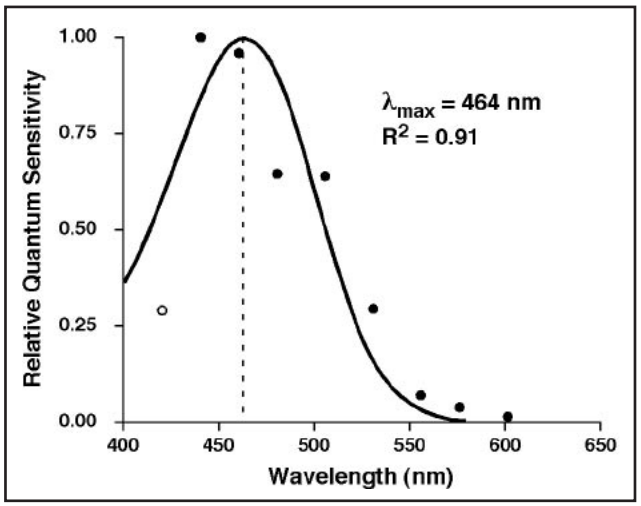

Figure 1. This figure illustrates the action spectrum for percent control-adjusted melatonin suppression in humans, with the dashed line indicating the calculated peak spectral sensitivity at 464 nm. The dark circles indicate the half-saturation constants of wavelengths of 440, 460, 480, 505, 530, 555, 575 and 600 nm, all of which were normalized to the maximum response and plotted as log relative sensitivity. The open circle represents the estimated half-saturation constant derived from an incomplete set of 420 nm data, based on a single light exposure and a control night. The solid curve represents the best-fit template for vitamin A_1 retinaldehyde photopigments, which predicts a peak spectral absorbance of 464 nm [52]. There is a high coefficient of correlation for fitting an opsin template to the melatonin suppression data (R^2 = 0.91). This figure is from Brainard et al. [30] and is reprinted with permission (Copyright 2001 by the Society for Neuroscience).

This study tested different monochromatic wavelengths of light at varying intensities and found that levels lower than 0.4 to 3.3 lux of monochromatic light in the blue wavelength region of the visible spectrum can significantly suppress melatonin in healthy humans [30]. Although similar light exposures may be very rare in ordinary domestic circumstances, that finding illustrates the high sensitivity to light of the human RHT and melatonin generating system when ocular exposure factors are optimized. There is also recent evidence to suggest that similarly low levels of white light (≤100 lux), may be enough to effect entrainment in humans as well [41, 51]. Table 1 provides the monochromatic light levels at eight tested visible wavelengths, each with narrow half-peak

Table 1. Radiometric and photometric equivalencies of light required to elicit the half-saturation constant (ED_{50}) of the percent-controlled adjusted melatonin suppression in humans at eight different wavelengths [30].

	440 nm	460 nm	480 nm	505 nm	530 nm	555 nm	575 nm	600 nm
Intensity ($\mu W/cm^2$)	2.42	2.41	3.43	3.28	6.75	27.7	46.6	110
Photon density (photons/(sec*cm^2))	5.35×10^{12}	5.59×10^{12}	8.28×10^{12}	8.33×10^{12}	1.801×10^{13}	7.75×10^{13}	1.35×10^{14}	3.33×10^{14}
Photopic lux (lm/m^2)	.39	1.01	3.29	9.21	39.3	188	290	475
Scotopic lux (Im/m^2)	13.5	23.3	46.2	55.2	92.4	192	132	67.9

bandwidths (10–14 nm), which were required to induce 50% melatonin suppression in humans [30]. This data demonstrates that much lower levels of light than initially thought can suppress high nocturnal melatonin levels, depending on the spectral qualities of the light source. In view of the possible link between light exposure, melatonin suppression and cancer risk, it is important to begin considering the consequences of nighttime light exposure with specific attention to the spectral characteristics of the source.

When fully characterizing a given light exposure, spectral qualities are an important consideration, particularly when examining photobiological responses. Therefore, direct measurement is commonly determined as a function of wavelength, in the form of spectral irradiance or spectral photon flux density. Although these measures are comprehensive, a single numerical characterization of light would be more convenient for purposes of interpretation and comparison. In the case of describing a light source with a narrow spectral bandwidth, total power per unit area or total photon flux per unit area is an adequate way to quantify the light. However, if the spectral bandwidth is wide, this is not an adequate measure because photobiological responses are variable in their sensitivity to different wavelengths. A numerical characterization of the light can be obtained by weighing the spectral values by an action spectrum appropriate to the effect under consideration. For example, in characterizing light for visual responses, there are standard defined spectral weighting functions for rods (night or scotopic vision) and cones (day or photopic vision).

In 1980, when light induced melatonin suppression was first observed, there were no defined action spectra for circadian regulation or melatonin suppression in humans [35]. Consequently, photopic measures of light were often used as a surrogate measure in human studies of circadian and neuroendocrine physiology. In an effort to place the results of a recent human melatonin action spectra in context with previously published studies, both radiometric and photometric measures have been provided in Table 1. Now that action spectra for human melatonin suppression have been published [30, 50], agreement upon a standard action spectrum would allow for a common basis for evaluation and comparison that would be both convenient and comprehensive in its consideration of spectral influences.

Five recent action spectra developed in separate animal and human studies may be relevant to understanding the potential role of light exposure in cancer development. Across these action spectra, a common reasonably narrow 446–484 nm region of peak sensitivity was identified for melatonin suppression in humans [30, 50], electroretinogram B-waves in humans [53], pupillary constriction in rd/rl mice [54], and direct retinal ganglion cell response to light stimuli in rats [55]. Although caution must be taken in interpreting these studies in relation to one another as they each examine distinct physiological responses in different species, all of the action spectra suggest the involvement of a novel photopigment in circadian phototransduction and other non-visual, ocular-mediated responses.

Other studies have identified a variety of novel candidate photopigments including vertebrate ancient opsin [56], encephalopsin [57], cryptochrome [58], and melanopsin [59, 60]. Among these novel opsins, melanopsin has been strongly implicated in circadian phototranduction. Melanopsin has been found in both the rodent and human retina [59, 60] and was further localized in the retinal ganglion cell bodies (RGCs) that project to the SCN [61, 62] as well as in an extensive retinal ganglion cell dendritic arbor [63]. In rats, ganglion cells with projections to the SCN were intrinsically responsive to light, and the light response mimicked that of photic entrainment and melatonin suppression [55]. These same photosensitive RGCs also contain melanopsin [64]. Together, the aforementioned studies indicate that these melanopsin-positive ganglion cells may be the primary photoreceptors involved in circadian regulation and perhaps, other non-visual responses in mammals.

Rapid progress is being made towards elucidating photic input for circadian regulation. As studies continue to clarify connections between light, melatonin and breast cancer risk, defining the basic related physiology becomes increasingly important. Visual performance, rather than circadian function, has traditionally been the primary focus of architectural lighting strategies. Failing to consider the impact of light on the human circadian system when developing lighting standards may result in a disturbance of homeostasis and in turn, a breakdown in physical health. Physiological consequences may not be limited to conditions such as sleeping disorders and winter depression, but may extend to breast cancer and other hormone-sensitive cancers. Less than 100 lux of polychromatic white light is sufficient to cause melatonin suppression in an acute fashion and phase shift circadian rhythms. That means that even common nighttime activities such as a late night out, use of the restroom during normal sleep times and mid-night awaking to check on a baby, may result in exposures to light of high enough levels to disrupt normal circadian cycles. The door has been opened to identifying the specific relevance of this information to cancer risk. Ultimately, it is critical to reevaluate the way lighting is employed for illuminating the indoor and outdoor environment.

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