Circadian rhythms are variations in physiology and behavior that persist with a cycle length close to 24 hours even in the absence of periodic environmental stimuli. It is hypothesized that this system evolved to predict and therefore optimally time the behavior and physiology of the organism to the environmental periodicity associated with the earth’s rotation. Because the cycle length, or period, of this endogenous timing system is near, but not exactly, 24 hours in most organisms, circadian rhythms must be synchronized or entrained to the 24-hour day on a regular basis. In most

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organisms, this process of entrainment occurs through regular exposure to light and darkness.

Early reports from studies of human circadian rhythms had suggested that humans were unlike other organisms, being relatively insensitive to light and more sensitive to social cues to entrain their circadian systems. However, subsequent studies, and reanalysis of results from those early studies, have found that the human circadian system is like that of other organisms in its organization and in its response to light, and is as sensitive to light as the circadian systems of other diurnal organisms. In this article, we review the results of studies over the past 25 years conducted in our laboratory and in those of others investigating the effects of light on the human circadian timing system.

NEUROANATOMY OF THE MAMMALIAN CIRCADIAN SYSTEM

Studies published in the early 1970s established the suprachiasmatic nucleus of the hypothalamus as the central circadian pacemaker in mammals.1–5 This pacemaker is composed of individual cells that, when isolated, can oscillate independently with a near-24-hour period.5,6 The suprachiasmatic nucleus receives direct input from the retina,7–9 providing a mechanism by which entrainment to light-dark cycles occurs. Investigators have recently described a subset of retinal ganglion cells that serve as photoreceptors for circadian and other non–image-forming responses (NIFs).10–12 These specialized retinal ganglion cells are distributed throughout the retina, project to the suprachiasmatic nucleus, are photosensitive, and contain melanopsin as their photopigment.13,14 While the photosensitive retinal ganglion cells can mediate circadian responses to light, evidence suggests that rod and cone photoreceptors can also play a role in circadian responses to light.15,16 The relative contribution of different photoreceptors to circadian responses is not yet well understood and is an area of intense research. It is likely that the intensity, spectral distribution, and temporal pattern of light can all affect the relative contribution of different photoreceptors to circadian responses. The same neuroanatomical features of the circadian system described in mammals are also present in humans.17–24

PHASE-DEPENDENT RESPONSE OF THE HUMAN CIRCADIAN SYSTEM TO LIGHT

Studies of the effects of light on the circadian system of insects, plants, and animals conducted from the late 1950s through the 1970s demonstrated that the timing of a light stimulus has an important influence on the direction and magnitude of response to that stimulus.25–28 Those studies indicated that the circadian system of both nocturnal and diurnal organisms is most sensitive to light during the biological night. Because humans sleep throughout most of their biological night, testing the influence of light on the human circadian system requires that in the sleep-wake cycle be shifted to deliver the light stimulus at the time of highest expected sensitivity. Because of prior reports suggesting that social cues influenced human circadian rhythms, that manipulation of sleep-wake timing was a concern in the earliest human light studies.29,30 For those reasons, we therefore conducted one of our earliest studies of the effect of light on the human circadian system on a subject whose circadian temperature rhythm had an unusual phase relationship to her sleep-wake cycle.31 We identified a subject whose sleep-wake cycle timing was fairly normal, but whose circadian core body temperature rhythm was several hours earlier than normal, resulting in much of her biological night occurring before the time she went to bed. In the experiment we conducted, the subject was exposed to several hours of light every evening for a week, and the timing of her rhythms of core body temperature and plasma cortisol were assessed before and after that week of evening light exposure. Both rhythms were shifted by approximately 6 hours, and examination of temperature data collected throughout the experiment suggested that the shift had already occurred after only 2 days.

This finding that light could have this rapid and strong effect on the timing of human circadian rhythms led us to conduct a series of studies in normal young adults to whom we applied a series of light stimuli over 2 to 3 days.32,33 In those studies performed in the late 1980s, we held the intensity, spectral distribution, and duration of the light stimulus constant, but varied the time at which the initial stimulus was applied. To do this, we had to shift the timing of the sleep-wake cycle so as to be able to present light stimuli across the entire 24-hour circadian cycle. In the course of doing these initial experiments, we were attempting to produce a phase-response curve (PRC).28 Our results were not surprising in some ways, but surprising in others. We found that humans, like other organisms, are most sensitive to light stimuli during the biological night, and far less sensitive to light in the middle of the biological day.32,34 We also found that when humans are exposed to a light stimulus in the late-biological-day/
early-biological-night, that stimulus produces a phase-delay shift (a shift to a later hour), and light stimuli presented in the late-biological-night/early-biological-day produce phase-advance shifts (shifts to an earlier hour).

What was somewhat unexpected in those studies was the large magnitude (up to 12 hours) of the phase shifts we were able to achieve, and the PRC that was developed from those three-cycle light stimuli was a type 0 (strong) PRC. A type 0 PRC is characterized by large phase shifts of 12 hours forward or backward, with no “cross-over” point between maximal delays and maximal advances. Type 0 resetting also implied that the phase shift had been produced via changing the amplitude of oscillation of the underlying pacemaker. When we subsequently conducted additional experiments to test the phase shifts that could be achieved with a two-cycle stimulus, we found that in some studies we could markedly reduce the amplitude of the core body temperature and cortisol rhythms. This finding suggested that the stimulus affected the amplitude of the underlying circadian pacemaker, lending additional support to the idea that the phase shifts to the strong three-cycle stimulus were type 0.

Since describing that PRC to a strong light stimulus, we and others have conducted PRCs to stimuli consisting of one light pulse. In the late 1990s, we constructed a human PRC study to a single 6.5-hour light stimulus. Results from those studies indicated a type 1 PRC, with a shape and magnitude consistent with type 1 PRCs from other organisms. Type 1 PRCs are characterized by a lower amplitude than type 0 with smaller maximal phase shifts, as well as by a crossover point between maximal delays and advances. In the human PRC to the 6.7-hour stimulus, the maximal phase shifts were 2 to 3 hours. There was a phase-delay region in the late-biological-day/early-biological-night, a phase-advance region in the early biological day, small phase shifts during the middle of the biological day, and a transition point toward the end of the biological night (Fig. 1).

Evidence from studies in insects shows that both type 0 and type 1 PRCs are possible in the same species, with the PRC type dependent on the strength of the light stimulus, and the organisms in which type 0 resetting has been demonstrated also show type 1 resetting to a weaker stimulus. In fact, the type 1 and type 0 PRCs of humans are remarkably similar to those of mosquitoes (see article by Czeisler and Wright for illustration of the human and mosquito PRCs).

Additional studies and analyses conducted in our laboratory have also revealed additional features of the human phase-dependent response to light. We have found that humans, like other diurnal species, are sensitive to light throughout the biological day, with little evidence of a so-called “dead zone” (a segment of the PRC during the biological day when no responses are observed). Our analyses have also found that phase shifts to light in humans appear to occur rapidly, with little evidence of transients. Together, these studies of the phase-dependent response of humans to light have reinforced the idea that the human circadian system is like that of other organisms.

### INTENSITY-DEPENDENT RESPONSE OF THE HUMAN CIRCADIAN SYSTEM TO LIGHT

Reports from studies in nonhuman organisms indicated that the circadian system showed intensity-dependent responses to light stimuli, in
addition to its phase-dependent responses to light. Investigation of the intensity-response relationship to light is typically done by applying light stimuli of varying intensities but of the same duration and spectral composition at a fixed circadian phase. Early reports from human studies had demonstrated that varying the intensity of a light stimulus would produce different amounts of suppression of the pineal hormone melatonin.58–61 Based on this animal and human evidence, we conducted a series of studies, beginning in the late 1980s,62 to test the ability of different intensities of light to phase shift the human circadian system.

In the first series of studies, we applied a three-cycle 5-hour light stimulus in the early biological day (the phase-advance portion of the PRC), and studied groups of subjects at several different illuminance levels (0, 12, 180, 600, 1260, and 9500 lux; Fig. 2). In those studies,53–65 we found that the groups exposed to light greater than room-light level showed a significant phase-advance shift, while the groups exposed to darkness or dim light (the 12-lux group) for the same three-cycle 5-hour stimulus timing drifted to a later phase consistent with the longer-than-24-hour period of the human circadian system.66 The 0-lux and 12-lux control groups also confirmed that the phase shifts produced by the light were mainly due to the light exposure itself, and not to the shift in the timing of the rest-activity schedule.67

Subsequently, we conducted another study testing the effect that a single light-exposure would have on the human circadian system when the illuminance was varied.68 In this study, we used a 6.5-hour light stimulus ranging from 3 to 9100 lux, applied in the late-biological-day/early-biological-night, so as to produce phase-delay shifts. We found that the resetting response and melatonin suppression was related in a nonlinear way to illuminance, with minimal responses below 100 lux and saturating responses above approximately 1000 lux. The best model fit to the data was from a four-parameter logistic model, which predicted a half-maximal response of approximately 100 lux, in the range of normal indoor light.68 A similar study conducted in healthy older subjects found similar responses to low and high levels of illumination, with a suggestion of slightly less sensitivity in the older subjects compared with that in the younger adults.69

In the one-pulse study in young adults, we also examined the relationship between illuminance and measures of alertness, and found that brighter light had greater effects on subjective and objective measures of alertness.70

Findings from all of these studies indicate that the human circadian system can be sensitive to rather dim levels of light, including candlelight.71 In fact, in the one-pulse study by Zeitzer and colleagues,68 phase shifts of 50% magnitude of the maximal shift (obtained with a 9100-lux stimulus) were obtained with stimuli of only about 1% of that intensity (~100 lux). However, we should note that the light stimuli in these studies were presented after exposure to many hours of very dim light or darkness, and, as we discuss below, this prior exposure to dim light likely sensitized the system. Thus, while an approximately 100-lux light pulse applied after several hours of very dim light

Fig. 2. Phase shifts (A) and melatonin suppression (B) in response to a three-cycle 5-hour light stimulus in young adults. The magnitude of the phase shift (in hours) is plotted with respect to the illuminance of the light stimulus (in lux). Symbols represent mean (± standard error of the mean) responses from each group of seven to nine subjects. The solid line represents a three-parameter logistic curve fit to the data, and the upper and lower 95% confidence intervals of this fit are shown in the dashed lines. (From Zeitzer JM, Khalsa SB, Boivin DB, et al. Temporal dynamics of late-night photic stimulation of the human circadian timing system. Am J Physiol 2005;289(3):R839–44; with permission.)
does have a significant phase-shifting and melatonin-suppressing effect in humans, the same light pulse applied against a brighter background would likely produce a smaller effect.

**RESPONSE OF THE HUMAN CIRCADIAN SYSTEM TO INTERMITTENT BRIGHT-LIGHT EXPOSURE**

Studies of light effects in mammals had demonstrated that brief pulses of light could affect the circadian system, and that the system appeared to integrate brief light pulses applied in sequence.46,55,72 We conducted experiments to explore whether the human circadian system is responsive to short-duration stimuli, and if the human circadian system is capable of integrating short-light stimuli,73,74 In the first such experiment,73 we used a three-cycle light stimulus applied in the phase-advance region (late-biological-night/early-biological-day) of the PRC, and tested two different light-stimulus patterns. The first pattern used four periods of light stimuli, each about 46 minutes, alternating with episodes of darkness, each about 44 minutes, so the entire pattern took 5 hours. The second light-stimulus pattern used briefer stimuli, with 13 5.3-minute periods of light stimuli alternating with 19.7-minute episodes of darkness. We compared the results of these two intermittent-light patterns with results from two groups in which we used a continuous 5-hour bright-light stimulus or a continuous 5-hour darkness stimulus.67 Even though the duration of bright light in the two intermittent-light groups was only 63% or 31% of that for the continuous-light group, respectively, we still observed significant phase-advance shifts (Fig. 3). The intermittent-light group that received 63% of the light duration showed phase shifts that were not significantly different from those for the continuous-light group, with a response approximately 88% of that of the continuous-light group. The intermittent-light group with the shorter light duration (31%) showed phase advances that were approximately 70% of the magnitude of the continuous-light group. These findings demonstrated that humans were responsive to shorter durations of bright-light exposure than had been previously recognized, and that the magnitude of the response was related in a nonlinear way to the duration of light contained within the stimulus.75,76

We also conducted an experiment testing the effects of an intermittent-light stimulus using a one-cycle light stimulus.74 In that study, we used a 6.5-hour stimulus presented in the phase-delay region (early biological night), and compared subjects exposed to continuous bright light, continuous very dim light, and intermittent light. The intermittent-light pattern consisted of six 15-minute bright-light pulses separated by 60 minutes of very dim light, and therefore contained 23% of the duration of the continuous bright-light stimulus. We found that both groups exposed to light phase delay shifted by a significant amount, and that the magnitude of the phase delay was not significantly different between the two groups, with approximately 75% of the resetting response achieved with 23% of the bright-light duration. When suppression of melatonin by the intermittent-light stimuli was examined, we found that melatonin was suppressed within 5 minutes of the start of each light stimulus, that each subsequent light pulse suppressed melatonin by a similar percentage, and that melatonin levels began to increase within 10 minutes after each light pulse ended.77

The finding from these studies—that the human circadian system is responsive to very short pulses of light—has many practical implications. It suggests that light treatments can be shortened or interrupted without reducing their effectiveness,
and it also suggests that brief exposures to bright light may greatly influence entrainment to the 24-hour day. In fact, studies of natural light exposure in humans living in a number of different cities have found that most people get relatively little bright-light exposure. How such patterns of brief and intermittent exposure to outdoor levels of light influence phase angle of entrainment in modern humans is currently not well understood, but available evidence suggests that prolonged exposure to outdoor light each day can have a significant influence on both sleep timing and the timing of hormonal secretion.

Intermittent bright-light stimuli have been tested as a method to adapt the circadian rhythms of shift workers to a night-work–day-sleep schedule. Reports from such studies have indicated that intermittent bright light during night work can aid in adjusting the circadian system to a night work schedule although the bright-light groups in those studies were also required to be in darkness at specified daytime sleep times. Given that the scheduling of daytime darkness/sleep can itself aid in adaptation to a night work schedule, it is not clear whether it was the intermittent bright light, or the combination of intermittent light and scheduled sleep/darkness that produced better adjustment to the night work schedule.

**WAVELENGTH SENSITIVITY OF THE HUMAN CIRCADIAN SYSTEM**

Photic resetting of the circadian system is part of a larger class of NIFs to retinal light exposure that have been observed in both humans and in other mammals. After studies in animals had suggested a role for a nonrod, noncone photoreceptor in circadian responses to light, melanopsin was identified as the photopigment present in those specialized photoreceptors. Studies of light suppression of melatonin secretion in humans had identified a short-wavelength peak in spectral sensitivity of that response, suggesting that human NIF responses were also mediated by a melanopsinlike photopigment. In fact, several years earlier, we had reported that some blind humans could show NIF responses to light, retaining an ability to show melatonin suppression in response to ocular light exposure at night and that light could phase-shift the circadian rhythms in some blind individuals.

To explore whether human phase-shifting to light would show a short-wavelength sensitivity, a study was conducted in our laboratory in which a 6.5-hour exposure to monochromatic light was applied in the phase-delay region in sighted human subjects. Responses to monochromatic light of 460 nm and 555 nm of equal photon density were compared, and we observed that both phase-shifting and melatonin suppression were significantly greater in the subjects exposed to 460-nm light than in those who received 555-nm light. We also found that during the 6.5-hour light exposure, subjects exposed to the 460-nm light rated themselves as significantly more alert and showed faster reaction times, fewer lapses of attention, less electroencephalographic delta power, and more electroencephalographic high-alpha power than subjects exposed to 555-nm light. This was consistent with a greater alerting effect of the short-wavelength light. More recently, a study conducted in our laboratory reported that NIFs to light in two blind individuals was short-wavelength sensitive.

While these studies provide additional evidence that the human circadian system includes a short-wavelength–sensitive photoreceptor, as in other mammals, they do not rule out the role of visual photoreceptors in mediating circadian responses to light in humans. The relative contribution of different photoreceptors to circadian light responses is not yet well understood, and may depend on the intensity and duration of exposure.

**ADAPTATION OF THE HUMAN CIRCADIAN SYSTEM TO PRIOR LIGHT-DARK EXPOSURE**

Studies in humans and animals have provided evidence that prior exposure to light and darkness influences the response of the circadian system to light. We have conducted several recent studies to examine systematically how the duration and relative intensity of prior light exposure affect the subsequent response to a light pulse. In a study we conducted recently, we exposed subjects to a 6.5-hour 200-lux light stimulus during the biological nighttime, and measured the degree of melatonin suppression. Before the light stimulus, subjects were in a background light that was very dim (~0.5 lux) or of room intensity (200 lux, the same intensity as the light stimulus) for 15 hours. Exposure to the dim background resulted in significantly greater melatonin suppression in response to the 200-lux light stimulus than did exposure to 200-lux background light. The design of that study did not allow for an estimate of phase-shifting response, but a subsequent study conducted in our laboratory using a modified design has examined both melatonin suppression and phase-shifting responses to a light stimulus following a dim-light or a room-light background. Preliminary results from that recent study show phase-shifting results consistent...
with the melatonin-suppression findings from our earlier report.111

Studies in circadian photoreceptors suggest a mechanism by which the response observed in human studies may occur. Those studies have demonstrated that the response of those photoreceptors is influenced by prior light history, demonstrating larger responses to light stimuli after dim-light exposure, and reduced responsiveness to light stimuli after bright background-light exposure.110

Together, these findings suggest that the overall 24-hour pattern of light and darkness to which humans are exposed plays a role in subsequent sensitivity to light exposure, and thus in entrainment. These findings also suggest that the circadian system of individuals who get little bright-light exposure may become more sensitive to moderate levels of light.105 Given that most studies show that modern humans get relatively little bright-light exposure and instead spend most of their waking day in light of indoor intensity,79–83 these findings may have very important practical relevance for most humans.

**ENTRAINMENT OF THE HUMAN CIRCADIAN SYSTEM BY LIGHT**

As we outlined above, regular exposure to light and darkness is the primary synchronizer of the human circadian system to the solar day. On average, the period of the human circadian system is longer than 24 hours.66,71,78,113–119 This means that for the circadian system to remain in synchrony with the external environment, it must for most people be reset by a small phase-advance shift each day. For individuals whose circadian period is shorter than 24 hours, entrainment is achieved through a phase-delay shift.120

Entrainment theory states that the range of entrainment is related to the strength of the synchronizing signal, meaning that a weak synchronizer will be able to entrain individuals whose periods are very close to 24 hours, but a stronger synchronizer is required to entrain those individuals whose periods are further over or under 24 hours.35,121 Furthermore, this theory holds that the phase angle of entrainment is related to the strength of the synchronizing signal, and evidence for this has been obtained in animals.121–123

By the late 1990s, studies by our group and those of others had demonstrated that humans show a range of circadian periods close to, but on average slightly longer than, 24 hours,66,113–117 and also that humans show differences in phase angle of entrainment.124–126 We had also reported that in young humans there is a relationship between circadian period and phase angle of entrainment,127 in accordance with entrainment theory. We therefore embarked on several studies to explore entrainment in humans.

In the first such study, we examined whether humans could entrain to a very weak synchronizer (light of ~1.5 lux in the angle of gaze), and tested that ability using three different day lengths.71 We found that most (five of six) subjects tested could entrain to a 24.0-hour day in this very weak synchronizer, but that subjects studied on a 23.5- or 24.5-hour day length did not remain entrained.

We also conducted two other studies in which we examined how phase angle of entrainment in humans is related to circadian period, and how light intensity affects this relationship.78,119 In the first of these studies, phase angle was assessed following a variety of routines, including a normal routine at home with uncontrolled lighting, following exposure to a very strong synchronizer throughout the waking day for 5 days, and after 24 hours in very dim (~1.5 lux in the angle of gaze) light. We found, as in our prior study,127 that phase angle of entrainment is significantly associated with circadian period, such that individuals with shorter periods have a longer interval between evening melatonin onset and usual bedtime than those individuals with longer periods.119 We also found that when a very strong synchronizer was applied, the range of phase angles was reduced, but the relationship between phase angle and period was still present.

In a subsequent entrainment study, we examined the ability of synchronizers of different strengths to entrain human circadian rhythms to a longer-than-24-hour day.78 In this study, we first assessed the period of each subject, and then randomized them to one of three groups, each with a different synchronizer strength. The synchronizers were then applied during a month when the each subject was scheduled to a day length 1 hour longer than the subject’s circadian period, so that the entrainment challenge was the same for all subjects. We found that most (three of four) subjects living in 25 lux of light were unable to entrain to the imposed day that was 1 hour longer than their circadian period, but all subjects living under 100 lux of light were able to entrain. As would be predicted by entrainment theory, the subjects who entrained to the longer day showed a phase angle that was different from the one they had at the beginning of the study.

Together, these entrainment studies demonstrated that the human circadian system is much like that of other organisms, and that light strongly...
influences the phase angle of entrainment in humans. This information has implications for understanding and developing treatments for circadian-rhythm sleep disorders.128,129

SUMMARY

As we have outlined above, over the past 3 decades studies in our laboratory and elsewhere have revealed a wealth of information about how light affects the human circadian system. Knowledge from these studies has improved our understanding of entrainment of human circadian rhythms to the 24-hour environment, has revealed important insights into circadian-rhythm sleep disorders, and has allowed for the design of light-treatment regimens for night workers, jet travelers, and patients with circadian-rhythm sleep disorders.89,90,130–135

Additional laboratory and field studies are still necessary to better understand some features of the human circadian response to light. We are only beginning to understand how prior exposure to light affects the subsequent response to a light stimulus, and our understanding of how light exposure can affect the period of the human circadian system is also limited.136 In addition, little is known about individual differences in circadian sensitivity to light, nor do we understand how polymorphisms in so-called “clock genes” (or other genes) affect sensitivity to light. Furthermore, while some of our knowledge has been translated into light-treatment regimens for circadian-rhythm disorders, many of the current treatments are impractical, and development and testing of lighting devices and treatment plans that optimize outcomes with shorter and more effective exposures are required. Such studies are time consuming and expensive to conduct in human subjects, but additional well-controlled laboratory-based studies where light-response phenotyping and genotyping are conducted in tandem are still necessary to fully understand the effects of light on the human circadian system and to translate this knowledge into optimized light treatments.

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REFERENCES


95. Lucas RJ, Foster RG. Neither functional rod photoreceptors nor rod or cone outer segments are required for the photic inhibition of pineal melatonin. Endocrinology 1999;140(4):1520–4.

