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Effect of Light on Human Circadian Physiology

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Synopsis

The circadian system in animals and humans, being near but not exactly 24-hours in cycle length, must be reset on a daily basis in order to remain in synchrony with external environmental time. This process of entrainment is achieved in most mammals through regular exposure to light and darkness. In this chapter, we review the results of studies conducted in our laboratory and others over the past 25 years in which the effects of light on the human circadian timing system were investigated. These studies have revealed, how the timing, intensity, duration, and wavelength of light affect the human biological clock. Our most recent studies also demonstrate that there is much yet to learn about the effects of light on the human circadian timing system.

Keywords

biological rhythm; core body temperature; illuminance; melatonin; phase response curve

Introduction

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 in order 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, in most organisms, not exactly 24 hours, circadian rhythms must be synchronized or entrained to the 24-hour day on a regular basis. In most 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 re-analysis of results from those early studies, have found that the human circadian system is like that of other organisms in its organization and its response to light, and is as sensitive to light as other diurnal organisms. In this chapter we review the results of studies conducted in our laboratory and others over the past 25 years in which the effects of light on the human circadian timing system were investigated.

Neuroanatomy of the mammalian circadian system

Studies published in the early 1970's established the suprachiasmatic nucleus of the hypothalamus as the central circadian pacemaker in mammals (1–5). This pacemaker is comprised of individual cells which, when isolated, can oscillate independently with a near-24-hour period (5;6). The SCN receives direct input from the retina (7–9), providing a mechanism by which entrainment to light-dark cycles occurs. Recently, a subset of retinal ganglion cells has been described that serve as photoreceptors for circadian and other non-image-forming responses (10–12). These specialized retinal ganglion cells are distributed throughout the retina, project to the SCN, are photosensitive, and contain melanopsin as their photopigment (13;14). While the photosensitive retinal ganglion cells can mediate circadian responses to light, there is also evidence that rod and cone photoreceptors can 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 this is an area of intense research currently. 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 1950's through the 1970's had 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 therefore required that in the sleep-wake cycle be shifted in order to deliver the light stimulus at the time of highest expected sensitivity. That manipulation of sleep-wake timing was a concern in the earliest human light studies, because of prior reports suggesting that social cues influenced human circadian rhythms (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 prior to 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 in which we applied a series of light stimuli over 2–3 days (32;33;33). In those studies carried out in the late 1980's, 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 in some ways were not surprising, but in other ways were. 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 3-cycle light stimuli was a type 0 (strong) PRC. A type 0 PRC is characterized by large phase shifts of + 12 hours, with no “cross-over” point between maximal delays and maximal advances (35). Type 0 resetting also implied that the phase shift has been produced via changing the amplitude of oscillation of the underlying pacemaker (36–39). When we subsequently conducted additional experiments to test the phase shifts that could be achieved with a 2-cycle stimulus, we found that in some studies we could markedly reduce the amplitude of the core body temperature and cortisol rhythms (40). This finding suggested that the amplitude of the underlying pacemaker was affected by the stimulus, lending additional support to the idea that the phase shifts to the strong 3-cycle stimulus were type 0 (41).

Since describing that PRC to a strong light stimulus, we and others have conducted PRCs to single light pulse stimuli (42;43;131;132). In the late 1990's, we constructed a human PRC

study to a single 6.7-hour light stimulus (42). 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 cross-over point between maximal delays and advances. In the human PRC to the 6.7-hour stimulus, the maximal phase shifts were 2–3 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 towards the end of the biological night [see Figure 1, reproduced from (42)].

There is evidence from studies in insects 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 (35;38;39). In fact, the type 1 and type 0 PRCs of humans are remarkably similar to those from the mosquito (44) [see (45) 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 (46), are sensitive to light throughout the biological day (34), 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 (34;47). 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 (48).

Intensity-dependent response of the human circadian system to light

Reports from studies in non-human organisms indicated that the circadian system showed intensity-dependent responses to light stimuli (25;49–55), 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 the same duration and spectral composition at a fixed circadian phase, but varying the intensity of the light. 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 (56–59). Based on this animal and human evidence, we conducted a series of studies, beginning in the late 1980's (60), 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 3-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 9,500 lux; see Figure 2, reproduced from (63)]. In those studies (61–63), 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 3-cycle 5-hour stimulus timing drifted to a later phase consistent with the longer than 24-hour period of the human circadian system (64). 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 (65).

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 (66). In this study, we used a 6.5-hour light stimulus ranging from 3 to 9,100 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 non-linear way to illuminance, with minimal

responses below 100 lux and saturating responses above ~1,000 lux. The best model fit to the data was from a 4-parameter logistic model, which predicted a half-maximal response of ~100 lux, in the range of normal indoor light (66). 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 the younger adults (67).

In the 1-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 (68).

Findings from all of these studies indicate that the human circadian system can be sensitive to rather dim levels of light, including candlelight (110). In fact, in the 1-pulse study by Zeitzer et al. (66), phase shifts of 50% magnitude of the maximal shift (obtained with a 9,100 lux stimulus) were obtained with stimuli of only ~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 and/or darkness, and as we discuss below, this prior exposure to dim light likely sensitized the system. Thus, while a ~100 lux light pulse applied after several hours of very dim light 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 (44;53;69). 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 (70;71). In the first such experiment (70), we used a 3-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 ~46-minute light stimuli interspersed with ~44-minute episodes of darkness, such that the entire pattern took 5 hours. The second light stimulus pattern used briefer stimuli, with 13 5.3-minute light stimuli interspersed 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 (65). Even though the duration of bright light in the two intermittent light groups was only 63% or 31% of the continuous light group, respectively, we still observed significant phase advance shifts [see Figure 3, reproduced from (70)]. The intermittent light group that received 63% of the light duration showed phase shifts that were not significantly different from the continuous bright 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 non-linear way to the duration of light contained within the stimulus (72;73).

We also conducted an experiment testing the effects of an intermittent light stimulus using a 1-cycle light stimulus (71). 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 were 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 was ended (74).

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 entrainment to the 24-hour day may be greatly influenced by brief exposures to bright light (34;75). 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 (76–80). 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 (81–83).

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 (133;134), 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 (127;128), it is not clear whether it was the intermittent bright light, or the combination of intermittent light and scheduled sleep/darkness that produced greater 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 non-image-forming responses (NIF) to retinal light exposure which have been observed in both humans and in other mammals. After studies in animals had suggested a role for a non-rod, non-cone photoreceptor in circadian responses to light, melanopsin was identified as the photopigment present in those specialized photoreceptors (10–13;23;84–87). Studies of light suppression of melatonin secretion in humans had identified a short wavelength peak in spectral sensitivity of that response (88;89), suggesting that human NIF responses were also mediated by a melanopsin-like photopigment. In fact, several years earlier, we had reported that some visually blind humans could show NIF responses to light, retaining an ability to show melatonin suppression in response to ocular light exposure at night (90), and that light could phase-shift the circadian rhythms in some blind individuals (91).

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 (92). Responses to monochromatic light of 460nm and 555nm of equal photon density were compared, and we observed that both phase-shifting and melatonin suppression were significantly greater in the subjects exposed to 460nm light than to those who received 555nm light. We also found that during the 6.5-hour light exposure, subjects exposed to the 460nm light rated themselves as significantly more alert, showed faster reaction times and fewer lapses of attention, and showed less EEG delta power and more EEG high alpha power than subjects exposed to 555nm light, consistent with a greater alerting effect of the short wavelength light (93). More recently, a study conducted in our laboratory has reported that non-image-forming responses to light in two visually-blind individuals was short-wavelength sensitive (24).

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 (15;16;94;95). 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 the response of the circadian system to light is influenced by prior exposure to light and darkness (96–102). We have conducted several recent studies in order to examine systematically how the duration and relative intensity of prior light exposure affect the subsequent response to a light pulse (103;104). 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 (103). 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 (104) show phase shifting results consistent with the melatonin suppression findings from our earlier report (103).

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 are 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 (102).

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 to 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 (97). 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 (76–80), 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 (64;75;105–112). This means that in order that the circadian system remains in synchrony with the external environment, in most people it must 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 (136).

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 away from 24 hours (35;113). Furthermore, this theory holds that the phase angle of entrainment is related to the strength of the synchronizing signal, and evidence for this had been obtained in animals (113–115).

By the late 1990's, studies conducted by our group and others had demonstrated that humans show a range of circadian periods close to, but on average slightly longer than 24 hours (64; 105–109), and also that humans show differences in phase angle of entrainment (116–118). We had also reported that in young humans there is a relationship between circadian period and phase angle of entrainment (119), 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 (110). 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 this relationship is affected by light intensity (75;112). In the first of these studies, phase angle was assessed following variety of routines, including a normal routine at home with uncontrolled lighting, following exposure to a very strong synchronizer throughout the waking day for five days, and after 24 hours in very dim (~1.5 lux in the angle of gaze) light. We found, as in our prior study (119), 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 (112). 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 (75). In this study, we first assessed the period of each subject, and then randomized them to one of three different synchronizer strength groups. The synchronizers were then applied during a month when the each subject was scheduled to a day length one hour longer than his 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 one 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 different phase angle than they had at the beginning of the study.

Together, these entrainment studies demonstrated that the human circadian system is very much like that of other organisms, and that phase angle of entrainment in humans is strongly influenced by light. This information has implications for understanding and developing treatments for circadian rhythm sleep disorders (120;121).

Summary

As we have outlined above, over the past three decades studies conducted in our laboratory and others have revealed a wealth of information about how the human circadian system is affected by light. The 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 (122–129).

Additional laboratory-based 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 (135). In addition, very little is known currently 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 therefore translate this knowledge into optimized light treatments.

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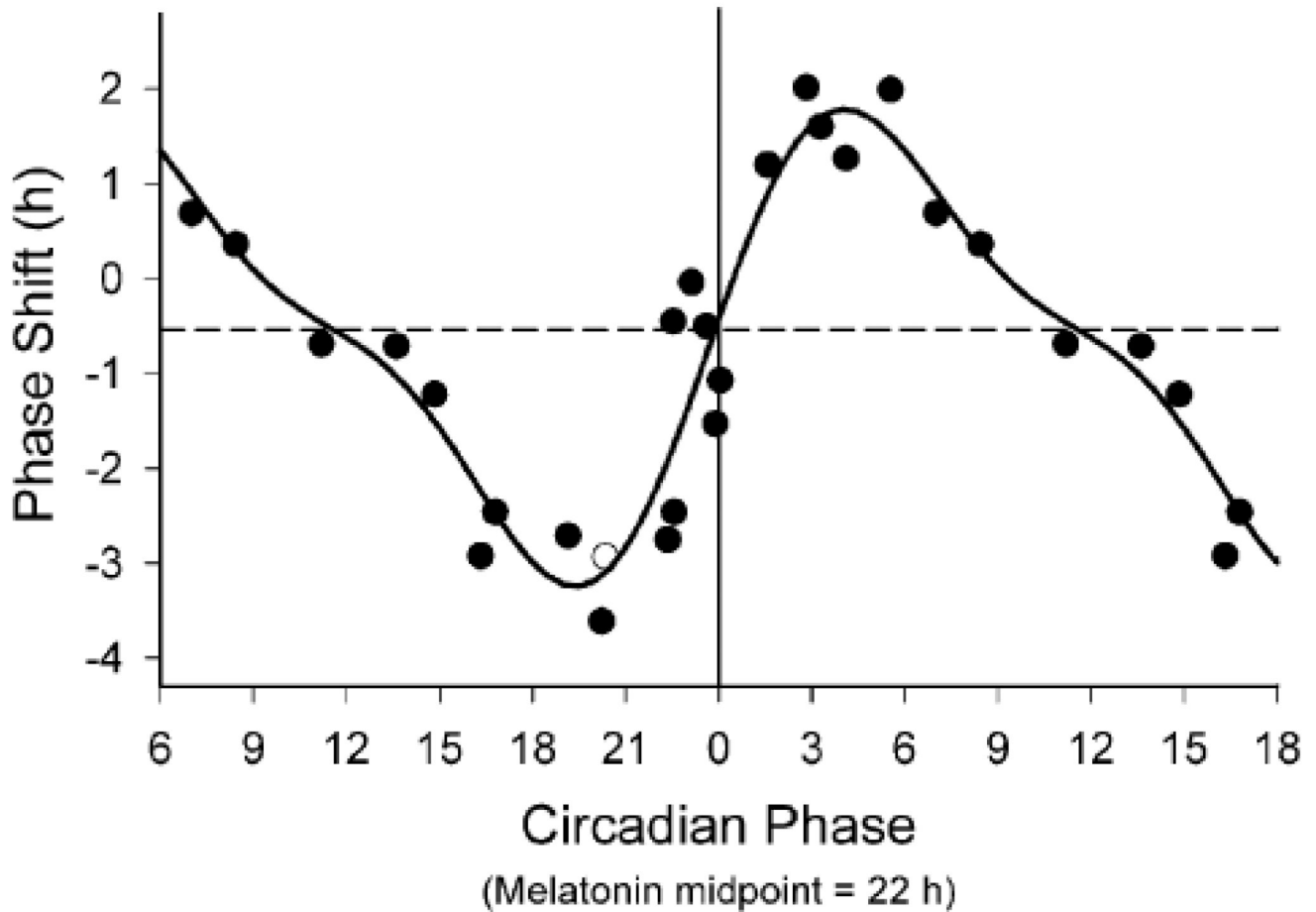


Figure 1.

Phase response curve to a single 6.5-hour episode of bright light in young adults. Phase shifts (in hours) of the plasma melatonin rhythm are plotted with respect to the circadian phase at which the center of the 6.5-hour light stimulus was presented. By convention, phase delay shifts (shifts to a later hour) are plotted as negative numbers, while phase advance shifts (shifts to an earlier hour) are plotted as positive numbers. Phase shift magnitude was determined by assessing phase before and after the light stimulus. Circadian phase of the light stimulus was defined relative to the midpoint of the plasma melatonin rhythm (defined as 22h) assessed just prior to the stimulus. Data from circadian phase 6–18 are double-plotted for better visualization. The open circle represents a subject whose phase shift was determined using salivary melatonin. The solid line represents a best-fit dual harmonic function to the data points. The dashed horizontal line represents the assumed 0.54-hour average phase delay drift of the human circadian pacemaker between the pre- and post-stimulus phase assessments. Figure reproduced with permission from Reference 42 [Khalsa SBS, Jewett ME, Cajochen C, and Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol (Lond)* 2003; 549(Pt 3):945–952].

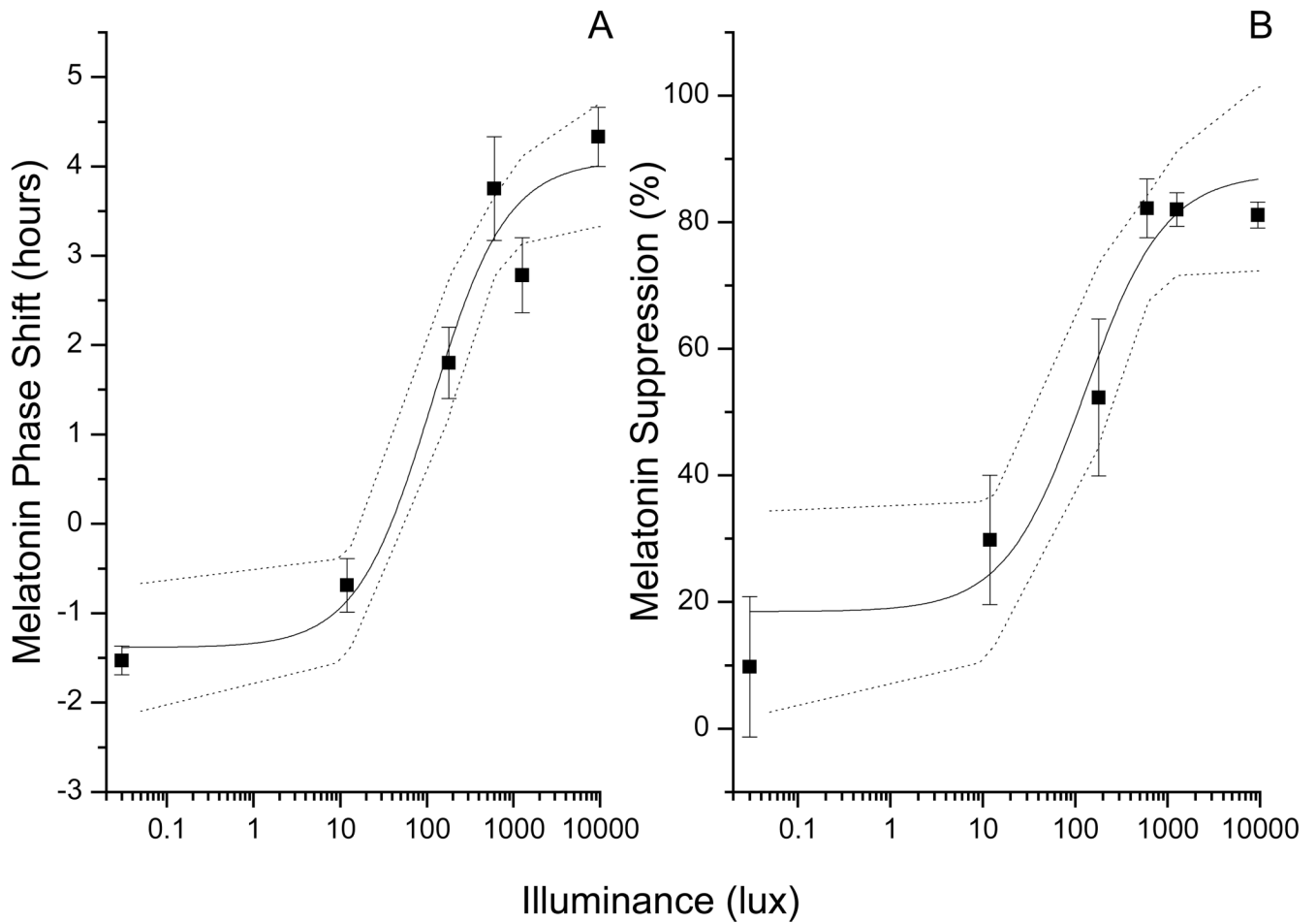


Figure 2.

Phase shifts (panel A) and melatonin suppression (Panel B) in response to a 3-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 (\pm s.e.m.) responses from each group of 7–9 subjects. The solid line represents a 3-parameter logistic curve fit to the data, and the upper and lower 95% confidence intervals of this fit are shown in the dashed lines. Figure reproduced with permission from Reference 63 [Zeitzer JM, Khalsa SB, Boivin DB, Duffy JF, Shanahan TL, Kronauer RE, and Czeisler CA. Temporal dynamics of late-night photic stimulation of the human circadian timing system. *Am J Physiol* 2005; 289 (3):R839–R844].

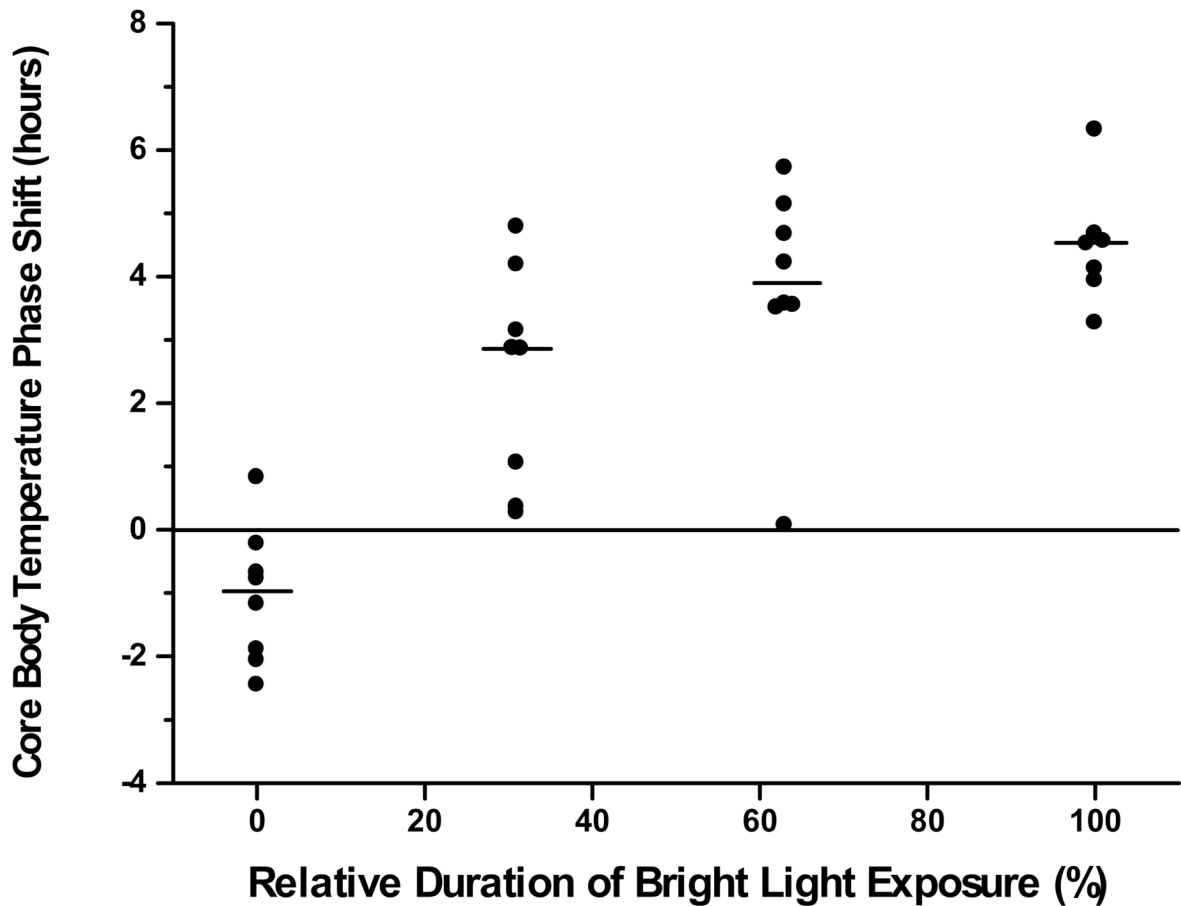


Figure 3.

Phase resetting responses to a 3-cycle 5-hour stimulus in young adults. The magnitude of the phase shift (in hours) is plotted with respect to the relative duration of the bright light exposure. The 0% group was exposed to complete darkness throughout the 5-hour stimulus and the 100% group was exposed to continuous bright light throughout the stimulus. Two groups received intermittent bright light exposure during the 5-hour stimulus: 5.3 minutes of bright light interspersed with 19.7 minutes of darkness (31% relative duration group); or 46 minutes of bright light interspersed with 44 minutes of darkness (63% relative duration group). Each point represents the response from 1 subject, and the horizontal bars represent the median phase shift for the group. Figure reproduced with permission from Reference 70 [Rimmer DW, Boivin DB, Shanahan TL, Kronauer RE, Duffy JF, and Czeisler CA. Dynamic resetting of the human circadian pacemaker by intermittent bright light. *Am J Physiol* 2000; 279(5):R1574–R1579]