Dynamic resetting of the human circadian pacemaker by intermittent bright light

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Rimmer, David W., Diane B. Boivin, Theresa L. Shanahan, Richard E. Kronauer, Jeanne F. Duffy, and Charles A. Czeisler. Dynamic resetting of the human circadian pacemaker by intermittent bright light. Am J Physiol Regulatory Integrative Comp Physiol 279: R1574–R1579, 2000.—In humans, experimental studies of circadian resetting typically have been limited to lengthy episodes of exposure to continuous bright light. To evaluate the time course of the human endogenous circadian pacemaker’s resetting response to brief episodes of intermittent bright light, we studied 16 subjects assigned to one of two intermittent lighting conditions in which the subjects were presented with intermittent episodes of bright-light exposure at 25- or 90-min intervals. The effective duration of bright-light exposure was 31% or 63% compared with a continuous 5-h bright-light stimulus. Exposure to intermittent bright light elicited almost as great a resetting response compared with 5 h of continuous bright light. We conclude that exposure to intermittent bright light produces robust phase shifts of the endogenous circadian pacemaker. Furthermore, these results demonstrate that humans, like other species, exhibit an enhanced sensitivity to the initial minutes of bright-light exposure.

circadian rhythms; core body temperature; phototherapy

Many advances have been made in understanding photic resetting of the human circadian pacemaker since it was initially recognized that light is the principal circadian synchronizer in humans (9, 12, 14, 18, 27, 34, 41). Photic induction of circadian phase shifts has been characterized extensively and is known to depend on several variables including the timing, duration, and intensity of retinal light exposure. Techniques of bright light administration gleaned from these principles have been implemented successfully not only in the laboratory setting but also in the treatment of a variety of disorders including maladaptation to night shift work, delayed and advanced sleep phase syndrome, circadian rhythm sleep disorders, dyssomnia associated with transmeridian travel and spaceflight, as well as age-related early morning awakening (3, 4, 7, 8, 10, 13, 17, 23, 34, 38, 40, 41). However, the use of bright-light therapy in these settings typically has consisted of 2- to 8-h continuous exposures. The imposition of time constraints involved in such extended exposures obviates the need to develop, on the one hand, more efficient means of delivering bright-light therapy, whereas on the other hand, retaining the ability to induce phase shifts of comparable magnitude to those obtained through extended exposures.

Much of the evidence supporting the notion that the endogenous circadian pacemaker may be sensitive to shorter durations of light exposure comes from animal models. In 1991, Nelson and Takahashi (35) demonstrated that the action of light as a synchronizer of the circadian clock in the golden hamster Mesocricetus auratus was most efficient during the first few minutes of the application and that further extension of the stimulus produced little additional phase shift. This finding was consistent with photic resetting properties observed in the mosquito (37). Furthermore, it has been reported that the circadian system of mice can integrate a chain of 60 very brief (2 ms) light pulses to cause circadian phase shifts of up to 2 h (42). Yet, the temporal dynamics of the circadian phase resetting response to light in humans remains unquantified. This is particularly notable because exposure to bright light is typically intermittent in everyday life (21, 26, 36, 39). Therefore, to characterize whether humans, like rodents and mosquitoes, have enhanced sensitivity to the initial minutes of intermittent light exposure, we undertook experiments to examine whether repeated brief exposures to ~9,500 lx of light produce robust phase shifts of the circadian timing system. We compared the phase shifts produced by those brief, repeated light exposures to those elicited by continuous light exposure and by darkness to estimate the temporal dynamics of the human circadian response to light. Our results reveal that the endogenous circadian timing system of humans is far more sensitive to shorter-duration light exposure than was previously recognized.

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MATERIALS AND METHODS

Subjects. Sixteen healthy men (24 ± 2.1 yr, means ± SD) were recruited for study using newspaper advertisements and billboard flyers. All subjects were free from any acute or chronic physical or psychiatric disorders. Medical suitability was determined on the basis of medical history, physical examination, ophthalmologic examination, and blood and urine chemistries. Psychological screening questionnaires, including the Minnesota Multiphasic Personality Inventory and the Beck Depression Inventory and State Anxiety Scale were used to exclude subjects with evidence of psychopathology from participation in the study. Individuals with a history of drug dependency, psychiatric illness, or affective disorder such as major depression or manic-depressive illness, were excluded from study. Subjects were asked to refrain from using alcohol, nicotine, prescription drugs, dietary supplements, and caffeine throughout the course of the study; urinary toxicological analysis was performed to ensure that subjects were drug free on admission to the laboratory. All subjects studied reported no recent history of regular nightshift work, and none reported crossing more than one time zone in the previous 3 mo. Subjects were asked to maintain a regular sleep-wake schedule for 3 wk at home before the study, such that their habitual bedtimes and wake times occurred at the same time (±30 min) each day and were 8 h apart. Compliance was verified by sleep-wake logs and wrist actigraphy monitoring for the week before the study. The protocols used were reviewed and approved by the Human Research Committee at the Brigham and Women’s Hospital, and each subject gave written informed consent before the start of the inpatient portion of the protocol.

Experimental protocol. Subjects underwent an experimental protocol designed to measure the phase-shifting effects of intermittent light on the endogenous circadian core body temperature cycle. All studies were performed in the Environmental Scheduling Facility of the General Clinical Research Center of the Brigham and Women’s Hospital. On empanelment in the 2-wk study, each subject underwent 3 adaptation days, with the time of their 8-h sleep episode schedule based on their habitual bedtime and wake time obtained from the prestudy sleep-wake logs. Beginning at wake time on the fourth day, subjects underwent a constant-routine (CR) procedure (detailed below) that consisted of 30–33 h of enforced wakefulness to assess the phase of the endogenous circadian core body temperature rhythm. The CR continued until 9.5 h after the fitted minimum of the core body temperature rhythm on day 5, at which time subjects were allowed to sleep for 8 h. For the next 3 consecutive days, subjects were then scheduled to undergo one of two intermittent bright-light conditions (detailed below) followed by a final CR assessment of endogenous circadian phase that lasted 40–50 h (Fig. 1).

From admission to the laboratory until 1.5 h before bedtime on day 3, subjects lived in ~150 lx of light during waking hours. From that point forward, room light intensity was lowered to ~10–15 lx during waking hours (except during bright-light-exposure episodes) for the remainder of the study. All sleep episodes were conducted in <0.02 lx (all reported light intensities were measured in the angle of gaze).

CR. We used the CR procedure to reveal the endogenous component of the circadian core body temperature rhythm. This methodology is a modification of the original technique used by Mills et al. (32) and has been successfully used to minimize or distribute evenly the potential masking effects associated with changes in activity, posture, sleep-wake state, diet, and ambient temperature across the circadian cycle (9, 12, 15, 33). When successfully employed, this technique affords an assessment of the output of endogenous circadian pacemaker, as reflected by the core body temperature rhythm. The CR procedure in these studies consisted of a regimen of enforced semirecumbent wakefulness with activity restricted to prevent changes in body posture. Daily caloric intake was calculated using the Wilmore nomogram (44) that was adjusted upward by an activity factor of 10% to maintain a consistent metabolic state across circadian phases. Sustenance was provided in the form of hourly snacks and liquid aliquots containing ~150 mmol of sodium and 100 mmol of potassium per 24-h period. A technician was present throughout the CRs to ensure compliance with the posture, activity level, and constant wakefulness aspects of the protocol.

Lighting regimen. Subjects were assigned to one of two intermittent lighting conditions that consisted of a three-cycle, 5-h episode of exposure to bright light (~9,500 lx in the angle of gaze) interrupted by episodes of complete darkness. This episode was centered on average 1.51 ± 0.08 h (means ± SD) after the initial endogenous temperature minimum and administered against a background of dim light (~10–15 lx). Within each 5-h episode, darkness episodes were repeated at 90- or 25-min intervals (duty cycle; Fig. 2, c and d). Subject comfort required that the light-dark transitions be effected with moderate stepwise changes that were spaced uniformly in time. As a result, the subjects were in darkness for ~44 min of the 90-min duty cycle or 19.7 min of the 25-min duty cycle. The effective duration of bright-light exposure for each 5-h intermittent stimulus together with the 25-min transitions before and after the 5-h stimulus was 63% or 31%, respectively, compared with the continuous bright-light protocol (see below). Results obtained from these two groups of subjects were compared with historical data from 15 volunteers (21.67 ± 3.54 yr, mean ± SD) who participated in the
same experimental protocol but were exposed to a 5-h stimulus consisting of either continuous (100%) bright light (Fig. 2b) or continuous (0%) darkness (control; Fig. 2e) (16).

Physiological monitoring. The bright-light stimuli were administered using ceiling-mounted cool-white fluorescent lamps (North American Philips Lighting, Bloomfield, NJ). Light measurements were performed using a research photometer (model 1700 and SED (SEL) 038/Y 7859/W 3339 detector; International Light, Newburyport, MA) held at the forehead and directed in the line of gaze. Subjects were outfitted with clear goggles throughout the 5-h intermittent light episodes (model #S379; Uvex Safety, Smithfield, RI) to exclude ultraviolet exposure.

Throughout the entire study, subjects were maintained in an environment free from time cues, and social contact was limited to the laboratory personnel who were specially trained to apply the physiological monitoring devices, administer light stimuli, ensure wakefulness, and shield the subjects from temporal information.

Core body temperature was recorded via disposable rectal thermistors (Yellow Springs Instrument, Yellow Springs, OH), and room temperature was recorded by a surface thermistor and maintained at 29.6 ± 0.9°C (mean ± SD). Both the core body temperature and room temperature were recorded at 1-min intervals by means of a real-time, online data-acquisition system using IBM PC-compatible, Pentium-based computers.

Statistical analysis. Circadian phase was estimated from the core body temperature data derived from the CRs by a dual-harmonic regression plus correlated noise model fit to the data by a nonlinear least-squares procedure (6). The first 5 h of CR temperature data were excluded from analysis to minimize the masking effects resulting from the transition from sleep to wake and postural changes associated with beginning the CR. Phase shifts were calculated as the difference (in hours) in the time of the fitted core body temperature minima between the first and second CRs. By convention, phase advances (to an earlier hour) are represented as positive phase shifts, whereas phase delays (to a later hour) are negative phase shifts. An ANOVA, with planned tests for linear and quadratic trends, as well as post hoc pairwise comparisons using Tukey’s method, were used to evaluate the effect of the intervention regimen on phase shifts between groups of subjects. In addition, the data were compared with the resetting responses predicted for the intermittent light stimulus by a mathematical model of the effect of light on the human circadian pacemaker (22), in which it was presumed that any given duration of light exposure exerts an intensity-dependent direct drive on the pacemaker, independent of the duration of prior light exposure (30).

RESULTS

As previously reported at that phase of light administration (12), all light-exposed groups demonstrated phase advances of their endogenous circadian rhythm of core body temperature. The median phase-advance shift observed was +2.87 h in the group of subjects exposed to the intermittent 31% bright-light duty schedule; +3.90 h in the group exposed to the intermittent 63% bright-light duty schedule; and +4.52 h in the group exposed to the 100% continuous bright-light stimulus, respectively (Fig. 3). A median phase delay of −0.97 h was observed in the 0% group of subjects exposed to continuous darkness, consistent with the slightly longer-than-24-h period of the endogenous circadian pacemaker (11, 16). Thus, compared with the
control 0% condition (darkness), the 31% intermittent bright-light duty schedule, the 63% intermittent bright-light duty schedule, and the 100% continuous bright-light stimulus duty schedule produced median phase shifts of +3.84, +4.87, and +5.51 h (individual phase shifts are reported in Table 1). The planned ANOVA revealed both a significant linear trend ($P < 0.0001$) and a significant quadratic trend ($P = 0.0104$), indicating that there was a significant nonlinear relationship between the relative duration of the bright-light exposure and the resetting response. The post hoc ANOVA for pairwise comparisons using Tukey’s method revealed that 1) the phase advance shifts in all light-exposed groups were significantly different from the change in phase observed for the 0% control group of subjects exposed to darkness ($P < 0.01$ in all cases); 2) the phase advances observed for the 63% intermittent bright-light group were not significantly different from those observed in the group exposed to 100% continuous bright light; and 3) the phase advances observed for the 31% intermittent bright-light group were significantly less than from those of the 100% continuous bright-light group ($P < 0.05$) but were not significantly different from the 63% bright-light group.

Figure 4 illustrates how these resetting responses compare with those predicted for the intermittent light stimulus by the direct drive model of the effect of light on the human circadian pacemaker (22).

DISCUSSION

This is the first laboratory-based study designed to quantify the temporal dynamics of circadian phase resetting by intermittent bright light in humans. Our findings demonstrate that the response of the human circadian pacemaker to short-duration light pulses is not different from those observed in other organisms (35, 37, 42) and necessitate the refinement of previous models describing human sensitivity to light.

Our results suggest that an intermittent bright-light stimulus, interrupted by intervals of complete darkness that substantially exceed the duration of the light exposure, can significantly phase shift the human circadian pacemaker. Surprisingly, when the bright-light exposure occupied only 31% of the stimulus, 70% of the median resetting response was preserved compared with the continuous stimulus. Furthermore, when the bright-light exposure occupied only 63% of the stimulus, nearly 90% of the median resetting response was preserved compared with the continuous stimulus. The results from the latter group are especially revealing. Although 37% of light was eliminated, only a 10% price was paid in the phase-shifting response. Such results are inconsistent with the “direct-drive” model that we had proposed, in which the effectiveness of bright light in phase shifting the endogenous circadian pacemaker was homogenous throughout the duration of the stimulus.

We have thus now proposed two alternative modifications to the direct-drive model to reconcile these new findings. The first alternative is the “maintained-drive” model, which embodies two rate constants, $\alpha$ representing the turn-on process (when the lights are turned on) and $\beta$ representing the persistence after the turn-off process (when the lights are turned off) (28, 29). This model postulates that light produces a drive on

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the endogenous pacemaker that persists or is maintained for a period of time after it is turned off, decaying only gradually with an extended time course. Similarly, when a light stimulus is initiated, a period of time elapses before full phase-shifting strength is attained. The second alternative, the “dynamic-stimulus” model, postulates that during dark episodes, a potential for photic drive is stored and that this potential is tapped at the start of light exposure with rate constant α and is reconstituted (restored) with a rate constant β (28, 29). During an extended light episode, the phase-shifting drive potential declines (with a time constant τ) to a low asymptotic level (αβ/α + β) corresponding to a balance between utilization and reconstitution. That is, the drive rate onto the circadian pacemaker is limited by the restoration process. Thus, when light is turned off, the phase-shifting drive stops completely, but the restoration of drive potential continues at the β rate, thereby priming the system for the next light episode.

We have shown mathematically (28, 29) that the temporal pattern of drive for the maintained-drive model can be determined by passing the drive pattern from the dynamic-stimulus model through a “leaky” integrator of time constant β⁻¹. Thus, in the sense of cumulative drive, the two new models are equivalent, but important distinctions remain. Compared with the dynamic-stimulus temporal-drive pattern, the pattern of the maintained-drive model is significantly delayed by the time β⁻¹ = 2.2 h, too long to account for the initial strong phase-shifting response presently observed (29). Because the dynamic-stimulus model is more consistent with the prompt biochemical responses (Fos protein) (20) to light observed in mammalian suprachiasmatic nuclei, it is the one we adopted.

The current results, as anticipated by the dynamic-stimulus model, demonstrate that the initial strength of the photic drive produced by the bright-light stimulus is very strong after several hours of dim light exposure. As the bright-light exposure is maintained, the drive strength declines (with a time constant of ~20 min) to an asymptotic level (αβ/α + β) corresponding to a balance between utilization and reconstitution. Thus, the initial strength of the drive after several hours of dim light is approximately six times the strength of the drive after 1 h of bright-light exposure (28, 29). These results suggest that, as in the golden hamster and mosquito, there is a strong phase-resetting response to the initial minutes of a light stimulus followed by a much weaker continuing response as the light duration is increased. This concept is supported by both Brainard et al. (5), who demonstrated that intermittent bright light, which is conveyed to the pineal gland through the circadian pacemaker (25, 31), is capable of inducing significant suppression of plasma melatonin levels in humans and by Baehr et al. (1), who in a lab/field study reported significant phase-delay shifts in groups exposed to intermittent bright light during simulated night shifts compared with those exposed to dim light.

**Perspectives**

Our findings demonstrate that humans are much more sensitive to the phase-resetting effects of brief intermittent exposures to light than was previously recognized (26, 43) and reinforce the concept that the mechanisms by which human circadian rhythms are entrained by light are not qualitatively different from those of other mammals (14). Our study provides evidence that intermittent light exposure, even to as little as repeated 5-min intervals of bright light, can produce circadian resetting effects nearly as great as those observed with a continuous 5-h bright-light exposure. These findings, together with the recognition that humans are sensitive to the phase-resetting effects of light throughout the subjective day (24), indicate that the brief intermittent exposures to bright light that we typically experience in everyday life (21, 36, 39) may have a much greater impact on circadian entrainment than was previously recognized (19, 26, 36, 39, 43). Given that photic resetting responses can also be achieved in humans at much lower light intensities (3, 45), these data suggest that sporadic nocturnal light exposure, such as that which occurs to a wide variety of people ranging from hospitalized patients to astronauts orbiting the Earth, may have more of an adverse circadian phase-shifting effect than previously anticipated. These data also have practical implications and suggest that a less-restrictive bright-light treatment regimen can be used to reset the circadian pacemaker in populations such as night workers or transmeridian travelers and to treat patients with seasonal affective disorders or circadian rhythm sleep disorders.

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**REFERENCES**


INTERMITTENT LIGHT RESETS THE HUMAN CIRCADIAN PACEMAKER


