Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phase in humans

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Gronfier, Claude, Kenneth P. Wright Jr., Richard E. Kronauer, Megan E. Jewett, and Charles A. Czeisler. Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phase in humans. Am J Physiol Endocrinol Metab 287: E174–E181, 2004. First published March 23, 2004; 10.1152/ajpendo.00385.2003.—It has been shown in animal studies that exposure to brief pulses of bright light can phase shift the circadian pacemaker and that the resetting action of light is most efficient during the first minutes of light exposure. In humans, multiple consecutive days of exposure to brief bright light pulses have been shown to phase shift the circadian pacemaker. The aim of the present study was to determine whether a single sequence of brief bright light pulses administered during the early biological night would phase delay the human circadian pacemaker. Twenty-one healthy young subjects underwent a 6.5-h light exposure session in one of three randomly assigned conditions: 1) continuous bright light of ~9,500 lux, 2) intermittent bright light (six 15-min bright light pulses of ~9,500 lux separated by 60 min of very dim light of ~1 lux), and 3) continuous very dim light of ~1 lux. Twenty subjects were included in the analysis. Core body temperature (CBT) and melatonin were used as phase markers of the circadian pacemaker. Phase delays of CBT and melatonin rhythms in response to intermittent bright light pulses were comparable to those measured after continuous bright light exposure, even though the total exposure to the intermittent bright light represented only 23% of the 6.5-h continuous exposure. These results demonstrate that a single sequence of intermittent bright light pulses can phase delay the human circadian pacemaker and show that intermittent pulses have a greater resetting efficacy on a per minute basis than does continuous exposure.

melatonin; circadian pacemaker; photoreception; phase shift
results, we anticipated a robust phase delay in the groups of subjects exposed to both continuous (33) and intermittent (45) bright light compared with small drifts in phase in the group of control subjects exposed to continuous very dim light due to the near-24-h period of the human circadian pacemaker (13, 33, 34, 54). In addition, on the basis of a mathematical model of the effect of light on the human circadian pacemaker developed by Kronauer and coworkers (32, 38, 39), we predicted that the resetting effect of the intermittent light exposure would be more efficient than continuous bright light exposure, as measured by the amount of shift induced per minute of bright light exposure.

MATERIALS AND METHODS

Subjects

Twenty-one healthy subjects participated in the study; 20 subjects [24.3 ± 3.9 (SD) yr, 15 males, 6 females, body mass index 22.8 ± 2.3 (SD) kg/m²] were included in the analysis due to noncompliance to constant routine procedures by one subject. The subjects had no medical, psychiatric, or sleep disorders as determined by history, physical examination, electrocardiogram, and blood and urine biochemical screening tests, and psychological screening questionnaires (Minnesota Multiphasic Personality Inventory and Beck Depression Inventory). A staff psychologist interviewed subjects and those with a history of or a current psychiatric pathology were excluded. Subjects reported that they were not taking any medication and were instructed to abstain from the use of alcohol, nicotine, recreational drugs, and foods or beverages containing caffeine for 3 wk before the study. All participants were drug free at the time of study as verified by a comprehensive toxic analysis conducted upon admission to the laboratory. All experimental procedures were carried out in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by the Human Research Committee at the Brigham and Women’s Hospital. Before beginning the protocol, all participants gave informed, written consent.

Overall Study Design

Subjects were required to maintain a regular 8:16-h sleep-wake schedule at home for ≥3 wk before admission to the laboratory. To ensure compliance with this protocol, subjects were required to call into a date/time-stamped answering machine just before going to bed and immediately upon awakening, and the times were compared with sleep-wake logs on the day of admission. In addition, wrist activity and light exposure were monitored for 1 wk immediately before admission to the laboratory (Actiwatch-L; Mini Mitter, Sunriver, OR) and were used to verify the stability of their sleep-wake cycle during that last week and throughout the entire inpatient protocol.

Upon admission to the study on experimental day 1, subjects were maintained in an environment free from external time cues, including clocks, radios, television, visitors, and sunlight. Subjects maintained contact with staff members specifically trained to avoid communicating time of day or the nature of the experimental conditions to the subjects. Subjects were adapted to the laboratory with 3 baseline days (days 1–3), during which time they continued to sleep and wake at their habitual times (Fig. 1). To assess their endogenous circadian phase before the light stimulus and to appropriately center the light stimulus during the following scheduled episodes of wakefulness, subjects underwent a 26.2-h initial constant routine (CR1; procedure described below) from day 4 to day 5. The duration of the constant routine, as well as the associated shift of the sleep episodes 4 and 5 (see Fig. 1), was designed so that the 6.5-h light exposure session (centered in the middle of the wake period) would coincide with the delay portion of the human phase-response curve (33) and was started 9.05 h before habitual bedtime and ended 2.55 h before habitual wake time [corresponding to a center at ∼3.5 h before the subjects’ core body temperature minimum (CBTmin)].

On day 5, subjects were randomly assigned to one of the three light exposure conditions (described below). Then, they were scheduled to a final constant routine of 64-h duration (days 6–9) to reassess their endogenous circadian phase and thereby estimate the phase shift from the initial constant routine. Subjects were then discharged on day 10, after an ∼22-h recovery sleep episode.

During wake episodes, subjects were free to move about the suite as desired, except that they were asked not to lie down, nap, or exercise. Subjects’ compliance with the protocol was monitored by means of closed-circuit cameras and frequent interaction with technicians.

The experimental suites were equipped with ceiling-mounted cool-white (4,100 K) fluorescent lamps (T8 and T80; Phillips, Eindhoven, The Netherlands). A computer system automatically turned the lighting to the required preset intensity at the scheduled times. Maximum light intensities, as measured vertically at a height of ∼1.83 m with an IL1400 photometer (International Light, Newburyport, MA), were ∼190 lux during the waking hours of the 3 baseline days (∼90 lux measured horizontally at a height of ∼1.37 m); <8 lux (∼1.5 lux measured horizontally at a height of ∼1.37 m) during the constant routines and the day of light exposure; and, depending on the experimental condition (described below), <1 lux (∼0.5 lux measured horizontally at a height of ∼1.37 m) or ∼9,500 lux (in the direction of gaze at a wall-mounted target) during the light exposure session. Sleep episodes were conducted in darkness. The experimental suites were equipped with hand-held terminals for online event recording, a porthole for 24-h blood sample collection with minimal sleep disturbance, a video camera, and a voice-activated audio system.

Constant-Routine Procedure

The constant-routine (CR) procedure was used to assess the phase of two markers of the endogenous circadian pacemaker: the core body

![Fig. 1. Raster plot of the 10-day experimental protocol for subject 19a1. Scheduled sleep episodes (8 h in darkness) are illustrated as black bars. During baseline days (days 1–3), subjects were exposed to ≤90 lux during wakefulness (16 h). For the remainder of the study, except during the light exposure session, subjects were exposed to ∼1.5 lux during wakefulness (gray bars). An ∼26.2-h constant routine (CR1) was scheduled on days 4–5. Light exposure session (white bar) was scheduled on days 5–6 and consisted of 6.5 h of exposure centered 5.8 h before habitual wake time (i.e., started ∼1.1 h before habitual bedtime and ended ∼2.6 h before habitual wake time). After the light exposure day, subjects underwent a 64-h CR (CR2) and were discharged after an ∼22-h recovery sleep episode. Δ, Dim-light melatonin onsets (DLMOn25%) in CR1 and CR2. For this subject, the light exposure (continuous bright light (BL) condition) generated a phase delay of 3.15 h in the DLMOn25%.

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temperature rhythm and the melatonin rhythm. The methodology that we used involved a refinement of a technique first proposed by Mills et al. (41), according to which the subjects are studied under constant environmental and behavioral conditions to eliminate or distribute across the circadian cycle the physiological responses evoked by environmental or behavioral stimuli, such as sleeping, eating, and changes in posture (22). The CR consisted of a regimen of enforced wakefulness in a semirecumbent posture in constant dim illumination of \(-1.5 \text{ lux}\). Subjects were required to maintain a very low level of physical activity and were not permitted to change their posture throughout the CR. This posture was also maintained for urine samples and bowel movements. Nutritional intake was divided into hourly isocaloric snacks to maintain an equal caloric intake across the circadian cycle. Caloric requirements were calculated with use of the Wilmore nomogram (53) to determine the basal metabolic rate and were adjusted upward by a 10% activity factor. Fluid intake was calculated for each subject to account for the sedentary nature of the CR. A staff member monitored the subject to help maintain wakefulness and to ensure compliance with the posture and activity level requirements.

**Light Exposure Conditions**

Subjects were randomly assigned to one of the three light exposure conditions (Fig. 2). The light exposure session of 6.5 h duration was centered 5.8 h before habitual wake time (i.e., it started \(-1.1 \text{ h}\) before habitual bedtime and ended \(-2.6 \text{ h}\) before habitual waketime) and therefore \(-3.5 \text{ h}\) before CRCT (23). The three conditions were as follows: continuous bright light (BL) of \(-9,500 \text{ lux} \), defined as 100% bright light; intermittent bright light (IBL), consisting of six 15-min bright light pulses of \(-9,500 \text{ lux} \) separated by 60 min of very dim light (\(<1 \text{ lux}\) ), defined as 23% bright light; and continuous very dim light (VDL) of \(<1 \text{ lux}\) , defined as 0% bright light. In all three conditions, the 30 min before and the 30 min after the light exposure session were conducted in \(<1 \text{ lux}\) . Seven subjects were randomized to each condition. Subjects were seated in a chair from 2 h before until 2 h after the end of the light exposure session. A technician was present at all times during the light exposure session to ensure compliance with the protocol. During the light exposure sessions, subjects were instructed to fix their gaze on a target mounted on the wall of their suite for 5 of every 10 min and then allow free gaze for 5 of every 10 min to ensure consistency of light exposure among subjects. This alternating fixed- and free-gaze episodes continued during the entire duration of the light exposure sessions. Light intensity measurements were taken in the direction of gaze every 5 min to ensure that subjects were exposed to the appropriate light intensity for the appropriate duration. Clear polycarbonate lenses filtered 99.9% of the light in the UV range from the light source. In addition, all subjects wore clear goggles (model no. S379, luminous transmittance 90%, UV absorption >99%; Uvex Safety, Smithfield, RI) during the exposure sessions to bright light for additional protection against UV exposure.

**Data Collection**

**Temperature data.** A real-time, online data acquisition system utilizing IBM PC-compatible computers was employed to monitor and collect temperature data. CBT was recorded continuously via a disposable rectal thermostor (Yellow Springs Instrument, Yellow Springs, OH), and room temperature was recorded by means of a permanent air temperature thermistor; both were recorded every minute.

**Hormonal data.** Blood samples were collected every 40 min during constant routines through an indwelling intravenous catheter that was inserted into a forearm vein on day 2 of the study, and every 5 to 10 min during the light exposure session (data will be presented elsewhere). A solution of heparinized saline (0.45% sodium chloride, 10 U heparin/ml) was infused at a slow rate (20 ml/h, 200 IU heparin/h) between blood samples. We provided participants with ferrous gluconate (324 mg) pills to be taken at breakfast and dinner 1) for a minimum of 1 wk before participation in the inpatient research protocol, 2) during the inpatient portion of the protocol, and 3) for 3 wk after completion of the protocol. Subjects’ hemoglobin levels were tested every 1–2 days to ensure appropriate levels (>11.0 for men, >10.3 for women). Blood samples were collected in ethylenediaminetetraacetic-K₂ tubes and rapidly centrifuged at 4°C, and the plasma was stored at or below \(-25°C\) until assayed. Samples were assayed for melatonin by use of radioimmunoassay techniques (Diagnostech/Pharmasan, Osceola, WI). The assay sensitivity was 2.5 pg/ml. The average intra-assay coefficients of variation were 6.4% below 50 pmol/l and 4.9% above.

**Estimation of Circadian Phase**

For temperature data collected during constant routines, a nonlinear least squares dual-harmonic regression model with correlated noise (8) was used. The time of the fitted CRCT was defined as the marker of the temperature phase. Data collected during the first 5 h of the CRs were excluded to minimize potential masking effects from the preceding sleep episode or from changes in posture from flat to the semirecumbent CR posture. To minimize uncertainty in the phase estimate, subjects for whom amplitude of the temperature rhythm was below 0.14°C were not included in the analysis (24) (Table 1). To minimize the effect of interindividual differences in circadian period on the phase shift assessments, only the first circadian oscillation of melatonin and CBT of the final CR was included in the analysis, and phase was estimated on the same time window length as for CR1.

For melatonin data, a three-harmonics least squares regression analysis was applied to data collected during CR1 (Fig. 3, thick line) to estimate the amplitude of each subject’s melatonin rhythm (Fig. 3, dashed line). A threshold of 25% of the peak-to-trough amplitude of the fitted curve (54) was calculated (Fig. 3, dotted line) and applied to data of CR1 and CR2 (first circadian oscillation considered). Three markers of melatonin phase were computed for each CR data: 1) the midpoint (MP₂₅%) between 2) the upward dim-light melatonin onset (DLMO₂₅%) and 3) the downward dim-light melatonin offset (DLMO₂₅%) crossings of this 25% threshold.

Phase shifts of temperature and melatonin rhythms were calculated as the difference between the phase in CR1 and the phase in CR2.

![Fig. 2. Light exposure conditions. Subjects were exposed either to 6.5 h of BL (\(-9,500 \text{ lux}\) ), intermittent bright light (IBL; six 15-min bright light (\(-9,500 \text{ lux}\) ) pulses separated by 60 min of very dim light (\(<1 \text{ lux}\) ), or to very dim light (VDL) (\(<1 \text{ lux}\) ).](image-url)
Table 1. Timing of LES and individual phase shifts of endogenous circadian rhythms of temperature and melatonin in BL, IBL, and VDL exposure groups

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<tr>
<th>Subject Code</th>
<th>Sex</th>
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<th>LES (clocktime)</th>
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<td>DLMOn25% End</td>
<td>CBTmin DLMOn25% DLMOff25%</td>
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LES, light exposure sessions; CBTmin, core body temperature minimum; DLMOn25%, dim-light melatonin onset; MP25%, midpoint; DLMOff25%, DLM offset; BL, continuous bright light; IBL, intermittent bright light; VDL, very dim light. By convention, phase delays are negative (−) shifts; phase advances are positive shifts. Note that, because of the low amplitude of their CBT rhythms, phase shifts of CBTmin are not given for subjects 2008 and 2041, and the center of the light exposure sessions relative to CBTmin is not given for subject 2008. Because of missing blood samples, melatonin MP25% and DLMOff25% could not be calculated for subject 2056. Centers of the light exposure sessions and phase shifts are given in hours.

Fig. 3. Method used for melatonin phase assessment using DLMOn25%, DLM offset (DLMOff25%), and midpoint (MP25%) phase markers. Thick line, the 3-harmonics fitted curve; dashed line, the amplitude of the fitted curve; dotted line, 25% of the amplitude. The figure also illustrates the bright light exposure session (L.E.S.)-induced melatonin suppression. The study days corresponding to the profile are given at the top of the figure.
RESULTS

The light stimulus was, on average, centered 3.15 ± 0.72 h after DLMO_{25\%} and 3.39 ± 1.28 h before CBT_{min} [i.e., it started on average 5 min (0.09 ± 0.72 h) before DLMO_{25\%} and ended 5 min (0.09 ± 1.56 h) after CBT_{min}; Table 1]. There were no significant differences among the three groups in the initial phases of the temperature and melatonin rhythms at which the light intervention occurred. There were minimal changes in phase observed in the control group of subjects exposed to VDL (median phase change of +0.44 h for CBT_{min} and −0.31 h for DLMO_{25\%}; Fig. 4). A significantly greater phase delay was observed in subjects exposed either to BL [median phase delay = −2.70 h for CBT_{min} (P < 0.0002 vs. controls), 3.03 h for DLMO_{25\%} (P < 0.0002 vs. controls), −2.71 h for MP_{25\%} (P < 0.0002 vs. controls), and −2.38 h for DLMO_{25\%} (P = 0.0003 vs. controls)] or to IBL [median phase delay = −1.73 h for CBT_{min} (P < 0.0003 vs. controls), −2.34 h for DLMO_{5\%} (P < 0.0002 vs. controls), −2.30 h for MP_{25\%} (P < 0.0002 vs. controls), and −1.63 h for DLMO_{25\%} (P = 0.001 vs. controls)]. As expected for the selected phase of light exposure, the BL and IBL groups demonstrated phase delays of their endogenous circadian rhythms of core body temperature and melatonin (Fig. 4).

Although the phase shifts observed in the IBL group were slightly smaller than those observed in the BL group, no statistical differences were found for any marker (Fig. 4).

The resetting responses measured with CBT_{min} were more variable than those measured with melatonin (Table 1); however, we found highly significant and positive linear relationships between the markers of the two rhythms (r_{CBT_{min}/DLMO_{25\%}} = 0.896, r_{CBT_{min}/MP_{25\%}} = 0.871, and r_{CBT_{min}/DLMO_{25\%}} = 0.779; P < 0.0001 for all three correlation coefficients).

We found no significant linear correlation between observed melatonin phase shifts and the initial phases of light exposure (\phi_{init}) within the limited range of initial phases to which subjects were exposed within each condition (r_{\phi_{init}/DLMO_{25\%}} = 0.182, r_{\phi_{init}/MP_{25\%}} = 0.071, r_{\phi_{init}/DLMO_{25\%}} = 0.031; P nonsignificant for all 3 correlation coefficients).

In appraising the variability of the phase shift data presented here (Table 1), we recognize three independent variability sources whose variances should sum: 1) noise in the individual phase assessments whose difference comprises the phases shift, 2) intersubject differences in the endogenous circadian period that lead to different phase drifts over the two cycles of shift assessments, and 3) intersubject differences in photic response arising either from sensitivity differences or from differences in the timing of the stimulus. Klerman et al. (36) found that the method of single-phase assessment yielding the lowest variance was a normalized level crossing on the rising front of the melatonin pulse. This variance could be as low as 0.04 h^2 (50th %ile) so that, for phase shifts, the variance might be 0.08 h^2. For our results, the DLMO_{25\%} does indeed give consistently the lowest variance estimates. Czeisler et al. (13) estimated the standard deviation of circadian period for young adults to be 0.13 h so that a two-cycle phase drift would show a variance of 0.07 h^2. We recognize that variance estimates are extremely unreliable for data groups of six or seven members.

### Statistical Analysis

Repeated-measures ANOVA (condition × phase marker) with Greenhouse-Geisser correction (only original degrees of freedom are reported), and Tukey’s tests for post hoc multiple comparisons were used to compare phase shifts between phase markers, with H_0: μDLMO_{25\%} = μMP_{25\%} = μDLMO_{25\%} = μCBT_{min}. Pearson correlations were calculated between phase shifts and initial phases of light exposure, between CBT_{min} and melatonin phase shifts, and between phase shifts of the melatonin phase markers (DLMO_{25\%} and DLMO_{25\%}).
However, the value of 0.15 h² for the VDL condition is consistent with the sum of 0.08 and 0.07 h² for sources 1 and 2 described above. The variance of 0.20 h² for the BL condition suggests that perhaps as little as 0.05 h² might be ascribed to source 3. However, by this reasoning, the variance of 0.12 h² for the IBL condition is inexplicably small and may represent a remarkably homogeneous subject group with little difference in endogenous circadian period.

DISCUSSION

The present results demonstrate that a single sequence of IBL exposure is effective in inducing phase delays of the human circadian timing system. The phase delays observed after IBL exposure were comparable to those measured after BL exposure (Fig. 4), even though the BL represented only 23% of the 6.5-h light exposure session. Given that the median phase delay measured with DLMOn25% was −3.03 h under BL condition (6.5 h of BL), and −2.34 h in the IBL (1.5 h of bright light) condition, the phase-resetting ability of IBL exposure, when the reference −0.31-h phase shift measured in the control VDL condition was taken into account, was 3.2 times greater than that of BL exposure on a per minute basis of BL exposure.

The small change in phase observed in the control group may be attributed to the longer-than-24-h period of the circadian timing system. The phase delays observed after IBL and BL exposures were significant from those after BL exposure, and phase delay shifts after IBL and BL exposures were significantly greater than those after VDL exposure.

The mathematical model developed by Kronauer and colleagues (32, 38, 39) predicts that the phase shift after IBL would be ≈70% of that after BL. In fact, we found that IBL was 69% as effective in shifting CBTmin, 74% as effective in shifting DLMOn25%, and −2.34 h in the IBL (1.5 h of bright light) condition, the phase-resetting ability of IBL exposure, when the reference −0.31-h phase shift measured in the control VDL condition was taken into account, was 3.2 times greater than that of BL exposure on a per minute basis of BL exposure.

The present experiment was designed with several objectives. The first was to expose subjects to a single sequence of bright light pulses, as opposed to multiple sequences of exposure over several days. A second was to extend the range of the duration of near darkness from the former range of 20–45 min to 60 min. A third was to study a short duty cycle of 0.23. Both of these changes in intermittent light patterns, besides improving the accuracy of rate estimate, increase the practical usefulness of intermittent light intervention. Our fourth goal was to validate Kronauer’s mathematical model of resetting efficacy of intermittent bright light (32, 38, 39); simulations based on existing rate estimates indicated that the pattern of light exposure used in this experiment would produce −70% of the resetting drive onto the circadian pacemaker achieved by continuous bright light.

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temporal range required either to support or to reject this possibility. The response dynamics of rods and cones to light make them unlikely to embody process L. Further investigations, however, including exposures to intermittent light of different duty cycles and different wavelengths, are required to clarify this point.

These findings have important implications, as they provide a greater understanding of the effects of brief episodes of light on the human circadian timing system and suggest that the intermittent exposure to bright light that occurs in everyday life (47) may have a much greater impact on circadian entrainment than previously recognized. The present results also indicate that brief episodes of light exposure may be a cost- and time-effective way of resetting the circadian timing system in humans. Such strategies could be used not only to treat circadian misalignment related to the low light intensities (20, 54) associated with space missions, but also, as shown in the field setting, in which subjects are exposed to conflicting cues, to treat circadian misalignment associated with transmeridian travel, shiftwork (3, 7, 10, 31), and circadian sleep disorders such as advanced and delayed sleep phase syndrome.

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