EXPOSURE TO BRIGHT LIGHT AND DARKNESS TO TREAT PHYSIOLOGIC MALADAPTATION TO NIGHT WORK

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Abstract Working at night results in a misalignment between the sleep-wake cycle and the output of the hypothalamic pacemaker that regulates the circadian rhythms of certain physiologic and behavioral variables. We evaluated whether such physiologic maladaptation to nighttime work could be prevented effectively by a treatment regimen of exposure to bright light during the night and darkness during the day. We assessed the functioning of the circadian pacemaker in five control and five treatment studies in order to assess the extent of adaptation in eight normal young men to a week of night work.

In the control studies, on the sixth consecutive night of sedentary work in ordinary light (approximately 150 lux), the mean (±SEM) nadir of the endogenous temperature cycle continued to occur during the night (at 03:31±0:56 hours), indicating a lack of circadian adaptation to the nighttime work schedule. In contrast, the subjects in the treatment studies were exposed to bright light (7000 to 12,000 lux) at night and to nearly complete darkness during the day, and the temperature nadir shifted after four days of treatment to a significantly later, midafternoon hour (14:53±0:32; P<0.0001), indicating a successful circadian adaptation to daytime sleep and nighttime work. There were concomitant shifts in the 24-hour patterns of plasma cortisol concentration, urinary excretion rate, subjective assessment of alertness, and cognitive performance in the treatment studies. These shifts resulted in a significant improvement in both alertness and cognitive performance in the treatment group during the night-shift hours.

We conclude that maladaptation of the human circadian system to night work, with its associated decline in alertness, performance, and quality of daytime sleep, can be treated effectively with scheduled exposure to bright light at night and darkness during the day. (N Engl J Med 1990; 322:1253-9.)

A PROXIMATELY 7.3 million Americans work at night, either on permanent shifts or on schedules requiring a rotation of day, evening, and night work. These workers forgo nocturnal sleep and then attempt to sleep during daylight hours. Yet, as Benedict first noted at the turn of the century, a complete physiologic adaptation of endogenous circadian rhythms to such inversion of the daily routine does not occur even after years of permanent night-time work. Physiologic maladaptation to an inverted schedule results in diminished alertness and performance during nighttime work, with attendant increases in the number of fatigue-related accidents during nighttime hours. Then, despite the nocturnal deprivation of sleep, these workers typically experience daytime insomnia. Long-term exposure to variable work schedules that include work at night is also associated with an increased risk of cardiovascular disease, gastrointestinal illness, reproductive dysfunction in women, and sleep disorder. Improvements in performance and well-being have been achieved as a result of modifications in work-schedule design, but true physiologic adaptation to night work under field conditions has not previously been demonstrated.

During the past 20 years, considerable progress has been made in understanding the underlying neurophysiologic processes that regulate adaptation to the periodic aspects of the external environment. Studies involving ablation, transplantation, and other procedures have demonstrated that the suprachiasmatic nuclei of the hypothalamus serve as the principal pacemaker of the circadian timing system in mammals. A specialized retinohypothalamic tract links the retina to these nuclei, forming a nonvisual photoreceptive system that mediates the synchronization, or entrainment, of the circadian pacemaker with the light-dark cycle. Even though corresponding structures subserving rhythmicity and photic entrain-
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ment in the brain have been identified, it was thought that the human circadian pacemaker was uniquely insensitive to light and that it instead relied on "social contacts" to achieve synchrony with the 24-hour day. However, we have demonstrated that the light-dark cycle has a direct synchronizing effect on the human circadian pacemaker. Furthermore, we have recently discovered that properly timed exposure to bright light and darkness can reset the pacemaker by as much as 12 hours within two to three days. We found that the pacemaker's resetting response to bright light depends on the timing of the average midpoint of the total daily exposure to light, after weighting for brightness. Therefore, the bright light to which night-shift workers are often exposed during the day (e.g., during the return home from work) may prevent them from adapting to night work. On the basis of these results, we designed a pattern of exposure to bright light and darkness in the work and home environments by which the phase of the pacemaker can be reset rapidly and effectively in persons who work at night, even if they are exposed to natural light on the way home from work each morning.

Methods

Subjects

Ten two-week studies were conducted in eight healthy men, 22 to 29 years old. The subjects had no medical, psychiatric, or sleep disorders as determined from their medical histories, physical examinations, chest radiographs, electrocardiograms, biochemical screening tests, and psychological screening questionnaires (the Minnesota Multiphasic Personality Inventory). None had worked regularly at night on a permanent or rotating shift within the preceding year, and none had traveled to another time zone during the previous six weeks. They were not taking any medications and were instructed to abstain from the use of alcohol, recreational drugs, and products containing caffeine for the duration of the study. Urinary toxicologic screening was used to verify that they were drug-free at the time of the study.

The first two subjects participated in the control study and then in the treatment study, after an interval of three to five weeks during which they lived at home and maintained a schedule of regular daytime activity and nocturnal sleep. To facilitate recruitment the remaining six men were asked to participate in only one study; each was randomly assigned to either the control study or the treatment study after the successful completion of an initial evaluation of his circadian phase.

All the studies were carried out in the summer, to avoid seasonal variation in exposure to outdoor light during the week of night work. The experimental procedures and the procedure for obtaining informed consent were approved by the Committee for the Protection of Human Subjects from Research Risks of Brigham and Women's Hospital. Written informed consent was obtained from each man before participation in the study.

Overall Study Design

Five control and five treatment studies were performed; each consisted of one week of ambulatory recording of base-line temperature, physical activity, and heart rate, followed by a week of night-shift work. The men lived at home throughout each study, reporting for "work" in the laboratory each night of the second week. To evaluate the extent of physiologic adaptation to nighttime work, the output of the circadian pacemaker was evaluated during the first and sixth consecutive night shifts. On those nights, and during each of the immediately preceding days, the activity of the subjects was restricted to the enforced semirecumbent wakefulness of a laboratory constant routine as described below. Both the control and the treatment protocols are shown in Figure 1.

During the week of base-line recording, the men maintained regular bedtimes and waking times (within a range of ± 1 hour). Their subjective sleep—wake logs were verified for accuracy by comparison with the results of continuous ambulatory monitoring of wrist activity, heart rate, and body temperature (PMS-8 Recorder, Vitalog, Redwood City, Calif.) throughout both weeks of the study. In the case of two men (one control and one treatment subject) whose behavior during the study did not conform to the protocol, the results were excluded before the outcome of their experimental trials was determined.

On the second through the fifth nights of work, the men reported to the laboratory at 23:45 hours and spent the eight hours between midnight and 08:00 seated at a desk. On those four nights, the men in the treatment studies were exposed to bright light (7000 to 12,000 lux, an intensity comparable to that of natural sunlight just after dawn) between 00:15 and 07:45 hours, whereas those in the control studies were exposed to ordinary room light (approximately 150 lux). All subjects completed cognitive-performance tasks hourly...

Figure 1. Overall Study Protocol (Middle Panels) and Changes in Temperature Recorded during the First and Sixth Night Shifts (Upper and Lower Panels) in One Man during a Control Study and a Treatment Study.

Solid bars indicate daily sleep episodes, open bars constant routines, and circled x's the initial and final endogenous circadian temperature nadirs as derived from the temperature data (vertical dashed lines) measured during the constant routine. During the second through fifth nights of work (midnight to 08:00 hours), the men were exposed either to ordinary indoor light (approximately 150 lux; stippled box) in the control studies or to bright light (7000 to 12,000 lux; solar symbol in the open box) in the treatment studies. To facilitate visual comparisons, segments of the temperature data have been double-plotted.
during this time and subjective assessments of alertness and mood every 20 minutes. They were otherwise free to do their own work and were given dinner and a snack during each night shift. In all but two trials, the subjects (one in the control study and one in the treatment study) consumed their meals at times of their own choosing. A technician monitored the subjects throughout each night shift to ensure that they remained awake.

After each night shift, the men left the laboratory and traveled home. They were thus exposed to outdoor light each morning during this travel time. The men in the treatment studies were instructed to remain in the dark from 09:00 to 17:00 hours each day, in bedrooms in which the windows were covered with opaque material to exclude sunlight. In contrast, the men in the control studies were not scheduled to remain in the dark at any particular time each day, although most did use their existing window shades or curtains while they slept, at times of their own choosing. No other restrictions were placed on the activities of the subjects in either group during their "nonwork" hours. All were provided with a breakfast and a lunch to take home and eat at will.

Assessment of Endogenous Circadian Phase

Previous attempts to evaluate the extent of circadian adaptation to night work have been complicated by the masking effects of activity on the physiologic variables monitored. In this study, the constant-routine method was used to reveal the endogenous component of the body-temperature rhythm, an established marker of the endogenous circadian pacemaker.11-13 During the constant-routine procedure, we determined the endogenous circadian phase (the particular point at which a regularly recurring event occurs in an intrinsic oscillatory process) at which the nadir of the daily body-temperature cycle occurred. Our method involved an extension and refinement of a technique first proposed by Mills et al.,14 according to which the subjects are studied under constant environmental and behavioral conditions in order to eliminate (or distribute across the circadian cycle) the physiologic responses evoked by environmental or behavioral stimuli, such as sleeping, eating, changing posture, and changing light levels. During all the constant-routine studies, the men were restricted to absolute, semicircadian bedding time in a room with constant indoor lighting (approximately 150 lux) and required to remain awake. Wakefulness was monitored by a research technician and verified by continuous polysonmographic recording.16 During the constant routine, the men’s daily nutritional and electrolyte needs were met by identical hourly snacks, with approximately 150 mmol of sodium and approximately 100 mmol of potassium evenly distributed over the 24-hour period. The caloric requirements for weight maintenance were calculated with use of the Wilmore nomogram17 to determine the basal metabolic rate; they were then adjusted upward by a 10 percent activity factor. Since the constant-routine procedure required that the subjects lose at least one night of sleep, it was carried out concurrently with the first and sixth night shifts. Each constant routine was begun just after the subject awakened on the day of the shift, and it continued for as long as was necessary (at least 21 hours) to determine accurately the endogenous circadian temperature nadir. In two subjects (one in the control study and one in the treatment study), an additional 24 hours was required for this determination during the final constant routine.

Physiologic and Behavioral Measures

Throughout each constant routine, the core body temperature of the subject was recorded at one-minute intervals from a disposable thermometer (Yellow Springs Instrument Company, Yellow Springs, Ohio) inserted 10 cm into the rectum. In addition, blood samples were collected in syringes and transferred to heparin-coated tubes every 15 to 25 minutes on a randomized sampling schedule from an indwelling intravenous catheter with side holes (Deseret Medical, Sandy, Utah) that was placed in a forearm vein;18 the samples were chilled immediately and centrifuged within two hours, the plasma was frozen at −20°C. The plasma cortisol concentrations were measured within five months of sample collection by an 11β-hydroxy-coated tube radioimmunoassay procedure (Diagnostic Products, Los An-
ation in the endogenous circadian temperature cycle were made with use of Student's unpaired t-test (parametric analysis), with confirmation of significant results by the Wilcoxon rank-sum test. All statistical analyses were two-tailed.

Finally, in both groups the body temperatures, subjective-alertness and cognitive-performance scores, urinary excretion rates, and plasma cortisol concentrations were averaged according to the time of day during the initial constant routines and compared with the averages for the same times of day during the final constant routines. For the less frequently sampled among these variables (subjective alertness, cognitive performance, and urinary excretion rate), the mean value of the data for each man was calculated every two hours, and an average for all subjects was obtained; for the remaining variables (body temperature and plasma cortisol concentration), the mean (±SEM) value for all subjects was calculated at regular intervals (every 100 minutes).

**RESULTS**

**Sleep–Wake Schedules**

During the week of base-line recording, each man maintained a regular sleep–wake schedule consistent with that required for regular daytime work. There were no significant differences between the control and the treatment studies with respect to either the average (±SEM) bedtime (00:22±0.18 vs. 00:04±0.21 hours) or the average waking time (07:48±0.19 vs. 07:33±0.29 hours) during the week of base-line recording.

During the scheduled night shifts the men in both studies slept during daytime hours, as shown in Figure 1. However, the men in the treatment studies slept an average of two hours longer per day than the men in the control studies after each of the second through the fifth nights of work (7.7±0.1 vs. 5.7±0.5 hours per day; P = 0.0103), as reported in their sleep–wake logs and independently verified on the basis of the monitoring data.

**Assessments of Endogenous Circadian Phase**

The mean initial nadir of the endogenous circadian temperature cycle occurred at 04:59 hours, 2.7 hours before the men's habitual waking time in the week before each study. There was no significant difference between control and treatment studies with respect to the timing of this nadir (P = 0.1564) (Fig. 2). In the control studies, the mean times of the initial and final nadirs of the endogenous circadian temperature cycle (04:38±0.11 vs. 03:31±0.56 hours) were similar. In contrast, in the treatment studies, the mean final temperature nadir occurred 9.6 hours later than the mean initial temperature nadir (14:53±0.32 vs. 05:19±0.23 hours; P<0.0001) (Fig. 2). The mean shift in the endogenous circadian temperature nadir between the first and sixth nights in the treatment group (−9.6±0.7 hours) was significantly greater than that in the control group (1.1±0.9 hours) (P<0.0001). Finally, the mean endogenous circadian temperature nadir on the sixth night occurred significantly later in the treatment studies than in the control studies (14:53±0.32 vs. 03:31±0.56 hours; P<0.0001).

These differences between the control and treatment groups were also statistically significant even when the data for one control trial and one treatment trial for each of the first two men (who participated in both the treatment and control studies) were excluded from the analysis. Finally, there was no significant difference between the mean amplitudes of the initial and final temperature wave forms in either the control or the treatment studies. However, for one man in the treatment study the amplitude of the cycles for temperature and plasma cortisol concentration was attenuated during the first 24 hours of the final constant routine; when the constant-runtime study was extended for an additional 24 hours, both the amplitude and phase shift of these variables were comparable with those of the other subjects in the treatment studies.

**24-Hour Patterns of Physiologic and Behavioral Variables**

The mean 24-hour patterns of core body temperature, subjective alertness assessments, cognitive performance, urinary excretion rate, and plasma cortisol concentrations during the initial constant routine in both the control and treatment studies had prominent circadian variations. The mean wave forms and timing for each of these variables during the initial constant routine were similar in the men who subsequently participated in the control and treatment studies and also resembled those reported previously.30,31,33,42 (Fig. 3). During the final constant routines, a persistent circadian rhythm was apparent in the average wave form for each variable in both groups. Furthermore, the internal temporal relation between these rhythms did not change during the final constant routine of the control and treatment studies. The relation of each of these average rhythms to the time of day did not change from the initial to the final constant routine.
the control studies, there was no significant difference in performance during the night-shift hours between the initial and the final constant routines (Fig. 3C). Similarly, the mean values for alertness were significantly higher during the night shift after the bright-light intervention in the treatment studies than they were before treatment (P = 0.0009) (Fig. 3G). Although the mean values for alertness during the night shift were also significantly higher in the control studies at the time of the final constant routine than at the time of the initial constant routine (P = 0.009) (Fig. 3B), the improvement was significantly greater in the treatment studies than in the control studies (31.5±7.8 vs. 13.4±6.3 mm, respectively; P = 0.004).

**Discussion**

Despite the high prevalence of night work in modern society, the physiologic response of the circadian timing system to the reversal it occasions in the sleep-wake schedule is poorly understood. This is largely because night workers are exposed to conflicting synchronizing cues: their work schedule demands activity at night and sleep during the day, whereas all other periodic environmental cues (in particular the light-dark cycle) are oriented toward activity during the day and sleep at night. Although some laboratory experiments have indicated considerable adaptation to a week of simulated nighttime work, those experiments were conducted in laboratories shielded from the environmental light-dark cycle to which shift workers are ordinarily exposed. Studies of shift workers exposed to normal periodic environmental cues have suggested that an incomplete adaptation to nighttime work occurs in persons who live at home and travel daily to work.

In this study, we attempted to resolve the dilemma by evaluating endogenous circadian rhythms under controlled laboratory conditions on the first and sixth night shifts in men otherwise living at home. The physiologic and behavioral data that we collected in the control studies demonstrate that under field conditions the circadian timing system fails to adapt to an inversion of the daily routine even after a week of night work. In fact, three of the five men had small maladaptive advances of the endogenous circadian phase on the sixth night shift as compared with the first. The failure of the circadian timing system to adapt to night-shift work in persons working in ordinary room light at night and sporadically exposed to bright outdoor light during the day is probably a consequence of the direct and powerful biologic effect of light on the human circadian pacemaker.

In contrast, in the treatment studies we found that four cycles of exposure to a properly designed regimen of bright light and darkness induced a complete physiologic adaptation to night work in the men living at home and traveling to and from work. The physiologic and behavioral adaptation to the night shift was evident with respect to all measured variables. The success of this experimental paradigm in inducing an ad-
Adaptation to an inversion of the sleep–wake schedule is rapid, with the finding that travelers adapt more rapidly to a time-zone shift if they remain outdoors on arrival rather than in their hotel rooms.14,26 and with recent studies suggesting that bright light is an effective synchronizer of circadian rhythms in human subjects.27,33 Our findings are comparable with the results of experiments conducted under conditions of 24-hour daylight in the Arctic, in which adaptation of the body-temperature cycle to a reversal of the activity–sleep schedule was achieved after only three to four days among subjects who concurrently reversed their exposure to the natural light–dark cycle by using blinds during daytime sleep.34 However, it should be noted that the resetting effect of light on the circadian pacemaker is critically dependent on the timing, intensity, and duration of the light exposure. The desired phase shift may not be achieved even with the same amount of exposure to bright light35 unless it is administered at appropriate times.29

The use of the constant-routine procedure allowed the extent of adaptation of both physiologic and behavioral variables to be evaluated in the control and treatment studies. The endogenous circadian rhythms of body temperature, plasma cortisol concentration, and urinary excretion rate all failed to adjust to the schedule of night work in the control studies, yet in the treatment studies they were all effectively synchronized with the night-work schedule. The indexes of alertness and performance remained at their lowest daily levels from midnight to 08:00 hours in the control studies, even after a week of nighttime work. In the treatment studies, these same indexes during the night were significantly improved, and there was a marked decline in alertness (or an increase in sleepiness) during the daytime, when night workers must attempt to sleep. This increase in daytime sleepiness is consistent with the shift in phase of the physiologic variables and may account for the significantly increased sleep time among the men in the treatment studies. Taken together, these data suggest that the schedule of light and darkness to which these men were exposed shifted a master circadian pacemaker that drives all these physiologic and behavioral rhythms.

Disalignment of the circadian phase and sleep deprivation are the principal factors contributing to the decrements in performance and increased accident rates associated with night-shift work.9 Therefore, the ability of exposure to light and darkness to adjust the circadian phase and improve the sleep of night-shift workers could have important implications for both industrial productivity and safety. Furthermore, since circadian-phase misalignment, sleep deprivation, or both may add to the deleterious consequences for health that are associated with nighttime work (such as digestive, cardiovascular, and sleep disorders), the ability to induce physiologic adaptation to such a schedule could also have important consequences for the health of night workers.

Although this study is a step toward the development of a practical treatment for maladaptation to nighttime work, a number of important questions remain to be answered. They concern the relative importance of exposure to bright light during nighttime work as compared with darkness during daytime sleep, variability both between individuals and according to age and sex in the phase-shifting response to bright light, and the number, duration, and intensity of light exposures needed to induce and maintain optimal physiologic adaptation to nighttime work.

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