Changes of the human core body temperature rhythm and sleep structure by 6-hour phase advance treatment under a natural light-dark cycle

Alterações do ritmo da temperatura central do corpo e da estrutura do sono por seis horas de tratamento de avanço de fase sob um ciclo claro-escuro natural

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ABSTRACT

Objectives: The purposes of this study were to reveal how far the core body temperature rhythm phase advances and the corresponding changes in sleep structure. The extremities of core body temperature rhythm shifts and nocturnal sleep structure changes were examined during 6 days of 6-hour phase advance treatment using bright light and melatonin under the natural light-dark cycle.

Methods: Six healthy males received phase advance treatments with 1 hour bright light exposure after waking, oral melatonin (1.0 mg) administered in the early evening, and advancement of environmental routines intended to advance the onset of the sleep period 1 hour per day. Core body temperature was recorded continuously for 8 days comprising adaptation, baseline, and 6 treatment days. Nighttime sleep quality was evaluated by polysomnography (PSG) on adaptation, baseline, night 3, and night 6.

Results: The core body temperature nadir in each day compared with baseline advanced significantly (p < 0.05). The mean nadir had advanced approximately 4.5 hours from baseline by day 6. The only significant change found in sleep structure was REM sleep duration, which was significantly decreased in day 6 compared with baseline (p < 0.05). Significant negative correlations existed between nadir phase advances and REM in baseline, day 3, and day 6 recordings.

Discussion: Thus, phase advances greater than 4 hours were possible under natural light-dark condition, although a phase shift of 1 hour per day may be too rapid to maintain normal sleep structure.

Keywords: body temperature, circadian rhythm, jet lag syndrome, polysomnography.

RESUMO

Objetivos: O objetivo deste estudo foi revelar como a temperatura corporal central avança em função da estrutura do sono. Alterações nos extremos da temperatura corporal central e na estrutura de sono foram examinadas durante seis dias de tratamento de avanço de fase por 6 horas, usando luz intensa e melatonina, sob um regime de ciclo claro-escuro natural.

Métodos: Seis homens saudáveis receberam tratamentos de avanço de fase com uma hora de exposição à luz intensa após o desperta, melatonina por via oral (1,0 mg) ao anoitecer, e o avanço das atividades rotineiras teve como objetivo avançar o início do sono em 1h por dia. A temperatura corporal central foi mensurada continuamente por oito dias, compreendendo período de adaptação, mediadas basais e seis dias de tratamento. O sono noturno foi avaliado por meio de polissonografia durante o período de adaptação, basal, noite 3 e noite 6.

Resultados: O nadir da temperatura corporal em cada dia, comparado com a medida basal, avançou significativamente (p < 0.05). O nadir médio avançou aproximadamente 4.5h desde a medida basal até o sexto dia. A única alteração significativa na estrutura do sono se deu na duração do estágio REM, o qual foi significativamente diminuído no sexto dia, em comparação com o basal. Correlações significativamente negativas foram observadas entre o nadir do avanço de fase e a porcentagem de sono REM na medida basal, no terceiro dia e no sexto dia.

Discussão: Avanços de fase maiores do que 4h foram possíveis em condições de ciclo claro-escuro naturais, embora um atraso de fase de 1h por dia seja rápido demais para manutenção da estrutura de sono normal.

Descritores: polissonografia, ritmo circadiano, síndrome do jet lag, temperatura corporal.

INTRODUCTION

International jet flights continue to greatly increase the number of people flying across multiple time zones. Jet lag has become a substantial, often critical issue for businessmen, tourists, and athletes.(1-3). Jet lag is caused by a misalignment between the destination time-zone’s life cycle and the persistence of a traveler’s endogenous circadian rhythms entrained in a different time zone.(4). Under natural conditions core body temperature, hormonal secretions, psychological and physical activity levels each exhibit variations with a period of about 24 hours.(5-7). The free-running periods of these rhythms are not completely 24 hours, but are continually re-entrained to the 24 hour day mainly by light exposure, and partially by rest-activity schedules and social interactions, maintaining proper phase relationships with the local life cycle.(8,9)

The symptoms of jet lag include insomnia, excessive daytime sleepiness, and feelings of fatigue. These symptoms, induced by the misalignment of established bodily rhythms in
a novel time zone are dissipated by gradual re-entrainment to the destination time, at a rate dependent on the magnitude of the time difference. Re-entrainment of endogenous circadian rhythms is typically slower after eastward rather than westward flights because the period of the biological rhythms is slightly longer than 24 hours, while the advanced local time at eastward destinations has effectively shortened the activity period\textsuperscript{[10-12]}. Conversely, traveling across eight time zones or more in an easterly direction can result in adaptation by phase delay rather than causing jet lag by phase advance\textsuperscript{[13,14]}.

Because sleep affects both the physical and psychological aspects of those who have to perform at important meetings or other competitions abroad, phase advancing preflight treatments that minimize their own sleep disturbances would be desirable for the best performance after eastward flight. In addition, when people travel further eastward, longer courses of phase advance pretreatment may be needed to minimize jet lag symptoms. However, there are few published studies of either long-term preflight treatment or of phase advance treatments that include detailed measurements of sleep structure.

The goal of eastward preflight treatment is to produce a phase advance in the timing of a traveler’s entrained biological rhythms. Endogenous circadian rhythms can be advanced by manipulating bright light exposure in the morning and by timed boosting of melatonin levels in the early evening. The desired timing of light exposure and/or melatonin is determined based on the phase response curve (PRC) to bright light or melatonin intake\textsuperscript{[13,16]}. Phase advance (and delay) effects of appropriately timed bright light exposure and melatonin intake have been well established\textsuperscript{[17,18]}.

Khalsa et al.\textsuperscript{[19]} showed that controlled bright light exposure can be used to advance or delay the endogenous melatonin rhythm depending on the phase stimulated. Additionally, Revell et al.\textsuperscript{[20]} demonstrated that the combination of afternoon 0.5mg oral melatonin intake after morning intermittent bright light was associated with advancing the sleep-wake cycle, inducing 50 minutes phase advance per day. In a recent study, Paul et al.\textsuperscript{[21]} examined whether 1 hour morning light exposure followed by afternoon oral melatonin intake had additive or synergistic effects on phase advance treatment. Their procedures yielded about a 1 hour phase advance and revealed that the combination of oral melatonin intake and light exposure was additive.

Sleep is not a unitary state, but a complex of fluctuating phenomena. There are two broad classes of sleep distinguished by their EEG, eye movement and muscle tone characteristics, and that these classes alternate dynamically in repetitions of a Non-REM/REM cycle throughout the sleep period, with the dissipation of slow-wave Non-REM and increasing amounts of REM across the cycles. The composition of sleep is also affected by the timing of its own internal processes. The regulation of sleep structure is affected by both homeostatic processes and circadian processes, which have been elaborated in a two-process model of sleep regulation\textsuperscript{[22]}.

Under both free-running and forced desynchrony protocols, it has been revealed that REM sleep propensity is closely tied to the time of the core body temperature nadir\textsuperscript{[23,26]}. Thus, it has been thought that the expression of REM sleep is most likely regulated by circadian processes whereas Non-REM sleep characteristics are more dependent on prior waking duration\textsuperscript{[20]}.

The purposes of the present study were to reveal how far the core body temperature rhythm phase advances over 6 treatment days under natural light-dark cycle conditions, and to evaluate the corresponding changes in sleep structure during such treatments to minimize jet lag effects.

METHODS

Subjects

6 healthy young males participated in this study. Subjects were between the ages of 23 and 26 years of age (mean ± SD = 24.0 ± 1.3), had scores on the Morningness-Eveningness Questionnaire (MEQ)\textsuperscript{[28]} of 48 ± 7.4 (none had extreme scores, 16-30 scores are extreme Eveningness and 70-86 scores are extreme Morningness), and had normal body mass indices (mean ± SD = 22.4 ± 3.4 kg/m\textsuperscript{2}). All were nonsmokers, none were shift workers, and none reported taking any medication or consuming any illicit drug as assessed by a physician’s check and their medical history. None had traveled across time zones during the 3 months prior to study. Subjects gave written informed consent for their participation in the study, which was approved by the Ethics Committee on Human Research of Waseda University.

Study design

The study was completed in the laboratory of Waseda University in Tokorozawa (E139.28, N35.48), Saitama, Japan between June and July in 2011. During this period, the times for sunrise and sunset in Tokorozawa were between 0424 hours and 0448 hours (mean ± SD = 0431 ± 0007), and 1848 hours and 1902 hours (mean ± SD = 1857 ± 0003 hours), respectively. For 1 week prior to the study, subjects were asked to maintain regular bedtimes and wake-up times. During that period, compliance was checked by sleep diaries and wrist-worn activity monitors (AWI, Minimitter, Respironics Inc., Bend, OR). Wrist activity was monitored throughout the study. The protocol consisted of 8 days, as shown in Figure 1. The first day was an adaptation day, and the second day was used as a baseline for subsequent comparisons. From the baseline to day 6, subjects received phase advance treatments in which the timings of light exposure, melatonin intake, sleep time, meal intake, and showering were advanced by 1 hour on each phase advancing treatment day.

Procedures

Subjects assembled in the laboratory at 1600 hours prior to the adaptation night, and inserted probes for rectal temperature recording. Core body temperature recordings began at 1700 hours on the adaptation afternoon. Subjects were fed at 1900 hours, took showers at 2030 hours, and were in bed between 2400 and 0800 hours for the adaptation night; feeding, showering and bed times were considered life cycle variables. Meals were served three times each day during the study, and each subject...
consumed approximately 2,200 kilocalories per day. Each day’s time in the shower was also uniform at 15 minutes. Subjects were asked to remain in bed for 8 hours each sleep period in the temperature controlled laboratory. Nighttime sleep structure was evaluated by polysonomography (PSG, described below) on nights before adaptation, baseline, day 3, and day 6.

Baseline was acquired on the same schedule as adaptation except for the addition of phase advance treatments upon awakening. Phase advance treatments were timed bright light exposure, oral melatonin administration, and life cycle advances. Bright light exposure was performed for 1 hour after waking. The light intensity was 7000 to 8000 lux depending on the angle of gaze, which was measured by the device (CENTER 337, MK Scientific Inc., Japan).

Subjects were permitted to eat and have conversation with an experimenter during the light sessions. Oral melatonin (1.0 mg) was administered at designated times. In baseline, light exposure occurred from 0810 to 0910 hours and melatonin intake was at 1600 hours. From day 2 forward, phase advance treatments and life cycle variables were each advanced 1 hour per day. Thus, for example, sleep time on night before day 6 was from 1800 to 0200 hours. Light exposure and melatonin intake were not performed on day 6.

This study was conducted under the natural light-dark cycle. Subjects were allowed to attend classes, walk outside, play computer games, and read books, although naps and exercise were prohibited throughout the study.

**Recording and data analysis**

Rectal temperature was recorded every 60 seconds by an ambulatory device (LT8A, Gram Corporation, Japan). Temperature was recorded continuously for 8 days. The temperature raw data for each day (24 hours) was then cosine-fitted and each temperature nadir was identified.

PSG recording was performed on the nights prior to the adaptation, baseline, day 3, and day 6 activity days. Scalp electroencephalograms (EEGs) from standard placements at F4, C4, and O2 (referred to linked mastoid electrodes; time constant = 0.5 sec), electrooculographic (EOG) horizontal and vertical eye movements (referenced to linked mastoid electrodes; time constant = 0.5 sec), and a chin surface electromyogram (EMG) (time constant = 1.5 sec) were digitally recorded for offline analysis. An ambulatory recording device sampling each channel at 500 Hz (Polymate II AP216; TEAC Corporation, Japan) was used for all PSG recordings. Visual sleep stages (wake, sleep stage 1, sleep stage 2, sleep stage 3, and sleep stage REM) scoring of each 30 sec PSG epoch was performed by an experimenter, following the American Academy of Sleep Medicine guidelines. Data from the nights before baseline, day 3, and day 6 were analyzed. The adaptation night was discarded from analysis.

Subjective sleepiness was assessed using a 100 mm visual analogue scale (VAS) completed by each subject just after the scheduled wake time and just before bedtime.

**Statistics**

SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for analysis. Time of the body temperature nadir, sleep parameters, and subjective sleepiness were analyzed using a single-factor, repeated-measures ANOVA. The Greenhouse-Geisser correction for repeated measures was applied to all ANOVAs. Significance was assessed with the Bonferroni significant difference test. The relationship of nadir phase advances and %REM between baseline, day 3, and day 6 used correlational analysis and ‘r’ represents Pearson’s correlation coefficient. Statistical significance was defined as the 95% level of confidence.

**RESULTS**

Figure 2 shows the changes of the temperature nadir on each study day. A single-factor, repeated-measures ANOVA performed on each nadir revealed significant differences ($F_{15} = 947.69, p < 0.001$). Post hoc analysis with the Bonferroni method confirmed that each nadir was significantly advanced compared to baseline ($p < 0.05$). Significant incrementing differences were also found from day 3 through day 6 compared to day 1, from day 4 through day 6 compared to day 2, day 5 and day 6 compared to day 3, day 5 and day 6 compared to day 4, and between day 5 and day 6 ($p < 0.01$). Nadirs in baseline and in day 6 were $0516 ± 0102$ hours and $0036 ± 0053$ hours, respectively. The mean nadir had advanced approximately 4.5 hours from baseline to day 6.

Figure 3 shows the corresponding changes in subjective sleepiness before bedtime and after each awakening. A single-factor, repeated-measures ANOVA revealed no significant differences. Means and standard deviations of PSG sleep structure characteristics during baseline, day 3, and day 6 nights are shown in Table 1. A single-factor, repeated-measures ANOVA and post hoc analysis with the Bonferroni method applied for each sleep characteristic revealed that the only significant difference was the decreased REM sleep duration between baseline and day 6 ($F_{15} = 196.31, p < 0.05$). Increased wake after sleep onset (WASO) and decreased sleep efficiency (SE) were also noted as suspect, but not statistically significant.
exposure after awakening followed by administration of oral melatonin (1.0 mg) after 8 hours, in combination with advancing environmental feeding, showering and bed times. Compared with baseline, significant temperature nadir phase advances were observed on all experimental days ($p < 0.05$). Significant step-wise differences were also found from day 3 through day 6 compared to day 1, from day 4 through day 6 compared to day 2, day 5 and day 6 compared to day 3, day 5 and day 6 compared to day 4, and between day 5 and day 6 ($p < 0.01$).

Thus, we succeeded in advancing core body temperature with phase advance treatments. However, although sleep phase advanced 6 hours, the difference of temperature nadir timing between baseline and day 6 was only approximately 4.5 hours. This indicates that the body temperature rhythm was not completely synchronized with sleep phase. Although there was no overall statistically significant change, sleep efficiency on the third night was still 90.3% (compared to 96.9% baseline value), but only 78.2% on the sixth night. As found for core body temperature phase, the biological rhythm reflected in sleep structure after 6 days of phase advancing treatment also might not have completely synchronized with the scheduled sleep phase.

One of the reasons for this imperfect synchronization may be that this phase advance schedule was too rapid for the...
body clock to follow. It is also possible that further core body temperature rhythm advance was prevented by the ongoing stability of natural light conditions. In later experimental days, subjects went to bed in the early evening, having spent their wakingbrightly-lit circumstances during their intended phase-delay period before going to bed. Past studies indicated that even room lighting levels could entrain the core body temperature rhythm to local time\(^{(25,30)}\). Experiments have also shown that avoiding light exposure during phase delay periods, for example by wearing sun-glasses, could enhance the advancement of circadian rhythms\(^{(25)}\).

Eastman et al. compared sleep schedules advanced by 1 hour per day with 2 hours per day on 3 treatment days. They reported subjective sleepiness after wake time was not different between groups throughout the experiment\(^{(32)}\). However, since they did not record PSG, any physiological changes in sleep structure were unknown. In the present study, we found no significant changes in subjective sleepiness before bedtime and after wake time after each intervention (Figure 3), indicating the phase advance treatments did not lead to major subjective sleep disturbances. However, PSG measurement on baseline, day 3, and day 6 revealed that REM sleep duration was significantly decreased on day 6 compared to baseline \((p<0.05)\).

If an internal circadian phase for REM propensity completely followed the phase advance treatments, %REM should have remained consistent. Therefore, the obtained relationship between nadir phase advances and %REM in baseline, day 3, and day 6 indicates the dissociation of REM sleep propensity and the body temperature rhythm (Figure 4). Non-REM sleep duration did not find significantly different throughout the treatment period, perhaps because unlike REM sleep the regulation of Non-REM sleep has only slight relevance to circadian phase\(^{(28)}\). On the other hand, significant differences were found in REM sleep duration and the correlation between temperature nadir phase advances and %REM in baseline, day 3, and day 6 \((r=-0.499, p<0.05)\).

We interpret these results to reflect misalignment between the core body temperature rhythm and scheduled sleep-wake cycle. Although REM sleep duration did not find significantly in the first 3 days of the treatment period, 6 days of treatment induced significant misalignment between endogenous rhythms and scheduled life cycle interventions.

CONCLUSION

In conclusion, 1 hour of bright (7000 to 8000 lux) light exposure after waking followed by oral melatonin (1.0 mg) intake later in the day, in the context of life cycle variable advancement induced an approximately 4.5 hour temperature nadir phase advance during otherwise unchanged environmental activities under natural lighting. However, PSG measurement revealed significantly decreased REM sleep duration in day 6 compared to baseline \((p<0.05)\). These results suggest that more than four hours of phase advance is possible under natural light-dark conditions. However, phase shifting 1 hour per day may be too quick to preserve the normal sleep structure. Such preservation might be more feasible if the treatment advances phase less than 1 hour (e.g. 30 min) a day, and the total phase shift is up to 4 hours. Since sleep inhibition, the major alternative procedure to minimize anticipated jet lag, may itself induce degradation of daytime performance and motivation\(^{(35)}\), the present results support the design of phase advance protocols that are practical for those who need to be working during the days while preparing to avoid jet-lag problems. Indeed, the participant’s size was small, but this study was valuable results towards the application of avoiding jet-lag problems. A further obvious conclusion might be obtained by increasing participants.

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References


