A LARGE NUMBER of experimental studies have shown that the ability to initiate and maintain sleep is at least partially controlled by thermoregulatory processes. Studies of transmeridian travel, shift-work, and time-free environments indicate that variations in core temperature (Tc) can alter the initiation, duration, and evolution of sleep processes. The observed relationship between Tc and sleep appears straightforward, as shown by the temporal association of sleep initiation and termination with the circadian rhythm of Tc. For example, within a 24-hour period, sleep is most likely to be initiated when Tc is declining or is lowest, and least likely when temperature is rising or highest. Conversely, the probability of sleep termination is highest during the peak or rising part of the Tc rhythm and lowest near the trough or declining portion of the temperature curve.

These observations are further supported by the observation that, the rise in Tc, which is usually associated with the end of the sleep period, typically occurs earlier in certain populations who suffer from premature termination of sleep. An early rise in Tc may be induced pharmacologically or with heating protocols. However, the same observation typically can be made during the sleep periods of specific groups, including the elderly, shift-workers, and transmeridian travellers. Taken together, the results of these studies suggest that elevated core temperature may underlie some of the sleep disruption observed in these groups.
clearly co-vary in subjects studied in time-free environments, however, many other physiological measures also free-run with Tc and may also influence sleep. Similarly, drugs known to affect temperature, such as caffeine, aspirin and alcohol, have other non-specific actions so it is unclear whether observed effects on sleep are direct, or due to indirect effects on physiological systems such as thermoregulation.

Finally, studies involving heating protocols typically have produced large changes in Tc (up to 2.5 °C), which are considerably higher than would occur under average physiological conditions (e.g., moderate exercise) and certainly greater than the circadian variation in unmasked Tc (0.5 - 0.75 °C). For example, one previous study increased subjects’ Tc by up to 2.5 °C using a high humidity microenvironment with an ambient temperature of 39 °C. Such an increase would normally only be seen with fever or extreme exercise.

The aim of our study was to determine whether we could produce an increase in core temperature, within the circadian range, during nocturnal sleep. Furthermore, we wished to investigate any effects of this core temperature increase on nocturnal sleep.

METHODS

Subjects

Sixteen subjects (9 male, 7 female) aged between 18 and 23 years (mean±SD: 20.5±1.2 yrs) gave informed consent to participate in this study. The study was approved by the Human Research Ethics committee at the Queen Elizabeth Hospital, Adelaide, South Australia. A 14-day sleep diary and general health questionnaire were employed to ensure that subjects had a regular sleep pattern and no concurrent medical or psychiatric complaints. Subjects were required to abstain from intense exercise and drugs known to affect sleep or thermoregulation (e.g., alcohol, caffeine, and aspirin) for the duration of the study. Information regarding menstrual phase was obtained during screening and general health questionnaire were employed to ensure no concurrent medical or psychiatric complaints.

Procedure

The experiment was performed on three non-consecutive nights to allow a recovery sleep night, outside of the laboratory, between experimental conditions. The first experimental night served as an adaptation to the laboratory environment and the protocol used in the study. Subjects then completed counter-balanced baseline and experimental (heat) conditions on the Second and Third nights of the study.

Subjects reported to the laboratory at 1930h, and prior to 2200h, were fitted with electrodes to allow polysomnographic (PSG) recording of the night’s sleep. Subjects lay in bed and self-selected lights out from 2330h.

A standard PSG montage of electrodes was used, including EEG (C3-A2 and O2-A1), EOG and facial EMG. PSG data were acquired using a Sleep Analysing Computer (SAC 847) from Oxford Medical Inc., Oxford, UK. The SAC 847 samples at 500 Hz and stores data at 250 Hz within a 70 Hz bandwidth, with a low-filter-cut-off of 0.33 Hz. PSG recordings were later manually scored in 30-second epochs according to the criteria of Rechtschaffen and Kales by two independent observers.

Subjects were required to collect a urine sample across each sleep period. A sample of this urine was later assayed for a melatonin metabolite, 6-sulphatoxymelatonin (aMT6s). Previous research has shown that urinary aMT6s levels are closely related to plasma melatonin levels. The amount of aMT6s released across the night was used as an indicator of melatonin secretion across the sleep period.

Rectal core temperature was measured continuously using a rectal thermistor (YSI-4400 series, Yellow Springs Instruments, OR) connected to an ambulatory temperature recorder (Mini-logger, Mini-Mitter Co., Sunriver, OR). Core temperature and PSG recordings commenced at 2230h and continued until subjects’ terminal awakening.

During the experimental condition, beds were heated with an electric blanket (Riviera, Model MB, 32V, 138W) located between the mattress and bottom sheet. Heat was applied from 0230h until termination of the sleep period (i.e., the morning awakening). The blankets were modified by The Queen Elizabeth Hospital Biomedical Engineering Department to eliminate electromagnetic interference with the PSG equipment. This was achieved by rectification and regulation of the AC to a low voltage DC current. Modification of the blankets was designed to eliminate any low frequency electromagnetic fields that have been shown to suppress slow wave sleep. In the baseline condition, the blanket was on the bed but was not switched on.

Data Analysis

Core temperature data were averaged into 30 minute bins and individual temperature values were expressed relative to the temperature at 0230h. Using the SAC software, hourly sleep reports were generated for the period 2330 to 0630h. All sleep and temperature measures were analysed using a two factor (condition x time) repeated measures ANOVA. Planned means comparisons were used to determine when significant temperature and sleep differences occurred due to the experimental treatment. Significance was achieved at a=0.05.

RESULTS

Rectal Core Temperature
Heating applied from 0230h was associated with a significant increase in rectal core temperature of 0.18±0.03 °C (mean±SEM) from 0400 to 0700h relative to Baseline (p<0.05). As shown in Figure 1, a significant increase in mean Tc was observed after 90 minutes of heating and was maintained for the remainder of the sleep period (p<0.05).

**Polysomnographic Measures**

Repeated measures ANOVA showed significant condition by time interactions (all p<0.05) for Stage 0 (wake), stage 1, the number of stage changes, and sleep efficiency (% of sleep period time spent sleeping). There were no significant changes in stage 2, slow wave, or REM sleep, nor in movement time or number/duration of arousals. Figure 2 shows the effects of heating from 0230-0630h on the hourly sleep measures for which significant main effects were observed. The amount of Stage 0 and sleep efficiency were significantly different between conditions at all time points from 0230h. In addition, significant differences between conditions were observed at 0430h for stage 1 sleep and at 0230h and 0530h for the number of stage changes.

Table 1 shows that heating was associated with a significant decrease in sleep efficiency between 0230 and 0700h (mean±SD: 5.5±0.9%). The amount of total wakefulness (or stage 0), stage 1 sleep, and the number of stage changes between the baseline and treatment conditions all significantly increased. The amount of stage 2 sleep, slow wave sleep (SWS), rapid eye movement (REM) sleep, movement time, and the number and duration of arousals remained unchanged by heating.

**Analysis of Arousals and ATc during Arousals**

Repeated measures ANOVA showed that there were no significant effects of the experimental condition on arousal duration. The mean duration of arousal in the baseline condition was 1.38±0.70 minutes (mean±SEM) for the “before 0230h” period and 2.44±2.91 minutes in the “after 0230h” period. The mean duration of arousal in the experimental condition was 4.56±2.47 minutes (mean±SEM) for the “before 0230h” period and 3.75±1.23 minutes in the “after 0230h” period.

Similarly, ANOVA results showed that there were no significant effects of the experimental condition on the number of arousals. However, there was a strong trend towards an increase in the number of arousals (p=0.054). The mean number of arousals in the baseline condition was 0.38±0.18 (mean±SEM) for the “before 0230h” period and 0.63±0.38 in the “after 0230h” period. The mean number of arousals in the experimental condition was 0.75±0.49 (mean±SEM) for the “before 0230h” period and 3.25±0.84 in the “after 0230h” period.

Although a strong trend toward increased number of arousals was observed, repeated measures ANOVA showed that there were no significant effects of arousals on Tc. The mean core temperature change during arousal in the baseline condition was -0.007±0.007 °C (mean±SEM) for the
“before 0230h” period and 0.008±0.007 °C for the “after 0230h.” The mean core temperature change during arousal in the experimental condition was -0.028±0.02 °C for the “before 0230h” period and 0.0003±0.012 °C for the “after 0230h.”

Analysis of Melatonin Metabolite (aMT6s) Secretion between Conditions

Repeated measures ANOVA results showed that there were no significant effects of the experimental condition on 6-sulphatoxymelatonin (aMT6s) secretion. The mean level of aMT6s secretion was 33.9±4.6 nmoles (mean±SEM) for the baseline condition and 37.5±3.8 nmoles in the experimental condition.

DISCUSSION

The present study indicated that direct heating of subjects from 0230h during the sleep period was associated with a significant Tc increase of approximately 0.2 °C. A significant difference from baseline Tc was achieved within 90 minutes of the electric blanket being turned on and the elevation in Tc was maintained for the remainder of the sleep period. This Tc increase represents 15-20% of the circadian peak-to-trough amplitude observed in the Tc rhythm of young, healthy individuals.27

Compared to baseline, the treatment condition produced no significant changes in the secretion of the melatonin metabolite aMT6s. Even with a larger number of subjects, no significant change would be expected. This is as expected as there is no suggestion from the literature that melatonin can be manipulated via changes in Tc.

The treatment condition produced a significant disruption of sleep. Specifically, the amount of wakefulness, stage 1 sleep and number of stage changes increased significantly. Following heating, the amount of wakefulness increased almost three-fold compared to baseline. Consequently, sleep efficiency decreased nearly 6% to below 90%. Such a level of disruption is comparable with that observed in clinical insomnia.32

Previous heating protocols have typically increased Tc by up to 2-2.5 °C before sleep or during brief awakenings.11,17,28-30 However, such relative temperature increases are significantly greater than observed under normal environmental or physiological conditions (e.g., high ambient temperature or moderate exercise). Therefore, the Tc increases in previous studies may have produced large homeostatic responses to preserve normal physiological function. By comparison, Tc elevations observed in this study may better reflect those associated with circadian disruption, such as results from shiftwork and transmeridian travel. Similar changes in Tc have been achieved using timed bright light exposure in young adults, which phase-shifts the circadian system.31 Thus, the current protocol may be further developed as another method to “age young sleep,” although it is likely that the underlying Tc rhythm is masked and not phase-shifted by the heating protocol.

Previous studies using heating or exercise prior to sleep produce elevations in temperature that are not maintained throughout the entire sleep period. Any elevation in Tc produced prior to sleep, is more likely to affect sleep initiation than the current protocol. This is due to the connection of sleep initiation with rate-of-decline in Tc.6 In addition, it is likely that any effect of heating prior to sleep is confounded by the fact that the shape of temperature rhythm across the sleep period is altered relative to a normal rhythm. That is, the temperature may be relatively higher in the first part of the night and relatively lower in the later part of the night. The current protocol was successful in producing Tc elevations of both similar magnitude and duration as those seen in clinical populations (Figure 1).

Interestingly, during the experimental condition, a decrease in sleep efficiency occurred without any change in the number or duration of arousals across the sleep period. However, there was a strong trend (p=0.054) for an increase in the number of arousals. This could be interpreted to mean that increasing Tc does not affect sleep initiation but may affect the maintenance of sleep. The inverse of this, that declining temperature facilitates the maintenance of sleep, has previously been reported. It must be noted, however, that most studies to suggest this have been carried out using artificially induced insomnia,33 or insomnias related to chronobiological disorders.34,35

It is important to understand the exact relationship between the increase in Tc and the increase in sleep disruption. The question to be answered is “does the heating directly cause the sleep disruption, or, is the disruption mediated via such an outcome as increased wakefulness due to being too hot?”. There is clear evidence to suggest that Tc can be relatively increased (up to 0.05 °C, see Figure 2 in 36) by 20 minutes of continuous wakefulness. However, the increases observed during these 20 minute awakenings (for testing sessions) were not significant. In addition, the temperature changes during the 20 minute awakenings were not analysed independently of the temperature changes which occurred during the 20 minute testing sessions during the day. This previous research suggests that increases in Tc can be induced purely by keeping individuals awake for 20 minutes during the sleep period. However, the findings of the current study showed no trends or significant changes in Tc during awakening. It is also important to note that all of the awakenings present in the data, only three are greater than 20 minutes in duration. The changes in temperature across these three periods were -0.15, -0.05, and 0.05 °C respectively. For these samples at least, it is unlikely that awakenings contributed to any increases in Tc due to the experimental condition.
The results of this study indicate that the experimental heating protocol was not associated with an increase in the number or duration of arousals from sleep. In addition, there were no increases in Tc that occurred during the arousal. Therefore, the increases in Tc during the experimental condition appear to be due to subjects being heated and not because they spend more time awake. This is further supported by the fact that melatonin levels were not effected by the heating (i.e., suggestions that changes in melatonin secretion due to heating could underlie temperature changes are unfounded). Therefore, it can be suggested from the results that the heating protocol produced an increase in subject’s core body temperature and that this led to a disruption of sleep. It can also be suggested that this disruption of sleep was not mediated via an increase in wakefulness or a suppression of melatonin secretion. Thus, the results of the current study suggest that increased nocturnal Tc alone is associated with disrupted sleep. There are very few reported studies involving sustained heating during sleep. There are very few reported studies involving sustained heating during sleep, due to methodological technical issues and not because they spend more time awake. This is further supported by the fact that melatonin levels were not effected by the heating (i.e., suggestions that changes in melatonin secretion due to heating could underlie temperature changes are unfounded). Therefore, it can be suggested from the results that the heating protocol produced an increase in subject’s core body temperature and that this led to a disruption of sleep. It can also be suggested that this disruption of sleep was not mediated via an increase in wakefulness or a suppression of melatonin secretion.

The means by which increasing Tc influences sleep is not yet known. It has previously been suggested that the circadian rhythm of sleep/wakefulness appears to result from both circadian control of body Tc and circadian processes governing the sleep/wake cycle. However, the results of the present study, as well as those of Karacan and colleagues strongly support the suggestion that sleep is directly influenced by core body temperature. It may even be the case that the unmasked circadian Tc rhythm is a major contributor to the circadian sleep/wake rhythm.

In summary, the possible relationship between Tc and sleep quality has typically been inferred from results of studies involving indirect manipulation of temperature. The current study, however, provides supporting evidence for this relationship by more directly manipulating Tc. Increased nocturnal Tc of similar magnitude and duration to that observed in the present study have been observed in poor sleepers. If elevated Tc contributes to poor sleep, then direct manipulation of Tc may be of possible clinical benefit in the treatment of sleep disturbances. For future research, elevations in core temperature within the physiological range could be induced using the current methodology. The utility of such elevations for research purposes may allow better understanding of core temperature related insomnia or the effects of shiftwork and jet-lag.

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