Symposium: Circadian Influences on Sleep

Sleep dominates our daily life and is yet so little understood. Why do we sleep, what triggers our sleep, what induces our awakening. What are the essentials of sleep structure and sleep quality. How is sleep modulated by a circadian signal. In this symposium several aspects of sleep are discussed ranging from the circadian sleep structure, the interaction with deep body temperature and the changes that occur at ageing to the effects of shift work.

Circadian Aspects of the Sleep Structure

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Introduction

Normally, sleep stage structure has been studied in major sleep episodes either at night, or at different times of day (1,2) or at different phase positions in the circadian temperature cycle in the absence of the natural 24-hour day (3,4). In isolation studies, the sleep structure of the major sleep episodes is measured during free-running circadian cycles (5,6,7). It has been shown, that in addition to sleep onset and sleep duration, sleep stage structure exhibits a circadian variation. Nevertheless, this finding refers only to major sleep episodes and does not take into account that sleep regulation may be an ongoing process.

Recently it has been shown that a monophasic circadian sleep/wake sequence model may not be sufficient to explain basic sleep/wake regulation (8). Thus, to view sleep as on ongoing process, the analysis of sleep cannot be based on data from experiments where sleep is restricted to the normal night phase. One experimental design, which allows the spontaneous expression of sleep and wakefulness is the constant bedrest design. In this condition, subjects not only sleep ad lib. while isolated from the natural environment, but had also no behavioral alternatives to sleep while lying continuously in bed. By eliminating the external influences on sleep, the more endogenous aspect of sleep regulation can be analyzed from an ongoing sleep process. However, this procedure has been shown to lead to an increase in the amount of sleep (9). To control for this variation in the amount of sleep, modifications of the experimental design have been carried out. In the following experiment, in addition to a constant bedrest condition, an increase in the need for sleep was achieved by including two total sleep deprivation conditions, which differed in their respective durations. To control for the possibility of sleep satiation, an intermittent bedrest condition was included, where the constant bedrest condition was interrupted every four hour for 2,5 hours, which gave an ultradian pattern to the permanent sleep restriction schedule over the entire experimental episode.

Method

Twenty healthy volunteers (11 females, 9 males; ages 17-46, mean 36,2 years) participated in this study. Each of the subjects underwent session #1 and #2, while ten of them in addition underwent session #3 and #4 in the sleep laboratory. All sessions started at 2300 h for all subjects and lasted 32 hours. The four conditions were as follows:

Session #1: **Condition "S"** (sleep): Session with constant bedrest throughout the entire 32 hours.

Session #2: **Condition "SD"** (sleep deprivation): Session began with 8 hours of total sleep deprivation followed by constant bedrest for the remaining 24 hours.

Session #3: **Condition "PSD"** (prolonged sleep deprivation): Session began with 10 hours of total sleep deprivation followed by 22 hours of constant bedrest.

Session #4: **Condition "IB"** (intermittent bedrest): condition "S" was interrupted every 4 hour for 2,5 hours of forced wakefulness in the same environment, followed by 1,5 hour of bedrest condition. This sequence continued throughout the 32 hours of the experimental condition.

During every section of "constant bedrest" the subjects had to lie continuously in bed, where they could take their snacks ad libitum.

The control of the dim illumination in the room was at the discretion of the subject, who had no knowledge of the time of day. Subjects were not allowed to read, write, listen to music, or exercise. It was possible for the experimenter to communicate with subjects (e.g. regarding experimental instructions) by an intercom system. The following measurements were recorded continuously: EEG, EOG, EMG, rectal temperature and wrist activity. The sequence of the two conditions S and SD was randomized for all twenty subjects. Ten subjects randomly chosen from the overall group underwent condition PSD after the condition S and SD. Condition IB was carried out last.

Results

Total Sleep Time: In session S the subjects slept an average of 18.1 h, in session SD, with the 8 h sleep deprivation 15,9 h, in session PSD 14,0 h (10 hours sleep deprivation) and in session IB with the scheduled short sleep episodes 9,0 h of the 12 h of total bedrest. Thus, the sleep restriction is relatively compensated by an increase in sleep during the possible available time (condition S: 57 %, SD: 66 %, PSD: 64 % and in IB: 75 % of the respective bedrest episode (absolute values see: Figure 1; top left, with the course of the cumulative values of total sleep time; TST). The distribution of sleep over day and night can be seen in Figure 1; bottom left, with the mean hourly values expressed in relative amount per hour (sleep efficiency; SE). In all sessions the amount of sleep showed a decrease during the day-phase until the early evening, where a clear trough is to be seen.

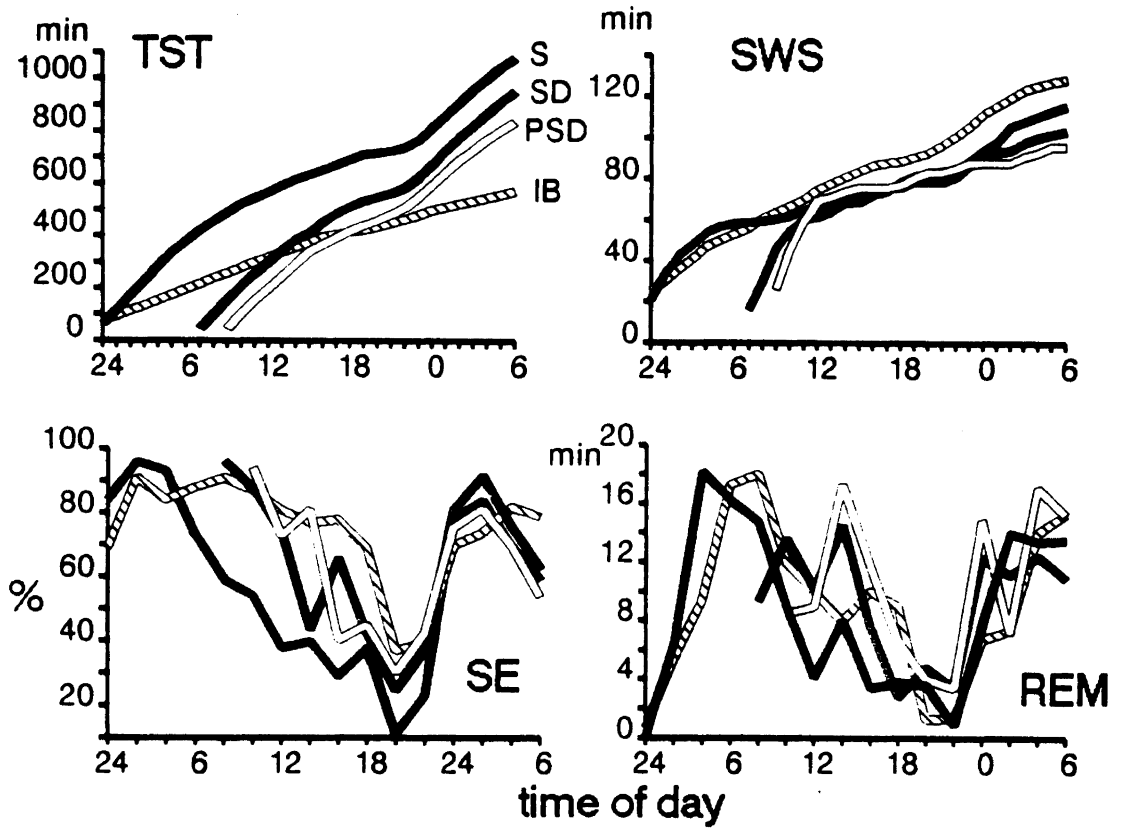

Fig. 1. Cumulative amount of (top left) total sleep (TST; total sleep time) and of (top right) slow wave sleep (SWS). Two-hourly mean values of the (bottom left) relative amount of sleep (SE; sleep efficiency) and (bottom right) REM sleep in the four different conditions. Condition **S**: constant bedrest with Sleep ad lib; **SD**: constant bedrest with 8 h Sleep Deprivation; **PSD**: constant bedrest with a Prolonged Sleep Deprivation of 10 h and **IB**: Intermittent Bedrest.

In the further course, the amount of sleep increases with a steep rise to the high values of the second night.

REM sleep

The amount of REM sleep changed with the values of TST. In condition S the subjects showed a mean of 246 min, in SD 203 min, in PSD 186 min and IB 108 min. This resulted in relative values of S 23 %, SD 21 %, PSD 22 % and IB 20 %. These differences in relative values were not significant. The course of REM sleep showed a reduction over the day. The afternoon and especially the early evening was characterized by a minimum of REM sleep. That this circadian variation is not only due to the reduction in total sleep time can be seen by matching morning (0600-1000 h) and evening (1800-2200 h) sleep episodes of equal duration (condition IB); the differences in the amounts of REM sleep persist (23,2 % versus 14,7 %). Sleep deprivation does not significantly change the relative amount nor the circadian variation.

SWS

The cumulative amount of SWS is remarkable similar in all conditions (Figure 1, top right). The absolute values are comparable with (S 115 min, SD 104 min, PSD 102 min, IB 128 min) and the relative values are with S 10 %, SD 11 %, PSD 12 % and IB 24 % only for the latter condition different. This result supports the finding of the cumulative values: with restriction of sleep, the absolute amount of SWS remains relatively constant. This can only be achieved by increasing the relative amount which results in up to 50 % of SWS occurring within one NREM-episode. After sleep deprivation the deficit in SWS is compensated after about 4 h of sleep. The amount of SWS is solely dependent on prior wakefulness (within certain limits) and does not show a circadian variation (10). Following the high amount after sleep onset, the occurrence of SWS remains relatively low (with random fluctuations) providing that there is not a longer episode of wakefulness, which in itself leads to an increase in SWS in the subsequent sleep episode. This relationship can also be seen by the slightly higher amount of SWS in condition IB. The interruptions of sleep lead to higher SWS-values compared to the spontaneous course of sleep.

Discussion

Constant bedrest in an unscheduled environment with no behavioral options to sleep resulted in the intended increased amount of sleep. The focus of the experiment was how this additional sleep and its structure was distributed over the experimental period. In addition it could be assessed, how different intensities in the need for sleep changed this sleep pattern.

In constant bedrest, the normal 24-hour distribution of sleeping and waking persisted with a high amount of sleep during the night phase and a low amount during the day. This low amount of day sleep does not show an equal distribution; it varies predictable over the day. The high amount of sleep of the first night decreases throughout the day until it reaches a minimum in the early evening, where a sharp rise in sleep propensity leads to the high amount of sleep in the second night. That this decrease of spontaneous day sleep is not due to sleep satiation can be concluded from the intermittent bedrest study, where the subjects were restricted in their sleep length. This result is in agreement with studies with scheduled short sleep episodes which showed a similar course of sleep tendency (4,11). The early evening is characterized by a remarkable low amount of sleep just before the main peak in sleep onset. This phase has been described as the "forbidden zone" for sleep, and occurs just before the nocturnal "sleep gate" (11). The present findings support this interpretation. From these studies it can be concluded that the circadian variation of sleep propensity is not limited to the nocturnal placement of the major sleep episodes but is also seen during the diurnal period. Beside the most robust characteristic of day sleep propensity (forbidden zone), an ultradian variation has also been described (8,12).

The characteristic pattern with the typical late afternoon dip is still to be seen in conditions where the normal circadian pattern is disturbed by preceding sleep

deprivation. The distribution of the recovery sleep is strongly influenced by the persistence of a controlling circadian mechanism. Nevertheless, the increased need for sleep at the time of the sleep "forbidden zone" leads to a less pronounced trough in sleep propensity. This result questions the term "forbidden zone for sleep" since the increased need for sleep (a homeostatic influence) seems to allow sleep even at the circadian minimum of sleep propensity. Therefore the "forbidden zone" refers only to the circadian influence. Normally, under non-sleep deprived conditions, the circadian factor is in relative terms, dominant over the homeostatic component.

In this study the occurrence of sleep is, especially at different times of day, characterized by short sleep episodes. Thus, conclusions regarding the sleep stage structure of sleep should be limited to such brief sleep episodes and not be generalized to sleep regulation per se. This is especially true for the distribution of REM sleep. The present finding shows, that the absolute amount of REM sleep is in synchrony with the amount of TST. But in addition, REM sleep (at sleep onset) shows a circadian variation independent from the circadian course of TST. The conclusion can only be, that at the beginning of a sleep episode a circadian modulated mechanism influences the sleep stage structure (10), while the succeeding NREM-REM cycles are not controlled by this regulatory mechanism. This conclusion is supported by further studies which demonstrated, that only the first NREM-REM cycle shows a circadian fluctuation (6,13).

The course of SWS shows the well-known independence from the duration of a sleep episode. SWS occurs at the beginning of sleep, independent from the circadian phase. Its amount depends on the duration of preceding wakefulness. Thus, a loss of SWS is compensated by increased amount of SWS, leading to a compensation within the first hours of sleep. As has been shown earlier (10), a periodic influence in the occurrence of SWS is not supported by this study.

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How Stable is the Clock in Humans?

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It is generally accepted that a measured circadian rhythm consists of two components; an endogenous component due to the internal oscillator(s) – the body clock – and an exogenous component produced by an individual's lifestyle and environment. For rectal temperature, the exogenous or masking effects include rises in body temperature produced by different types of activity, and falls produced by sleep (1). Thus, in spite of the observation that circadian rhythms are normally adjusted to a 24-h day, it is not known to what extent this phase stability reflects entrainment of the body clock and/or a reproducibility of exogenous factors.

Our purification method (2) enables an estimate to be made of the endogenous component of the circadian rhythm in individuals living a normal schedule and in the presence of masking factors. We have used the method to estimate the phase of the endogenous component of the rectal temperature rhythm in up to 22 successive days in 13 healthy subjects.

Eleven of these subjects were studied in our Isolation Unit. They lived a conventional lifestyle with regard to hours of sleep and waking, and times of meals. The confines of the Unit meant that their daytime activities were sedentary. Two further subjects who also kept an activity log were studied living normally with their families. Rectal temperature was measured throughout and hourly records have been used in the present analysis.

s of temperature dah and the times of sleep and different types of activity and adjusts the raw data in accord with the subject's activities during the previous hour. It then assesses the phases of the purified rhythm in comparison with a standard rhythm – "normative endogenous data", obtained from subjects in whom masking effects were minimal. The phase of the purified rhythm and size of masking effects are calculated by finding the combination which minimizes the summed squared deviations between this purified rhythm and the standard rhythm. As a control, the phase of