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Dijk, Derk Jan; Beersma, Domien G.M.; Daan, Serge; Lewy, Alfred J.

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# Bright morning light advances the human circadian system without affecting NREM sleep homeostasis

DERK JAN DIJK, DOMIEN G. M. BEERSMA, SERGE DAAN, AND ALFRED J. LEWY
*Departments of Biological Psychiatry and of Zoology, University of Groningen,*
*9713 EZ Groningen, The Netherlands; and Department of Psychiatry,*
*The Oregon Health Sciences University, Portland, Oregon 97201*

DIJK, DERK JAN, DOMIEN G. M. BEERSMA, SERGE DAAN, AND ALFRED J. LEWY. *Bright morning light advances the human circadian system without affecting NREM sleep homeostasis.* Am. J. Physiol. 256 (Regulatory Integrative Comp. Physiol. 25): R106–R111, 1989.—Eight male subjects were exposed to either bright light or dim light between 0600 and 0900 h for 3 consecutive days each. Relative to the dim light condition, the bright light treatment advanced the evening rise in plasma melatonin and the time of sleep termination (sleep onset was held constant) for on average ~1 h. The magnitude of the advance of the plasma melatonin rise was dependent on its phase in dim light. The reduction in sleep duration was at the expense of rapid-eye-movement (REM) sleep. Spectral analysis of the sleep electroencephalogram (EEG) revealed that the advance of the circadian pacemaker did not affect EEG power densities between 0.25 and 15.0 Hz during either non-REM or REM sleep. The data show that shifting the human circadian pacemaker by 1 h does not affect non-REM sleep homeostasis. These findings are in accordance with the predictions of the two-process model of sleep regulation.

light; sleep; melatonin; circadian rhythms; electroencephalogram; spectral analysis; two-process model

THE TIMING OF human sleep has been the subject of various theoretical models. Two models have been published recently (9, 17). In the model of Kronauer et al. (17) two self-sustaining circadian pacemakers ($x$ and $y$) interact to generate the sleep-wake cycle. The $x$ or deep oscillator, located outside the suprachiasmatic nuclei (SCN), is reflected in the endogenous component of the body temperature rhythm and rapid-eye-movement (REM) sleep propensity, whereas the $y$ oscillator is thought to regulate the rhythm in slow-wave sleep (SWS). In the original formulation (17) sleep occurs during the central two-thirds of the trough in $y$, whereas in a more recent formulation sleep ends when $y$ upwardly crosses its mean value and sleep begins approximately one-third of a $y$-cycle earlier (14).

In the two-process model (3, 8, 9) the alternation between sleep and wakefulness results from the interaction of a circadian process (process C), which is generated by the circadian pacemaker located in the SCN, and an hourglass process. This latter process, called process S, keeps track of the history of sleep and wakefulness and thereby monitors the physiological need for sleep. Sleep is initiated when S reaches an upper threshold, after

which S decays during sleep until a lower threshold is reached and sleep is terminated. Both thresholds together are called process C and are modulated by the circadian pacemaker. The minima and maxima coincide roughly with the minimum and maximum of the body temperature rhythm, respectively. Under normal conditions waking up occurs on the rising part of the lower threshold, which coincides with the rising part of the body temperature curve (15). The time course of process S can be monitored by spectral analysis of the electroencephalogram (EEG) during non-REM (NREM) sleep. Power densities of the $\delta$ and $\theta$ frequencies decay exponentially during sleep, reflecting the diminishing sleep need (4, 12). The build up of process S has been quantified by measuring power density at the beginning of a sleep episode as a function of the duration of the preceding wake episode. This EEG parameter indeed does increase monotonically as the duration of prior wakefulness increases without any sign of circadian modulation (11).

Because in both models the sleep-wake cycle is governed by circadian pacemakers with intrinsic periods deviating from 24 h, pathways by which zeitgebers exert period and phase control over these pacemakers have been postulated. In the Kronauer model (14, 17) it is assumed that zeitgebers act on the $y$ (the sleep wake) oscillator, which in turn influences the $x$ (body temperature) oscillator. In contrast, in the two-process model it is assumed that zeitgebers act directly on the pacemaker that generates the C process (2, 9). Because under steady-state conditions process S is virtually phase locked to process C, changes in the period or phase of the C process will lead to similar changes in the sleep-wake cycle.

There has been some discussion over the nature of the zeitgebers for the human circadian system. Social cues have long been considered powerful zeitgebers (28), but more recent experiments indicated that light also in humans, as in other mammals, acts as a zeitgeber (6, 21, 29). The discovery that light of an intensity much higher than ordinary room light suppresses the nightime melatonin secretion in humans (22) inspired further experiments in which the influence of bright light on the human circadian system was investigated. It was shown that the rise in plasma melatonin, which can be considered a reliable marker of the phase of the circadian pacemaker, could be shifted by shifting dawn and dusk even when

the timing of sleep was held constant (21). These results indicate that the zeitgeber acts on the deep oscillator directly. An experiment by Czeisler et al. (5) in which the phases of the body temperature and cortisol rhythms in a single subject were delayed after repetitive exposure to bright light in the evening is consistent with this hypothesis. Because in this experiment the timing of sleep was also fixed, it was indeed concluded that "Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle" (5), as was postulated in the two-process model (8, 9).

The next question is how shifts of the circadian pacemaker affect sleep timing. The two-process model predicts that if the history of sleeping and waking is kept constant an advance of process C will result in an earlier interception of S and the lower threshold of C, and thus an earlier termination of sleep at a slightly higher value of S. The model further predicts that the time course of integral EEG power density during sleep, which is thought to reflect process S, is not affected.

We indeed found that repetitive exposure to bright light in the early morning, which resulted in an advance of the rise of body temperature during sleep, did advance wake up time, whereas the time course of integral EEG power density, which is mainly a reflection of the time course of the lowest EEG frequencies (4), was not affected (13). Whether power densities of specific sleep EEG frequencies were affected was not analyzed. Furthermore no data are available on how an advance of the circadian pacemaker affects the duration of the various sleep stages.

In the present study we analyzed the time course of REM and NREM sleep and the spectral EEG composition after bright or dim light treatment. We report that bright light shifted circadian phase as assayed by melatonin, without exerting discernible effects on any sleep parameter except (REM) sleep duration.

METHODS

The experiment was carried out in February and March at the department of Biological Psychiatry. Eight male subjects [age 23.1 ± 2.5 (SD) yr] were selected. All had regular sleep habits and were free of sleep complaints. They were exposed to two light conditions in a balanced crossover design. In both conditions the subjects came to the laboratory on four consecutive evenings. During the first three evenings they sat from 1900 to 2200 h in a darkened room at a light intensity of 1 lx. From 2200 until 0600 h they were allowed to sleep in a completely darkened room. Between 0600 and 0900 h, they sat awake in a laboratory room exposed to 1 lx (candle light) in the dim light condition or to 2,000 lx (measured at eye level) in the bright light condition. During the bright light exposure the subjects were sitting in front of a light screen consisting of 16 white fluorescent tubes (vita light) tubes. The dimensions of the screen were width 242 and height 120 cm. The screen was elevated 65 cm above floor level. The distance between the subjects and the light source was 1 m. During the light exposure the subjects were allowed to read. They were under continuous surveillance to avoid eye

closure or sleep. After 0900 h the subjects left the laboratory. During the morning and evening hours the subjects filled out the Stanford Sleepiness Scale (16) every hour. Each morning the subjective sleep quality was measured by the Groningen sleep complaints scale (23). This is a 14-item scale constructed by means of a Mokken-scale analysis. High scores indicate low subjective sleep quality. The interval between the two conditions was 3 wk. On the fourth evening of both conditions subjects entered the laboratory at 1800 h. Light intensity was 1 lx. From 1900 to 2300 h blood samples were collected every 30 min by venous puncture. These were centrifuged immediately, and the plasma was stored at −20°C.

On the fourth evening the subjects went to bed at 2400 h. To assess the spontaneous termination of sleep, the subjects were instructed not to rise until they felt refreshed. They slept in a darkened room without knowledge of clock time.

EEG, electromyogram (EMG), electroculogram (EOG), and body temperature were recorded. The EEG was derived from C3-A2 and C4-A1. The subjects were adapted to the electrodes during the third night. The EEG was recorded at a paper speed of 10 mm/s. Paper recordings were scored per 30-s epoch according to the criteria of Rechtschaffen and Kales (24). After low-pass filtering at 25 Hz (24 dB/oct) both EEG signals were digitized with a sampling rate of 64 Hz. The EMG, EOG, and a time signal were also digitized and stored on magnetic tape together with the EEG data. Both EEG signals were subjected to spectral analysis by a fast Fourier transformation (FFT) on a PDP11/34 computer. Power densities between 0.25 and 15.0 Hz were calculated per 4-s periods, resulting in a 0.25-Hz bin width. The data were reduced to 1-Hz bins by adding power densities of adjacent frequencies. The visual scorings of the EEGs were also fed into the computer. This enabled us to calculate power densities per sleep stage and to remove movement time epochs. Brief disruptions of EEG signals were removed automatically on the basis of the value of the rectified EMG.

The blood samples were coded and sent deeply frozen to Portland, where plasma melatonin levels were assayed by means of gas chromatography-mass spectrometry. By this method plasma levels as low as 1 pg/ml can be detected. The within-assay variability is ~6% (19). The onset of melatonin secretion is probably the most reliable marker of the phase of the melatonin rhythm, since changes in sensitivity throughout the night in the β-adrenergic receptors of the pineal gland may influence the apparent time of the maximum melatonin secretion (cf. 18). Furthermore, maximum plasma melatonin levels were reached after subjects went to sleep (19). Therefore the phase of the melatonin rhythm was defined as the time at which plasma melatonin concentration reached or exceeded the 10-pg level (dim light melatonin onset, DLMO). The phase of the melatonin onset was determined without knowledge of the treatment, to the nearest quarter of an hour, by linear interpolation.

RESULTS

*DLMO.* Figure 1 depicts the clock time of the DLMO in the eight individuals after morning exposure to dim
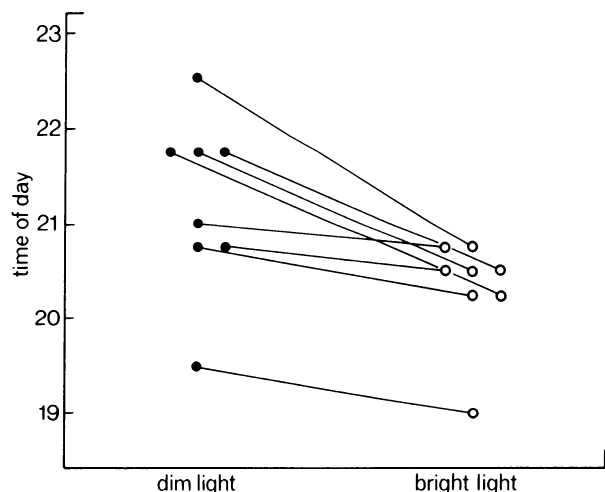
FIG. 1. Dim light melatonin onset after repetitive exposure to dim or bright light.

TABLE 1. *Subjective sleep complaints during two treatments*

| Condition | Night | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| n | 8 | 8 | 8 | 5 |
| Dim light | 4.1±1.6 | 3.1±2.4 | 3.6±2.5 | 2.2±0.8 |
| n | 8 | 8 | 8 | 7 |
| Bright light | 3.8±2.0 | 3.5±2.4 | 2.5±1.6 | 1.4±1.8 |

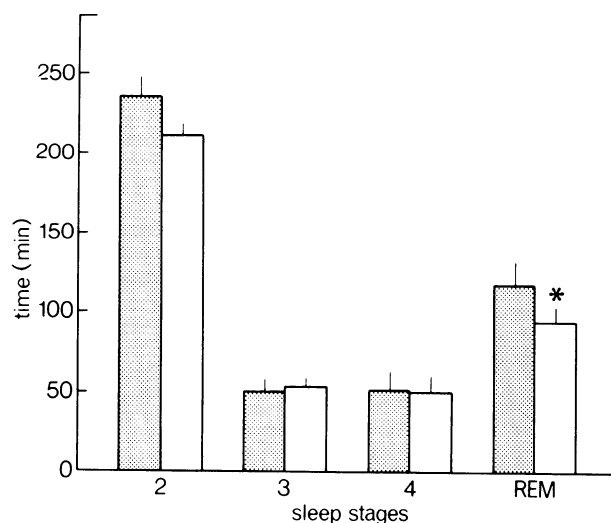Values are means ± SD; $n$, no. of subjects. Figures represent scores on the Groningen sleep complaints scale.



FIG. 2. Sleep stages after exposure to dim (stippled bars) or bright light (open bars). Bars indicate SE; $n = 8$ in both conditions. * $P < 0.05$.

light and after morning exposure to bright light. In the dim light condition the interindividual variation is considerable. The earliest DLMO was at 1930 h, whereas the latest DLMO was at 2230 h. On average plasma melatonin reached the 10-pg level at 2113 h ± 55 (SD) min. After repetitive exposure to bright light the interindividual variation was reduced [mean 2019 h ± 34 (SD) min, range 1900–2045]. In all eight subjects the time at which plasma melatonin reached the 10-pg criterion was advanced after treatment with bright light, compared with the dim light treatment. Figure 1 further suggests that the magnitude of the advance (DLMO time after dim light minus DLMO time after bright light) is related to the phase of the DLMO after the dim light treatment. Maximum advances are observed in those subjects in whom the DLMO was late after the dim light treatment. Statistical analysis of this relation is difficult, since stochastic variation will result in correlations between dependent variables. The correlation between the advance of the DLMO (calculated as time of DLMO after dim light minus time of DLMO after bright light) and the time of DLMO after dim light indeed is significantly positive ($r = 0.807$; df = 6; $P < 0.05$). That this is not only due to stochastic variation is suggested by a significant correlation of the DLMO times for the two conditions ($r = 0.779$; df = 6; $P < 0.05$). This indicates that the contribution of stochastic intraindividual variation is restricted.

*Subjective sleep quality.* Subjective sleep quality was assessed after all nights in the laboratory by means of the Groningen sleep complaints scale. The minimum score on this scale is 0, whereas the maximum score is 14. High scores indicate low sleep quality. In both conditions sleep complaints tended to decrease in the course of the experiment, although not significantly [$F(3, 21) = 2.79$; $P > 0.05$; two-factor analysis of variance (ANOVA) for repeated measures on both factors]. Between the two conditions no significant differences could be detected [$F(1, 7) = 2.72$; $P > 0.05$; Table 1].

*Sleep stages.* The effects of light treatment on the spontaneous termination of sleep have been reported elsewhere (13). After exposure to bright light, a more rapid accumulation of stages 0, 1, and movement time was observed, indicating an advance of the waking up tendency. If sleep end was operationally defined as the first 15-min interval without any epoch of stage 2, 3, 4, or REM sleep, sleep duration was significantly reduced after exposure to bright light by 54 min on average ($P < 0.05$). Figure 2 shows the time spent in the various sleep stages between sleep onset and sleep end. Time spent in both stage 3 and stage 4 was virtually identical for the two conditions. After exposure to bright light, time in stage 2 was insignificantly reduced. The total amount of REM sleep, however, was significantly smaller after the bright light treatment compared with dim light treatment [94.0 ± 29 vs. 116.8 ± 37.5 (SD) min; $P < 0.05$, Wilcoxon matched-pairs test]. The latency to REM sleep was not significantly different for the two conditions, although the median REM latency was somewhat smaller after the exposure to bright light (89.0 and 110.5 min for the bright and dim light condition, respectively). For an analysis of the temporal distribution of REM sleep, time in REM sleep was accumulated for the first 390 min and plotted at 30-min intervals (Fig. 3). The 390-min cutoff was chosen because all subjects slept that long. No clear-cut differences in the rate of accumulation between the two conditions did emerge.

The percentage of time spent in the various sleep stages mentioned was in no case significantly different between the two conditions.

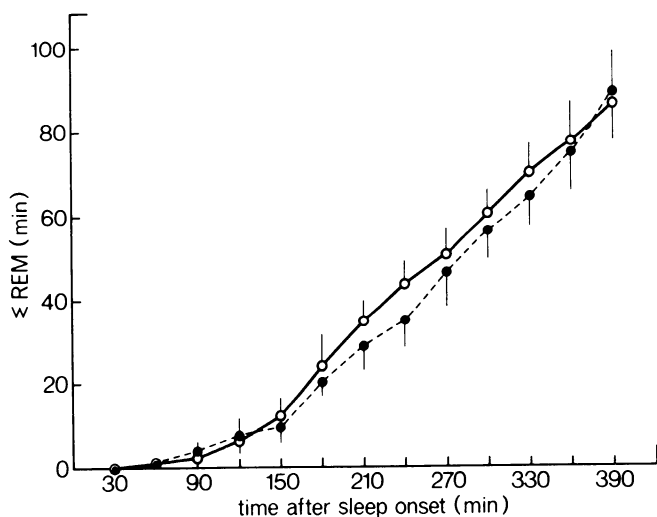*EEG power density.* Integral EEG power density (0.25–

FIG. 3. Accumulation of REM sleep during first 390 min of sleep. Open symbols, bright light; filled symbols, dim light. Bars indicate SE.

15.0 Hz) during stages 1, 2, 3, 4, and REM sleep was accumulated from sleep onset to sleep end, resulting in EEG energy. The integral EEG power density represents essentially the activity in the slow-wave range (4). Because large differences in the absolute power densities existed between individuals, EEG energy was expressed relative to the EEG energy accumulated from sleep onset to sleep end during the night after the dim light treatment (=100%). After exposure to bright light the total EEG energy amounted to 94.8 ± 17.6%. This was, however, not significantly different from 100%. The decay of power density over successive NREM-REM cycles is essentially exponential (4). So the integration of power density over time should result in a saturating exponential curve. Therefore the time course of the accumulation of EEG energy was analyzed by fitting an exponential saturating curve, $E(t) = A[1 - e^{-r^*(t-t_0)}]$ to the data, using a least square criterion. $E(t)$ represents energy accumulated at time $t$. $A$ represents the asymptote, r the inverse of the time constant, $t_0$ allows the fitted curve to be different from 0 at $t = 0$, and $t$ represents time. The resulting decay rates, r, were 0.245 and 0.239°log units/h for the dim and bright light condition, respectively. The percentage of the total variance accounted for by the fitted curve was 91 and 87% for the dim and bright light data, respectively.

For a further analysis of the effects of treatment on the sleep EEG, power densities were calculated per 1-Hz bin during REM sleep and NREM sleep (stage 1 not included) separately, for the first 390 min of sleep. In all subjects, power density in each frequency bin was expressed relative to power density during either NREM or REM sleep in the first 390 min of sleep after the dim light treatment (=100%). By this method both interindividual differences in power density, differences in power density between NREM and REM sleep, and differences in power density between the various frequencies are eliminated. Because in both conditions only the first 390 min of sleep were included, differences between the two treatments cannot be attributed to the difference in sleep duration. The results of these analyses

are depicted in Fig. 4. During neither REM sleep nor NREM sleep did power density in any of the frequencies analyzed differ significantly between the two conditions. Only small deviations from the 100% level can be observed.

*Sleep duration and phase of melatonin onset.* For an analysis of the relations between the phase of the dim light melatonin onset and the spontaneous termination of sleep, Pearson's correlation between the clocktimes of sleep end and of the DLMO were calculated for all 16 nights: $r = 0.216$, df = 14, $P > 0.1$ (see Table 2 for the individual values). If the small variation in sleep onset times was accounted for by calculating the correlation between sleep duration and DLMO the correlation was 0.152 (df = 14, $P > 0.1$). Finally the correlation between the change in sleep duration and the change in the DLMO between the two treatments was calculated. This correlation was not significant ($r = -0.141$, df = 6, $P > 0.1$). So neither variation in the phase of melatonin onset
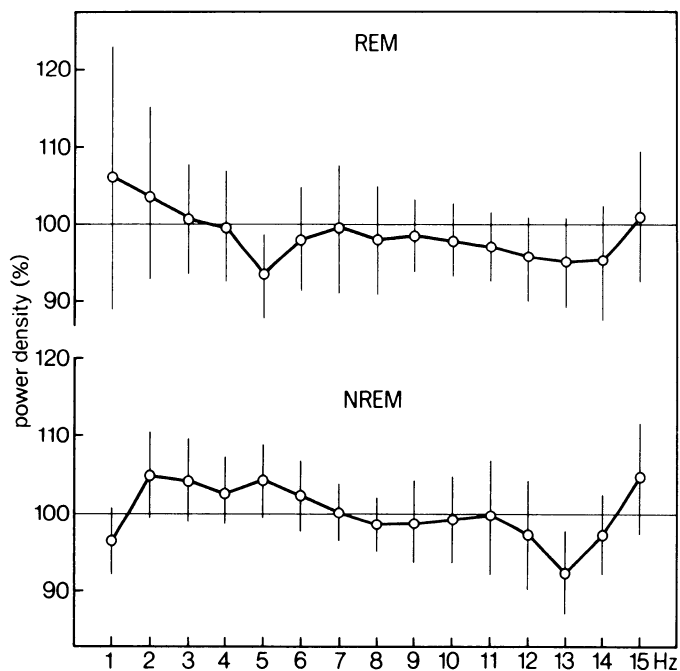


FIG. 4. Power densities during rapid-eye-movement (REM; *top*) and non-REM sleep (*bottom*) during first 390 min of sleep after repetitive exposure to bright light. 100% = power density after exposure to dim light. Bars indicate SE; $n = 8$ in both conditions.

TABLE 2. *Clock times of DLMO, sleep onset and sleep end after dim light and bright light exposure*

| Subject | Dim Light | | | Bright Light | | |
|---|---|---|---|---|---|---|
| | DLMO | Sleep onset | Sleep end | DLMO | Sleep onset | Sleep end |
| 1 | 2145 | 0021 | 0909 | 2015 | 0013 | 0822 |
| 2 | 1930 | 0015 | 0820 | 1900 | 0021 | 0758 |
| 3 | 2045 | 0015 | 1008 | 2015 | 0010 | 0717 |
| 4 | 2100 | 0029 | 0857 | 2045 | 0019 | 0732 |
| 5 | 2145 | 0021 | 0750 | 2030 | 0017 | 0812 |
| 6 | 2045 | 0029 | 0751 | 2030 | 0028 | 0746 |
| 7 | 2230 | 0026 | 0753 | 2045 | 0035 | 0704 |
| 8 | 2145 | 0034 | 0926 | 2030 | 0019 | 0735 |

Clock times of sleep onset and sleep end have been rounded off to nearest minute. DLMO, dim light melatonin onset.

nor the change of this phase in response to light treatment explained much of the variance in sleep duration or its change during the experiment.

## DISCUSSION

*Melatonin.* The observed advance of the rise of plasma melatonin in the evening after repetitive exposure to bright light in the morning is in accordance with the findings reported by Lewy et al (20, 21). Because in the present experiment as well sleep times were fixed and identical during the two treatments, the observed advance in the DMLO indicates that the circadian pacemaker by which the melatonin rhythm is driven can be phase advanced by bright light pulses in the early morning, while during the treatment days the sleep-wake cycle is fixed. This finding is in accordance with those by Lewy et al. (20, 21). We reported earlier that the rise of body temperature at the end of the night was also advanced after the exposure to bright light in the early morning (13). Czeisler et al. (5) reported that bright light in the evening phase delayed the body temperature and cortisol rhythm. So it is now well established that the effects of bright light on the phase of the circadian rhythms of at least three physiological variables are not entirely mediated through the sleep-wake cycle.

The magnitude of the phase shift of the DLMO correlated with the phase of the DLMO after exposure to dim light. The trivial statistical explanation that correlations between dependent stochastic variables turn significant is unlikely, since the correlation of the DLMO phase of individuals was significant over the two conditions. An alternative explanation is that the small advance observed in those subjects in whom the DLMO is already early after the dim light treatment is caused by the exposure to normal daylight in the afternoon. This light may either prevent the phase advance of the circadian pacemaker driving the melatonin rhythm or mask the advance by direct suppression of the melatonin production. A third possibility is that the particular part of the phase-response curve exposed to light differs between the subjects with early and late DLMO after exposure to dim light. From the present data it cannot be concluded which hypothesis is most likely to be true. Interestingly though, in patients suffering from seasonal affective disorders the DLMO is delayed relative to normal controls (20). This delayed DLMO can be normalized by light treatment. Compared with the normal controls, the induced phase advance in these patients was much larger. The observed relation between initial phase and phase shift within the present sample of normal subjects may reflect a similar underlying mechanism.

*Sleep parameters.* The advance of the DLMO and body temperature rise induced by the bright light treatment was accompanied by an advance of the spontaneous termination of sleep. The resulting reduction of sleep duration did not affect the amount of stages 3 and 4, which are predominantly present at the beginning of a sleep episode (30). This finding is in accordance with the results reported by Akerstedt and Gillberg (1). In their experiment a large variation in sleep duration was observed when sleep was initiated at different circadian phases. They did not, however, report a significant circadian variation in SWS. Also in experiments in which sleep duration was limited during several nights the duration of SWS was not reduced (26). After the bright light treatment the somewhat smaller amount of stage 2, which is usually predominant in the later part of a sleep episode, is reminiscent of the reduction in stage 2 in the experiments of both Akerstedt and Gillberg and Webb (1, 26). The reduction in the total amount of REM sleep in the present experiment is also in accordance with the findings in the studies cited. The absence of an effect on the percentage of REM sleep and on REM latency was also reported by Akerstedt and Gillberg (1). However, an increase in the percentage of REM sleep at the beginning of sleep and a reduction of REM latency have been reported under conditions of temporal isolation (7, 31). Under these circumstances the minimum of the body temperature rhythm shifts to the beginning of the major sleep episode. The failure to find an effect of phase advancing the circadian rhythm of body temperature and melatonin on the percentage of REM sleep, the time course of REM sleep, and REM latency may have been due to the relatively small advance induced in this experiment (1 vs. 4–5 h in free-running experiments). In the Akerstedt and Gillberg experiment the absence of a circadian modulation of REM latency may be due to the interaction of circadian REM propensity and pressure for SWS that increases with increasing duration of prior wakefulness. The present data support the notion that NREM sleep and especially deep NREM sleep (SWS) is regulated very accurately by a homeostatic control mechanism, whereas the amount of REM sleep is to a large extent directly determined by sleep duration.

The analysis of power densities during NREM and REM sleep in the frequency range from 0.25 to 15.0 Hz during the first 390 min of sleep revealed that the light treatment did not affect any of the EEG frequencies analyzed during either NREM or REM sleep. The analysis of the effects of light treatment on the time course of integrated EEG energy, which is largely determined by slow-wave activity, resulted in similar decay rates for the two conditions (0.245 and 0.239 °log units for the dim and bright light condition, respectively). So, in accordance with findings on SWS (25, 27), the different phase relation between sleep and the circadian system did not affect the time course of EEG power density. In terms of the two-process model of sleep regulation, this indicates that the time course of process S is not dependent on the circadian phase of sleep onset. The decay rates obtained in the present study are very similar to the decay rates derived from Borbély's data (0.238) (9) and data from a previous experiment (0.243) (12). In a previous experiment (12) we showed that EEG power density is proportional to the first derivative of S with respect to time. So the somewhat smaller total amount of EEG energy that accumulated during sleep after the bright light treatment can be interpreted as a higher level of S at which sleep termination occurs when the lower threshold is advanced. The absence of a significant correlation between the shift of the DLMO and the change in sleep duration may be explained by the noise that is superimposed on

the wake up threshold (9). Alternatively it could be explained by assuming that light exposure not only shifts the phase of the C process but also changes the shape of the threshold. This suggestion can be derived from a model of the circadian pacemaker in which two coupled oscillators constitute this pacemaker (10). Increase in day length by bright light in the early morning will change the phase relation between the two oscillators, which may result in a change in the shape of various circadian rhythms, including the wake up threshold.

Although in the present experiment the circadian pacemaker was advanced by only 1 h, the data are in accordance with the predictions of the two-process model of sleep regulation. An advance of the circadian pacemaker was induced by exposure to bright light in the early morning. This effect of light was not mediated through the sleep-wake cycle. The advance of the circadian pacemaker resulted in a reduction of sleep duration. This reduction in sleep duration was not accompanied by any change in EEG power density or its time course. These data indicate the independency of the events within NREM sleep from the circadian system and the strong influence of the circadian system on the termination of the sleep process. Experiments in which more dramatic shifts of the human circadian pacemaker are induced may further elucidate these interactions.

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