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Effect of the shift of the sleep-wake cycle on three robust endocrine markers of the circadian clock

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Goichot, Bernard, Laurence Weibel, Florian Chapotot, Claude Gronfier, François Piquard, and Gabrielle Brandenberger. Effect of the shift of the sleep-wake cycle on three robust endocrine markers of the circadian clock. *Am. J. Physiol.* 275 (*Endocrinol. Metab.* 38): E243–E248, 1998.—To determine the effect of a phase shift in sleep on the circadian clock, thyroid-stimulating hormone (TSH), cortisol, and melatonin, three robust markers of the circadian clock, were analyzed using a 10-min blood sampling procedure. In an initial experiment eight subjects were studied during two experimental sessions: once under baseline conditions with normal nighttime sleep from 2300 to 0700 (baseline) and once after a night of sleep deprivation followed by daytime sleep from 0700 to 1500 (*day 1*). In a second experiment, carried out on seven subjects, the 24-h hormone profiles of the first day (*day 1*) were compared with those of the second day (*day 2*) of the sleep shift. During the night of sleep deprivation (*day 1*) the TSH surge was higher than during baseline conditions, whereas melatonin and cortisol rhythms remained unaffected. On *day 2* the amplitude of the nocturnal TSH surge was reduced in comparison to *day 1*, whereas the amplitudes of melatonin and cortisol rhythms were unchanged. There was a clear phase shift in the three endocrine rhythms. Triiodothyronine levels were slightly higher in the morning after the first night of sleep deprivation. These results demonstrate that 2 consecutive days of sleep shift are sufficient to affect the timing of the commonly accepted circadian markers, suggesting the existence of a rapid resetting effect on the circadian clock. TSH reacts in a distinctive manner to the sleep-wake cycle manipulation by modulating the amplitude of the nocturnal surge. This amplitude modulation is probably an integral part of the phase-shifting mechanisms controlled by the circadian clock.

thyroid-stimulating hormone; melatonin; cortisol; circadian rhythms

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UNDER NORMAL CONDITIONS many physiological functions display circadian rhythms. These rhythms are driven by an endogenous biological clock and synchronized on the 24-h period by environmental clues. Two kinds of stimuli synchronize endogenous rhythms in humans: the light-dark cycle, which is the most important "zeitgeber" in humans (13, 24), and various non-photic stimuli, predominantly social factors (5, 21). Several factors have been described as accelerating synchronization. Bright-light exposure (12, 13, 24), melatonin (4, 14), hypnotic drugs (20), and physical exercise (32, 33) have a measurable effect on the markers of circadian clock in the 24 h after the stimulus.

Previous studies involving one abrupt shift in the sleep-wake cycle have shown that the time necessary for an endocrine rhythm to adapt to a newly imposed sleep-wake cycle depends on the hormone. Sleep-dependent hormonal rhythms, such as prolactin and growth hormone, adapt more rapidly than the circadian rhythms of melatonin and cortisol, so that these latter rhythms are usually considered to be the best endocrine markers of the circadian clock (10, 28). The thyroid-stimulating hormone (TSH) rhythm has been described as reacting in a distinctive manner to an abrupt shift in the sleep period. In the case of sleep deprivation, the amplitude of the circadian surge markedly increases and the maximum occurs later in the night than in the case of normal nocturnal sleep (25), so that it is generally assumed that sleep exerts an inhibitory effect on the circadian rhythm of TSH.

To better understand how neuroendocrine rhythms adapt to chronobiological challenges, we conducted an experiment involving 2 successive days of sleep shifts, with no other confounding influences. We performed a concomitant analysis of the 24-h profiles of melatonin, cortisol, and TSH. This study allows us to characterize for the first time the effect of 2 consecutive days of a sleep-wake cycle manipulation on the circadian clock.

SUBJECTS AND METHODS

Subjects. Fifteen healthy male subjects, aged 23–30 yr old, participated in the experiment. All gave their informed consent, and the local ethics committee approved the protocol. The subjects participated in the study after medical examination and screening tests. All had regular sleep-wake habits, and none was taking medication.

The study was conducted in two parts. In the first experiment eight young, healthy male subjects were studied during a 24-h period from 1900 to 1900, once with sleep being permitted between 2300 and 0700 (baseline) and another time (1 mo later) with sleep being permitted between 0700 and 1500 (first day of the shift, *day 1*). This experiment was preceded by an habituation night from 2300 to 0700. The experiments were randomized.

In the second experiment seven different subjects were studied from 1900 to 1900 with sleep being permitted from 0700 to 1500. This experiment was preceded by two different sleep periods: in one case the subjects slept during the day before the experiment (from 0700 to 1500) and were then studied from 1900 to 1900, i.e., during the first day of the shift (*day 1*); in the other case they slept during the day before the experiment (from 0700 to 1500) and the subjects were then studied from 1900 to 1900, i.e., during the second day of the shift (*day 2*).

The experiments were carried out in a sound-proof, air-conditioned sleep room. The subjects remained supine throughout the investigation and for 4 h before the beginning of the experiment. During awakening, measured light intensity was maintained below 100 lux, and darkness was created during the sleep periods. When awake, the subjects were

allowed to read and watch television. During the night of sleep deprivation, they were kept under continuous surveillance and conversed with a member of the laboratory staff.

A catheter was inserted into an antecubital vein 3 h before the beginning of the experiment, and blood was pumped continuously in an adjoining room and sampled into 10-min aliquots from 1900 to 1900. Blood was immediately centrifuged, and plasma was stored at $-25°C$ until analysis. Blood was sampled at hourly intervals for free (F) thyroid hormone measurements, thyroxine (T_4) and triiodothyronine (T_3)(FT_4 and FT_3). A nasogastric tube was used for continuous enteral nutrition, which began 4 h before blood sampling (Sondalis, ISO, Sopharga, Puteaux, France; 50% carbohydrate, 35% fat, 15% protein, 1 kcal/ml and 90 ml/h). Electrodes for polysomnography were applied 2 h before the beginning of the sleep recordings.

Hormone assays. TSH was measured by a commercial immunoradiometric assay kit (Incstar, Stillwater, MN). The intra-assay coefficient of variation (CV) was 6.0% for concentrations between 0.05 and 0.5 mU/l and 3.0% for concentrations between 0.5 and 10 mU/l. The interassay CV was 8.4% for concentrations between 0.05 and 0.5 mU/l and 4.0% for concentrations between 0.5 and 10.0 mU/l. The detection limit was 0.013 mU/l. No sample fell below this detection limit. Cortisol was measured by RIA (Ciba Corning Diagnostics) with a detection limit of 0.2 μg/dl. The intra-assay CV was 4.0% above 6 μg/dl and 10.0% for levels below. The interassay CV was 5.2% for levels above 6 μg/dl and 11.5% for levels below. FT_4 and FT_3 were assayed by RIA (Magic, Ciba Corning Diagnostics). The intra-assay CV was 4.9% for concentrations between 1.0 and 4.0 pg/ml and 2.6% for concentrations between 4.0 and 8.0 pg/ml for FT_3, and 6% for concentrations between 1.0 and 2.0 ng/dl for FT_4. The detection limit was 0.16 pg/ml for FT_3 and 0.09 ng/dl for FT_4. Plasma melatonin was measured by an RIA kit (ImmunoBiological Laboratories, Hamburg, Germany). The detection limit was 2.5 pg/ml. The intra-assay CV was 10% below 20 pg/ml, 7% between 20 and 120 pg/ml, and 20% above 120 pg/ml. The interassay CV was 13% below 20 pg/ml, 10% between 20 and 120 pg/ml, and 26% above 120 pg/ml. All samples from a given subject were measured in the same assay.

Data analysis. Each individual TSH, melatonin, and cortisol profile was submitted to a detailed analysis, including evaluation of circadian parameters. The wave shape of each profile was quantified by a smooth curve using a robust locally weighted regression procedure proposed by Cleveland (11). For each hormone the best circadian markers were used to assess any changes in the rhythm (31).

For each of the three rhythms, the acrophase and nadir were defined as the time of occurrence of maximum and minimum, respectively, in the best-fit curve. The duration of the surge is the lag between the onset and the offset, and the mean amplitude was defined as the difference between the value at acrophase and the value at nadir.

The onset of the circadian rise of TSH was defined as the time when the value of the best-fit curve reached the value of the daytime nadir plus 25% of the difference between the value at the acrophase and the value at the nadir (31). The offset of the circadian rise of TSH was defined as the time when the value of the best-fit curve reached the value of the daytime maximum minus 25% of the difference between the value at the acrophase and the value of the nadir.

For melatonin the onset of the rise was defined as the time when the value of the best-fit curve exceeded the mean of the 10 lowest consecutive melatonin values of the 24-h profile plus 2 SD in at least 10 consecutive samples. The offset of the rise was defined as the time when the value of the best-fit

curve reached the mean of the 10 lowest consecutive melatonin values of the 24-h profile plus 2 SD in at least 10 consecutive samples (23).

For cortisol the quiescent period was defined as starting when concentrations <50% of the 24-h mean were observed for at least six consecutive samples and ending when concentrations >50% of the 24-h mean were observed in six consecutive samples (15).

The fluctuations of thyroid hormone concentrations were studied using ANOVA for repeated measures, with time and condition (nocturnal or diurnal sleep) as dependent factors. Mean comparisons between the two conditions were conducted using a Wilcoxon signed-rank test with a threshold of significance at 0.05. All analyses were conducted using BMDP software (BMDP Statistical Software, Los Angeles, CA). All values are expressed as means $\pm$ SE.

RESULTS

First experiment: baseline vs. 1st day of shift. Mean 24-h TSH, cortisol, and melatonin profiles during baseline conditions and during the first sleep shift (*day 1*) are shown in Fig. 1. As expected, TSH reached higher levels during the first night of sleep deprivation compared with baseline, so that the amplitude of the TSH rhythm differed between the two conditions (1.01 $\pm$ 0.12 vs. 2.12 $\pm$ 0.20 mU/l, $P < 0.01$). On *day 1* the timing of the circadian markers of the TSH rhythm remained unaffected by the sleep shift. Cortisol and melatonin rhythms remained unchanged. There were in particular no differences displayed by the two rhythms in temporal characteristics for the two conditions (Table 1). In particular, the amplitudes of both cortisol (18.4 $\pm$ 0.9 vs. 18.4 $\pm$ 1.4 μg/dl) and melatonin (87.0 $\pm$ 19.4 vs. 84.4 $\pm$ 22.7 pg/ml) rhythms were similar in the two conditions.

Second experiment: 1st vs. 2nd day of shift. Mean TSH, melatonin, and cortisol profiles during the 1st and 2nd days of the sleep shift are shown in Fig. 2. The temporal markers of the TSH rhythm were shifted during *day 2* compared with *day 1* (Table 2). The onset of the surge was delayed by 2 h 53 min $\pm$ 40 min, but the duration of the surge did not differ between the two conditions (12 h 17 min $\pm$ 36 min vs. 13 h 20 min $\pm$ 73 min, not significant). The amplitude of the TSH surge was markedly decreased during *day 2* (1.47 $\pm$ 0.19 vs. 0.84 $\pm$ 0.11 mU/l, $P < 0.05$). The onset of the melatonin surge was shifted on *day 2* compared with *day 1* (2148 $\pm$ 16 min vs. 2345 $\pm$ 32 min, $P < 0.05$). The cortisol rhythm was also affected by the sleep shift. The beginning of the quiescent period of cortisol secretion was delayed on *day 2* compared with *day 1* (2052 $\pm$ 23 min vs. 2222 $\pm$ 35 min, $P < 0.05$), as well as the acrophase of the rhythm (0812 $\pm$ 54 min vs. 1421 $\pm$ 67 min, $P < 0.05$). However, no differences in the amplitude of the melatonin and the cortisol rhythms were observed in the two conditions.

During this second experiment, thyroid hormones were measured hourly (Fig. 3) to determine whether the variations of TSH rhythm amplitude could be the consequence of variations in the negative feedback of thyroid hormones on TSH secretion. There was no significant variation of FT_4 during the 24 h. ANOVA for
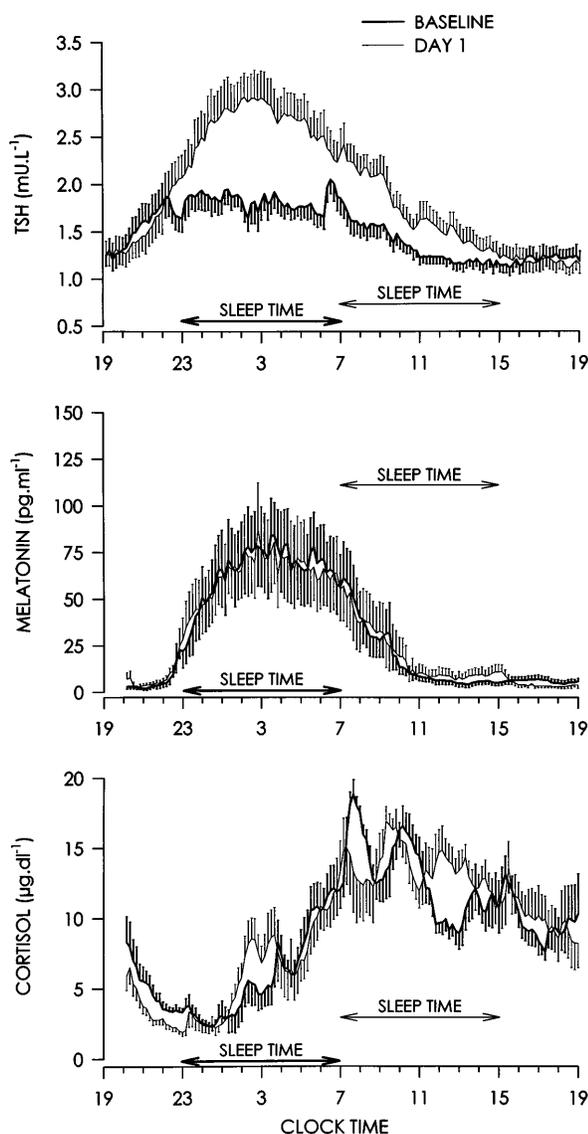
Fig. 1. Mean 24-h rhythms of thyroid-stimulating hormone (TSH), melatonin, and cortisol in 8 subjects during baseline and during 1st day of sleep shift.

repeated measures of FT_3 showed a highly significant effect of time ($P < 0.0001$), with no effect of condition ($P = 0.27$) and with an interaction between time and condition at the limit of significance ($P < 0.05$). This indicated that the fluctuations of FT_3 during the 24 h depended on the condition. Visual analysis of the FT_3 profiles indicated higher levels following the first night of sleep deprivation between 0900 and 1500.

DISCUSSION

The major finding of this study is that 2 days of abrupt sleep shift suffice to partially shift the 24-h rhythms of TSH, melatonin, and cortisol, three robust markers of the circadian pacemaker. To our knowledge this is the first report that argues in favor of the hypothesis that 2 days of sleep shift have a direct resetting effect on the circadian clock. Compared with melatonin and cortisol rhythms, the distinctive feature

of TSH is the way in which the TSH rhythm reacts to manipulation of the sleep-wake cycle. In addition to a shift of its temporal markers, i.e., the onset of the nocturnal surge and the acrophase of the rhythm, adaptation of the TSH rhythm also relies on an amplitude modulation with a return to baseline level of the nocturnal surge during the second day of the shift. It seems unlikely that the slight increase in FT_3 observed in the morning after the first night of sleep deprivation should exert an enhanced negative feedback on TSH secretion the following night.

It is known that the endocrine rhythms are more or less rapidly displaced after shifts in the sleep-wake cycle. Previous studies on jet lag and other studies in which a single shift in the sleep period was used have reported that sleep-dependent hormone rhythms, i.e., prolactin and growth hormone, adapt more rapidly than the endocrine rhythms under circadian influence, i.e., melatonin and cortisol. In the present study, we demonstrate that an abrupt sleep shift, in itself, without any other confounding influences, i.e., light, posture, and meals, can, after 2 days, directly act on the circadian clock. This effect is independent of the relationships between sleep and hormone secretion, because TSH is closely related to sleep as a whole and to sleep structure (17, 18), whereas cortisol is less so and melatonin not at all.

The regulation of the amplitude of the TSH surge in both healthy and diseased individuals is not completely understood but seems to be of critical importance for thyroid economy (8, 9, 19). It has been previously reported that the time of sleep determines the maximum of the surge and modulates its amplitude. In the case of sleep deprivation, the TSH maximum is delayed and reaches higher levels. When sleep deprivation lasts

Table 1. *Characteristics of 3 endocrine rhythms in 8 subjects during baseline and 1st day of sleep shift*

	Baseline	*Day 1*
TSH		
Onset of surge	2120 ± 32 min	2215 ± 24 min
Offset of surge	1152 ± 45 min	1158 ± 32 min
Duration of surge	14 h 32 min ± 45 min	13 h 43 min ± 32 min
Amplitude, mU/l	1.01 ± 0.12	$2.12 \pm 0.20*$
Melatonin		
Onset of surge	2223 ± 16 min	2219 ± 17 min
Offset of surge	1023 ± 37 min	1024 ± 53 min
Duration of surge	12 h ± 38 min	12 h 5 min ± 52 min
Amplitude, pg/ml	87.0 ± 19.4	84.4 ± 22.7
Cortisol		
Beginning of quiescent period	2119 ± 17 min	2040 ± 11 min
End of quiescent period	0236 ± 21 min	0205 ± 25 min
Duration of quiescent period	5 h 14 min ± 30 min	5 h 25 min ± 32 min
Acrophage	0754 ± 14 min	0838 ± 31 min
Amplitude, µg/dl	18.4 ± 0.9	18.4 ± 1.4

TSH, thyroid-stimulating hormone. Times of "onset" and "offset" and beginning and end of quiescent period are times of day. $*P < 0.01$.
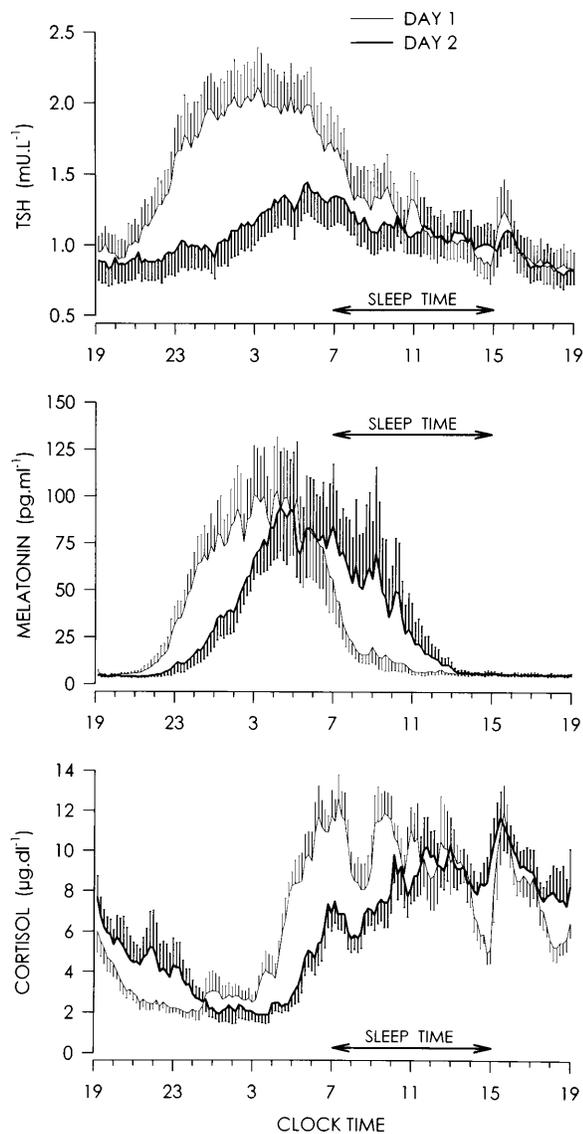
Fig. 2. Mean 24-h rhythms of TSH, melatonin, and cortisol in 7 subjects during 1st and 2nd days of sleep shift.

Table 2. *Characteristics of 3 endocrine rhythms in 7 subjects during 1st and 2nd days of sleep shift*

	Day 1	Day 2
TSH		
Onset of surge	2128 ± 26 min	0021 ± 54 min*
Offset of surge	0945 ± 37 min	1332 ± 74 min*
Duration of surge	12 h 17 min ± 36 min	13 h 20 min ± 73 min
Amplitude, mU/l	1.47 ± 0.19	0.84 ± 0.11*
Melatonin		
Onset of surge	2148 ± 16 min	2345 ± 32 min*
Offset of surge	1042 ± 26 min	1132 ± 38 min*
Duration of surge	12 h 56 min ± 15 min	11 h 47 min ± 21 min
Amplitude, pg/ml	103.5 ± 25.6	103.1 ± 32.1
Cortisol		
Beginning of quiescent period	2052 ± 23 min	2222 ± 35 min*
End of quiescent period	0236 ± 43 min	0334 ± 74 min
Duration of quiescent period	5 h 44 min ± 46 min	5 h 11 min ± 64 min
Acrophase	0812 ± 54 min	1421 ± 67 min*
Amplitude, µg/dl	13.6 ± 0.9	13.2 ± 0.6

* $P < 0.05$.

tions, such as central or peripheral hypothyroidism (2), chirurgical stress (7), poorly controlled diabetes (6), or the sick euthyroid syndrome (1, 16, 27), the amplitude of the TSH rhythm has also been shown to be decreased. The mechanisms of this decreased surge amplitude seem to involve abnormal regulation by the hypothalamo-pituitary axis, as well as abnormal peripheral T_4 to T_3 conversion (16). Because T_3 is decreased in these situations, negative feedback by thyroid hormones cannot be implicated in the decrease of the TSH surge.

It seems unlikely that the TSH surge enhanced during sleep deprivation should act on the temporal characteristics of the melatonin and cortisol rhythms
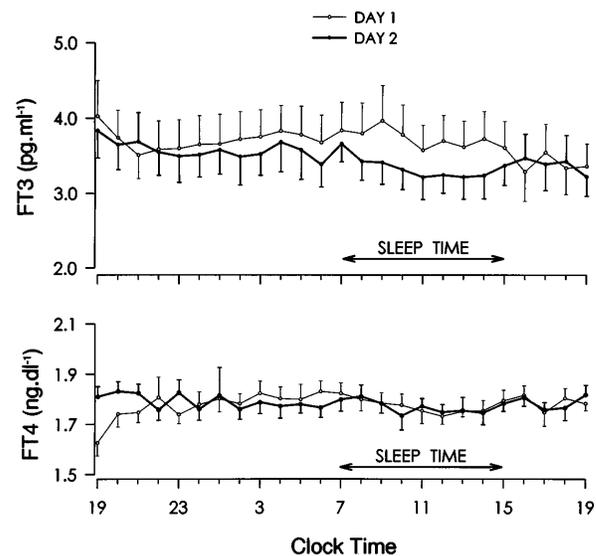
several days, the circadian TSH rhythm persists but its amplitude progressively decreases (3, 25, 26). These results have been interpreted as reflecting a decrease in vigilance and a tendency to sleepiness resulting from prolonged sleep deprivation (3). However, the decrease in amplitude of the TSH surge has also been observed by Parker et al. (25) despite the absence of sleep deprivation. It could also be suggested that the metabolic and thermoregulatory modifications induced by a shift in the sleep period could explain the changes in the amplitude of the TSH surge, but no experimental evidence has been provided as yet. Also, some authors hypothesized that the decreased nocturnal surge after a sleep shift or a period of sleep deprivation is the consequence of enhanced negative feedback by thyroid hormones, which increased after sleep deprivation (30). In our opinion, it is unlikely that the small increase in FT_3 observed by us in the morning could inhibit TSH levels the following night. In several pathological situa-

Fig. 3. Mean 24-h rhythms of free thyroid hormones in 7 subjects during 1st and 2nd days of sleep shift. FT_3, triiodothyronine; FT_4, thyroxine.

the following day. There is currently no evidence for an effect of thyroid hormones on the circadian clock. A direct effect of TSH on the clock should have been observed in patients having increased TSH levels, but this, to our knowledge, has not been reported. However, one cannot exclude the possibility that the effect of the shift on TSH amplitude, as well as the effect observed on the temporal characteristics of the three endocrine rhythms, may be related to a direct effect of the abrupt sleep shift on the circadian pacemaker. Manipulation of the circadian system using bright light exposure has been reported in some cases to modify the amplitude of biological rhythms. In particular, Jewett et al. (22) reported that bright-light exposure provokes a clear shift of the cortisol rhythm together with a reduction of the rhythm amplitude. More recently, Hirschfeld et al. (20) demonstrated that an 8-h advance in the sleep period resulted in an increased amplitude of the TSH rhythm. This enhanced amplitude was followed by a slight ascending trend in total T_3 concentrations but without evidence of a subsequent negative feedback on TSH secretion. Treatment with bright light or zolpidem limited this increase of TSH with no effect on T_3 levels. Comparing these results to our own, it appears that the effect on the amplitude of the TSH rhythm depends on the direction of the shift. On the other hand, Van Cauter et al. (29), using bright light applied at different moments of the day during a constant routine procedure, showed an effect of the light exposure on the temporal parameters of the TSH rhythm but without evidence of any effect on the surge amplitude. The inconsistencies between these studies clearly show that the exact significance of the amplitude modulation of the TSH surge is not yet clearly understood. The physiological meaning of this adaptation remains unclear because the effects on thyroid hormone levels are weak. A role of the modification of the amplitude of the TSH rhythm after advanced or delayed shifts in the subjective signs of jet lag syndrome has been suggested (20). It remains to be determined whether stimulation of TSH to avoid the decrease of the surge following phase delay would also have a symptomatic effect. This could offer new perspectives in the exploration and the treatment of the decreased TSH surge observed in nonthyroidal illnesses.

In conclusion, the present results suggest that the sleep-wake cycle can be considered as a zeitgeber for the circadian clock, as indicated by the shift of the three endocrine rhythms. TSH reacts in distinctive manner to this shift with a modulation of the amplitude of its rhythm, which depends on the direction of the shift. This modulation seems to be an integral part of the phase-shifting mechanisms controlled by the circadian clock.

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