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Circadian Rhythms of Melatonin, Thyroid-Stimulating Hormone and Body Temperature: Relationships among those Rhythms and Effect of Sleep-Wake Cycle

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Plasma melatonin, thyroid-stimulating hormone (TSH) and body temperature were measured simultaneously and continuously before and after the sleep-wake cycle was shifted in 4 healthy males and changes in the circadian rhythm itself and in the phase relationship among these circadian rhythms were determined. Normal sleep-wake cycle (sleep hours: 2300-0700) was delayed by 10 h (sleep hours: 0900-1700) during the experiment. Even after this shift the typical melatonin rhythm was maintained: low during daytime and high during night. The melatonin rhythm was gradually delayed day by day. The TSH rhythm was also maintained fundamentally during 3 consecutive days of altered sleep-wake cycle. The phase was also delayed gradually but remarkably. The daily rhythm of body temperature was changed by the alteration of sleep-wake cycle. The body temperature began to decrease at the similar clock time as in the control but the decline during night awake period was less steep and the lowered body temperature persisted during sleep. The hormonal profiles during the days of shifted sleep-wake cycle suggest that plasma melatonin and TSH rhythms are basically regulated by an endogenous biological clock. The parallel phase shift of melatonin and TSH upon the change in sleep-wake cycle suggests that a common unitary pacemaker probably regulates these two rhythms. The reversal phase relationship between body temperature and melatonin suggests that melatonin may have a hypothermic effect on body temperature. The altered body temperature rhythm suggests that the awake status during night may inhibit the circadian decrease in body temperature and that sleep sustains the lowered body temperature. It is probable but uncertain that there are causal relationships among sleep, melatonin, TSH, and body temperature.

Under normal conditions, many physiological functions including plasma melatonin level, thyroid stimulating hormone (TSH) level and body temperature display circadian rhythms in the organism. These rhythms are driven by an endogenous biological clock, are synchronized on a 24 h period by environmental or internal cues such as light-dark cycle and sleep-activity cycle, and follow a phase shift of the synchronizer (Mills et al., 1978; Lewy et al., 1980; Tagahashi and Zatz, 1982; Czeisler et al., 1989; Minor et al., 1991; Allan and Czeisler, 1994; Arendt, 2000).

These circadian rhythms of the physiological functions are under constant phase relation to the others, which may be necessary for optimal functioning of various physiological systems. A change in the sleep-wake cycle results in disturbance of circadian rhythms (Mills et al., 1978; Moor-Ede and Richardson, 1985; Goichot et al., 1998) and gives rise to stress, and physiological adaptation is difficult (Winfree, 1982; Linda and Charmane, 1993)

Plasma melatonin levels in normal human are very low during daytime but increase significantly and remain elevated during night sleep, falling sharply to daytime values in the morning (Arendt, 1988, 2000). The physiological significance of melatonin could be revealed from the effects of the hormone on temperature (Cagnacci et al., 1992; Weibel et al., 1997), or induction of sleepiness (Leproult et al., 1997). It has been revealed that melatonin performs an important role in forming physiological rhythms and its synthesis as well as secretion is regulated by light and stress (Lewy et al., 1980; Czeiler et al., 1989; Sack et al., 1992; Van Reeth et al., 1994; Weibel et al., 1997).

TSH promotes growth and development of thyroid and stimulates the secretion of the thyroid hormones, which in turn modulates energy metabolism. A

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circadian rhythm of TSH secretion is established in animal and man with an acrophase during the night (Parker et al., 1976; Brabant et al., 1990; Van Treuer et al., 1996; Fukuda et al., 1997). Sleep is known to exert a modulatory effect on the TSH release, but the exact temporal relationship between sleep and the TSH level and its role on the nightly TSH increase still controversial (Parker et al., 1987; Allen and Czeisler, 1994).

Body temperature shows a circadian change: high during active period and low during night sleep. Strong interaction between body temperature and sleep is known to occur in human (Leproult et al., 1997). It is also known that melatonin acts as a modulator of thermo-regulation (Weibel et al., 1997).

The similar pattern of circadian rhythms of melatonin and TSH and the existence of constancy in the phases of melatonin, TSH and body temperature give rise to the possibility that there may be a causality in the relations among melatonin, TSH, body temperature, and sleep. The thermo-modulation effects of melatonin, TSH and sleep partly support this possibility. It is, however, not clear whether the rhythms of TSH and body temperature are entrained or modulated by melatonin rhythm or independently by the Zeitgeber, sleep-activity cycle.

To ascertain the relations among the rhythms of melatonin, TSH and body temperature, the sleep-wake cycle was abruptly changed from 2300-0700 to 0900-1700 and resulting changes in the circadian rhythms and temporal changes in the phase relationships were determined. The relationship between melatonin and TSH was maintained before and after the cycle shift whereas the relationships between body temperature and melatonin and between body temperature and TSH were somehow modulated.

Materials and Methods

Subjects

Four healthy male subjects, aged 20-22 yr old and weighing 60-70 kg, participated in this experiment. All subjects were nonsmokers and had no personal histories of psychiatric illness, endocrine illness or sleep disorder. They were prohibited from drinking alcohol and coffee, exercise, and drug during the experimental period.

Experimental protocol

For 3 wk before the experiment, healthy male subjects were maintained on a sleep cycle between 2300 and 0700 on clock time. During the experimental days, sleep was deprived at the first night and sleep time was shifted to 0900-1700. During their usual sleep period (2300-0700) they were forced to stay awake under bright fluorescent light and activities such as reading without exercise was allowed.

Blood sampling

In the control experiment, blood sampling was performed through an indwelling catheter in the forearm vein, starting from 1000 until 0700 on the following day at 2 or 4 h intervals. During the 3 d experiment, a 24 h blood sampling was done through an indwelling catheter in the forearm vein, starting from 2100. Samples were collected at 4 h intervals during the period when the hormonal levels were known to be steady and low, and at 2 or 3 h intervals during the period when hormone levels changed. Each blood sample was collected in an blood collection tube and immediately centrifuged. The plasma samples were stored at -70℃ until determination of melatonin and TSH concentrations by radioimmunoassay.

Hormone assays

Assays for plasma melatonin and TSH were subsequently done in the Green Cross Laboratory, Gwangju and Seoul. Samples from the same individual were used for both assays.

Plasma melatonin levels were measured using a melatonin direct ^{125}I-RIA kit (Diagnos Tech International Co.). This antiserum has been validated for the direct assay in human plasma using an iodinated melatonin tracer. The lower limit of sensitivity was 1.5 pg/mL. Plasma concentrations of TSH were measured by an immunoradiometric assay system utilizing two high-affinity monoclonal antibodies forming a sandwich with TSH (TSH IRMA Kit; Immunotech Co.). The lowest level of sensitivity is 0.025 μI.U./mL. The mean intra-assay coefficient of variation is 6.1%.

Body temperature measurement

Oral temperature was measured with a standard mercury thermometer every 2 to 4 h at the time of blood sampling for 1 control day and 3 continuous experimental days.

Results

Melatonin

Mean profiles of plasma melatonin obtained in the 4 subjects during the control day and 3 consecutive days of shifted sleep-wake cycle are shown in Fig. 1. In the control day-active subjects, the typical circadian melatonin rhythm was observed: melatonin was maintained at a low level during the day, began to rise in the evening (2000), increased abruptly just after the entry into sleep, reached the peak at 0200 and then decreased steeply to the basal level in the morning. The mean amplitude of the plasma melatonin was 47.5 ± 8.7 pg/mL. All individuals showed the similar pattern of daily rhythmic change, but the amplitude was variable from one individual to another (individual data not shown).

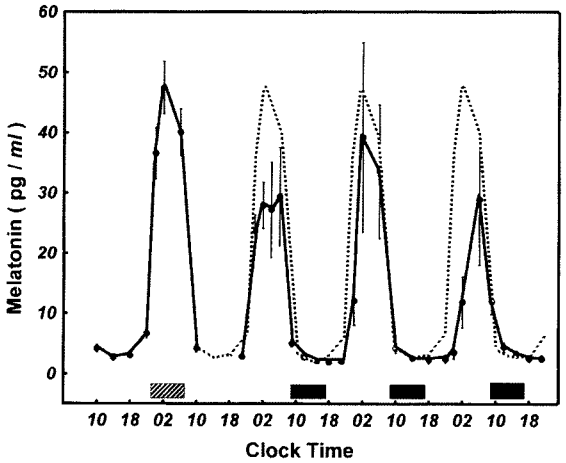

Fig. 1. Profiles of plasma melatonin levels during sleep-wake cycle change. In the following figures, for clear comparison, the control trace is superimposed (dotted line) on each of the days of sleep-wake cycle shifted. Note that the value at 1000 in control was replotted again at 1000 on the following day for completion and clear demonstration of the rhythm. The hatched bar (▨) and solid bar (■) indicate the sleep period in control (2300-0700) and in sleep shift experiment (0900-1700), respectively. Data are mean ± S.E. of four subjects.

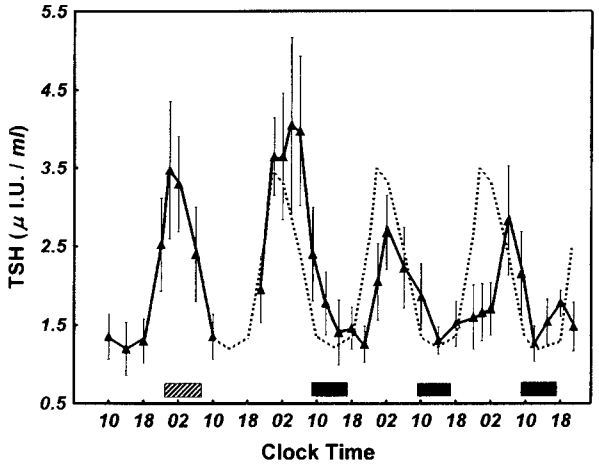

Fig. 2. Profiles of plasma TSH levels during sleep-wake cycle change. Data are mean values ± S.E. of four subjects. ▨ : sleep in control (2300-0700), ■ : sleep in experiment (0900-1700).

To facilitate comparison, the control rhythm was superimposed (dotted line) on the experimental. The control melatonin waveform was maintained in all 4 subjects imposed to a new sleep wake cycle (data not shown). The rhythms, however, became delayed daily and a clear phase shift in melatonin rhythm was observed on day 3 of the altered sleep-wake cycle, reflecting restoration of its phase relationship to sleep-wake cycle. Although the typical nocturnal peak appeared to persist during the sleep shift days, the peak values of melatonin were reduced during the night of sleep deprivation (day 1) and thereafter in 3 of 4 subjects.

These results suggest that the change in sleep-wake cycle did not disturb the fundamental melatonin rhythm, but shifted the melatonin rhythm to the right (delayed).

Thyroid stimulating hormone

Fig. 2 shows the daily plasma TSH rhythms obtained in the 4 subjects during normal sleep-wake cycle and following delayed sleep-wake cycle. TSH increased episodically at night. In the control with constant routine sleep-activity, the low basal values were maintained during the daytime, a rise occurred at 1800 with the maximum value observed at 2400 just after the onset of sleep, and the TSH level decreased gradually to the basal level at 1000. The usual TSH rhythm was maintained in all subjects with delayed sleep wake cycle (individual trace not shown). The superimposed rhythms in Fig. 2 show that the rhythms gradually become delayed with the cycle shift. Contrary to melatonin, the typical nocturnal peak values were slightly higher than the control on the first day of sleep shift in 3 individuals (individual data not shown).

These results suggest that the delay in sleep cycle did not disturb the fundamental TSH rhythm, but caused the TSH rhythm to be delayed and affected the amplitude of the rhythm.

Body temperature

As shown in Fig. 3, the body temperature showed dual phases: high during active period and low during sleep. Upon entry into sleep the body temperature decreased by about 1.5℃, from 37℃ to 35.5℃. Immediately following arousal the body temperatures were quickly restored to the level of active period and this was sustained during the daytime, forming a wide plateau and a steep valley in the shape of circadian variation.

Upon shift to sleep the circadian shape changed to a wide trough and a narrow peak. In sleep delayed individuals the body temperatures began to decrease similarly at 2200 as in control condition. When the subjects stayed awake during usual bedtime hours, the body temperature decreased as usual, suggesting that an internal clock regulates the body temperature rhythm. When the subjects entered into sleep during the usual active period, the lowered body temperature was maintained; it did not rise to the usual awake level shown in the control, indicating that it is modulated by sleep. Contrary to the control, the body temperature did not further decrease upon entrance into sleep. Because of overall effects of circadian clock and sleep, the decline of temperature did not seem as steep as in control. The temperature decreased rather gradually through the awake period in the night and the lowered body temperature was maintained during the sleep time (0900-1700) in daytime, forming a long basin. After waking up the temperature rapidly reached the peak and entered into a decline phase without the high plateau period, forming narrow steep peaks. Thus, in

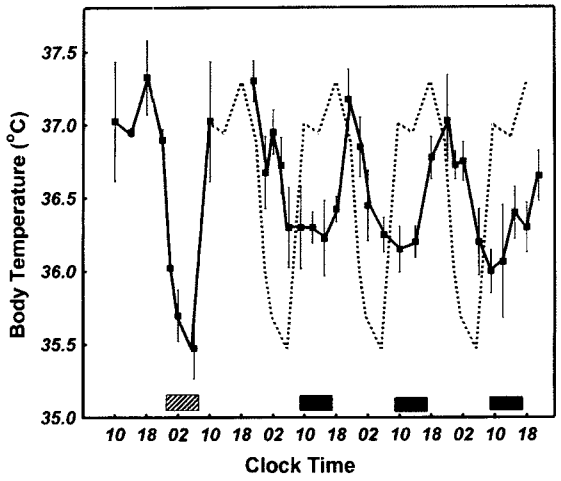

Fig. 3. Profiles of body temperature levels observed before and after the shift of sleep-wake cycle. Data are mean values ± S.E. of four subjects. ▨ : sleep in control (2300-0700), ■ : sleep in experiment (0900-1700).

the altered body temperature rhythm there appeared a long basin persisting from the night until arousal from the sleep and a narrow peak in the night.

In contrast to the melatonin and TSH rhythms, the body temperature rhythm was considerably affected by a newly imposed sleep-activity cycle (Fig. 3), indicating that the sleep-activity cycle is an important factor modulating body temperature.

Relationships among melatonin, TSH, and body temperature

Many physiological oscillating parameters as well as the Zeitgeber should be synchronized with one another for the optimal body function. Possible relationships among melatonin, TSH and body temperature were analyzed.

The data of melatonin in Fig. 1 and TSH in Fig. 2 were superimposed in Fig. 4A. These two levels changed quite in parallel throughout the day in the normal sleep-activity condition. There was, however, a small difference in the rhythmic change: TSH began to increase a little earlier than melatonin and also began to decrease earlier than melatonin. During the days of shifted sleep-wake cycle these episodic changes were maintained in parallel, and following the alteration of sleep-wake cycle the rhythms of melatonin and TSH were concomitantly delayed in a similar manner, suggesting a correlation between plasma melatonin and TSH levels.

Fig. 4B shows the changes in plasma melatonin levels and body temperatures. These rhythms changed opposite to each other in normal sleep-wake condition: body temperature was high during active period and low during sleep, whereas melatonin levels were low during day time and high during sleep. Upon the alteration of sleep-wake cycle, the opposite phase

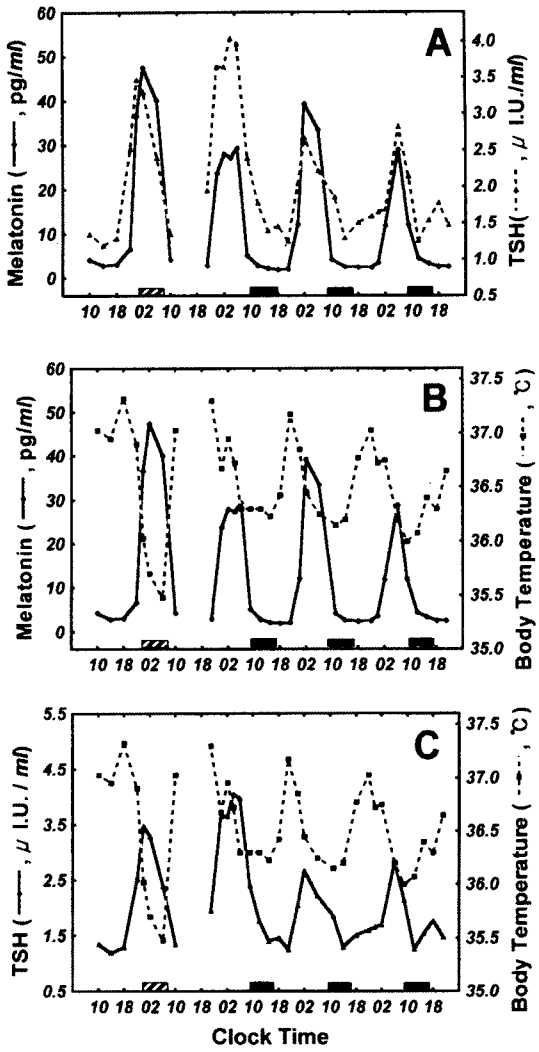

Fig. 4. Phase relationships between plasma melatonin and TSH (A), melatonin and body temperature (B), and TSH and body temperature (C). The values of melatonin, TSH, and temperature are adopted from those in Fig. 1, 2 and 3, respectively. ▨ : sleep in control (2300-0700), ■ : sleep in experiment (0900-1700).

relationship was a little estranged. At about 2200 melatonin began to increase and body temperature began to decrease as in control. The increment of melatonin was lower than the control and the decrease in body temperature was not so steep as in control. The plasma melatonin levels were restored to the basal level as in the control during day sleep period, whereas the low body temperatures were sustained during the sleep period in daytime. Thus, during daytime sleep plasma melatonin levels and body temperature were relatively low. This different responses during daytime sleep made the phases uncoupled, but the fact that melatonin began to increase when body temperature began to decrease indicates that the basic mirror phase relation persisted during the days of shifted sleep-activity cycle.

The traces of TSH in Fig. 2 and the body temperature in Fig. 3 were superimposed in Fig. 4C. The phase relation between TSH and body temperature was very similar to that of melatonin and body temperature in Fig. 4B. TSH and body temperature varied in a mirror image, with significant negative correlations: the body temperature was high when the TSH level was low, and vice versa in control. When the subjects were imposed to the shifted sleep-wake cycle, the low body temperature sustained during daytime sleep period made a small discrepancy in the opposite phase relation. The fundamental reversal relation, however, persisted during the sleep shifted days: when body temperature began to decrease, the plasma TSH level started to increase.

Discussion

Sleep-wake cycle and the circadian rhythms of melatonin and TSH

This study demonstrates that the circadian rhythms of melatonin and TSH were sustained even after the abrupt shift in sleep period by a 10 h delay. The nocturnal peaks of melatonin and TSH during sleep in the control were gradually delayed toward the shifted sleep period day by day. The clear phase shifts were found on day 3 after the sleep shift in melatonin and TSH. There was no evident change in the waveform of melatonin and TSH rhythms. These results indicate that the rhythms of melatonin and TSH are regulated mainly by internal circadian clock, but could be modulated by external cues. The delay in the rhythms can be interpreted as an indication of restorative processes of daily rhythmic change. The sustained circadian rhythms and gradual phase shift in the melatonin and TSH rhythms were also observed by others (Weibel et al., 1997; Goichot et al., 1998).

In contrast to the maintenance of phase of rhythms, the peak values were altered. The melatonin peak values decreased after the shift of sleep period in 3 out of 4 individuals, except for one who showed similar peak values. The decrease in the night peak may reflect inhibition of the nocturnal production of melatonin by the fluorescent light illumination (Lewy et al., 1980). The TSH peak levels increased on the first sleep deprived night and decreased thereafter to below the control peak in 3 individuals. The increase in the TSH peak level during the night of sleep deprivation has also been observed by Goichot et al. (1998).

The sustained low level of melatonin during daytime sleep suggests that melatonin synthesis was not turned on directly by sleep entry or by darkness. The internal clock, which may be synchronized to light-dark cycle, may act as a timer to switch on the synthesis of melatonin.

The results that the TSH level began to increase in the evening and turned to decrease after the entry into sleep suggest the possibility that the darkening switches on and the entrance into sleep switches off or has an inhibitory influence on the synthesis or secretion of TSH. However, the normal decline of TSH in experimental condition ruled out the possible involvement of sleep, raising a possibility that some internal timer may turn off TSH synthesis. The rhythms gradually moved to the direction adjusting the altered sleep period, indicating that the TSH rhythm became adjusted to the altered sleep-wake cycle, even though the process was very slow.

Relationship between melatonin and TSH rhythms

It may be necessary to maintain a constant phase relation between the rhythms for the proper physiological functioning of the various systems. The results show that the temporal phase relationship between melatonin and TSH persisted even after the sudden 10 h-delay in sleep. Upon this alteration of sleep-wake cycle, the rhythms of melatonin and TSH were concomitantly delayed in a similar manner. This parallel changes suggests a strong possible correlation between the melatonin and TSH rhythms. But TSH began to increase, reached at the peak values and entered a decline phase earlier than melatonin, suggesting that melatonin may not be the central controller or Zeitgeber on the TSH rhythm change. The disparity of the ratio betweem TSH and melatonin on days 1 and 2 after sleep shift supports the above suggestion.

It is more likely that the two rhythms are regulated by a common internal pacemaker via different pathways and thus, they are modulated to be different by the shift in sleep-wake cycle. This notion is consistent with the early studies in humans that indicated different circadian rhythms might be controlled by different circadian pacemakers (Aschoff and Wever, 1976). The present results suggest that the sleep-wake cycle can be considered as a weak Zeitgeber for the circadian clock, as indicated by the shift in the two endocrine rhythms. The slow adaptation of hormone rhythms in the present study applying on the abrupt shift in the sleep-wake cycle suggests that perfect adaptation by these hormone rhythms to a newly imposed sleep-wake cycle may require long time. The necessary time to be adapted may depend on the hormones (Mills et al., 1978; Van Cauter et al., 1994; Goichot et al., 1998).

Sleep-wake cycle and the body temperature rhythm

The body temperature was maintained high during the active period. It declined sharply to the nadir after the onset of sleep and was restored sharply to the day level (around 37℃) immediately after arousal, forming a deep and steep valley during sleep in the rhythmic phase. The shape was reversed with the 10 h-delayed shift in the sleep-wake cycle to narrow peaks and relatively wide troughs. This result indicates that the

body temperature rhythm was severely affected by the external cue, sleep-wake state, and that sleep has a potent modulating effect on body temperature as observed in by others (Reinberg et al., 1984; Franken et al., 1992).

The sleep shift was sufficient to partially shift the circadian rhythms of the body temperature and modulate the shape and magnitude of daily changes in the body temperature. Thermosensitive preoptic-anterior hypothalamus (PO/AH) neurons receive synaptic input from ascending pathways associated with states of arousal and sleep (Glotzbach and Heller, 1984). This could explain changes in body temperature associated with sleep and circadian rhythm.

It should be noted that the time that the body temperature begain to decline in the sleep shift condition was the same as that in control. This suggests that the body temperature rhythm or at least the internal circadian clock controls the process that turns down the body temperature either directly or indirectly.

Suprachiasmic nuclei (SCN) neurons in rat (a nocturnal animal) show a circadian change in neural activity with thermosensitivity high at night (Derambure and Boulant, 1994). If SCN neurons, which produce circadian rhythms in several regulatory systems, synaptically influence PO/AH neurons, the circadian changes in SCN thermosensitivity may account for the interactions between body temperature and circadian rhythms. Since lighting conditions and the length of day influence SCN activity, SCN-PO/AH interactions may be an additional factor linking photoperiod and temperature as a neural mechanism for seasonal adaptation to thermal conditions.

Melatonin, TSH and body temperature

The inverse relationship between melatonin and body temperature shown in Fig. 4B raises the possibility that the decrease in body temperature is resulted from the increase in plasma melatonin level which is regulated by internal biological clock. The hypothermic effect of melatonin reported in human (Cagnacci et al., 1992; Deacon and Arendt, 1995) supports this possibility. The slightly higher body temperature during day sleep could also be explained by the hypothermic effect of melatonin.

On the relationship between melatonin and body temperature, one group suggested the notion that the two rhythms are regulated by a single central pacemaker (Weibel et al., 1997) and the other group suggested that the body temperature rhythm could be shifted independently of the melatonin rhythm (Honma et al., 1992). The present results show that the inverse phase relationship between melatonin and body temperature was dissociated upon the shift in sleep-wake cycle, supporting the possibility that the two rhythms are regulated independently. In constrast, as discussed earlier the timing and the maintained inverse relation when the melatonin began to increase and body temperature began to decrease support that the body temperature rhythm is basically regulated by an internal clock directly and/or via melatonin pathway presumed in the previous studies (Van Cauter et al., 1994).

The discrepancy in the sleep effect, the remarkable hypothermic effect on body temperature with no effect on the melatonin rhythm may induce the dissociation of phase relation. Since there is no experimental evidence that melatonin influences the thermoregulatory centers in the hypothalamus, the phase relationship may be derived from independent circadian regulatory pathways.

TSH rhythm also seems to have an inverse relationship with the body temperature rhythm in human. TSH may affect the body temperature via regulation of the levels of thyroid hormones. It is well known that TSH stimulates the production of thyroid hormones, which in turn stimulates calorigenesis and heat production in most cells resulting in an increase in body temperature. The secretion of TSH is regulated primarily by thyrotropin-releasing hormone (TRH) produced by hypothalamus. The secretion of TRH is influenced by the inputs from the temperature regulatory centers in the hypothalamus, which in turn receive information concerning changes in body temperature. The increase in body temperature has a negative effect on TRH and TSH secretion and thus a reverse phase relationship between TSH and body temperature was expected. However, whether there is a causal relationship or it happens to be mere chance is uncertain. The temporal dissociation of TSH and body temperature rhythms after the sleep shift may result from the different responses to the altered sleep-wake cycle: body temperature is modulated profoundly whereas TSH rhythms is affected little by the sleep-wake cycle.

In conclusion, the present study has provided that circadian rhythms of melatonin and TSH are regulated fundamentally by an internal clock but are modulated by the sleep-wake cycle. There is a close relationship between melatonin and TSH rhythms. The body temperature rhythm seems to be basically regulated by internal clock but directly modulated by sleep-wake cycle and affected by melatonin and TSH rhythms. There are inverse phase relationships between body temperature and plasma hormones, melatonin and TSH in subjects having a normal sleep-wake cycle.

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