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Sleep Propensity Free-Runs with the Temperature, Melatonin and Cortisol Rhythms in a Totally Blind Person

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Summary: In previous studies, we found that many totally blind people have free-running melatonin rhythms, but that free-running melatonin rhythms were not necessarily associated with periodic insomnia and daytime sleepiness. Thus, it was not clear if the circadian sleep propensity rhythm was free-running with the other circadian rhythms. In the present study, we report that the sleep propensity rhythm (as defined by an ultrashort sleep–wake schedule) free-ran with the melatonin, temperature and cortisol rhythms in a 44-year-old totally blind man even though he maintained a conventional sleep schedule and did not complain of clinically significant insomnia or excessive daytime sleepiness. **Key Words:** Blindness—Melatonin—Circadian rhythms—Temperature—Sleep disorders—Cortisol.

In our recent study of 20 totally blind people, free-running melatonin and cortisol rhythms were common (11 of 20), even for subjects in which sleep patterns were quite regular and at conventional nighttime hours (1). Thus it appears that most blind people maintain a roughly 24-hour sleep–wake schedule, even when their other rhythms are free-running. One cannot infer, however, that their underlying sleep propensity rhythm is entrained; sleep times could be structured by informational time cues, and homeostatic mechanisms (i.e. the development of a "sleep debt") could produce periodic sleepiness independent of circadian mechanisms. The main question addressed in this study was whether the endogenously generated sleep propensity rhythm free-ran with the other free-running circadian rhythms in a blind subject with an overt 24-hour sleep–wake pattern. To our knowledge, this is the first case report of melatonin, core temperature, cortisol production and sleep propensity measured concurrently in the same human subject.

METHODS

The subject was a 44-year-old totally blind man who had been employed as a radio dispatcher in the past but was unemployed at the time of the study; nevertheless, he maintained a consistent nighttime sleep and daytime activity schedule. He had been blind since birth due to retrolental fibroplasia and had no subjective light perception and no pupillary reflex. He was otherwise physically healthy and did not have subjective sleep complaints.

Prior to beginning the study of multiple rhythms, we collected daily sleep diary data for 2 months and 24-hour melatonin profiles every 2–3 weeks.

We measured the timing of his sleep propensity weekly with the ultrashort sleep–wake schedule developed by P. Lavie (2,3). We also monitored sleep with standard sleep polysomnographic (PSG) recordings weekly. For these procedures, as well as for blood sampling and temperature monitoring, he was admitted to the general Clinical Research Center (CRC) at Oregon Health Science Center where he maintained the following weekly schedule for 5 consecutive weeks:

Day 1 (Friday: PSG day): Subject arrived at the CRC in the evening approximately 1 hour prior to his usual bedtime (23:00) and was prepared for standard PSG recordings including electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG) and electrocardiogram (ECG). PSG was performed from 11:00 p.m. to 7:00 a.m. Sleep records were scored according to the usual criteria (4) with the exception that rapid eye movement (REM) sleep had to be scored without depending on EOG (EEG voltage and waveform, atonia and EMG twitches were used to score REM sleep).

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Day 2 (Saturday: Constant routine day): The constant routine protocol is a technique that has been used in a number of chronobiology laboratories to minimize the masking effects of sleep and exercise on core body temperature (5,6). As required by the protocol, the subject was kept awake (total sleep deprivation), recumbent (except to go to the bathroom) and quiet for 26 hours. He received isocaloric feedings every 2 hours. During the constant routine, we measured rectal temperature every 5 minutes via a rectal probe (Yellow Springs thermistor, Minimitter DataLogger). In addition, we obtained blood samples hourly, which were later assayed for plasma melatonin and cortisol concentrations. For blood sampling, an intravenous catheter was inserted into a forearm vein, and 5 cc were drawn at hourly intervals for 24 hours for 3 of the test days and for 12 hours (to capture the onset of melatonin production) for 2 of the test days. Melatonin was assayed using a radioimmunoassay (RIA) recently developed by Schumacher (7). Critical data points used to define the melatonin onset were confirmed by reassay using the highly sensitive and specific gas chromatographic negative ion mass spectrometric developed by Lewy and Markey (8). The time at which melatonin concentrations rose above a 10-pg/ml threshold (melatonin onset time) was used as the primary marker for circadian phase. Cortisol was measured using a commercial coated-tube RIA assay kit (Diagnostic Products Corp., Los Angeles, CA).

Day 3 (Sunday: Sleep propensity rhythm day): After the constant routine study (26 hours sleep deprivation), the subject was fitted with electrodes to record EEG, EOG and EMG. At 9:00 a.m., he began a schedule of 7-minute nap opportunities alternating with 13 minutes of enforced wakefulness (7/13 ultrashort sleep–wake paradigm) for 24 hours (72 trials) (2,3). Every 20 minutes he was instructed to lie in bed in a sound-attenuated bedroom and attempt to sleep. Sleep recordings were carried out during the 7-minute nap opportunities to determine amount of sleep as well as the sleep stage. At the end of each nap, no matter how much he had slept, he was requested to leave the bedroom. During the 13-minute awake period, he was free to move about quietly. Light snacks and soft drinks were provided every 2 hours. The 7-minute sleep records were scored in 30-second epochs for sleep stage according to the criteria described above (4).

Days 4–7 (Monday through Thursday: Recovery days): On these days, the subject was "on pass" to his own apartment. After a day or two of rest to allow recovery from the period of sleep deprivation, the subject returned to his usual schedule.

This weekly cycle was repeated five times. However, sleep data (both PSG and naps) were discarded from the first week because of missing data and because the sleep propensity measures appeared to be influenced by the stress of the experimental procedures.

RESULTS

Preliminary results of this study have been presented previously (9).

Sleep diary data

Figure 1 presents the data from the sleep diary study. Melatonin rhythms were free-running with a stable period of 24.65 hours, but sleep times remained on an approximate 24-hour schedule.

Sleep propensity rhythm

Figure 2 presents the sleep durations for each nap opportunity (total minutes of each stage) double-plotted in relation to clock time. The "sleep gate" [the first trial containing at least 50% sleep of any sleep stage (2)] delayed 3.67–4.33 hours each week (average 0.59 hours each day). Also in Fig. 2, melatonin onsets are double-plotted for 4 consecutive weeks during which his melatonin rhythm delayed 4.0 hours per week (average 0.57 hours each day). The sleep propensity rhythm clearly free-runs in parallel with the melatonin rhythm.

Melatonin, temperature and cortisol rhythms

In order to better understand the phase relationships between the melatonin and the temperature and cortisol rhythms, the data for all five days were plotted on "circadian time" by considering the melatonin onset time to be the beginning of the "circadian day" (Fig. 3). Sleep propensity is lowest just before the rise in melatonin production and rises in parallel to the rise in melatonin levels. However, sleep propensity does not appear to fall until melatonin has reached daytime levels.

The timing of the temperature maximum and the cortisol nadir appeared to coincide with the melatonin onset time, while the timing of the temperature nadir and the cortisol maximum appear to coincide with melatonin "offset" (the time that melatonin dropped below the 10 pg/ml threshold). Sleep propensity is greatest when temperature is declining and cortisol is rising.

PSG

In the standard sleep PSGs, sleep efficiency was good on the second and third week (99% and 82%, respec-

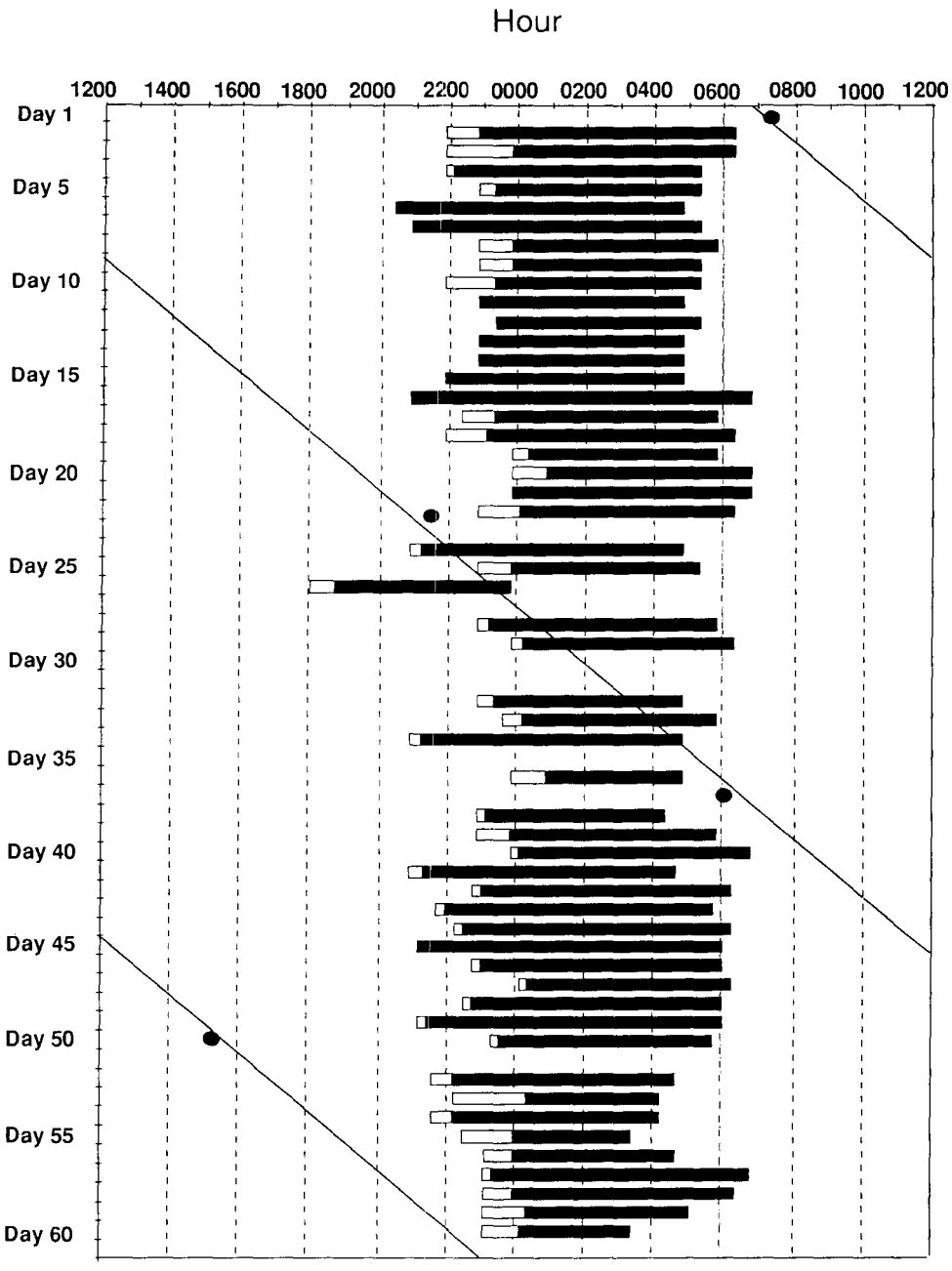

FIG. 1. Sleep diary data are plotted for a 60-day period. Each bar represents a time in bed, and the darkened portion represents the estimated time asleep. The times when melatonin increased above the 10 pg/ml threshold, i.e. the "melatonin onsets", are represented by the filled circles, and the lines connecting them represent the estimated (interpolated) times for the melatonin onsets on the intervening days. Although the melatonin rhythm is free-running, sleep times remain relatively constant over the 60-day period.

tively) when melatonin onset times were close to the normal phase for sighted people (6:00 and 10:00 p.m.). On the other hand, sleep efficiency was reduced (62% and 75%) on the fourth and fifth week when melatonin onset time was delayed with respect to usual sleep times (2:30 and 6:00 a.m.). There was no correlation between sleep architecture and the phase of the free-running melatonin rhythm; however, the number of nights sampled may have been too small to detect a difference.

DISCUSSION

Circadian rhythms in blind people

Miles et al. (10) described the first case of a totally blind person with free-running rhythms who suffered from periodic insomnia and daytime sleepiness when his endogenous rhythms were out of phase with his preferred sleep times. Despite heroic attempts to entrain his sleep rhythm, he was not able to sleep on a

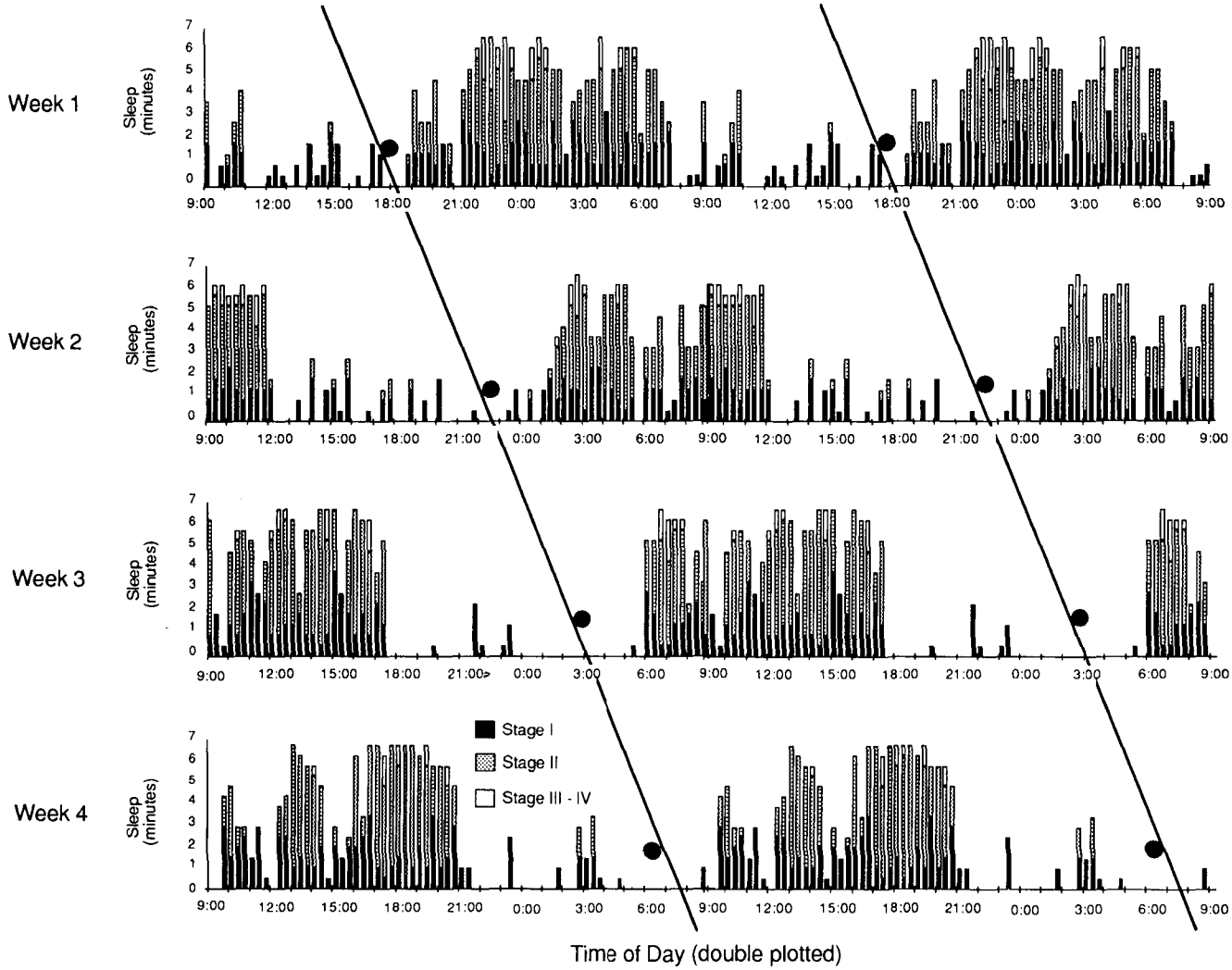

FIG. 2. The sleep propensity rhythm was measured for a 24-hour period on 4 consecutive weeks using the protocol developed by Lavie (see text). Each column represents the total sleep time for a given 7-minute nap opportunity and is subdivided according to the proportion of stages I, II and III–IV sleep observed in each nap. Sleep propensity is operationally defined as the total accumulation of sleep during each nap; thus, the height of the column is proportional to the sleep propensity. There were 72 nap opportunities during each 24-hour test period, and the data are double-plotted to better show the circadian pattern. The times when melatonin increased above the 10-pg/ml threshold, i.e. the "melatonin onsets", are represented by the filled circles. Sleep propensity appears to free-run in parallel with the melatonin rhythm.

24-hour schedule. Orth et al. (11) reported free-running cortisol rhythms in a blind person who was studied in the hospital for 50 days; the circadian period of her cortisol rhythm was 24.5 hours while her sleep–wake cycle had a circadian period of exactly 24.0 hours. No mention is made of sleep-related symptoms. Lewy and Newsome first documented free-running melatonin rhythms in a blind subject (12); this man had recurrent sleep complaints that appeared to be explained by his circadian desynchrony. In our study of totally blind subjects, 3 of 20 (all with free-running rhythms) complained of periodic insomnia of disabling intensity. Surveys of blind people for sleep complaints have found a higher than average frequency of symptoms (13,14). In summary, it appears that sleep problems do not typically bring totally blind people to a physician and most blind people keep fairly regular hours; however, some blind people have symptomatic periodic insomnia and daytime sleepiness, which is sometimes disabling and presumably related to free-running circadian rhythms, including a free-running sleep propensity rhythm that beats in and out of phase with the 24-hour geophysical and social day.

Our data document that the underlying sleep propensity rhythm is "phase locked" with the other free-running rhythms in at least this one blind subject. The fact that his habitual sleep pattern followed a 24-hour cycle underscores the importance of other factors besides circadian phase in determining actual sleep times; homeostatic mechanisms [i.e. the build-up of a sleep debt (15)], as well as the choice of bed time, presumably influenced by social convention, appeared to exert

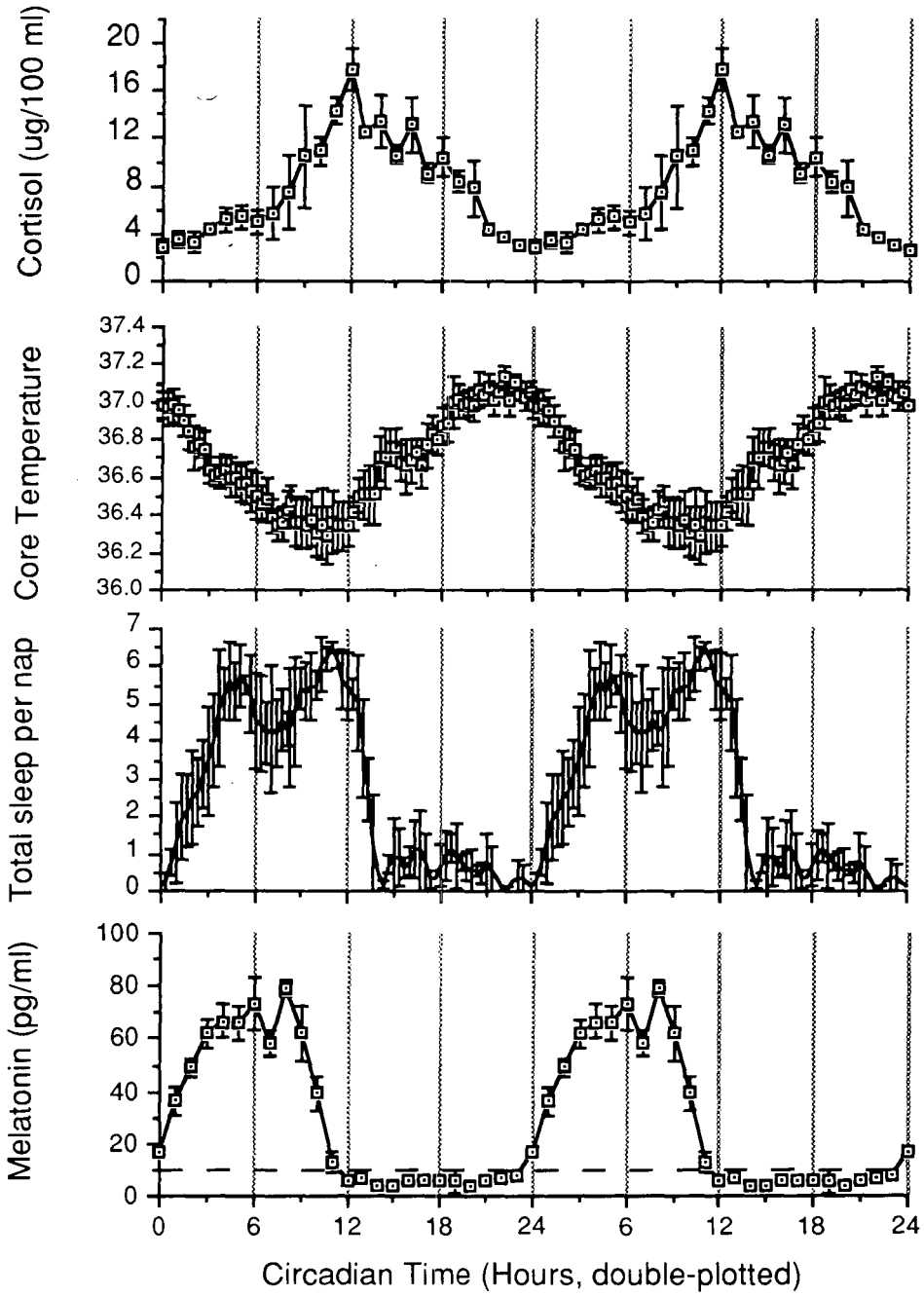

FIG. 3. Plasma cortisol concentration, core body temperature, total sleep per 7-minute-nap (sleep propensity) and melatonin concentration are double-plotted on "circadian time", using the onset of melatonin production (the time when melatonin concentration rises above the 10-pg/ml level) as the beginning of each "circadian day". Data from five test days are averaged, except for sleep propensity, which in the first week was omitted because of technical problems. The timing of the temperature maximum and the cortisol nadir appeared to coincide with the melatonin onset time, whereas the timing of the temperature nadir and the cortisol maximum appear to coincide with melatonin "offset" (the time that melatonin dropped below the 10-pg/ml threshold). Sleep propensity is greatest when melatonin production is active, temperature is declining and cortisol is rising.

enough influence on his overt sleep behavior to maintain a conventional day-active, night-sleep pattern. However, PSG data suggest that sleeping out of phase with the underlying sleep propensity rhythm extracts a cost in sleep efficiency. In some blind people, this desynchrony is the likely cause for periodic insomnia and daytime sleepiness. It remains unclear why some blind people are able to tolerate circadian desynchrony while others cannot. Dawson and Campbell have suggested the concept of "phase tolerance" in which adequate sleep may not require complete alignment of the sleep period with the circadian timekeeping system (16).

Recently, Martens et al. (17) reported regularly re-

peating cycles in sleep architecture in a blind man with free-running temperature rhythms who was monitored for 103 nights. REM propensity appeared to be a function of circadian phase, as was shown previously in temporal isolation studies (18), but the pattern of slow-wave sleep was more variable, perhaps because it is related more to homeostatic than to circadian mechanisms.

The use of ultrashort sleep schedule as a measurement of circadian sleep propensity

The "7/13 ultrashort sleep schedule" protocol designed by Lavie permits the extraction of the circadian component from the other influences on sleep. Sleepiness is sampled with sufficient frequency to provide a highly resolved measure of the phase of the sleep propensity rhythm; furthermore, sleep debt is held roughly constant because the subject is sleep-deprived for 24 hours prior to beginning the protocol, and during the protocol, does not accumulate enough sleep to reverse the initial sleep deprivation. Previous studies by Lavie et al. (3) discriminating sleep propensity between "owls" and "larks" suggested that the 7/13 schedule might be a useful marker for circadian rhythms generally; however, other marker data were not available for comparison.

In a more recent study of normally entrained sighted subjects, Tzischinsky and Lavie (19) found a correlation between the timing of the "sleep gate" as determined by the 7/13 schedule and the acrophase in the urinary excretion of the primary metabolite of melatonin, a finding consistent with our data.

Is melatonin a somnogenic hormone?

Our data demonstrate a strong correlation between the timing of melatonin production and sleepiness, but the design of the study does not demonstrate causality. Almost from the time that melatonin was discovered, there has been speculation that melatonin has a sleep-inducing effect and may be responsible, at least in part, for normal nocturnal sleepiness (20,21). Melatonin administration studies by James et al. (22,23) appeared to refute the earlier evidence that melatonin was hypnogenic; however, in these studies melatonin was administered to subjects with presumably normal endogenous melatonin production. Thus a more cogent experiment may be to administer melatonin under conditions in which endogenous melatonin production is lacking or suppressed, for example in the elderly.

Recently, melatonin administration has been shown to reduce core body temperature (24,25). Because a fall in temperature is frequently associated with sleepiness, this finding suggests an indirect mechanism by which melatonin may increase sleep propensity.

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