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Melatonin Rhythms in Delayed Sleep Phase Syndrome

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Abstract The aim of this study was to compare circadian and sleep characteristics between patients with delayed sleep phase syndrome (DSPS) and healthy controls. The authors studied 8 DSPS patients and 15 normal controls. Serum melatonin concentration was assessed every hour for 24 h under dim light conditions. The sleep phase and the melatonin rhythm in DSPS patients were significantly delayed compared to those in normal controls. Sleep length was significantly greater in DSPS patients compared to that in controls, but the duration of melatonin secretion did not differ between the two groups. The final awakening, relative to melatonin onset, melatonin midpoint, and melatonin offset, was significantly longer in DSPS patients than in controls. By contrast, the timing of sleep onset relative to melatonin rhythm did not differ between the two groups. The authors found a significant positive correlation between sleep phase markers and melatonin phase markers in DSPS. They postulate that a delayed circadian pacemaker may be responsible for delayed sleep phase syndrome. The alteration of phase angle between melatonin rhythm and sleep phase suggested that not only the delay of the circadian clock but also a functional disturbance of the sleep-wake mechanism underlies DSPS.

Key words sleep disorder, delayed sleep phase syndrome, DSPS, melatonin, circadian rhythm, light

INTRODUCTION

Delayed sleep phase syndrome (DSPS) was first defined by Weitzman et al. (1979) as a chronic sleep onset insomnia that is due to a consistent delay of sleep timing. The International Classification of Sleep Disorders (ICSD) (Diagnostic Classification Steering Committee, 1990) has classified DSPS as a circadian rhythm sleep disorder. Functional abnormalities of the circadian pacemaker have been assumed to underlie this syndrome, but its detailed pathophysiology has not yet been established.

Several authors have investigated DSPS sufferers’ core body temperatures and/or hormonal rhythms as circadian phase markers, but the results have been conflicting, in part due to lack of a comparative study. Ozaki et al. (1996) indicated that the nadir of DSPS patients is significantly delayed compared to that of normal individuals. Alvarez et al. (1992) suggested that the profile of plasma melatonin release in DSPS patients lies within the normal range, whereas Oren et al. (1995) documented a delayed melatonin rhythm in a patient with DSPS.

Hoban et al. (1989), Ozaki et al. (1996), and Uchiyama et al. (1996) showed that the phase angle between circadian pacemaker and sleep episode is thought to affect circadian rhythm sleep disorders. In these studies, it was pointed out that a sleep episode may be more delayed compared to the circadian pacemaker in patients with persistent sleep phase delay.
whereas the ICSD has stated that the temperature nadir of the DSPS sufferer is delayed into the latter part of his or her sleep episode.

In the study described here, we investigated the plasma melatonin profiles of DSPS patients and healthy normal controls under well-controlled conditions. The difference in phase angle between the circadian pacemaker and sleep phase is of particular interest in this study.

PATIENTS AND METHODS

We studied 8 patients with DSPS and 15 normal controls, all of whom gave their informed consent before entering the study. The patient group consisted of 7 males and 1 female, age 15 to 36 years, in whom DSPS was diagnosed according to ICSD criteria. We carried out the present study before the patients had undergone any therapeutic interventions. No patient had been given any medication, had the habit of drinking alcohol before bedtime, or abused alcohol or other psychotropic drugs. The clinical features of the patients are summarized in Table 1. We conducted a semistructured psychiatric interview and found no Axis I or III disorders of DSM-IV (American Psychiatric Association, 1994). No patient had a medical disorder, a history of developmental problems, or a severe somatic disease. All of the patients had experienced either occupational or educational difficulties. Because of their inability to keep to desired sleep-wake schedules, Cases 1 and 4 could attend their workplaces only during the afternoon, and Cases 2 and 8 could not engage in regular employment.

The controls were healthy volunteers (5 males and 10 females, ages 20 to 23 years) without any sleep disorders or any histories of using psychoactive drugs. They had regular sleep-wake habits but no remarkable weekday-weekend differences in sleep length or remarkable irregularity due to work schedules. None of the controls had difficulty in waking up at the desired wake time. The basal body temperature data of the female participants were used to know the phases of their menstrual cycles. We carried out the present study in the follicular phase. We instructed all of the participants to keep sleep logs for more than 4 weeks and to wear wrist activity recorders (Actigraph, AMI, New York). We confirmed that no marked day-to-day variations in their sleep-wake schedules occurred and that their own sleep schedules were not markedly constrained by their work schedules.

Sleep onset and offset times were determined visually from the sleep logs in 15-min bins by one of the investigators, who was unaware of the conditions of the participants. The actigram data confirmed the reliability of the sleep log data.

The medians of sleep onset and sleep offset times for 2 weeks prior to the experimental session were used as the participants’ markers of habitual sleep schedule. To obtain circadian melatonin profiles, blood samples were taken every hour under dim light conditions for 24 h from the participants’ rise time through indwelling venous catheters with a heparin lock. Plasma melatonin levels were assayed by radioimmunoassay (Bühlmann melatonin radioimmunoassay test kit, Schönenbuch, Switzerland). To avoid sunlight before initiation of blood sampling, participants came to the laboratory 4 to 5 h prior to their habitual bedtimes. During their habitual sleep times, some patients stayed awake under dim light conditions (< 10 lux), but other patients did not tolerate sleep deprivation. Finally, 10 controls and 5 patients completed sleep deprivation, and others slept in a dark sound-attenuated bedroom. All of the data were analyzed together because under dim light conditions, melatonin concentrations are unlikely to be influenced by sleep (Hoban et al., 1990; Lewy et al., 1993). During melatonin measurement, the participants were kept in

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Gender</th>
<th>Age at Study (years)</th>
<th>Age at Onset (years)</th>
<th>Sleep Onset Time (hours)</th>
<th>Sleep Offset Time (hours)</th>
<th>Total Sleep Time (hours)</th>
<th>Social Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>30</td>
<td>28</td>
<td>6.5</td>
<td>16.0</td>
<td>9.5</td>
<td>Occupational difficulties</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>24</td>
<td>17</td>
<td>4.0</td>
<td>12.0</td>
<td>8.0</td>
<td>Loss of employment</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>20</td>
<td>17</td>
<td>6.0</td>
<td>15.5</td>
<td>9.0</td>
<td>Poor attendance at school</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>26</td>
<td>24</td>
<td>2.0</td>
<td>12.0</td>
<td>10.0</td>
<td>Occupational difficulties</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>32</td>
<td>27</td>
<td>6.8</td>
<td>16.4</td>
<td>9.6</td>
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</tr>
<tr>
<td>6</td>
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<td>31</td>
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<td>3.0</td>
<td>10.5</td>
<td>7.0</td>
<td>Occupational difficulties</td>
</tr>
<tr>
<td>7</td>
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<td>15</td>
<td>14</td>
<td>2.1</td>
<td>12.0</td>
<td>9.9</td>
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</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>36</td>
<td>25</td>
<td>4.5</td>
<td>12.0</td>
<td>7.4</td>
<td>Loss of employment</td>
</tr>
</tbody>
</table>
a dark room (< 10 lux). When participants left the room for urination/defecation, they wore dark goggles, which attenuated light less than 10 lux coming into the eyes.

The melatonin onset time (melatonin onset) and melatonin offset time (melatonin offset) were determined visually as the crossing time of the raw data and the midrange of peak concentration. The melatonin duration was defined as the period between melatonin onset and offset. The melatonin midpoint time (midpoint) was obtained by averaging melatonin onset and melatonin offset. To investigate the timing of sleep onset or offset relative to melatonin rhythm, we subtracted melatonin phase markers from sleep onset or offset.

A t-test was used to perform a between-groups comparison. Correlation coefficients were calculated using Spearman’s rank correlation coefficient (StatView, ver. 4.51.1, Abacys Concepts, Berkeley, CA).

RESULTS

The melatonin profiles and habitual sleep episodes of the DSPS patients and the controls are shown in double-plot format in Fig. 1. Melatonin concentration is expressed as the percentages of participants’ peak values. The melatonin rhythm and the sleep phase in DSPS patients were markedly delayed compared to those in normal controls.

The sleep and circadian parameters of both the DSPS patients and the normal controls, together with the between-groups comparison, are given in Table 2. The sleep onset and offset times were delayed significantly in DSPS patients compared to those in normal controls (sleep onset time: 4.5 ± 0.7 h vs. 0.7 ± 0.2 h, p < .0001; sleep offset time: 13.3 ± 0.8 h vs. 7.6 ± 0.3 h, p < .0001). The sleep length was significantly longer in DSPS patients than in controls (8.8 ± 0.4 h vs. 6.9 ± 0.2 h, p < .0001). The melatonin onset and melatonin offset were delayed significantly in DSPS patients compared to those in controls (melatonin onset: 4.3 ± 0.7 h vs. 0.6 ± 0.4 h, p < .0001; melatonin offset: 12.4 ± 0.8 h vs. 8.2 ± 0.3 h, p < .0001). The melatonin midpoints also were delayed significantly in DSPS patients compared to those in controls (8.4 ± 0.8 h vs. 4.4 ± 0.3 h, p < .0001). The melatonin duration did not differ between the two groups (8.1 ± 0.2 h vs. 7.6 ± 0.3 h).

The timing of sleep onset and offset relative to melatonin rhythm is given in Table 3. The timing of sleep onset relative to melatonin rhythm did not differ between the groups. By contrast, the timings of sleep offset relative to melatonin onset, melatonin midpoint, and melatonin offset were significantly longer in DSPS patients than in normal controls (p < .01, p < .01, and p < .05, respectively).

In DSPS patients, we calculated the Spearman’s rank correlation coefficient between sleep parameters (sleep onset and sleep offset) and melatonin phase markers and found significant positive correlations: sleep onset versus melatonin onset, rho = .95, p = .01; sleep onset versus melatonin offset, rho = .80, p = .34; sleep offset versus melatonin onset, rho = .82, p = .04; and sleep offset versus melatonin offset, rho = .76, p = .05.

DISCUSSION

In the present study, the phase markers of melatonin rhythm were significantly delayed in patients with DSPS compared to those in normal controls. In previous studies, data regarding the circadian position of melatonin rhythm in DSPS appear to be conflicting. Oren et al. (1995) reported that melatonin and temperature rhythms were delayed in a woman suffering from DSPS. Conversely, Alvarez et al. (1992) reported that melatonin rhythm was normal in 14 patients with DSPS. Under normal daylight conditions, the normal melatonin rhythm of the DSPS sufferers studied by Alvarez et al. might have been influenced by the light
conditions. By contrast, in Oren et al.’s (1995) study and the present study, melatonin rhythm was assessed with the participants under constant dim light conditions. Indeed, we can explain the contrasting results on melatonin rhythm by considering the light conditions under which prior studies have been conducted. Under dim light conditions, the melatonin rhythm has been considered to represent the oscillation of circadian pacemakers (Lewy et al., 1993). In DSPS patients, the melatonin rhythm is likely to be delayed. The observation of a delayed melatonin rhythm in DSPS patients under dim light conditions might indicate a phase delay of the patients’ circadian pacemakers. Likewise, in the non-24-h sleep-wake syndrome, under dim light conditions, melatonin rhythms are free running in parallel to the sleep-wake rhythm (Nakagawa et al., 1992). Previously reported delayed temperature rhythms in DSPS patients also support this notion. A significant correlation between sleep parameters and melatonin phase markers in DSPS patients suggests that a delayed circadian pacemaker is responsible for the delayed sleep phase.

In the present study, the position of sleep onset time relative to melatonin rhythm did not differ between the patients and the controls, whereas the timing of sleep offset relative to melatonin rhythm was significantly delayed in DSPS patients compared to that in controls. These data suggest that in DSPS patients, only sleep offset is delayed relative to the circadian pacemaker. In other human experimental studies, a phase-resetting effect of bright light pulses on the circadian system has been demonstrated (Czeisler et al., 1989; Dijik et al., 1991; Minors et al., 1991; Cauter et al., 1993). Bright light pulses given slightly before the body temperature nadir phase-delayed the temperature rhythm, whereas bright light pulses given slightly after the body temperature nadir phase-advanced the temperature rhythm. Sleep offset that is delayed relative to the circadian pacemaker in DSPS patients may prevent the phase-advance portion of the phase response curve (PRC) (Lewy et al., 1984) from being illuminated. Hoban et al. (1989) having observed delayed sleep onset relative to melatonin rhythm in a patient with non-24-h sleep-wake syndrome, postulated that the delay in sleep phase relative to the circadian pacemaker might make the patient sleep through the phase-advance portion of the PRC to light. Ozaki et al. (1996) reported that the interval from the core body temperature nadir to sleep offset was significantly longer in DSPS patients than in controls. However, these investigators did not confirm that those findings might be related to the circadian pacemaker because the core body temperature rhythm was measured during a normal routine, and the masking effects (Minors and Waterhouse, 1989; Folkard et al., 1991; Barrett et al., 1993; Carrier and Monk, 1997) of exercise, sleep, and ambient light on temperature curves were not fully excluded. Thus, the present results represent the first documentation that the phase relationship between sleep and the circadian pacemaker is altered in DSPS patients and that this might explain patients’ inability to properly phase-advance the sleep episode.

The study presented here revealed that the sleep length of DSPS patients is significantly longer than
that of normal controls but that the duration of melatonin secretion does not differ between the two groups. These findings suggest that not only the delay of the circadian clock but also a functional disturbance in the sleep-wake mechanism underlies DSPS. Wehr et al. (1993) studied the relationship between photoperiod and sleep length. They demonstrated that sleep length was greater after exposure to long nights than after exposure to short nights. In DSPS patients, delayed sleep offset may be responsible for the shortening of the photoperiod, and this might be responsible for their greater sleep durations.

REFERENCES


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