Phase-advance shifts of human circadian pacemaker are accelerated by daytime physical exercise

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Miyazaki, Toshihiko, Satoko Hashimoto, Satoru Masubuchi, Sato Honma, and Ken-Ichi Honma. Phase-advance shifts of human circadian pacemaker are accelerated by daytime physical exercise. Am J Physiol Regulatory Integrative Comp Physiol 281: R197–R205, 2001.—Effects of forced sleep-wake schedules with and without physical exercise were examined on the human circadian pacemaker under dim light conditions. Subjects spent 15 days in an isolation facility separately without knowing the time of day and followed a forced sleep-wake schedule of a 23 h 40-min period for 12 cycles, and physical exercise was imposed twice per waking period for 2 h each with bicycle- or rowing-type ergometers. As a result, plasma melatonin rhythm was significantly phase advanced with physical exercise, whereas it was not changed without exercise. The difference in phase was already significant 6 days after the start of exercise. The amplitude of melatonin rhythm was not affected. A single pulse of physical exercise in the afternoon or at midnight significantly phase delayed the melatonin rhythms when compared with the prepulse phase, but the amount of phase shift was not different from that observed in the sedentary controls. These findings indicate that physical exercise accelerates phase-advance shifts of the human circadian pacemaker associated with the forced sleep-wake schedule.

delay shifts of the core body temperature rhythm associated with simulated night shifts (9). These findings suggest that physical exercise somehow has an impact on the human circadian pacemaker. But it is not known whether physical exercise contributes to entrainment of the human circadian pacemaker to the day-night alternation, because it is a phase-advance shift not a phase delay that is necessary for the human circadian pacemaker, which possesses an intrinsic period longer than 24 h (7, 10, 27), to entrain to a 24-h cycle.

On the other hand, entrainment can be accelerated by shortening the circadian period of pacemaker, whereby the daily phase shift necessary for entrainment becomes smaller. Beersma and Hiddinga (2) examined the effect of physical exercise during wakefulness on the circadian period of core body temperature with a desynchronization protocol of 20-h intervals. They did not find a statistically significant difference in the period between the forced schedules with and without exercise. Physical exercise under free-running conditions also failed to change the circadian period of body temperature (29). However, in these studies, physical exercise was designed to cover all phases of the circadian pacemaker (2) or a particular part of the circadian phase (29), so that the possibility was not excluded that the phase-dependent effect of physical exercise was missed. Actually, Buxton et al. (4) predicted a phase-response curve for physical exercise in which a phase-advance portion was located at noon.

In the present study, we reexamined the entraining effect of physical exercise on the human circadian rhythm using a forced sleep-wake schedule of a period of 23 h and 40 min under dim light conditions (<10 lx). This external periodicity requires a phase-advance shift of >1 h/day for full entrainment of the circadian pacemaker. The rationale for using this periodicity was to reveal the phase-advance effect of physical exercise, if any, by a relatively short-term experiment. Because the free running period of the human circadian pacemaker is longer than, but close to, 24 h under dim light conditions (17), especially immediately after release into free running (10), the expected phase shift...
in the control experiment is only a few hours at most in 12 days. The phase difference to be tested at the end of experiment should be large enough between the control and experimental groups; otherwise the entraining effect of physical exercise would be missed. In the experimental design mentioned above, the overall displacement (phase-advance shift) of sleep time is 4 h in 12 cycles. In addition, a single pulse of physical exercise given at different times of day was examined for its phase-shifting effects on the plasma melatonin rhythm to discover the mechanism of entrainment by physical exercise.

SUBJECTS AND METHODS

Subjects and Facility

Forty-six healthy subjects of both sexes (42 men, 4 women) participated in the present study as paid volunteers. Two persons participated twice in different experiments. They ranged in age from 20 to 28 yr (the average, 23.2 ± 2.1 yr) and passed a routine medical examination. Subjects who had been abroad or had a job in the early morning or at night within 4 wk before the experiment were excluded. The study was approved by the ethical committee of Hokkaido University Graduate School of Medicine.

The subjects were asked to try to go to bed at midnight for 7 days before the start of experiment and to keep sleep diaries. They stayed in a temporal isolation facility either for 3 days or for 15 days without knowing the time of day. The facility consists of four isolation units. Each two units are connected by a common room where the subjects performed physical exercise. The common room is also isolated from outside. The isolation unit consists of a living room with kitchen and a bathroom, as described elsewhere (14). The main illumination was supplied from the ceiling, but there were accessory lights at bed, bathroom, and desk. The light intensity of the rooms for physical exercise as well as the isolation units was kept at 50 lx at the head level of a standing subject, but the actual light intensity received by the subjects was <10 lx when measured with a photosensor (actirum) placed on the forehead. The intensity of accessory lights was <10 lx in the ordinary position.

Experimental Protocols

Two different experiments were carried out: forced sleep-wake schedules with and without physical exercise (experiment 1) and a single pulse of physical exercise at three different times of day (experiment 2).

Experiment 1: forced sleep-wake schedule with and without physical exercise. Four series of experiments were carried out. In each series, four subjects were studied, two performing physical exercise and the other two being sedentary.

The subjects entered the isolation facility at 1700 on the 1st day. A serial blood sampling was started at 1800 for 24 h at 1-h intervals. On the 1st night, the subjects were instructed to go to bed at their habitual sleep times and allowed to wake up at their preferred times. From the 2nd night, a forced sleep-wake schedule with a period of 23 h and 40 min (8-h rest and 15 h 40-min wake periods) was imposed for 12 cycles. The time of retirement at the 2nd night (1st night of forced schedule) was scheduled at 2400 and the wake-up time at 0800, both of which were phase advanced by 20 min every day. On the last day of the forced schedule (day 14), the subjects went to bed at 2000 and got up at 0400. The subjects were notified by phone to prepare for sleep 30 min before the scheduled time for retirement and again to go to bed at the scheduled sleep time. They were required to remain in bed lying down until the scheduled wake-up time, except when using the bathroom. Immediately before retirement, the room illumination and accessory lights were turned off. At the scheduled wake-up time, the subjects were awakened by a morning call and required to get out of bed. The room illumination and accessory bed lights were turned on. They performed physical exercise twice a day during the waking period from day 3 to day 14. The morning exercise was started 3 h after waking up, and the afternoon exercise was 2 h after the end of morning exercise (7 h after waking up). Physical exercise and rest (sitting in a chair) were carried out in the common rooms. Except for physical exercise or rest period, the subjects were not allowed to leave the living room. They were called by phone for exercise 15 min before the scheduled time. At other times, the subjects listened to music or watched videotapes. Reading was not impossible, but difficult, under the dim light conditions. Napping was not allowed. Performance tests (modified Pouly test with a computer display and a 10-key board) and questionnaires asking about physical as well as emotional state were undertaken at every micturition and at meal times. Meals were supplied 30 min after wake up, 30 min after the morning exercise (5 h and 30 min after wake up), and 3 h after the afternoon exercise (12 h after wake up). The total calories per day were ~2,500 kcal. In addition to the regular meals, the subjects were allowed to take snacks and softdrinks. Serial blood samplings were performed on day 8 starting at 1600 until 2100 on the following day and on day 14 from 1400 until 2000 on the next day. Physical exercise was not performed on day 15. The experimental protocol is illustrated in Fig. 1.

Experiment 2: a single pulse of physical exercise. This experiment consisted of four sessions performed on different days: the control session without physical exercise, the morning session with exercise from 0900 to 1100, the afternoon session from 1500 to 1700, and the night session from 0000 to 0200. In each session, eight subjects participated. Subjects did not participate in different sessions. The conditions, facilities, and equipment were the same as in experiment 1. The subjects were required to go to bed at 1100 and wake up at 0700 on the first night but decided the times of retirement
and getting up on the following nights by themselves. Meals were supplied at the regular times: 0730, 1230, and 1830.

In the control and morning sessions, the subjects entered the isolation facility at 1700 on the 1st day, and a serial blood sampling was started at 1800 and ended at 1800 on the 3rd day (48 h). In the morning session, the subjects performed physical exercise from 0900 to 1100 on the second day. In the afternoon session, the subjects entered the facility at 1100 on the 1st day, and a serial blood sampling was started at 1200 and continued to 1200 on the 3rd day (48 h). Subjects performed physical exercise from 1500 to 1700 on the 2nd day. In the night session, the subjects entered in the facility at 1700 on the 1st day, and a serial blood sampling was started at 1800 and ended at 1800 on the 4th day (72 h). Subjects performed physical exercise from 0000 to 0200 on the 3rd day (i.e., the 2nd night).

Physical Exercise

Two subjects performed physical exercise for 2 h, and the other two sat quietly in chairs for the same period. Every time, the staff instructed them on how to perform the physical exercise. Physical exercise was done with bicycle- and rowing-type ergometers. When the subjects used a bicycle-type ergometer in the morning, they would use a rowing-type ergometer in the afternoon and vice versa. They performed physical exercise for 15 min at a heart rate of 140 beats/min, followed by 15 min rest. This pattern was repeated four times in 2 h. Heart rate was monitored by the heart rate monitor (Polar PE3000), and the staff advised the subjects of the strength of exercise. In experiment 2, only a bicycle-type ergometer was used for physical exercise.

Measurement of Plasma Melatonin and Rectal Temperature

Blood (~3 ml) was sampled at 1-h intervals through an indwelling catheter with a heparin lock placed in the forearm vein. Immediately after sampling, plasma was separated by centrifugation and stored at −40°C until the determination of melatonin by radioimmunoassay (11). The intra- and interassay variances of the melatonin assay were 6.7 and 7.0%, respectively. Rectal temperature was measured continuously by a thermistor probe with a line connected to a computer in the operation room, to which a record was fed every 30 s.

Data Analysis

The phase and amplitude of plasma melatonin rhythm were analyzed by a geometric method reported previously (11). The original rhythm was transformed by a three-point moving average method. The difference between the maximum and minimum values of a smooth 24-h rhythm was defined as the amplitude of the rhythm. The ascending phase was defined as the time when a horizontal line through the midpoint of the maximum and minimum values (middle line) crossed the ascending limb of the nocturnal melatonin rise, and the descending phase was defined as the time when the middle line crossed the descending limb of melatonin rhythm. The peak phase was the midpoint between the ascending and descending phases. The amount of phase shift of the plasma melatonin rhythm was calculated for the first half (from day 2 to day 8), the second half (from day 9 to day 15), and the whole session, using the peak phase as a reference. The amplitude of the individual melatonin rhythm was calculated as follows. The melatonin rhythms in individuals were standardized in such a way that each melatonin value was expressed as a percentage of the peak value on day 1. The amplitude was defined as the difference between the daytime minimum value and the peak value and expressed as percent peak value.

The rectal temperature rhythm in experiment 1 was analyzed as follows. Rectal temperature recorded every 10 min was transformed to two states, a higher and lower temperature than the mean body temperature. The mean body temperature was calculated using data for 14 days (from day 2 to day 15). For this calculation, temperature values during physical exercise and shower taking were omitted. In experiment 2, differences in rectal temperature between the exercise and control days were calculated based on local time.

Statistics

A two-way ANOVA with post hoc t-tests was used for comparison of melatonin rhythm parameters with and without exercise under the forced sleep-wake schedule in experiment 1. Repeated t-tests were used for comparison of phases of melatonin rhythms and rectal temperature between the control and exercise days in experiment 2.

Table 1. Phases and phase shifts of individual melatonin rhythms with and without exercise

<table>
<thead>
<tr>
<th>Subject</th>
<th>AB</th>
<th>OG</th>
<th>KK</th>
<th>NG</th>
<th>TB</th>
<th>ZN</th>
<th>TS</th>
<th>SK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>5.41</td>
<td>6.21</td>
<td>4.00</td>
<td>7.69</td>
<td>2.18</td>
<td>4.26</td>
<td>3.56</td>
<td>6.79</td>
</tr>
<tr>
<td>Day 8</td>
<td>5.46</td>
<td>7.04</td>
<td>3.90</td>
<td>7.25</td>
<td>3.61</td>
<td>5.57</td>
<td>5.16</td>
<td>12.32</td>
</tr>
<tr>
<td>Day 14</td>
<td>6.81</td>
<td>7.07</td>
<td>2.84</td>
<td>6.05</td>
<td>3.01</td>
<td>8.32</td>
<td>4.82</td>
<td>19.00</td>
</tr>
<tr>
<td>Day phase shift (days 1–8)</td>
<td>−0.05</td>
<td>−0.83</td>
<td>0.10</td>
<td>0.44</td>
<td>−1.43</td>
<td>−1.31</td>
<td>−1.60</td>
<td>−5.53</td>
</tr>
<tr>
<td>Day phase shift (days 1–14)</td>
<td>−1.40</td>
<td>−0.86</td>
<td>1.17</td>
<td>1.64</td>
<td>−0.83</td>
<td>−4.05</td>
<td>−1.26</td>
<td>−12.21</td>
</tr>
<tr>
<td>With exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>5.42</td>
<td>3.06</td>
<td>3.64</td>
<td>2.32</td>
<td>4.88</td>
<td>6.57</td>
<td>4.94</td>
<td>7.26</td>
</tr>
<tr>
<td>Day 8</td>
<td>4.90</td>
<td>2.67</td>
<td>3.76</td>
<td>2.75</td>
<td>3.85</td>
<td>5.57</td>
<td>1.15</td>
<td>9.96</td>
</tr>
<tr>
<td>Day 14</td>
<td>5.00</td>
<td>1.32</td>
<td>1.79</td>
<td>0.88</td>
<td>4.87</td>
<td>3.54</td>
<td>2.21</td>
<td>13.60</td>
</tr>
<tr>
<td>Day phase shift (days 1–8)</td>
<td>0.51</td>
<td>0.38</td>
<td>−0.11</td>
<td>−0.43</td>
<td>1.02</td>
<td>1.00</td>
<td>3.79</td>
<td>−2.70</td>
</tr>
<tr>
<td>Day phase shift (days 1–14)</td>
<td>0.41</td>
<td>1.75</td>
<td>1.85</td>
<td>1.44</td>
<td>0.01</td>
<td>3.03</td>
<td>2.73</td>
<td>−6.34</td>
</tr>
</tbody>
</table>

Values are peak phase of melatonin rhythm. Results from SK and PS are not used for statistics. *P < 0.05, †P < 0.01 vs. without exercise.
RESULTS

Table 1 demonstrates the amounts of phase shift in individual melatonin rhythm in experiment 1, and Fig. 2 illustrates the averaged melatonin rhythms with and without physical exercise. The peak phases of individual melatonin rhythm on day 1 were located from 2.32 to 6.57 h, with an average value of 4.40 h (SE 0.56 h) in the subjects performing exercise, and from 2.18 to 7.69 h with an average of 4.76 h (SE 0.69 h) in the subjects being quiet. There was no statistically significant difference in the initial phase between the two groups (t-test). In one subject from each group (YS, SK), the melatonin rhythm showed a large phase-delay shift in the course of experiment, and the amounts of phase shift were significantly different from the means of respective groups (Smirnoff’s test). Therefore, these values were not included in the following analyses. The average phase shift of the melatonin peak for the entire period was +1.60 h (n = 7, SE 0.42 h) with physical exercise and −0.80 h (n = 7, SE 0.71 h) without exercise. A positive sign indicates a phase-advance shift and a negative sign a phase-delay shift. The difference in phases is statistically significant (2-way ANOVA, P < 0.01). The phase shift of the melatonin peak was already significantly different in the first 6 days (t-test, P < 0.05). The phase shift at that time was +0.88 h (SE 0.53 h) with physical exercise and −0.67 (SE 0.31 h) without exercise. The rate of phase shift seemed to be different when the ascending and descending phases of nocturnal melatonin rise were compared. The ascending phase in the group with physical exercise was significantly phase advanced already on day 8 from that in the group without exercise (−0.59 ± 0.56 vs. 1.21 ± 0.47 h, P < 0.05), whereas the difference in the descending phase was not statistically significant. On the other hand, differences in both the ascending and descending phases were statistically significant on day 14 (ascending; −1.50 ± 0.69 vs. 1.19 ± 0.70 h, P < 0.05; descending; 7.13 ± 0.77 vs. 9.93 ± 1.01 h, P < 0.05).

Calculated from the phase shifts of melatonin peak, the period of melatonin rhythm during the forced sleep-wake schedule was 23.88 h (SE 0.04 h) with physical exercise and 24.06 h (SE 0.06 h) without exercise. The difference was small but statistically significant (P < 0.01). The amplitude of melatonin rhythm had a tendency to decrease in the course of experiment, but statistically significant differences were not detected either among days or between the groups.

Figures 3 and 4 illustrate the peak phase of melatonin rhythm and the transformed rectal temperature rhythms in all subjects in experiment 1. Except for one subject from each group (YS and SK), the lower part of body temperature coincided for the most part with the scheduled sleep time or slightly deviated from it. In subjects YS and SK, the lower temperature part and the peak phase of melatonin rhythm were substantially phase delayed.

Figure 5 and Table 2 demonstrate the effects of single pulses of physical exercise at different times of day on the onset, peak, and offset phases of the plasma melatonin rhythm (experiment 2). There was no difference in the phases of melatonin rhythm after the control and morning pulses. Statistically significant phase delays were detected in the peak phase after the afternoon pulse and all three phases after the night pulse. In the latter case, the three phases were compared between days 1 and 3, because physical exercise on day 2 could shift the melatonin rhythm immediately so that the shape of nocturnal melatonin rise would be changed, which might blur the phases of the melatonin...
rhythm, and because physical exercise might change the level of plasma melatonin per se (5), which, however, was not the case in the present study. Plasma melatonin levels were not changed significantly during exercise or within 3 h after physical exercise (data not shown). On the other hand, the amount of phase shift in any of three exercise sessions was not significantly different from that observed in the sedentary control session.

Figure 6 illustrates differences in rectal temperature between the day of exercise and of rest. Rectal temperature increased during physical exercise and decreased afterward even below the level of the sedentary day (postexercise hypothermia). The biphasic effects of physical exercise on rectal temperature seem to depend on the time of day when exercise was done. The increase in rectal temperature during exercise at midnight (1.22 ± 0.17°C) was significantly larger than that in the afternoon (0.72 ± 0.08°C, \( P < 0.05 \)) but not that in the morning (0.79 ± 0.15°C). On the other hand, the postexercise hypothermia seemed to last longer in the morning session (for ~8 h) than in the afternoon (for ~4 h) and night sessions (postexercise hypothermia was lacking).

**DISCUSSION**

In the present study, physical exercise in the daytime accelerated phase-advance shifts of the human circadian pacemaker under the forced sleep-wake period of 23 h and 40 min. The peak phase of plasma melatonin rhythm was significantly phase advanced by 1.60 h (SE 0.42) in 12 cycles with physical exercise, whereas the peak phase was slightly but not significantly delayed without exercise (−0.80 ± 0.71 h). The phase difference between exercise and rest was statistically significant. With physical exercise, the circadian body temperature rhythm also seemed to catch up with the forced schedule better than without exercise. To our knowledge, this is the first report in which physical exercise was demonstrated to phase advance the human circadian pacemaker.

The mechanism by which physical exercise phase advanced the pacemaker is not known. Previously, physical exercise at midnight was demonstrated to phase delay the circadian pacemaker in humans (4, 26) and accelerate the adaptation of core body temperature rhythm to a 9-h phase-delayed sleep (9). From the partial phase-response curve for physical activity, Buxton et al. (4) predicted that the phase-advancing effect of physical exercise could be observed at noon. In the present study, a single pulse of moderate physical exercise given either in the morning or afternoon hours did not yield a significant phase-advance shift (Fig. 5). However, the present findings do not exclude the possibility that a single pulse of physical exercise at the right time of day might phase advance the human
circadian pacemaker, because an expected phase shift by a single pulse is \(-0.12\) h, which is too small to be detected by the plasma melatonin rhythms.

Alternatively, physical exercise may shorten the endogenous period of the human circadian pacemaker, which makes the circadian pacemaker entrain more easily to the forced sleep schedule. Wever (29) examined the effects of physical workload on the free run period in human subjects and failed to find statistically significant changes in the period. Beersma and Hiddinga (2) also studied the effects of physical activity on the human circadian period by a desynchrony protocol of a forced sleep-wake cycle with a 20-h period. Although they could not find statistically significant effects of physical activity, the circadian period of core body temperature showed a tendency to shorten. Core body temperature is known to be masked by sleep and wakefulness, which might blur the effects of exercise (28). Rectal temperature was influenced not only during physical exercise but also for a relatively long period after exercise (Fig. 6). On this reason, the plasma melatonin rhythm was used in the present study as a marker of the circadian pacemaker, which is known to escape from many masking factors, except for bright light (12).

Exogenous melatonin in the late afternoon phase advanced the human circadian pacemaker (15, 16). Moreover, daytime physical exercise was reported to Fig. 4. Two-state expression of rectal temperature and the peak phase of plasma melatonin in subjects under the forced schedule without physical exercise. Shaded area, hypothermic period; ○, peak phase of melatonin rhythm. Solid bars, rest period.

Fig. 5. Effects of a single pulse of physical exercise at different times of day on plasma melatonin rhythm. ○, Melatonin rhythm on the day before physical exercise; ●, melatonin rhythm on the day of physical exercise (control, morning, afternoon pulse) or on the day after physical exercise (night pulse). The melatonin values are expressed by the mean and SE (n = 8).
increase plasma melatonin levels (5, 24, 25), which might account for the phase-shifting effect of physical exercise. However, this possibility is unlikely, because single trials of physical exercise did not change plasma melatonin levels (data not shown). Alternatively, physical exercise may increase the sensitivity to light and thereby accelerate the light-induced phase-advance shift. This possibility is not excluded completely but is unlikely, because the light intensity actually received by the subjects was 10 lx, which seems to be under the threshold for the phase-resetting capability of light (3).

Daytime physical exercise might increase the arousal state of subjects (23) and strengthen the sleep-wakefulness rhythm that feeds back onto the circadian pacemaker. In nocturnal rodents, the feedback of physical activity onto the circadian pacemaker is well established (1, 30). In this context, the phase shifts of melatonin rhythm observed without exercise are interesting. The phase of the melatonin rhythm was not changed at all for 12 cycles under the forced sleep-wake schedule without exercise, which indicates the period of circadian rhythm is very close to 24 h. This finding could be interpreted in two different ways. The circadian pacemaker was desynchronized from the sleep-wake cycle and exhibited the endogenous periodicity close to 24 h. Czeisler et al. (7) reported the circadian period in humans was very close to 24 h, as estimated by a desynchrony protocol. Similar results were also obtained by other authors (17). Alternatively, the present finding could be interpreted to indicate that the forced sleep-wake schedule itself had an impact on the free run period of the human circadian pacemaker. Recently, we observed free running melatonin rhythms with the mean circadian period of 24.47 h in sighted subjects subjected under lights of <1 lx (unpublished observation). A similar value was reported in blind subjects whose circadian rhythms were free running under temporal isolation (27). If we take this value as an endogenous circadian period, the forced sleep-wake itself has a potency to affect the human circadian pacemaker.

Table 2. Phases and phase shifts of melatonin rhythm after a single pulse of exercise at different times of day

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Phase shift</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>-0.93 ± 0.79</td>
<td>-0.77 ± 0.77</td>
<td>-0.16 ± 0.16</td>
</tr>
<tr>
<td><strong>Peak</strong></td>
<td>3.00 ± 0.65</td>
<td>3.11 ± 0.66</td>
<td>-0.11 ± 0.12</td>
</tr>
<tr>
<td><strong>Offset</strong></td>
<td>6.94 ± 0.57</td>
<td>7.12 ± 0.65</td>
<td>-0.18 ± 0.18</td>
</tr>
</tbody>
</table>

Values are means ± SE in phase of reference point each day. Day 1 is the prepulse day and day 2 is the pulse day. Day 1, day 2, and day 3 are the prepulse, pulse, and postpulse days, respectively. *P < 0.05, †P < 0.01 vs. 1st day.

Fig. 6. Effects of a single pulse of physical exercise at different times of day on rectal temperature. Solid bars, times of physical exercise; open bars, sleep. Each horizontal bar at the sleep onset and end indicates SE. Changes in rectal temperature are expressed with the mean and SE (n = 8). Horizontal bars indicate the portion where rectal temperature decreases significantly below the control level (P < 0.05).
Complete entrainment was not established in the present study even with physical exercise. If the circadian pacemaker is fully entrained by the forced sleep-wake schedule with physical exercise, a phase-advance shift of 4 h would be expected in 12 cycles, which was not the case. In the present study, physical exercise was given intermittently at the strength of 140 beats/min in heart rate twice in the daytime. A failure of complete entrainment might be due to the strength of zeitgeber or to possible conflicting effects produced by double zeitgeber pulses. The phase-delaying effect of physical exercise depended on the strength and duration of exercise (4). The phase-shifting effects of bright light were reported to decrease when given intermittently (21). On the other hand, it is well established that the zeitgeber effect is dependent on the phase of the circadian pacemaker in which the zeitgeber was given (20). Although the amount of phase shift yielded by a pulse of exercise in the afternoon was not significantly different from that in the sedentary control, afternoon exercises might exert conflicting effects on the circadian pacemaker so that the overall effect was diminished. These issues are the targets of future studies.

Whatever the mechanism might be, physical exercise can facilitate the entrainment of human circadian pacemaker to a forced sleep-wake schedule under dim light conditions. The implications of this finding are not trivial, because they suggest that physical exercise is helpful for entrainment to the natural 24-h periodicity if one could not get enough light. Especially for people with delayed sleep phase or non-24-h sleep-wake syndromes, daytime physical exercise might have therapeutic value.

A pulse of physical exercise at any time of day failed to change the amount of phase shift of plasma melatonin rhythm observed in the control session (Table 2). These results are inconsistent with previous reports in which physical exercise at midnight significantly phase delayed the melatonin rhythm (4, 26). In the present study, physical exercise at midnight significantly phase delayed the three phases of plasma melatonin rhythm when compared with the prepulse phase, whereas the amount of phase shift was not different from that in the sedentary control session. The discrepancy between the previous and present results could be explained, at least in part, by the frequency of blood sampling for the determination of plasma melatonin. More frequent blood sampling in the previous studies may provide melatonin rhythms capable of being analyzed with a higher time resolution than the present study.

On the other hand, a single pulse of physical exercise showed dual effects on rectal temperature: increase during exercise and decrease for several hours after exercise (Fig. 6). The effects seem to be phase dependent. The largest increase was observed in the night session (1.22°C), whereas the longest after-exercise hypothermia was detected in the morning session (∼8 h). The mechanisms for these phenomena are not known, but the findings suggest care in interpretation of rectal temperature rhythms on which physical exercise exerts dual effects in a phase-dependent manner.

**Perspectives**

Light is known to be a strong regulator for the human circadian pacemaker and is used as a therapy for circadian rhythm disorders such as delayed sleep-phase syndrome and non-24-h sleep-wake syndrome. Physical exercise, although less effective, is also capable of facilitating the entrainment of the human circadian rhythm and may be useful in cases in which lights are not available, e.g., blind people or people in space where lights are very expensive. In space, the natural 24-h periodicity is lacking and one may follow an artificial (forced) sleep-wake schedule with a period that deviates more or less from the endogenous circadian periods in individual astronauts. Light is very expensive in space and may not be available for resetting the astronauts’ circadian pacemakers. Timed physical exercise may be helpful for them.

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