REVIEW ARTICLE

Effects of physical exercise on human circadian rhythms

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Abstract

Bright light is the principal zeitgeber for the biological clock in mammals, including humans. But there is a line of evidence that non-photic stimuli such as physical activity play an important role in entrainment. Scheduled physical activity, such as wheel and forced treadmill running, has been reported to phase-shift and entrain the circadian rhythm in rodent species. In humans, several studies have reported the phase-shifting effects of physical exercise. A single bout of physical exercise at night was demonstrated to phase-delay the circadian rhythm in plasma melatonin. However, for the entrainment of human circadian rhythm, a phase-advance shift is needed. Previously, we demonstrated that scheduled physical exercise in the waking period facilitated the entrainment of plasma melatonin rhythm to the sleep/wake schedule of 23 h 40 min. This result suggested that timed physical exercise produced phase-advance shifts. A regular physical exercise also facilitated entrainment of the circadian rhythms associated with acute phase-delay shifts of the sleep/wake and light/dark schedule. These findings suggest that physical exercise is useful to adjust the circadian rhythm to external time cues, especially for totally blind people and elderly people.

Key words: circadian rhythm, entrainment, human, phase shift, physical exercise.

INTRODUCTION

The performance as well as the effects of physical exercise are known to depend on the time of day when the exercise is performed.[1,2] The biological clock is generally involved in such time-of-day effects, but the precise mechanisms for these particular issues are not known.

The circadian pacemaker, the central structure of the biological clock, is located in the hypothalamic suprachiasmatic nucleus (SCN) in mammals and is entrained by a light/dark cycle through the photic input from the retina. The SCN consists of ca 8000 neurons on each side and most of them show robust circadian oscillations in neural activity with a period slightly different from exactly 24 h.[3,4]

When healthy, sighted people are shielded from a 24-h light/dark cycle without knowledge of the time of day, their endogenous circadian rhythms such as plasma melatonin and core body temperature free run with a period that is not exactly 24 h. Therefore, to adjust to the 24 h local environmental time, our biological clock must make a phase-advance shift by about 1 h every day. It has been demonstrated that natural sunlight is the principal zeitgeber for the human biological clock, and morning bright light phase advances and evening bright light phase delays the circadian clock (Fig. 1).[5,6] However, approximately half of blind people have been reported to show normal entrainment of the circadian rhythm in plasma melatonin, but the other half exhibited altered or free-running rhythms.[8] In addition, non-photic stimuli such as a forced sleep/wake schedule has been reported to synchronize the endogenous circadian rhythms of totally blind individuals with a non-24 h schedule while living in a constant condition of dim light.[9] This finding supports an idea that the non-photic stimuli act as a time cue for the human biological clock. Is physical exercise able to entrain the mammalian biological clock? It is well known that physical activity, such as wheel and forced treadmill running, phase shifts and entrains the circadian rhythms in rodent species. Several studies have assessed the effectiveness of physical exercise as a phase-resetting cue (non-photic zeitgeber) in humans as well.[10,11]

PHYSICAL EXERCISE AND CIRCADIAN RHYTHM IN NOCTURNAL RODENTS

Physical activity such as wheel running and forced treadmill running phase-shifts the circadian rhythms in nocturnal rodents.[12–14] Briefly, free-running rhythms under constant dark or light in several rodent species were phase shifted or entrained by the periodical induction of running wheels in a cage.[15–21] In addition, the period of free-running rhythms was shortened by access to a running wheel.[17,22,23] A complete phase response curve (PRC) for a 3-h pulse of novelty-induced wheel running was demonstrated in the Syrian hamster.[15] The PRC shows a prominent phase-advance portion in the subjective day (rest phase) and small delay portion in the late subjective night. These findings indicate that physical exercise is able to entrain circadian rhythms in nocturnal rodents. However, the critical variable for clock resetting associated with wheel running remains unknown. Possible explanations for clock resetting by non-photic stimuli in rodent species have been advanced. For example, physical activity affects the SCN circadian pacemaker via the geniculo-hypothalamic tract.[24] Neurotransmitters such as neuropeptide-Y (NPY) and serotonin have been proposed to mediate non-photic effects of physical activity.[25–27] Physical activity increases an arousal state, which may eventually feed back though the NPY pathway from the intergeniculate leaflet to the SCN, and/or through the serotonergic afferents from the raphe nuclei.[13,28]

It has been suggested that the elevation in body temperature may act as an input to the circadian pacemaker of mammals, since temperature is a strong zeitgeber for non-mammalian vertebrates and insects.

Physical activity increases core body temperature, the level of which is circadian phase-dependent, and the increment is larger in the rest phase than in active phase in mammals including humans.[29,30] In the PRC for 3-h wheel running in the Syrian hamster,[15] the maximum phase-advance shift is observed during the middle of the inactivity phase, which corresponds to the phase of temperature trough and to the phase exhibiting the largest increment of body temperature by 4-h wheel running.[29] These results do not contradict the notion that physical exercise phase-shifts the pacemaker by changing the body temperature. On the other hand, injections of the benzodiazepine, triazolam, induce phase shifts in the circadian rhythm of hamsters by acutely increasing their locomotor activity.[31,32] The PRC for the triazolam injection is similar to that for wheel-running[31] but the increase in body temperature is not the signal mediating the phase-shifting effects of triazolam,[32] because triazolam increases body temperature in both restrained and unrestrained animals but phase-shifts the circadian rhythms only observed in unrestrained animals.[32] Furthermore, Mrosovsky and Biello (1994) suggested that it is not running per se that is critical for phase shifting the pacemaker but it may be the motivational context for running.[33] Therefore, at present, there is limited and small evidence that a change in the body temperature is the mediator of the phase shift induced by physical activity.

Further studies are needed to fully understand the mechanism of clock resetting by physical exercise in rodents and the relation between photic and non-photic entrainments.

EFFECTS OF PHYSICAL EXERCISE ON HUMAN CIRCADIAN RHYTHMS

A single bout of physical exercise

In hamsters, increased physical activity by 3-h wheel running during the rest period is associated with phase advance shifts of the biological clock. Van Reeth *et al.*(1994) examined whether or not physical exercise induced phase-advance shifts in humans when carried out in a usual rest period (nocturnal sleep time).[10] In this study, the circadian rhythms in plasma melatonin were assessed twice under constant routine conditions, once in the absence of physical exercise and once with low intensity physical exercise of 3-h duration [40–60% of peak oxygen uptake (VO_2)]. The light condition was constant dim light exposure (<300 lux). The phase shifts were measured on the 1st day after physical exercise. The timing of the physical exercise ranged from −5 to +4 h around the trough of the core body temperature rhythm. A single bout of exercise induced a robust phase-delay shift. The result was inconsistent with the rodent data. Using the same protocol, Buxton *et al.* (1997) reported that physical exercise with a higher intensity (75% of peak VO_2) and a shorter duration (1 h) elicited significant phase-delay shifts when exercise were cantered at a clock time of 0100 under dim light (70–80 lux).11 The timing of the onset of the nocturnal elevations of plasma melatonin was used to estimate the circadian phase before and after stimulus. The mean phase delay shifts were −23 ± SE 10 min without exercise, −63 ± SE 8 min with low intensity exercise of 3 h, and −55 ± SE 15 min with high intensity exercise of 1 h, respectively. These results suggested that a low intensity of physical exercise was enough to shift the human circadian clock. Recently, Buxton *et al.* (2003) extended the experiment and demonstrated a PRC for physical exercise (the data combined with 3-h low intensity exercise and 1-h high intensity exercise).[34] This PRC revealed phase-advance shifts by physical exercise in the evening and phase-delay shifts in the subjective night. In addition, they indicated that physical exercise in the morning and afternoon had no effect on the circadian phase.

The question arises as to whether the phase-advance shift by a single bout of exercise in the evening was really due to the change in the circadian pacemaker, since the phase determination was made at 1 to 2 circadian cycles immediately after the physical exercise. Indeed, a phase-advance shift was obtained one cycle after the exercise session (30 ± SE 15 min), but a larger phase-delay shift (−66 ± SE 9 min) occurred on the following day. Previously we examined the phase-shifting effects of a single bout of physical exercise.[35] In this experiment, the subjects stayed three nights in the isolation facility. On Day 1, the pre-exercise circadian phase was obtained. On the Day 2, a single bout of 2 h of physical exercise (intensity heart rate at 140 beat/min) was imposed at one of the three times of day (morning 9:00–11:00, afternoon 15:00–17:00 and night 00:00–02:00). As a result, there was a slight but significant phase-delay shift of circadian rhythm in plasma melatonin when physical exercise was performed in the afternoon and at night. However, the amount of the phase shift was not significantly different from that of the control subjects who stayed in the same isolation facility for three days without exercise.[35]

Beersma and Hiddinga (1998) examined the effects of a single bout of physical exercise on the intrinsic period (τ) of the human circadian pacemaker using a T-cycle experimental procedure.[36] Using a 20-h forced desynchrony protocol (13.5 h for wakefulness and 6.5 h for sleep), three experiments were conducted under dim light conditions (under 10 lux), with and without physical exercise. The subjects performed two types of physical exercise using a cycle ergometer, with intermediate and high intensity for a half hour per 2 h of each waking time. They did not observe a significant effect of physical exercise on the τ. In this study, the τ was assessed by the demasked core body temperature rhythm, which showed a larger variability in estimating the circadian phase. Further research is needed to detect the effect of physical exercise on the τ of human circadian pacemaker.

The mechanism induced a single bout of physical exercise to phase shift the circadian rhythm is not yet known. It is well established that the increase of rectal temperature by physical exercise is greater in the early morning than in the afternoon and late evening.[37–39]

Hypothermia after a single bout of physical exercise was observed longer in the morning than in the afternoon and night.[35]

Recently, Kobayshi *et al.* (2005) examined the effects of a single bout of physical exercise for 1 h with a strength of 50–60% VO_2 maximum at three different time of day (morning 07:40–08:40, evening 16:30–17:30, late evening 20:30–21:30) on the night’s sleep.[40]

They reported that 1 h physical exercise, when carried out in the late evening, significantly shortened sleep latency and increased slow-wave sleep compared with any other timed exercise. Furthermore, Tanaka *et al.* (2001) have demonstrated that the intervention such as a short nap after lunch (30 min between 13:00 and 15:00) and moderate intensity of exercise in the evening (30 min from 17:00) was effective in improving sleep quality for elderly people who have difficulty in sleeping.[41] They have suggested that the quality of the daytime arousal of the elderly people was improved by exercise in the evening.[41] However, other previous studies have reported that moderate intensity exercise in the morning or afternoon improved shorter sleep latency[42–44] and more slow-wave sleep.[42,45]

Since these studies did not measure the circadian rhythm maker, it is not known that the subject's circadian pacemaker would really phase-advance shift as a result of physical exercise. The precise mechanism of these time-dependent phenomena is not yet known. However, a change of body temperature and subjective arousal by physical exercise cannot be excluded as a possible factor which may entrain the circadian pacemaker.

Daily bouts of physical exercise

Previously, we reported that daily bouts of physical exercise advanced the human circadian pacemaker.[35] In this experiment, physical exercise was imposed regularly on subjects whose sleep/wake schedule was phase advanced by 20 min everyday (Fig. 2). The subjects performed physical exercise with the bicycle ergometer for 2 h twice during the waking period. The morning exercise started at 3 h after wake up and the afternoon exercise started within 2 h after the end of the morning exercise (7 h after wake up). In the control experiment, the subjects were sitting in a chair at the same time of day as physical exercise. The light intensity was less than 10 lux. The circadian rhythm in plasma melatonin was phase-advanced significantly in the subjects who took regular physical exercise during the waking period, whereas the melatonin rhythm was not shifted in the subjects without taking exercise (Fig. 3). These findings indicate that regular physical exercise has a potential to entrain the human circadian pacemaker. However, it is not known whether the phase shift is due to the direct effect of physical exercise, or the effect of some other factors associated with physical exercise, such as the increase in body temperature.

Possible explanations for the phase-advance shift observed in a double-session exercise study were; (i) the physical exercise phase-advanced the circadian rhythm; or (ii) the physical exercise increased the arousal level, which resulted in phase-advance shifts.

The question now arises as to why regular exercise during the waking period induces phase-advance shifts,[35] which is inconsistent with the PRC reported by Buxton *et al.* (2003).[34] According to the PRC, physical exercise beginning in the middle of the day produces a phase delay, rather than a phase-advance shift. Therefore we constructed a partial PRC using the previous experiment,[35] and found that physical exercise around 8 h after the melatonin peak produced phase-advance shifts (Fig. 4). Since the time of physical exercise did not cover the whole circadian phase, we need to complete the PRC for physical exercise.

Physical exercise facilitate re-entrainment

Shift workers and transmeridian travelers are exposed to the abnormal light/dark cycles and a change in the phase relationship between sleep and the endogenous circadian rhythm. The internal and external desynchronizations induce various symptoms including fatigue, headaches, irritability, loss of concentration, gastrointestinal disorders and sleep problems (sleep loss, premature awakening). In addition, the maximum performance of physical exercise also declines as a result of jet lag.[46] There is a question as to whether physical exercise facilitates the resynchronization of the circadian rhythm to a new time zone. In the animal study using Syrian hamsters, Mrosovsky and Salmon (1987) revealed that a single pulse of 3-h wheel running in the middle of the rest period facilitated resynchronization to an 8-h phase-advance shift of the light/dark cycle.[47] In humans, Klein and Wegman (1974) and Shiota *et al.* (1996) have reported that outdoor exercise had some effect on the resynchronization of circadian rhythms in urinary 17-hydroxy corticosteroids and catecholamine exertion to a new time zone. However, the light condition was not controlled in these studies.[48,49] Recently, Barger *et al.*(2004) have examined whether physical exercise of moderate intensity (65–75% heart rate maximum) facilitated resynchronization to a new sleep/wake cycle (9-h delay of the subject's habitual sleep episode).[50] Subjects carried out physical exercise for seven days following the 9-h phase delay of the sleep/wake schedule, while the control subjects were just sitting on the bicycle. The light intensity was strictly controlled to 0.65 lux at the standing position (angle of gaze). The mean phase shift of the rising phase of plasma melatonin was significantly greater in the subjects doing physical exercise (−3.17 ± SE 00.49 h) than in the control (−1.67 ± SE 00.45 h). In this experiment, physical exercise was done 4.2–6.7 h after the rising phase of plasma melatonin. Thus, daily bouts of physical exercise facilitated the resynchronization of the melatonin rhythm after a phase-delay shift of sleep/wake cycle. On the other hand, physical exercise was reported to have no or a very small effects on the resynchronization of circadian rhythms to a shift schedule.[51, 52] Both studies simulated shift work with consecutive day/night shift work (9-h delay from habitual sleep time). In one study, [51] during the 8 days of night work, physical exercise at 50–60% of maximal heart rate was imposed for a 15-min duration in the first three days. A larger phase delay shift was observed in the temperature rhythm of the subjects doing physical exercise, but it was not significantly different from that in the control subjects (−6.6 ± SD 2.5 vs −4.2 ± SD 3.4 h). In the other study, [52] intermittent physical exercise (6 bouts, 15-min long each, at 50–60% of maximal heart rate) occurred during the first 6 h of the first three night shifts. Exercise neither facilitated nor inhibited the phase shift induced by bright light. In both experiments, physical exercise was performed in the subjective night when the phase-delay shift was expected.[34] Similarly, Youngstedt *et al.* (2002) failed to find an additive effect of physical exercise on bright light-induced phase shifts.[53]

EFFECT OF PHYSICAL EXERCISE IN ELDERLY PEOPLE

Almost all studies examining the effects of physical exercise on circadian rhythms have been conducted in young, healthy subjects. In elderly people, the circadian rhythms in entrainment tend to phase advance as compared with those in young subjects.[54–58] In addition, the amplitude of circadian melatonin and core body temperature rhythms are low in elderly people.[54–56, 59, 60] Notably, the phase relationship between sleep and the circadian rhythm of minimum core body temperature was reported to change in elderly people. The mechanisms for these changes are not well understood. One study addressed the issue and found that nocturnal physical exercise induced phase-delay shifts of the circadian rhythm in plasma melatonin in elderly male and female subjects.[61] Phase shifts were also observed by a single bout of physical exercise. Although the phase shift in elderly people was not consistent in direction [(phase advance (n = 2), phase delay (n = 5), no phase shift (n = 1)], the result suggests that physical exercise is useful in elderly people to adjust circadian rhythms to the environmental cycle.

CONCLUSION

Nocturnal physical exercise induces significant phase delay shifts in the human circadian pacemaker. However, the effects of a single bout of physical exercise in the daytime were not consistent among studies. On the other hand, daily bouts of physical exercise facilitated re-entrainment of the circadian melatonin rhythm to advance or delay the sleep/wake cycle. These results suggest that timed and regular physical exercise is useful for the entrainment of the circadian rhythms in blind people, shift workers, and jet-lagged travelers. However, the optimal conditions of physical exercise still remain to be clarified.

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FIGURE LEGENDS

Figure 1 A human phase response curve for bright light which is measured under free-running conditions. The two results[5,6] represented by open and closed circles, respectively, are combined (adapted from Beersma and Daan, 1993).[7]

Figure 2 Experimental protocol for scheduled sleep/wake cycle with the period of 23 h 40 min (modified from Miyazaki *et al.,* 2001).[35] Solid bars; rest period, hatched bars; 2 h physical exercise twice a day. The period indicated by the two arrows is the time of serial blood sampling. The phase angle difference was calculated between the plasma melatonin peak (downward triangles at Day 2 and Day 9) and midpoint of physical exercise twice a day during a waking period (upward triangles at Day 2 and Day 9). For calculating the phase difference, the melatonin peak at Day 1 was used as the substitute for the melatonin peak at Day 2 (see Fig. 4).

Figure 3 Plasma melatonin rhythms on Day 1, Day 8 and Day 14 of the experiment of the scheduled sleep/wake cycle. The circadian rhythm in plasma melatonin was phase advanced significantly in subjects doing physical exercise （●）, whereas the melatonin rhythm did not shift in the subjects not doing exercise (○) (adapted from Miyazaki *et al.* 2001).[35]

Figure 4 A partial phase-response curve to physical exercise twice a day during the waking period and control condition without physical exercise from the shortened T cycle experiment.[35] The phase shift derived from melatonin data from Day 1 to Day 8 and from Day 9 to Day 15 are plotted vs the mid-point of timing of stimulus relative to estimated timing of melatonin peak for each subject on Day 2 and on Day 9. By convention, phase advances are defined as positive numbers and phase delays as negative numbers. The right panel shows the phase response to control conditions studied in the absence of physical exercise. Open circles (○) represent the timing of the mid-point of rest conditions on Day 2 vs the phase shift of plasma melatonin from Day 1 to Day 8, and open triangles (△) represent the timing of rest conditions on Day 9 vs the phase shift from Day 9 to Day 15. The left panel shows the phase response to 2 h of physical exercise twice a day. The filled circles (●) indicate the timing of exercise twice on Day 2 vs the phase shift of plasma melatonin from Day 1 to Day 8, and the filled triangles (▲) indicate the timing of exercise on Day 9 vs the phase shift from Day 9 to Day 15.

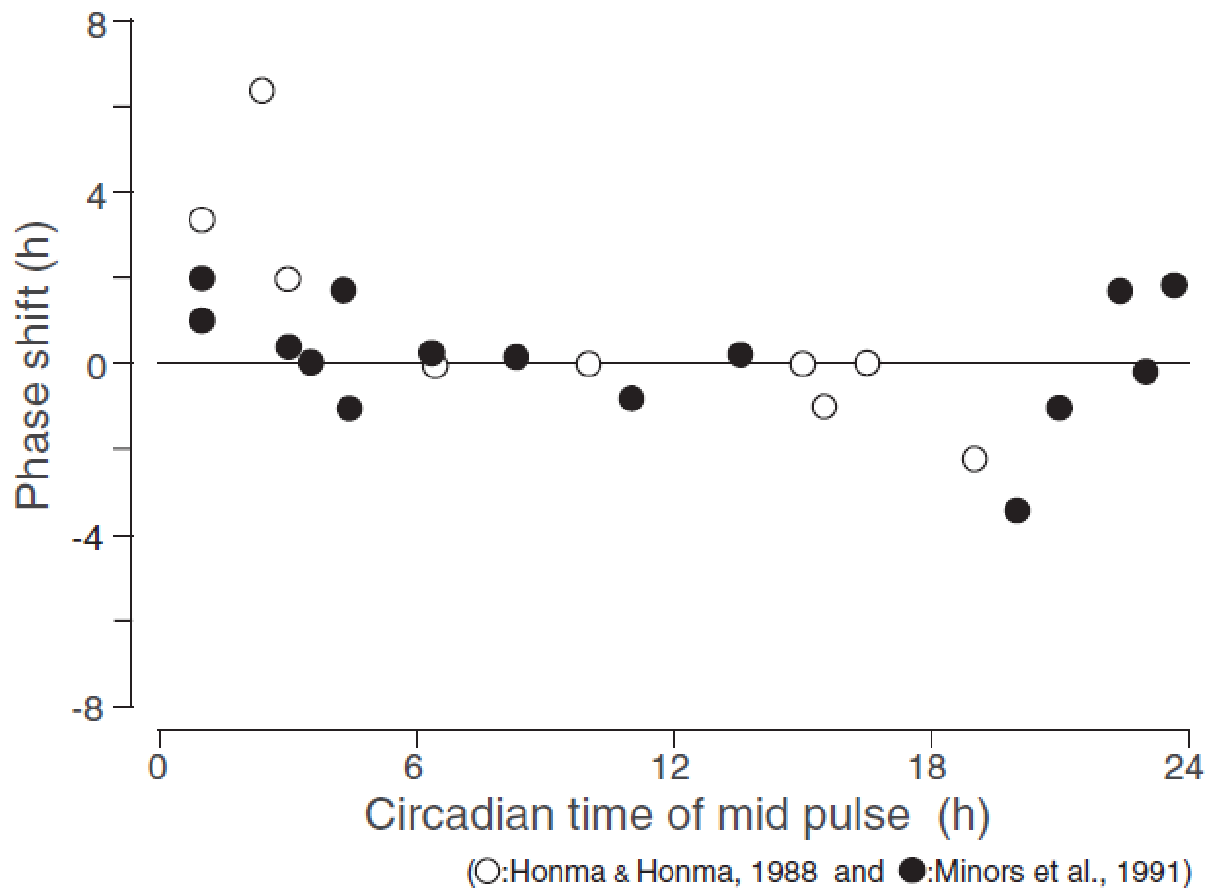
8
4
0
-4
-8
Phase shift (h)
0
6
12
18
24
Circadian time of mid pulse (h)
(○:Honma & Honma, 1988 and ●:Minors et al., 1991)

Figure 1

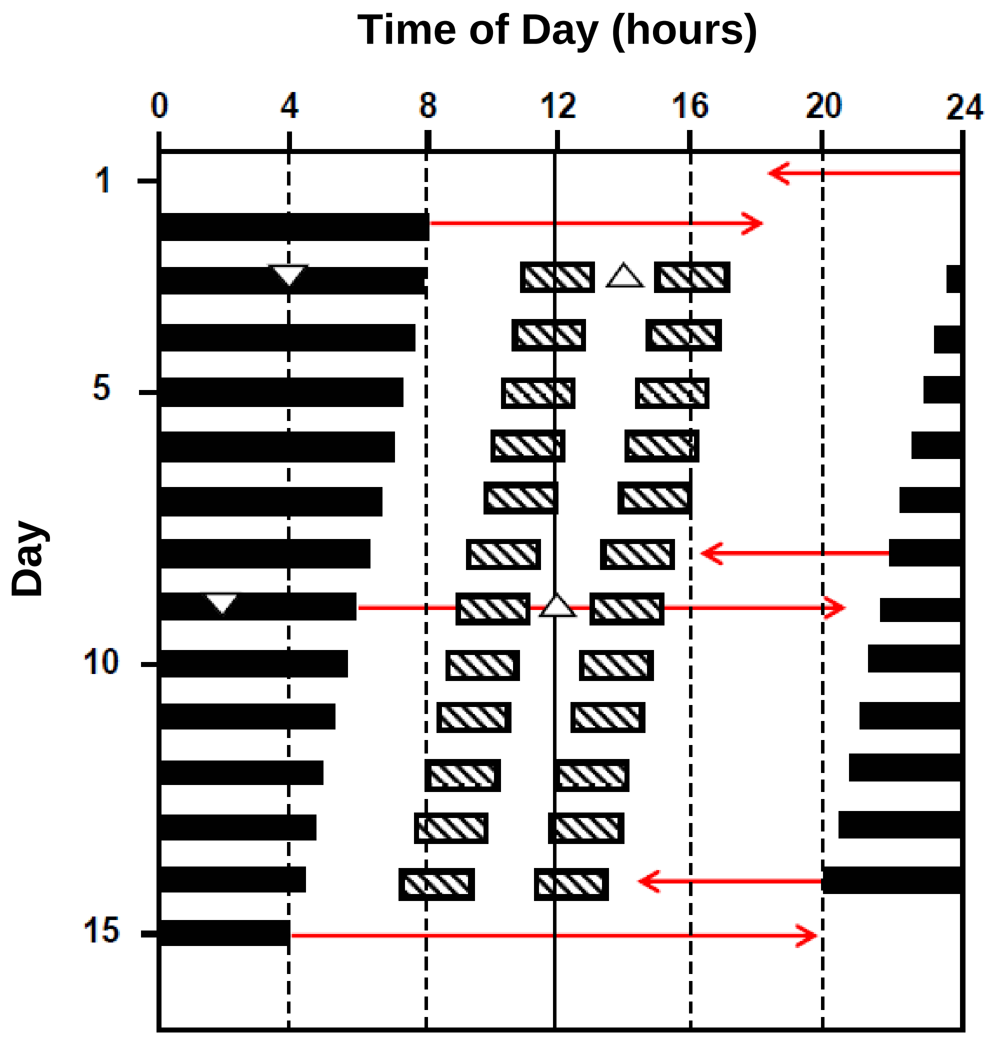

Figure 2

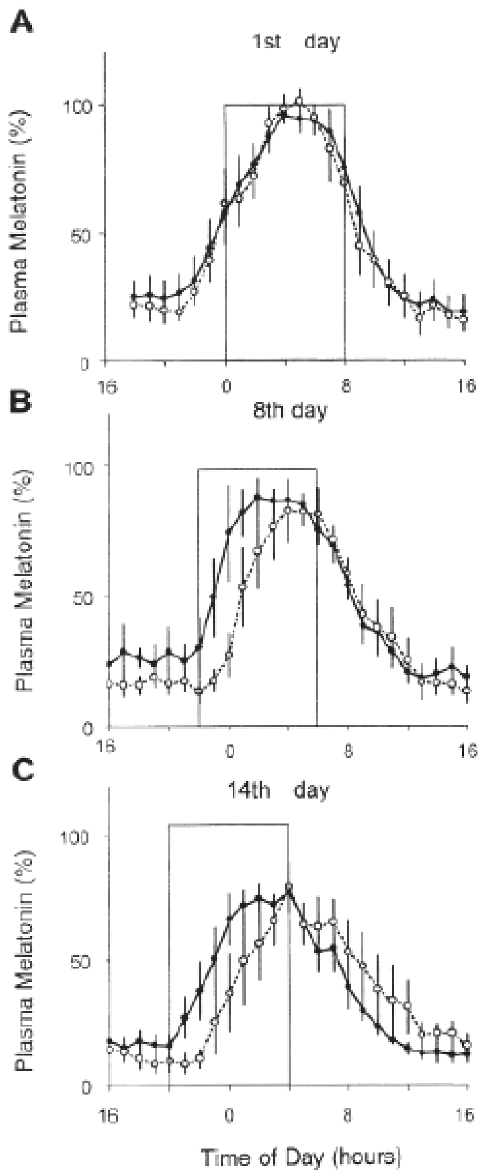
A
1st day
B
8th day
C
14th day
Plasma Melatonin (%)
100
50
0
16
0
8
16
Time of Day (hours)

Figure 3

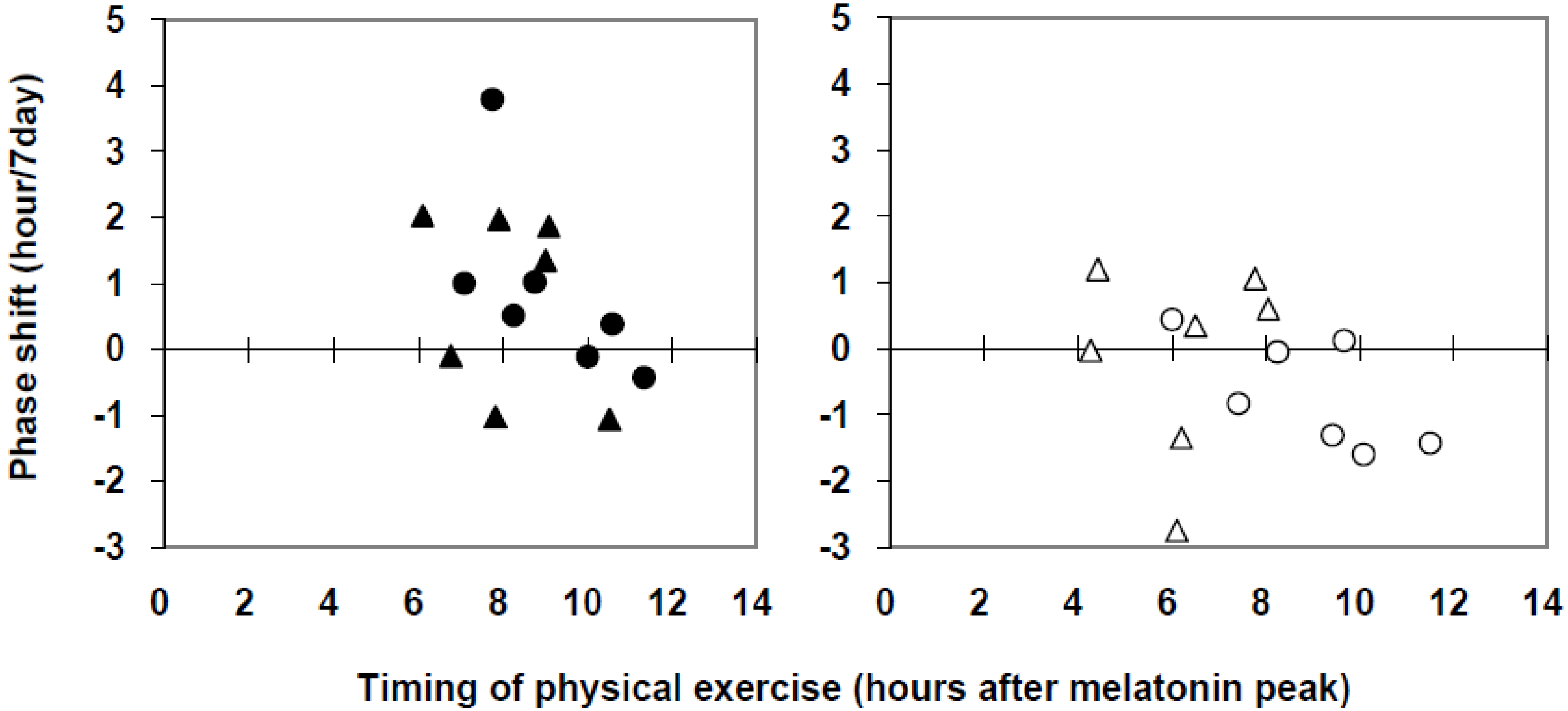
Phase shift (hour/7day)
5
4
3
2
1
0
-1
-2
-3
0
2
4
6
8
10
12
14
Timing of physical exercise (hours after melatonin peak)

Figure 4