Phase-dependent shift of free-running human circadian rhythms in response to a single bright light pulse

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Summary. Responsiveness of free-running human circadian rhythms to a single pulse of bright light was examined in a temporal isolation unit. Bright light (5000 lx) of either 3 or 6 h duration, applied during the early subjective day, produced phase-advance shifts in both the sleep-wake cycle and the rhythm of rectal temperature; the light pulse had essentially no effect on the phase of the circadian rhythms, when it was introduced during the late subjective day or the early subjective night. The results indicate that bright light can reset the human circadian pacemaker.
Key words. Human circadian rhythm; bright light pulse; phase-shift; temporal isolation; phase response curve.

Since DeCoursey[1] observed phase-dependent shifts of free-running circadian rhythms brought about by a single light pulse, phase response curves (PRC) have been reported in many species except for humans. PRCs are more or less similar in shape whether they are obtained from uni- or multi-cellular organisms, from diurnally or nocturnally active species[2]. It has been a matter of debate whether human circadian rhythms are reset by light, as suggested so far by indirect evidence[3]. Recently we reported that free-running human circadian rhythms in sleep-wakefulness and rectal temperature were entrained by an artificial bright light cycle under temporal isolation[4]. From the phase relation between the circadian rhythms and the light cycle, bright light in the early subjective day was assumed to produce a phase-advance shift of the circadian pacemaker. On the other hand, Czeisler and coworkers[5] demonstrated a 6-h phase-delay shift in body temperature and serum cortisol rhythms brought about by 4-h pulses of bright light applied repeatedly prior to the normal bedtime. The phase-shift occurred independent of the sleep-wake cycle. These observations suggested the presence of a phase response curve for light in human circadian system. In the present study, we examined the responsiveness of human circadian rhythms to a single bright light pulse under temporal isolation.

Four young male subjects separately spent 3 weeks in an isolation unit without knowledge of time. The sleep-wake cycle, the rectal temperature and several behavior patterns such as meal intake were monitored as described previously[4]. Sleep episodes in routine life were recorded for at least one week before and after the experiment. There were two kinds of illumination in the unit, one with ordinary fluorescent light and the other one with fluorescent bright light. The intensity of the ordinary light was 300–500 lx at the level of the head in the living room, the kitchen, and the toilet. The subject was allowed to use the ordinary lights at any time. The instrument for bright light was located on the ceiling of the living room and could be controlled only from outside the unit; its intensity was 5000 lx at the level of the desk and 500 lx at the position of a pillow on the bed. About one week after the beginning of an experiment, the living room was illuminated by the bright light for either 3 or 6 h (light pulse). One week later, the room was illuminated again. To two subjects (A and B), a pulse of bright light was applied during the early subjective day. The onset of the light pulse was scheduled to coincide with the expected time of waking as estimated by extrapolation of an eye-fitted line through the preceding ends of sleep episodes. For two other subjects (C and D), the light pulse was introduced during the late subjective day or the early subjective night. The phases of the sleep-wake cycle and the temperature rhythm were determined by visual inspection before and after the light pulse. Figure 1 demonstrates the results obtained from subjects A and B, to whom light pulses were applied in the early subjective day. The sleep rhythm in subject A was split into two sleep episodes of similar duration on the day following the first 6-h light pulse. One sleep episode occurred about 7 h earlier than expected (phase-advanced component), and the other one seemingly took place as a continuation of the previous rhythm. On the following days, however, the major sleep episodes were observed as a persistence of the phase-advanced component, so that in the steady state, the sleep rhythm was phase-advanced by about 7 h. The temperature rhythm also phase-advanced after the light pulse, but the extent of the phase shift was smaller than that of the sleep rhythm. The period of the sleep rhythm was roughly 24.9 h before the light pulse and 26.0 h after the pulse. The phase relation between the sleep and temperature rhythms also seemed to change after the pulse. The splitting of the sleep rhythm and eventual phase advance shifts of both circadian rhythms were confirmed in this particular subject by the second pulse which was shortened to 3 h. In this case, the changes in the sleep rhythm occurred on the second day after the light pulse (day 17). However, the phase-shift of the temperature rhythm seemed to occur already on the first day (day 16). On the second day (day 17), the sleep rhythm was split into two major sleep episodes, with fragmentation of sleep in the phase-advanced component. The amount of phase shift was approximately 7 h. In contrast, the phase-advance shift of the temperature rhythm was completed already on the second day, so that there was a transient internal dissociation between the sleep and temperature rhythms after the light pulses. The phase relation was reestablished on the 4th day (day 19).

Similar phase-advance shifts of the circadian rhythms by bright light pulses were also observed in subject B. This subject had an intrinsic period of 25.6 h before the light pulse. After the first light pulse, both circadian rhythms phase-advanced immediately. The amount of the phase shift was about 7 h on the first day (day 8), but only about 5 h after the circadian rhythms reached a steady state of free-run (day 9–day 13). In this case, splitting of the sleep rhythm was not evident. After the second light pulse, the temperature rhythm phase advanced by a maximum on the first day after the pulse (day 14), whereas there was no concomitant phase shift of the sleep rhythm. The duration of sleep was shortened on the next day, but the phase of sleep remained as a continuation of the previous rhythm. The sleep onset phase-advanced gradually in the following couple of days, and caught up with the phase of the temperature rhythm. The phase relation seemed to become normal on the 4th day after the pulse (day 17). The amount of steady state phase shift was approximately 4 h.

Figure 2 illustrates results from the two subjects to whom bright light pulses were applied during the late subjective day (subject C) or the early subjective night (subject D). The period of the circadian rhythm was 24.9 h in subject C and 25.3 h in subject D, respectively. In subject C, a bright light pulse of 3 h duration had no effect on the circadian rhythms, except for slight phase-advance shifts of the sleep episode and the temperature minimum on that specific day. The second light pulse of 6 h duration had some effects on the sleep rhythm. The sleep episode on the day of light pulse (day 16)

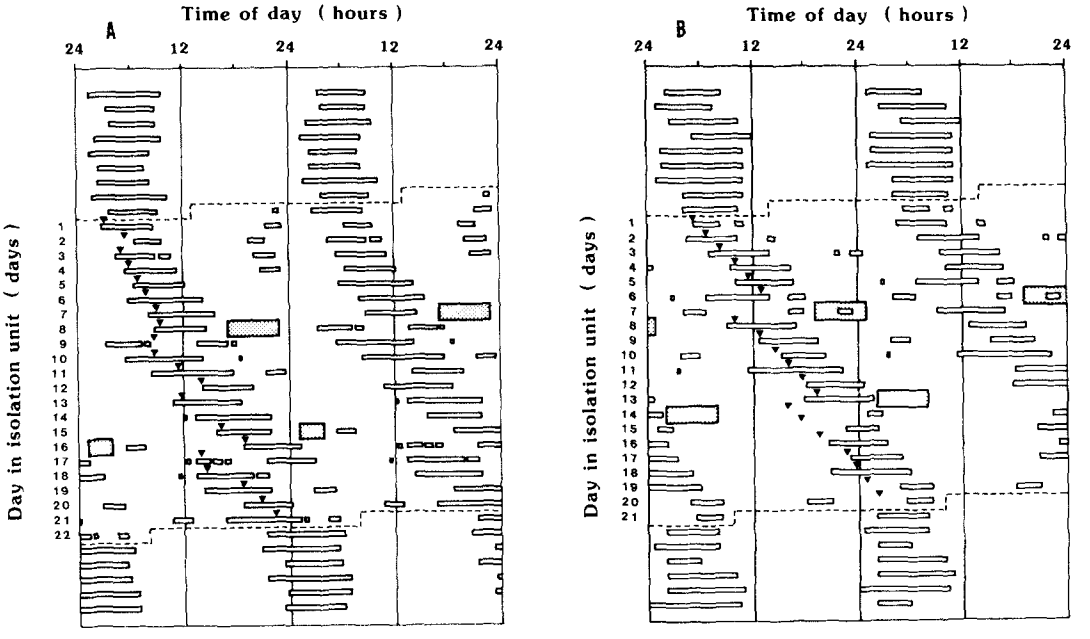

Figure 1. Double-plotted sleep rhythms and the daily positions of the rectal temperature minimum in two male subjects (A, 22 y; B, 25 y) in a temporal isolation unit. A horizontal open bar indicates a sleep episode and a closed triangle a time of the temperature minimum in a cycle. Shadowed squares indicate bright light pulses. A long square is a pulse of 6 h duration and a short is that of 3 h. Sleep episodes before and after the isolation experiment are indicated above and below the dotted lines, respectively.

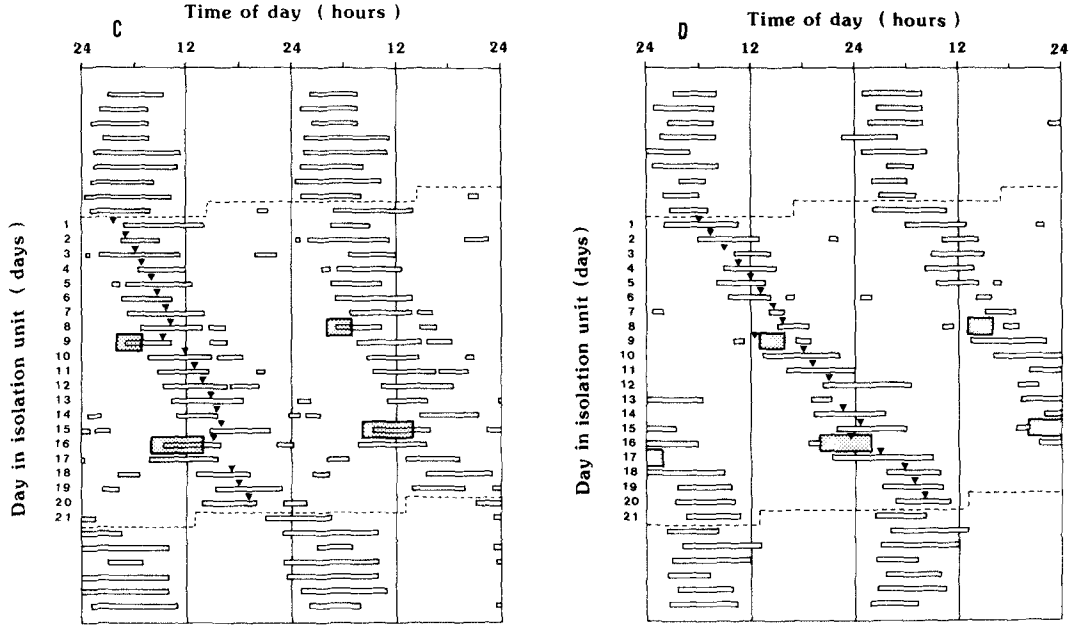

Figure 2. Double-plotted sleep rhythms and the daily positions of the rectal temperature minimum in two male subjects (C, 21 y; D 21 y). See also the legend to figure 1.

phase-advanced again, and that on the second day (day 17) phase-advanced further. But the major sleep episodes on the following days returned to the phase which could be predicted from the previous rhythm. The phase of the temperature rhythm was essentially unaffected by the light pulse. The sleep of subject D was relatively short and the rhythm was not very regular. The light pulses of either duration did not seem to have any significant effect on the phases of either circadian rhythm.

Although the present study is qualitative rather than quantitative, the findings demonstrate phase-shifts of free-running human circadian rhythms in response to a single light pulse. The shift depended on the phase of circadian rhythm when the pulse was given. PRCs of diurnally active animals have a phase-advance portion from the late subjective night to the early subjective day, and a phase-delay portion from the late subjective day to the early subjective night[6]. The presence of a phase-advance portion in a human PRC for light is suggested by our previous finding that human circadian rhythms were entrained by an artificial bright light cycle under temporal isolation[4]. Since the intrinsic period of human circadian rhythms is mostly longer than 24 h[7], a phase-advance

portion is necessary for entrainment to a 24-h light-dark cycle[2].

On the other hand, the light pulse applied from the late subjective day to the early subjective night had very small effects on the phases of the two circadian rhythms. Previously, Wever et al.[8] determined the range of entrainment of body temperature rhythm to artificial bright light cycles; the upper limit for it was 29.0 h. From these figures, a delay shift of about 4 h is expected. The absence of prominent delay shifts in the present study is contradictory to the finding of Czeisler et al.[5], in which a bright light of 4 h duration, applied for one week to an elderly woman before going to bed, produced a 6-h delay shift of temperature and serum cortisol rhythms. One possible explanation for this discrepancy is a difference in the intensity of bright light used. In Czeisler's experiment, the subject was exposed to bright light of 7,000–12,000 lx continuously for 4 h, while in the present study, the intensity was 5000 lx and the subject was allowed to sleep during the light pulse. In fact, subject C slept in bright light, which might reduce the phase-shifting effect of the bright light pulse. This explanation, however, is not possible for subject D, who did not sleep during bright light pulses. Another explanation for the disagreement is a difference in the intrinsic period of the circadian rhythm, which was shorter than 24 h in Czeisler's subject and was longer than 24 h in ours. The phase-delay portion in a PRC is important for the circadian rhythm to entrain to a 24-h light cycle, whose intrinsic period is shorter than 24 h.

Another interesting finding of the present study is a demonstration of internal dissociation between the sleep and temperature rhythms after a bright light pulse. The temperature rhythm phase-advanced always soon after the light pulse, while the sleep rhythm phase-advanced sometimes with transients. Different mechanisms have been suggested to be involved in the circadian sleep and temperature rhythms[9], and are still a matter of debate[10]. A large phase-angle difference between the sleep and temperature rhythms on the first day of internal dissociation may suggest that the oscillatory mechanism for the temperature rhythm reacts to light directly, while that for the sleep rhythm responds to it indirectly. The phase shift of the sleep rhythm can be interpreted as a result of secondary interaction with the temperature rhythm which phase-shifted primarily. However, a possibility remains that both mechanisms react to light, but differently.

Splitting of the sleep rhythm after a light pulse was an unexpected result, and raises a possibility of a two-oscillatory pacemaking system, as has been suggested for activity rhythms in rodents[11].

1 DeCoursey, P., Science *131* (1960) 3.
2 Pittendrigh, C.S., in: Handbook of Behavioral Biology, vol. 4, Biological Rhythms, p. 95. Ed. J. Aschoff. Plenum Press, New York 1981.
3 Lewy, A.J., Wehr, T.A., Goodwin, F.K., Newsome, D.A., and Markey, S.P., Science *210* (1980) 1267.
4 Honma, K., Honma, S., and Wada, T., Experientia *43* (1987) 572.
5 Czeisler, C.A., Allan, J.S., Strogatz, S.H., Ronda, J.M., Sanchez, R., Rios, C.D., Freitag, W.O., Richardson, G.S., and Kronauer, R.E., Science *233* (1986) 667.
6 Kram, K.R., J. interdisc. Cycle Res. *7* (1976) 127.
7 Wever, R.A., The Circadian System of Man. Springer-Verlag, New York 1979.
8 Wever, R.A., Polasek, J., and Wildgruber, C.M., Pflügers Arch. *396* (1983) 85.
9 Aschoff, J., Science *148* (1965) 1427.
10 Moore-Ede, M.C., and Czeisler, C.A., Mathematical Models of the Circadian Sleep-Wake Cycle. Raven Press, New York 1984.
11 Pittendrigh, C.S., and Daan, S., J. comp. Physiol. *106* (1976) 333.

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Age-related disappearance of Mayer-like heart rate waves

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Summary. Healthy elderly subjects (≥ 65 years) did not show the prominent low frequency (0.07–0.09 Hz) heart rate oscillations (Mayer waves) recorded in young adults immediately following passive upright tilt. This difference may be related to altered autonomic function with physiologic aging.

Key words. Aging; autonomic nervous system; heart rate variability; Mayer waves.

Acute intravascular volume shifts due to postural change or blood loss may induce relatively low frequency (~ 0.02–0.10 Hz) oscillations in systemic arterial blood pressure[1–5]. Periodic fluctuations of this kind, termed Mayer waves[6,7], are coherent with oscillations in heart rate which have been observed in healthy human subjects following passive upright tilt[5]. Although their precise mechanism is unknown, these heart rate variations apparently require functionally intact parasympathetic and sympathetic nervous systems[5,8]. We postulated that autonomic changes associated with physiologic aging[9–12] would alter this oscillatory behavior. Spectral analysis of post-tilt heart rate data demonstrated a loss of the Mayer-like waves in healthy elderly subjects.

The study groups consisted of 6 normal male volunteers (ages 22–26 years) and 8 healthy, older subjects (5 males, 3 females; ages 65–84 years) on no medication. As previously described[13], subjects underwent a 60° upright tilt over 9 s using the Stryker Circu-electric bed. A lead II electrocardiogram was recorded continuously beginning just prior to tilt and for 3 min post-tilt.

All young subjects showed prominent heart rate oscillations beginning shortly after tilt and persisting to the end of the observation period with a spectral peak at about 0.07–0.09 Hz. Oscillations at this frequency were absent or markedly attentuated in all elderly subjects (fig. 1). Principal component analysis[14] of the heart rate spectra showed a clear separation of the two groups related to the absence of the relatively low frequency oscillations in the elderly subjects (fig. 2). Cuff systolic blood pressure levels (Dinamap Automatic Sphygmomanometer) at 1, 2 and 3 min post-tilt were not significantly different from pre-tilt levels in either group[13].

Dynamic changes associated with physiologic aging are incompletely understood. Attenuation of both sympathetic and parasympathetic function has been described in older individuals[9,11,12]. Heart rate variability under resting condi-