Basic concepts and unique feature of human circadian rhythms: Implications for human health

Yujiro Yamanaka

Affiliations: YY is with the Laboratory of Life and Health Science, Hokkaido University Graduate School of Education and the Research and Education Center for Brain Science, Hokkaido University, Sapporo, Hokkaido, Japan

Correspondence: Yamanaka Y, Laboratory of Life & Health Sciences, Graduate School of Education, Hokkaido University, at North-11, West-7, Kita-Ku, Sapporo, 060-0811, Japan. Phone: +81-11-706-3077. Email: y-yu2ro@edu.hokudai.ac.jp

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Abstract

Most of all physiological function and behavior demonstrate robust 24 h rhythmicity (circadian rhythm) in the real world. These rhythms persist under constant condition, but the period is slightly longer than 24 h, suggesting that circadian rhythms are endogenously driven by an internal, self-sustained oscillator. In mammals including humans, the central circadian pacemaker is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Although the primary zeitgeber for the SCN circadian pacemaker is bright sunlight, non-photic time cues such as strict schedule and timed exercise affect somehow on the circadian rhythms in humans. The most unique feature of the human circadian system is the so-called spontaneous internal desynchronization between the sleep-wake cycle and core body temperature rhythm under the constant condition and partial entrainment of the sleep-wake cycle to non-photic time cues. Therefore, experimental and clinical studies in the human circadian rhythms should pay careful attention to unique feature of our internal biological clock and circadian rhythms. This review covers the basic concept and unique feature of the human circadian system, the underlying mechanism causing phase adjustment of the circadian rhythms by light and non-photic time cues (e.g., physical exercise), and the effect of eating behavior (e.g., chewing frequency) on circadian rhythm of glucose metabolism.

INTRODUCTION

Circadian rhythms, approximately 24 h fluctuation in physiology and behavior, are regulated by the circadian clock system which consists of the central and peripheral circadian oscillators. In mammals, the central circadian pacemaker is located in the suprachiasmatic nucleus (SCN) of anterior hypothalamus[1], whereas the peripheral clocks in the various peripheral organs (e.g., liver, lung, and skeletal muscle)[2] and extra-SCN brain regions[3]. Although the period of circadian rhythm is 24 h under the presence of light-dark cycles, the rhythm still remains under constant conditions (e.g., temporal isolation facility) which defined as the free-running rhythm. The free-running rhythm of circadian rhythm is slightly longer than 24 h (ca. 25 h)[4]. Therefore, circadian pacemaker in the SCN entrains to a 24 h natural light-dark cycle by exposure to a bright light in the morning[5]. Afterward, the external time information is transmitted to the peripheral clocks through the neural/humoral pathways from the SCN pacemaker[6,7]. As a result, the circadian pacemaker regulates and maintains internal temporal order of physiological function in the organism[8].

Stable entrainment of the human circadian clock to both an environmental light-dark cycle and social schedule is necessary for our normal physiological and psychological functions. Circadian misalignment and disruption of circadian rhythms are associated with a higher prevalence/development of sleep disorders, metabolic diseases (e.g., obesity and type2 diabetes, cardiovascular diseases (e.g., hypertension) and mood disturbance[9-11]. In order to reduce the circadian rhythms related health problems, people need to understand a basic and unique feature of the internal body clock system and underlying mechanism causing phase adjustment of the circadian rhythms by light and social (non-photic) behavior (e.g., daily life schedule, physical exercise, meal). This review covers 1) basic concept and unique feature of the human circadian system, 2) underlying mechanism of phase-adjustment circadian rhythm by light and exercise, and 3) effect of eating behavior on circadian rhythm in postprandial glucose metabolism.

BASIC AND UNIQUE FEATURE OF HUMAN CIRCADIAN RHYTHMS

The human circadian rhythm under the temporal isolation facility

Under normal condition, the circadian pacemaker entrains to an environmental light-dark cycle and generates 24 h fluctuation in physiology and behavior. In addition, circadian rhythms free-run under constant condition without any time cues and the period is slightly longer than 24 h. The mean free-running period of rectal temperature was 25.0 ± 0.50 SD h (n = 147)[4].

Spontaneous internal desynchronization is the most unique feature of the human circadian system. Subjects living in isolation facility without any time cues show the free-running rhythm with a period of about 25 h. But, in sometimes, the rhythms spontaneously desynchronized between the sleep-wake cycle and rectal temperature rhythm[12]. After the occurring internal desynchronization, the sleep-wake cycle became slower with a period of more than 30 h or more fast rhythm with a period of 20 h. Contrary to the sleep-wake cycle, the rhythm of rectal temperature maintained a period of about 25 h. In addition, the internal desynchronization is also occurred between the sleep-wake cycle and circadian rhythm of plasma melatonin[13]. The phenomenon of spontaneous internal desynchronization supports the idea that human circadian system is consist from two distinct circadian oscillators which separately regulate circadian rhythm of rectal temperature and plasma melatonin and sleep-wake cycle[14] (Figure 1). The oscillator for rectal temperature and plasma melatonin is located in the central circadian pacemaker in the suprachiasmatic nucleus of hypothalamus. The localization of oscillator for sleep-wake cycle is still unknown in humans, but it is probably located in the extra-SCN brain regions[15].

Photic entrainment

The free-running period of the human circadian clock is normally longer than 24 h, and so a phase advance is needed every day to entrain the clock to the 24-h environmental LD cycle. Bright light (natural sunlight) is a primary zeitgeber (entraining agent) for the circadian clock in humans. Figure 2 demonstrates so called light phase-response curve (PRC) produced by a single 3-h pulse of bright light at about 5,000 lux)[16, 17]. The PRC was obtained from subjects staying in an isolation facility under free-running conditions. In this PRC, the phase-advance portion coincides with late subjective night and early subjective morning, the phase-delay portion with early subjective night, and the middle of subjective day is a dead-zone when bright light does not produce a significant phase shift (dead-zone). Under normal circumstances, therefore, our circadian clock is entrained to a 24-h LD cycle by a phase advance caused by exposure to natural sunlight in the morning after waking up.

Physical exercise as a non-photic zeitgeber for human circadian rhythms

As for the effect of regular physical exercise on the circadian rhythm, there is good evidence that the circadian rhythm of plasma melatonin in totally blind persons and in sighted subjects under dim light condition entrained to a strict sleep-wake schedule shorter than 24 h (23.6 and 23.8 h) with a daily exercise[18, 19]. From these previous findings suggest that daily physical exercise affects the human circadian pacemaker whereas, somewhat paradoxically, studies using a strict sleep-wake schedule did not provide support for phase-shifting effects and/or entrainment caused by the sleep-wake cycle.

With regard to an attempt to resolve this paradox, Yamanaka et al. previously examined the effect of regular physical exercise on re-entrainment of the sleep-wake cycle and the circadian rhythm of plasma melatonin to an 8-h phase advance of the sleep-wake schedule under dim light conditions[20]. In this study, the subjects' sleep-wake schedule was phase-advanced by 8 h from its habitual value for 4 days. The exercise group performed interval exercise (15 min of running alternating with 15 min of rest) for 2 h upon a cycle ergometer twice a day after the wake period had been advanced. The control group sat quietly on a chair during the same period. At the end of the 4 days, the subjects were released into free-running conditions. By measuring the phase position of sleep-wake cycle and circadian rhythm of plasma melatonin on the first day of the free-running conditions, the re-entrainment of these rhythms to the advanced sleep schedule could be evaluated. It was demonstrated that daily physical exercise facilitated the re-entrainment of the sleep-wake cycle but not of the circadian rhythm of plasma melatonin, indicating that so-called partial entrainment (entrainment of partition) of sleep-wake cycle to non-photic time cue was observed in the exercise group (Figure 3). In contrast to this advanced sleep schedule, Barger et al. reported that regular physical exercise at midnight produced a greater phase delay and facilitated re-entrainment to a 9-h phase-delay in the sleep-wake schedule under dim light conditions[21]. These findings suggest that the direction of the phase shift of melatonin produced by exercise is different from that produced by the change of sleep-wake schedule. In other words, daily physical exercise might affect the circadian rhythm of plasma melatonin only indirectly. Physical exercise acts upon the oscillator controlling the sleep-wake cycle. This oscillator then acting upon the oscillator that is responsible for the circadian rhythm of melatonin.

Effect of physical exercise under bright light on circadian rhythms

As noted above, daily physical exercise acts as non-photic zeitgeber for the sleep-wake cycle rather than the circadian rhythm of plasma melatonin, whereas bright light acts as a zeitgeber for circadian rhythms in general. In the normal world, however, the combined effects of bright light (natural sunlight and artificial light) and non-photic cues (such as social schedule and physical exercise) on circadian rhythms should be considered. Yamanaka et al.[22] have been investigated whether or not physical exercise under bright light of 5000 lux facilitated the re-entrainment of circadian rhythms to an 8-h advance of the sleep schedule, using a similar experimental protocol to that used previously[20]. Physical exercise under bright light significantly accelerated re-entrainment to the advanced schedule of not only the sleep-wake cycle but also the circadian rhythm of plasma melatonin (Figure 3). By contrast, the subjects who did not perform physical exercise also showed the re-entrainment of sleep-wake cycle, but did not show a significant phase shift from the baseline values in their circadian rhythm of plasma melatonin. That is, internal desynchronization between the sleep-wake cycle and the circadian rhythm of plasma melatonin had occurred in the control group. These two studies[20, 22] indicate that the effect of physical exercise on the human circadian system is dependent on the light conditions when the exercise is performed.

EFFECT OF EATING BEHAVIOR ON CIRCADIAN RHYTHM OF POSTPRANDIAL GLUCOSE METABOLISM

Regarding the circadian rhythm of glucose metabolism in humans and animals, glucose tolerance and insulin sensitivity shows circadian rhythm with higher in the morning than in the evening. Blood glucose levels are higher in oral glucose tolerance tests (OGTTs) or a mixed meal consumption test conducted in the afternoon and evening than in those conducted in the morning, whereas insulin secretions, especially early-phase of insulin secretion, are higher in the morning than in the evening[23, 24]. Alternative mechanism of lower insulin sensitivity in the evening is reported to be associated with the circadian rhythm of free-fatty acid concentration[25].

Epidemiological studies demonstrate that eating behaviors such as time of meal and number of chew food are associated with risk of obesity and type2 diabetes. Slow eating and chewing food well increase dietary induced thermogenesis (DIT)[26] and appetite reducing hormone secretions (PYY and GLP1)[27], and decrease hunger hormone (ghrelin)[27]. In recently, we could reveal that effect of mastication on postprandial glucose metabolism is dependent on time of day and frequency of mastication[28]. In this study, healthy male subjects consumed a high carbohydrate food (200g rice) with 10 or 40 chew per mouthful at 0800 h and 2000 h. The results reveal that morning mastication but not evening decreases postprandial blood glucose concentrations (Figure 4A) and increases insulin secretion at 30 min (Figure 4B) and so-called the insulinogenic index as a marker of early-phase β-cell function (Figure 4C). It still unknown the alternative mechanism involved in the morning mastication enhanced early phase insulin secretion. There are two possible hypotheses that mastication could increase insulin-mediated glucose metabolism. The first is that mastication enhances so-called preabsorptive insulin response within a few minutes of ingestion[29], which the intraoral sensory stimulation from food elicits insulin secretion through the release of acetylcholine from the vagus nerve to the pancreas[30]. The other is that mastication may increase insulin secretion after eating, since it has been reported that the amount of DIT is positively correlated with insulin secretion after eating[31,32]. Furthermore, the amount of DIT shows circadian rhythm with higher in the morning and lower in the evening[33]. Thus, it is reasonable to assume that the morning mastication improve insulin secretion before and after food consumption. Clinically, impairment of early-phase insulin secretion is considered an early marker of β-cell dysfunction and the development of type 2 diabetes [34-36]. In recently, there are many studies in the field of "Chrono-Nutrition" that examine effect of time-of-day of meal intake and its association with energy metabolism and rising incidence of obesity and type 2 diabetes. Further studies would be needed to pay attention to the combined effect time-of-day of meal intake and of eating behavior on human health.

CONCLUSIONS

From the previous and recent studies in temporal isolation facility, we can further understanding on the human circadian system. In modern society, especially urban city, internal/external desynchronizations of circadian rhythms are caused by not only individual lifestyle choices (activity and eating patterns) but also it's responsible for occupational demands such as night shift work. The desynchronization of circadian rhythm induces impairment of energy metabolism and decreases insulin secretion in response to meal consumption. Further studies would be needed for clarity the association between desynchronization of circadian rhythm and the human health, and the strategy for preventing the desynchronization of circadian rhythm.

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Figure legends

Figure 1 Two oscillator model of human circadian rhythms[14]

Figure 2 Effect of physical exercise on the reentrainment of sleep-wake cycle and circadian rhythm of plasma melatonin under different light condition[20, 22]

Representative recordings of sleep-wake cycle, peak phase of plasma melatonin, and two state rhythm of rectal temperature in no-exercise subjects (A, C) and exercise subjects (B, D) under dim light (A, B) and bright light (C, D) conditions. Black horizontal bars indicate the sleep periods. Open circles indicate the peak phase of plasma melatonin rhythms measured on the baseline, the last day of shift schedule, and the last day of free-run, respectively. The two-state rectal temperature rhythm is expressed in a raster plot, and the shaded area indicates the lower temperature state, which were lower than the mean of all records throughout the experiment. Square columns in panel B indicate the periods of exercise of 2 h duration.

Figure 3 Effects of mastication on postprandial glucose level and insulin secretion after high-carbohydrate food consumption[28]

Glucose (A), insulin (B) and insulinogenic indices (C) in the morning and evening. The insulinogenic index [Δ insulin (0-30 min)/Δ glucose (0-30 min)] was calculated from the glucose concentrations and insulin secretions in each condition. Data are represented as mean ± SEM (n = 9) and were analyzed using two-way repeated measures ANOVA and post hoc Bonferroni test or the paired t test. E-10, 10 chews in the evening; E-40, 40 chews in the evening; iAUC, incremental area under the curve; M-10, 10 chews in the morning; M-40, 40 chews in the morning; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; M-40 vs. E-40. #$p = 0.06$, †$p < 0.05$; M-10 vs. M-40.

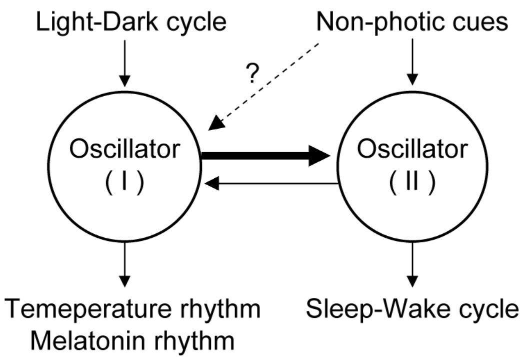
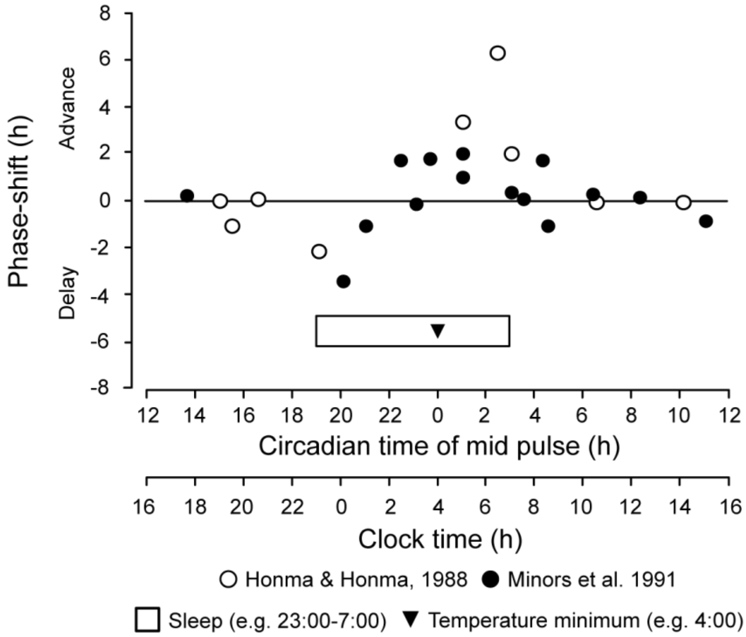
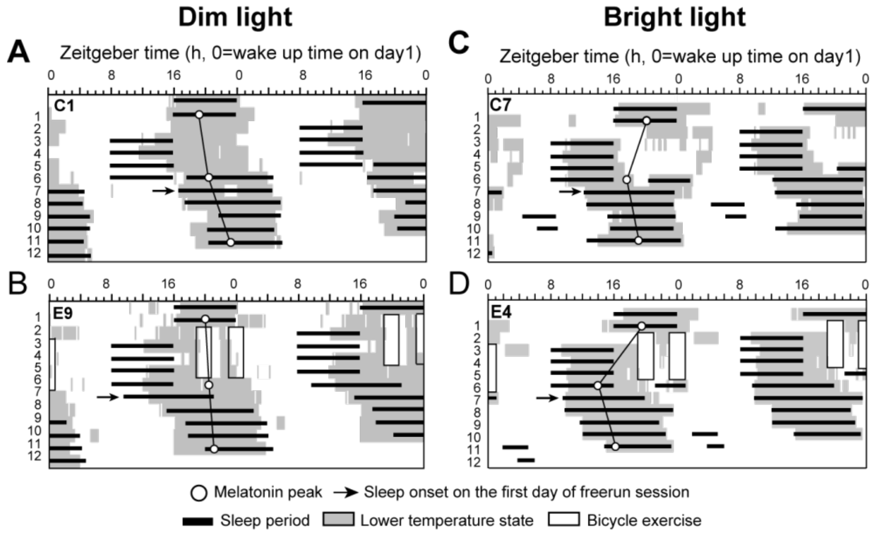

Light-Dark cycle
Non-photic cues
?
Oscillator
(I)
Oscillator
(II)
Temeperature rhythm
Melatonin rhythm
Sleep-Wake cycle

Figure 1



Phase-shift (h)
Advance
Delay
8
6
4
2
0
-2
-4
-6
-8
12 14 16 18 20 22 0 2 4 6 8 10 12
Circadian time of mid pulse (h)
16 18 20 22 0 2 4 6 8 10 12 14 16
Clock time (h)
Honma & Honma, 1988
Minors et al. 1991
Sleep (e.g. 23:00-7:00)
Temperature minimum (e.g. 4:00)

Figure 2



Dim light
Bright light
A
B
C
D
Zeitgeber time (h, 0=wake up time on day1)
C1
E9
C7
E4
Melatonin peak
Sleep onset on the first day of freerun session
Sleep period
Lower temperature state
Bicycle exercise

Figure 3

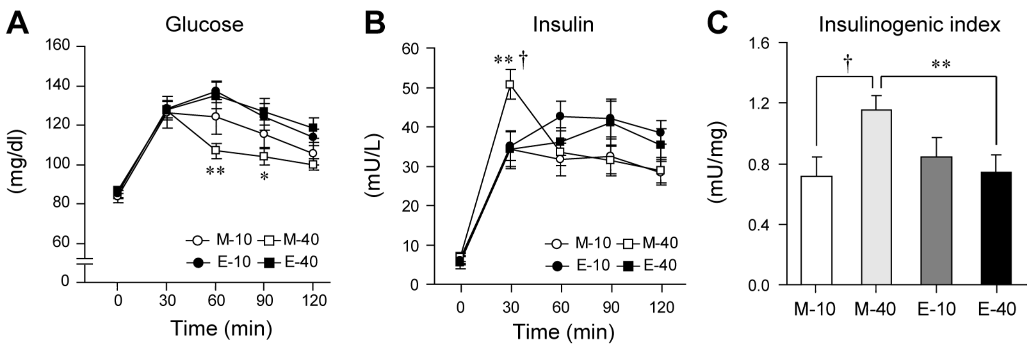

A
Glucose
160
140
120
100
80
60
0
(mg/dl)
0
30
60
90
120
Time (min)
**
*
M-10
M-40
E-10
E-40
B
Insulin
60
50
40
30
20
10
0
(mU/L)
** †
0
30
60
90
120
Time (min)
M-10
M-40
E-10
E-40
C
Insulinogenic index
1.6
1.2
0.8
0.4
0.0
(mU/mg)
†
**
M-10
M-40
E-10
E-40

Figure 4