REVIEW ARTICLE

Sleep-wake cycles in Humans

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Abstract

Sleep-wake cycles in human are unique in several aspects. First, human sleep and wakefulness are mostly consolidated except for the infantile and senile periods. Second, the sleep-wake cycle is synchronized because of the circadian rhythms in plasma melatonin and deep body temperature. Third, the polysomnography-based structure as well as the length of sleep depends on the circadian phase. The sleep-wake cycle is entrained by non-photic time cues independent of the circadian pacemaker. Some of these characteristics are easily understood by assuming that the specific oscillator in the circadian domain regulates sleep and wakefulness. The animal model for the human circadian system is advanced and the brain dopaminergic mechanism is strongly suggested to be site of the oscillator(s) regulating the sleep-wake cycle.

Keywords: Sleep wake cycle, circadian phase, internal desynchronization, circadian, oscillation.

Consolidated sleep and wakefulness

Sleep and wakefulness in adult humans are consolidated, with one continuous sleep episode and a persisting wakefulness in the day. Such consolidated sleep and wakefulness are characteristic in humans, whereas a large number of animal species show fragmented sleep and wakefulness, though keeping the dominancy of either nocturnality or diurnality. In humans, consolidated sleep and wakefulness develops several months after birth and,[1] become fragmented again in aged persons[2]. In some degenerative illnesses such as Parkinson's disease, fragmentation of sleep and wakefulness was evident and is accompanied by lowering daytime activity and increasing nighttime awake periods[3].

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As demonstrated later, the length as well as the propensity of spontaneous sleep depends on the circadian phase[4,5]. When sleep occurs at the circadian peak of deep body temperature, the sleep length is longest; up to 16 hours. On the other hand, when sleep occurs at the trough of body temperature, the sleep is shortest down to 3 hours. The length of sleep and wakefulness also depends on the time of year[6]. Sleep is shortest in summer time and longest in winter. The seasonality in the length of sleep or wakefulness is likely due to photoperiod or length of day time, rather than ambient temperature[6]. There is some evidence that two different circadian oscillators are involved in the seasonal changes of the length of sleep or wakefulness[7].

Internal desynchronization

Daily sleep and wakefulness are principally regulated by the circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN)[8]. The SCN circadian pacemaker is entrained by a light-dark cycle through

optic pathways called the retino-hypothalamic tract. On the other hand, it is well documented that succeeding sleep and wakefulness cycles depend to some extent on a proceeding alternative. In 1965, J. Aschoff and his colleagues[9] demonstrated for the first time dissociation between the circadian rhythms and sleep-wake cycle in a single subject whose circadian system was free-running under temporal isolation. The sleep-wake cycle free-run has a period far longer than 24 hour, while the circadian rhythm in deep body temperature showed a free-running period close to 24 hour (Figure 1). Such dissociation was called 'internal' desynchronization. On the other hand, the term, 'external desynchronization', is used for the circadian rhythms which are desynchronized from `external` cycles (local time) when they are free-running. Prior to full manifestation of spontaneous internal desynchornization, a phenomenon called 'internal dissociation' occurs in which the phase-relation is substantially changed between the sleep-onset and the circadian rhythm in deep body temperature[10]. In normal sleep at night, the trough of body temperature rhythm is located a few hours before spontaneous awake. However, under internal dissociation, the temperature trough is located at the sleep-onset. Therefore, sleep starts from the trough of deep-body temperature.

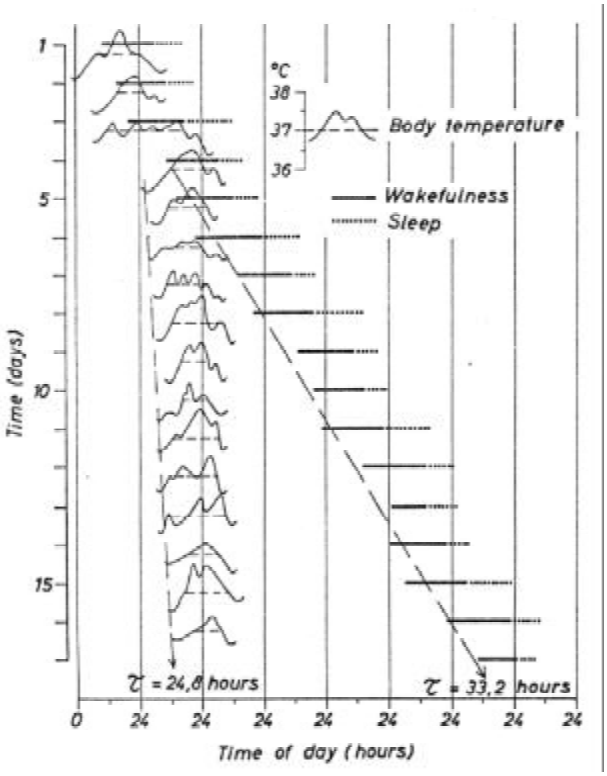

Figure 1: Internal desynchronization

Spontaneous internal desynchronization has been categorized into two types; one is a type in which the period of sleep-wake cycle is shorter than the 24 hours with the average length of 17.9 hours, and the other is a type in which the period of sleep-wake cycle is longer than 24 hours with the average length of 34.0 hours[10]. Changes in the length of 'a subjective day' were mainly due to changes in the length of wakefulness. The wake period in a subjective day was lengthened by 8.5 hours on average in the former type, and shortened by 6.6 hours in the latter. In the former type, one of the two alternating sleep episodes could be a nap. However, this interpretation is not accepted because the subjects took three meals during a short waking period, suggesting a substantially altered time sense. During internal desyncrhonization, most subjects complain of poor sleep and daytime sleepiness. Spontaneous internal desynchronization occurs not only between sleep-wake cycles and circadian rhythms in deep body temperature but also between sleep-wake cycles and other circadian rhythms such as in plasma melatonin[11]. Plasma melatonin levels are low during wakefulness and high during sleep. However, under internal desynchronization, the melatonin level could be high during wakefulness and low during sleep. About 20% of subjects show internal desynchronization during a relatively short-tem temporal isolation[10], but almost all subjects suffered from desynchronization in a long-term isolation over several months. Spontaneous internal desynchronization has not been reported in mammals other than humans.

Even under internal desynchronization, sleep-wake cycles and circadian rhythms in deep body temperature are not completely independent but interact with each other[4,5]. Figure 2 illustrates the relationship between sleep onset and sleep length in association with circadian rhythms in deep body temperature. During internal desynchronization, sleep starts more frequently during the decreasing phase of deep body temperature than the increasing phase, and sleep length is longest when sleep starts at the circadian peak of body temperature and shortest when starts at the trough. The mechanism for the systematic changes in sleep propensity and sleep length in reference to the circadian phase is unknown but is probably related with two circadian oscillators regulating the sleep-onset and awaking respectively. This is discussed in more details in a later section.

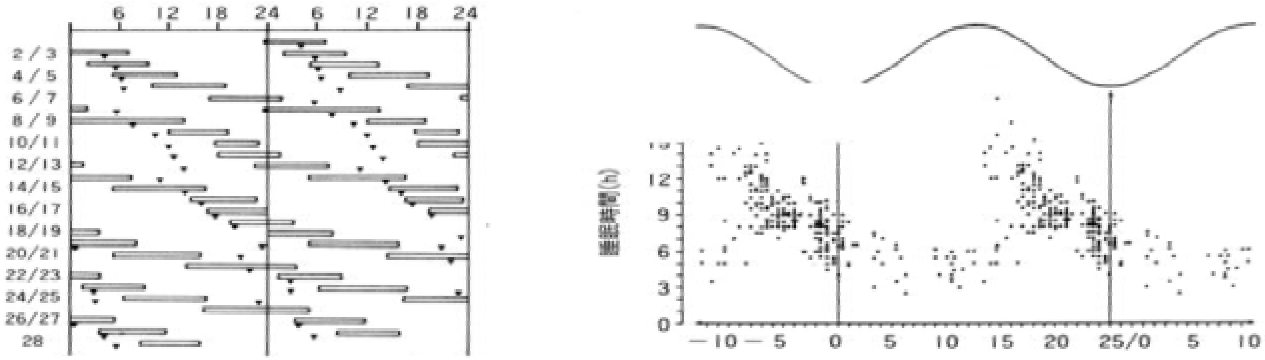

Figure 2: Propensity of sleep and sleep length in association with circadian rhythms in body temperature

Circabidian rhythm

Circabidian rhythms is a sleep-wake cycle with a period extended up to a. 50 hours (double circadian = circabidian), in which the length of wakefulness and sleep is about twice as long as usual[10]. By contrast, rhythms in deep body temperature keep circadian periods. As a result, the phase-relation is not changed between sleep-wake cycles and body temperature rhythms, but sleep appears to coincide with every second temperature trough (Figure 3)[12]. Most interestingly, the subjects do not recognize theirwaking period being extended twice as much as usual and regard an extreme long day as a usual day. They take three meals during the prolonged waking period, and keep diary as a single day. Their time sense is substantially changed J. Aschoff and his colleagues[13] examined time sense of subject under spontaneous internal desynchronization and circabidian rhythm. They found that a short-term time estimation (min) was not changed but a long-term time estimation (hour) was significantly changed and positively correlated with the length of waking period (Fig. 4).

The longer the waking period becomes, the shorter is the subject's estimate of the same time laps (or the longer the subject produce the time for same time laps). Underestimation of time laps is not a result of a prolonged waking period but likely a cause of extended waking period, since the time sense is already changed in the morning of a long day under internal desynchronization. The interval between the wake-up time and the time of breakfast is already positively correlated with the waking period of that day. The extended waking time is not the extension of wakefulness beyond a usual time to go-to-bed, but seems to be due to slow down of the angler velocity of oscillation underlying wakefulness.

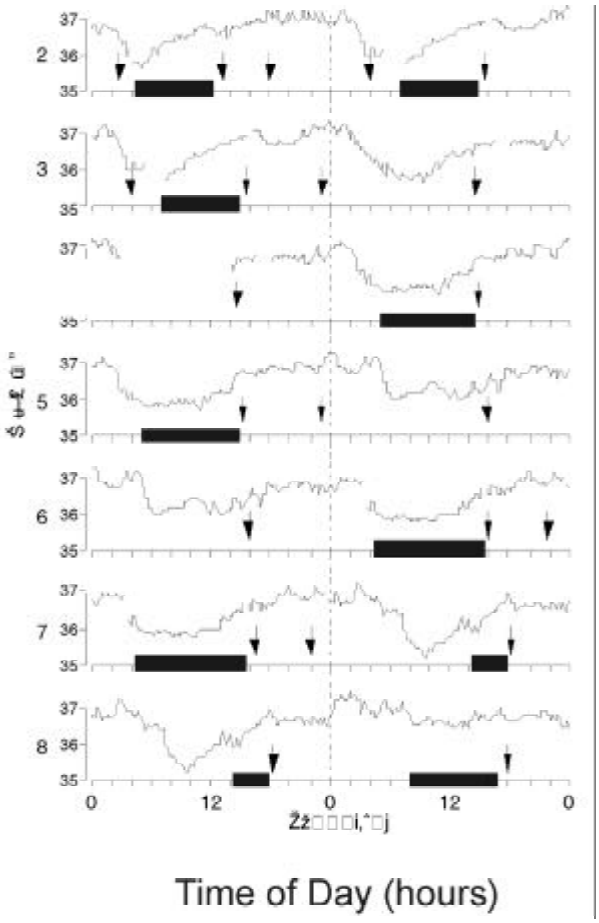

Figure 3: Circabidian rhythm

Photic and Non-photic entrainment

Human circadian rhythms are entrained by a light-dark cycle[14]. However, the circadian rhythms need far more brighter lights for entrainment than other mammals such as rats and mice do. Before the concept of photic

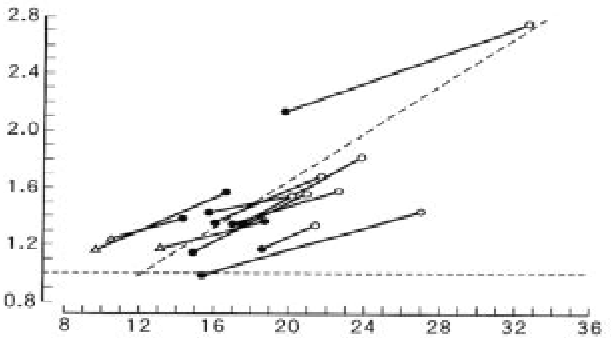

Figure 4: Time sense in internal desynchronization

entrainment is generally accepted for humans, a major zeitgeber (time cue) for human circadian rhythms were thought be social factors such as scheduled works[15]. On the other hand, the sleep-wake cycle in a totally blind person was reported to be entrained in 24 h days[16]. Furthermore, partial entrainment or entrainment by partition was reported in a sighted person, in which sleep-wake cycles are entrained by 24 h days, while circadian rhythms in plasma melatonin are free-running [17]. These reports suggest differential time cues for sleep-wake cycles and circadian rhythms, but the possibility is not excluded that sleep and wakefulness are directly induced by 24 h schedules (masking). Entrainment is accomplished through an oscillatory mechanism, while masking is a direct effect of external stimuli on sleep or wakefulness without affecting the underling oscillatory system. The two modes, entrainment and masking, could be experimentally differentiated. Hashimoto et al[18] examined this issue in subjects isolated from external time cues and demonstrated for the first time partial entrainment of human sleep-wake cycles (Figure 5). They observed entrainment of sleep-wake cycles to phase-

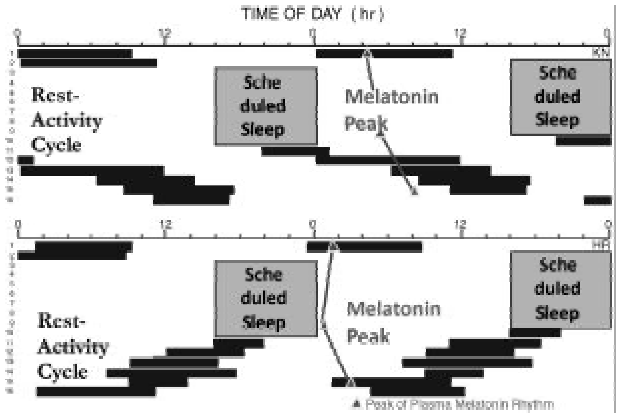

Figure 5: Entrainment of sleep-wake cycle to non-photic time cues

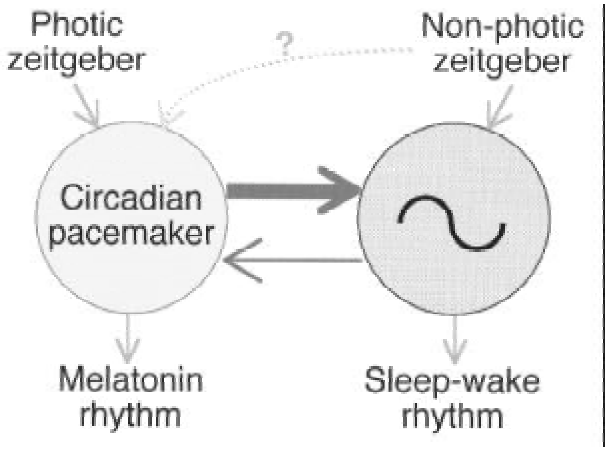

Figure 6: Two oscillator model of human circadian system

advanced sleep schedule by 8 hour from the routine life, and free-running of plasma melatonin rhythms during the schedule. Entrainment was assessed by the initial phase position of sleep-wake cycle in the subsequent free-run session. Desynchronizated two rhythms during forced sleep schedule were gradually re-synchronized in the course of free-run and finally established a usual phase-relationship. The findings strongly support the two oscillator hypothesis for the human circadian system.

Two oscillator hypothesis

As mentioned already, internal desynchronization, circabidian rhythms and partial entrainment are unique for the human circadian system. These phenomena, in the author's knowledge, have never been observed in other mammals. Several models based on two oscillator hypothesis have been advanced[19]. Our model postulates two mutually coupled oscillators; one oscillator denoted as Oscillator I drives the circadian rhythms in plasma melatonin and deep body temperature, which is identical to the circadian pacemaker located in the SCN and entrained by light-dark cycles, and the other denoted as Oscillator II drives sleep-wake cycles, which is entrained by non-photic time cues but neither the site nor the mechanism of oscillation of which is known (20) (Figure 6).

When the two oscillators are coupled to each other, they behave as one coupled oscillator, but when the mutual coupling is disrupted, internal desynchronization or partial entrainment may happen. The coupling strength from Oscillator I to Oscillator II seems to be stronger than the opposite direction, since the extent of

period change is much larger for Oscillator II than for Oscillator I when internal desynchronization occurs.

Animal model for human sleep-wake cycle

In order to characterize the above mentioned two oscillators in humans, we need to study animal models. Methamphetamine (MAP), a competitive antagonist of dopamine active dopamine active transporter (DA), is known to stimulate DA receptors by inhibiting DA re-uptake[21]. Administration of MAP dissolved in drinking water consolidates nocturnal behaviors of rats under light-dark (LD) cycles and phase-delayed circadian behavior rhythm. Eventually, the circadian behavior rhythms were desynchronized from LD cycles and free-ran with a period longer than 24 hours[22]. The free-running behavior rhythms were, however, modified periodically by LD cycles, showing signs of relative coordination. It turned out soon that free-running of behavior rhythms by MAP was not due to free-running of the circadian pacemaker located in the SCN, but the rhythms generated by MAP, since similar behavior rhythms were detected in rats with bilateral SCN lesions [23]. Following studies (24) revealed that the period of MAP-induced behavior rhythm was does-dependently increased by MAP, continuous infusion of MAP by means of osmotic mini pump induced behavior rhythms in SCN lesioned rats, and occasionally circabidian rhythms appeared by MAP treatment. MAP-induced behavior rhythms were entrained by non-photic time cues such as restricted daily feeding. These initial findings already indicated the existence of an oscillation(s) in the circadian domain which was induced by prolonged MAP treatment and independent of the light-entrainable SCN circadian pacemaker. A more recent study (25) demonstrated a partial entrainment of circadian system in MAP treated rats, in which the circadian melatonin rhythm was entrained by LD cycles, while the behavior rhythm was externally desynchronized (Figure 7). Thus, the MAP-induced behavior rhythm shows consolidated sleep and wakefulness, internal desynchronization (partial entrainment), circabidian rhythm, and non-photic entrainment, which are characteristics of human sleep-wake cycles. Thus, the MAP treated rats could be regarded as the animal model of human circadian system.

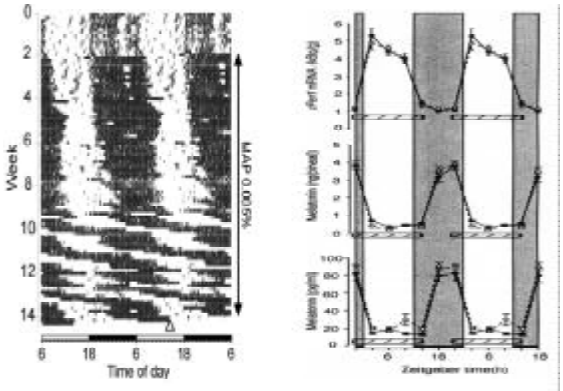

Figure 7: Partial entrainment of circadian system in MAP treated rats

A hierarchical multi-oscillator system regulation sleep-wake cycle

According to current understanding, the circadian rhythm is generated by a positive-negative feedback loop in which 4 families of clock genes, *Per(s)*, *Cry(s)*, *Bmal1*, *Clock*, are involved[26]. Expressions of clock genes show robust circadian rhythms. These are detected not only in the SCN but also in other tissues and organs. When the circadian system of rats was internally desynchronized by MAP treatment, the circadian rhythms in clock gene expression in several brain areas were also desynchronized from the SCN circadian pacemaker[25]. The circadian clock gene expression rhythm in the SCN was kept entrained by LD cycles, while those in the parietal cortex (CP) and caudate-putamen (CPU) were completely phase-reversed similar to MAP-induced behavior rhythms. These results do not necessarily indicate the site of MAP-induced oscillation, since it is not known whether the phase reversal of clock gene expression reflected the MAP-induced oscillation or simply behavior rhythms.

Taking advantage of bioluminescence reporter for clock gene expression, it is now possible to monitor the circadian oscillation in cultured tissues. This technology was used to explore the site and mechanism of MAP-induced oscillation[27,28]. Discrete brain areas were obtained from MAP treated rats and cultured to monitor the circadian oscillations for several cycles. Circadian oscillations in the extra-SCN regions, especially in the brain dopaminergic system are substantially affected by MAP-treatment (Figure 8). The circadian oscillations in these regions were not only desynchronized from the SCN circadian oscillation but also re-organized to function as a coupled oscillator which most likely regulates the MAP-induced behavior rhythms. We call this coupled

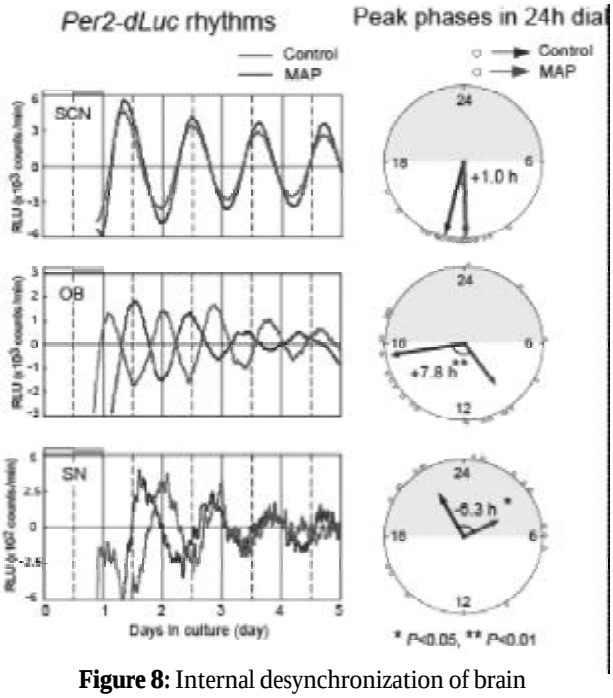

Figure 8: Internal desynchronization of brain oscillation by MAP

oscillator as MAP-induced oscillator (MAO). Thus, the MAO may consist of multiple circadian oscillators located mainly in the central dopaminergic regions and interact with the SCN circadian pacemaker. The mechanisms of mutual coupling for building the MAO, of expression in behavior by the MAO and of the interaction with the SCN circadian pacemaker remain elucidated.

Is the human Oscillator II MAO?

Now the question arises whether the human Oscillator II regulating sleep-wake cycles is MAO or not. We have no answer yet. However, if the consolidated wakefulness in humans is a sign of enhanced dopaminergic activity in the brain, the possibility of MAO as the responsible oscillator for sleep-wake cycles would be greatly increased. On the other hand, circadian rhythms in Parkinson's disease could be a good counterpart model, in which neuronal degeneration occurs mainly in the brain dopaminergic system whose circadian system could be monitored relatively easily[3]. As mentioned already, the sleep-wake cycle of Parkinson's disease is characterized by fragmentation, lowering daytime activities and causing frequent awakenings after sleep-onset.

References

1. **Majid Mirmiran**, Yolanda GH Maas and Ronald L Ariagno. Development of fetal and neonatal sleep and circadian rhythms. *Sleep Medicine Reviews* 7(4): 321-334, 2003.
2. **Youn-Lu Huang**, Rong-Yu Liu, Qing-Song Wang, Wus JW van Someren, Hao Xu and Jiang-Ning Zhou. Age-associated difference in circadian sleep-wake and rest-activity rhythms. *Physiology and Behavior*, 76:597-603, 2002.
3. **JJ van Hilten**, HAM Middelkoop, GA Kerkhof, RAC Roos. A nnew approach in the assessment of motor activity in Parkinson's disease. *J Neurology Neurosurgery and Psychiatry* 54:976-979, 1991.
4. **Czeisler CA**, Weitzman ED, Moore-Ede MC, Zimmerman, JC and Knauer RS. Human sleep: its duration and organization depend on its circadian phase. Science 210;1264-1267, 1980.
5. **Zulley J.**, Wever R., Aschoff, J. The dependency of onset and duration of sleep on the circadian rhythm of rectal temperature. *Pflugers Arch*, 391:314-318, 1981.
6. **Honma K**, Honma S, Kohsaka M and Fukuda, N. Seasonal variation in the human circadian rhythm: dissociation between sleep and temperature. *Am J Physiol*, 262:R885-R891, 1992.
7. **Wehr TA**, Schwartz PJ, Turner EH, Feldman-Naim S, Drake CL, and Rosenthal NE. Bimodal patterns of human melatonin secretion consistent with a two-oscillator model of regulation. *Neurosci Lett* 194: 105-108, 1995.
8. **Klein DC**, Moore RY, Reppert SM *Suprachiasmatic Nucleus: the Mind's Clock* Oxford University Press, New York, 1991.
9. **Aschoff J.** Circadian rhythms in man: a self-sustained oscillator with an inherent frequency underlies human 24-hour periodicity. Science 148: 1427-1432, 1965.
10. **RA Wever**. The Circadian System of Man. Results of Experiments under Temporal Isolation, Springer-Verlag, New York, 1979.
11. **Honma K**, Hashimoto S, Endo T and Honma S. Light and plasma melatonin rhythm in humans. *Biol Signals* 6:307-312, 1997.
12. **Honma K.**, Honma S. and T. Wada. Circabidian rhythm; its appearance and disappearance in association with a bright light pulse. *Experientia* 44:981-983, 1988.
13. **Aschoff J.** Human perception of short and long time intervals: its correlation with body temperature and the duration of wake time. *J Biol Rhythm* 13:437-442, 1998.
14. **Honma K**, Honma S, and Wada T. Entrainment of human circadian rhythms by artificial bright light cycles. Experientia 43: 572-574, 1987.
15. **Aschoff J**, M. Fatranska, H. Giedke, P. Doerr, D.Stamm, and H.Wieser. Human circadian rhythms in continuous darkness: entrainment by social cues. Science, 171:213-215, 1971.
16. **Klein T**, Martens H, Dijk DJ, Kronauer RE, Deely EW, Czeisler CA. Circadian sleep regulation in the absence of light perception: Chronic non-24-hour circadian rhythm sleep disorder in a blind man with a regular 24-hour sleep-wake

schedule. *Sleep* 16:333-343, 1993.

17. **Hashimoto S**, Nakamura K, Honma S and Honma K. Free-running circadian rhythm of melatonin in a sighted man despite a 24-hour sleep pattern: A non-24-hour circadian syndrome. *Psychiat. Clinical Neurosciences* 51:109-114, 1997.
18. **Hashimoto S**, Nakamura K, Honma S, and Honma K. Non-photic entrainment of human rest-activity cycle independent of circadian pacemaker. *Sleep and Biological Rhythms*. 2004; 2: 29-36.
19. **Moore-Ede M** and Czeisler CA (eds), Mathematical Models of the Circadian Sleep-Wake Cycle, Raven Press, New York, 1984.
20. **Honma K**, Hashimoto S, Endo T and Honma S. Internal Desynchronization of the human circadian system. In: Circadian Clocks and Entrainment, (eds) K. Honma and S. Honma, Hokkaido Univ Press, Sapporo, pp.101-113, 1998.
21. **Fleckenstein AE**, Volz TJ, Riddle EL, Gibb JW and Hanson GR. New insights into the mechanism of action of amphetamine. *Annu Rev Pharmacol Toxicol*, 47:681-698, 2007.
22. **Honma K**, Honma S. Hiroshige T. Disorganization of the rat activity rhythm by chronic treatment with methamphetamine. Physiol Behav. 1986; 36: 687-691.
23. **Honma K**, Honma S and Hiroshige T. Activity rhythms in the circadian domain appear in suprachiasmatic nuclei lesioned rats given methamphetamine. *Physiol Behav* 40: 767-774, 1987.
24. **Honma K**, and S. Honma. The SCN independent clocks, methamphetamine and food restriction. *Eur J Neurosci*. 2009; 30: 1707-1717.
25. **Masubuchi S**, Honma S, Abe H, et al. Clock genes outside the suprachiasmatic nucleus involved in manifestation of locomotor activity rhythm in rats. *Eur J Neurosci*. 2000; 12: 4206-4214.
26. **Reppert SM** and Weaver,D.R.: Coordination of circadian timing in mammals. Nature, 418:935-941, 2002.
27. **Natsubori A**, et al. Differential responses of circadian *Per2* expression rhythms in discrete brain areas to daily injection of methamphetamine and restricted feeding in rats. *Eur J Neurosci*,37:251-258, 2013.
28. **Natubori A**, Honma K and Honma S. Differential responses of circadian Per2 rhythms in cultured slices of discrete brain areas from rats showing internal desynchronization by methamphetamine. *Eur J Neruosci*, 37:2013.