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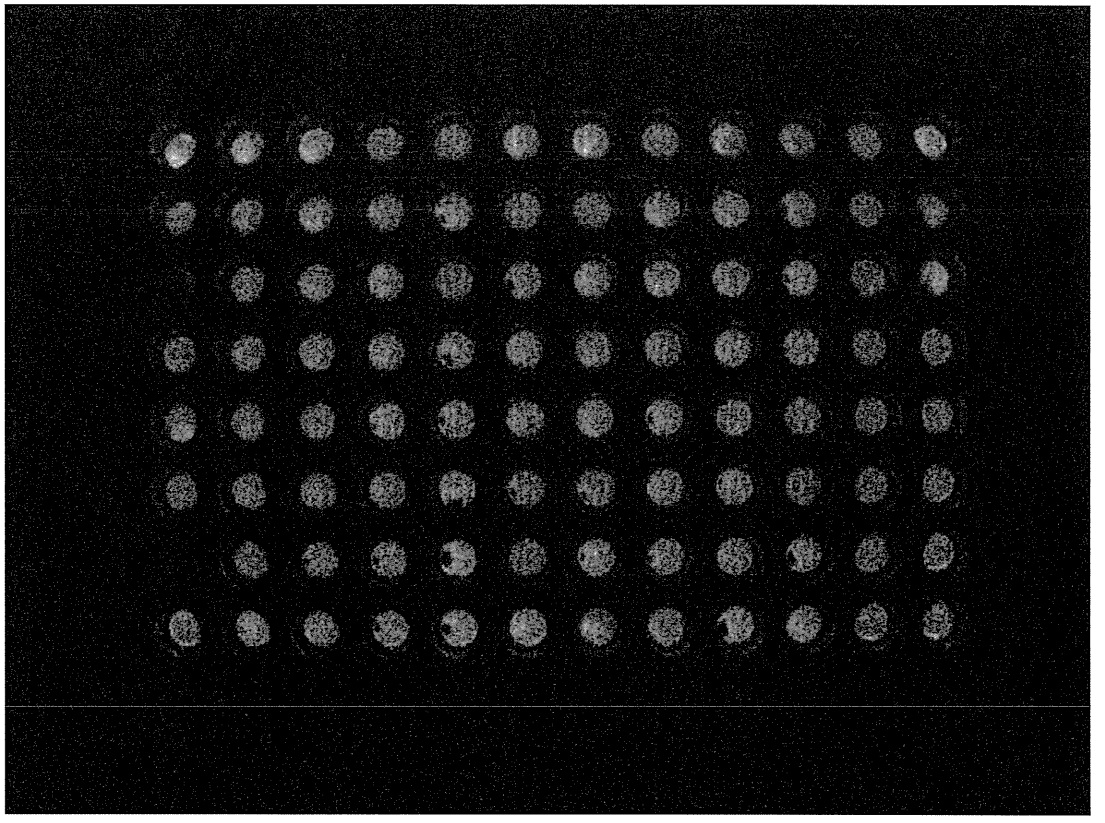

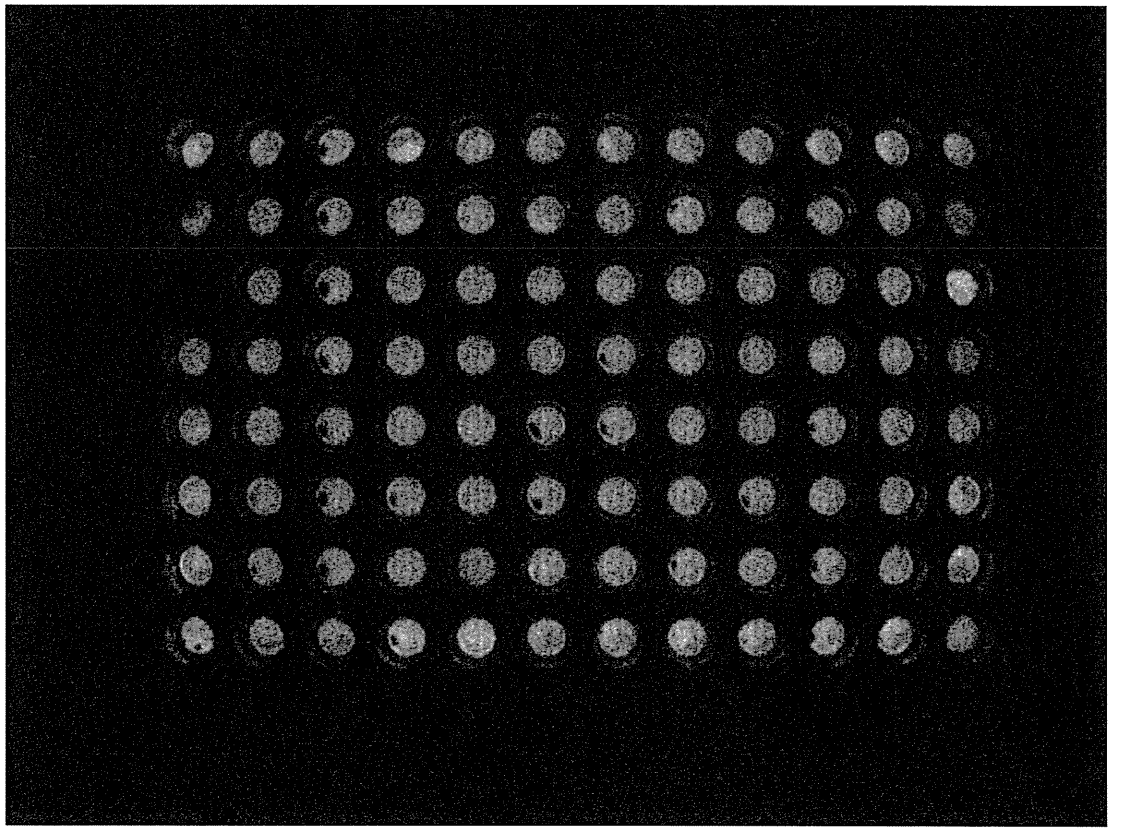

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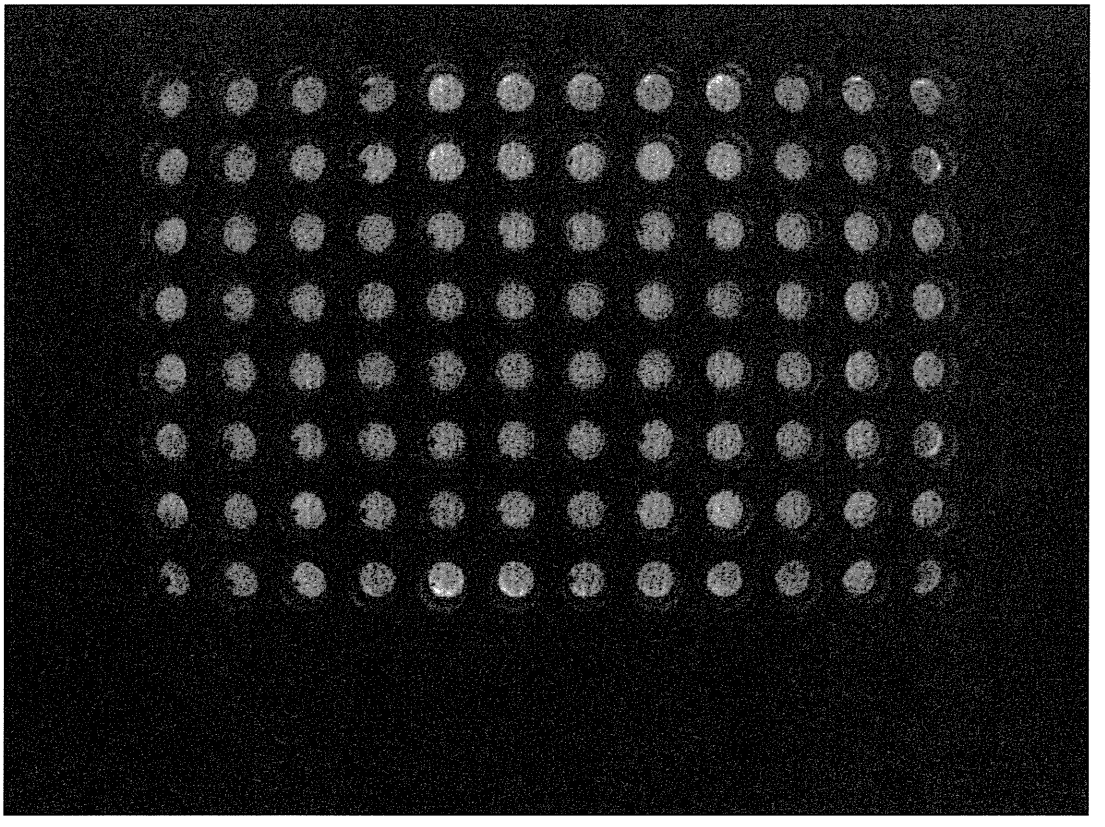

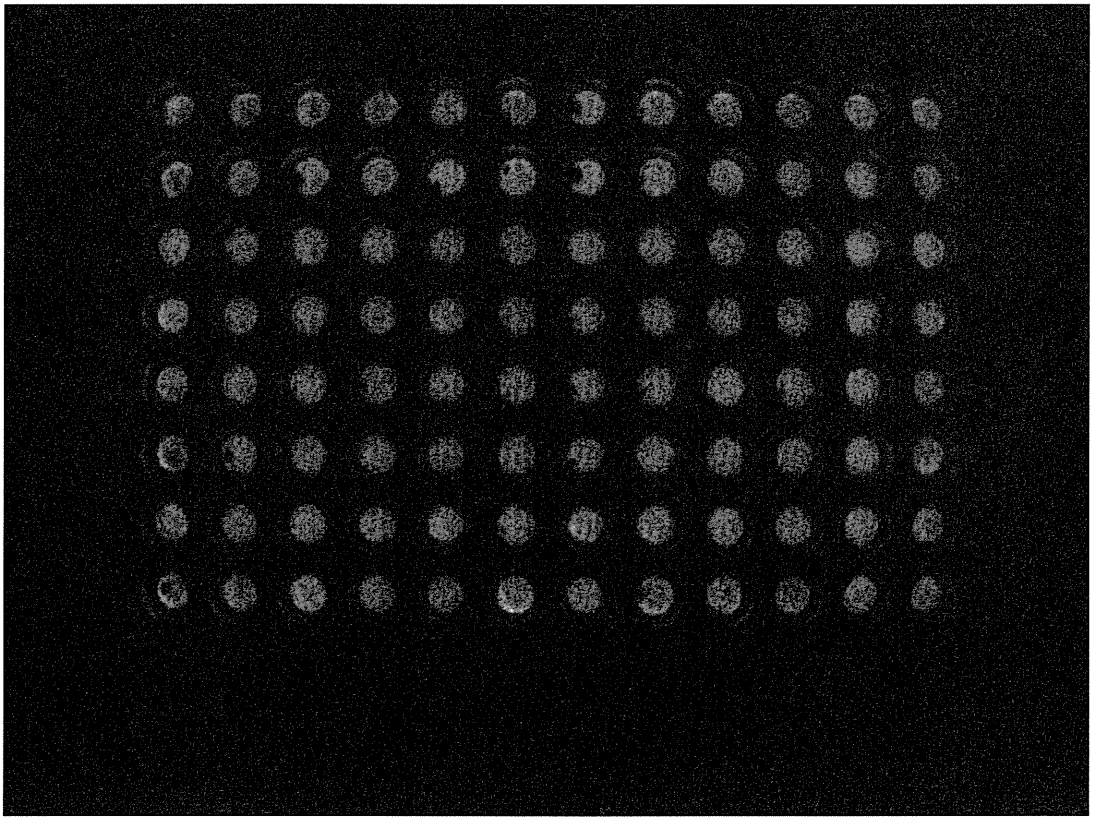

II.　研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hida, A., Kitamura, S. & Mishima, K.	Pathophysiology and pathogenesis of circadian rhythm sleep disorders	Journal of Physiological Anthropology	31	7	2012
Hida, A., Kitamura, S., Enomoto, M., Nozaki, K., Moriguchi, Y., Echizenya, M., Kusanagi, H. & Mishima, K.	Individual traits and environmental factors influencing sleep timing: a study of 225 Japanese couples, Chronobiology international.	Chronobiology International	29	220-6	2012
肥田昌子、三島和夫	気分障害と生物時計システムーリズム異常をもたらす生物時計機能障害評価法	医学のあゆみ	239	907-11	2011
肥田昌子、三島和夫	概日リズム睡眠障害の病態生理研究の動向	日本生物学的精神医学会誌	22	165-70	2011

肥田昌子、三島和夫	認知症患者の概日リズムの乱れに対するメラトニン治療の効果ーせん妄に対しても効果はあるか？	Cognition and Dementia	10	62-3	2011
肥田昌子	概日リズム睡眠障害の病態生理	睡眠医療	5	11-5	2011
Aritake-Okada S, Higuchi S, Suzuki H, Kuriyama K, Enomoto M, Soshi T, Kitamura S, Watanabe M, Hida A, Matsuura M, Uchiyama M, Mishima K	Diurnal fluctuations in subjective sleep time in humans	Neurosci Res	68	225-31	2010
Kitamura S, Hida A, Watanabe M, Enomoto M, Aritake-Okada S, Moriguchi Y, Kamei Y, Mishima K	Evening preference is related to the incidence of depressive states independent of sleep-wake conditions	Chronobiol Int	27	1797-812	2010

III.　研究成果の刊行物・別刷

Hida et al. Journal of Physiological Anthropology 2012, 31:7
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REVIEW Open Access

Pathophysiology and pathogenesis of circadian rhythm sleep disorders

Akiko Hida*, Shingo Kitamura and Kazuo Mishima

Abstract

Metabolic, physiological and behavioral processes exhibit 24-hour rhythms in most organisms, including humans. These rhythms are driven by a system of self-sustained clocks and are entrained by environmental cues such as light-dark cycles as well as food intake. In mammals, the circadian clock system is hierarchically organized such that the master clock in the suprachiasmatic nuclei of the hypothalamus integrates environmental information and synchronizes the phase of oscillators in peripheral tissues. The transcription and translation feedback loops of multiple clock genes are involved in the molecular mechanism of the circadian system. Disturbed circadian rhythms are known to be closely related to many diseases, including sleep disorders. Advanced sleep phase type, delayed sleep phase type and nonentrained type of circadian rhythm sleep disorders (CRSDs) are thought to result from disorganization of the circadian system. Evaluation of circadian phenotypes is indispensable to understanding the pathophysiology of CRSD. It is laborious and costly to assess an individual's circadian properties precisely, however, because the subject is usually required to stay in a laboratory environment free from external cues and masking effects for a minimum of several weeks. More convenient measurements of circadian rhythms are therefore needed to reduce patients' burden. In this review, we discuss the pathophysiology and pathogenesis of CRSD as well as surrogate measurements for assessing an individual's circadian phenotype.

Keywords: circadian, sleep, surrogate measurement, clock gene expression, biopsy sample

Mammalian circadian clock system

The circadian clock system regulates daily rhythms of physiology and behavior, such as the sleep-wake cycle and hormonal secretion, body temperature and mood [1]. These rhythms are entrained by environmental cues, light-dark (LD) cycles and food intake. In mammals, the master clock in the suprachiasmatic nuclei (SCN) of the hypothalamus incorporates environmental information and coordinates the phase of oscillators in peripheral cells, tissues and organs [2,3]. Light is one of the most potent environmental cues that enable the organisms to adapt to the 24-hour environmental LD cycle. Photic signals are delivered from the eye to the SCN via the retinohypothalamic tract, thereby mediating the entrainment of the circadian clock system [4]. The circadian clock system involves transcription-translation negative feedback loops of multiple clock genes and posttranscriptional modification and degradation of clock proteins [4-6] (Figure 1). The basic helix-loop-helix and Per-Arnt-Sim transcription factors CLOCK and BMAL1 form heterodimers and activate transcription of *Period 1* (*Per1*), *Per2*, *Per3*, *Cryptochrome 1* (*Cry1*), *Cry2* and *retinoid-related orphan receptor α* (*Rorα*), *Rorβ*, *Rorγ*, *Rev-Erbα* and *Rev-Erbβ* by binding to E-box motifs on their promoter regions. PER and CRY proteins gradually accumulate in the cytoplasm and phosphorylation of PER and CRY occurs with casein kinase Iδ (CKIδ) and CKIε. PER, CRY and CKI proteins form complexes that translocate to the nucleus and interact with CLOCK-BMAL1 heterodimers, thereby inhibiting transcription of the *Per*, *Cry*, *Ror* and *Rev-Erb* genes. Meanwhile, *Bmal1* transcription is regulated positively by retinoid-related orphan receptor (ROR) and negatively by REV-ERB via the ROR element (RORE) motif on the *Bmal1* promoter.

Circadian rhythm sleep disorders

A two-process model is a major model of sleep regulation. Two components, homeostatic drive and circadian

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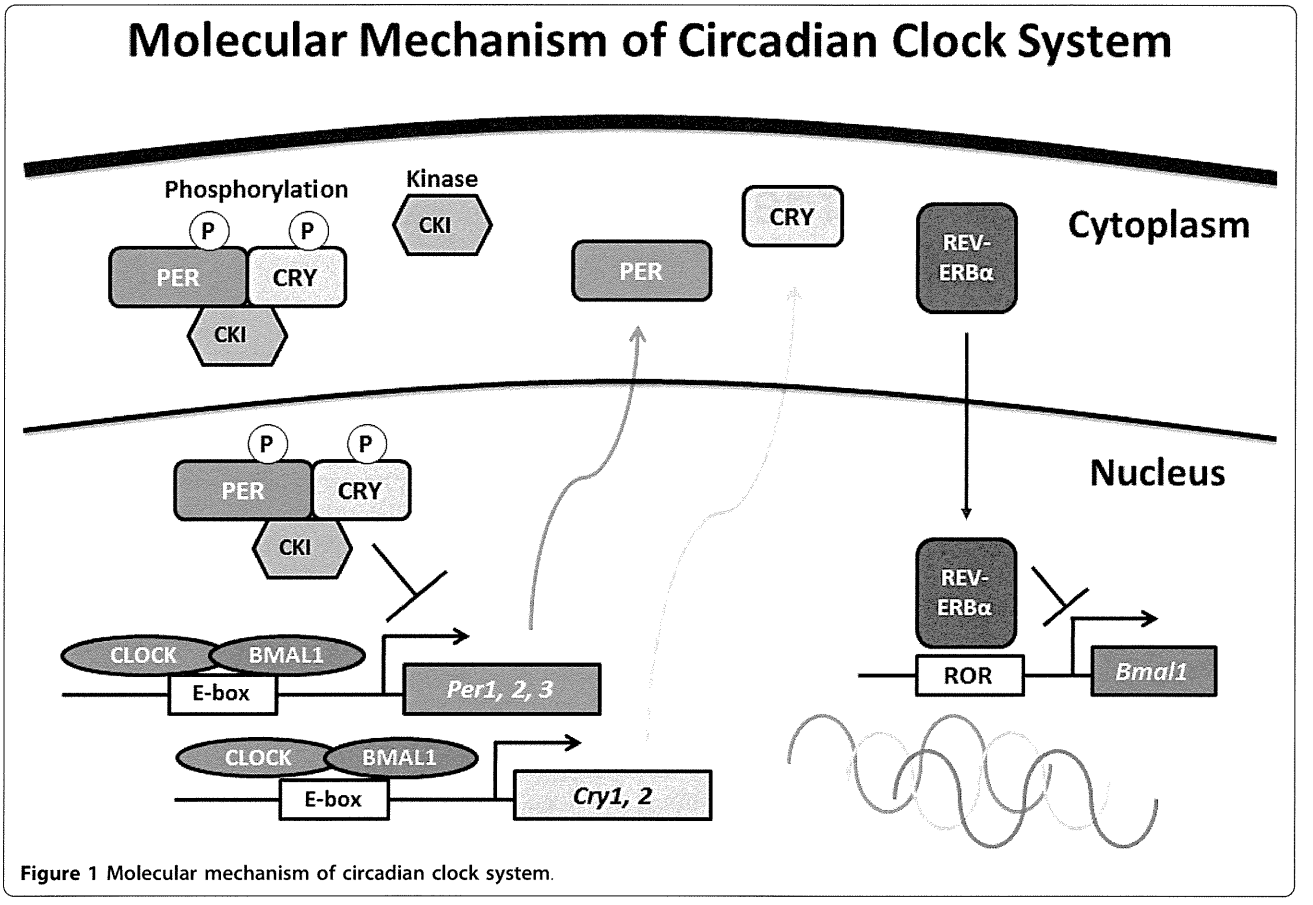

Figure 1 Molecular mechanism of circadian clock system.

drive, interact with each other and regulate the sleep-wake cycle [7]. The sleep-wake cycle is controlled by sleep homeostasis. The desire to sleep increases gradually with extended wakefulness and decreases during sleep. Additionally, sleep and wakefulness occur in turn, and the timing of their occurrence is controlled by the circadian clock system. Circadian rhythm sleep disorders (CRSDs) are defined by a persistently or recurrently disturbed sleep pattern. CRSD is attributed etiologically to alterations of the circadian timekeeping system and/or a misalignment between endogenous circadian rhythm and exogenous factors that affect sleep timing [8]. The intrinsic circadian period (τ, the free-running period of circadian rhythms in the absence of external cues) is considered to be a critical factor in the pathophysiology of CRSD [9,10].

Familial advanced sleep phase type

Familial advanced sleep phase type (FASPT) is an autosomal dominant genetic disease characterized by extremely early involuntary sleep timing. A missense mutation in the *PER2* gene has been identified in a large pedigree with FASPT. This mutation caused a change from serine to glycine at amino acid 662 (S662G) located in the CKIε binding domain of the PER2 protein and resulted in decreased PER2 phosphorylation [11]. Transgenic mice carrying the mutant S662G *PER2* gene showed a shorter free-running period, τ [12]. In addition, a missense mutation in the *CKIδ* gene was found in another FASPT pedigree. The substitution of threonine with alanine at amino acid 44 of CKIδ reduced enzymatic activity of CKIδ, leading to decreased phosphorylation level of PER2, a target of CKI [13]. The CKIδ T44A mutation shortened τ, as well as the PER2 S662G mutation, in mice. It was previously proposed that decreased phosphorylation of PER2 stabilizes the PER2 protein, thereby enhancing nuclear accumulation of PER2 and leading to a shorter circadian period. Recent studies, however, have shown that decreased PER2 phosphorylation enhances destabilization of PER2 by increasing turnover and degradation of PER2 [14,15]. These findings suggest that the shortening of τ observed in the FASPT models results from enhanced turnover of nuclear PER2 caused either by increased degradation or by reduced nuclear retention. FASPT patients have been reported to have a shorter period of physiological rhythms [16]. Several studies have indicated that the phosphorylation status of circadian clock proteins plays

a critical role in regulating circadian periods [17,18]. Altered τ seems to contribute to the pathogenesis of CRSD.

Delayed sleep phase type

Delayed sleep phase type (DSPT) is characterized by the inability to fall asleep and awaken at a desired time, leading to significantly later sleep onset and wake times. The pathophysiology of DSPT is attributed to longer τ, misaligned phase relationship between endogenous clock and sleep-wake cycles, reduced photic entrainment and/or altered sleep homeostasis. The human *PER3* gene has multiple missense polymorphisms that cause amino acid substitution and a variable number tandem repeat (VNTR) polymorphism that encodes either four or five copies of eighteen amino acids [19]. Association studies have shown that the longer allele (five copies) in *PER3* VNTR polymorphism (*PER3*^{5}) is associated with extreme morning preference and that the shorter allele (four copies) is associated with extreme evening preference and DSPT [20]. *PER3*^{5} homozygotes have been reported to show increased slow-wave sleep in non-rapid eye movement sleep and θ/α activity during wakefulness compared to homozygotes for *PER3*^{4} [21]. These results suggest that the *PER3* polymorphism may be linked to homeostatic regulation of human sleep. The mouse *Per3* gene was thought to be dispensable for circadian rhythm, as PER3-deficient mice did not show altered expression patterns of circadian clock genes in the SCN or altered behavioral rhythm [22]. However, PER3-deficient mice have recently been reported to have a shorter τ and advanced phase of *Per1* rhythm in peripheral tissues compared to wild-type mice. The results suggest that *Per3* may play a role in regulating circadian rhythms in the periphery [23]. Another group has found that PER3-deficient mice had a lower light sensitivity and suggested that *Per3* may be involved in the light input pathway [24]. These findings imply that the function of the *PER3* gene may contribute to the interaction between the circadian system and sleep homeostasis.

Nonentrained type (free-running type)

Nonentrained type is characterized by sleep timing that occurs with a 30-minute to 1-hour delay each day. Nonentrained sleep-wake patterns are usually observed in totally blind people [25-27], whereas the nonentrained patterns are rarely observed in sighted people. It is likely that blind individuals have free-running rhythms due to the loss of photic reception (photic entrainment). Because the τ in humans is not extensively longer than 24 hours (average τ = 24.18 hours) [28] and sighted people are capable of perceiving photic signals, impaired photic entrainment as well as prolonged τ may underlie the pathophysiology of sighted patients with the nonentrained type.

Evaluation of individual circadian phenotypes

FASPT, DSPT and nonentrained type of CRSDs are thought to result from malfunction and/or maladaptation of the circadian system. Evaluation of an individual's circadian phenotype is indispensable to understanding the pathophysiology of CRSD. Individual subjects are required to stay in a laboratory environment free from external cues during a couple of weeks' time to assess circadian rhythms precisely [28-30]. First, rhythmic characteristics of physiological functions (core body temperature, plasma melatonin and plasma cortisol levels) are measured to estimate individual circadian phases. Blood samples are collected over a 40-hour period under constant routine (CR) conditions where masking effects (for example, physical movement, food intake, ambient temperature and light intensity) are minimized (first CR). Next, patients undergo a 28-hour forced desynchrony (FD) protocol (9.33-hour sleep and 18.67-hour wake cycle) followed by a 40-hour CR (second CR). Individual circadian phases are assessed again during the second CR. The intrinsic circadian period, τ, is determined by the difference in circadian phase between the first and second CRs. As described herein, the CR and FD protocols are laborious and costly to perform in a clinical setting. More convenient measurements of circadian phenotypes are required to reduce the patients' burden.

Surrogate measurements for assessing circadian phenotypes

Most cells in peripheral tissues as well as cells in the SCN are equipped with circadian clock components. Brown *et al.* developed a lentiviral luminescence assay system using biopsy samples to measure individual circadian rhythms in fibroblasts [31]. Primary cells derived from skin biopsy samples were introduced with a circadian reporter: the *Bmal1* promoter-driven luciferase gene (*Bmal1-luc*). The luciferase activity under the control of the *Bmal1* promoter showed robust daily rhythms in individual primary fibroblast cells. *Bmal1-luc* rhythms were monitored for several days, and rhythmic characteristics of the luminescence rhythms were evaluated. Independently, we measured clock gene expression in primary fibroblast cells established from individual skin biopsies and observed robust *Bmal1-luc* rhythms (Figure 2). Brown *et al.* found that extreme morning types had shorter periods of fibroblast rhythms compared to extreme evening types [32]. Furthermore, they compared the period length of fibroblast rhythms with that of physiological rhythms in the same subjects and observed a significant correlation between the two

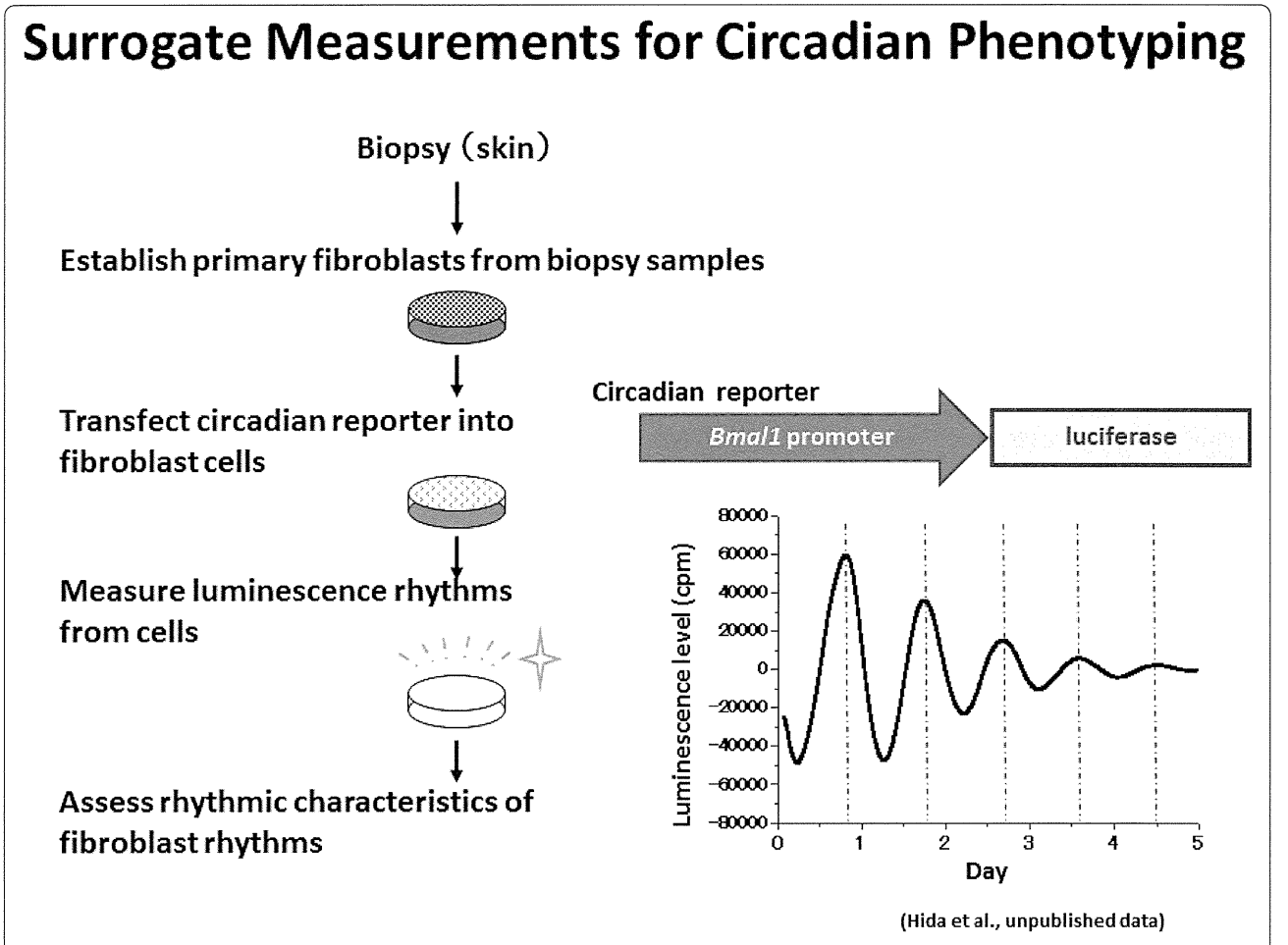

Figure 2 Surrogate measurements for circadian phenotypes.

rhythms. However, they did not observe long fibroblast periods in blind subjects, who had significantly longer physiological rhythms than sighted subjects [33]. The prolonged physiological period observed in the blind subjects may be caused by their previous sleep-wake cycles under constant darkness. The unaltered fibroblast period may be attributed to experimental conditions. Although the reason for this discrepancy is not yet fully understood and further studies are required, surrogate measurements using fibroblast cells should be a powerful tool for assessing individual circadian properties.

Conclusions

Evaluation of circadian phenotypes is indispensable to understanding the pathophysiology and pathogenesis of CRSD. Because conventional protocols for examining individual circadian characteristics are laborious and costly, more convenient measurement methods are required in the clinical setting. The circadian reporter *Bmal1-luc* showed robust daily rhythms in primary fibroblast cells derived from individual skin biopsies. The fibroblast rhythms are associated with chronotypes (morningness vs eveningness preference) and physiological rhythms. Surrogate measurements using fibroblast cells would be a powerful tool for the assessment of individual circadian properties and could lead to providing personalized medicine for CRSD.

Acknowledgements

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Authors' contributions

AH wrote the manuscript and performed circadian phenotyping. SK and KM edited the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Individual Traits and Environmental Factors Influencing Sleep Timing: A Study of 225 Japanese Couples

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Behavioral and physiological processes, such as sleep-wakefulness, thermoregulation, and hormone secretion, exhibit 24-h rhythms in most organisms. These biological rhythms are driven by the circadian clock system and are entrained by the external environment, which in the case of humans includes social time schedules. Couples might be ideal experimental subjects to discriminate between individual traits and environmental factors, as they share lifestyle habits but not genetic backgrounds. In this study, sleep timing was compared between married Japanese couples (n = 225) who had lived together for 1 yr or more (mean 17 yrs). Additionally, the authors evaluated the influence of individual traits and environmental factors on an individual's sleep timing per each couple. The results reveal that the sleep timings of a couple are mainly associated with the chronotypes of the husband and wife, whereas the sleep timings are significantly influenced by certain environmental factors. The findings suggest that chronotype remains one of the major determinants of an individual's sleep onset and wake times. Understanding an individual's chronotype may help improve the quality of life issues surrounding sleep. (Author correspondence: mishima@ncnp.go.jp)

Keywords: Chronotype, Circadian rhythms, Lifestyle habit, Society, Spouse

INTRODUCTION

The preferred timing of daily activities shows great variation among individuals. The type of individual difference known as morningness-eveningness preference (chronoytpe) has been well studied by questionnaires, including the 19-item self-report Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (Horne & Östberg, 1976). Morning types fall asleep and get up earlier than intermediate types, and still earlier than evening types (Horne & Östberg, 1976; Kerkhof, 1998; Tzischinsky & Shochat, 2011). Similarly, phases of physiological rhythms, such as core body temperature and the secretion of melatonin, cortisol, or thyroid-stimulating hormone, are advanced in morning types compared to intermediate types, and more so compared to evening types (Baehr et al., 2000; Duffy et al., 1999). Another questionnaire, the Munich ChronoType Questionnaire (MCTQ), developed by Roenneberg et al. (2003), collects data on actual sleep and wake times on work days and free days, and studies by Roenneberg et al. and others have shown age- and sex-related differences in chronotype (Adan & Natale, 2002; Carskadon et al., 1998; Randler, 2008, Roenneberg, 2004; Roenneberg et al., 2004). People have an early chronotype in childhood, which becomes later during puberty and adolescence, before returning to an earlier one, with an early sleep timing, in the late 20s. Generally, males prefer evening activities, whereas females prefer morning ones, but this sex-related difference disappears in the elderly (Foster & Roenneberg, 2008; Roenneberg et al., 2003). An individual's chronotype has also been shown to depend on dawn/dusk times, and the human circadian clock is predominantly entrained to sun time (Martinez-Nicolas et al., 2011; Roenneberg et al., 2007). These findings suggest that chronotype is associated with the circadian clock system.

The daily rhythms of behavior and physiology driven by the circadian clock system are entrained to environmental cues, such as light exposure, food intake, and work schedules, enabling us to adapt to changes in the external environment (Foster & Roenneberg, 2008; Gachon et al., 2004; Pittendrigh & Daan; 1974, Takahashi

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et al., 2008). Sleep-wake timing is one such rhythm that is influenced by both the circadian clock system and the external environment. Due to new social needs, most people in modern society are expected to adjust themselves to different time schedules (Åkerstedt et al., 2010; Wittmann et al., 2006). In this sense, environmental factors such as social time cues and lifestyle habits might strongly impact on an individual's sleep timing.

Couples might be ideal experimental subjects to discriminate between individual traits and environmental factors, as they share lifestyle habits, but not genetic backgrounds as in the case of twins (Barclay et al., 2010). Accordingly, in this study we evaluated the individual differences in sleep timing by comparing sleep onset time, wake time, and mid-sleep time between the spouses of 225 married couples who shared daily routines and housing for longer than or equal to a 1-yr period (average 17 yrs). Furthermore, we assessed the influence of individual traits (age, chronotype, and depressive mood) and environmental factors (work schedule, spouse's sleep timing, and lifestyle habits) on the determination of sleep onset and wake times.

METHODS

Subjects

The study population consisted of 225 married couples, part of a larger cohort of 1814 Japanese participants studied by Kitamura et al. (2010). The mean ± SD age of the husbands and wives were 44.39 ± 10.69 yrs and 42.12 ± 10.05 yrs, respectively (range 22–73 yrs and 21–72 yrs, respectively). The couples had lived together for between 1 and 48 yrs (mean ± SD: 17.04 ± 10.72 yrs), ate meals together 0–21 (mean ± SD: 9.51 ± 4.18) times/wk, and shared a bedroom 87.11% of the time. In relation to work patterns, 43 males (19.1% of husbands) and 81 females (36.0% of wives) were nightshift workers 1–2 times/wk, 12 males (5.3% of husbands) and 22 females (9.8% of wives) 3–4 times/wk, 9 males (4.0% of husband) and 5 female (2.2% of wives) ≥5 times/wk. The protocol was approved by the Institutional Ethics Committee of National Center of Neurology and Psychiatry. Written informed consent was obtained from each subject. The protocol and all the procedures were in agreement with the Declaration of Helsinki and met the ethical standards of the journal (Portaluppi et al., 2010).

Self-Assessment

The Japanese versions of all the listed questionnaires were used in this study. The Horne-Östberg MEQ (Horne & Östberg, 1976) was administered to assess subjects' diurnal preferences; its validity was previously confirmed in a Japanese population (Ishihara et al., 1984). Since chronotypes have been shown to change with age, age-adjusted MEQ scores were used to rate individuals' chronotypes: age-adjusted MEQ scores of 16–41 denote evening types, 42–58 denote intermediate types, and 59–86 denote morning types. Sleep quality and depressive mood were evaluated by the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977), respectively, to assess the presence/absence of depression and sleep disorders that could strongly modify the sleep state in each subject. A PSQI total score >5 was considered indicative of poor sleep quality, and a CES-D score ≥16 was considered indicative of depressive symptomatology.

Statistical Analysis

Sleep onset time (SOT) and wake time (WT) for the past month were determined by the values given in the PSQI. The sleep parameters were not obtained separately for work days or free days. Mid-sleep time (MT) was calculated as the midpoint between sleep onset time and wake time. Pearson's correlation analysis was performed to ascertain whether sleep onset time, wake time, or mid-sleep time was correlated between husband and wife, and to determine if the number of years each couple lived together correlated with absolute differences between husband and wife in terms of sleep onset time (ΔSO), wake time (ΔWT), or mid-sleep time (ΔMT). Statistical analyses were performed using SPSS version 11. Noncontinuous variables were analyzed as categorical data. Full model multiple regression analysis was performed to assess the influence of individual traits and external factors on a husband's or wife's sleep timing (sleep onset time or wake time) between spouses for the 225 couples. Variables tested in the analysis for individual traits were (i) age, (ii) chronotype, and (iii) presence of depressive mood (CES-D); and for environmental factors: (i) shiftwork schedule, (ii) spouse's shiftwork schedule, (iii) spouse's sleep onset time, (iv) spouse's wake time, (v) sharing a bedroom (not a sharing a bed but sleeping in the same room as is common in Japanese culture), (vi) number of years living together, and (vii) number of times/wk eating meals (breakfast, lunch, and supper) together. The variables of "chronotype" and "presence of depressive mood" were categorized according to the cutoff points described above in the section on Self-Assessment, and the variables of "shiftwork schedule," "spouse's shiftwork schedule," and "spouse's wake time" were categorized as described above in the section on Subjects. Variables with a p value <.05 were considered to be statistically significant.

RESULTS

Among the total of 450 participants, 79 males (35.1% of husbands) and 62 females (27.6% of wives) were defined as morning types (M), 125 males (55.6% of husbands) and 154 females (68.4% of wives) as intermediate types (I), and 21 males (9.3% of husbands) and 9 females (4.0% of wives) as evening types (E). Fifty-six males (24.9% of husbands) and 79 females (35.1% of wives) had poor sleep quality. In addition, 40 males (17.8% of husbands) and 63 females (28.0% of wives) had depressive mood. Out of the 225 couples, 120 (53.3%) had the same chronotypes (husband and wife: 26 M-M, 93 I-I, and 1

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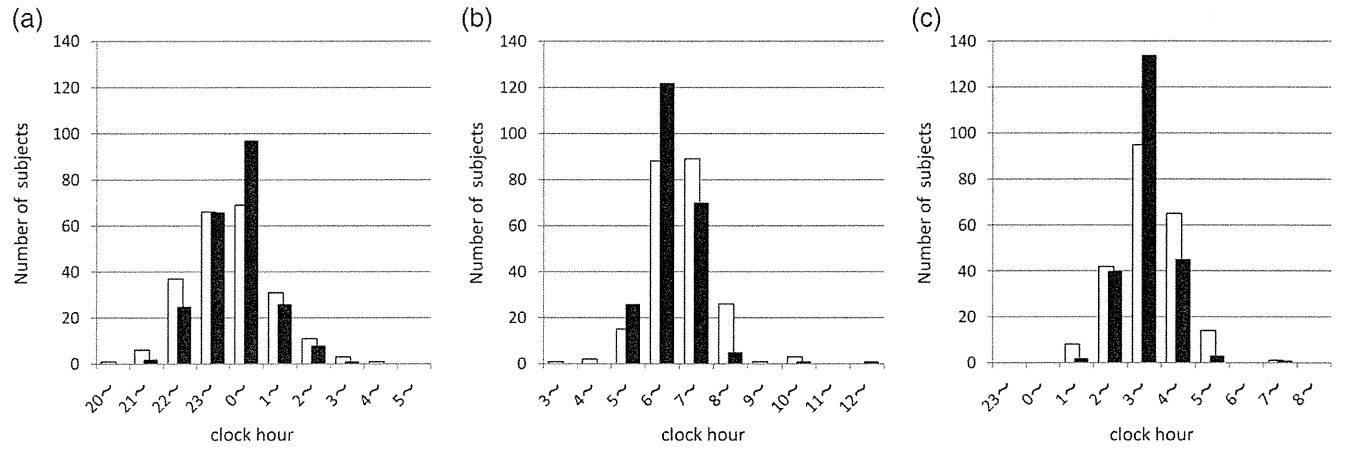

FIGURE 1. Frequency distribution of sleep onset time (A), wake time, (B), and mid-sleep time (C) for 225 husbands (open bar) and their wives (black bar) in our study sample. (A) Husband's sleep onset times ranged from 19:45 to 04:00 h, whereas wife's ranged from 20:35 to 02:30 h. (B) Husband's wake times ranged from 03:00 to 10:00 h, whereas wife's ranged from 04:30 to 11:30 h. (C) Husband's mid-sleep times ranged from 00:05 to 06:45 h, whereas wife's ranged from 00:43 to 07:00 h.

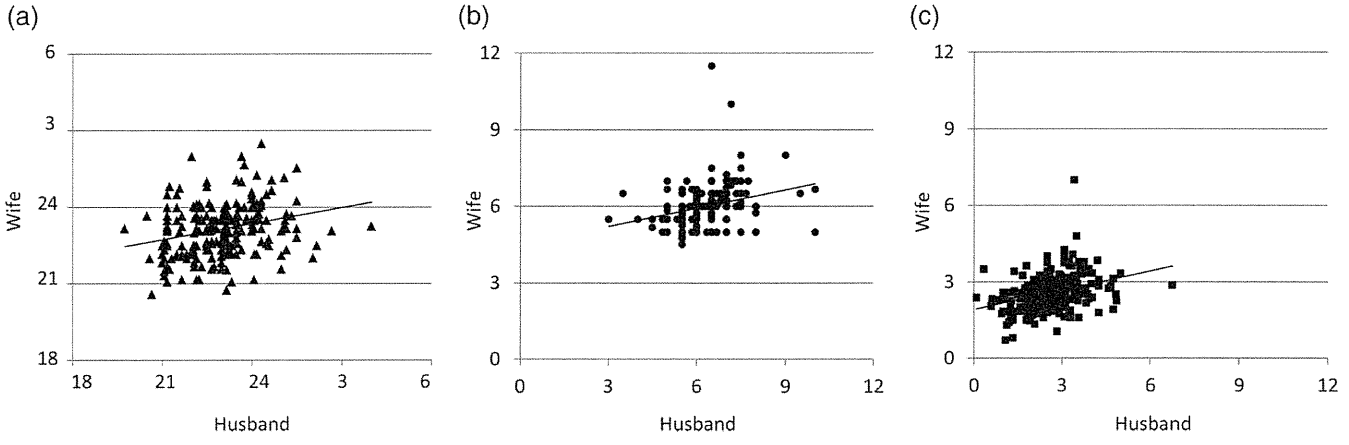

FIGURE 2. Comparison of (A) sleep onset time, (B) wake time, and (C) mid-sleep time between the husband (x-axis) and wife (y-axis) of 225 couples. Positive correlation was found between husband and wife's sleep onset times ($R = .259$, $p < .001$), wake times ($R = .285$, $p < .001$), and mid-sleep times ($R = .345$, $p < .001$).

E-E), whereas 105 (46.7%) had different chronotypes (husband and wife: 48 M-I, 5 M-E, 29 I-M, 3 I-E, 7 E-M, and 13 E-I). Couples did not differ by chronotype distribution ($\chi^2_4 = 5.30$, $p = .258$), and neither sleep quality distribution ($\chi^2_1 = .043$, $p = .837$) nor depressive mood distribution ($\chi^2_1 = .216$, $p = .642$) differed for the various combinations of chronotypes between husband and wife.

Sleep timing followed a normal distribution and varied widely among individuals (Figure 1). Husband's sleep onset time ranged from 19:45 to 04:00 h (mean ± SD: 23:00 ± 01:16 h), wake time from 03:00 to 10:00 h (mean ± SD: 06:21 ± 00:54 h), and mid-sleep time from 00:05 to 06:45 h (mean ± SD: 02:40 ± 00:57 h), whereas the corresponding values for the wife were 20:35 to 02:30 h (mean ± SD: 23:08 ± 01:01 h), 04:30 to 11:30 h (mean ± SD: 06:01 ± 00:46 h), and 00:43 to 07:00 h (mean ± SD: 02:35 ± 00:42 h). Sleep onset time, wake time, and mid-sleep time were compared between the husband and wife for each couple (Figure 2). A positive correlation was seen between spouses for sleep onset time ($R = .259$, $p < .001$), wake time ($R = .285$, $p < .001$), and mid-sleep time ($R = .345$, $p < .001$). On the contrary, there was no correlation between spouses for age-adjusted MEQ score ($R = .078$, $p = .244$). The absolute difference between spouses in terms of SO, WT, and MT (i.e., ΔSO, ΔMT, and ΔWT) ranged from .00 to 4.75 h (mean ± SD: 1.03 ± .95 h), from .00 to 5.00 h (mean ± SD: .72 ± .77 h), and from .00 to 3.88 h (mean ± SD: .72 ± .65 h), respectively. No significant correlation was seen between years living together and ΔSO ($R = .069$, $p = .303$), ΔWT ($R = -.064$, $p = .341$), or ΔMT ($R = -.006$, $p = .928$) (Figure 3).

Table 1 lists the influence of individual traits and environmental factors on husband's sleep timing. Husband's SOT was mainly influenced by his chronotype, followed by number of meals/wk eaten together. Husband's SOT was not related to his age, his depressive mood, his or his wife's shiftwork schedule, wife's SOT, wife's WT, sharing a bedroom, or years living together.

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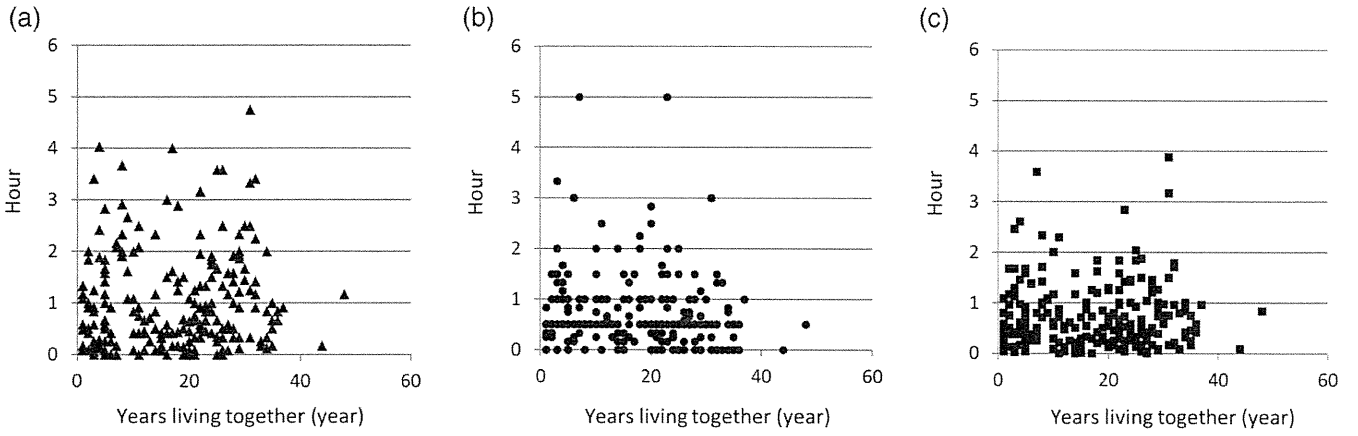

FIGURE 3. Comparison of absolute differences between husband and wife in (A) sleep onset time (ΔSO), (B) wake time (ΔWT), and (C) mid-sleep time (ΔMT) with number of years the couple had lived together. The years of living together did not correlate closely with either ΔSO ($R = .069$, $p = .303$), ΔWT ($R = -.064$, $p = .341$), or ΔMT ($R = -.006$, $p = .928$).

Similarly, husband's WT was mainly influenced by his own chronotype, followed by his wife's WT. No relationship was found between husband's WT and his age, his depressive mood, his or his wife's shiftwork schedule, wife's SOT, sharing a bedroom, years living together, or number of meals/wk eaten together. Overall, husband's SOT and WT were mainly and strongly associated with his chronotype.

Table 2lists the influence of individual traits and environmental factors on wife's sleep timing. Wife's SOT was mainly influenced by her chronotype, followed by husband's shiftwork schedule and husband's SOT. Her SOT showed no relationship with her age, her depressive mood, her shiftwork schedule, husband's WT, sharing a bedroom, years living together, or number of meal eaten times/wk together. Wife's WT was influenced mainly by her chronotype, followed by number of meals/wk eaten together and husband's WT. In contrast, wife's age, her depressive mood, her and her husband's shiftwork schedules, husband's SOT, sharing a bedroom, and years living together were not related to her WT. Overall, wife's sleep timing was

TABLE 1. Influence of individual traits and environmental factors on husband's sleep timing

Husband's sleep onset time	β	p
Age	0.199	0.195
Chronotype	0.537	**<.001**
Depressive mood	−0.028	0.602
Shiftwork schedule	−0.045	0.416
Wife's shiftwork schedule	−0.043	0.445
Wife's sleep onset time	0.106	0.061
Wife's wake time	0.095	0.095
Sharing bedroom	0.035	0.514
Years living together	−0.204	0.180
Meal times a week together	−0.157	**0.007**
$R = 0.649$; $F(10,214) = 15.601$; $p < 0.001$		
Husband's wake time	β	p
Age	−0.259	0.101
Chronotype	0.435	**<0.001**
Depressive mood	0.078	0.155
Shiftwork schedule	0.072	0.210
Wife's shiftwork schedule	0.016	0.781
Wife's sleep onset time	0.066	0.255
Wife's wake time	0.124	**0.034**
Sharing bedroom	0.086	0.121
Years living together	0.130	0.404
Meal times a week together	−0.068	0.253
$R = .623$; $F(10,214) = 13.589$; $p < .001$		

Note: Boldface = significance.

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TABLE 2. Influence of individual traits and environmental factors on wife's sleep timing

Wife's sleep onset time	β	p
Age	0.112	0.511
Chronotype	0.209	**0.002**
Depressive mood	0.117	0.063
Shiftwork schedule	0.028	0.680
Husband's shiftwork schedule	−0.176	**0.008**
Husband's sleep onset time	0.179	**0.023**
Husband's wake time	0.111	0.160
Sharing bedroom	−0.029	0.647
Years living together	−0.015	0.929
Meal times a week together	0.020	0.777
$R = 0.413$; $F(10,214) = 4.404$; $p < 0.001$		

Wife's wake time	β	p
Age	−0.074	0.650
Chronotype	0.372	**<0.001**
Depressive mood	0.015	0.805
Shiftwork schedule	−0.001	0.991
Husband's shiftwork schedule	0.080	0.201
Husband's sleep onset time	0.076	0.305
Husband's wake time	0.173	**0.022**
Sharing bedroom	−0.001	0.990
Years living together	−0.023	0.887
Meal times a week together	0.181	**0.008**
$R = 0.503$; $F(10,214) = 7.248$; $p < 0.001$		

Note: Boldface = significance.

mainly associated with her chronotype and with her husband's sleep timing.

DISCUSSION

We found that sleep onset time, wake time, and midsleep time did correlate significantly, but not strongly, between husbands and wives who shared daily routines and housing. Furthermore, years living together showed no significant correlation with the differences in sleep timing between husband and wife. Multiple regression analysis showed that an individual's sleep timing was mainly influenced by chronotype. No significant correlation was found between the husband and wife's chronotype in this study. This is in contrast to other studies reporting a significant correlation, although the correlation is thought to be based on initial assortative mating rather than interaction during marriage (Hur et al., 1998; Randler & Kretz, 2011). Taken together, the results suggest that a couple's sleep timings do not synchronize the longer they live together, and thus the saying "Like husband, like wife" may not simply apply in the specific case of sleep habits.

Environmental factors (work schedule, spouse's sleep timing, lifestyle, etc.) have been reported to interfere with individual sleep-wake cycles (Leonhard & Randler, 2009; Meadows et al., 2009; Wittmann et al., 2006; Yamazaki et al., 2005). The data presented here also indicate that spouse's sleep timing, spouse's shiftwork schedule, and number of meals/wk eaten together influence the sleep timing. Notably, wife's SOT was associated with spouse's shiftwork schedule and SOT, although husband's SOT was not. The wife tended to go to bed earlier if her husband was a nightshift worker, and go to bed later if her husband went to bed later. Living together with a spouse appears to be a strong factor influencing women's sleep timing. Most couples sleep with a steady partner, and they report being less satisfied when sleeping alone (Troxel et al., 2007, 2010). It is likely that a husband and wife go to bed together (same timing) if they have a good marital relationship. Troxel et al. showed a bidirectional link between sleep and closeness of the couple's relationship (Hasler & Troxel, 2010; Troxel, 2010); couples with matched sleep-wake timing report a better relationship than those with unmatched sleep-wake timing. These findings imply that the association between sleep and relationship quality might explain the influence of "spouse" on an individual's sleep timing.

There are some limitations in this study. The survey was performed using self-rating questionnaires in a cross-sectional and retrospective design. The present results would have been strengthened if additional data had been collected using other tools, such as sleep logs or actigraphs, and if the study had been conducted in a prospective and longitudinal manner. Also, Leonhard and Randler (2009) have reported that children are a

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strong factor influencing their mother's sleep timing; our data did not include information about children (number, age, sex, etc.). In addition, a major model for sleep regulation is a two-process model, where the two components of circadian drive and homeostatic drive interact with each other to regulate the sleep-wake cycle (Daan et al., 1984). As individual differences in nocturnal sleep pressure have some influence on the preferred timing of the sleep-wake cycles (Mongrain et al., 2006), data on homeostatic drive (slow-wave activity in non-rapid eye movement sleep, etc.) would have provided a better understanding of an individual's sleep timing.

CONCLUSION

The present findings demonstrate that chronotype is the major factor influencing an individual's sleep timing, followed by spouse's sleep timing, spouse's work schedule, or number of meals/wk eaten together. This study suggests that an individual's sleep timing is strongly associated with individual traits and chronotype, although environmental factors do significantly influence sleep onset and wake times. Our findings imply that recognizing an individual's chronotype may help promote better physical, emotional, and mental well-being by improving quality of life issues surrounding sleep.

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Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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気分障害と生物時計システム
——リズム異常をもたらす生物時計機能障害の評価法
Mood disorder and circadian clock system

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◎睡眠覚醒リズムの異常，不眠，過眠などの睡眠障害は，一般の生活者から精神・神経疾患患者まで幅広く認められる．とくに，睡眠覚醒リズムの異常は，うつ病などの気分障害から統合失調症，自閉症を含む多くの精神疾患で併存することが知られている．昼夜逆転による生活リズムの乱れは患者のQOLを低下させるのみならず，精神疾患の再発を助長し，社会復帰を阻害している大きな要因のひとつとなっている．また現代社会では，一般生活者の多くも生活の夜型化やシフトワークなど不規則な生活リズムに悩まされている．このようなリズム異常の背景には，生体リズムを制御する生物時計システムが密接に関係していると考えられており，精神疾患にみられるリズム異常の病態を正しく理解するためには，患者個人の生物時計機能の障害を正確に評価する必要がある．本稿では気分障害に伴うリズム異常の分子病態，ならびに生体組織を利用した患者の生物時計機能の測定法について紹介する．

Key word：気分障害，生体リズム，生物時計，評価方法，生体組織

生体リズムを制御する生物時計システム

睡眠覚醒，メラトニン・コルチゾール分泌量，体温，気分の変動といった行動，内分泌系，代謝系，精神機能系の活動には，約1日24時間を周期とした日内変動が存在する．このリズムは概日リズムとよばれ，哺乳類では脳視床下部・視交叉上核(suprachiasmatic nucleus：SCN)に存在する生物時計(中枢時計)によって駆動し[1]，明暗サイクルや摂食タイミングなどの外因性シグナルにリセットされ，24時間周期の明暗サイクル(昼夜リズム)へ同調する．もっとも強力な同調因子である環境光は，その時刻情報(明期，すなわち昼であること)を網膜視床下部路を経由してSCNへ直接伝え，中枢リズムの位相を同調することで，個体の生体リズムを環境変化に順応させる．このように生物時計システムは，①環境情報の変化を時計本体に伝える入力部，②システムの中枢をなし自律的な24時間リズムを形成する時計本体，そして③時計から発振される概日性シグナルにより生理機能リズムを駆動する出力部から構成されている[2,3]．生物時計機能は中枢のみならず，ほとんどの組織・器官の細胞にも備わっており(末梢時計)，中枢時計から発振される概日サイクルが末梢時計リズムを統合している[4]．

生物時計の分子メカニズム

生物時計システムにかかわるほとんどの遺伝子は，中枢時計SCNにおいて約24時間の転写日周リズムを示し，この時計遺伝子群の転写・翻訳制御にかかわるフィードバックループが生物時計システムの中核をなす[5]．また，リン酸化やユビキチネーションといった蛋白修飾も概日リズムの形成に重要な役割を担っている．転写因子CLOCKとBMAL1はヘテロダイマーを形成し，E-box配

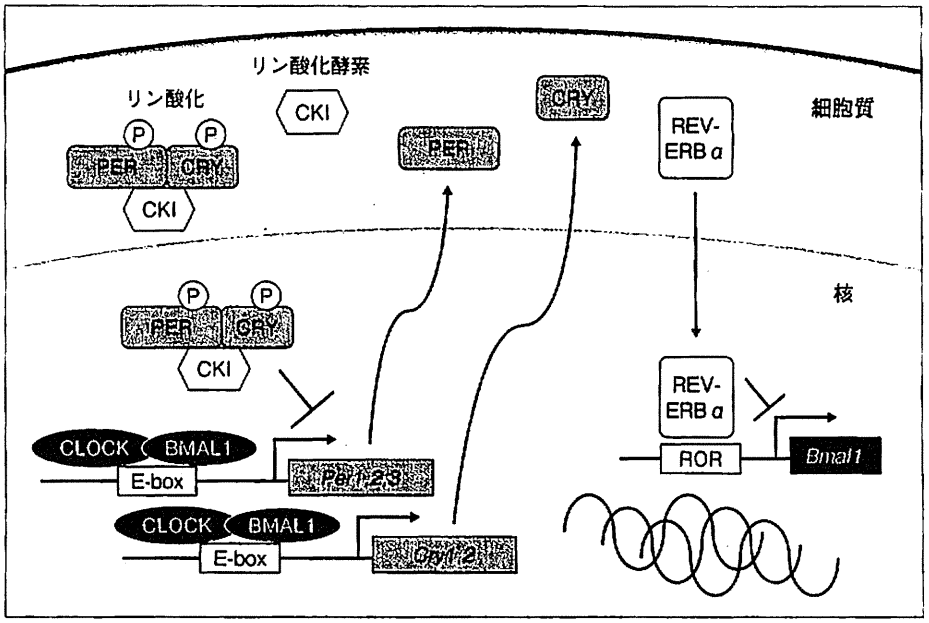

図 1　生物時計システムの分子メカニズム

列を介して DNA に結合することで，時計遺伝子群である *Per*(*Period*)*1*，*Per2*，*Per3*，*Cry*(*Cryptochrome*)*1*，*Cry2* やレチノイン酸関連核内受容体 *Rorα*，*Rorβ*，*Rorγ*，*Rev-Erbα*，*Rev-Erbβ* などの転写を活性化する．転写翻訳後，時計遺伝子産物 PER は CK I (casein kinase I) によりリン酸化修飾を受け，ある定まった量に達したところで CRY と複合体を形成し核内へと移行する．そして，PER：CRY 複合体は CLOCK：BMAL1 によって活性化された自らの転写を抑制するネガティブフィードバックを形成する．一方，同様に CLOCK：BMAL1 の制御下にある核内受容体である RORα と REV-ERBα は，*Bmal1* プロモーター上に存在する RORE 配列に結合し，RORα は *Bmal1* の転写を活性化し，REV-ERBα は *Bmal1* の転写を抑制することが知られている(図 1)．

気分障害とリズム異常

気分障害に特徴的な臨床病態のひとつとして，症状の周期性があげられる．たとえば，冬季うつ病ではうつ症状に季節性が認められる．また，躁うつ病では躁症状とうつ症状が短期間に頻回に切り替わるなど，より短い周期性を示すことが知られている．また，うつ病では午前中に症状が強いなど日内変動が認められることが多い．このほか数多くの先行研究により，冬季うつ病や躁うつ病患者では気分調整の異常に加えて，生物時計の調節障害が併存していることが明らかにされている[6]．たとえば，気分障害患者では睡眠覚醒リズムの異常や概日リズム周期の短縮など，さまざまな生理機能リズムの位相異常が高頻度に伴うことが知られている[7,8]．

また，気分障害の治療には選択的セロトニン再取込み阻害薬などの抗うつ薬と並んで，光療法も効果的であることが知られている[9]．光は生物時計システムをリセットさせるもっとも強力な同調因子であり，生体のリズム位相を前進あるいは後退させ，位相を調整することができる．冬季うつ病患者に対しても春の訪れを知らせるような光照射を(30 分ほど)行うだけで十分な抗うつ作用があるといわれている[10,11]．このように，光は生体リズム同調能と抗うつ効果をあわせもつ作用因子であり，リズム異常を伴う気分障害にとって非常に有効な治療法と考えられる．

気分調節と生物時計

気分障害の発症にはセロトニン・ノルアドレナリン・ドパミンなどのモノアミン神経系の機能障