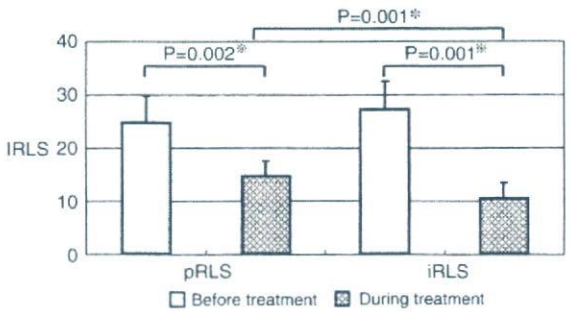

Fig. 3. Comparison of the change in IRLS during treatment in each patient group. Scores of IRLS were not different between pRLS and iRLS before treatment. After starting the treatment on RLS, the score was significantly improved in both groups (Wilcoxon's ranking sum test, pRLS; $p=0.002$, iRLS; $p=0.001$). During treatment, the pRLS scores were significantly higher than that of iRLS (Mann–Whitney U test, $p=0.001$). Scores are shown as mean±S.D. * indicates a significant difference between two groups by Mann–Whitney U test. ※ indicates a significant difference between before and during treatment in each group by Wilcox ranking sum test.

vs the iRLS group, despite the absence of a statistically significant gender difference. Regarding family history of RLS, the rate was significantly lower in pRLS patients ($p=0.036$). As for iron variables, serum values of iron and feritin did not differ between groups. Regarding subjective sleep disturbance measures, PSQI and IRLS results did not differ between the two groups (Table 1).

Comparison of PSG parameters showed no difference in the variables between the two groups, with the exception of the PLM index (PLMI), which was significantly lower in the pRLS patients ($p=0.002$). Fewer pRLS patients had pathological PLMI (PLMI>5) [18] compared with iRLS patients ($p=0.011$). The PLMS-related arousal index was also smaller in pRLS than in iRLS patients, but the difference did not reach significance ($p=0.058$). As for the results of the SIT, neither the SIT index nor the maximal values of the VAS differed between the two groups (Table 2).

RLS symptoms of all patients in both groups were treated with DA and/or CLZ. In pRLS patients, the doses of these medications were apparently higher than those in the iRLS patients both before and during treatment for RLS (Table. 3). However, the dose increase in the amount of DA during treatment for RLS in the pRLS group was not different from that used in the iRLS group. On the other hand, doses of CLZ were twice as high in the pRLS group compared to the iRLS group (Table 3). As shown in Fig. 3, significant improvement of IRLS after treatment was noted in both groups. However, IRLS scores after treatment were significantly higher in the pRLS group compared with the iRLS group ($p=0.001$) (Fig. 3).

4. Discussion

In our sample, the occurrence of RLS was mostly concentrated in the period within 5 years after the onset of PD. RLS symptoms did not precede PD symptoms in pRLS patients, indicating that RLS does not appear to be a predictor of PD. These findings were consistent with our previous results obtained from an epidemiological survey [11], and we speculated that RLS was a PD comorbidity occurring mainly in the early years of the disease, despite the lack of a relationship between the severity of RLS and PD.

Our patients with pRLS showed a remarkably low rate of RLS family history, as we reported previously [11]. This finding indicated that the occurrence of pRLS was strongly related to the disease mechanism of PD itself, rather than to a genetic basis. On the other hand, half of the iRLS patients with idiopathic RLS had a positive family history. This finding is compatible with reports showing a genetic predisposition in iRLS [22].

From the results of both subjective parameters, including the IRLS and PSQI, as well as findings of both the SIT and PSG, it was revealed that the severity of RLS symptoms and their influence on subjective and objective sleep quality are quite similar between the two patient groups. The length of RLS morbidity was shorter in pRLS patients than in iRLS patients. These results, taken together with the fact that pRLS patients were already taking dopaminergic agents, which are known to alleviate RLS symptoms, suggest that it is possible that RLS in patients with PD might progress faster and become more serious in the absence of treatment with dopaminergic drugs than in iRLS. Regarding PLMI, the value before treatment for RLS was significantly smaller in pRLS than iRLS. With regard to this point, Wetter et al. reported that drug-free PD patients showed increased PLMI [23]. The reason for the discrepancy between the two studies is unclear. However, it is plausible that the PLMs in pRLS patients had been suppressed already by DA medications before initiation of treatment focusing on the RLS.

When speculating on the mechanism of RLS in patients with PD, the finding that RLS symptoms appeared after the initiation of DA in more than half of the patients with pRLS and the high age at onset of the disorder should be taken into consideration. We speculated that high prevalence and early aggravation of the disorder under DA medication in pRLS patients can be attributed to a large extent to the confluence of degeneration of dopaminergic neurons due to PD and physiological aging. Although the diencephalospinal dopamine pathway is rarely pathologically involved in idiopathic PD [24,25], this circuit is a plausible substrate in iRLS and almost 20% of PD patients [26–28]. Moreover, somatic motor neuron activity is known to be mediated through the diencephalospinal tract [29]. We believe that the frequent occurrence of RLS in PD patients is strongly related to the degeneration of this pathway. After further increases in the dose of DA and/or CLZ for the treatment of RLS, both of which are well known to be effective treatment in the disorder [30–32], symptoms of RLS in the patients with pRLS were more severe than in those with iRLS, although the doses of both drug types were quite similar between the two groups. From this finding, we want to raise the

possibility that RLS symptoms in pRLS are refractory to standard treatment [12] due to irreversible degeneration of the dopaminergic system. However, we should consider the smaller percentage increase in the dose of DA in pRLS patients, because they had been medicated with DA already. Future research is necessary to draw a conclusion about this point.

The results of this study indicated that pRLS could be a pathological condition, in which the severity of RLS itself is similar (or greater) compared to that of iRLS. However, our study suffers from a limitation that all of our pRLS patients were receiving treatment with DA at the investigation. Accordingly, the results obtained in our pRLS patients were likely to be affected by the actions of these medications (i.e., RLS symptoms could be alleviated [33] or augmented [34] by using DA in some patients). To make a comparison of the true characteristics between these two groups, the inclusion of drug-free patients would be desirable, but is unfortunately next to impossible.

However, we can emphasize that many pRLS patients in clinical settings are elderly, and RLS in this group occurs in the early years of PD without a genetic predisposition. Moreover, the response to standard treatment for RLS could be poorer in this group. A better alternative for treatment would be desirable in the treatment-resistant group.

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CLINICAL REVIEW

Circadian rhythm sleep disorders: Characteristics and entrainment pathology in delayed sleep phase and non-24 sleep–wake syndrome ☆

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KEYWORDS
Non-24-h sleep–wake rhythm;
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Body temperature;
Depression;
Sleep homeostasis

Summary This paper presents a clinical review of delayed sleep phase syndrome (DSPS) and non-24-h sleep–wake syndrome (non-24). These syndromes seem to be common and under-recognized in society, not only in the blind, but also typically emerging during adolescence. Both types of syndrome can appear alternatively or intermittently in an individual patient. Psychiatric problems are also common in both syndromes. DSPS and non-24 could share a common circadian rhythm pathology in terms of clinical process and biological evidence. The biological basis is characterized by a longer sleep period, a prolonged interval from the body temperature nadir-to-sleep offset, a relatively advanced temperature rhythm, lower sleep propensity after total sleep deprivation, and higher sensitivity to light than in normal controls.

There are multiple lines of evidence suggesting dysfunctions at the behavioral, physiological and genetic levels. Treatment procedures and prevention of the syndromes require further attention using behavioral, environmental, and psychiatric approaches, since an increasing number of patients in modern society suffer from these disorders.

Introduction

The sleep–wake rhythm in humans is regulated by the circadian timing system, and disorders of this system are known as circadian rhythm sleep disorders (CRSD), which can have multiple etiology but result in maladjustment of the biological clock with respect to the environment. Persons suffering from these sleep disorders develop an inability to

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASPS, advanced sleep phase syndrome; BT, body temperature; CRSD, circadian rhythm sleep disorder; DSPS, delayed sleep phase syndrome; M-E, morningness-eveningness; Non-24, non-24-h sleep–wake syndrome; NOS, not otherwise specified; PRC, phase response curve

☆ Dedicated to Anna Wirz-Justice in recognition of her contributions to the field made during her career at the Psychiatric University Clinics Basel.

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fall asleep at the desired time at night and to wake up at the desired time in the morning. They usually force themselves to adjust to the environmental light–dark (or social) cycle, but are not often successful and may develop physical and psychological complaints during waking hours, i.e. sleepiness, fatigue, headache, decreased appetite, or depressed mood.

Patients with CRSD often have difficulty maintaining ordinary social lives, and some of them lose their jobs or fail to attend school. There has been an increasing awareness of persistent CRSDs. In our 24-h society, under conditions that may disrupt normal day–night activities, such as shift work, transmeridian flight, or exposure to bright light late at night, desynchronization of circadian rhythms can occur, resulting in CRSD.

The pathophysiology or pathogenesis of CRSD has not been fully elucidated and it cannot be subsumed under a single disorder. The syndrome is thought to be multifactorial: social, psychological, and environmental factors as well as biological factors have all been proposed to play important roles in the onset and development of symptoms, but no single factor is sufficient to explain it.

This review focuses on clinical studies of delayed sleep phase syndrome (DSPS) and non-24 h sleep–wake rhythm (non-24), which are representative syndromes in CRSD, from the viewpoints of prevalence, comorbidity, treatment strategies and pathophysiology, and proposes future research directions.

Classification of circadian rhythm sleep disorders

Circadian rhythm sleep disorders can be divided into two major groups (1): those occurring when the physical environment is altered relative to internal circadian timing (e.g. shift work, jetlag); and (2) those occurring when the circadian timing system is altered relative to the external environment (e.g. delayed sleep phase syndrome, non-24, advanced sleep phase syndrome, irregular sleep–wake rhythm). The general criteria for CRSD in the International Classification of Sleep Disorders (ICSD)[1] are defined in Table 1.

Table 1 General criteria for circadian rhythm sleep disorder.

A.	There is a persistent or recurrent pattern of sleep disturbance due primarily to one of the following:
i.	Alterations of the circadian timekeeping system.
ii.	Misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.
B.	The circadian related sleep disruption leads to insomnia, excessive daytime sleepiness, or both.
C.	The sleep disturbance is associated with impairment of social, occupational, or other areas of functioning.

Delayed sleep phase syndrome (CRSD, delayed sleep phase type)

Delayed sleep phase syndrome is caused by an abnormally delayed circadian clock.[2] Sleep onset and wake-up times are both significantly delayed in comparison with conventional sleep–wake times. Typically, patients with DSPS do not get sleepy until the early morning hours, and then sleep until the late morning or early afternoon. In addition to their delayed sleep period, a variety of circadian rhythms such as plasma melatonin, urinary melatonin metabolite excretion, and core body temperature have been reported to be significantly delayed in patients with DSPS.[3–6] DSPS patients are often characterized as "night owls", and when tested with chronotype questionnaires to determine morningness and eveningness, they score on the eveningness end of the scale. Once asleep, provided they are allowed to sleep at their own selected times, they will have normal quality sleep with normal sleep architecture, which will last for a normal time unless it is interrupted by external disturbances.[2] The continuing mismatch between the daily schedule required by the social environment and the individual's circadian sleep–wake pattern creates major social, work, and academic problems. This discrepancy has been given the appropriate and pictorial name of "social jet lag".[7] Sometimes DSPS patients complain of headache, loss of appetite, depressed mood, and loss of concentration. These symptoms could be caused by forced awakening in the morning to adjust their daily lives to social demands.

Evening-type individuals and patients with DSPS share many similar characteristics.[8] However, it is still unclear whether extreme evening-type and DSPS individuals share a common pathology or lie on a continuum. Several published investigations of early and late chronotypes have provided new perspectives on circadian and homeostatic regulation, which are important for addressing the nature of DSPS.[9–15]

Non-24-h sleep–wake syndrome (CRSD, free-running type, non-entrained type, hypernychthemeral syndrome)

Non-24 has been reported to be a rare condition characterized by a chronic steady pattern of about 1-h delays in spontaneous sleep onset and wake-up times in individuals living under normal environmental conditions. It occurs because the intrinsic circadian pacemaker is no longer entrained to a 24-h period and is free running with a non-24-h period, usually slightly longer than 24 h. Because most individuals are usually required to maintain a regular sleep–wake schedule, the clinical picture is of periodically recurring problems with sleep initiation, sleep maintenance, and rising, as the circadian cycle of wakefulness and sleep propensity moves in and out of synchrony with a fixed sleep period time.

Most individuals with non-entrained circadian rhythms are totally blind[16–22] and the failure to entrain circadian rhythms is related to the lack of photic input to the circadian pacemaker. Although the disorder has been considered rare in sighted people, it has been reported to occur in such individuals,[23–34] and most studies of such patients have been individual case reports. Affected patients have not usually been previously properly diagnosed and treated. Social and behavioral factors may contribute to its development. Hayakawa et al.[35] conducted a large-cohort study of sighted patients suffering from non-24, which indicated that, as well as DSPS, the disorder is not rare in individuals in their teens and 20s. This study provided important information on clinical characteristics, which will be discussed later.

Prevalence of CRSD

Although no study has systematically investigated all age groups, the incidence of DSPS has been found to be low in the general population in Japan: 0.13% among all individuals aged 15–54 years.[36] In adolescents, DSPS is reportedly a common cause of insomnia.[37–39] In Norway, 0.17% of DSPS cases were found in an epidemiological study of CRSD.[40] In Japan, symptoms in half of all adult patients with DSPS begin in childhood or adolescence,[41] and may be triggered by a long vacation (day–night reversal) or by exhausting preparation for university exams. The number of cases of DSPS and related disorders seems to have increased in the last few decades, due to many aspects of modern life such as watching TV, playing computer games, or night work, all resulting in a delay of sleep onset time.[42,43] Some of the individuals affected in this way show clear symptoms of DSPS. The frequency of DSPS patients presenting at sleep disorder clinics has been reported to be 6.7–16%.[2,44] Many of these patients seem to have an unsatisfactory and low quality of life.

Dagan and Eisensterin[45] found that among 322 patients with CRSD, 84.6% had DSPS and 12.3% had non-24. Yamadera et al.[41] reported 90 cases (74%) of DSPS and 13 cases (11%) of non-24 among 121 cases of CRSD. Kamei et al.,[46] in an intensive follow-up study of 90 CRSD patients, reported that 64 (71%) had DSPS, and 21 had non-24 (23%). All these reports suggest that DSPS is the most common syndrome in patients with CRSD.

Treatment strategies

Light therapy

It is well accepted that exposure to bright light can dramatically influence both the amplitude and phase of human circadian rhythms, and there is growing evidence that light may affect human physiology and behavior through non-circadian mechanisms as well.

In humans and other mammals, the daily light–dark cycle is a major synchronizer responsible for entrainment of circadian rhythms to the 24-h day, and phase response curves (PRC) to light have been obtained.[47–49] Since in healthy subjects the minimum core body temperature occurs approximately 1–2 h before the habitual time of awakening, the most sensitive phase of PRC to light coincides with sleep, and the timing of the monophasic sleep–wake cycle itself is a major determinant of light input to the pacemaker. Exploiting these responses of the human PRC to light, light therapy for CRSD has been carried out.

Morning bright-light therapy should be applied during the phase-advance period of the PRC, starting with immediate treatment upon spontaneous awakening for several days, advancing the treatment time in increments of about 15–30 min, and applying the treatment for several days at each new time. When the desired wake-up time has been achieved, morning light treatment should be maintained at this constant time.

These procedures are based on findings of previous research. In a clinical setting, there are many limitations to these idealized methods. Further investigations of potentially beneficial approaches should be carried out systematically

with respect to light intensity, timing and duration of light exposure. Ideally, for chronobiological treatments of CRSD, individual evaluation of biological clock time is needed. This can be estimated by measuring the dim light melatonin onset (DLMO)[50] in plasma or saliva. Since this is not always possible before treatment begins, indirect information of body clock time can be rapidly estimated using the (corrected) mid-sleep time as elucidated in the Munich Chronotype Questionnaire[7] (see Roenneberg et al., this issue).

Melatonin treatment

The pineal hormone melatonin manifests a marked circadian rhythm, opposite in phase to the core body temperature rhythm. The general pattern of the PRC to melatonin suggests a near mirror image of the PRC to light: melatonin administered in the early evening induces a phase-advance, and in the early morning, a phase-delay. The circadian phase-shifting properties of melatonin have been applied to several clinical disorders, such as non-24 blind patients with CRSD.[51–60]

Sighted patients with non-24 or DSPS have also been treated successfully by melatonin administration.[61–65] For these disorders it is important to know DLMO before the start of melatonin treatment.[62,63] Melatonin treatment is most effective if administered 5 or 6 h before DLMO.[64] Furthermore, timing correctly according to DLMO may predict the efficacy of melatonin treatment in childhood DSPS.[65]

The efficacy of melatonin for DSPS has been confirmed by placebo-controlled studies.[66–68] Kayumov et al.[68] reported the efficacy of 5 mg of melatonin for some symptoms of DSPS, as confirmed by both objective and subjective measures, in a randomized, double-blind, placebo-controlled crossover study. However, a systematic method has not been established in clinical practice. Further study of the necessity for a daily melatonin profile to correctly time melatonin administration is needed. Although dosage is still an unclear issue, there is a tendency towards using much lower (approximately physiological) dosages.

Combined treatments based on chronobiology

Bright-light therapy and melatonin are known to be effective for DSPS and non-24. However, many patients do not properly respond to these treatments. Combined treatments with melatonin administration before bedtime and bright-light therapy early in the morning have been effective in some patients.[31]

Such a treatment strategy for CRSD has been proposed.[69] As a first step, it is important to reset daily-life schedules and regulate the lighting environment. Chronotherapy[70] may be useful prior to light therapy or melatonin therapy to obtain the desired sleep–wake schedule with one caveat. Although delaying both bedtime and waking time by 3 h, repeated daily until rotation around the clock can achieve the desired sleep–wake schedule, this delaying chronotherapy could lead to non-24 by allowing the system to slip around the clock and cause dangerous situations. Bright-light and/or melatonin treatment are effective for stabilizing the desired sleep–wake schedule. After the patient reaches the target bedtime, and hence rising time, there is a need for rigid adherence to the new schedule. Lighting should be dim for at least several hours before bedtime and should be as bright as possible upon wake time. The use of blue-light filtered sunglasses in the evening might be a useful strategy.[71]

Comorbidity and psychiatric symptoms

Some reports have indicated that depression is the most common psychopathology associated with DSPS.[44,72] However, the relationship between psychiatric symptoms and the biological background of CRSD has not been elucidated.

In our cohort study of 150 consecutive cases,[73] 70% were diagnosed as primary CRSD and the remaining 30% as psychiatric diseases (depression, personality disorders, anxiety disorders, or schizophrenia).

A large cohort study of 57 sighted patients with non-24[35] conducted over a 10-year period has provided important clinical information. The onset of non-24 had occurred during the teenage years in 63% of the cohort. Psychiatric disorders had preceded the onset of non-24 in 16 patients (28%); of the remaining 41 patients, 14 (34%) developed major depression after the onset of non-24.

These studies suggest that there may be a close relationship between psychiatric symptoms and CRSD. Withdrawal from a normal social life due to psychiatric problems is one of the etiologic factors of CRSD. Sighted patients with non-24 may have preceding schizophrenia, bipolar disorder, depression, obsessive–compulsive disorder or schizoid personality.[24,26,27,33] Hayakawa reported that among patients who had no psychiatric problems before the onset of non-24, 34% developed major

depression thereafter. In these patients, the symptoms of depression were exacerbated when their sleep episodes occurred out of phase (i.e., when they slept during the daytime) and were slightly ameliorated when their sleep episode occurred in phase (i.e., when they slept during the night). This suggests the importance of correct phase relationships for good mood, and also that a reduction in exposure to sunlight may be a cause of depression, as described with respect to seasonal affective disorder.[74]

Some patients suffer from both depressive mood and DSPS,[73] and do not respond to antidepressants. However, intensive treatments for sleep disorders using bright light and/or melatonin are simultaneously beneficial for improving the depressive symptoms.[73] These findings indicate that CRSD and depression could share a common pathology on a chronobiological basis.

There have been various studies on the relationship between biological rhythms and depression. Some of the evidence suggests that late rising itself may predispose to depression. Wehr et al.[75] have introduced the circadian-rhythm phase-advance hypothesis, which infers that, in depression, the circadian rhythm is phase-advanced relative to the (delayed) sleep phase. Our previous studies[73,76] have revealed that the sleep phase was delayed relative to the melatonin rhythm in patients with CRSD as compared with controls. Delay of the sleep phase relative to the circadian pacemaker may be an etiologic factor of the depression associated with CRSD. Another possible trigger for this depression is the social disruption caused by CRSD.

Several disorders are also associated with DSPS, i.e., chronic or mild traumatic brain injuries[77–80] and headache.[81] Furthermore, idiopathic sleep onset insomnia in children is strongly associated with DSPS and responds very well to melatonin treatment,[82,83] as does the chronic idiopathic sleep onset insomnia in children with attention-deficit/hyperactivity disorder (ADHD).[84,85]

These recent studies have suggested an association between comorbid diseases and CRSDs, although the mechanisms underlying this association remain to be elucidated.

Biological basis and pathogenesis of CRSD

The exact mechanisms responsible for DSPS are unknown, but are surely multiple in origin. In particular, an abnormal interaction between the endogenous circadian rhythm and the sleep homeostatic process that regulates sleep and wakefulness plays an essential role in the pathophysiology of delayed sleep phase-type CRDS. Altered phase relationships relative to the light–dark cycle are a common feature in patients with delayed sleep disorders.

Voluntary wakefulness until late at night and waking up late in the morning may create an abnormal relationship between the endogenous circadian rhythm and sleep homeostasis. Several factors may contribute to the development of such disorders in these patients, for example changes in the characteristic features of the PRC, or light sensitivity, resulting in melatonin suppression.

Several biological factors possibly related to the pathogenesis of CRSD are as follows.

Sleep length

The mean habitual sleep length in patients with CRSD has been reported to be longer than that in controls; 9–10 h (9.0 ± 1.3 h; mean ± SD) in non-24.[32,35] The circadian periods of the sleep–wake cycles in patients with non-24 are between 24.5 and 25 h (24.8 ± 0.4 h; mean ± SD).

The longer sleep duration in DSPS than in healthy individuals could be socially disadvantageous because of delayed waking in the morning as well as inability to fall asleep at the desired time and staying up late at night.

Temperature rhythm and sleep phase in CRSD

Studies conducted in a time-cue-free isolation environment have demonstrated that sleep onset times cluster around the core body temperature (BT) trough.[86] The BT trough in patients with DSPS and non-24 in our study, which appeared relatively earlier in the sleep period, may indicate a common basis between what happens to humans under temporal isolation and the pathophysiology of these circadian disorders. Studies on the relationship between sleep and temperature in normal controls, and patients with DSPS and non-24 in a semi-constant routine environment have confirmed that (i) sleep length and the interval between the BT trough and sleep offset are significantly longer in non-24 patients than in DSPS patients, and that these values are significantly longer in both types of patients than in controls, and (ii) further analysis of the relative time of the BT trough in the sleep period has shown that it occurs significantly earlier in non-24 and DSPS patients than in controls.[87,88]

Deformity of the phase-advance portion

In humans, the average free-running period of the sleep–wake cycle is somewhat longer than 24 h.[84,87,88] Therefore, to be entrained to the 24-h day, the circadian pacemaker needs to be phase-advanced regularly each day. This capacity of the circadian pacemaker to phase-advance or phase-delay is well described in PRCs.[47,48] Khalsa et al. conducted an intensive study of human PRCs under highly controlled conditions and obtained a comprehensive characterization; phase delays occurred when the light stimulus was applied before the critical phase at the core body temperature minimum and phase advances occurred when the light stimulus was applied after the critical phase in a day, without a dead zone.[49] The shape of the PRC represents a subject's resetting capability. Alternatively, PRCs indicate a range of period lengths to which the circadian pacemaker can be entrained. This range is estimated to be between 23 and 26 h.[89] A more recent study indicates that the range is much smaller with a period of nearly 24 h.[90]

Czeisler et al.[70] have hypothesized that patients with DSPS may have an abnormally small advance portion of the PRC. This means that the range of period length to which the patient can be entrained is limited. This hypothesis can explain the potential resetting capacity of DSPS patients to accomplish a phase-advance equal to the difference between their endogenous free-running period and the 24-h day, as well as their lack of capacity to phase-advance their daily sleep episode to an earlier clock time.

If the PRC has an even smaller phase-advance portion, the patient fails to entrain even to the 24-h day and displays a sleep–wake cycle longer than 24 h (non-24). This might provide an explanation for a patient's failure to entrain to an environmental light–dark cycle. However, no clinical studies have confirmed these hypotheses.

Homeostatic process and circadian rhythm in CRSD

In CRSD, persistent sleep disorders are considered to be due to alterations of the circadian time-keeping system, and the basic homeostatic mechanisms seem to be normal as long as the patients are able to sleep at their desired time of day. However, some patients with CRSD complain of sleep disturbance-associated impairment of social or occupational functioning even if they are allowed to sleep. In such patients, alterations in the length of the circadian period or in the recovery of sleep function after sleep loss could be contributory factors to the development of DSPS. On the basis of this hypothesis, Uchiyama et al.[88] conducted a 24-h sleep deprivation study of patients with DSPS and non-24 under an ultra-short sleep–wake schedule. This revealed that recovery daytime sleep after 24-h sleep deprivation did not occur in these patients. The finding suggests that they may have problems related to the process of sleep homeostasis, which involves accumulating sleep pressure during sleep deprivation, and/or releasing sleep pressure after sleep deprivation. Control subjects can phase-advance sleep onset by increasing homeostatic sleep pressure, while DSPS and non-24 patients fail to advance sleep onset even after sleep deprivation.

In control subjects, after melatonin production has been initiated, sleep propensity increases in parallel with melatonin production, whereas in patients there is a lag of several hours between the onset of melatonin production and that of a major sleep episode. The lag is longer in non-24 than in DSPS. These findings indicate that there may be a phase alteration between the sleep–wake cycle and the circadian pacemaker in DSPS and non-24.

Light sensitivity to melatonin suppression

Czeisler et al.[91] have reported that some totally blind patients display suppression of melatonin secretion when their eyes are exposed to bright light. Such blind patients who displayed light-induced melatonin suppression were free from sleep disturbances, whereas most of those who did not suffered from sleep disturbances, including failure to entrain to a 24-h day. This might provide an explanation for the well-acknowledged clinical fact that some blind patients show loss of entrainment to a 24-h day (non-24), while others can maintain circadian entrainment even at a normal phase. In blind patients, as in all humans, the non-visual retinohypothalamic pathway conveying light information to the suprachiasmatic nuclei seems to play an exclusive role, and may in some patients still be functional even though their visual acuity is zero.

Patients with DSPS fail to synchronize their 24-h cycle at an appropriate phase relationship to the environment, perhaps because of reduced sensitivity to environmental cues, notably light–dark cycles.

Some sighted patients with non-24 have been reported to have decreased sensitivity to the light-induced melatonin-suppression test.[92,93] This

decreased sensitivity to light may play an important role in the failure to entrain.

Aoki et al.[94,95] undertook a series of experiments to investigate the effect of light on melatonin suppression. The studies confirmed that minimum light intensity decreased as duration of exposure increased, indicating that less light intensity than previously reported could suffice for melatonin suppression, and that melatonin suppression in response to light was significantly greater in patients with DSPS than in controls, suggesting hypersensitivity to light in DSPS patients. These results are incompatible with former studies.[91–93] Hypersensitivity of melatonin suppression or of the circadian pacemaker to light may play an important role in the etiology of DSPS; evening light could easily phase-delay or free-run in DSPS or non-24 patients.

Possible hypothesis for the pathology of DSPS and non-24

The longer BT nadir-to-sleep offset interval in DSPS and non-24 compared with control subjects[87] suggests that the effectiveness of the phase-advance portion of the PRC in the morning (rising time) may be masked by the longer sleep episodes, and that consequently, the sleep phase may remain delayed in DSPS patients and show further delay in non-24 patients. This hypothesis contends that the difference between DSPS and non-24 lies in the masking of the phase-advance portion. This may also provide an explanation for the fact that a DSPS-like sleep pattern and a non-24-like sleep pattern can appear in the same patient. Evening bright-light exposure at bedtime could easily trigger phase-delay in DSPS and non-24 patients, since the phase-delay portion of the PRC in the evening (bedtime) may be exposed by the later sleep episode. Furthermore, higher sensitivity to light for melatonin suppression[95] could facilitate the delay of sleep onset even more.

Findings obtained using an ultra-short sleep–wake schedule[88] also support this hypothesis in terms of homeostatic considerations. Normal controls are expected to have two different means of phase-advancing their sleep onset time: increasing homeostatic sleep pressure by sleep deprivation, and phase-advancing the pacemaker by morning light. In contrast, patients are likely to have difficulty in elevating homeostatic sleep pressure. Thus, the only way for such patients to phase-advance sleep timing is to phase-advance the pacemaker.

Genetic factors in the etiology of DSPS and non-24

As with many other types of disease, the genetic basis for CRSD has been investigated. Patients with advanced sleep phase syndrome (ASPS) are reported to have polymorphism in the circadian clock gene.[96,97] The role of the 3111 CLOCK gene in DSPS has been supported by Iwase et al.,[98] and in the human period 3 gene, one of the haplotypes is significantly associated with DSPS.[99] So far, there have been few studies on the circadian period in DSPS and non-24 under a time-free environment, and there are no data to support the hypothesis of a longer period in DSPS and non-24 than in normal subjects. In a clinical study,[35] the period of non-24 patients was shown to be 24.3–24.8 h, which is within the normal range.

Studies of genetic factors associated with light sensitivity could provide further information on the pathogenesis of CRSD, and whether CRSD can be explained by behavioral levels of day/night exposure. Polymorphisms of the period gene may also discriminate between extreme morning and evening types.[100,101] Jones et al.[102] reported age-related changes in the association between a polymorphism in the PER3 gene, and suggested this might explain the evening-preference of younger individuals. Matsuo et al.[103] reported a novel single nucleotide polymorphism in hPer2 associated with diurnal preference in a healthy population. These lines of research could help to clarify whether DSPS is an extreme expression of "eveningness".

Accumulating studies of chronotype[8–11,13–15] have suggested similarities or differences in evening-preference individuals and DSPS patients using chronobiological markers, i.e., EEG records, body temperature and/or melatonin. Baehr et al.[13] reported that evening-type individuals slept during the earlier part of their body temperature curve, similar to DSPS patients, and Liu et al.[104] obtained supporting results in terms of melatonin peak time. Mongrain et al.[105] conducted an intensive investigation of circadian and homeostatic sleep regulation in individuals with either morningness or eveningness preference and concluded that the two regulatory mechanisms differ in the two groups. These studies may provide new insights into the biological basis of why morning-preference individuals are unsuited for night work because of their higher sleep propensity in the evening.

Future considerations

As increasing numbers of patients are presenting with CRSD, there is a need for multidirectional

studies for elucidating the pathophysiology and establishing practical treatments. This review has presented several hypotheses based on our own research. Figure 1 is a schematic representation of CRSD research projects dealing with multiple factors: biological, environmental and/or psychiatric. Such research may help to raise social awareness of CRSD, and its appropriate treatment and prospective prevention in the future.

Patients with CRSD who have psychiatric, psychological or personality disorders have usually been overlooked when treatments are being considered. However, many of these patients, especially those with depression, can be improved by chronobiological treatments. This suggests a close relationship between psychiatric diseases and CRSD. Personality factors related to CRSD should also be considered when designing suitable treatments.[106,107] Increasing numbers of studies have indicated that CRSD can occur in childhood, or can be associated with ADHD, traumatic brain injury or headache. Further studies are needed to clarify the relationship between CRSD and various comorbidities. These lines of research could reveal new aspects that are relevant from the viewpoint of both psychiatry and human chronobiology.

Practice points

1. In clinical practice, a detailed psychiatric interview should be conducted to clarify any comorbidity of CRSD with psychiatric disorders.
2. Patients with psychiatric symptoms should be treated using psychiatric and chronobiological methods, and efforts should be made to find any relationship between psychiatric symptoms and CRSDs.
3. Recognition of the relatively widespread prevalence of DSPS and non-24 should be considered in the discussion of later school starting times, which ironically are most likely to affect those suffering from this type of disorder.

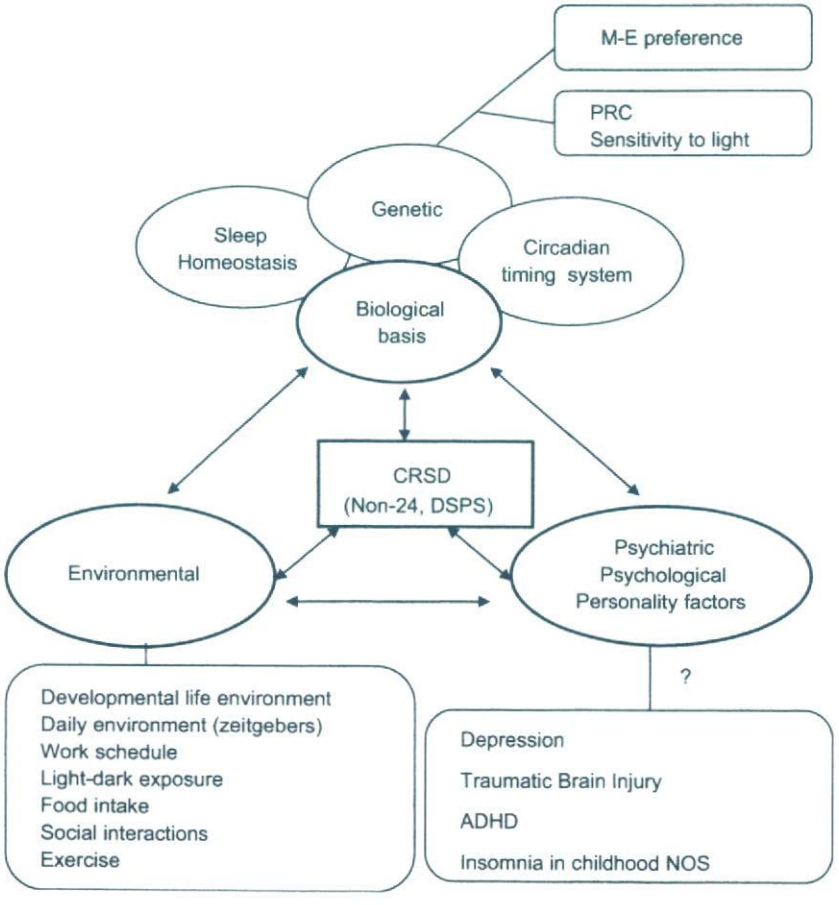

Figure 1 The future direction of CRSD research. ADHD, attention-deficit/hyperactivity disorder; CRSD, circadian rhythm sleep disorder; M-E, morningness-eveningness; NOS, not otherwise specified; PRC, phase response cure.

4. As many measured data as possible on the circadian rhythms of the sleep–wake cycle, body temperature, and/or melatonin level should be obtained in a patient suspected to suffer from CRSD to facilitate appropriate treatment with light and/or melatonin.

Research agenda

1. Cohort study of sleep hours, sleep timing, sleep disturbance and lighting conditions. This could provide information on the environmental, social, and biological basis of CRSD.
2. Obtain information on lifestyle, morningness and eveningness preference throughout development, from the neonatal period through to childhood and adolescence.
3. Future research into the roles of the circadian pacemaker and homeostatic sleep pressure in the emergence of CRSD.
4. Studies of acquisition of the PRC in patients with CRSD to elucidate the pathophysiology of CRSD and to devise practical treatment.
5. Investigation of light-induced phase shifts to test the hypothesis that patients with DSPS show hypersensitivity to night-time light exposure. According to this hypothesis, evening light exposure is particularly important in precipitating DSPS in predisposed persons.
6. The possible roles of conditioned insomnia and inadequate sleep hygiene in the exacerbation of DSPS.

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Acute effects of zolpidem on daytime alertness, psychomotor and physical performance

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Abstract

In a double-blind cross-over study, seven athletes received zolpidem (10 mg) or placebo in two sessions over two nights. Residual effects on subsequent daytime functions were evaluated objectively by measuring psychomotor and physical performance using a combined test of finger dexterity, a simple discriminatory reaction test, critical flicker fusion test (CFF), vertical jump, and 50-m sprint, as well as subjectively, by visual analog scales. Zolpidem shortened self-estimated sleep latency and increased total sleep at nighttime. There was no change in alertness and fatigue scales on the following day in the zolpidem session, but realm of daytime well-being was slightly worsened. The CFF test showed significantly better results in the zolpidem group than in the placebo group. Zolpidem did not have effects in athletic evaluation. Zolpidem has a hypnotic activity without disturbing psychomotor and physical performance on the following day when given to healthy adults, suggesting zolpidem may be used in healthy athletes to adjust their extrinsic sleep disturbances and their consecutive psychomotor and physical impairments.

Keywords: Zolpidem; Critical flicker fusion (CFF) test; Well-being

1. Introduction

It is well known that physical activity or athletic ability cannot be exhibited to its full extent when the subject has a sleep disturbance or insufficient sleep the prior night (Leger et al., 2005). Distinguished athletes for international competitions may also suffer from jet lag, and this is also likely to interfere with their performances. In the past, attempts to use hypnotics for athletes to overcome sleep disturbances the night before sports events were often unsuccessful due to carryover effects of the drug on the following day (Charles et al., 1987; Grobler et al., 2000). Several authors examined effects of sleep deficiency (Mougin et al., 1991; Meney et al., 1998) and circadian rhythm adjustment (Youngstedt and O'Connor, 1999) on performances. Meney et al. (1998) concluded that sleep deprivation has a negative effect on mood and physical parameters in healthy students, although there were considerable inter-individual variations in response to sleep-loss among the subjects.

Recently, several short-acting nonbenzodiazepine hypnotics with different chemical structures (such as zopiclone, zolpidem, zaleplon) that potentiate gamma-aminobutyric acid (GABA) neurotransmission by acting on the GABAA-benzodiazepine receptor complex, have been introduced and are widely used for treatments of acute and chronic insomnia (Leger et al., 2005; Terzano et al., 2003).

Among them, zolpidem is an imidazopyridine with the shortest half-life ($T_{1/2}$ = 1.5–2.4 h) (Terzano et al., 2003). Zolpidem is known to have almost no affinity to benzodiazepine ω2 receptor on GABAA receptor subunit and therefore has less muscle relaxant effect compared as conventional benzodiazepine hypnotics (Terzano et al., 2003). The efficacy of zolpidem on sleep latency and sleep efficiency was assessed in

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1997 by meta-analysis on 16,944 subjects, and adverse effects were reported only in 1.1% (Nowell et al., 1997). Zolpidem has also been shown to be an effective treatment for insomnia when used intermittently (i.e., as-needed basis), and there is no need to increase the prescription dose (Hajak et al., 2002). Thus, the hypnotic effect and its safety profile is well established. Since zolpidem has a short life and no muscle relation effects, it may be also more suitable for the treatment of extrinsic sleep disturbances in athletes.

In the present study, we therefore evaluated acute effects of zolpidem (10 mg) on sleep at night and psychomotor function, physical activity and subjective evaluation on the next day, in healthy university students.

2. Methods

2.1. Subjects

The subjects enrolled in the study included eight healthy male university students (members of the volley-ball team, age: range 18–23; mean ± S.D., 19.8 ± 1.8). All subjects enrolled were right handed. From each subject, the informed consent on the participation in the study was obtained by document after full explanation of the experimental protocol and the aim of the study. This experiment protocol was approved by Akita University Ethical Committee.

Subjects were screened by medical history and physical examinations including any history of severe physical or mental disorder, as well as history of alcohol or drug abuse. Subjects agreed not to use any prescribed medications for a 2-week period prior to the study and they refrained from any alcohol consumption for at least 48 h before testing. On the test days, subjects were not allowed to drink any beverages containing caffeine or to have naps until the end of testing, and they fasted for at least 4 h prior to treatment.

2.2. Procedure

Each subject has both placebo and drug sessions, according to a cross-over double-blind design. Zolpidem or placebo (gelatin capsule) was orally given to each subject in two sessions over two nights with 1-week wash-out period between the sessions. We tested single night administration effect of zolpidem or placebo over following daytime performance. The hypnotic was taken immediately before going to bed (23:00 h) at their own home, and subjects were instructed to get up at 7:00 a.m. the next day. To investigate the remaining effect of the medication on the next day, psychomotor and physical performance tests were carried out at 9:00, 13:00 and 17:00 h, respectively. For subjective evaluation, self-evaluation was performed at the time of getting up in the next morning and every hour from 7:00 to 22:00 h.

2.3. Psychomotor and physical performance tests

The performances tests included a combined test for finger dexterity (CTFD), a simple discriminatory reaction test (SDR), critical flicker fusion test (CFF), vertical jump (VJ), and 50-m sprint in our laboratory and university gymnasium.

The CTFD is a subscale of psychomotor performance tests (an occupational aptitudes test) to estimate finger dexterity. CTFD was performed using a metallic pegboard with 100 holes and 50 pegs and 50 washers. Subjects are required to take a peg on the right hand, and to pick out a washer from a column with the left hand (all subjects enrolled were right handed), then to combine a peg and a washer, and lastly to put those into the holes for ninety seconds. Data was recorded on the numbers of these pegs placed in the holes.

The SDR test is a performance test program (Human Response Checker), a software by NoruPro Light systems™. The test measured the reaction time and the eye-hand coordination skill of the subjects. Subjects were required immediately to right click when a blue circle was lighted and to left click when a white circle was lighted.

CFF tests were conducted by binocular determination of critical flicker fusion frequency. Individual thresholds were determined by the method of limits on three ascending and three descending scales.

For the VJ, the subjects were required to jump with their feet together and to touch a graduated scale drawn on the wall. Mean height for three consecutive jumps was recorded. Finally, the subjects ran a distance of 50 m two times and their mean times were recorded.

Prior to the study, the subjects underwent an extensive training session to preclude learning effects.

2.4. Subjective evaluation

On the first morning after the drug intake, the subjects fulfilled a sleep assessment questionnaire including total sleep time (TST), sleep latency (SL), the number of awakenings, the minutes from awakening to getting out of bed, depth of sleep and mood of awakening. The scale's of sleep and mood of awakening were "deep (5)–light (1)", "good (5)–bad (1)". Every hour from 7:00 to 22:00 h, the subjects evaluated their sleepiness by means of the Stanford sleepiness scale (SSS) (Hoddes et al., 1973) alertness, well-being and fatigue with visual analogue scale (VAS). The scale's extremes were; "very alert–very drowsy", "very good–very bad" and" very tired–very rested".

2.5. Statistical analysis

The repeated-measures ANOVA with a grouping factor (placebo vs. drug sessions) for psychomotor and physical tests was conducted to verify main effects and interactions of time and/or drug. Wilcoxon's signed rank test and paired t-test were used for analyzing subjective evaluation. SSS and VAS were analyzed with repeated-measures three-way ANOVA and main effects and interactions of time or/and drug were verified. Data are presented as mean ± S.E. A p-value less than 0.05 was considered significant.

3. Results

Since one of the eight subjects dropped out of this study between the first and second session because of a training accident unrelated to this study, the analysis of this study was performed on the remaining seven subjects.

3.1. Psychomotor and physical performance tests

The means and standard errors on measures (S.E.M.) of CTFD, SDR, CFF, VJ and 50-m sprint are shown in Table 1.

The results of the CFF test, analyzed by a repeated-measures ANOVA, were significantly better in the zolpidem group than in the placebo group; the main effects of drug ($F = 8.51, p = 0.03$) as well as time ($F = 14.41, p = 0.01$) were significant, but not for the interaction with drug and time.

CTFD, CFF, and the number of answers of SDR showed the significant main effect of time by repeated ANOVAs, but not for the drug effect or the interaction. The VJ and the 50-m sprint did not show any significant differences. Fig. 1 indicates the performance changes with time of CFF.

3.2. Subjective evaluation

Sleep assessment data are summarized in Table 2. In the subjective evaluations, TST was 53 min longer in the zolpidem group ($t = 3.31, p = 0.02$). The time of SL was 32 min shorter in the zolpidem group compared to the placebo group ($t = -2.58$, $p = 0.04$).

Table 1
Psychomotor and physical performance tests

	Zolpidem		Placebo		Interaction	Drug main	Time main
	Mean	S.E.M.	Mean	S.E.M.	Drug × time F	Effect F	Effect F
Combined test for finger dexterity (CTFD) (*n*)	41.19	1.63	39.19	1.97	0.16	0.89	31.76**
CFF (Hz)	39.69	1.14	37.77	0.84	2.59	8.51*	14.04**
Simple discriminatory reaction test (SDR)							
Rate correct response (%)	95.52	2.32	97.30	1.24	0.67	3.11	0.91
Number of answers (*n*)	50.19	0.19	50.43	0.26	0.07	3.95	11.14**
False responses (n)	0.76	0.20	0.71	0.34	0.77	0.08	0.73
Number of responses (*n*)	1.24	1.18	0.24	0.26	0.47	2.86	1.42
Vertical jump (VJ) (cm)	61.05	2.25	60.70	2.28	1.55	1.65	0.82
Fifty-meters sprint (s)	7.44	0.11	7.40	0.10	2.20	0.03	0.55

Psychomotor and physical performance tests were carried out at 9:00, 13:00 and 17:00 h, respectively. Data were analyzed by repeated-measures ANNOVA with a grouping factor (placebo vs. drug group). The results of the CFF test were significantly better in the zolpidem group than in the placebo group.
* $p < 0.05$.
** $p < 0.01$.

In self-evaluation SSS, alertness, well-being and fatigue showed significant main effects of time ($F = 6.49$, $F = 5.53$, $F = 3.04$, $F = 2.64$, all $p = 0.001$) (Table 2). The means of well-being of self-evaluation with VAS showed a significant main effect of drug ($F = 8.34$, $p = 0.001$) (Table 2), and placebo group were better than zolpidem with well-being (Fig. 2).

4. Discussion

In the current study, we observed that zolpidem (10 mg, $T_{1/2} = 1.5$–2.4 h, $\omega 1 \gg \omega 2$) (Terzano et al., 2003) given at night in eight healthy adults enhanced nighttime sleep and improved CFF test performance the following day compared to the placebo session.

Two groups had previously evaluated the use of hypnotics on athletes and its effects on psychomotor function and physical activity tests performed on the next day. Charles et al. (1987) reported on the use of nitrazepam (10 mg, $T_{1/2} = 30$ h, ω receptor selectivity (ωRS): non-selective) that there were no changes in the results of psychomotor function while a remarkable carryover effect (negative effects on awakening and integrity of behavior following wakefulness) was observed. Tafti et al. (1992) used zopiclone (7.5 mg, $T_{1/2} = 4$–5 h, $\omega 1 > \omega 2$)(Terzano et al., 2003) and found some favorable effects on self-estimated sleep quality and daytime sleepiness. However, psychomotor and physical performance tests did not show any significant difference between effects by zopiclone and placebo groups. Therefore, our finding of a significant improvement of CFF in the zolpidem group is remarkable.

The CFF is a sensitive tool to measure arousal levels in humans and a useful index for subjective drowsiness (Smith and Misiak, 1976; Hindmarch, 1982). Smith and Misiak (1976) reported that psychostimulant drugs significantly increase CFF while hypnotics decrease it. Regarding the effects of anxyolytic benzodiazepines on CFF test in the previous reports, CFF results in the medicated groups were generally lower than or equal to those of control groups (Holmberg, 1982; Maddock et al., 1993).

While one study had shown that zopiclone (Tafti et al., 1992) showed no significant differences on the mean of the CFF, Mizuki et al. (1987) verified some residual effects of zopiclone (10 mg) and nitrazepam (10 mg) and found that both decreased the CFF. In contrast, Charles et al. (1987) also estimated adverse effect on athletes' performance with nitrazepam

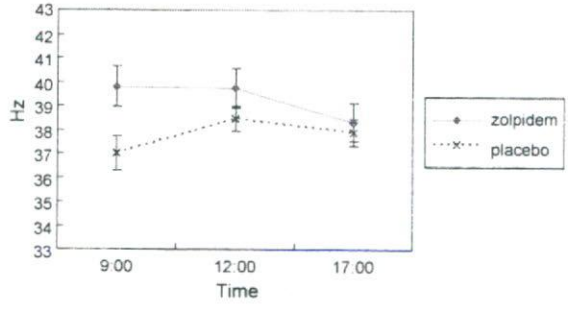

Fig. 1. Effects of a nighttime administration of zolpidem on CFF on the following day. Significant main effects of drug and time on CFF were obtained by repeated-measures ANOVA ($p < 0.05$).

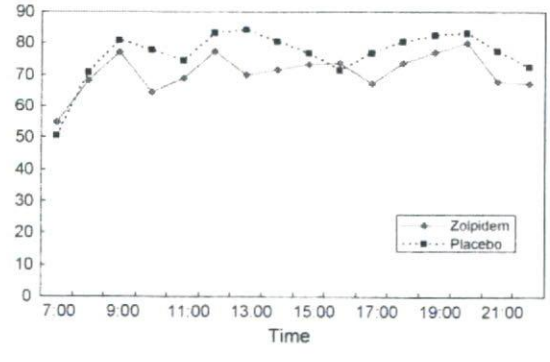

Fig. 2. Effects of a nighttime administration of zolpidem on well-being on the following day. Significant main effects of time ($F = 3.04$, $p = 0.001$) and drug ($F = 8.34$, $p = 0.001$) on well-being were observed. Placebo group had better well-being than zolpidem group.

Table 2
Subjective evaluation

	Zolpidem		Placebo		Paired *t*/Wilcoxon signed-ranks *t*	Interaction	Drug main	Time main
	Mean	S.E.M.	Mean	S.E.M.	*t*/*z*	Drug × time *F*	Effect *F*	Effect *F*
Total sleep time (TST) (min)	447.43	9.16	395.00	12.58	3.31*			
Sleep latency (SL) (min)	19.00	4.86	50.71	13.56	−2.58*			
Number of awakenings (*n*)	1.57	0.53	2.57	0.61	−1.15			
The minutes from awakening to getting out of the bed (min)	10.86	3.62	14.29	4.14	−0.77			
Depth of sleep	3.57	0.37	3.14	0.34	−0.76			
Mood of awakening	2.86	0.26	3.14	0.34	−0.71			
Stanford sleepiness scale (SSS)	2.54	0.28	2.52	0.29		1.25	0.04	6.49**
Alertness (VAS)	70.76	9.42	75.17	7.78		0.65	3.53	5.53**
Well-being (VAS)	70.72	25.43	76.38	16.51		0.41	8.34**	3.04**
Fatigue (VAS)	62.39	9.33	64.54	8.05		0.94	1.34	2.64**

TST and the following five evaluations were asked at the time of getting up in the next morning. The scale's extreme depth of sleep and mood of awakening were "deep (5)–light (1)", "good (5)–bad (1)". SSS and VAS were asked every hour from 7:00 to 22:00 h and were analyzed by repeated-measures ANOVA with a grouping factor (placebo vs. drug group). The scale's of VAS extremes were "very alert–very drowsy", "very good–very bad" and "very tired–very rested". TST was 53 min longer in the zolpidem group. The time of SL was 32 min shorter in the zolpidem group compared with the placebo group. SSS, alertness, well-being and fatigue showed significant main effects of time. The well-being showed a significant main effect of drug ($F = 8.34$, $p = 0.001$).

* $p < 0.05$.

** $p < 0.01$.

(10 mg), temazepam (30 mg, $T_{1/2} = 5.3$ h, $\omega 1 = \omega 2$) and for placebo administration, no significant differences between CFF scores were observed. These results suggest that effects on the CFF of hypnotics may be varied depending on the compound and their half lives and dosage (Smith and Misiak, 1976; Mizuki et al., 1987; Bensimon et al., 1990; Berlin et al., 1993).

Several researchers also reported effects of zolpidem on the CFF. Richens et al. (1993) studied rebound insomnia following cessation of zolpidem and showed that the data of CFF was not significantly different at 9 and 11 h after administration. Bensimon et al. (1990) reported that 20 mg of zolpidem administration brought significantly higher score of CFF than that of flunitrazepam 2 mg ($T_{1/2} = 21.5$ h, ωRS: non-selective) at 10 h after administration. However, they did not check the significant differences in CFF between zolpidem and placebo administrations. Berlin et al. (1993) reported that the score of the CFF at 1.5 h after zolpidem treatment (10 mg) was significantly lower compared to that with placebo treatment but was recovered to the same level as placebo at 4 h after administration. Interestingly, 6–8 h after administration, the score with zolpidem treatment was higher than that with placebo, although the difference was not significant. Improvements of CFF in later hours in this study as well as those in the following morning might be due to the hyperarousal state withdrawal from the zolpidem administration, though hyperarousal was not detected by visual analog scales in our study.

As previously demonstrated by nocturnal polysomnographic study (10 mg, zolpidem) in normal healthy adults (Uchimura et al., 2006), and meta-analysis study with objective and/or subjective evaluations (Nowell et al., 1997), the results of our subjective sleep evaluations also suggest that zolpidem (10 mg) significantly shortened sleep latency and prolonged total sleep time. Therefore, the refreshment of the good nocturnal sleep due to hypnotic administration may also likely contribute to the enhancement of CFF.

Several researchers studied the residual effects of zolpidem. The withdrawal symptoms of zolpidem abuse, such as tremor, agitation, anxiety and seizure were reported (Madrak and Rosenberg, 2001; Roger et al., 1993) to be the same as withdrawal symptoms of benzodiazepines (Chouinard, 2004). Roger et al. (1993) reported "diurnal agitation" as the residual effects of regularly used zolpidem in the elderly people with insomnia. Although none of the subjects claimed any of these side effects, the score of well-being is better in the placebo group than zolpidem group. The functional significance of this result is not known at this moment, and one study rather reported that well-being was enhanced by continuous zolpidem (5 or 10 mg) administration with healthy volunteers who do shifted night work (Hart et al., 2003). Our subjects never took a hypnotic before the enrolment of this study, and they may have felt anxious with subjective feeling if they received hypnotic the night before. As we described before, zolpidem is considered free from residual effects, such as on mood, anxiety, and malaise (Terzano et al., 2003; Bensimon et al., 1990; Allain et al., 2003), consistent with the results that no subjects reported fatigue nor any other side effects.

The limitation of this study are (i) this experiment was conducted in home condition without polysomnography, (ii) the assessment of nocturnal sleep was made only based on subjective scales.

In conclusion, zolpidem has a hypnotic activity without disturbing psychomotor and physical performance on the following day when given to healthy adults. Zolpidem (and other short half-life hyponotics) may therefore be used in healthy subjects, including athletes, to adjust their extrinsic sleep disturbances and their consecutive psychomotor and physical impairments.

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