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 timekeeping 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.

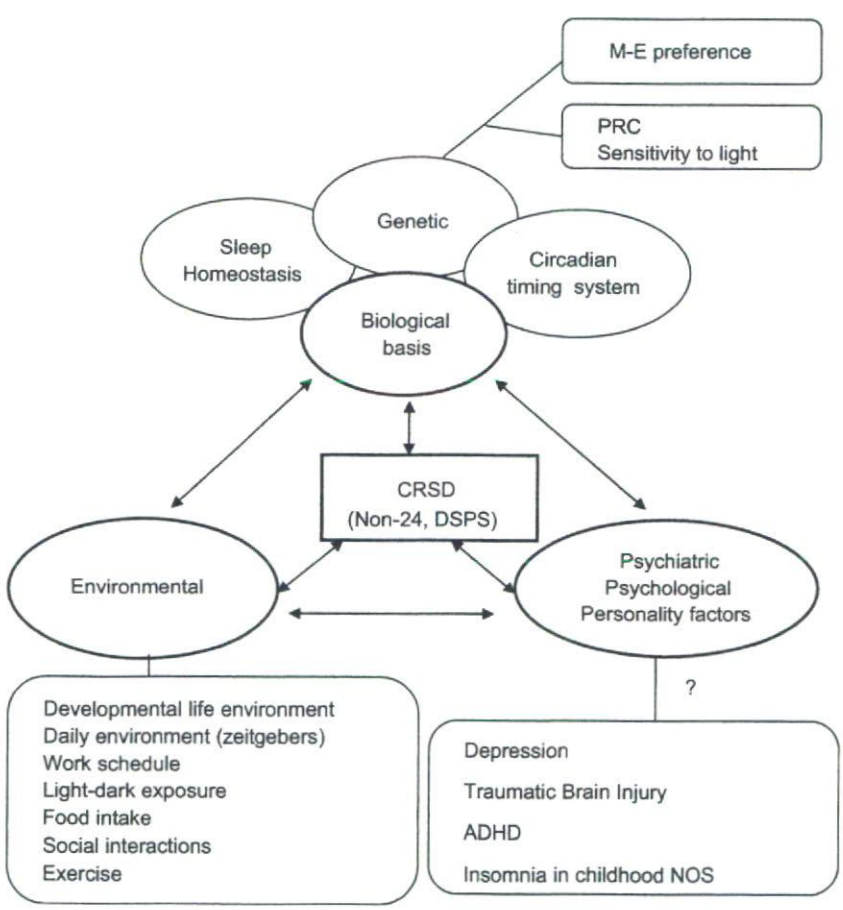

Figure 1 The future direction of CRSD research. ADHD, attention-deficit/hyperactivity disorder; CRSD, circadian rhythm sleep disorder; M-E, morningness-eveningness; NOS, not otherwise specified; PRC, phase response cure.

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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ORIGINAL ARTICLE

Low-dose oral risperidone lengthened sleep duration in healthy participants

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Abstract

We examined the effects of low-dose oral risperidone (RIS) on nocturnal sleep in healthy participants. This study was performed in a placebo-controlled manner in 10 healthy male volunteers (mean age, 23.6 years), with administration of 0.5 mg of RIS oral solution or a placebo in the morning or evening for 2 consecutive days. Each night, polysomnography (PSG) was performed, and PSG data during non-rapid-eye movement (REM) sleep were processed by power spectral analysis. An evening administration of 0.5 mg RIS significantly increased total sleep time, sleep efficiency and sleep stage 3, and significantly decreased total waking time and waking after sleep onset ($P < 0.05$). A morning administration of 0.5 mg RIS significantly increased sleep stage 3 ($P < 0.05$). According to power spectral analysis, the evening administration of RIS significantly increased the theta power ($P < 0.05$) and decreased the beta power ($P < 0.05$) during non-REM sleep. The administration of 0.5 mg oral RIS increases sleep stage 3 and increases total sleep time following evening administration.

Key words: healthy human, polysomnography, risperidone, serotonin, sleep architecture.

INTRODUCTION

Insomnia is a common symptom affecting many patients with mental disorders.[1] Benzodiazepine-based hypnotics represent the first-line medication for the treatment of insomnia. However, some patients develop a tolerance to benzodiazepines.[2] Moreover, benzodiazepines do not lengthen the duration of slow-wave sleep (SWS) and even attenuate SWS, although they usually lengthen sleep duration.[3] This is not a desirable effect, since SWS is reportedly pivotal for cognitive function after sleep.[4] Sleep-inducing drugs with the ability to prolong SWS would probably be preferable in the treatment of insomnia.

Haloperiodol, a traditional antipsychotic, has been shown to induce SWS in patients with schizophrenia after the administration of a high dose.[5] The fact that psychotropic drugs other than benzodiazepine can increase SWS fraction is noteworthy.

The newly developed antipsychotic risperidone (RIS) is not only an antagonist of dopamine D_2 receptors, but also potently antagonizes 5-hydroxytryptamine (5-HT) receptors. The serotonin system has also been shown to be involved in sleep physiology, and antiserotonergic drugs such as ritanserine have been shown to improve sleep quality by increasing SWS.[6] These lines of evidence suggest that a drug that antagonizes both serotonin and dopamine receptors could favorably affect sleep for the treatment of insomnia. Low-dose RIS reportedly increases SWS in animals.[7] The current study examined

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how the administration low-dose RIS affects sleep architecture in healthy humans, with special reference to differences in effect between the morning and the evening administration.

METHODS

Participants

The participants comprised 10 healthy male volunteers (mean age, 23.6 years; range, 21–28 years, mean height ±SD, 173.9 ± 4.8 cm, mean weight ±SD, 67.0 ± 5.2 kg). Prior to enrollment in the study, all the participants underwent medical and psychiatric screening by an experienced medical doctor to ensure they had no past or present history of sleep disturbance, psychiatric disorders or major physical illness. No participants were taking medications during or 3 months prior to this study, and all were directed to refrain from alcohol consumption or intense physical exercise from the day before the experiment to the end of each session. Informed consent was obtained from each participant before the experiment. At the beginning of this study, the participants were informed of the possibility of adverse effects after the administration of RIS, such as extra-pyramidal symptoms, hangovers, lethargy and sleepiness during the experimental period. The participants were also required to inform the researchers if they experienced any such adverse effects. This study was approved by the Ethics Committee of Shiga University of Medical Science.

Examination schedule

All participants underwent three sets on 2 consecutive nights of polysomnography (PSG) examinations. Each set was separated by a >2-week period of drug washout. Either 0.5 mg of RIS oral solution in a beverage or the beverage alone (the placebo) was given on 2 consecutive days in three kinds of session: the placebo session; the evening RIS session; or the morning RIS session. The beverage with or without RIS was administrated at both 09.00 and 21.00 hours for a total of four times during each session over 2 days. In the evening RIS session, the placebo was administrated at 09.00 hours and the RIS-containing beverage was administrated at 21.00 hours. In the morning RIS session, the RIS-containing beverage was administrated at 09.00 hours and the placebo was administrated at 21.00 hours. These three sessions were performed in a counter-balanced order. The following experimental conditions were made in a crossover design, and all procedures were performed in a double-blinded manner. During study nights, participants were allowed to sleep in bed at 22.30 hours in a quiet, dark examination room until 06.00 hours.

PSG was performed every six nights, using a Grass-Telefactor PSG TWin version 3 (Astro-med, West Warwick, RI 02893, USA). Each recording performed during the first night for each of the three sessions was discarded from further analysis to avoid any first-night effect. Electroencephalography (EEG) signals were recorded for two EEG derivations of the International 10–20 system (C3-A2 and C4-A1). An electrooculography (EOG) was recorded from a pair of electrodes placed above and below the left eye, and a horizontal EOG was recorded from a pair of electrodes placed 1 cm lateral to the right and left outer canthus. An electromyography (EMG) was recorded from the submental muscle. The recording passband was 0.5–70 Hz for the EEG.

At the end of each recording session, the participants were asked to score how well they had slept on a 10-point scale (from "much worse than usual, 1" to "much better than usual, 10"). They were also required to keep a daily sleep log diary for 16 days, seven days prior to and following each two-day session, in order to estimate their subjective sleep duration.

Sleep architecture analysis

The PSG data from each second night were analyzed further. The sleep stages were visually scored every 30 s epoch by a technician using standardized criteria and blinded to the experimental conditions.[8] Based on these records, sleep parameters such as the total sleep time, sleep onset latency, rapid eye movement (REM) latency, and duration of each sleep stage were derived.

For spectral analysis, a fast Fourier transform was performed on consecutive artifact-free 2 s epochs with a frequency resolution of 0.5 Hz. A Hanning window was used, as a signal processing technique that attenuates the contributions of data from the ends of each epoch, thus minimizing spurious frequencies in analysis that might arise from an abrupt transition to the analysis epoch. Power spectra of 15 consecutive 2 s epochs were averaged to match corresponding sleep stages. Epochs containing artifacts were considered as missing data to preserve sleep continuity in the analysis. EEG signals recorded from C3-A2 deviation during non-REM sleep (sleep stages 2, 3 and 4) were analyzed as absolute powers and classified into four frequency bands (delta: 0.5–3.5 Hz; theta: 4.0–7.5 Hz; alpha: 8.0–12.5 Hz;

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Table 1 Sleep parameters for the second night in three conditions ($n = 10$)

Sleep parameter	Placebo (mean ± SEM)	M-RIS (mean ± SEM)	E-RIS (mean ± SEM)
Total sleep time	405.2 ± 7.0	403.5 ± 7.4	424.9 ± 4.9**
Stage 1 (min)	34.6 ± 4.6	38.4 ± 4.8	35.6 ± 5.6
Stage 1 (%)	8.5 ± 1.1	9.5 ± 1.1	8.4 ± 1.3
Stage 2 (min)	231.3 ± 6.4	222.5 ± 7.4	243.4 ± 8.3
Stage 2 (%)	57.3 ± 2.1	55.3 ± 2.2	57.3 ± 1.9
Stage 3 (min)	20.0 ± 3.0	25.2 ± 3.5*	27.9 ± 4.3*
Stage 3 (%)	5.0 ± 0.8	6.3 ± 0.9*	6.6 ± 1.0*
Stage 4 (min)	26.1 ± 7.3	21.7 ± 6.6	21.5 ± 6.9
Stage 4 (%)	6.4 ± 1.8	5.3 ± 1.6	5.0 ± 1.6
SWS (min)	46.1 ± 9.2	46.9 ± 7.8	49.3 ± 9.0
SWS (%)	11.4 ± 2.2	11.6 ± 1.9	11.5 ± 2.1
REM sleep (min)	93.2 ± 9.3	95.8 ± 9.0	96.7 ± 6.1
REM sleep (%)	22.8 ± 2.1	23.6 ± 1.9	22.8 ± 1.5
WASO (min)	29.0 ± 5.1	30.6 ± 5.2	16.4 ± 2.4**
Sleep latency (min)	17.4 ± 6.7	22.8 ± 11.1	10.2 ± 3.4
REM latency (min)	86.9 ± 7.4	78.7 ± 12.8	91.2 ± 13.7
Sleep efficiency (%)	89.8 ± 1.6	88.4 ± 2.3	94.3 ± 1.1**

Results of the Wilcoxon signed-rank test. *Significant difference from placebo condition: $P < 0.05$. **Significant difference in evening administrated risperidone (E-RIS) condition from both placebo condition and morning -risperidone (M-RIS) condition: $P < 0.05$. REM, rapid eye movement; SWS, slow-wave sleep; WASO, waking after sleep onset.

beta: 13.0–30 Hz). Relative delta, theta, alpha and beta powers expressed as a percentage of the total power (0.5–30 Hz) for each 30 s epoch were also calculated.

Statistical analysis

Data were analyzed using SPSS for Windows (Version 12.0J; SPSS, Chicago, Il, USA.). Each variable of sleep architecture among the three conditions was assessed using Friedman's analysis. When significant differences were identified, post hoc Wilcoxon signed-rank testing was performed to detect the conditions contributing to the difference. The results of power spectra between the condition in which the placebo was administrated and the condition in which 0.5 mg RIS was administrated in the evening were compared by paired *t*-testing.

RESULTS

Subjective sleep quality

When RIS was administered in the morning (as compared with those given a placebo), three of the 10 participants reported improved subjective sleep quality, five participants reported no change and two reported impaired subjective sleep quality. Conversely, when RIS was administered in the evening (as compared to the placebo group), four participants reported improved subjective sleep quality, four reported no change, and two reported impaired sleep quality. Moreover, when RIS was administered in the evening (as compared with that given RIS in the morning), four participants reported improved subjective sleep quality, three reported no change, and three reported impaired sleep quality. In terms of subjective sleep quality, no significant differences were identified among the three conditions. No adverse effects such as extra-pyramidal symptoms, hangovers or sedation were reported by the participants during the entire experimental period. According to the subjective sleep log diaries, no significant differences of sleep duration were detected among the three periods; pre-administration, administration and post-administration (data not shown).

Sleep architecture

To estimate objective changes in sleep parameters in morning and evening administration of the drug, RIS-administered conditions were compared with those of the placebo-administered condition (Table 1). In the morning-administered condition (M-RIS), sleep parameters did not significantly change except for duration of sleep stage 3 compared with the placebo condition,

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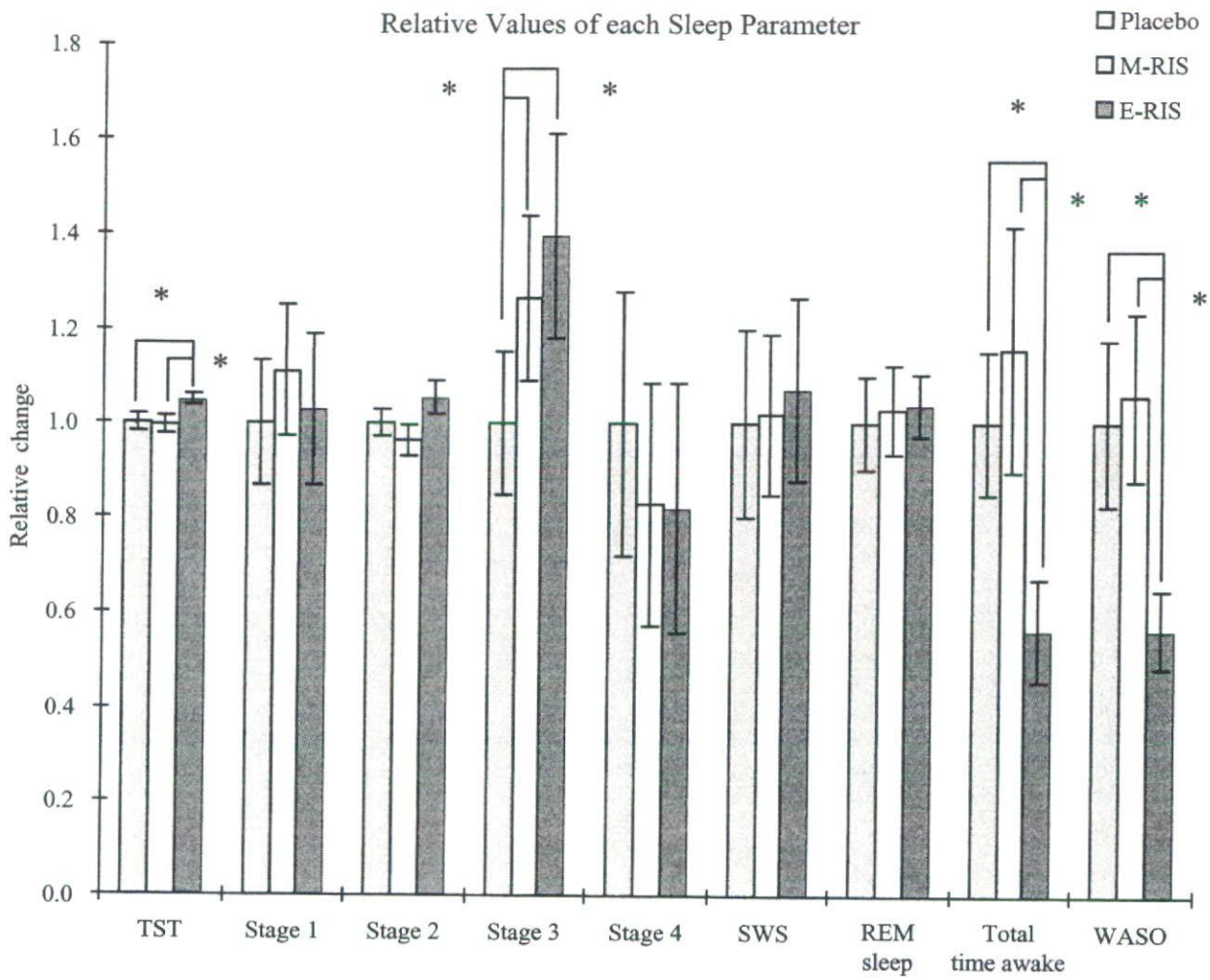

Figure 1 Relative values of each sleep parameter (min), compared with placebo condition. Results of the Wilcoxon signed-rank test, significantly different from placebo condition: $^*P < 0.05$. E-RIS, evening risperidone; M-RIS, morning risperidone; REM, rapid eye movement; TST, total sleep time; WASO, waking after sleep onset.

when it was increased by 26.3% compared with the placebo (placebo, 20.0 ± 3.0 min; M-RIS, 25.2 ± 3.5 min; $P = 0.032$) and this change was disproportional to the shortened total sleep time (Fig. 1). In the evening-administered condition (E-RIS), the total sleep time was increased by 4.9% compared with the placebo condition (placebo, 405.2 ± 7.0 min; E-RIS, 424.9 ± 4.9 min; $P = 0.028$). This change in E-RIS condition was accompanied by increased sleep efficiency (placebo, 89.8 ± 1.6%; E-RIS, 94.3 ± 1.1%; $P = 0.022$) and a significant decrease in waking after sleep onset (WASO) (placebo, 29.0 ± 5.1 min; E-RIS, 16.4 ± 2.4 min; $P = 0.024$).

Sleep stage 3 was also significantly increased in the E-RIS condition compared with the placebo (placebo, 20.0 ± 3.0 min; E-RIS, 27.9 ± 4.3 min; $P = 0.038$). Compared with the M-RIS condition, WASO and total waking time were significantly decreased and total sleep time and sleep efficiency were significantly increased in the E-RIS condition.

Power spectral analysis

Marked differences in sleep parameters were apparent between the placebo and E-RIS conditions, so EEG signals in these two conditions were subjected to further

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Table 2 Absolute and relative powers for second nights in two conditions during non-REM sleep ($n = 10$)

	Placebo (mean ± SD)	E-RIS (mean ± SD)	*t*-test
Absolute power			
Delta activity (μV^2)	251.2 ± 85.9	269.1 ± 73.2	ns
Theta activity (μV^2)	38.0 ± 11.3	44.0 ± 14.6*	$P = 0.005$
Alpha activity (μV^2)	18.0 ± 5.6	19.7 ± 7.9	ns
Beta activity (μV^2)	15.5 ± 8.0	12.3 ± 4.3	ns
Relative power			
Delta activity (%)	77.5 ± 3.8	78.0 ± 4.0	ns
Theta activity (%)	12.0 ± 2.5	12.7 ± 2.5*	$P = 0.016$
Alpha activity (%)	5.7 ± 1.3	5.6 ± 1.5	ns
Beta activity (%)	4.9 ± 2.0	3.7 ± 1.4*	$P = 0.024$

Results of the paired *t*-test, significantly different: *$P < 0.05$. ns, no significance. E-RIS, evening risperidone (E-RIS)

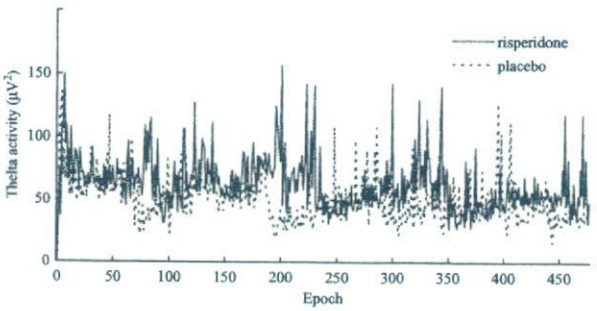

Figure 2 Time course of absolute power in the theta band during non-rapid eye movement (non-REM) sleep for one representative participant. The solid line shows absolute power under the evening risperidone condition. The dotted line shows absolute power in the placebo condition. One epoch corresponds to 30 s.

analysis of power spectra in four frequency bands. Absolute power in the theta band was larger in the E-RIS condition than in the placebo (placebo, 38.0 ± 11.3 μV^2; E-RIS, 44.0 ± 14.6 μV^2; $P = 0.005$) (Table 2). Relative power in the theta band was also larger in the E-RIS condition than in the placebo (placebo, 12.0 ± 2.5%; E-RIS, 12.7 ± 2.5%; $P = 0.016$), and absolute power in the beta band was smaller in the E-RIS condition than in the placebo (placebo, 4.9 ± 2.0%; E-RIS, 3.7 ± 1.4%; $P = 0.024$) (Table 2). Figure 2 illustrates the time course of absolute power in the theta band during non-REM sleep of a representative participant in the E-RIS condition. Predominance in absolute power in the theta band under the E-RIS condition was preserved when EEG signals were divided into former and latter halves of the study night (data not shown).

DISCUSSION

Our study indicated that a 2-day administration of low-dose RIS before sleep effectively lengthens sleep duration and sleep stage 3 in healthy humans. These tendencies were not observed in the M-RIS condition except for sleep stage 3.

RIS shares some profiles with its ancestor drugs, haloperidol and ritanserine. The former is a dopamine D_2 receptor blocker and the latter is a 5-$HT_{2A/2C}$ receptor blocker. A previous investigation has indicated that haloperidol can increase total sleep time and sleep stage 3 in schizophrenic patients, although no change was found with regard to total SWS.[5] This result is consistent with our findings, although the study was conducted under conditions of differing participants and doses. Since the Maixner *et al.* study employed a rather high dose of haloperidol (mean dose, 11.7 mg/day), our findings are interesting in that even a low dose of RIS changed sleep architecture. Although differences in studies between healthy participants and patients should be taken into consideration, the relatively strong effects on sleep by RIS may be attributable to antiserotonergic effects that haloperidol lacks. According to previous research, antiserotonergic effects reportedly enhance slow-wave activity in sleep. Solomon *et al.* reported that the 5-HT_2 receptor antagonist increased the SWS fraction in healthy humans.[9] Moreover, the administration of 5-$HT_{2A/2C}$ receptor antagonists, such as ritanserin, increased SWS in a dose-related manner.[10] In these studies, the balanced effects on 5-HT_{2A} and 5-HT_{2C} receptors were suggested to be crucial to enhance SWS, particularly by antagonizing 5-HT_{2C} receptors. A single administration of another antipsychotic agent, olanzapine (5–10 mg), produced dose-related increases in SWS

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in healthy volunteers, in addition to decreases in REM sleep.[11] Sharpley *et al.* reported that the increases in SWS seen with olanzapine were probably attributable to 5-HT_{2C} receptor blockade. In our results, low-dose RIS increased only sleep stage 3 in non-REM sleep, and this might be due to its relatively stronger effects against 5-HT_{2A} receptors compared to 5-HT_{2C} receptors.[12] In addition, when the EEG signals were analyzed in detail by spectral analysis, we found that power in the theta band was increased, whereas that of the delta band was left unchanged in the E-RIS condition. The result of delta power in the E-RIS condition compared with placebo was consistent with the result of stage analysis, in which sleep stage 4 or SWS was not increased in the E-RIS condition. To the best of our knowledge, no study has determined how theta power contributes to sleep physiology. The functional relevance of the increased theta power found in E-RIS thus remains unclear.

Although few studies have been conducted to examine how RIS affects human sleep, Sharpley *et al.* reported that single administration of 1 mg of RIS before sleep resulted in significant suppression of REM sleep without any other significant changes to sleep architecture in humans.[13] This result was inconsistent with our results, but some conditions did differ between these studies, including dose of RIS. REM sleep suppression is associated with making norepinephrine and 5-HT neurotransmission more effective and also with muscarinic cholinergic blockade.[14] Conversely, the 5-$HT_{2A/2C}$ receptor blocker ritanserine does not suppress REM sleep in healthy humans.[6] Idazoxan, an α2-adrenoceptor antagonist, suppresses REM sleep probably by facilitating norepinephrine and 5-HT neurotransmission.[15] Accordingly, REM sleep suppression is partly caused by such anti-adrenergic effects of RIS, which has some antagonist activity at noradrenergic α2-adrenoceptors.[12] The lack of REM sleep suppression in our study might be due to the low dose of RIS, which may reduce the anti-adrenergic effects. An animal study showed that dose of RIS is crucial for the effects on sleep.[7] In that report, the administration of low-dose RIS (0.01–0.16 mg/kg) resulted in significantly increased SWS in rats, although high-dose RIS (0.63–2.5 mg/kg) induced opposite effects. Although doses in rodents cannot be directly extrapolated to humans, similar effects may be observed in other species. However, RIS may also affect sleep in an opposite according to dose.

Timing of medication is one of the concerns in clinical situations, particularly when sleep is regarded as one of the treatment targets. To examine the function of the RIS-administered situation, we administered the drug for 2 consecutive days in our study. Our data revealed that the effects on sleep are stronger for RIS administered just before sleep onset. Plasma levels of RIS from the oral solution reportedly peak 1 h after administration with a serum half-life of 4 h in the Japanese population.[16] This pharmacodynamic profile offers a good explanation of our results. An explanation for the isolated prolongation of sleep stage 3 in the M-RIS group might be the plasma levels of RIS's major active metabolite, 9-hydroxyrisperidone, which peak 3 h after administration with a serum half-life of 21 h.[16] Furthermore, this metabolite's activity is reported by some researchers to be of an almost equal or somewhat weaker strength to the activity of RIS. Although we should be cautious in applying findings from healthy humans to patients, the dependence of RIS effects on the timing of administration should be noticed in clinical situations in which RIS is subscribed to treat both sleep disturbance and psychiatric symptoms. Furthermore, compared with olanzapine, another antipsychotic agent that reportedly increases SWS in humans, RIS might be more appropriate due to the shorter serum half-life and might display fewer adverse effects such as hangovers and drowsiness.[16,17]

In conclusion, our study indicated that RIS has no significant effect on the amount of SWS, but increases both total sleep time and sleep stage 3, particularly when administered shortly before sleep. Moreover, no increase in sleep stage 2 was noted, contrasting with findings for the administration of traditional hypnotics. However, the current study displayed the limitations of a small sample size and a lack of strict control for different daytime activities among participants, which may bias efficacy findings. Further study is needed to establish the possible availability of RIS as a hypnotic.

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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.
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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

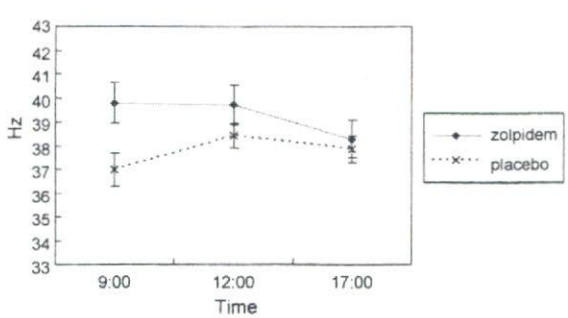

Fig. 1. Effects of a nighttime administration of zolpidem on CFF on the following day. Significant main effects of drug and time on CFF were obtained by repeated-measures ANOVA ($p < 0.05$).

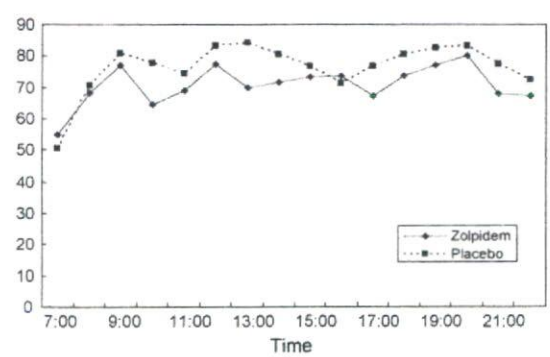

Fig. 2. Effects of a nighttime administration of zolpidem on well-being on the following day. Significant main effects of time ($F = 3.04$, $p = 0.001$) and drug ($F = 8.34$, $p = 0.001$) on well-being were observed. Placebo group had better well-being than zolpidem group.