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MELATONIN AND CIRCADIAN SLEEP DISORDERS

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Summary

When administered to humans the pineal hormone melatonin can phase shift a number of circadian rhythms. This property has prompted the investigation of exogenous melatonin in sleep disorders known to have an underlying chronophysiological basis (i.e. circadian rhythm sleep disorders). Both in field and simulated studies of jet lag and shift work suitably timed melatonin improved sleep and, in some cases, hastened readaptation of the circadian rhythms following the phase shift. Melatonin treatment has also been evaluated in the circadian sleep disorders, delayed sleep phase syndrome (DSPS) and non-24-hour sleep wake disorder. Compared with placebo, melatonin advanced the sleep period in subjects with DSPS. Melatonin also improved a number of sleep parameters in blind subjects suffering from non-24-hour sleep wake disorder. In addition, studies investigating circadian rhythm abnormalities in untreated blind individuals point to an association between the endogenous melatonin rhythm and sleep/napping patterns.

Introduction

The hormone melatonin (N-acetyl-5-methoxytryptamine) is synthesised primarily in the pineal gland and, to a lesser extent, in the retina. From unicellular algae to man, there is a day/night rhythm in melatonin production with peak levels occurring during the period of darkness (review 2).

The melatonin rhythm is endogenously generated by the circadian pacemaker localised in the hypothalamic suprachiasmatic nuclei (SCN). Light acting via retinal photoreceptors and a nonvisual retinohypothalamic tract (RHT) entrains SCN activity and consequently the melatonin rhythm to a 24 hour cycle. Daily and seasonal changes in light/dark cycles are capable of inducing changes in the SCN circadian pacemaker cells which, via a neural output pathway, affect the pattern of melatonin secretion and other output circadian rhythms such as core body temperature, cortisol and sleep/wake cycle. For example, the duration of nocturnal melatonin secretion increases in response to lengthening of the night and this melatonin signal conveys information about season to the organism (8, 33, 35).

As an endocrine signal reflecting the photoperiod, melatonin acts as a time cue for the organisation of daily (circadian) and annual (circannual) events. The high affinity melatonin receptors in the SCN (mel_{1a}/mel_{1b}) and the hypothalamic pars tuberalis (mel_{1a}) are the presumed sites of melatonin's circadian and reproductive effects, respectively (32). Melatonin has two distinct effects on the SCN: an acute inhibitory effect on neuronal firing (28) and a phase shifting effect on the SCN electrical activity rhythm (29). Recent studies using mice with targeted disruption of the mel_{1a} receptor suggest that melatonin's acute inhibitory effect and its phase shifting effect are mediated by mel_{1a} and mel_{1b} receptors, respectively (24). It may be that these receptors also mediate the reported acute and phase shifting effects of exogenous melatonin in humans.

The time giving (*zeitgeber*) properties of melatonin have a number of potential therapeutic applications from control of breeding cycles in seasonal breeders such as sheep to resynchronisation of body rhythms following an abrupt shift of time (in time zone travel, night shift work).

This review describes the results from our laboratory in investigating the effects of exogenous melatonin administration on sleep and other circadian rhythms in subjects with circadian sleep disorders. Studies in blind subjects with non-24-hour sleep-wake disorders have also allowed assessment of the relationship between the endogenous melatonin rhythm and the sleep/wake cycle.

Phase Shifting Effects of Exogenous Melatonin

Early work showed that early evening administration (17.00 h) of melatonin (2 mg daily for 4 weeks) produced a phase advance in the timing of sleep and the endogenous melatonin rhythm in healthy subjects (6, 36). Later studies showed that a single dose of melatonin (5 mg at 17.00 h) was capable of producing an advance in the onset of the endogenous melatonin rhythm and core body temperature rhythm (13). These effects of exogenous melatonin were later shown to be dose-dependent (10). In addition to its phase shifting effect exogenous melatonin also has an acute effect (induces sleepiness, reduces core body temperature and alertness) which is dose-dependent (13).

The phase shifting effects of melatonin on endogenous circadian rhythms is dependent upon the time of its administration. This effect is described by a phase response curve: melatonin given in the late subjective day produces phase advances, melatonin given in the late subjective night produces phase delays (22, 23, 30, 37). For subjects who are entrained to their light/dark cycle this phase response curve is useful to determine the time melatonin should be administered to produce the necessary phase shift. For example, subjects wishing to phase advance their circadian rhythms (required when flying eastwards across time zones) should take melatonin in the early evening.

Circadian Rhythm Sleep Disorders

According to the International Classification of Sleep Disorders (19), circadian rhythm sleep disorders are characterised by a mismatch between the subject's sleep pattern and "that which is desired or the societal norm". Two of the circadian rhythm sleep disorders result from a shift in time (Time zone change (jet lag) syndrome and Shift work sleep disorder). The other circadian rhythm sleep disorders are Irregular sleep-wake pattern, Delayed sleep phase syndrome (DSPS), Advanced sleep phase syndrome (ASPS) and Non-24-hour sleep-wake disorder. These sleep disorders may have an internal (e.g. neurological disease) and/or an external cause (e.g. environment).

Effect of Exogenous Melatonin on Circadian Sleep Disorders

Time Zone Change (Jet Lag) Syndrome

Melatonin administration has been investigated in both field (3,4) and simulated (12) studies of jet lag. Following an eastward flight across 8 time zones, melatonin timed to phase advance (5 mg at 18.00 h local time for 3 days before flight and at bedtime (23.00 h) in the new time zone for 4 days post flight) significantly alleviated subjective feelings of jet lag compared to subjects treated with placebo. Melatonin significantly reduced sleep latency and improved subjective sleep quality post flight. The treatment also hastened the rate of resynchronisation of the endogenous melatonin and cortisol rhythms. Since this early study evaluation of melatonin on self-rated jet lag has continued. To date 10 studies have been published, 8 of which have shown melatonin to be effective (see references in 7). Results from our placebo-controlled and uncontrolled studies (melatonin $n = 474$, placebo $n = 112$) show that melatonin reduces self-rated jet lag by 50% in the majority of subjects (7). The effect of melatonin was independent of subject gender and direction of travel but was significantly more effective after flights over more than 8 time zones. Side effects were minimal (7).

Simulated phase shift studies have supported the field study results. Following a rapid 9-h advance shift and using a double blind placebo-controlled crossover design, melatonin administration (5 mg at 23.00 h for 3 days post phase shift) significantly improved sleep (quality, duration and night awakenings), daytime mood and alertness compared with placebo (12). This effect of melatonin occurred immediately post phase shift suggesting an acute effect on the sleep/wake cycle followed by a hastened adaptation of the endogenous melatonin rhythm.

Overall our and most of the other studies suggest that if correctly timed melatonin will alleviate the symptoms of jet lag (disturbed night sleep, increased daytime sleepiness) in the majority of subjects (see references in 7). The optimum way to ensure correct timing is to administer melatonin in relation to each individuals' own circadian phase. Determination of a subject's circadian

phase, however, requires strict experimental conditions which are not practical in field studies. Thus as a minimum requirement subjects should be entrained to the pre-flight environment so that the timing of the melatonin treatment is approximately at the subjects' correct circadian phase. The importance of subject entrainment is emphasised by a recent study in which subjects not synchronised to the pre-flight environment appeared not to benefit from melatonin treatment (34).

Shift Work Sleep Disorder

There are few studies investigating the effect of melatonin on shift work sleep disorder experienced by rotating shift workers in the field. In a pilot study we gave melatonin (5 mg daily for 10 days) or placebo to workers following a 8-h night shift (18). Melatonin taken at their "bedtime" (approximately 07.00 h) significantly increased day sleep duration, improved subjective sleep quality and increased alertness during the night shift.

Models simulating the phase shift experienced by a fully adapted night worker returning to a day shift or vice versa have been developed in our laboratory (11, 14) in order to investigate the effect of exogenous melatonin and/or light treatment on sleep and the readaptation process following phase shift (12, results described above).

Delayed Sleep Phase Syndrome (DSPS)

In delayed sleep phase syndrome (DSPS) sleep is delayed in relation to desired clock time (19). Subjects are unable to fall asleep until between 02.00 and 06.00 h and have difficulty awakening in the morning to fulfil social/work obligations. In a randomised, double-blind, placebo-controlled trial, melatonin was administered (5 mg daily at 22.00 h for 4 weeks) to 8 patients with DSPS (9). Melatonin treatment significantly advanced the time of sleep onset and wake time with no overall change in sleep duration.

In a recent single case we have tried another approach. A blind man with DSPS and a delayed melatonin rhythm (mean peak time of secretion 14 h 15 min) was given melatonin (5 mg) or placebo for 28 days. The time of administration was advanced by one hour for the first 5 days and then held constant. This staggered treatment regimen attempted to account for the possible cumulative phase advances from each melatonin dose. In this subject melatonin significantly advanced sleep onset, delayed sleep offset, increased night sleep duration and reduced daytime napping compared with placebo given in a similar timed manner (unpublished results, Lockley, Skene, Arendt). Further studies using this approach are required both in blind and sighted DSPS sufferers.

Advanced Sleep Phase Syndrome

In advanced sleep phase syndrome (ASPS) the sleep episode is advanced relative to the desired clock time (19). Subjects complain of excessive evening sleepiness and early morning wakening. To date no controlled studies of the

effectiveness of melatonin in ASPS have been performed in our laboratory. Theoretically melatonin should be taken in the early morning, i.e. timed to produce a phase delay.

Non-24-hour Sleep Wake Disorder

In this disorder the sleep/wake cycle occurs at a period different from 24 hours, i.e. it is free running. This sleep disorder occurs mainly in blind subjects and is characterised by bouts of good sleep when their circadian clock is in phase with the 24-hour world and bouts of disturbed sleep when they are out of phase. We have recently completed a study of blind subjects ($n = 49$) with different degrees of visual loss and have shown that those subjects with no conscious light perception (NPL) are more likely to have free running sleep and other circadian rhythms (26) supporting the idea that the light/dark cycle is a major time cue in humans, which, via the retina-RHT pathway, entrains the SCN pacemaker.

We were the first to investigate the effect of melatonin on the sleep/wake cycle of a blind person with free running circadian rhythms. Melatonin given daily at bedtime (approximately 23.00 h) for 4 weeks stabilised sleep onset, increased night sleep duration and reduced daytime sleepiness compared with placebo (5). Studies assessing melatonin's effect on non 24-hour sleep in blind individuals have continued (1, 7). As not all blind subjects appeared to benefit from the treatment (e.g. only 6 out of 13 subjects had an improvement in one or more of the sleep parameters) (1, 7), we are presently conducting studies where melatonin is accurately timed according to each individual's own circadian phase in the hope of optimising melatonin's effectiveness. The subjects' circadian phase (assessed by the timing of the urinary 6-sulphatoxymelatonin rhythm) is determined just prior to melatonin administration and the first dose of melatonin (5 mg) taken when the subject's 6-sulphatoxymelatonin peak is in a normal phase position (04.00 h). To date 3 male NPL subjects with free running non 24-hour 6-sulphatoxymelatonin rhythms have been given melatonin (5 mg daily at 21.00 h) in a single-blind, placebo crossover design (7, Lockley, Skene, Arendt unpublished data). Melatonin administration continued throughout a full circadian cycle, length of treatment thus varied between 35 and 60 days depending upon the individuals' period length ($\tau = 24.37, 24.50$ and 24.68 for the 3 subjects). Preliminary analysis shows that compared with placebo, melatonin improved subjective sleep quality, reduced sleep latency and reduced the number and duration of daytime naps. Figure 1 shows the sleep/wake profile of one NPL subject (male, aged 34 with a free running 6-sulphatoxymelatonin rhythm, $\tau 24.68$) following melatonin or placebo treatment.

Although the above experiments show an action of melatonin on sleep parameters whether melatonin is capable of entraining the free running circadian rhythms in these subjects remains an open question. In our original case study (5, 17) melatonin failed to entrain the subject's free running rhythms in core

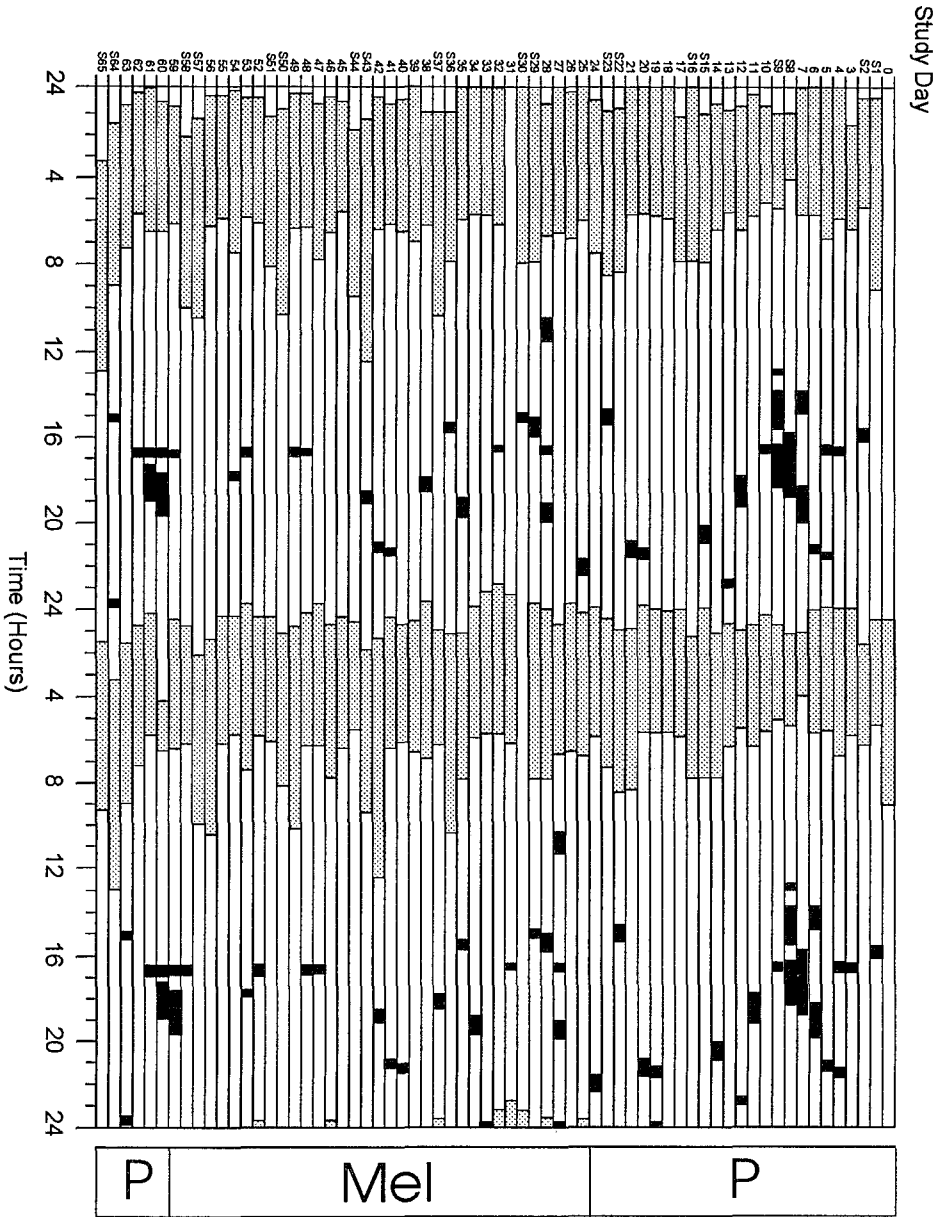


Figure 1. Double plot of subjective sleep profile of a blind man with no conscious light perception (NPL) and a free running 6-sulphatoxymelatonin rhythm (period length 24.68 h). Melatonin (5 mg) was administered daily at 21.00 h for a full circadian cycle (35 days) between days 25 and 59. During days 1 to 24 and 60 to 66 placebo was given. The Y axis shows sequential study days, 'S' indicating weekend days. The shaded grey bars show sleep onset and sleep offset times, the black bars show self-rated naps. Melatonin treatment significantly advanced sleep onset and reduced daytime napping in this subject.

body temperature and cortisol. Our present studies in free running blind subjects are designed to investigate this issue further.

Experiments on sighted subjects kept in constant dim light (< 8 lux) and partial temporal isolation have also been performed to assess the ability of melatonin treatment to entrain free running circadian rhythms (30). In a randomised double-blind crossover design volunteers received 5 mg melatonin at 20.00 h for 15 days followed by placebo for 15 days, or vice versa. In these trials melatonin stabilised the sleep/wake cycle in most of the subjects. However, in a proportion of subjects melatonin treatment produced fragmented sleep (30, 31). Melatonin's effect on the core body temperature rhythm was not consistent between subjects. During melatonin administration a shortening of the period of the temperature rhythm was observed in some individuals suggesting a weak zeitgeber effect.

Role of Endogenous Melatonin in Sleep

The role of endogenous melatonin in human sleep is difficult to investigate without control of lighting and complicated experimental designs, such as "7/13" ultra-short sleep/wake paradigm (20) or fractional desynchronisation studies (16). Using these approaches an association between the circadian rhythm in sleep propensity and melatonin has been shown (reviews 15, 21)

Our studies in the blind support a possible association between the endogenous melatonin rhythm and sleep propensity. Blind subjects with abnormal melatonin rhythms (free running or abnormally timed) had significantly more daytime naps of a longer duration than those with entrained, normally timed melatonin rhythms (Fig 2). The increased daytime sleepiness was associated with a melatonin rhythm out of phase with the 24 hour world (27). Blind subjects with no conscious light perception and free running circadian rhythms are ideal to investigate the possible relationship between the endogenous melatonin rhythm and the sleep/wake cycle as they eliminate the need for constant dark conditions and lengthy isolation experiments. Using these subjects the quality/timing of sleep can be evaluated at each phase of the circadian cycle. Preliminary analysis of this has shown that night sleep is reduced, and daytime napping increased when the melatonin rhythm is abnormally timed (25, 27).

Conclusions

The ability of appropriately timed exogenous melatonin to phase shift circadian rhythms suggests it will be of use in sleep disorders that have an underlying chronobiological basis. Field and simulated studies investigating the effect of exogenous melatonin administration in circadian rhythm sleep disorders broadly support this proposal. Knowledge of the individual's circadian phase prior to treatment will allow accurate timing of the melatonin dose in order to achieve the desired phase shift.

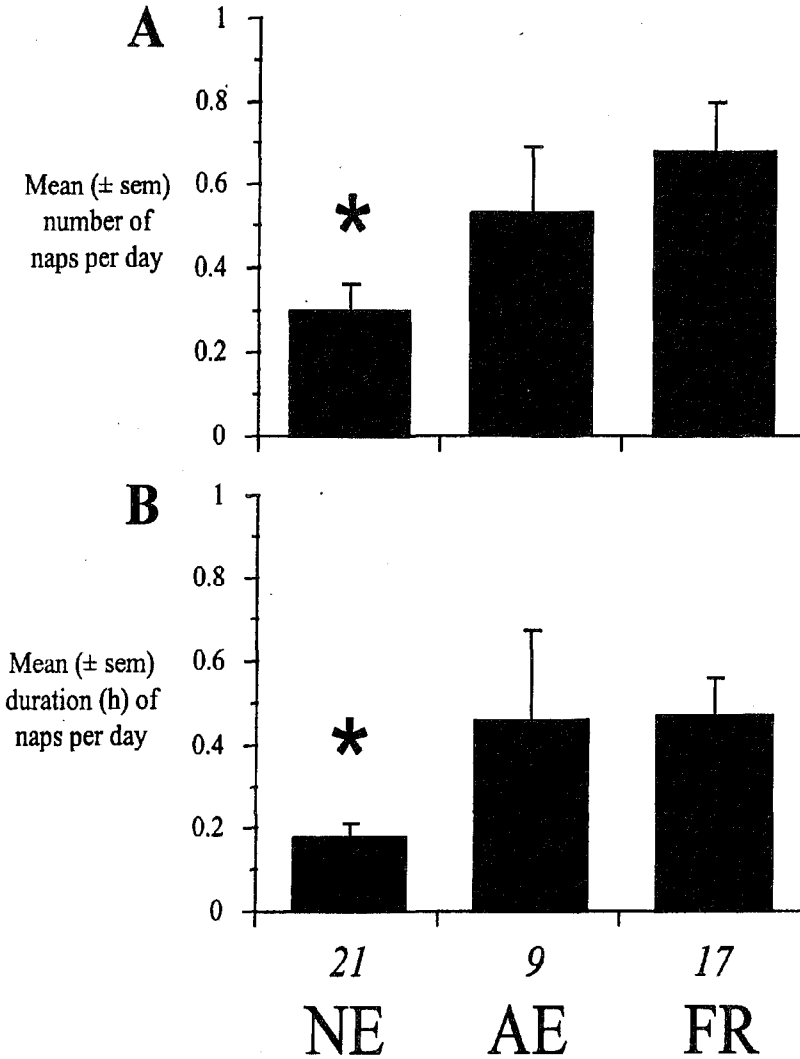


Figure 2. The number (a) and duration (b) of self-rated naps in blind subjects with normally entrained (NE), abnormally entrained (AE) or free-running (FR) 6-sulphatoxymelatonin rhythms. The numbers in italics represent the number of subjects per subgroup.

* $P < 0.05$ compared with the other subgroups.

The role of endogenous melatonin in sleep is less clear cut at present. Although studies show an association between the endogenous melatonin rhythm and some circadian sleep processes, cause and effect have not been proven. It is possible that the reported correlation between melatonin and sleep merely reflects two output rhythms driven by a single SCN oscillator.

Acknowledgements

Research carried out in the authors' laboratory is funded by The Wellcome Trust, Medical Research Council, European Commission BIOMED 2 Programme, Ministry of Defence, Servier Research and Development, South Thames Regional Health Authority, and Stockgrand Ltd. Their financial support is gratefully acknowledged.

References

1. Aldhous M.E., Arendt J.: Assessment of melatonin rhythms and the sleep-wake cycle in blind subjects. *Adv. Pineal Res.*, 1993, 5, 307-309.
2. Arendt J.: *Melatonin and the Mammalian Pineal Gland*. Chapman and Hall, Cambridge, 1995.
3. Arendt J., Aldhous M., English J., Marks V., Arendt J.H.: Some effects of jet lag and their alleviation by melatonin. *Ergonomics*, 1987, 30, 1379-1393.
4. Arendt J., Aldhous M., Marks V.: Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. *Brit. Med. J.*, 1986, 292, 1170.
5. Arendt J., Aldhous M., Wright J.: Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment. *Lancet*, 1988, 339, 772-773.
6. Arendt J., Borbely A.A., Franey C., Wright, J.: The effects of chronic, small doses of melatonin given in the late afternoon on fatigue in man: a preliminary study. *Neurosci. Lett.*, 1984, 45, 317-321.
7. Arendt J., Skene D.J., Middleton B., Lockley S.W., Deacon S.: Efficacy of melatonin treatment in jet lag, shift work, and blindness. *J. Biol. Rhythms*, 1997, 12, 604-617.
8. Bartness T.J., Goldman B.D.: Mammalian pineal melatonin: A clock for all seasons. *Experientia*, 1989, 45, 939-945.
9. Dahlitz M., Alvarez B., Vignau J., English J., Arendt J., Parkes J.D.: Delayed sleep phase syndrome response to melatonin. *Lancet*, 1991, 337, 1121-1124.
10. Deacon S., Arendt, J.: Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. *Brain Res.*, 1995, 688, 77-85.
11. Deacon S., Arendt J.: Adapting to phase shifts, I. An experimental model for jet lag and shift work. *Physiol. Behav.*, 1996, 59, 665-673.
12. Deacon S., Arendt J.: Adapting to phase shifts, II. Effects of melatonin and conflicting light treatment. *Physiol. Behav.*, 1996, 59, 675-682.
13. Deacon S.J., English J., Arendt J.: Acute phase-shifting effects of melatonin associated with suppression of core body temperature in humans. *Neurosci. Lett.*, 1994, 178, 32-34.
14. Deacon S., Skene D., Arendt J.: Use of light and/or melatonin in adaptation to phase shifts. In: Holick M.F., Jung E.G. (eds.): *Biologic effects of light 1995*. Walter de Gruyter, Berlin, 1996, 398-405.
15. Dijk D.-J., Cajochen C.: Melatonin and the circadian regulation of sleep initiation, consolidation, structure, and the sleep EEG. *J. Biol. Rhythms*, 1997, 12, 627-635.
16. Dijk D.J., Czeisler C.A.: Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J. Neurosci.*, 1995, 15, 3526-3538.

17. Folkard S., Arendt J., Aldhous M., Kennet H.: Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. *Neurosci. Lett.*, 1990, 113, 193-198.
18. Folkard S., Arendt J., Clark M.: Can melatonin improve shift workers tolerance of the night shift? Some preliminary findings. *Chronobiol. Int.*, 1993, 10, 315-320.
19. International Classification of Sleep Disorders: Diagnostic and Coding Manual. Diagnostic Classification Steering Committee, Thorpy M.J. (ed.). Allen Press Inc., Lawrence, Kansas, 1990.
20. Lavie P.: Ultrashort sleep-waking schedule. III. „Gates” and „forbidden” zones for sleep. *Electroencephal. Clin. Neurophysiol.*, 1986, 63, 414-425.
21. Lavie P.: Melatonin: Role in gating nocturnal rise in sleep propensity. *J. Biol. Rhythms*, 1997, 12, 657-665.
22. Lewy A.J., Ahmed S., Jackson J.M.L., Sack R.L.: Melatonin shifts human circadian rhythms according to a phase-response curve. *Chronobiol. Int.*, 1992, 9, 380-392.
23. Lewy A.J., Sack R.L.: Exogenous melatonin's phase shifting effects on the endogenous melatonin profile in sighted humans: A brief review and critique of the literature. *J. Biol. Rhythms*, 1997, 12, 588-594.
24. Liu C, Weaver D.R., Jin X., Shearman L.P., Pieschi R.L., Gribkoff V.K., Reppert S.M.: Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron*, 1997, 19, 91-102.
25. Lockley S.W., Skene D.J., Arendt J.: Changes in sleep in relation to circadian phase in the blind. In: Touitou Y. (ed.): *Excerpta Medica International Congress Series (ICS)*. Elsevier Science, Amsterdam, 1998, in press.
26. Lockley S.W., Skene D.J., Arendt J., Tabandeh H., Bird A.C., DeFrance R.: Relationship between melatonin rhythms and visual loss in the blind. *J. Clin. Endocrinol. Metab.*, 1997, 82, 3763-3770.
27. Lockley S.W., Skene D.J., Tabandeh H., Bird A.C., DeFrance R., Arendt, J.: Relationship between napping and melatonin in the blind. *J. Biol. Rhythms*, 1997, 12, 16-25.
28. Mason R., Brooks A.: The electrophysiological effects of melatonin and a putative antagonist (N-acetyltryptamine) on rat suprachiasmatic neurones in vitro. *Neurosci. Lett.*, 1988, 95, 296-301.
29. McArthur A.J., Gillette M.U., Prosser, R.A.: Melatonin directly resets the rat suprachiasmatic circadian clock in vitro. *Brain Res.*, 1991, 565, 158-161.
30. Middleton B., Arendt J., Stone B.M.: Complex effects of melatonin on human circadian rhythms in constant dim light. *J. Biol. Rhythms*, 1997, 12, 467-477.
31. Middleton B.A., Stone B.M., Arendt J.: Melatonin and fragmented sleep patterns. *Lancet*, 1996, 348, 551-552.
32. Reppert S.M., Weaver D.R.: Melatonin madness. *Cell*, 1995, 83, 1059-1062.
33. Rollag M.D., Niswender G.D.: Radioimmunoassay of serum concentrations of melatonin in sheep exposed to different lighting regimens. *Endocrinology*, 1976, 98, 482-489.
34. Spitzer R.L., Terman M., Malt U., Singer F., Terman J.S., Williams J.B.W., Lewy A.J.: Failure of melatonin to affect jet lag in a randomised double blind trial. *Society for Light Treatment and Biological Rhythms*, 1997, abstracts, vol. 9.
35. Wehr T.A., Moul D.E., Giesen H.A., Seidel J.A., Barker C., Bender C.: Conservation of photoperiod-response mechanisms in humans. *Am. J. Physiol. (Reg. Integr. Comp. Physiol.)*, 1993, 265, R846-R857.
36. Wright J., Aldhous M., Franey C., English J., Arendt, J.: The effects of exogenous melatonin on endocrine function in man. *Clin. Endocrinol.*, 1986, 24, 375-382.
37. Zaidan R., Geoffriau M., Brun J., Taillard J., Bureau C., Chazot G., Claustrat B.: Melatonin is able to influence its secretion in humans: Description of a phase-response curve. *Neuroendocrinology*, 1994, 60, 105-112.