Visual impairment and circadian rhythm disorders

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Many aspects of human physiology and behavior are dominated by 24-hour circadian rhythms that have a major impact on our health and well-being, including the sleep-wake cycle, alertness and performance patterns, and many daily hormone profiles. These rhythms are spontaneously generated by an internal "pacemaker" in the hypothalamus, and daily light exposure to the eyes is required to keep these circadian rhythms synchronized both internally and with the external environment. Sighted individuals take this daily synchronization process for granted, although they experience some of the consequences of circadian desynchrony when "jetlagged" or working night shifts. Most blind people with no perception of light, however, experience continual circadian desynchrony through a failure of light information to reach the hypothalamic circadian clock, resulting in cyclical episodes of poor sleep and daytime dysfunction. Daily melatonin administration, which provides a replacement synchronizing daily "time cue," is a promising therapeutic strategy, although optimal treatment dose and timing remain to be determined.

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Many aspects of human physiology and behavior are dominated by 24-hour rhythms that have a major impact on our health and well-being. For example, sleep-wake cycles, alertness and performance patterns, core body temperature rhythms, and the production of hormones such as melatonin and cortisol are all regulated by an endogenous near-24-hour oscillator in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The cells in these nuclei spontaneously generate rhythms with a period close to, but not exactly, 24 hours, and in order for the circadian pacemaker to ensure that physiology and behavior are appropriately timed to anticipate events in the outside world, environmental time cues must be able to reset this internal clock to 24 hours. The major environmental time cue that resets these rhythms in mammals is the 24-hour light-dark cycle generated by the earth's axial rotation. Light information is captured exclusively by the eyes using specialized retinal photoreceptors and transduced directly to the SCN via a dedicated neural pathway, the retinohypothalamic tract (RHT). Each day the light-dark cycle resets the internal clock, which in turn synchronizes the physiology and behavior controlled by the clock.

The major biochemical correlate of the light-dark cycle is provided by the pineal melatonin rhythm. Under normal light-dark conditions, melatonin is produced only

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during the night, and provides an internal representation of the environmental photoperiod, specifically night-length. The synthesis and timing of melatonin production requires an afferent signal from the SCN which projects to the pineal gland via the paraventricular nucleus and the superior cervical ganglion. Light exposure during the night also inhibits melatonin production acutely and provides an indirect assessment of light input to the SCN via the RHT *(Figure 1)*.[1-4] Given the close temporal relationship between the SCN and melatonin production, the melatonin rhythm is often used as a marker of circadian phase and the melatonin suppression response as a proxy for RHT-SCN-pineal integrity and sensitivity.

The role of light in circadian entrainment

Under normal conditions, the vital importance of daily light-dark exposure to entrain circadian rhythms is taken for granted. For example, although not consciously perceived, the ability to sleep at night and be awake in the day is largely controlled by the circadian system, which promotes sleep during the night and wakefulness during the day via alterations in efferent signals from the SCN to other hypothalamic areas controlling sleep-wake states.[5] The difficulties associated with trying to sleep during the day or be awake at night at the "wrong" circadian time is readily observed in sighted people following rapid transmeridian travel ("jet lag")[6] or in night-shift workers.[7] When traveling across multiple time zones, or when changing from a day to a night shift, the change in the timing of the light-dark exposure is too rapid for the internal circadian pacemaker to synchronize to immediately. A 12-hour shift in sleep timing or time zone may take as long as 2 weeks to become resynchronized to,[8] and often shift times or the time zone are changed again before adaptation has occurred. Consequently, the individual's sleep pattern becomes desynchronized from the circadian system and, in the case of shift workers, daytime sleep duration is short, sleep efficiency is poor, and night-time waking alertness and performance are impaired,[9] accounting for the high

incidence of accidents and injuries experienced by night-shift workers.[10] Other functions also become desynchronized under such conditions, for example, postprandial
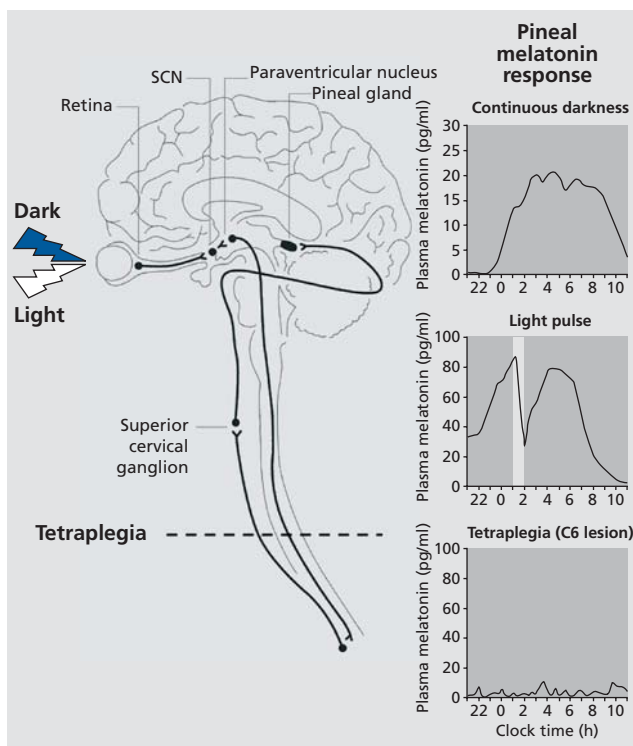
Figure 1. Neuroanatomy of the circadian system. Light is detected by specialized retinal photoreceptors and transduced to the circadian pacemaker in the hypothalamic suprachiasmatic nuclei (SCN) via the monosynaptic retinohypothalamic tract (RHT). SCN efferents project to the pineal gland via the paraventricular nucleus (PVN) and the superior cervical ganglion (SCG). Under normal light-dark conditions, the pineal melatonin rhythm peaks at night during the dark phase with the duration of melatonin production reflecting the scotoperiod (night-duration) (top panel). When the eyes are exposed to light at night, however, melatonin production is immediately suppressed, recovering once the light is switched off (middle panel). The "melatonin suppression test" confirms the functional integrity of the retina-RHT-SCN-PVN-SCG-pineal pathway. In individuals in whom the upper spinal cord has been severed, for example in tetraplegic patients, the signal from the SCN cannot reach the pineal gland and no rhythmic production of melatonin is possible (lower panel). Circadian rhythms in other parameters that do not require the SCN-SCG pathway, such as cortisol and TSH rhythms, remain fully intact in tetraplegic patients.[1,2]

Adapted from reference 3: Wehr TA, Duncan WC Jr, Sher L, et al. A circadian signal of change of season in patients with seasonal affective disorder. *Arch Gen Psychiatry* 2001;58:1108-1114. Copyright © American Medical Association 2001; and from reference 4: Zeitzer JM, Ayas NT, Shea SA, Brown R, Czeisler CA Absence of detectable melatonin and preservation of cortisol and thyrotropin rhythms in tetraplegia. *J Clin Endocrinol Metab.* 2000;85:2189-2196. Copyright © Endocrine Society 2000

metabolism. When meals are taken during the biological night, they cannot be metabolized as efficiently as when eaten during the day, and consequently postprandial levels of glucose, insulin, and fats are elevated.[11-13] In the long term, the regular impairment of metabolism induced over years of shiftwork may lead to chronically elevated circulating levels of insulin and fat, and may increase the risk of developing insulin resistance, diabetes, or cardiovascular disease.[14] Gastrointestinal discomfort is also a common complaint in jet lag,[15] most likely due to the temporal misalignment of circadian oscillators in peripheral tissues (eg, the liver, kidney, esophagus, and stomach) that have recently been identified (for review see ref 16).

The potential importance of light in human circadian entrainment was first explored in cave experiments, where investigators measured rhythms in physiology and behavior when shielded from the solar day (although dim artificial light was generally available).[17,18] These studies indicated that the circadian pacemaker did not oscillate exactly on a 24-hour day, but had a circadian period (τ) that was on average slightly longer than 24 hours. Studies of subjects kept in temporal isolation,[19] in dim light-dark cycles,[20,21] or on very long (eg, 28-h, 30-h, 42.85 h) or very short (eg, 11-h, 20-h) day-lengths outside the range of entrainment of the biological clock have also shown that the period of the circadian clock is not exactly 24 hours in humans (average ~24.2 h)[22,23] similarly to that in other mammals. Under such nonentrained conditions, the rhythms controlled by the circadian system "free-run" at the endogenous period of the biological clock. For example, if a person's nonentrained period is 24.5 h, the sleep-wake cycle and other rhythms will also cycle with a period of 24.5 h and the subject will therefore go to sleep 0.5 hours later each day, when measured using the 24-hour clock (see below).

Real-world environments where altered light-dark exposure can result in circadian desynchrony in sighted individuals include submarines, where the dim light levels and rapidly rotating duty cycles cause the circadian system to "free-run" with a non-24-hour cycle[24]; during spaceflight, where unusual light-dark exposure, combined with imposed non-24-hour "workdays," cause disruption to circadian rhythms and sleep[25,26]; and during polar winters where, in the absence of any environmental light-dark cycle, inadequate or poorly timed artificial light exposure can fail to entrain circadian rhythms in sleep, performance, and metabolism.[27-29] Although the light-dark cycle is the primary environmental time cue, "nonphotic"

time cues, such as sleep, exercise, food, and some drugs, are also able to reset the circadian pacemaker (for review see ref 30), and are potentially important for blind patients (see below).

The effect of visual impairment on circadian entrainment

Early studies of hormone rhythm disorders in the blind

If ocular light exposure is the most important environmental circadian synchronizer, the obvious question is, what happens to the circadian rhythms in visually impaired people? Abnormal hormonal patterns have been reported in some visually impaired patients for more than five decades. In the 1940s, Remler recognized that some blind patients had normal 24-hour rhythms whereas some had inverted rhythms in rectal temperature, heart rate, blood pressure, and urinary excretion (1948[31] cited in Hollwich and Dieckhues[32]). Subsequently, Orth and Island,[33] Kreiger and Rizzo,[34] Bodenheimer et al,[35] and D'Allessandro et al[36] all found irregularities in the plasma profiles of corticosteroid production in a majority of blind subjects. Orth and Island[33] studied three subjects with no conscious perception of light (NPL) and demonstrated a normal, an abnormal, and a free-running rhythm of 17-hydroxycorticosteroid (17-OHCS) production in these subjects. Kreiger and Rizzo[34] showed that five out of seven blind subjects with light perception (LP) and nine of 12 NPL subjects had abnormal 11-hydroxycorticosteroid (11-OHCS) rhythms. Similarly, Bodenheimer et al[35] reported that grouped data of 24-h cortisol measurements from seven NPL subjects showed a phase difference compared with sighted controls. D'Allessandro et al[36] presented mean plasma cortisol data from 11 NPL patients that did not show 24-h rhythmicity. All the studies emphasized the importance of light in modulating the secretion of corticosteroids and noted a split of these rhythms from the sleep-wake cycle. Similarly, irregularities of sleep and its timing were related to an abnormal phase of rectal temperature.[37,38] The rhythm of excretion rates of electrolytes (Na+, Cl-, K+) was also shown to be abnormally timed with a reduced amplitude in the blind.[39,40]

Several early studies did not find any irregularities in the rhythms of blind individuals, however. Migeon et al[41] failed to find any differences in the diurnal pattern of plasma and urinary excretion of 17-OHCS between sighted subjects, night workers, and blind subjects with

no conscious light perception (NPL), although a reduction in the amplitude of plasma 17-OHCS was observed in the blind people. Weitzman et al[42] found normal cortisol and growth hormone rhythms in seven NPL subjects comparable to sighted individuals. Similarly, Scheving et al[43] found no phase difference in the epinephrine and norepinephrine rhythms of 14 blind subjects compared with sighted subjects, although there was an increase in the mesor of norepinephrine levels in these subjects.

A large study of the "endocrine system" of several hundred blind individuals was conducted by Hollwich and Dieckhues.[32] They found abnormalities in a wide variety of biochemical measurements in totally blind subjects (n=220) compared with those with severely impaired vision (n=140) and sighted subjects (n=50). These changes included reduced serum levels of glucose, protein, cortisol, sodium, and raised levels of creatinine and potassium which were mirrored in urinary analysis. Unfortunately, samples were taken only once or overnight, and did not take into account any age or circadian phase differences between individuals. They did postulate the existence, however, of an "excitatory effect" of light on the hypothalamus via an "energetic pathway of the optic system, ...independent of the visual pathway" that stimulated "releasing factors" from the hypothalamus that regulated hormone levels, an observation that correctly anticipated confirmation of a physiologically distinct retinohypothalamic tract. Hollwich and Dieckhues also concluded that the reduction in metabolic activity in the blind accounted for the complaints of blind patients (including diminished physical capacity, insomnia, autonomic and emotional disturbances, desynchrony, and circadian rhythm sleep disorders). The failure to follow circadian rhythms longitudinally within individuals, however, limited the interpretation of these early studies.

The first report of melatonin rhythms in the blind was made by Smith and colleagues who showed that four blind men had higher day- than night-time melatonin levels,[44] the opposite of what would be expected in sighted subjects *(Figure 1)*. Subsequently, Lewy and Newsome[45] investigated plasma melatonin profiles in 10 blind subjects (9 NPL, 1 LP) and showed that six subjects had an abnormally timed melatonin rhythm, three of these being phase-advanced and three being phase-delayed. Longitudinal follow-up of two of these patients showed one subject with a stable but abnormally entrained melatonin rhythm (peak time 10.00-12.00 h, an approximate delay of 8 hours compared with normal) and the other subject had a free-run-

ning melatonin rhythm with a period of 24.7 h.[45] The same group later conducted a more extensive longitudinal study of the plasma melatonin rhythms in 20 NPL subjects,[46] and confirmed a heterogeneous distribution of melatonin rhythm types. Three subjects had normally phased melatonin rhythms, three were abnormally entrained, and 11 had free-running melatonin rhythms with periods ranging from 23.86 to 25.08 h.[46] The remaining three subjects appeared to be arrhythmic.

Early studies of sleep disorders in the blind

Another prediction that can be made if light is important for circadian entrainment is that sleep disorders would be more prevalent in blind compared with sighted subjects, or in those without light perception, as compared with those with some degree of light perception. Several epidemiological studies have investigated these hypotheses. Miles and Wilson first reported that 76% of blind subjects with a range of visual loss complained of a sleep-wake disorder (n=50).[47] Additionally, 40% of subjects recognized that the symptoms were cyclic or episodic, an important characteristic of circadian rhythm sleep disorders (see below). Sasaki et al[48] demonstrated a lower incidence of sleep-wake complaints (40%) in 73 blind teenagers, although they did postulate that an increase in sleep disorder (delayed sleep phase syndrome and non-24-h sleep-wake rhythm) was associated with a decrease in light perception. More recently, Leger et al[49] reported on the results of a postal study in ~800 blind individuals, who were age, sex- and location-matched with sighted controls. Overall, significantly more of the blind individuals were said to have at least one sleep disorder (83%—at least one of latency, night-time and early-morning awakenings, reduced sleep duration or quality) and in addition, 17% of the subjects fulfilled the criteria for diagnosis of free-running sleep patterns.[50] Unfortunately, no information was provided about the severity of visual loss in individuals with "free-running" sleep or on any relationship between sleep disorder and visual acuity. A similar-sized postal study of UK guide-dog owners (n=1139) was also conducted in the UK by Moseley et al[51] who reported a low prevalence of subjective disorder overall (18%) which reduced to 14% in subjects who did not report being depressed (n=981). The methodology for sleep assessment was not described, and the authors stated that sleep disorders were likely to be due to other factors than circadian rhythm disorders caused by loss of light perception.

In order to address whether sleep disorders were associated with loss of light perception, we conducted a survey of 388 registered blind individuals with a range of visual acuities (n=54 with no perception of light [NPL] and n=330 with visual acuity from 20/200 vision to light perception only [LP]).[52] Sleep disorders were assessed using the Pittsburgh Sleep Quality Index (PSQI score > 5) and subjects with depressive symptoms were excluded. Disturbance of sleep was recorded in nearly 50% (189/388) of the blind subjects overall. The prevalence was higher (66%) and the sleep disturbance was more severe (mean PSQI ± SD = 8.1 ± 1.1); however, in the NPL group compared with those blind subjects with a visual acuity of LP or better (46%, mean PSQI =5.8 ± 0.4), or sighted controls (9%, mean PSQI =2.9 ± 0.5; n=44).[52] These data are consistent with the hypothesis that reduced photic input to the circadian pacemaker may increase the risk of circadian rhythm sleep disorders.

Circadian rhythm disorders in the blind

The first study to describe conclusively that circadian rhythm disorders per se occurred in the blind was conducted by Miles et al in 1977.[53] They showed that a blind man with no conscious perception of light (NPL) had nonentrained "free-running" sleep-wake, temperature, alertness, performance, cortisol and urinary excretion rhythms with a period (τ) of 24.9 hours when the subject lived freely without restriction. Similarly, Orth et al[54] demonstrated a free-running cortisol rhythm with a period of 24.5 h in a 52-year-old woman with NPL, and other cases reported similar results in sleep and/or hormonal rhythms.[55-59] These periodicities persisted despite attempts to entrain the rhythms using a strict regime of bedtime, meals, and activity, or knowledge of clock time. In order to extend these findings, in 1994 we started a series of studies to investigate in more detail the relationship between visual impairment and circadian rhythm disorders under real-world conditions.[60-62] To date, we have studied 67 blind adults (aged 17 to 74 years; 48 males, 19 females) with varying visual acuities using a home-based protocol where subjects are asked to maintain a daily sleep log for at least 4 weeks, and wear an activity monitor continuously.[63] For 48 hours per week, most subjects are also asked to rate their alertness and mood every 2 hours while awake using four 9-point Likert scales, and complete a four-choice serial auditory reaction time test after each alertness rating. Finally, they

are asked to collect their urine for the same 48 hours in 4-hourly episodes while awake plus an 8-hourly collec-
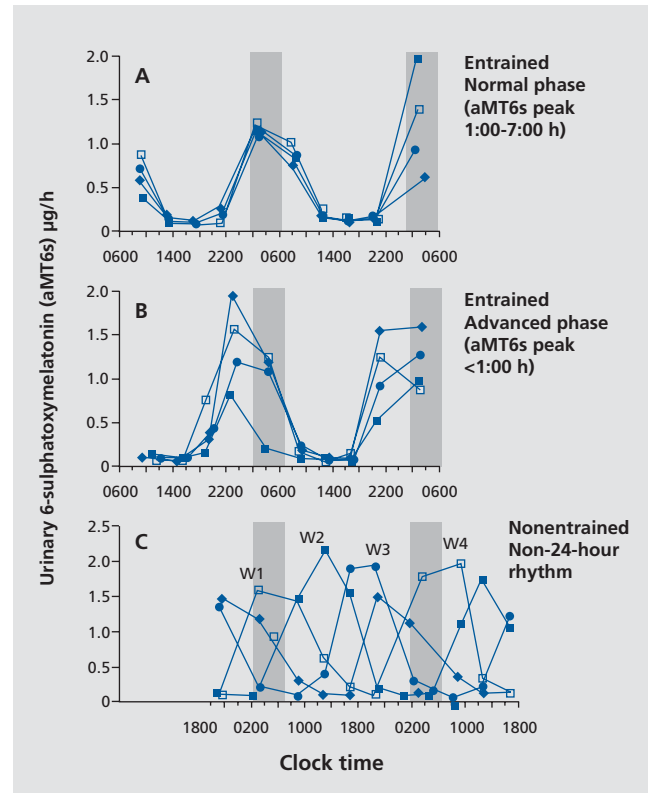

Figure 2. Characterizing circadian phase using urinary aMT6s rhythms. Examples of urinary aMT6s rhythms measured for 48 hours over 4 consecutive weeks are shown for three representative blind subjects. Panel A shows a normally entrained aMT6s rhythm with a normal night-time peak (grey bar, normal range 1:00-7:00 h), that remains remarkably stable from week to week, despite the study being conducted by the subject at home. A proportion of subjects exhibit stable 24-hour rhythms but are entrained to an abnormally advanced or delayed phase. Panel B shows an advanced subject who has an aMT6s rhythm peaking relatively early compared with normal. Panel C shows the most common rhythm type observed in subjects with no conscious perception of light (NPL), namely a nonentrained "free-running" rhythm. While the rhythm may initially appear arrhythmic, closer inspection shows that the aMT6s peak is changing from week to week over the 4-week study (W1-W4), getting relatively later each week, and thereby exhibiting a circadian period >24 hours (τ=24.7 h in this case). In these cases, longitudinal assessment over several weeks or even months, if the endogenous period is very close to 24 hours, is required to distinguish the nonentrained rhythm from a normally or abnormally entrained stable rhythm.

tion overnight, record the volume by weight, and retain a sample for analysis. The urine samples are analyzed for 6-sulphatoxymelatonin (aMT6s) *(Figure 2)*,[64] the major urinary metabolite of melatonin, or cortisol, which provide a reliable marker of circadian phase.[27,64-66]

The incidence of circadian rhythm disorders is related to the degree of visual acuity. Of the 30 individuals with light perception (LP; 19 males, 11 females), 77% had normally entrained aMT6s rhythms, and four (13%) had abnormally phased rhythms (2 advanced and 2 delayed). Two subjects had no detectable rhythm and one subject with minimal LP in one eye only exhibited a free running aMT6s rhythm ($\tau = 24.62$ h). Conversely, the majority of NPL subjects (76%) had abnormal aMT6s rhythms (either abnormally entrained or "free running"). Of those NPL subjects with at least one eye, 11 (46%) had free-running aMT6s rhythms (τ range = 23.92-24.79 h), 5 (21%) were abnormally phased (3 advanced, 2 delayed) and 7 (29%) were normally entrained. One subject had no significant rhythm. One subject with small vestigial eyes located under the skin (cryptophthalmos) also had normal aMT6s and cortisol rhythms. All of the bilaterally enucleated subjects (n=12) exhibited free-running rhythms with periods ranging from 24.13 to 24.81 h.

Although abnormal timing of hormonal patterns can confirm the presence of a circadian rhythm disorder, patients complain about the resultant circadian rhythm *sleep* disorder, and disturbed sleep is the most commonly reported symptom associated with misaligned circadian rhythms *(Figures 3 and 4)*.[62,67] Irregularities of sleep and its timing were previously related to an abnormal phase of the rectal temperature rhythm[37,38] and in 1990, Martens et al reported that 71% of NPL subjects (n=16) complained of a chronic sleep disorder associated with increased sleep episodes and increased daytime sleep.[68] We have extended these findings and showed that sleep depends on circadian phase,[69] even under real-world conditions.[62] In entrained subjects, the timing of sleep was highly correlated with the timing of the aMT6s rhythm such that subjects with advanced aMT6s rhythms had a relatively earlier sleep time and subjects with delayed aMT6s rhythms had a later sleep time *(Figure 4)*.[62] In "free-running" subjects, a more complicated pattern emerges where sleep exhibits a non-24-hour pattern that cycles in and out of synchrony with the 24-hour social day on which most subjects try to live *(Figure 3B)*. The episode of poor sleep is characterized by short duration night-time sleep and a high propensity for daytime naps,
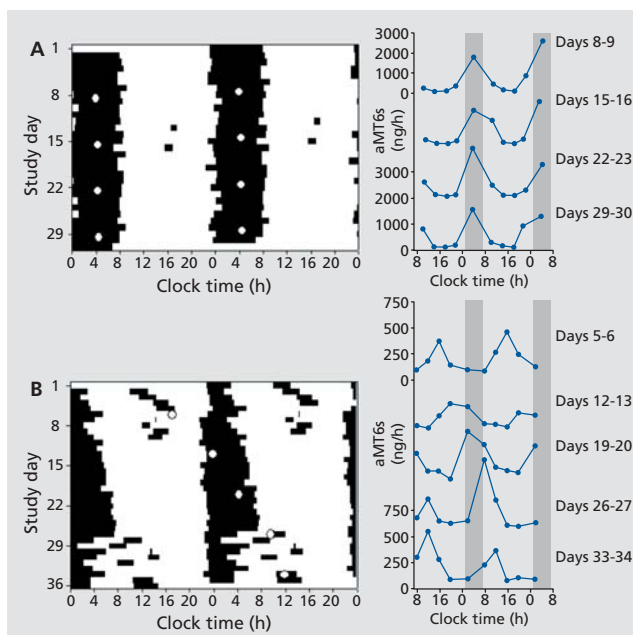
Figure 3. Circadian rhythms of sleep and melatonin in two blind subjects. The left-hand panels show subjective sleep times (■) over 4 to 5 weeks, double-plotted according to time of day (abscissa) and study day (ordinate). Subjects also collected sequential 4- to 8-hourly urine samples for 48 hours per week and the peak time of urinary 6-sulphatoxymelatonin (aMT6s) production each week (O) is plotted. The right-hand panels show the weekly rhythms of urinary aMT6s production (●) that correspond to the peak times shown and the gray bars represent the normal range of peak production for aMT6s (1:00-7:00 h).

Panel A shows data from a visually impaired female aged 35 years with a visual acuity allowing her to detect hand movements only and normal circadian rhythms (Subject 21). Both the sleep-wake cycle and aMT6s rhythm remain entrained to 24 hours (A, left panel) with normal night-time production of melatonin (A, right panel) and such rhythms would be typical of most sighted subjects. Note that her visual impairment, while severely disrupting the visual system, does not affect the circadian photoreception system, illustrating the functional separation of the visual and circadian photoreceptor systems. Panel B shows the rhythms from a 66-year-old totally blind man with one eye and no conscious light perception (Subject 20). He exhibits a sleep-wake cycle and melatonin rhythm that is not entrained to 24 hours. The aMT6s rhythm exhibits a non-24-hour period ($\tau = 24.68$ h) which clearly delays from week-to-week and is not entrained to the night (B, right panel). Similarly, the sleep pattern show a cyclic sleep disorder characteristic of "non-24-hour sleep-wake disorder," with recurrent episodes of disturbed night-time sleep and many daytime naps when melatonin peaks during the day (eg, Days 1 to 8, or 28 to 35) that alternate with episodes of good sleep and high day-time alertness when the melatonin is produced during the night (eg, Days 10-25) (B, left panel).

the timing of which coincides with the aMT6s peak as the circadian system drives sleepiness during the biological (but not social) night.[62,70] The cyclic sleep-wake pattern, formally termed "non-24-hour sleep-wake disorder,"[50] persists ad infinitum and can be extremely disruptive and debilitating, especially in individuals with periods very close to 24 hours, when sleep can remain misaligned from the circadian cycle for many months.

In addition to affecting sleep, circadian rhythm disorders also impact waking function. In addition to the high propensity for naps during the day,[70] subjects also rate themselves more sleepy and more miserable and perform worst when they are awake at an adverse circadian phase.[71] In entrained subjects, the daily profile of sleepiness, mood, and performance depends on the circadian phase of the wake episode, such that advanced subjects feel better in the early part of the day and worse late in the day, whereas delayed subjects report feeling very sleepy for the first half of the day, but then gradually getting better as the day goes on. These alertness and performance profiles are similar to those experienced by extreme "morning" and "evening" types who also sleep and wake at relatively abnormal circadian phases.[72] In free-running subjects, the rhythms in alertness and performance also free-run, as first shown in the case by Miles et al,[53] such that subjects report feeling the worst when awake at the time of peak aMT6s production and best when awake at

a normal circadian phase, when no aMT6s is being produced, as occurs in most sighted subjects.

The effect of light in the blind

The effect of visual impairment on circadian photoreception

The impact of different types of visual impairment on the circadian system has been used as an indirect method to assess the photoreceptor systems mediating circadian and other nonvisual responses to light. Firstly, these studies have shown that eyes are required for circadian photoreception; individuals without eyes, either through bilateral enucleation or as a result of developmental disorders, are unable to entrain their circadian pacemaker to the 24-hour light-dark cycle.[61] Similarly, the majority of totally blind individuals who retain their eyes but cannot consciously perceive light also exhibit circadian rhythms that are not entrained to the 24-hour light-dark cycle, as described above.

Disorders of the visual system do not always attenuate the circadian effects of light, however, demonstrating a functional separation of the visual and circadian photoreception systems. As outlined previously, the majority of legally blind individuals who retain some degree of light perception, even with very little usable vision in some cases, have
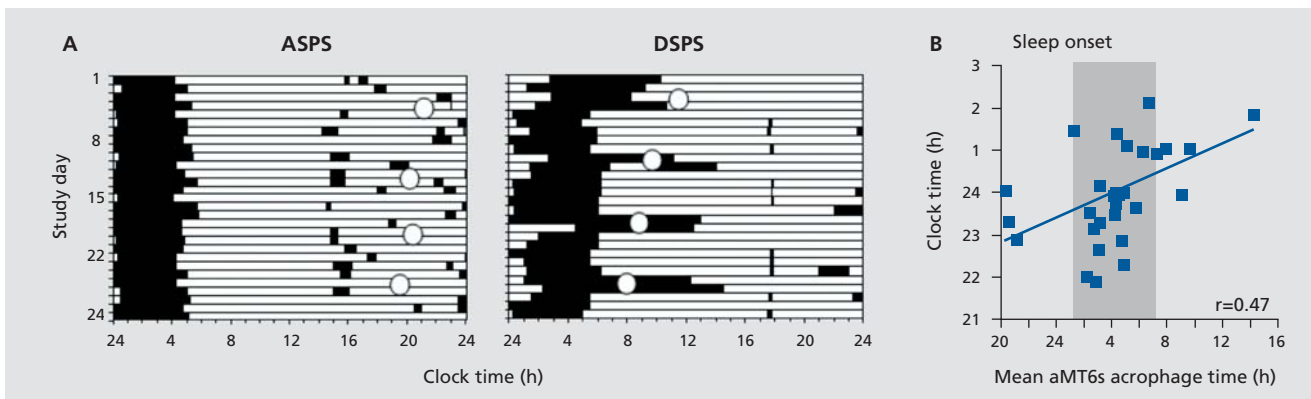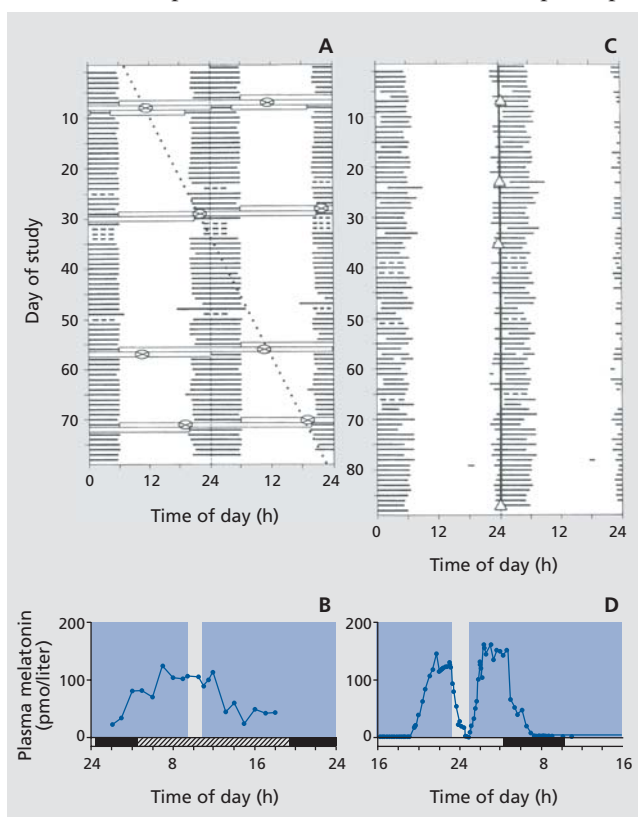
Figure 4. Relationship between sleep timing and circadian phase in entrained blind subjects. Panel A shows subjective sleep (■) and urinary 6-sulphatoxymelatonin rhythm (O) timing over 4 weeks (study day on ordinate axis, clock time on abscissa) in two blind subjects, one with advanced sleep phase syndrome (ASPS) and one with delayed sleep phase syndrome (DSPS). In the ASPS subject, the advanced aMT6s peak (~20:00 h, 8 hours earlier than normal) is associated with many daytime naps in the late afternoon and early evening, as the circadian system attempts to initiate sleep during the biological night, and an early wake-time from the main sleep episode. The DSPS subject exhibits a relatively delayed sleep onset time on most days, but shows a particularly delayed sleep pattern during weekends when not having to set an alarm for work, as on other days. Panel B shows the correlation between the timing of the aMT6s peak (abscissa) and sleep onset time (ordinate) in visually impaired entrained subjects, illustrating the change in sleep timing associated with altered circadian phase.

Adapted from reference 62: Lockley SW, Skene DJ, Butler LJ, Arendt J. Sleep and activity rhythms are related to circadian phase in the blind. *Sleep*. 1999;22:616-623. Copyright © Associated Professional Sleep Societies 1999

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normally entrained circadian rhythms.[61] Primary loss of the central or peripheral visual fields is also not associated with circadian rhythm disorders,[61,63] suggesting that the circadian photoreceptor system is less sensitive to the spatial distribution and intensity of light than vision. Color blindness, a more specific lesion of the three-cone photopic

visual system, also does not attenuate circadian responses to light, as measured by acute suppression of pineal melatonin,[73] suggesting that the cones are not the primary photoreceptors mediating this response. Finally, and most definitively, it has been demonstrated that a small proportion of blind people without light perception retain normal circadian phase-shifting and melatonin suppression responses to light, even in the absence of any functional rods or cones, as assessed by conscious ability to detect light, visually-evoked potentials, or electroretinogram *(Figure 5)*.[74,75] As expected if their eyes contained fully functional circadian photoreceptors, these individuals exhibit normally entrained 24-hour rhythms under real-world conditions and do not report sleep disorders.[74] The effects of light in these subjects are mediated exclusively via the eyes as, when their eyes are covered, the effects of light are inhibited. Thus, circadian photoreception can be maintained in some humans in the absence of a functional visual system, as has also been shown in transgenic and developmental rodent models of blindness (for review see ref 76). While intact circadian photoreception explains the normally entrained 24-hour rhythms in about 20% of entrained NPL subjects, most blind people who exhibit 24-hour rhythms are not affected by light ([63], Lockley et al, unpublished results) and are either entrained by nonphotic time cues (see below) or have a period very close or equal to 24 hours.

Spectral sensitivity of circadian photoreception

The neuroanatomical basis and photoreceptor mechanisms underlying the functional separation of visual and

Figure 5. Absence and presence of circadian photoreception in two totally blind subjects. Panels A and C: Subjects completed daily sleep and nap diaries for ~11 to 12 weeks and their sleep times (solid lines) are double-plotted according to convention in *Figure 3*. Subjects also had their circadian phase measured at regular intervals from either core body temperature minimum (⊕ Panel A) or plasma melatonin onset (Δ Panel C). Panels B and D show the results of a melatonin suppression test during which the subjects' eyes were exposed to bright white light (6000 to 13 700 lux) for 90 to 100 minutes during plasma melatonin production.
Panels A and B show the sleep–wake pattern and melatonin suppression response for a 70-year-old blind man with congenital glaucoma. He retained both eyes but reported no conscious light perception. Electroretinogram (ERG) and visually evoked potential (VEP) responses were not detectable. As shown in Panel A, the subject's circadian system was not entrained to the light-dark cycle and the core body temperature rhythm exhibited a non-24-hour period. Consistent with the lack of entrainment by light, light exposure did not have any effect on the melatonin rhythm, confirming that the retina-SCN-pineal pathway was not functional in this patient.
Panels C and D show the sleep-wake pattern and melatonin suppression results for a 21-year-old woman with Leber's congenital amaurosis, a type of retinal dystrophy. The ERG was undetectable but an abnormal VEP was recorded. As shown in Panel C, the sleep-wake cycle was normal with stable entrainment to 24 hours. The melatonin suppression response was clearly positive, with an immediate suppression of melatonin at lights on (open bar) which ceased once the bright lights were switched off. Despite the subject's lack of conscious light perception, light was still able to stimulate the retina-SCN-pineal pathway; covering the eyes prevented the response. The normal sleep-wake cycle, coupled with the positive melatonin suppression test, indicated that light was able to entrain the circadian system of this totally blind woman. Note: a similar sleep-wake pattern but accompanied by a negative melatonin suppression test would indicate that (i) the subject was entrained to 24 hours by a nonphotic time cues or (ii) the subject's endogenous circadian period was exactly 24 hours. SCN, suprachiasmatic nucleus

nonvisual responses to light have been discovered (for reviews see refs 76,77). Briefly, a novel opsin, melanopsin, has been located in specialized retinal ganglion cells that are directly sensitive to light and project to the brain areas mediating these nonvisual effects of light (eg, SCN for circadian and melatonin responses, olivary pretectal nuclei for pupil constriction responses). The cells are most sensitive to short-wavelength (blue) light ~480 nm and the absorption spectrum of melanopsin is distinct from the absorption spectra for the rods or cones. Animals that have had their melanopsin "knocked out" can still retain some circadian responses to light, showing that the traditional visual system likely contributes to these effects, but the melanopsin-driven system appears to be the primary phototransducer for the circadian effects of light. Action spectra for the behavioral effects of light in rodents and primates (eg, circadian phase resetting, pupil constriction) also show a peak sensitivity of ~480 nm, matching the cellular spectral sensitivity, as do action spectra for melatonin suppression and pupil responses in humans.[78-80] Circadian phase resetting and the alerting effects of light are also short-wavelength sensitive in humans,[81-86] suggesting that the novel non-rod, non-cone photoreceptor system primarily mediates a wide range of nonvisual effects of light. These findings are consistent with those in blind humans described above, who retain circadian responses to light despite absent or attenuated rod and cone function.

The effect of nonphotic time cues in the blind

Although light is the most powerful environmental time cue, nonphotic time cues are able to affect the circadian pacemaker.[30] In sighted subjects, the timing of sleep,[87] exercise,[88,89] and carbohydrate intake,[90] but not knowledge of clock time,[91] have been shown to phase-shift the circadian clock. Other potential nonphotic synchronizers include social interaction and olfactory cues.[30]

In the absence of light input to the clock, nonphotic time cues are obviously a potential therapeutic option to treat non-24-hour circadian rhythms disorder in the blind. There are currently no therapeutic guidelines, but some preliminary research suggests that it may be beneficial for patients to try to maintain a regular 24-hour schedule. Klerman and colleagues[92] showed that the circadian system of a blind man with a period of 24.1 h became entrained when he lived on a 23.8 h "day." All aspects of his schedule were shifted simultaneously in this protocol,

including the sleep-wake cycle, meal times, activity, posture, and interaction with staff, precluding identification of the effective time signal, but collectively at least they were able to induce a phase advance. Other attempts to entrain circadian rhythms in blind people using a "potential complex *zeitgeber*," including exercise (bicycle riding, 50 W over 15 mins), a strict social routine, a cold shower, and a heavy protein breakfast[37] appeared to have induced a shift in the timing of sleep and temperature rhythms, although it is not clear whether entrainment occurred. The relative weakness of nonphotic time cues is readily observed; however, in the majority of totally blind people who are not entrained when living in society (see above), where they are exposed to many 24-hour time cues such as work or school schedules, mealtimes, sleep-wake schedules, activity, alarm clocks, family and social interaction, and so on. The inability to entrain to these schedules is dependent on an individual's intrinsic circadian period as the weak nonphotic time cues with have narrow "limits of entrainment," the range of periods over which nonphotic cues can have an effect. If an individual's circadian period is too far from 24 hours, the weak nonphotic time signals will be unable to entrain it.

Treatment of circadian rhythm disorders in the blind

While some other drugs have been shown to shift the timing of the clock (for review, see ref 30) the most promising therapeutic strategy for treatment of non-24-hour sleep-wake disorder is daily administration of melatonin. Although it was shown more than 20 years ago that melatonin treatment could entrain free-running rhythms in rats[93] and could cause phase advance shifts in humans,[94,95] demonstration of entrainment in free-running humans took longer to prove. Initial experiments using daily treatment with 5 mg or higher doses either failed to affect the circadian pacemaker at all[56,96] or shortened period without inducing entrainment.[97,98] These and other cases[99-104] did report some improvement or stabilization of the sleep-wake cycle in these patients,[105] most likely through the direct soporific effects of melatonin.[105-108]

In 1996, we began a re-examination of the entraining effects of melatonin in seven men with non-24-hour rhythms with a period >24 hours.[109] Five subjects received 5 mg melatonin PO or placebo at 21:00 h each for a full circadian beat cycle (35 to 71 days depending on their circadian period) and two additional subjects received

melatonin only in a single-blind design. Entrainment was assessed using urinary cortisol rhythms.[64] As their endogenous rhythms were longer than 24 hours, subjects required a daily phase advance (ie, a shift to an earlier time) to become entrained to 24 hours.

Three of the subjects exhibited entrained cortisol rhythms and one had a shortened period during treatment. The remaining three subjects were not affected by melatonin. Post-hoc analysis of melatonin treatment timing indicated that those subjects who failed to entrain had treatment initiated at a time that corresponded to the delay phase of the melatonin phase response curve (PRC)[110] (equivalent to ~1:00-13:00 h in a normally-entrained subject) where melatonin causes a phase delay shift (ie, to a later time), the opposite of that required to entrain. Surprisingly, the subjects did not entrain once they free-ran into the correct window to cause a phase advance, unlike previous animal models.[93] Those subjects who became entrained or had a shortened period had their treatment initiated during the phase-advance portion of the PRC (~13:00-1:00 h in normal subjects), a time consistent with the observed daily advance achieved. We hypothesized at the time that the inappropriate initial timing in the nonentrained subjects may have affected the sensitivity to melatonin (for example, by receptor downregulation) when the appropriate treatment time was reached.

Shortly following publication of these data, similar results were published by Sack and colleagues using a 10-mg dose of melatonin initiated during the phase-advance window, who also showed entrainment of plasma melatonin rhythms when assessed during temporary suspensions of melatonin treatment.[111] In addition, they demonstrated that the 10-mg dose could be gradually stepped down to 0.5 mg and entrainment could be maintained.[111] These data raised the question as to whether a 0.5-mg de novo dose could also reset the clock, and both we and others confirmed that it could.[112-114] This low dose was also more likely to entrain than treatment with higher doses
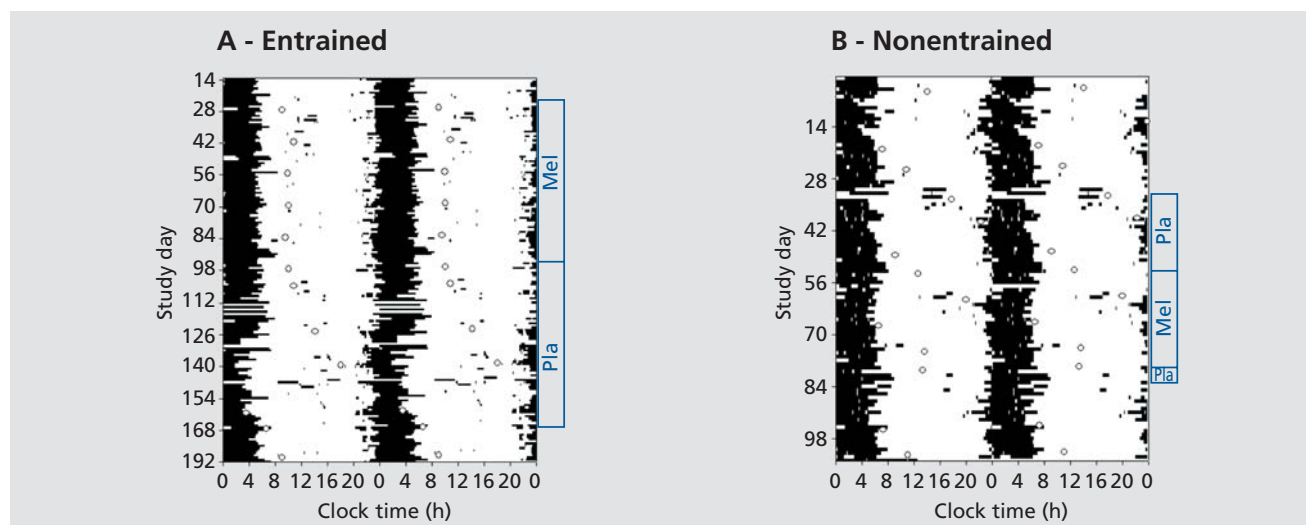
Figure 6. Entrainment of circadian rhythms in the blind with melatonin. This Figure shows the double-plotted sleep timing (■) and urinary cortisol peak times (O) for two totally blind men treated with 5 mg melatonin PO at 21:00 h for at least one circadian cycle in a placebo-controlled single-blind design. Sequential study days are plotted on the ordinate and clock time is plotted on the abscissa. The start and end of placebo (Pla) and melatonin (Mel) treatment are indicated by the boxes.

Panel A shows a subject who was entrained by melatonin treatment (S17). He exhibited a cortisol period of 24.3 h during placebo treatment but was fully entrained (τ=24.0 h) at a normal circadian phase (mean ± SD cortisol peak time =9.9±0.7 h)[67] during melatonin administration. The stabilized sleep-wake cycle observed during melatonin treatment becomes immediately disrupted upon cessation of treatment and reverts to the characteristic non-24-hour pattern, with cyclic episodes of good sleep at night and a small number of daytime naps followed by extremely disrupted night-time sleep and excessive day-time napping.

Panel B shows a subject who failed to entrain to melatonin treatment (S45) and who exhibited similar periods during melatonin (25.2 h) and placebo (24.9 h) administration, despite melatonin treatment for nearly two full circadian cycles. The persistent cyclic non-24-hour sleep disorder is apparent throughout both the placebo and melatonin treatment.

Reproduced in part from ref 109: Lockley SW, Skene DJ, James K, Thapan K, Wright J, Arendt J. Melatonin administration can entrain the free-running circadian system of blind subjects. *J Endocrinol*. 2000;164,:R1-R6. Copyright © Society for Endocrinology 2000

(5 to 20 mg) maybe through providing a more discreet time signal than a higher dose with a more prolonged duration in the circulation. The individual circadian period may also affect the likelihood of entrainment with melatonin,[115] as those subjects with periods furthest from 24 hours may be outside the range of entrainment for this relatively weak time cue. Inconsistencies still exist, however, as to whether the circadian time of initial treatment affects subsequent entrainment. In our studies, using both 5 and 0.5 mg melatonin, entrainment was more likely if treatment was initiated in the advance, compared with the delay, phase of the PRC in both between and within-subjects designs ([109,113], Lockley et al, unpublished results). At low doses, however, (0.5 mg or lower), melatonin treatment initiated at any circadian phase will eventually cause entrainment of the circadian pacemaker,[113-114,116] although there may be a delay until presumably the phase-advance part of the PRC is reached. Current consensus suggests, therefore, that smaller doses (up to 0.5 mg) may be preferable to larger doses, and that treatment timing should be timed initially to phase advance if possible (to achieve immediate entrainment *[Figure 6]*)[109] but if mistimed, may still eventually cause entrainment. Given melatonin's soporific properties, treatment should also be given close to the desired bedtime to ensure the alignment of the circadian and social day. Melatonin administration has also been explored for treatment of abnormal entrained phase disorders in the blind,[117] as well as sighted populations,[118] but appropriate timing may be even more important in these groups than non-24-hour sleep disorder.[119]

Conclusion

The detrimental effects of loss of light perception, or loss of eyes, on circadian rhythm entrainment, and subsequently sleep and waking function, are often inadequately recognized by physicians, families, friends, and employers, making it difficult for blind people to obtain the treatment and support required to deal with this highly prevalent condition. Our data confirm the anecdotal accounts from subjects, who describe fighting to stay awake at work, having problems maintaining concentration and memory during the day, or being overwhelmed with a desire to sleep at inappropriate times. These circadian rhythm sleep disorders are chronic, unrelenting, and currently difficult to manage with conventional approaches. Simply treating the sleep-wake symp-

toms, for example with a combination of daytime stimulants and night-time hypnotics, indicates an insufficient diagnosis and a failure to address the underlying cause of the condition. Correcting the underlying misalignment between circadian and sleep-wake cycles, for example using appropriately-timed melatonin treatment as described above, is fundamental for the optimal treatment of circadian rhythm sleep disorders.

Clinically, our data suggest that sleep disorders in visually impaired people with some degree of LP are not due to circadian desynchrony, and should therefore be investigated for other sleep disorders as in sighted subjects. Blind people with NPL who complain of sleep disorders, particularly episodic or cyclic insomnia and daytime sleepiness, should be studied longitudinally to confirm a circadian disorder diagnosis, using home-based sleep diary and urine assessments as described above.[61,62] If non-24-hour rhythms are confirmed, then treatment with low-dose (0.5 mg) melatonin at a fixed clock time close to bedtime is warranted. To enhance the chance of immediate entrainment, treatment should commence once the subject begins to slip out of a normal sleep phase, characterized by difficulty initiating sleep (long sleep latency) or difficulty getting up in the morning. In advanced or delayed sleep phase syndrome, melatonin treatment timing should be individually determined based on the extent of their abnormal phase according the melatonin PRC[110] and stepwise treatment for particularly advanced or delayed subjects may be warranted. In all of these disorders, daily melatonin treatment is a lifelong requirement, as once treatment is stopped, the circadian pacemaker will revert to its endogenous period or phase angle *(Figure 6)*. The safety profile of melatonin, while not assessed for very long-term use in humans, is good,[104,120,121] although care should be taken to ensure it is from a reliable source and pharmaceutical grade. In the near future, melatonin analogs will also become approved for this indication although as with melatonin, a correct initial diagnosis is required, and precise timing and dose remain to be determined. ❏

Clinical research

Deterioro visual y trastornos de los ritmos circadianos

Muchos aspectos fisiológicos y conductuales del ser humano están controlados por ritmos circadianos de 24 horas, los que tienen un gran impacto en nuestra salud y bienestar. Estos ritmos incluyen el ciclo sueño-vigilia, el alerta y los patrones de varias funciones, como también el perfil de secreción diaria de muchas hormonas. Estos ritmos se generan espontáneamente por un "marcapaso" interno en el hipotálamo y se requiere de la exposición de los ojos a la luz diurna para mantener estos ritmos circadianos sincronizados tanto internamente como con el ambiente externo. Los sujetos videntes tienen este proceso de sincronización asegurado, aunque ellos experimenten algunas de las consecuencias derivadas de la falta de sincronía cuando tienen un "jetlag" o trabajan en turnos nocturnos. La mayoría de las personas ciegas no percibe la luz; sin embargo, experimentan continuas faltas de sincronía circadiana debido a que falla la llegada de la información luminosa al reloj circadiano hipotalámico, lo que se traduce en episodios cíclicos de mal dormir y mal funcionamiento durante el día. La administración diaria de melatonina proporciona un sustituto para la sincronización diaria de la "clave temporal", y aunque constituye una estrategia terapéutica promisoria, aun falta determinar el momento más adecuado de la administración y la dosis terapéutica óptima.

Troubles du rythme circadien et déficit visuel

De nombreux aspects de la physiologie et du comportement humain sont dominés par les rythmes circadiens de 24 h qui ont un impact majeur sur notre santé et notre bien-être, notamment le cycle veille-sommeil, les variations quotidiennes des processus attentionnels et de performance, et la sécrétion de nombreuses hormones. Ces rythmes circadiens sont générés spontanément par un « pacemaker » interne situé dans l'hypothalamus. Une exposition quotidienne des yeux à la lumière est nécessaire pour conserver la synchronisation de ces rythmes à la fois entre eux et avec l'environnement externe. Les voyants considèrent cette synchronisation quotidienne comme évidente, tout en expérimentant certaines conséquences de la désynchronisation circadienne en cas de décalage horaire ou de travail en horaire posté. La plupart des aveugles, n'ayant aucune perception de lumière, subissent une désynchronisation circadienne permanente par impossibilité de l'information lumineuse d'atteindre l'horloge circadienne hypothalamique. Ceci conduit à des épisodes cycliques de mauvais sommeil et de mauvais fonctionnement diurne. En resynchronisant les plages horaires chaque jour, l'administration quotidienne de mélatonine est une stratégie thérapeutique prometteuse, bien qu'il faille encore en préciser l'horaire d'administration et la posologie optimale.

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