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Chronobiology of sleep in humans

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Abstract. Periodic circadian (24-h) cycles play an important role in daily hormonal and behavioural rhythms. Usually our sleep/wake cycle, temperature and melatonin rhythms are internally synchronized with a stable phase relationship. When there is a desynchrony between the sleep/wake cycle and circadian rhythm, sleep disorders such as advanced and delayed sleep phase syndrome can arise as well as transient chronobiologic disturbances, for example from jet lag and shift work. Appropriately timed bright light is effective in re-timing the circadian rhythm and sleep pattern to a more desired time, ameliorating these disturbances. Other less potent re-timing effects may also be obtained from the judicious use of melatonin and exercise.

Keywords. Sleep, circadian rhythms, zeitgebers, bright light, delayed sleep phase syndrome, advanced sleep phase syndrome.

Sleep/wake regulation

Our sleep/wake cycle is determined by the two independent but additive processes of homeostatic sleep drive and circadian influences. This model is elaborated in an accompanying article by Nakao. In brief, homeostatic process involves an increasing sleep drive that builds up during wake and is dissipated in sleep. The circadian process involves self-sustaining 24-h rhythms of physiological activity. The present article concerns the chronobiology of sleep and will elaborate the circadian rhythm influences on sleep. Circadian rhythms are ubiquitous and are significant biological regulators occurring in organisms ranging from unicellular organisms to humans. They play an important role in controlling daily hormonal and behavioural rhythms such as our core body temperature, cortisol and melatonin rhythms, sleep/wake cycle, subjective alertness and performance levels.

Phase relationships between rhythms

The sleep/wake cycle, body temperature and melatonin rhythms have a stable internal phase relationship with maximum sleepiness coinciding with the melatonin excretion peak and the core body temperature nadir in humans and other diurnal species. In a normally entrained individual (synchronized with the light/dark cycle), the major sleep period occurs during the hours of darkness, with sleep onset taking place about 23:00 h and wake-up time occurring about 07:00 h. Melatonin onset precedes sleep onset by about 2 h and about 7 h before core body temperature minimum [1, 2]. Melatonin excretion reaches a peak between 01:00 and 03:00 h and then decreases to barely detectable levels from about 09:00 h [3–5]. Core body temperature usually peaks in the early evening and then decreases to a nadir occurring between 03:00 and 06:00 h [6, 7]. Sleep onset is usually initiated about 5 to 6 h prior to the core body temperature nadir [8]. In young healthy volunteers with normal sleep patterns, there were strong associations between melatonin offset, the temperature minimum and wake up time, with wake up time occurring soon after the nadir of the core body temperature [9] (Fig. 1).

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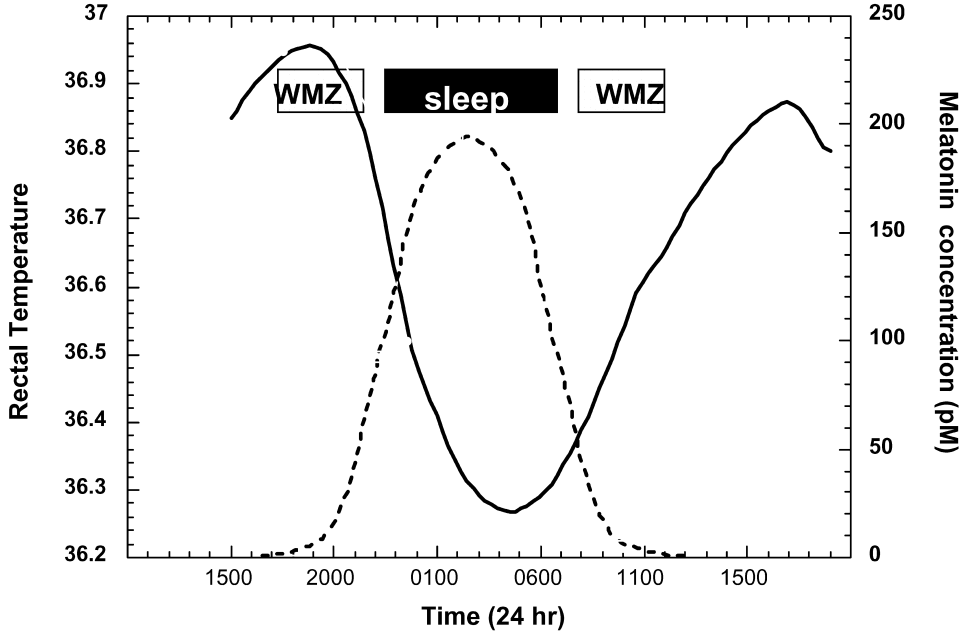

Figure 1. Graphical representation of the melatonin (dotted line) and core body temperature (solid line) rhythm over a 24-hour period with the major sleep episode indicated by the black bar and the wake maintenance zones by the shaded bars.

Effects of the circadian system on sleep

The propensity to fall asleep appears to be determined by the circadian system with the most rapid increase of sleep propensity occurring approximately 2 h after the onset of the secretion of nocturnal melatonin [10–12] and when core temperature is falling [13]. Sleep propensity is then high for a period of about 8 h with the maximum propensity at the time of the temperature nadir [14]. There also appears to be two 3-h periods when individuals are rarely able to fall asleep spontaneously [15, 16]. The first period, termed the 'wake maintenance zone', is centered approximately 6–9 h before the temperature minimum (about 19:00–22:00 h) with the second zone 4–7 h after the temperature minimum (about 09:00–12:00 h). This second zone, the 'wake-up' zone, usually occurs during the rising part of the temperature cycle and appears to be associated with an increased probability of awakening from sleep [17, 18].

Anatomy and functions of the clock

In humans, the circadian pacemaker is located in the suprachiasmatic nucleus (SCN), a small structure in the anterior hypothalamus, above the optic chiasma, on either side of the third ventricle [19, 20]. The SCN generates the endogenous rhythm with a period length (or time taken to complete a full cycle) of approximately 24.2 h [21]. Entrainment of the circadian pacemaker ('setting the clock time') is by photoperiodic information of light/dark cycle that is relayed to the SCN via the optic nerve (retinohypothalamic tract, RHT).

The human circadian pacemaker system is composed of photoreceptors and input pathways (RHT) that receive and transmit light cues, the SCN itself and output pathways from the SCN [22, 23]. Light/dark information is converted into action potentials by the photoreceptors in the retina and transmitted to the SCN via the RHT. From the SCN, rhythmic information reaches the pineal gland, a small pea-sized structure located close to the 3rd ventricle and ventrally to the splenium, and results in the synthesis and secretion of melatonin [22].

The role of melatonin is to convey information of the daily light/dark cycle to every tissue of the body [24]. Melatonin has been described as the 'hand' of the clock, as it not only responds to signals of the SCN but the endogenous melatonin rhythm can indicate the phase or time of the clock [25]. In humans, putative melatonin receptors have been located in the SCN and have been found to provide a feedback loop to the SCN. By way of this feedback loop, the circulating melatonin influences the SCN that in turn controls the timing of the secretion of melatonin from the pineal gland [26].

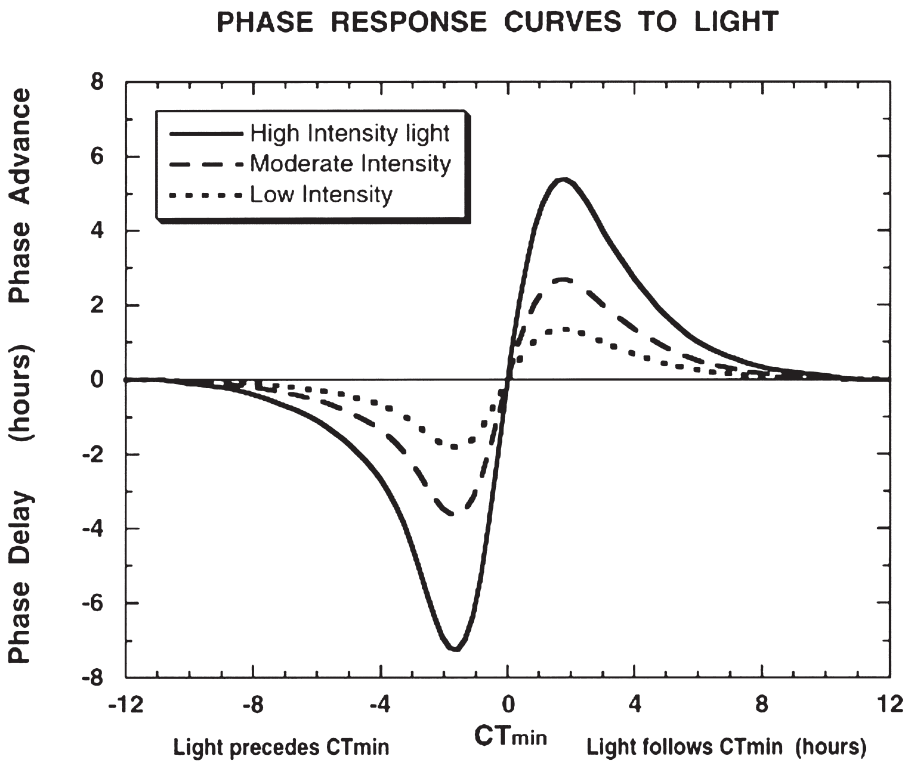

Figure 2. Graphical representation of the human phase response curve (PRC) for light Administration showing three phase response curves for the effects of three different levels of light intensities [From Ref 35 with permission].

Zeitgebers

The SCN is entrained or synchronized by environmental cues that are termed zeitgebers or 'time givers'. The most important time cue is the light/dark cycle; however, other zeitgebers include social cues such as eating and physical activity or internal zeitgebers such melatonin.

Light

Initial studies demonstrated the effect of bright white (broad-band) light in suppressing melatonin and the phase shifting of melatonin and temperature circadian rhythm in humans [27–29]. Recently, it was shown that the circadian system is more sensitive to shorter wavelength light (blue and green) than to the longer wavelengths (red). The timing, intensity and duration of a light pulse(s) as well as wavelength affect the ability of light to entrain the circadian pacemaker.

Timing

The timing of the light stimulus affects the magnitude of a phase shift. Lewy and colleagues [30] proposed that humans had a phase response curve (PRC) to light with the circadian system responding differently to light depending on its timing within the phase of the circadian cycle. Extensive studies have been carried out to elaborate the human phase response to bright light [31–34]. When light pulses have been administered on a single day or over consecutive days, it has been demonstrated that large phase shifts of the circadian rhythm occurred when the midpoint of the bright light pulse was centered close to the temperature minimum. To achieve a phase delay of the circadian rhythm, a light stimulus needs to be presented before the temperature nadir, and to attain a phase advance (or shift the clock time earlier), the stimulus is to be presented after the temperature nadir. Figure 2 is a graphical representation of the human PRC for light administration showing three phase response curves for the effects of three different levels of light intensities [35]. For all light intensities light presented before the temperature minimum phase delays and light after the temperature minimum phase advances, with the magnitude of the response greater for light presented closer to the temperature minimum.

Furthermore, the magnitude of the phase shift is dose-dependent as well as time-dependent. Minors and colleagues [33] found that when a light pulse was administered over three successive cycles, phase shifts of 4–7 h were induced compared with phase shifts of approximately 2 h following one light pulse.

Light intensity

Intensity also affects the magnitude of melatonin suppression and circadian phase change. Recent studies have demonstrated that the human circadian

pacemaker is more sensitive to light than originally determined by Lewy and colleagues [29]. Light intensities as low as 300–500 lux (a metric measure of illuminance) when administered during the rising phase of the melatonin excretion have suppressed melatonin [36–38] and delayed the melatonin rhythm [39].

Three 5-h pulses of indoor light intensity of about 180 lux, centred 1.5 h after the temperature minimum was able to induce a phase advance of the temperature and melatonin rhythms of 1.16 and 2.89 h, respectively [40–42]. These studies demonstrated that the degree of the resetting response (phase advance) of the core body temperature and melatonin rhythm increased with the intensity of illumination in a nonlinear function (i.e. increases from lower intensities of a given amount, say 500 lux, produced greater increase in phase change than the same increase in the high-intensity range).

Other researchers have found that the best model to fit the response of melatonin suppression and the phase resetting of melatonin and alertness to variations in light intensities was consistent with a logarithmic dose-response curve [43, 44]. When a longer duration of light pulse of 6.5 h was administered in the early subjective night, it was found that plasma melatonin concentrations were suppressed in a dose-dependent manner. From light of 9100 lux they obtained only twice the alerting response, melatonin suppression and phase delay obtained from 100 lux (about equivalent to dim indoor light illuminance).

The above studies demonstrate that nocturnal melatonin can be minimally suppressed by light as low as 200 lux and that melatonin suppression and phase resetting response occur in a dose-dependent manner, with higher intensities producing greater suppression. A further implication of these finding is that experiments determining the effect of light on melatonin and core body temperature rhythms should be carried out with the control condition light intensity lower than ordinary room illumination of 150 lux.

Light duration

Studies have produced modest 30 min phase delays of the melatonin rhythm with a 1-h single light pulse [39, 45]. Dawson and colleagues [46] were able to produce both phase delays and phase advances with a single 4-h light pulse of 12,000 lux. A phase delay of 2.4 h occurred when light was administered immediately prior to habitual bedtime and a phase advance of 1.5 h was induced following light exposure immediately following habitual wake-up time. In another study, when, a single 3-h light pulse of 5000 lux was presented at different circadian times relative to the temperature minimum, average phase delays and advances of one hour were produced with phase delays being larger than phase advances [47]. In general, the research suggests that longer duration light pulses produce greater circadian phase changes.

Light wavelength

Shorter wavelength light (blue and green) has been found to be more effective than longer wavelength light (yellow and red) in suppressing nocturnal melatonin secretion [48, 49] and phase changing the melatonin rhythm [50–52]. Two studies have established an action spectrum for nocturnal melatonin suppression [53, 54] with both demonstrating that the shorter wavelengths are the most potent wavelength region for regulating the human pineal gland.

Melatonin

Exogenous melatonin is a nonphotic zeitgeber with appropriately timed administration, being able to phase advance and phase delay the circadian system. Human phase response curves have been described [55–58] demonstrating that when melatonin is administered in the late afternoon or early evening, the melatonin rhythm will phase advance, as opposed to the phase delays seen in evening bright light exposure. Maximum advances occur when melatonin is given 3 h before the dim light melatonin onset [59], or about 5 h before one's habitual bedtime.

On the other hand, a delay in the melatonin onset has been demonstrated with melatonin administration in the morning [60]. Melatonin administered at about the time at which endogenous melatonin ceases (about 2 h before habitual wake time) will produce a melatonin rhythm delay. It should therefore be noted that the melatonin phase response curve is 180 degrees out of phase with light phase responses, with melatonin producing phase advances with early evening administration and phase delays with early morning administration.

Physical exercise

Nonphotic entrainment of the circadian system has also been demonstrated by appropriately timed single bouts (1–3 h) of moderate to high-intensity exercise [61–63]. Exercise during the late subjective day, before the onset of melatonin excretion, has been shown to produce a phase advance of the melatonin rhythm [63], whereas exercise during most of the subjective night produce phase delays [61–64].

Sleep-wake cycle

Two recent studies carried out under very dim light conditions have found that sleep itself may be a weak zeitgeber in humans. Under dim light of about 1.5 lux, Wright and colleagues [65] studied subjects for up to

55 days in the laboratory, and demonstrated that the activity-rest cycle was sufficient for entrainment to a 24-h day. Under near darkness (<0.2 lux) and while keeping behavioural factors such as meals and posture constant, Danilenko and colleagues [66] advanced the timing of sleep by 20 min each day. The core body temperature minimum and the dim light melatonin onset advanced relative to the control condition of fixed sleep; however, the effect size was only small to medium. Therefore, changing the timing of sleep alone has little effect on circadian timing if it does not coincide with a changed exposure to light.

Circadian rhythm sleep disorders

Disturbances of the relationship between components of the biological clock can be experienced chronically in some sleep disorders (delayed and advanced sleep phase syndrome) and transiently as occurs in jet lag and shift work. When sleep is attempted at a circadian time that is not optimal for the major sleep episode, the result can be either difficulty falling asleep or early morning awakenings. Both of these circadian rhythm sleep disturbances can result in a decrease of total sleep time and thus can impair alertness and overall well-being. Re-entrainment of the endogenous circadian pacemaker with appropriately timed bright light can alleviate these symptoms.

Delayed sleep phase syndrome

Diagnostic criteria [67] describe individuals with delayed sleep phase syndrome (DSPS) as having difficulty falling asleep at their desired bedtime and an inability to wake spontaneously at the desired time in the morning. For example, individuals with DSPS may wish to sleep between the hours of 23:00 and 07:00; however, according to their delayed circadian rhythm, their sleep period may actually occur between 02:00 and 10:00 h. Although they may have an inappropriately timed sleep period, individuals with DSPS usually have normal sleep architecture [68] and do not experience, for example, night-time awakenings. Prevalence rates for DSPS have ranged from 0.2–10% of the population [68–72]. The apparently large range of prevalence estimates may be due to variations in the severity criteria for the delayed sleep period. A recent study reported the habitual sleep onset times of 13 patients diagnosed with DSPS varied between about 23:45 and 05:15 h [73]. Thus less severe DSPS (i.e. 2–3 h delays of sleep period), while still producing a sleep/wake problem, could well be experienced by more than 10% of the population [69]. Weitzman and colleagues [68,72] first defined delayed sleep phase syndrome (DSPS). The major characteristics of DSPS were long sleep onset latencies with late sleep onset times. For example, if an individual was trying to fall asleep before midnight, then sleep latencies could be 2 h and longer. Often total sleep time would be prematurely interrupted due to the need to wake for social or work commitments. A reduced amount of sleep will result in daytime sleepiness, especially in the mornings, irritability and a lack of concentration, all of which could subsequently affect school and work performances as well as family life. Sleeping in (usually on weekends) to recover accumulated sleep debt further delays the circadian rhythm and exacerbates DSPS [74, 75].

If the core body temperature rhythm is phase delayed, then the 'wake maintenance' zone would also be delayed in clock time. For example, if the temperature minimum was delayed until, say, 08:00–09:00 h, the wakefulness zone would occur from 22:00 to 02:00 h, resulting in an inability to fall asleep at the 'desired time' [76]. Core body temperature and melatonin rhythms have been found to be delayed in individuals with sleep onset insomnia (difficulty initially falling asleep) and DSPS compared to control groups [77–80]. Morris and colleagues [77] found that volunteers who took longer than 45 min to fall asleep had a delay of their core body temperature markers approximately 2.5 h later than the control group. They were also attempting to fall asleep within their 'wake maintenance zone' of their delayed circadian rhythm in comparison to the control group, who had bedtimes closer to their body temperature minimums. Another study found that clients with DSPS had a significant delay of their sleep onset and offset times as well as circadian temperature nadirs compared with a control group [78]. Circadian melatonin plasma parameters of onset, acrophase (peak level) and offset have also been shown to be phase delayed in individuals with DSPS by up to 4 h [79–81]. Therefore, it appears the individuals with DSPS have a significant delay of their whole circadian system that impedes their ability to fall asleep at a normal bedtime.

A limited amount of studies have used bright light stimulation to advance the endogenous rhythm of individuals with DSPS [82–87]. In two pilot studies, we were able to advance the melatonin rhythm and sleep onset time of participants with DSPS by about 1 h following 1 week of morning bright light of 2500 lux [86] and advance the melatonin rhythm over 2.5 h after 1 week of 1000 lux blue light [88].

Exogenous melatonin has been administered to patients with DSPS. However, the varying doses, times and number of doses make it difficult to compare studies. Nevertheless, evening melatonin administration has resulted in phase advances [73, 81, 89], less daytime fatigue [90] and overall sleep

improvement [91]. A recent study with healthy adults [92] showed that the addition of evening melatonin to morning bright light therapy produces significantly greater phase advance than from morning bright light alone, suggesting that the effects of evening melatonin administration and morning light are additive.

Advanced sleep phase syndrome

The International Classification of Sleep Disorders nosology describes advanced sleep phase syndrome (ASPS) as a disorder in which the major sleep period is early or advanced in respect to the desired sleep/wake period [67]. Individuals with ASPS have overwhelming early evening sleepiness, an early sleep onset and morning awakening earlier than desired. They present with an inability to stay awake in the evening and/or with early morning awakening insomnia. For example, bedtimes could be as early as 19:00 and wake up times at 03.00 h. Although individuals with ASPS usually have no difficulty in initiating sleep, the tendency to feel sleepy and fall asleep early in the evening can be a social handicap. If the person attempts to delay bedtime by remaining active in the evening, awakening will still occur too early with an unwanted decrease of sleep time. Delaying bedtime until 22:00 h but a final wake-up time at 03:00 h will result in a total sleep time of only 5 h. This will inevitably lead to excessive daytime sleepiness, fatigue, moodiness and other symptoms of sleep deprivation such as lack of motivation and concentration. The prevalence rates of ASPS are unknown; however it appears to be reported more frequently in the middle-aged and older population [93].

In participants who experience early morning awakening insomnia, average wake-up times, circadian temperature and melatonin rhythms have been shown to be advanced compared with a control group of aged matched normal sleepers [94, 95]. Temperature minima ranged between midnight and 02:30 h, and urinary melatonin onset occurred early at about 21:00 h. If the temperature minimum is as early as midnight, then the 'wake-up' zone would also be advanced and could occur as early as 04:00 h, explaining the inability of individuals with ASPS to fall back to sleep in the mornings despite having only perhaps 5–6 h sleep.

In a recent study we demonstrated that evening bright light therapy is effective in phase delaying circadian parameters, including the sleep-wake cycle of individuals with early morning awakening insomnia and advanced sleep phase syndrome [96]. Subjects in the active condition were administered two evenings of bright (2500 lux) light from 20:00 h until midnight, close to their temperature minimum of 02:00 h. The average temperature minimum and dim light melatonin onset were delayed by about 2 h. Furthermore, there was also an improvement in sleep measures with a delay in wake-up time and an increase in total sleep time.

Jet lag

Although a transient problem, jet lag and the concomitant sleep, alertness and performance problems can have an effect on the individual as well as on businesses, governments and even sporting events [97]. Travellers and flight crew experience jet lag as they cross several time zones in a short period of time and experience a desynchrony between their endogenous circadian rhythm (still timed to their home environment) and the clock time of the new environment. One survey has found that up to 94% of passengers suffered jet lag, with 45% stating they found these symptoms severely disturbing [98].

The symptoms of jet lag due to this desynchrony include such sleep disturbances as difficulty initiating and maintaining sleep, and poor daytime functioning due to sleepiness, impaired alertness, fatigue, decrements in performance, lack of concentration and some gastrointestinal problems [99, 100].

Researchers have also found that chronic jet lag (long-term repeated desynchrony) experienced by flight crew may lead to temporal lobe atrophy and possibly some cognitive deficits in working memory and spatial learning [101, 102]. When flight crews have been monitored before, during and following multiple long-haul flights, their daytime sleep episodes were on average 41% shorter than night-time sleep episodes. And as the crew were unable to synchronize to the rapid time zone changes, the circadian nadir of alertness and performance could occur during flight [103, 104].

The severity of symptoms depends on the number of time zones crossed as well as the direction of the flight. Travellers flying east have more difficulty adjusting to the new time zone than travellers flying west, the latter requiring a delay of the circadian rhythm. As the period length of the human circadian rhythm is somewhat longer than 24 h, phase delaying the rhythm required following westward flight will take less time than the phase advance required after eastward flights. For the sleep-wake, temperature and other hormonal rhythms to gradually synchronize to the new environment, it can take about 1.5 days/h of adjustment [105]. One recent study of healthy top athletes found that, after a westward flight, jet lag symptoms persisted up to day 5–6, and up to day 7 following a eastward flight [106]. Training performance was at its lowest during the first 4 days after the westward flight.

Appropriately timed exposure to bright light and darkness as well as exogenous melatonin has been

found to be effective in treating jet lag. Exposure to daylight may be sufficient to entrain the circadian rhythms after eastward flights across four to eight time zones. However, artificial light would be necessary following westward flights when the most favourable time for light exposure would occur after sunset [107]. Researchers have proposed advancing the circadian rhythm prior to an eastward flight to avoid or at least minimize the symptoms of jet lag [108–110]. A combination of a gradual advance of the sleep schedule by 1 h each day over a 3-day period, with intermittent exposure to bright light in the morning [108, 109] and afternoon exogenous melatonin [92], can result in phase advances from 1.5 to 2.5 h. This advance of the circadian rhythms and sleep pattern will decrease the amount of phase change required upon arrival at the destination.

Shift work

Another self-imposed internal desynchronization between the endogenous circadian rhythms and sleep occurs chronically during shift work, resulting in insomnia during the daytime hours and excessive sleepiness during the nocturnal work time hours.

It has been estimated that approximately 5–10% of the population work night shift, typically between the hours of 22:00 and 06:00 h [111]. Of these night-shift workers, approximately 60% experience some type of sleep disturbance, with older shift workers generally less able to tolerate or recover from night shift than younger workers [14, 112].

Night shift workers need to be alert during the time that their sleepiness is actually increasing and core body temperature is falling. Generally the shift worker then attempts to initiate sleep between 8:00 and 10:00 a.m., just as body temperature is rising and at the time of the second 'wake maintenance' zone. This results in the shift worker experiencing difficulty falling asleep, as well as shortened and fragmented sleep, often with total sleep time reduced by 2–4 hours [105, 113].

Shift workers not only have to contend with sleeping in daylight hours but also with daytime noise and family commitments. Due to social and family pressures, shift workers often attempt to revert to normal life on their days off, which means attempting to sleep at night and be awake and alert during the day. In this way, the shift workers' circadian rhythms never fully adjust to their work, sleep and family schedules [114]. The negative impact of night shift work arises from sleep disturbances, impaired physical and psychological health [115] and disturbed social and family life [116]. Apart from daytime insomnia, shift workers experience diminished alertness during the night work period, and this can lead to poor performance, low productivity and fatigue-related work accidents Re-entrainment of the circadian rhythm can help night-shift workers to adapt to their new sleep/wake schedule. Simulated night-shift studies and field studies have demonstrated that appropriately timed bright light therapy can improve the adaptation to shift work [114, 117–120]. Intermittent exposure to bright light during the night shift, dark glasses in the morning [121, 122] and timed sleep scheduling [123] can produce a phase delay, with the temperature minimum occurring at the beginning of the sleep period instead of at the end of the night shift [121, 122]. Even partial re-entrainment has been shown to be sufficient to improve performance and mood measures [124].

Phase delays occurring in totally blind individuals

Difficulties maintaining entrainment to the day-night cycle have been reported in some totally blind individuals [125, 126]. This can lead to progressive phase delays so that for periods of time these individuals experience daytime sleepiness and insomnia, whereas a week or two later they will progressively delay until they are again sleeping well at night and are alert during the day. There is some evidence that appropriately timed administration of melatonin can entrain their rhythm to a 24-h cycle [127, 128].

Conclusion

Sleep occurs within a circadian chronobiological context. Sleep is enhanced at some circadian phases and impaired at others. There are sleep and chronobiological disorders such as jet lag and shift work that appear to be based on desynchrony between the sleep-wake cycle and circadian rhythm. Zeitgebers can retime the body's circadian system and thus re-synchronize the circadian rhythm with the sleep-wake cycle and ameliorate these disorders. The most potent retiming effect appears to be that of intense bright light, particularly in the blue and green wavelengths. Therefore the appropriate timing of exposure to bright light and darkness would be indicated as effective treatments of these disorders.

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