Light-induced Resetting of Circadian Rhythms in Humans

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ABSTRACT

Light is the most important environmental signal for synchronizing human circadian rhythms. The circadian system is normally synchronized with the solar day, ensuring that the sleep–wake cycle and endocrine rhythms are timed appropriately. However, exposure to electrical lighting can also reset circadian rhythms. In this short review, we discuss properties of light stimuli that are important for resetting the human circadian system. The direction and magnitude of light resetting are circadian phase-dependent, with exposure to light in the early biological night resulting in a phase-delay shift of circadian rhythms, and exposure to light in the late biological night and early morning resulting in a phase-advance shift. Circadian resetting responses can be enhanced by increasing the irradiance or duration of the light stimulus, or by using short-wavelength blue light to activate intrinsically photosensitive retinal ganglion cells that express the photopigment melanopsin. This knowledge can potentially be applied to improve light therapy for circadian rhythm sleep disorders, and to help reset circadian rhythms in individuals exposed to shift work or jet lag.

KEYWORDS: circadian, melatonin, shift work, jet lag

1. Introduction

In humans, exposure to light and darkness has a strong influence on the timing of circadian rhythms. The term circadian refers to rhythms that have a cycle length of about a day. Even in the absence of a light–dark cycle, humans exhibit behavioural and physiologic rhythms with a period close to, but not exactly, 24h\textsuperscript{1}. The circadian system therefore serves as an internal timekeeping system that needs to be adjusted each day in order to align with the solar day. This adjustment is achieved by light-induced resetting of the circadian system, ensuring that rhythms in sleep–wake, endocrine function, and metabolism are timed appropriately with the rising and setting of the sun. When a person is entrained to the solar day, the circadian system enables the body to anticipate daily changes in the environment, including the approach of dusk or dawn and food availability\textsuperscript{2}. For example, secretion of the sleep-promoting hormone melatonin usually begins a couple of hours before a person’s usual bedtime, which may serve to facilitate the transition to sleep. Melatonin levels are highest during the night and then begin to decrease prior to waking, while cortisol levels gradually increase across the night and reach their highest levels near wake time (Figure 1). The circadian system coordinates these changes to ensure that alertness is highest during the daytime and sleep occurs at night. If a person’s circadian system becomes misaligned with the light–dark cycle or his preferred sleep–wake pattern, disturbances in cognitive function and sleep can occur, e.g. in shift work or jet lag\textsuperscript{3}. Hence, the circadian system is important for maintaining normal human performance and sleep behaviour.

2. The suprachiasmatic nucleus (SCN) is a master clock that is reset by exposure to light

In mammals, the master circadian clock is located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. The SCN comprises pacemaker neurons that are responsible for generating circadian rhythms. Hence, damage to the SCN reduces or eliminates circadian expression of behavioural and endocrine rhythms\textsuperscript{4}. For example, it has been shown that daily patterns of sleep–wake behaviour and melatonin secretion are altered in patients who have a pituitary tumour that compresses the optic chiasm and SCN region\textsuperscript{5}. The SCN receives direct input from retinal ganglion cells\textsuperscript{6}, and this is the sole pathway by which light entrains circadian rhythms of behaviour\textsuperscript{7}. Notably, the photoreceptor pathway that mediates light-induced resetting of circadian rhythms is different from the pathway that mediates pattern-forming vision. This was suggested more than 20 years ago in experiments performed in blind individuals. In some blind patients with no light perception, it was shown that exposure to light at night inhibited melatonin synthesis\textsuperscript{8}. These individuals could also entrain normally under real world lighting conditions, suggesting that classical visual photoreceptors...
were not required for circadian light responses. Subsequently, it was shown that the retinohypothalamic projection to the SCN originates from a small population of intrinsically photosensitive retinal ganglion cells (ipRGCs) that expresses the photopigment melanopsin\(^9\). The ipRGCs are most sensitive to short-wavelength blue light (\(\lambda_{\text{max}}=480\,\text{nm}\)), but are also activated indirectly by rods and cones\(^{10,11}\). It is therefore likely that both rod-cone photoreceptors and melanopsin contribute to circadian light responses in humans with normal vision. Daily exposure to light resets the SCN neural activity rhythm, which in turn synchronizes behavioural and physiologic rhythms with the solar day (Figure 1).

3. Factors that influence the circadian resetting effects of light

3.1 Circadian phase of light exposure

The magnitude and direction of circadian resetting responses are dependent on the circadian phase (i.e., internal body time) at which the light stimulus occurs. The circadian system is most sensitive to light during the biological night, which corresponds to the usual hours of sleep in humans. Hence, going to bed late or waking up early, when combined with exposure to light, can result in resetting of circadian rhythms. Exposure to light in the early part of the biological night induces a phase delay shift of the human circadian system, which is equivalent to shifting circadian rhythms in the westward direction. As a consequence, the onset of melatonin secretion occurs at a later clock time on the day following exposure to light (Figure 2). By comparison, exposure to light in the late biological night or early morning induces a phase advance shift, which is equivalent to shifting circadian rhythms in the eastward direction. For such a light stimulus, melatonin secretion begins at an earlier clock time on the day after light exposure. The crossover point between phase delay shifts and phase advance shifts occurs in the middle of the night when the circadian rhythm of body temperature is near its minimum.

For experiments in which the resetting effects of a given light stimulus are examined across the circadian cycle, the data can be summarized by a phase-response curve (PRC). The PRC for exposure to a long-duration, bright light stimulus (6.7 h, \(-10,000\,\text{luc}\)) is characterized by weak "Type-1 resetting", in which the maximum phase delay shift is about \(-3\,\text{h}\) (by convention, phase delay shifts are assigned negative values), and the maximum phase advance shift is about \(+2\,\text{h}\)\(^{12}\). It is possible to achieve much larger phase shifts if more than one cycle of bright light is administered (i.e., exposure to light on consecutive nights). This is because exposure to light at night not only resets circadian rhythms, but also reduces circadian pacemaker amplitude\(^{13}\). As a result, further exposure to light can induce large "Type-0 resetting", in which it is possible to achieve phase shifts...
3.2 Dose-dependent effects of light on circadian resetting

The magnitude of light-induced circadian resetting depends on the intensity of the light stimulus. In studies that examined the effects of polychromatic white light on resetting of circadian rhythms, a non-linear dose-response curve was obtained, in which half-maximal resetting responses occurred for ~100–120lux of light, with light measurements taken at eye level. This result was obtained for a 3-cycle light stimulus (5-h stimulus on 3 consecutive days) administered during the phase advance region of the PRC\(^{17,18}\), as well as for a single-cycle light stimulus (6.5h) administered during the early biological night\(^{19}\). In the latter study, a saturating phase delay shift of about -3h was observed in response to -550lux of white light for young healthy subjects. In individuals aged ≥65 years who were exposed to similar experimental procedures, the half-maximal phase resetting response occurred for exposure to -260lux, suggesting that the sensitivity of circadian responses to light might be reduced in ageing\(^{20}\). Together, these studies demonstrate that the human circadian system responds to ordinary room light, and hence exposure to electrical lighting likely modulates circadian phase similar to the effects of natural light. Subsequent studies have also constructed irradiance response curves for circadian responses to different wavelengths of light\(^{21}\), demonstrating that exposure to short-wavelength light is highly effective at resetting human circadian rhythms (Figure 3), presumably due to activation of melanopsin-containing ipRGCs.

The magnitude of phase resetting can be increased by extending the duration of the light stimulus. This has been shown in studies comparing the effects of 1-h, 2-h, and 3-h pulses of bright white light (~2,000lux, ~4,000lux, or ~8,000lux) administered in the early biological night\(^{22}\). A non-linear increase in phase delay shifts was also observed in a study that examined the effects of increasing the duration of a polychromatic white light stimulus (~10,000lux for 12min, 1h, 2.5h, or 4h)\(^{23}\). Notably, when considered on a per-minute basis, the shorter-duration light stimuli were more effective than longer-duration light stimuli at resetting the circadian rhythm of melatonin. Comparable results were obtained in another study in which a 1-h bright white light stimulus (~10,000lux) induced a phase resetting response that was nearly 40% of the response to a 6.7-h light stimulus, despite representing only 15% of the stimulus duration\(^{20}\). These results indicate that the early part of a continuous light stimulus has greater resetting effects than the later part of the same stimulus, hence raising the possibility that a sequence of shorter light pulses might be more efficient at resetting circadian rhythms compared with continuous exposure to light. This has been explored by comparing circadian resetting responses for an alternating sequence of bright white light and darkness/dim light, relative to continuous exposure to bright light. In a pair of studies that examined long-duration light exposures (5h or 6.5h), it was found that intermittent light stimuli (e.g., ~10,000lux for 15min, followed by <3lux for 60min) induced phase shift responses that were nearly as large as those for continuous exposure to light\(^{25,26}\). This further suggests that short light pulses are effective at resetting circadian rhythms, which could prove beneficial for treating circadian misalignment associated with shift work or jet lag\(^{27,28}\).

3.3 Effects of different wavelengths of light on circadian resetting

Over the past 20 years, substantial progress has been made in characterizing the photoreceptor pathways that mediate circadian entrainment. As mentioned earlier, ipRGCs contain the photopigment melanopsin and project directly to the SCN. Melanopsin-dependent responses exhibit peak sensitivity to ~480nm light, but ipRGCs also receive input from rods and cones in the outer retina\(^{10,11}\). In mice, circadian responses to light are preserved in sightless mice with intact ipRGCs, as well as in melanopsin-deficient animals with intact rod-cone function\(^{29,30}\). Circadian phase resetting responses in mice are eliminated only when all photoreceptor types (i.e., rods, cones, & melanopsin) are rendered dysfunctional\(^{31,32}\). Hence, both melanopsin and visual photoreceptors contribute to circadian photoreception.
In humans, melanopsin and rod-cone contributions to circadian light responses are difficult to assess due to overlap of spectral sensitivity for the various photoreceptor types. However, melanopsin-dependent responses are relatively weak for longer-wavelength light in the visual spectrum. The contributions of melanopsin and cone photoreceptors to circadian photoreception can therefore be assessed by differences in the magnitude of circadian responses to shorter versus longer wavelengths of light. This was explored in a study that compared the phase delaying effects of 6.5h of exposure to narrow-bandwidth 460 nm light versus 555 nm light, with stimuli matched for photon density (10 nm half-peak bandwidth, \(2.8 \times 10^{13}\) photons cm\(^{-2}\) s\(^{-1}\)). Under these conditions, the magnitude of phase resetting was nearly twice as great for 460 nm light relative to 555 nm light (Figure 4A). Using similar methodology, a blind patient without a functional outer retina exhibited a phase delay shift of about −1.2h for the 460 nm light stimulus, whereas little or no response was observed for the 555 nm light stimulus. These findings suggest that melanopsin plays an important role in mediating human circadian responses to light.

There is also evidence, however, that cone photoreceptors contribute to circadian photoreception in humans. This was first suggested in a study in which early morning exposure to a red light stimulus on 3 consecutive days (~220lux) induced an average phase advance shift of about an hour. Recently, it was shown that exposure to 6h of narrow-bandwidth red light (631 nm, \(1.0 \times 10^{13}\) photons cm\(^{-2}\) s\(^{-1}\)) during the early biological night induced an average phase delay shift of nearly an hour (Figure 4B), and some participants exhibited phase shifts that were similar in magnitude to the resetting effects of bright white light or blue light. A role for cone photoreceptors in circadian photoreception is further supported by studies comparing irradiance-response curves to 460 nm light versus 555 nm light. It was found that the phase-delaying effects of 555 nm light at lower irradiances (<1.0 \times 10^{12}\) photons cm\(^{-2}\) s\(^{-1}\)) were too large relative to the 460 nm light stimulus to be explained solely by the activation of melanopsin. The sensitivity of melatonin suppression to 555 nm light also decayed exponentially relative to 460 nm light, suggesting that cone photoreceptors might contribute predominantly during the early part of a light exposure.

4. Light and circadian rhythms beyond the laboratory

4.1 Entrainment of circadian rhythms under real-world conditions

In the real world, there are many environmental factors that influence a person’s daily behavioural patterns and exposure to light. During a typical day, most people are exposed to multiple sources of electrical lighting including but not limited to ceiling lamps, street lamps, television screens, and tablets and smartphones. Many laboratory studies have characterized the phase resetting effects of light, but few studies have examined the effects of electrical lighting on human circadian entrainment under real-world conditions. A recent study compared the timing of circadian rhythms in a group of
of subjects who were exposed only to natural lighting (sunlight and fire light) as part of a camping trip in the Rocky Mountains, versus *ad libitum* access to electrical lighting under modern living conditions\(^{39}\). After exposure to each of these conditions, the melatonin rhythm was assessed in the laboratory. The onset of melatonin secretion occurred much earlier and closer to sunset after camping, suggesting that free access to electrical lighting has shifted our circadian clocks later than what would normally occur with natural lighting. Additionally, access to electrical lighting was associated with reduced exposure to sunlight during the daytime, but increased exposure to light after sunset. Although these results indicate that modern-day use of electrical lighting has affected the timing of circadian rhythms in humans, there is evidence that natural light is still a strong synchronizing stimulus. In a study that collected data on self-reported sleep behaviour in more than 20,000 individuals living within a single time zone in Germany, it was found that the timing of sleep varied systematically from east to west\(^{39}\), tracking the rising and setting of the sun. This finding suggests that sleep timing is not simply a consequence of social factors and school/work obligations. Despite our ability to manipulate our lighting environment using electrical lighting, exposure to natural light remains an important determinant of sleep–wake timing.

### 4.2 Treatment of circadian rhythm sleep disorders with light

In circadian rhythm sleep disorders, the sleep–wake cycle becomes misaligned with the circadian system and/or the environmental light–dark cycle. This results in insomnia, fatigue, and deterioration in neurobehavioral performance. These symptoms can be treated by using appropriately timed exposure to electrical lighting, in order to reset and synchronize circadian rhythms of sleepiness and alertness with the desired sleep–wake times of the patient\(^{40}\). As described above, the magnitude and direction of circadian resetting depend on the circadian phase of the light stimulus. This knowledge can be used to shift circadian rhythms earlier or later, as desired (Table 1). In patients with delayed sleep phase disorder (DSPD), the sleep period occurs much later than what is preferred. DSPD is associated with difficulty falling asleep (e.g., until 2:00 a.m. or later), as well as difficulty waking up in the morning. This often results in chronic partial sleep deprivation if the person with DSPD must report early for work or school on weekdays. Based on the human PRC, exposure to bright light therapy in the morning hours and avoidance of light in the late evening can help to reset the circadian system earlier. Clinical studies have demonstrated that early morning light therapy can be used as treatment for DSPD\(^{41}\), and the American Academy of Sleep Medicine recognizes light therapy as a complementary or alternative treatment option for DSPD\(^{42}\). Light therapy can also potentially be used to treat symptoms of advanced sleep phase disorder (ASPD), in which the sleep episode occurs much earlier than the patient’s desired sleep–wake schedule. Patients with ASPD experience difficulty remaining awake in the evening and have early morning awakenings during sleep. Hence, the desired outcome is a phase delay shift of the circadian system. This can be achieved by administering light therapy in the late evening hours and avoiding light in the early morning. Based on short-term clinical studies, evening light therapy has been shown to improve sleep efficiency and total sleep time, accompanied by a delay in melatonin and body temperature rhythms\(^{43}\).

Similar principles can be used for treating circadian misalignment associated with shift work and jet lag.

<table>
<thead>
<tr>
<th>Sleep problem/disorder</th>
<th>Symptoms</th>
<th>Desired outcome</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed Sleep Phase</td>
<td>Late sleep–wake times, sleep onset insomnia, difficulty waking up in the morning</td>
<td>Earlier sleep, phase advance shift</td>
<td>Morning bright light therapy after wake time, dim light before bedtime</td>
</tr>
<tr>
<td>Advanced Sleep Phase</td>
<td>Early sleep–wake times, difficulty remaining awake in the evening, early morning awakenings</td>
<td>Later sleep, phase delay shift</td>
<td>Evening bright light therapy before bedtime, dim light after waking up in the morning</td>
</tr>
<tr>
<td>Shift Work Sleep Disorder</td>
<td>Awakenings during daytime sleep, excessive sleepiness and fatigue during night shift</td>
<td>Adaptation to shift work, phase delay shift</td>
<td>Bright light therapy in evening/night, dim light after work, regular sleep–wake times</td>
</tr>
<tr>
<td>Jet Lag travel westward</td>
<td>Early morning awakenings, daytime sleepiness and fatigue</td>
<td>Phase delay shift</td>
<td>Evening bright light therapy before bedtime (home time), dim light after wake time</td>
</tr>
<tr>
<td>Jet Lag travel eastward</td>
<td>Sleep onset insomnia, difficulty waking up in the morning, daytime sleepiness and fatigue</td>
<td>Phase advance shift</td>
<td>Morning bright light therapy after wake time (home time), dim light before bedtime</td>
</tr>
</tbody>
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**Table 1 Application of light therapy for treating circadian desynchrony.**
Shift workers often complain of insomnia during daytime sleep and excessive sleepiness during the night shift. Physiologic adaptation to shift work is possible but requires strict adherence to regular sleep–wake times, exposure to adequate light during work shifts, and darkness during sleep. In a simulated shift work study, exposure to bright light during the work shift (−10,000lux) and sleep in darkness at home shifted circadian rhythms by several hours, whereas exposure to room light did not result in adaptation to shift work[40]. Field studies in night shift nurses have also shown that exposure to bright light in the evening and reduced morning light after the work shift (using sunglasses or tinted goggles) resulted in improved alertness during the night shift, increased daytime sleep, and large phase shifts in circadian rhythms of melatonin and body temperature[45, 46]. The effects of jet lag are similar to shift work. Following travel across time zones, there is a temporary misalignment between the circadian system and the pattern of light–dark and preferred sleep–wake times in the new time zone. Jet lag is associated with difficulty falling asleep following travel eastward, and early morning awakenings following travel westward. To accelerate adaptation following travel eastward, a phase advance shift is required for re-entrainment, which can be achieved by exposing oneself to bright light in the early morning (referenced to home time), and dim light in the hours preceding normal bedtime. For travel westward, a phase delay shift is required for circadian realignment, which can be achieved by exposure to bright light in the evening hours before sleep onset (referenced to home time), and dim light in the hours after awakening.

5. Conclusions

Remarkable progress has been made in understanding the effects of light on human circadian rhythms. Similar to other organisms, humans exhibit circadian phase-dependent resetting. The magnitude of phase shift responses depends on the intensity, duration, and wavelength of the light stimulus. These parameters can be manipulated to enhance or minimize the resetting effects of light. In the modern world, most individuals are exposed to a combination of natural light and electrical lighting on a daily basis. However, the combined effects of these light sources on circadian entrainment remains poorly understood, especially because exposure to lighting can vary markedly between individuals and from day-to-day in the same individual. More studies are needed to assess whether the amount of light emitted from personal electronic devices (e.g., computer screens, tablets, and smartphones) results in resetting of circadian rhythms under real-world conditions. The impact of irregular patterns of light exposure and sleep in non-shift workers is also relatively unexplored, but has potential implications for health and well-being. Many studies have shown that light therapy and light avoidance can be used to help treat sleep problems associated with circadian misalignment. As we learn more about the effects of light on human circadian rhythms, it is possible that these approaches can be optimized to improve clinical outcomes.

References


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