Entrainment of the Human Circadian System by Light

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Abstract The periodic light-dark cycle is the dominant environmental synchronizer used by humans to entrain to the geophysical 24-h day. Entrainment is a fundamental property of circadian systems by which the period of the internal clock (τ) is synchronized to the period of the entraining stimuli (T cycle). An important aspect of entrainment in humans is the maintenance of an appropriate phase relationship between the circadian system, the timing of sleep and wakefulness, and environmental time (a.k.a. the phase angle of entrainment) to maintain wakefulness throughout the day and consolidated sleep at night. In this article, we review these concepts and the methods for assessing circadian phase and period in humans, as well as discuss findings on the phase angle of entrainment in healthy adults. We review findings from studies that examine how the phase, intensity, duration, and spectral characteristics of light affect the response of the human biological clock and discuss studies on entrainment in humans, including recent studies of the minimum light intensity required for entrainment. We briefly review conditions and disorders in which failure of entrainment occurs. We provide an integrated perspective on circadian entrainment in humans with respect to recent advances in our knowledge of circadian period and of the effects of light on the biological clock in humans.

Key words light, human, entrainment, circadian rhythm, photic entrainment, period

Although much has been learned in the past 2 decades about the effects of light exposure on the circadian timing system in humans, very little is known about the strength or duration of light needed to entrain the human circadian clock to the 24-h day. The relative lack of research on the topic of photic entrainment in humans has resulted in part because such studies require subjects to remain in controlled laboratory conditions for weeks at a time. Furthermore, we are still learning about some of the more fundamental features of the human circadian system and how it responds to light, as well as what the period of the human circadian system is in the average healthy adult.

As we discuss below, this new knowledge has informed us about the average period of the human circadian system in healthy adults, information that in turn tells us about the magnitude of daily adjustment required to maintain entrainment. Studies of the effects of light on the human circadian system have provided new knowledge about the levels of light to which the system can respond and how it responds to

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JOURNAL OF BIOLOGICAL RHYTHMS, Vol. 20 No. 4, August 2005 326-338
DOI: 10.1177/0748730405277983

intermittent bright light exposure. This information, combined with field studies in which light exposure patterns of people following their normal routine are measured, has provided further insight into how modern humans are entrained by the light-dark cycle. Together, these recent human circadian studies have provided a foundation on which studies of human entrainment by light can be built. A more detailed discussion of these initial studies of human entrainment is below.

WHAT (BIOLOGICAL) TIME IS IT? ASSESSING CIRCADIAN PHASE IN HUMANS

Studies of circadian physiology in humans are more limited than those in animals by the experimental techniques that can be employed and by the types of data that can be collected. For example, it is not currently possible to measure the electrical activity of the SCN in a human, nor is it possible to place a cannula in the 3rd ventricle to infuse or withdraw substances from the human anterior hypothalamus. Thus, alternative methods for assessing internal biological time in human studies have been developed. The essence of such methods is to infer the status of the clock located in the SCN by measuring output rhythms driven by the clock. However, these output rhythms must be studied under controlled experimental conditions because the oscillation of most output rhythms is also influenced by periodic changes in behavior and/or the environment.

For example, most adult humans have a monophasic sleep-wake cycle, resulting in the influence of sleep and the associated postural changes and light exposure changes (due to closing the eyes) being distributed nonuniformly across the circadian cycle. This cycle is unlike the polyphasic sleep-wake cycles in rodents, in which there is a more even distribution of sleep and wakefulness across the circadian cycle and in which the postural changes associated with sleep are less dramatic. Other complications of measuring output rhythms rather than the direct activity of the clock are that output rhythms are influenced ("masked") differently by changes in behavior or posture, the influence of postural or behavioral changes on most rhythms is phase dependent (Dijk et al., 1998; Klerman et al., 1999; Waterhouse et al., 1999), and the masking effects caused by behavioral changes (such as those from the sleep-wake cycle) vary widely from person to person (Hiddinga et al., 1997; Dijk et al., 1998). Thus, to ensure that measurement of an observed rhythm can be assessed accurately as a marker of the output of the biological clock, the influence of behavioral and environmental factors must be controlled so that the endogenous component of that rhythm is revealed.

To address this issue, researchers conducting human circadian studies developed the constant routine (CR) procedure, in which the environment and the behavior of the subject are stringently controlled. Following an early CR-like protocol conducted by Aschoff (1995), Mills developed the CR protocol recognizing that removal of the masking effects of the sleep-wake cycle was a prerequisite for assessing the status of the clock following abrupt shifts of the sleep-wake/light-dark cycle. The essence of the CR is therefore to reduce or eliminate all periodic changes in behavior, in addition to maintaining a constant environment. Thus, the ideal CR keeps ambient lighting levels and room temperature constant, eliminates sleep and the behaviors associated with sleep (such as postural changes and eye closure), maintains low levels of activity and constant posture (even during bowel movements), and distributes food and fluid intake throughout day and night, with observations continued for an entire circadian cycle. Other methods of assessing circadian phase that do not use the labor-intensive methods of the CR or that do not require sleep deprivation have been proposed. Some of those methods include assessing phase by measuring melatonin onset in dim light (Lewy et al., 1999) or by attempting to mathematically extract underlying phase information from masked data. Using melatonin as a phase marker has the advantage that even though melatonin is influenced by changes in posture (Deacon and Arendt, 1994) and may also be influenced by sleep-wake state and/or activity (Ritz-De Cecco et al., 2001), it is less influenced by those behaviors than are the rhythms of temperature or other hormones. A disadvantage of using the DLMO method to measure phase is that it records only 1 portion of the 24-h rhythm, potentially missing changes in rhythm shape or amplitude that might be informative. Demasking methods for estimating phase have the disadvantage that the masking influence of posture, activity, or sleep on some rhythmic variables is phase dependent (Dijk et al., 1998; Klerman et al., 1999; Waterhouse et al., 1999).

LIGHT EFFECTS ON THE HUMAN BIOLOGICAL CLOCK

Specialized photoreceptors in the mammalian eye communicate information about environmental light to the circadian clock (located in the SCN) via a neuroanatomical pathway called the retinohypothalamic tract. These same structures are present in the human and are presumed to play similar roles in circadian photoreception and entrainment.

Studies conducted throughout the last quarter of the 20th century demonstrated that light is a powerful circadian synchronizer in humans. In the following text we will review major concepts and discuss recent developments regarding the influence of light on human circadian rhythms.

PHASE RESPONSE CURVES

The amount by which a discrete light pulse can change the timing of the circadian system is phase dependent, and this phase dependency is described by PRCs (Daan and Pittendrigh, 1976). PRCs to light share a number of features across species, including humans. Light pulses administered in the early night produce phase delays (shifts in timing to a later hour); light pulses administered in the late night/early morning produce phase advances (shifts in timing to an earlier hour). Depending on the species, light administered during the daytime may or may not produce a phase shift (Daan and Pittendrigh, 1976; Pohl, 1982). Although there have been reports from studies in humans that have concluded there is no significant phase-shifting response to midday light exposure (Dumont and Carrier, 1997), there is compelling evidence that the human circadian system is responsive to light throughout the waking day (Hashimoto et al., 1997; Jewett et al., 1997). In an analysis of more than 50 light exposure trials presented during the subjective day, there was no evidence of a "dead zone" in the PRC (Jewett et al., 1997), suggesting that light exposure throughout the waking day contributes to circadian entrainment in humans.

There are 2 general PRC morphologies: a low amplitude PRC with maximal phase shifts of a few hours (Type 1), and a high amplitude PRC with phase shifts as large as 12 h (Type 0) (Hastings and Sweeney, 1958; Winfree, 1980). In Type 0 resetting, the resetting stimulus affects both phase and amplitude, and a stimulus of appropriate strength applied at a critical phase can in theory reduce the amplitude of oscillation to zero (singularity) (Winfree, 1980; Kronauer et al., 1993; Lakin-Thomas, 1993). Both Type 1 and Type 0 PRCs have been observed in humans. A Type 0 PRC composed using 3 consecutive cycles of 5 h bright-light exposure (~7000-10,000 lux) has been reported (Czeisler et al., 1989), although whether responses to such a multiple-pulse stimulus can be classified as a Type 0 PRC has been debated by some (Beersma and Daan, 1993; Kronauer et al., 1993; Lakin-Thomas, 1993). In that PRC, stimuli centered in the late subjective night could elicit phase shifts of up to 12 h, whereas smaller phase shifts occurred when light exposure was centered at other times. The magnitude and shape of that Type 0 PRC for humans is qualitatively similar to the Type 0 PRCs reported for other species (Pittendrigh, 1960; Peterson, 1980; Gander and Lewis, 1983). Further support for the notion of Type 0 resetting in humans comes from a study in which the stimulus was reduced from 3 cycles to 2 cycles, producing amplitude reduction (Jewett et al., 1991). Single bright light exposures elicit phase shifts in humans consistent with a Type 1 PRC (Honma and Honma, 1988; Minors et al., 1991; Khalsa et al., 2003). A comprehensive human PRC to a single 6.7-h bright-light (9500 lux) pulse was published recently (Khalsa et al., 2003). The PRC showed maximum phase advances of ~2 h and maximum phase delays of ~3 h.

In both the Type I and Type 0 PRCs reported to date, the largest phase shifts in response to light are observed during the biological night, when humans are habitually asleep in the dark. Furthermore, these PRCs have been developed in response to light much brighter than normal indoor light. Although these laboratory PRCs have informed us about important aspects of the human circadian response to light, in most people entrainment is likely to occur in response to light exposure received during the subjective day and to light stimuli that consist of intermittent exposure to fewer than 2 h per day of bright outdoor light (Okudaira et al., 1983; Savides et al., 1986; Hébert et al., 1998) combined with much greater durations of indoor levels of light throughout the remainder of the waking day.

INTENSITY RESPONSE CURVES

The intensity of light to which we are exposed also influences the response, and systematic examinations of such effects are summarized in intensity response

curves (IRCs). There have been only a few systematic studies of the influence of intensity on the resetting response to light in humans, both reported in the 1990s. In 1 such study, an IRC to a multiple-cycle light stimulus presented in the phase advance region of the PRC (5.0-h light stimulus centered 1.5 h after initial core body temperature minimum) was constructed, and the magnitude of the resetting response was reported to increase with intensity in a nonlinear manner (Boivin et al., 1996). A single stimulus to light presented in the phase delay region (6.5-h light stimulus centered 3.5 h before initial core body temperature minimum) was also reported to induce a nonlinear IRC relationship between illuminance and the phase resetting response (Zeitzer et al., 2000). Furthermore, findings from that study indicated that as little as ~100 lux of light could produce half of the maximal phase delay shift to 10,000 lux of light and that 90% of the asymptotic maximum response could be achieved by 550 lux.

Results from the latter study suggested that humans were far more sensitive to light than had been previously thought. In another study of the phase-shifting effects of light, 3 cycles of exposure to 6.5 h of only ~12 lux per day was sufficient to produce a significant phase advance shift of the melatonin rhythm (Zeitzer et al., 1997; Wright and Czeisler, 2002) when compared with results from control subjects exposed to darkness (Duffy et al., 1996). Figure 1 shows a comparison of the dim light group with the darkness/control group, indicating that light as dim as 12 lux can have a significant effect on the human circadian system.

It should be noted that in the IRC studies described above, the background light to which the subjects were exposed was quite dim (less than 20 lux in the study by Boivin et al., and less than 5 lux in the study by Zeitzer et al.) and may well have influenced the results. In fact, in 2 recent studies (Hébert et al., 2002; Smith et al., 2004) it has been reported that the human circadian system shows adaptive responses to light history. Thus, while comparatively dim indoor light can influence the human circadian system and may play a role in entrainment, the absolute light levels to which an individual is exposed will probably influence the role that dim light plays in entrainment. These 2 IRC studies applied their stimuli during the early or late subjective night, and we do not know whether the IRC shape or half maximal response would be the same in response to stimuli applied at other phases.

INTERMITTENT LIGHT EXPOSURE

Light stimuli need not be continuous to have an effect on the human circadian system. Intermittent exposures to light have also been reported to induce robust phase shifts of the biological clock in humans. A series of shift-work studies have used intermittent exposure to light, combined in some cases with shielding the study participants from darkness at certain times, to speed adaptation to a night work schedule (Baehr et al., 1999; Boivin and James, 2002).

The human circadian system has been reported to integrate multiple exposures to as little as 5 min of bright light (5 min ~10,000 lux; 20 min darkness) presented during several hours to produce phase advances of the human circadian system (Kronauer et al., 1999). Those brief bright-light exposures, when presented during a 5-h interval on 3 successive days, were reported to be more effective per minute of exposure than were 5 h of continuous bright light (Rimmer et al., 2000). Another related study presented several 15-min bright-light exposures during a 6.5-h interval on a single day, and it was reported that the phase-delay shift to the intermittent bright light exposure was comparable to the phase shift measured after continuous bright-light exposure, even though the bright light represented only 23% of the 6.5-h continuous exposure (Gronfier et al., 2004). These laboratory studies of intermittent bright-light exposure suggest that the brief intermittent exposures to outdoor light that humans typically experience in everyday modern life (Okudaira et al., 1983; Savides et al., 1986; Hébert et al., 1998) may have a much greater impact on circadian entrainment than was recognized previously and further suggest that intermittent exposure to outdoor light plays an important role in entrainment.

SPECTRAL SENSITIVITY

Most of our understanding of the spectral sensitivity of the circadian system comes from studies of animals. Studies characterizing the effects of monochromatic light have found that shorter wavelength light is most effective at shifting circadian rhythms in nocturnal mammals. Humans also appear to be more sensitive to shorter wavelengths of visible light than to longer wavelengths. Initial studies of the effects of different wavelengths of light on humans used short-duration exposures to monochromatic light to conduct action spectra for melatonin suppression. Those

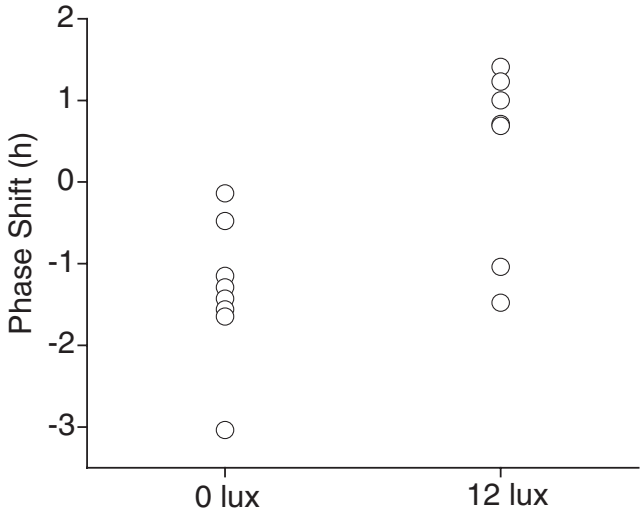

Figure 1. Phase shift of plasma melatonin rhythm to a dark (left) compared with a very dim light (right) stimulus. A 3-cycle 6.5-h stimulus was applied during the phase advance region of the PRC (centered ~1.5 h after the core body temperature nadir) and melatonin phase was measured in a constant routine before and after by calculating the time at which their melatonin onset rose above 25% of a 3-harmonic fit . Subjects in the dark/control stimulus group showed a –1.34 ± 0.87 h drift to a later phase across the 5 days between the initial and final phase assessment, consistent with a circadian period greater than 24.0 h. In contrast, subjects exposed to 12 lux of light during the stimulus time showed an average phase advance of 0.36 ± 1.14 h ($p < 0.05$). The significant difference in final phase between the 2 stimulus groups of 1.7 h indicates that light equivalent to candle light can influence the human biological clock and could play a role in entrainment. Data are from Duffy et al. (1996), Zeitzer et al. (1997), and Wright and Czeisler (2002).

studies found that light in the shorter wavelengths of the visible range (blue) was most effective at suppressing melatonin (Brainard et al., 1985; Brainard et al., 2001; Thapan et al., 2001).

More recently, studies of the spectral sensitivity of the human circadian system have examined the phase-shifting effects of different wavelengths of light. Those studies have examined the ability of different wavelengths of light to produce both phase-advance shifts (Warman et al., 2003; Wright et al., 2004) and phase-delay shifts (Wright and Lack, 2001; Lockley et al., 2003), and findings from those studies indicate that short wavelength light is more effective at producing circadian phase shifts than are longer wavelengths. Furthermore, shorter wavelength light is reported to be many times more effective at producing phase shifts than is broad-spectrum fluorescent light (Warman et al., 2003; Lockley et al., 2003) on a photon-by-photon basis.

These recent studies on the spectral sensitivity of the human circadian system indicate that the light *source* also plays an important role in circadian entrainment in humans. Humans as a species are unique in our exposure to artificial lighting, which has a spectral distribution unlike that of sunlight. Most humans experience only brief, intermittent exposure to natural sunlight (Okudaira et al., 1983; Savides et al., 1986; Hébert et al., 1998), spending much of their typical waking day in artificial light. Much remains to be learned about how the spectral composition of natural light versus that of artificial light affects the human circadian system, and how the relative balance of different light sources plays a role in human entrainment.

Furthermore, now that we know that the circadian photoreceptive system has a different spectral sensitivity than does the visual system, methods of measuring light that incorporate this knowledge will need to be developed so that light stimuli can be characterized accurately for their circadian effects.

MEASUREMENT OF HUMAN CIRCADIAN PERIOD

The finding that human circadian rhythms have a non-24-h period was first demonstrated in early cave and bunker studies (Aschoff and Wever, 1962; Colin et al., 1968). Those studies were carefully conducted in the absence of clocks, and participants were shielded from environmental and social time cues. However, unlike studies of the circadian system in other mammals, in most cases human participants were allowed access to artificial lights, which could be switched on upon awakening and off upon going to sleep.

In those early studies, it was reported that the period of the human sleep-wake cycle was significantly longer and more variable from day to day than the biological rhythms of most other mammals. Humans also showed a phenomenon termed "internal desynchronization" in many such studies (Aschoff et al., 1967). When internal desynchronization occurred, the period of the sleep-wake cycle demonstrated a variable and often extremely short or long period (much shorter or longer than 24 h), while the period of other rhythms controlled by the biological clock, such as the core temperature rhythm, showed a more stable period that was typically within ~1 h of 24 h.

It has since been established that allowing the participants in those studies access to artificial lighting

affected the period estimates derived from those early studies. The peak circadian drive for wakefulness occurs just before habitual bedtime (Czeisler et al., 1980; Zulley et al., 1981), and in the absence of knowledge of clock time, humans typically choose to remain awake beyond their typical bedtime. The peak circadian drive for sleep occurs near the end of the biological night close to the body temperature minimum (Dijk and Czeisler, 1994). Free-running humans often initiate sleep at this time, remaining asleep for the next 8 or more hours (Czeisler et al., 1980; Zulley et al., 1981). The choice to initiate sleep at this circadian time resulted in light exposure throughout most of the phase-delay portion of the PRC during wakefulness and darkness throughout most of the phase-advance portion of the PRC during sleep. In response to this pattern of light exposure, together with exposure to indoor levels of light now known to have significant effects on the human circadian system, the free-running study conditions resulted in artificially long period estimates (Klerman et al., 1996).

More recently, studies of sighted humans using the "forced desynchrony" protocol have been conducted to measure the period of the human circadian system without the confounding influence of self-selected sleep-wake/light-dark cycles. That protocol, which was first described by Nathaniel Kleitman in his seminal book in 1939, schedules participants to a sleep-wake/light-dark cycle length several hours shorter or longer than 24 and maintains the lighting at low levels during waking. The human biological clock cannot entrain to such a light-dark cycle, and the period of rhythms controlled by the clock (typically core temperature or melatonin) is then measured. Several research groups conducted forced desynchrony studies in sighted humans during the 1990s, and in all studies it was reported that period estimates that were much closer to 24 h than period estimates from free-run studies (Hiddinga et al., 1997; Carskadon et al., 1999; Czeisler et al., 1999; Wyatt et al., 1999; Wright et al., 2001). In fact, 3 subjects who were studied in both forced desynchrony and free-run studies were reported to have <24.5-h periods using the forced desynchrony protocol but near 25-h periods using a free-run protocol (Klerman et al., 1996).

Although some of the methodology used in early studies of the human circadian system is now known to have influenced the period measurements, those early studies were key in demonstrating that human biological rhythms, like those of other mammals, continue to cycle in the absence of periodic environmental cycles.

ENTRAINMENT STUDIES IN HUMANS

Although many studies have examined the phase resetting response to light in humans, very few studies have been conducted on photic entrainment of the human circadian pacemaker. As outlined above, entrainment in sighted people occurs via regular exposure to light and darkness. Evidence from forced desynchrony period assessment studies indicates that the average period in humans is ~24.2 h, implying that on average a 0.2-h (about 12 min) daily phase-advance shift must occur in the average person to allow him or her to remain entrained. Although the average period in sighted humans is ~24.2 h, the reported range of temperature periods in sighted humans, following release from entrainment to the 24-h day, is from 23.81 to 24.31 h (Czeisler et al., 1999; Wyatt et al., 1999; Wright et al., 2001), although additional unpublished results from our laboratory suggest that the range of periods in humans is larger. For the human circadian system to be entrained to the 24-h period of the environment (T cycle), small daily phase shifts ($\Delta\varphi$), or adjustments in timing between the period of the circadian clock and the period of the T cycle, must occur (i.e., entrainment occurs when $\tau - T + \Delta\varphi = 0$).

Figure 2 shows the range of daily adjustments needed to entrain subjects to the 24-h day based on period estimates derived from 3 forced desynchrony studies following release from entrainment to the 24-h day (Czeisler et al., 1999; Wyatt et al., 1999; Wright et al., 2001). As seen in the figure, approximately 25% of the individuals have an intrinsic period that is less than 24.0 h and thus require a daily lengthening, or delay, of their circadian clock to remain entrained to the 24-h day, whereas the majority of individuals tested have an intrinsic period that is longer than 24.0 h, requiring a daily shortening, or advance, of their clock to remain entrained.

These data indicate that the strength of photic (e.g., phase, duration, intensity) and of nonphotic synchronizers and the direction of the daily adjustment necessary to entrain humans to the 24-h day is dependent on interindividual differences in circadian period.

MINIMUM LIGHT INTENSITY REQUIRED FOR ENTRAINMENT

As described above, early human circadian research studies were influenced by lack of control over light exposure, and many of the early reports of light intensity and entrainment were affected by this.

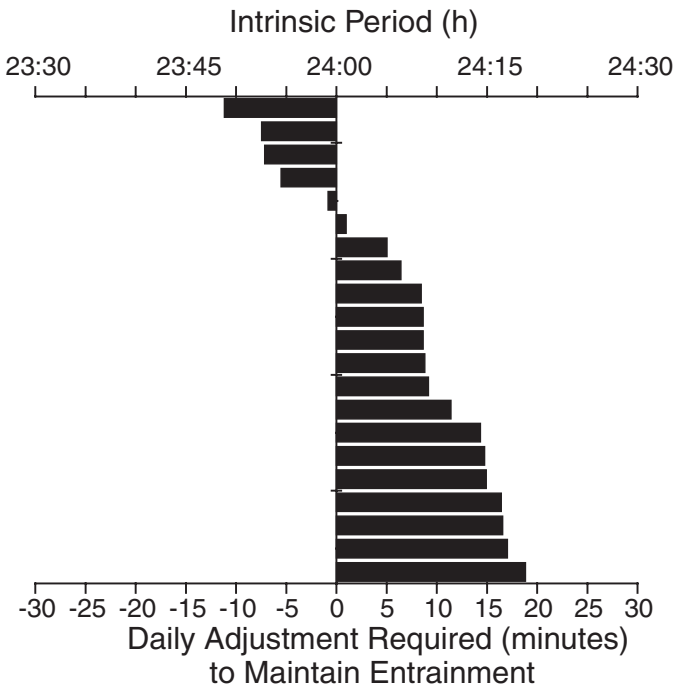

Figure 2. Range of daily adjustment needed to maintain entrainment for 21 young adults whose circadian period was assessed in a forced desynchrony study. Each of the healthy young adults was studied for at least 2 weeks in a forced desynchrony study designed to assess their circadian period after stable entrainment to the 24-h day. The range of periods observed in this group was 23.81 to 24.31 h (Czeisler et al., 1999; Wyatt et al., 1999; Wright et al., 2001). Five of the subjects had a period shorter than 24.0 h, requiring an average daily phase delay for entrainment, while the other 16 subjects had a period longer than 24.0 h, requiring a daily phase advance for entrainment. For this range of periods, the average daily adjustment for entrainment ranges from –12 min (delay) to +19 min (advance).

Early reports indicated that the minimum light intensity required for human entrainment was higher than 1000 lux, and many of the subsequent early studies of entrainment by light in humans used bright light because of that finding. The interpretation that bright light was necessary to entrain the human circadian clock was also based on the assumption that the average intrinsic circadian period in humans was ~25.0 h, necessitating on average a phase advance of 1 h per day to entrain to the 24-h day. As noted above, this interpretation and estimation of period is inconsistent with more recent findings (Hiddinga et al., 1997; Carskadon et al., 1999; Czeisler et al., 1999; Wyatt et al., 1999; Wright et al., 2001).

Early reports that subjects living in scheduled room light of ~300 lux and allowed to self-select their sleep-wake cycle did not remain entrained to the 24-h light-dark cycle (Aschoff et al., 1975; Wever, 1979) reinforced the notion that only bright light could affect human circadian rhythms. Wever (1989) also reported that 8 h of bright-light exposure (~4000 lux) could expand the physiologic range of entrainment, but concluded that light below 1500 lux exerted no direct physiologic effects other than through an influence on the timing of behavior (Wever et al., 1983). Honma et al. (1987) reported that a scheduled daily exposure to 8 h of bright light (~5000 lux) was able to entrain the timing of sleep and the temperature rhythm, even when subjects had access to supplemental lighting of ~300 to 500 lux.

Nakamura (1996) reported that the free-running temperature and melatonin rhythms of only 3 of 8 subjects were entrained to a 24.0-h imposed sleep-wake and light-dark schedule in ordinary room light, a finding inconsistent with our current knowledge about the significant influence of that level of light on the human biological clock and the average period of the human circadian system. However, that latter study lasted only 8 days and was preceded by a free-run in a self-selected light-dark cycle, a protocol that has been reported to alter the phase relationship between the temperature rhythm and the sleep-wake cycle (Czeisler, 1978; Wever, 1979) lasting at least 1 to 2 weeks. Thus, the design of that study, in which the initial free-run likely altered the phase relationship between the sleep-wake cycle and the biological clock combined with only 8 days of entrainment assessment, is a likely explanation for why their subjects did not appear to be able to be entrained by 200 lux of light.

More recently, an entrainment study in which a very weak circadian synchronizer was tested in humans was reported (Wright et al., 2001). That study examined entrainment to a 24.0-h light-dark/wake-sleep schedule using a light intensity of only ~1.5 lux in the angle of gaze, and the authors reported that dim light-dark cycle was sufficient to entrain 5 of their 6 subjects. Thus, either the very dim candlelight and/or nonphotic time cues appear to be sufficient to entrain the human circadian system. The range of periods of the 5 subjects who were entrained was from 23.88 to 24.14, indicating that the range of entrainment for this weak stimulus is at least ±7 min. Given the daily phase adjustment required to entrain to the 24.0-h day based

on the range of human periods observed in other studies (Fig. 2), it is evident that a stronger circadian synchronizer would be necessary to entrain all humans to the 24-h day.

In the study just described (Wright et al., 2001), the same very dim light level was used to test subjects for their ability to entrain to longer (24.6 h) or shorter (23.5 h) day lengths. None of the subjects tested were able to entrain to the short or long day, and thus stronger circadian synchronizers appear to be necessary to entrain the human circadian clock to non-24-h day lengths. As previously noted, the minimum strength of the environmental synchronizer necessary to re-entrain or capture the human circadian pacemaker after a perturbation such as an abrupt phase shift of the sleep-wake/light-dark cycle is unknown and may be also greater than that required to maintain ongoing circadian entrainment.

PHASE ANGLE OF ENTRAINMENT

During entrainment, the phase of a rhythm occurs at a similar time each day relative to environmental time (Pittendrigh and Daan, 1976b). The phase relationship between biological time and environmental time is referred to as the phase angle of entrainment. It has long been established that the phase angle of entrainment between the imposed light-dark cycle (T cycle) and an entrained rhythm is a function of the relatively stable difference in their periods; that is, $\psi = f(T - \tau)$ (Hoffmann, 1963; Pittendrigh and Daan, 1976b).

In humans, the phase relationship between sleep/darkness and the timing of melatonin secretion is the most well understood phase relationship that can inform us about entrainment. On average, the DLMO, defined as the time melatonin secretion exceeds either a fixed or relative threshold (Lewy et al., 1999) occurs ~2 h prior to habitual bedtime in people with stable entrainment (Wright et al., 2005). However, as is illustrated in Figure 3, there is a large range of DLMOs, even among healthy people with stable entrainment. These data indicate that it is unlikely that there is one ideal phase angle of entrainment for all humans, but rather that there is a range of normal phase angles that span approximately 75° of the circadian cycle, with this normal range determined in part by circadian period (Wright et al., 2005).

In fact, the phase angle of entrainment between DLMO and habitual sleep time/darkness has been shown to be positively and robustly related to circadian period in humans (Wright et al., 2005), with the strength of this relationship related to the strength of the entraining signal (light intensity) (Wright et al., 2001; Wright et al., 2005).

This relationship between phase angle of entrainment and period is likely to underlie individual differences in entrained phase in otherwise healthy humans, such as those observed between young adult "morning" and "evening" types (Kerkhof and van Dongen, 1996; Duffy et al., 1999; Baehr et al., 2000). While morning types awaken at an earlier clock time, they wake at a later biological time than do evening types. The chronobiological basis for this observed difference in entrained phase is likely to be a difference in period, given that variations in circadian period are correlated with morningness-eveningness and entrained phase in this same age group (Duffy and Czeisler, 2002).

Not all differences in phase angle of entrainment are likely to be due to period differences, however. For example, the difference in entrained phase between healthy older and young adults is unlikely to be explained by age-related differences in period (Czeisler et al., 1999), but instead may be due to age-related differences in the ability to maintain sleep at particular biological times (Duffy and Czeisler, 2002), resulting in different light-dark exposure patterns. Other factors, such as individual differences in light sensitivity or light exposure patterns, may also contribute to differences in entrained phase in humans. The ability to differentiate between the causal factors related to interindividual differences in entrained phase will be crucial in identifying the genes involved in circadian regulation in humans, as well as the polymorphisms and/or mutations that contribute to extremes of circadian behavior (Reid et al., 2004).

AFTEREFFECTS OF ENTRAINMENT

Aftereffects are the lingering influence of entrainment to a T cycle on the subsequent measurement of circadian period (Pittendrigh and Daan, 1976a) and are hypothesized to make it easier to maintain entrainment and prevent gross day-to-day adjustments of phase (Pittendrigh and Daan, 1976b). Aftereffects of entrainment on circadian period have been described in many species, and preliminary data from a recent study in humans indicates that aftereffects of entrainment to non-24-h days, as has been reported in animals, may also be present in humans (Scheer et al.,

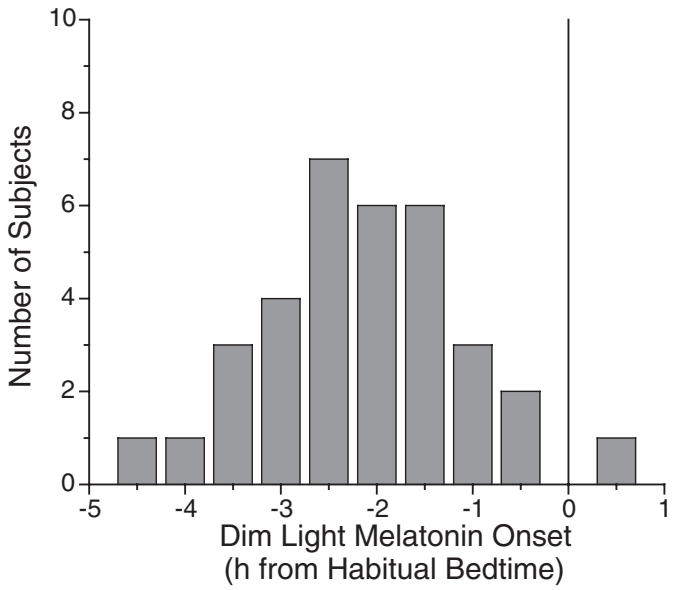

Figure 3. Histogram of DLMOs in a group of 34 healthy young adults with stable entrainment. Subjects maintained a regular light-dark/sleep-wake schedule at home for at least 3 weeks and entered the laboratory in the late morning, when collection of plasma samples in dim light began. The time at which their melatonin onset rose above 25% of a 3-harmonic fit (peak-trough) amplitude was calculated and is expressed relative to their usual bedtime. While the average was 2.15 ± 0.55 h and the median 2.25 h before usual bedtime, the range of DLMO was from ~4.5 h before to 0.55 h after usual bedtime, indicating the great variability in individual entrainment characteristics, even among humans who are healthy and have stable entrainment. Data redrawn from (Wright et al., 2005).

2005). It is possible that the observed near-24-h period of the human circadian system reported from sighted humans may result from prior entrainment to the 24-h day of Earth to which sighted humans are exposed throughout their entire lifetime, and aftereffects of entrainment to the 24-h day in sighted humans (and lack of such aftereffects in blind humans) may also explain the apparent difference in average circadian period between sighted and blind humans (Miles et al., 1977; Lockley et al., 1997).

WHEN ENTRAINMENT FAILS: CIRCADIAN RHYTHM SLEEP DISORDERS

Observations of the sleep-wake problems experienced by many blind people give us further insight into human entrainment. Many blind individuals complain of a cyclic sleep disorder, in which they are able to sleep at night and remain awake throughout the day for days or weeks at a time, but then at other times their nighttime sleep is disrupted and they have difficulty remaining alert throughout the day. Repeated observations of such blind people show that the timing of their circadian rhythms slowly drifts later week by week, indicating that they are not entrained (Sack et al., 1992; Klein et al., 1993; Czeisler et al., 1995; Lockley et al., 1997).

Results from nonentrained blind people indicate the importance of light in human entrainment. However, not all blind people show such cyclic sleep disorders. Although some apparently entrained blind people may not be totally blind, there are blind people with no conscious light perception who appear to be entrained. There are several possible explanations for why these totally blind individuals appear to be entrained. Some such individuals would be expected to have periods that are very near to 24 h, as is found in the sighted population. It is also possible that nonphotic cues may be sufficiently strong to entrain some blind individuals, especially those with periods within a limited range close to 24 h (see article in this issue by Mistlberger and Skene, 2005, for greater discussion of entrainment by nonphotic signals). Finally, a subset of blind people with no conscious light perception appears to retain a functional retinohypothalamic tract, as evidenced by the ability of a bright light pulse to suppress their melatonin secretion (Czeisler et al., 1995; Klerman et al., 2002). Thus, although they are visually blind, they retain circadian photoreception, and thus are able to entrain using light cues from the environment.

Failure of circadian entrainment is also observed in sighted humans. Sighted humans with non-24-h sleep-wake syndrome (American Academy of Sleep Medicine, 2000) experience cyclic sleep problems similar to that observed in blind individuals. Delayed sleep phase syndrome (DSPS) and advanced sleep phase syndrome (ASPS) are additional circadian rhythm sleep disorders in which the patient has stable entrainment but with an inappropriate phase relationship between biological time and socially acceptable time, resulting in their sleep occurring later (in DSPS) or earlier (in ASPS) than desired. Transient misalignment between biological and environmental time is observed during jet lag, whereby an abrupt shift in

environmental time occurs and the biological clock takes several days to re-entrain to the new light-dark cycle. Many shift workers who attempt to sleep during the day and work at night are not entrained to their night work schedule, experiencing a chronic mismatch between biological and environmental time. The mechanism(s) underlying the alterations in entrainment for circadian rhythm sleep disorders are poorly understood, and much additional research in this area is needed to better understand and develop effective treatments for these disorders (Wyatt, 2004). See the article by Eastman in this issue for additional discussion of jet lag and shift work.

Consequences of an inappropriate phase relationship between biological and environmental time include impaired alertness, memory, and performance, disturbed endocrine function, and upset gastrointestinal function. See the article by Klerman (2005) in this issue for greater discussion of circadian rhythm sleep disorders and their consequences.

FUTURE DIRECTIONS

As outlined above, great strides have been made during the past few decades in understanding the features of the human circadian system and how that system is influenced by light. There is compelling evidence that sighted humans are entrained by exposure to light and darkness, and it seems clear that all the light and darkness to which we are exposed throughout the day plays a role in entrainment. Our new understanding of the average circadian period in sighted humans indicates that most sighted persons must make adjustments of less than 30 min per day to remain entrained, and our knowledge of human sensitivity to light tells us that even light of indoor levels contributes to entrainment, and in some cases very dim light can be sufficient to maintain entrainment.

Despite all these recent advancements, much remains unknown about human entrainment. For example, we understand very little about the range of entrainment in humans and about how the strength of light stimuli are related to the range of entrainment. In the laboratory entrainment studies described above, the light stimuli were typically continuous during the waking day. However, in everyday life, humans are exposed to intermittent light stimuli of differing strengths during the waking day (and sometimes during the night), and we know little about how patterns of intermittent light exposure contribute to entrainment.

Our understanding of whether there are aftereffects of entrainment in humans is also quite limited. Although studies of aftereffects of entrainment to the 24-h day on measurement of circadian period may be impractical in sighted humans, studies of blind people may allow insight into whether aftereffects are present by comparing results from sighted and blind people studied under similar laboratory conditions.

Another area of light effects on the human circadian system that remains to be explored is adaptation to prior light exposure. Two recent studies, one a field study (Hébert et al., 2002) and the other a laboratory-based study (Smith et al., 2004) have provided evidence that the circadian photoreceptive system, like the visual system, shows adaptive responses to light history (Fain et al., 2001). Despite these 2 recent studies, we do not understand how the level of ambient light affects this adaptation response, nor do we know the duration of exposure to ambient lighting required to elicit adaptation responses. Furthermore, the dynamics of dim light sensitization have yet to be studied, and understanding how exposure to darkness and/or very dim light affects subsequent circadian responses to light will be important in our understanding of photic entrainment in humans.

The human circadian photoreceptive system, like that of other mammals, is differentially sensitive to short wavelength light in the blue range of the visible spectrum. The conventional measure of light intensity used in the literature, lux, is weighted toward the sensitivity of the human visible system, and thus cannot be used to quantify the circadian effects of light. We will therefore need to develop measures of light that take circadian sensitivity into account to describe accurately how light affects the human biological clock, and how the types of light to which humans are exposed (sunlight, artificial light from different sources) during the normal waking day play a role in entrainment.

ACKNOWLEDGMENTS

The authors thank M.J. Duverne for assistance in preparing the manuscript. Data presented in the figures were collected in studies supported by NIH grants MH45130, AG06072, AG09975, DK07529, and NASA Cooperative Agreement NCC9-58 with the

National Space Biomedical Research Institute; the studies were carried out in the Brigham and Women's Hospital General Clinical Research Center supported by RR02635. Jeanne F. Duffy is supported by NIH grants AG06072 and AT002571; Kenneth P. Wright, Jr. is supported by NIH grants HL73196, AG024621, and by the University of Colorado.

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