



Functional Genomics of Sleep and Circadian Rhythm Invited Review: Integration of human sleep-wake regulation and circadian rhythmicity

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Dijk, Derk-Jan, and Steven W. Lockley. Invited Review: Integration of human sleep-wake regulation and circadian rhythmicity. *J Appl Physiol* 92: 852–862, 2002; 10.1152/jappphysiol.00924.2001.—The human sleep-wake cycle is generated by a circadian process, originating from the suprachiasmatic nuclei, in interaction with a separate oscillatory process: the sleep homeostat. The sleep-wake cycle is normally timed to occur at a specific phase relative to the external cycle of light-dark exposure. It is also timed at a specific phase relative to internal circadian rhythms, such as the pineal melatonin rhythm, the circadian sleep-wake propensity rhythm, and the rhythm of responsiveness of the circadian pacemaker to light. Variations in these internal and external phase relationships, such as those that occur in blindness, aging, morning and evening, and advanced and delayed sleep-phase syndrome, lead to sleep disruptions and complaints. Changes in ocular circadian photoreception, interindividual variation in the near-24-h intrinsic period of the circadian pacemaker, and sleep homeostasis can contribute to variations in external and internal phase. Recent findings on the physiological and molecular-genetic correlates of circadian sleep disorders suggest that the timing of the sleep-wake cycle and circadian rhythms is closely integrated but is, in part, regulated differentially.

sleep homeostasis; entrainment; clock genes; blindness; aging

WE ARE ALL CONSCIOUS OF BEDTIME and wake time and the subjective quality of sleep. Our appreciation of the importance of the sleep-wake cycle is further enhanced when confronted with the consequences of its disruption. Disturbance in the timing of sleep cycles occurs, for example, in response to shift work, jet lag, long work hours, and social and family demands and leads to decrements in quality of life, performance, and health. Disorders of daily sleep patterns are also observed in blind individuals, in older people, and in sighted young individuals suffering from circadian sleep disorders. Such disorders often lead to the use of

sleep aids; hypnotics are among the most commonly prescribed medications.

Biological (circadian) clocks are thought to play an important role in the regulation of sleep-wake cycles and their disorders. Recently, remarkable progress has been made in the understanding of functions and mechanisms of circadian clocks in various model systems and at levels of description ranging from the intact organism to clock gene expression in vitro. Progress has also been made in our understanding of regulation of the timing of the human sleep-wake cycle and its integration with the timing of some endogenous circadian rhythms in endocrinology and physiology. The human sleep-wake cycle is not simply driven by the circadian pacemaker located in the suprachiasmatic nuclei (SCN) but instead is generated through interactions of circadian rhythmicity, a sleep-wake os-

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cillatory process (sleep homeostasis), circadian photoreception, as well as feedback from the sleep-wake cycle onto these processes (see Fig. 1). Alterations in these processes and their interactions may lead to sleep and wakefulness occurring at abnormal clock times (altered external timing) and/or out of phase with endogenous circadian rhythms (altered internal timing). Here we describe some recent developments related to the circadian sleep propensity rhythm, sleep homeostasis, and circadian photoreception.

SEPARATION OF CIRCADIAN AND SLEEP HOMEOSTATIC PROCESSES

It has long been recognized that, for an adequate description of the phenomenology of sleep-wake timing on an approximate daily time basis, two separate but interacting oscillatory processes need to be postulated: a strong circadian oscillator and a sleep-wake oscillatory process or sleep homeostat (for reviews, see Refs. 12, 14, and 15). Early key evidence for the existence of these two processes included the observation of spontaneous desynchrony between the sleep-wake cycle and the circadian rhythm of body temperature during classical temporal isolation studies (6, 30) and the circadian variation of sleep duration during experimentally displaced sleep (8). These data have been summarized in mathematical and conceptual models of the sleep-wake cycle in which the contribution of the two oscillatory processes to sleep timing was defined (13, 32, 63). Experimental human and animal work during the past two decades has confirmed such dual regulation of sleep timing by a circadian process and a relaxation-type sleep-wake oscillatory process. The latter process is also referred to as a sleep homeostat because, from a functional perspective, this oscillatory process regulates the average level of sleep debt. Sleep debt increases during wakefulness and dissipates during sleep. More recently, quantification of the relative contribution of these processes, by forced desynchrony of the sleep-wake cycle from the circadian process, has

shown that these processes contribute about equally to sleep consolidation and waking performance (36, 98). The relative contribution of these two processes to sleep structure and aspects of the electroencephalogram (EEG) during non-rapid eye movement (NREM) and rapid eye movement (REM) sleep varies widely (37, 41).

CIRCADIAN SLEEP-WAKE PROPENSITY SIGNAL

Lesions of the SCN in animals and a few clinical cases in which hypothalamic areas close to the SCN were damaged have demonstrated that the strong circadian process affecting sleep timing and sleep structure is generated by the SCN (27, 46, 87).¹ In humans, the SCN is thought to generate a wake or arousal signal that increases in strength throughout the biological day (i.e., during the habitual wake episode), peaking in the evening hours, at ~2200 h. The strength of this signal declines during the biological night [i.e., during the habitual sleep episode (36, 48)], to reach a minimum at ~0600 h, which coincides with the temperature nadir (36). In the absence of this circadian arousal signal, sleep-wake consolidation is lost and the monophasic sleep-wake cycle is replaced by a polyphasic sleep-wake cycle, presumably dictated primarily by sleep homeostasis. Thus the circadian pacemaker maintains timing of the sleep-wake cycle and consolidation of sleep-wake behavior by opposing the increase in (homeostatic) sleep need associated with sustained wakefulness. Experiments in which sleep was scheduled to occur at many circadian phases have demonstrated that a consolidated 8-h episode of sleep can only be obtained at one specific phase relationship between the sleep-wake cycle and endogenous circadian rhythmicity. Only when sleep is initiated ~6 h before the temperature nadir, i.e., shortly after the crest of the wake propensity rhythm, will sleep remain virtually uninterrupted for 8 h (see Fig. 2).

The circadian sleep-wake propensity rhythm could be generated by a circadian modulation of wake propensity, a circadian modulation of sleep propensity, or a circadian modulation of both. Evidence that the circadian pacemaker primarily affects wake propensity has been derived from studies in squirrel monkeys. SCN lesions lead to an increase in total sleep time per 24 h, in conjunction with the loss of circadian sleep timing (48). Such an increase in total sleep time suggests that promotion of wakefulness is absent in the absence of the SCN. On the other hand, both SCN lesion studies in animals and forced desynchrony studies in young and older healthy people support the view that the SCN also actively promotes sleep, in particular in the second half of the normal sleep episode (40, 97). Thus, in the intact squirrel monkey, wakefulness in the second half of the subjective night is at its lowest levels and well below the percentage of wakefulness

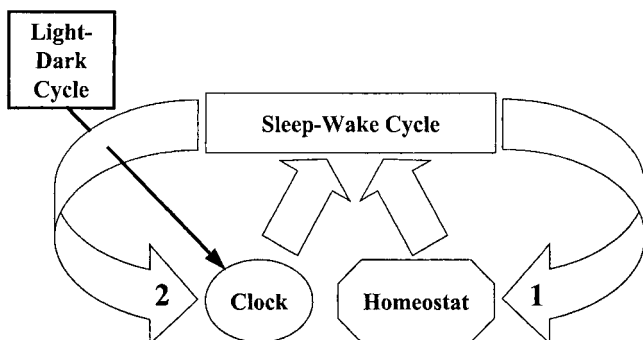


Fig. 1. A circadian pacemaker (clock), presumably located in the suprachiasmatic nuclei (SCN), and a sleep homeostat, presumably located outside the SCN, are two major determinants of the timing of the human sleep-wake cycle and sleep structure. The oscillation of the sleep homeostat is strongly, and maybe exclusively, determined by the sleep-wake cycle (arrow 1). Light input to the circadian clock is mediated by circadian photoreception. The sleep-wake cycle is a major determinant of light input to the clock (arrow 2).

¹We will use the term circadian process in the general context of this paper to mean the signal(s) that affect sleep propensity and sleep structure and originate from the circadian pacemaker, presumably located in the SCN.

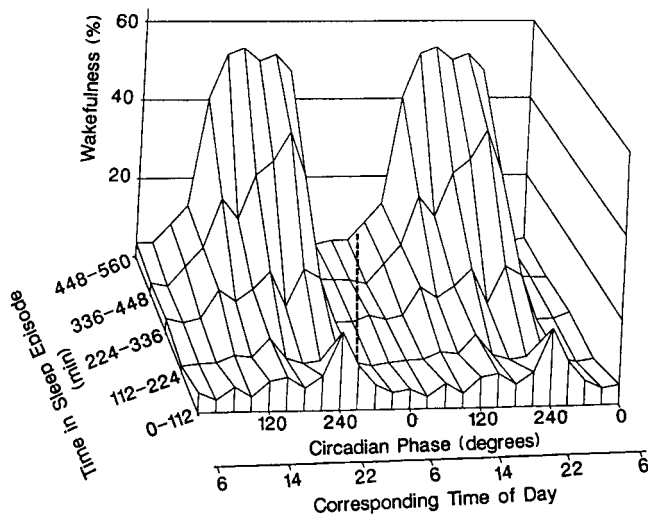


Fig. 2. Wakefulness in scheduled sleep episodes as a simultaneous function of time since start of sleep episode and circadian phase of the core body temperature rhythm. Consolidation of sleep for 8 h or more is only observed when sleep is initiated ~6–8 h before the temperature nadir (dashed line). [From Ref. 36 with permission.]

observed in the SCN-lesioned animal (48). Comparisons of the REM sleep rebound after REM sleep deprivation in control and SCN-lesioned rats have demonstrated that, during the major rest phase, the SCN actively promotes entry into REM sleep (97). In humans, sleep spindle activity is highest during the biological night. Furthermore, sleep latencies in older people are longer than in young people at around the temperature nadir but not at other circadian phases, suggesting that the active promotion of sleep by the SCN is diminished at this circadian phase in older people (40).

The waveform of the endogenously generated circadian sleep-wake propensity rhythm may change in response to variations in day length (photoperiod), such that after prolonged exposure to long dark episodes the internal biological night is extended (94, 95).

The circadian arousal and/or circadian hypnotic signal(s) could be humoral and/or neural. The circadian variation in sleep propensity is closely associated with the circadian rhythm of plasma melatonin (35, 68). Recent functional neuroanatomic studies have identified some of the pathways by which the SCN may transmit circadian information to sleep and arousal centers in the rat. Efferents from the SCN can modulate numerous systems, including the adrenergic, serotonergic, histaminergic, and the orexin systems (1, 7, 73, 75, 79). Deficiencies in the orexin system have been implicated in the sleep disorder narcolepsy (81, 82). Narcoleptic patients experience excessive daytime sleepiness and multiple sleep attacks during the day as though they were unable to maintain wakefulness. Edgar and colleagues (33) demonstrated that, whereas the timing of the circadian modulation of sleep propensity is normal, the strength of this signal, i.e., the promotion of wakefulness, appears to be markedly attenuated in narcoleptics. The recent insights derived

from studies of the orexin system in narcoleptic patients suggest that orexin may be a part of this circadian effector system.

MEDIATORS AND MARKERS OF SLEEP HOMEOSTASIS

Slow-wave sleep (SWS) and EEG slow-wave activity (SWA) during NREM sleep are the classical markers of the sleep homeostatic process. Increases in SWA and visually scored SWS after sleep deprivation are not obliterated in SCN-lesioned rodents (90). In humans, SWS and SWA decline during sleep independent of the circadian phase at which sleep occurs. Furthermore, the duration of wakefulness predicts how much SWS and SWA occur during sleep at all circadian phases (9, 34). Thus the localization of the sleep homeostat is likely to be distinct from the SCN and could be diffuse. There is now convincing evidence that the time course of the sleep homeostatic process can also be monitored during wakefulness in humans. Low-frequency components in the EEG increase as the duration of wakefulness progresses at all circadian phases (3, 19, 21, 49). Scheduling multiple naps during the day attenuates this increase in low-frequency activity during wakefulness (22). This is similar to the previously observed reduction of SWA during sleep following daytime naps (96). It thus appears that low-frequency components of EEG during wakefulness are closely associated with sleep homeostasis. Interestingly, the effects of wakefulness on both the sleep and wake EEG are most pronounced in frontal cortical areas of the brain (20, 21, 49, 50). Whether and how these local changes in the EEG are related to the circadian and sleep-wake-dependent modulation of performance remains to be established.

A number of hypotheses on the neurochemical basis of sleep homeostasis have been put forward (for review, see Ref. 16). There is now substantial evidence for a role of the neuromodulator adenosine in mediating sleep homeostatic signals. Levels of adenosine in basal forebrain areas increase during sustained wakefulness, and administration of adenosine to these brain areas leads to sleep (11). Such a role for adenosine would be consistent with the popular use of the adenosine antagonist caffeine to combat sleepiness. The kinetics of the sleep homeostatic process in mice, as indexed by EEG SWA, has been shown to be under strong genetic control. Quantitative trait loci analysis has identified genomic regions that contribute to this genetic control and that contain genes that regulate adenosine levels (52).

The concept that circadian and sleep homeostatic processes are functionally and anatomically distinct can be further investigated by studying sleep timing and structure and responses to challenges of the sleep homeostat in mammals with altered clock genes (99). The first of such studies indicated that sleep duration and the response to sleep loss may be affected by mutations of the murine *Clock* gene. Interestingly, REM sleep, the sleep stage most strongly regulated by circadian processes, is most modified in *Clock*-mutant mice (80). Some people

suffering from a human familial form of advanced sleep-phase syndrome (ASPS) have been shown to carry an altered *hPer2* gene (91), one of the key clock genes. It appears that in patients suffering from this disorder sleep structure is within the normal range (55, 84).

Clock genes may be involved in the generation of sleep-wake oscillatory processes. During pharmacologically induced desynchrony between rest-activity cycles and circadian rhythms in rats entrained to 24-h light-dark cycles, some clock genes (*rPer1*, *rPer2*, and *rBmal1*, but not *rClock*) in the parietal cortex and caudate putamen oscillate in synchrony with the rest-activity cycle. In contrast, clock gene expression in the SCN remained phase locked to the light-dark cycle and the rhythm of pineal melatonin (78). Alternatively, these extra-SCN rhythms in clock gene expression could be driven by the rest-activity cycle.

CIRCADIAN PHOTORECEPTION IN HUMANS

Although it was once thought that light was not a major synchronizer of human circadian rhythms, it has now been shown that multiple rhythms driven by the SCN, including the rhythms of sleep propensity and pineal melatonin, can be shifted by scheduled ocular light exposure (31). Current estimates of the sensitivity of the human circadian pacemaker to light indicate that ordinary room light exerts an effect that is 50% of the maximal effect induced by very bright indoor light (100). Similar high sensitivities have been obtained in dose-response studies of the direct effects of light on melatonin suppression, subjective alertness, and EEG and electrooculogram correlates of alertness (23). Such studies indicate that the range of illuminances (expressed in lux) over which light exerts a differential effect spans two to three log units. Such a small dynamic range has previously been observed for circadian responses in animal studies and is in accordance with the hypothesis that the effects of light on the circadian timing system are mediated by a photoreceptive system distinct from the system mediating vision (77).

Quantitative aspects of circadian photoreception such as the relationship between duration and intensity of light and the phase shifting effects are under intense investigation and have shown that the first minutes of light exposure are most effective (85). In mice, circadian phase shifting and neuroendocrine and pupillary responses to light can be elicited in the absence of rods and cones, suggesting that another ocular photoreceptor is involved in mediating these effects (53, 76). In humans, the spectral sensitivity of the circadian photoreceptive system has been investigated using light-induced melatonin suppression as the dependent variable. The assessment of the relative efficacy of different wavelengths of light varying from 420 to 600 nm on suppression of melatonin has now demonstrated that short wavelengths (blue light) are most effective in suppressing melatonin (18). A detailed analysis of these data suggested that neither rods nor cones primarily mediate the light-induced neuroendocrine response (17, 89). This neuroendocrine response is often used as a proxy for the circadian

phase shifting effects of light, but it remains to be established whether the spectral sensitivity for phase shifting is similar to that observed for melatonin suppression. Nevertheless, these data are the first compelling evidence that the human circadian photoreceptive system is distinct from the photoreceptive system involved in image formation. It has been hypothesized that melanopsin located in the ganglion cells of the human inner retina is the photopigment mediating these circadian light responses (83). The question of how this spectral sensitivity of the human circadian system is related to its entrainment to the natural light-dark cycle remains to be investigated.

Phase shifts of endogenous circadian rhythms, including the sleep propensity rhythm, can be induced by broad-spectrum light exposure even when the sleep-wake cycle is kept constant (31). Thus most of the effects of light on the circadian pacemaker are not necessarily mediated through the sleep-wake oscillator and are most likely mediated by the direct projection from the retinal ganglion cells to the SCN, the retino-hypothalamic tract. The sleep-wake cycle nevertheless plays an important role in regulating light input to the pacemaker because we close our eyes to sleep and open our eyes when awake (see Fig. 1). Consideration of the interaction between sleep-wake behavior and light input to the light-sensitive pacemaker may be important for the understanding of synchronization of the human circadian system. Previously, it was postulated that effects of light on the circadian pacemaker were in part mediated through a sleep-wake oscillator, which in turn would affect the circadian oscillator. Currently, the mechanisms by which light could exert such direct effects on the sleep-wake oscillatory process are unknown. Direct projections from the retina to extra-SCN hypothalamic areas, such as the ventrolateral preoptic area, which is known to contain sleep-active neurons (74), may play a role in mediating such effects of light. This view of entrainment by light via the sleep-wake oscillator also implies that the sleep-wake cycle exerts an influence on the circadian pacemaker. Experiments in which the sleep-wake cycle was inverted have shown that under these conditions the feedback effects are small (44). However, there is now growing evidence from both animal and human studies that such feedback from the sleep-wake cycle onto the SCN could nevertheless be significant, in particular for the maintenance of entrainment (5, 54, 62, 96a).

DETERMINANTS OF PHASE RELATIONSHIPS BETWEEN THE SLEEP-WAKE CYCLE, ENDOGENOUS CIRCADIAN RHYTHMS, AND THE ENVIRONMENT

In young healthy individuals without abnormalities in their sleep timing, sleep occurs during melatonin secretion and the trough of the endogenous circadian component of the temperature cycle. Sleep begins just after maximal circadian wake propensity and ends just after maximal circadian sleep propensity. Sleep also occurs at a specific phase relative to the circadian rhythm in response to light; the largest shifts of circa-

dian rhythmicity in response to ocular light exposure can be induced near the transition of wakefulness to sleep and vice versa (see Fig. 3). Determinants of the internal and external phase relationships between circadian rhythms, the sleep-wake cycle, and the external world include exposure and the responsiveness to light, the intrinsic period of the human circadian pacemaker, and the rate at which homeostatic sleep need builds up during wakefulness and dissipates during sleep.

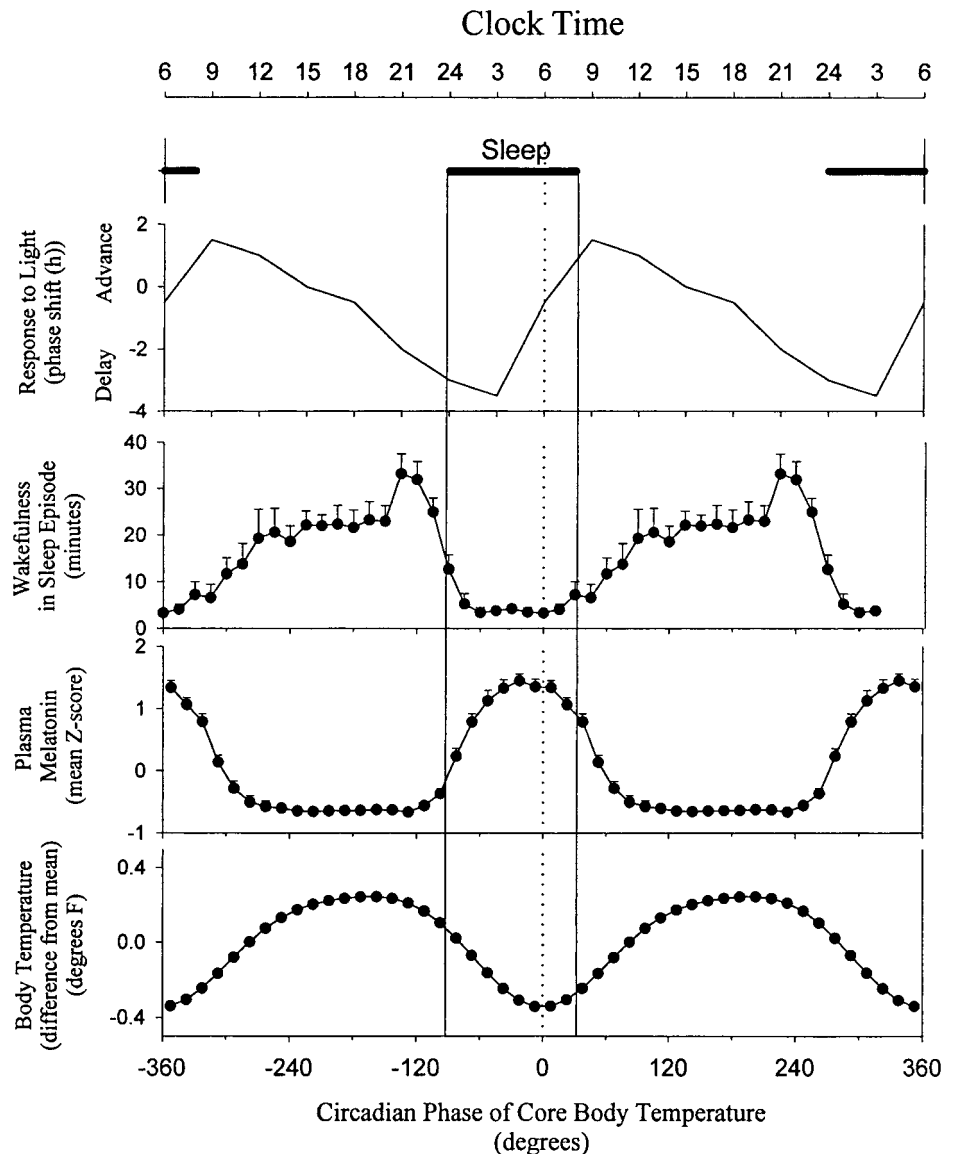
Can the variation in the phenomenology of sleep-wake timing be explained by variations in the intrinsic period of the circadian pacemaker, circadian photoreception and responsiveness of the circadian pacemaker to light, or changes in the sleep-homeostatic process?

INTRINSIC PERIOD OF THE HUMAN CIRCADIAN PACEMAKER: ASSOCIATION WITH INTERNAL AND EXTERNAL PHASE RELATIONSHIPS

The notion that the intrinsic period of the human circadian pacemaker is near 25 h has been recently

challenged. It was recognized that the exquisite sensitivity of the human circadian pacemaker to room levels of light may have affected the period estimate in the classical free running experiments from which the estimate of 25 h was derived (60). During the past decade, a number of laboratories have investigated this aspect of human circadian rhythmicity by assessing intrinsic periodicity under conditions in which the confounding effects of room light exposure were controlled. Such experiments in sighted subjects (young, older, or adolescent) and in blind adult subjects in whom the circadian system is not entrained yielded estimates of intrinsic period that are close to 24 h (see Refs. 26, 28, 38, 57, 69, and references therein). Relatively minor discrepancies between these estimates in populations of sighted and blind subjects may be related to selection of subjects included in the population average, aftereffects of entrainment to light on the observed period, study methodology, or differential control of potential nonphotic time cues (28). Experiments in

Fig. 3. Schematic representation of the timing of the habitual sleep episode in young adults relative to the circadian rhythm of core body temperature, plasma melatonin, wake propensity, and the responsiveness to light. The circadian variation in the responsiveness to light is a schematic representation (see Refs. 31 and 60 for review). Note that the maximum of the melatonin rhythm is located ~2 h before the nadir of the circadian temperature rhythm. Sleep disruption (wakefulness within scheduled sleep episodes) is maximal when sleep is scheduled just before the rise of melatonin. [Based on data published in Ref. 40.]



which the confounding effects of light were carefully controlled have now shown that, in young subjects, phase angle of entrainment is correlated with the intrinsic period of the circadian pacemaker. One estimate of the intrinsic period of the human circadian pacemaker under such conditions is 24 h and 11 min, with a remarkably small variation (SD of 8 min) (28). This small variation is nevertheless associated with entrained phase, such that a 6-min difference in intrinsic period leads to an approximately 1-h difference in entrained phase (45).

In healthy older people without sleep complaints and without sleep disorders, circadian rhythms of melatonin, core body temperature, and cortisol occur at an earlier clock time than that in young adults (25, 43, 45a). In older people, habitual wake time has been shown to also occur earlier relative to the core body temperature and plasma melatonin rhythms. This internal circadian phase advance of wake time has also been observed during forced desynchrony of the sleep-wake cycle and the endogenous circadian rhythm of plasma melatonin and core body temperature (40, 43, 45a). Therefore, the age-related change in the interaction of the sleep-wake oscillator and endogenous circadian rhythmicity is such that wake time is not only advanced with respect to clock time (altered external timing) but also advanced relative to internal circadian rhythms (altered internal timing). Although the advance of entrained phase (external timing) could theoretically be explained by an age-related reduction of the intrinsic period, the simultaneous advance of wake time relative to endogenous circadian rhythms could not. (A plot of the internal and external phase relationships in these two categories, compared with the theoretical changes in internal phase relationships due to changes in period, illustrates this point; see Fig. 4.) In addition, empirical assessments of the intrinsic period in young and older people have yielded identical estimates (28). Thus the age-related 1-h difference in the timing of the core body temperature and melatonin rhythm between young and older people cannot currently be accounted for by an age-related reduction in intrinsic period (28, 57), suggesting that changes in the period of the circadian system are not primarily responsible for the age-related changes in sleep timing. However, it may be worthwhile to point out that, according to the observed association between entrained phase and intrinsic period in young subjects, an age-related difference in intrinsic period of only ~6 min would be required to account for the age-related difference in entrained phase (45).

DIURNAL PREFERENCE

People vary in their diurnal preference for the timing of activity and sleep, and this preference is paralleled in their physiology. In morning types, wake time, the temperature nadir, and the plasma melatonin rhythm occur at earlier clock times than in evening types (10, 42, 58, 59). Sleep deprivation studies have indicated that the homeostatic aspect of sleep regulation is not markedly

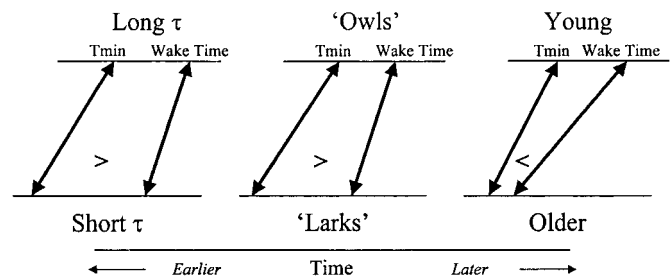


Fig. 4. Schematic representation of the differences in internal phase relationship between wake time and circadian rhythm of core body temperature between owls and larks and between young and older people, compared with theoretical phase relationships that could be expected in individuals with relatively longer or shorter intrinsic periods (τ) of the circadian pacemaker. T_{min}, circadian phase marker core body temperature minimum. Note that the relationship between T_{min} and wake time is not constant (i.e., parallel) in owls vs. larks, young vs. older age, and long vs. short τ , thus demonstrating changes in internal phase relationships between circadian and sleep rhythms.

different between morning and evening types (64). Furthermore, differences in the timing of circadian melatonin and core body temperature rhythms persist under constant routine conditions (in the absence of a sleep-wake cycle), demonstrating that such differences are not a direct consequence of altered sleep-wake timing. Examinations of the internal phase relationships between the sleep-wake cycle and endogenous circadian rhythms have led to the somewhat paradoxical conclusion that morning types, who wake up at an earlier clock time, wake later relative to the circadian cycle of temperature and melatonin (42). The opposite is true for evening types. As previously discussed, in young subjects, small variations in intrinsic period are correlated with variations in diurnal preference. A 6-min difference in intrinsic period is correlated with a change in Horne-Östberg rating (a measure of diurnal preference) by 5–10 points (out of 70-point range) (45). These data indicate that differences in intrinsic period of a magnitude smaller than those associated with clock mutants in rodents have significant consequences for sleep-wake timing and diurnal preference in humans. In fact, an association between diurnal preference and a polymorphism in the human *Clock* gene has been described (56).

ADVANCED AND DELAYED SLEEP PHASE SYNDROMES

ASPS and delayed sleep-phase syndromes (DSPS) are often thought to be associated with advanced and delayed timing of endogenous circadian rhythms, such as temperature and melatonin. Surprisingly, few studies have carefully characterized the circadian physiology in such sleep disorders.

In an examination of the internal and external phase relationships in DSPS patients, delayed bedtime, delayed wake time, and a later clock time for the onset and peak of the melatonin rhythm were reported (88, 92). In addition, bedtime and wake time were reportedly delayed relative to the melatonin rhythm. Therefore, DSPS patients appear not only to wake up at a later clock time but also at a later phase of the endog-

enous rhythm of melatonin and temperature. The observation is in contrast to evening types who wake up earlier in the endogenous circadian cycle. An association between DSPS and polymorphisms in the clock gene *hPer3* has been reported, suggesting that circadian processes may contribute to this condition (47).

The timing of sleep and circadian rhythms of temperature and melatonin in individuals suffering from familial forms of ASPS has been described. As may be expected, the timing of both sleep and endogenous circadian rhythms was advanced by as much as 4 h (55, 84). The internal phase relationships between sleep and the circadian rhythms of melatonin and temperature appeared normal in these patients. Sleep structure (i.e., SWS and REM sleep expressed as a percentage of total sleep time) also appeared normal, suggesting that the primary change in these patients is not associated with the sleep homeostatic facet of sleep-wake regulation but rather in the circadian aspect. So far, assessments of intrinsic period in the absence of the confounding effects of light are not available for such patients. The free-running period, assessed in a classical free-running paradigm, has been reported to be rather short in one patient (55). This may be related to the change in a *hPer2* phosphorylation site, which has been reported in a separate study for some but not all ASPS patients (91).

CHANGES IN CIRCADIAN PHOTORECEPTION IN AGING AND IN BLIND INDIVIDUALS?

Changes in circadian photoreception or changes in the responsiveness of the circadian pacemaker to light due to changes downstream from the circadian photoreceptors may contribute to variations in the entrained phase. Initial comparisons of the responsiveness to light in young and older healthy volunteers suggested that older people were somewhat less sensitive to light in the phase-advance portion of the phase response curve (PRC). The responsiveness to light in the phase-delay portion of the PRC was not significantly different (61). These findings are inconsistent with the hypothesis that changes in responsiveness of the pacemaker to light underlie the observed phase advance. The phase advance in older people may be mediated by the observed internal phase advance of wake time. As a result, this would increase light exposure in the phase-advance region of the PRC and would thereby contribute to the advance of endogenous circadian rhythms (43). This hypothesis highlights the potential role of sleep-wake behavior and changes in internal phase relationship between sleep and circadian rhythms in the determination of entrained phase.

Alteration of light input and the responsiveness of the oscillator to light have been indirectly examined in studies of circadian rhythms in blind subjects. Despite massive loss of visual function, the majority of blind individuals with some degree of light perception maintain normal circadian rhythmicity (29, 69, 72). Similar observations were reported for rodless mice (51). No significant associations have been observed between

circadian rhythm abnormalities and specific retinal abnormalities. In fact, within totally blind subjects, the best predictor of circadian rhythm disorders appears to be the lack of intact eyes (69), an observation which is consistent with the distinct nature of the circadian photoreceptive system. The report of several blind individuals who, despite having no conscious light perception, are sensitive to light-induced suppression of melatonin (29) is consistent with a functional circadian photoreceptive system. These subjects reported no cyclic sleep disorders and presumably have photically entrained circadian rhythms despite no visual function. Alternatively, the lack of association between retinal abnormalities and entrainment may be explained by the effects of nonphotic time cues (regular sleep-wake cycle, societal constraints, etc), exerting sufficient drive onto the pacemaker to maintain entrainment (62).

A variety of abnormal sleep-wake patterns, as well as internal and external phase relationships have been reported in totally blind subjects. Approximately 25% have normally timed hormonal rhythms relative to the light-dark cycle, clock time, and the sleep-wake cycle. A further 25% have hormonal rhythms entrained to an abnormal clock time but maintain more or less normal sleep timing. The remainder have nonentrained (non-24-h) hormonal rhythms and non-24-h sleep-wake cycles. These subjects attempt to maintain a normal internal phase relationship but are often unsuccessful because of the conflict between internal circadian timing and external 24-h time cues (70). Thus, in these totally blind subjects, not only do we observe abnormal phase relationships of endogenous circadian rhythms relative to clock time (altered external timing) but also highly abnormal internal and external phase relationships with respect to sleep timing (altered internal timing). Such observations represent the most extreme example of the consequences of altering the phase angle between sleep and the internal circadian system. Exogenous melatonin administration (5 or 10 mg/day) can be used to successfully treat non-24-h sleep-wake disorder (71, 86) and, if appropriately timed, can realign both abnormal internal phase relationships and the relationship between the circadian system and the external 24-h social day.

ALTERATIONS IN SLEEP HOMEOSTASIS

Self-reported sleep need and sleep duration are found to vary between individuals. First, sleep regulation in habitual short and long sleepers has been studied in the context of the circadian and homeostatic regulation of sleep. Analyses of both the sleep EEG and waking EEG indicate that short sleepers live under a higher homeostatic sleep pressure (2, 4). Second, sleep duration declines across the life span. It has been well documented that SWS and SWA decline with age (24, 93). These findings suggest that sleep need may decline with age. The age-related reduction in SWS and sleep duration is observed at all circadian phases, even when older subjects are scheduled to a rest-activity cycle

similar to young subjects (40) (see Fig. 5). Thus major differences in activity or daytime napping cannot be the primary cause of such changes. Analyses of awakenings in young and older subjects have further shown that it is primarily the consolidation of NREM sleep that is impaired in older subjects (39). Quantitative analyses of the EEG in young and older subjects have demonstrated that the age-related changes in the spectral composition of the EEG are a near-mirror image of the changes induced by an increase in homeostatic sleep pressure after sleep deprivation (24, 67) and opposite to the effects of the major inhibitory neurotransmitter GABA on the EEG (65). In addition, the age-related changes in the EEG appear most prominent in frontal cortical areas (66). These data are consistent with the hypothesis that the major aspect of age-related changes in human sleep are related to the extra-SCN sleep process. Whether this change reflects an age-related reduction in sleep need or age-related changes in the ability to maintain sleep remains unclear. Age-related changes in the circadian aspect of

sleep regulation appear limited to a reduction of the active promotion of sleep in the early morning (40).

CONCLUSION AND PERSPECTIVES

Human sleep-wake timing and circadian rhythmicity are closely interrelated but are, in part, separable and mediated by distinct processes. Consideration of both external and internal sleep timing may provide new parameters to quantify the phenomenology of normal and abnormal sleep regulation. Detailed description and controlled examination of both internal and external phase relationships and comprehensive description of sleep and circadian physiology could clarify the contribution of circadian processes, sleep homeostasis, and circadian photoreception and their molecular-genetic basis to the phenomenology of sleep timing. Examination of the impact of specific genotypes affecting sleep phenomenology on sleep physiology, circadian physiology, as well as circadian photoreception will undoubtedly lead to the discovery of new post-genomic physiology. This in turn may lead us to revise

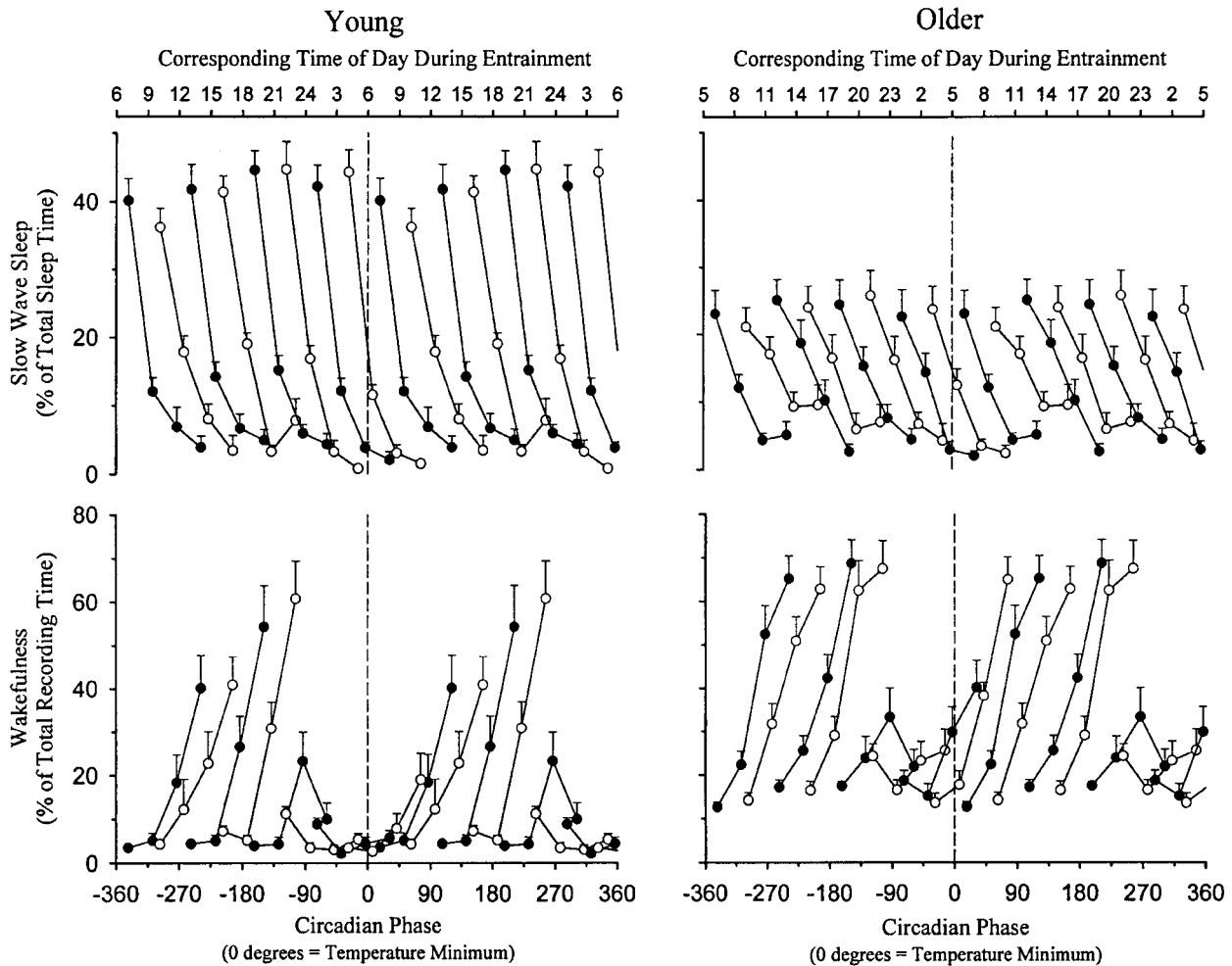


Fig. 5. Comparison of the time course of slow-wave sleep (SWS; top) and wakefulness (bottom) in sleep episodes scheduled at many circadian phases in young (left) and older (right) people. Note that in older people more wakefulness and less SWS within scheduled sleep episodes is present at all circadian phases. [From Ref. 38 with permission, based on data published in Ref. 40.]

or abandon current concepts and necessitate the design of new conceptual frameworks and therapeutic approaches for human sleep timing and its disorders.

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