Aging and Circadian Rhythms

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KEYWORDS

• Aging • Circadian • Human • Light • Melatonin • Sleep

KEY POINTS

- Sleep timing changes with age.
- The circadian system is a major sleep regulatory system.
- There are age-associated changes in human circadian rhythms.
- There are age-associated changes in components of the circadian system in both animals and humans.
- There is evidence for alterations in circadian rhythmicity contributing to age-related changes in sleep.

INTRODUCTION

Earlier Sleep Timing and Reduced Sleep Consolidation with Age

A common feature of aging is the advance of the timing of sleep to earlier hours,[1–7] often earlier than desired.[8–10] The sleep of older people is also characterized by an increased number of awakenings[11] and a reduction of the deeper stages of non–rapid eye movement (REM) sleep (also called slow wave sleep [SWS], stages 3 and 4 sleep).[12–31] These age-related changes are also associated with sleep complaints, with most studies finding that more than one-third of older adults report early morning awakening and/or difficulty maintaining sleep on a regular (several times per week) basis.[8–10,32–34] Although sleep disorders are far more prevalent in older adults,[35] even otherwise healthy older individuals also show characteristic changes in sleep, including reductions in SWS and sleep efficiency and increases in awakenings.[36–40] Age-related changes in sleep structure are seen even in middle-aged adults.[36–40]

Circadian Timing System Regulates Sleep Timing and Consolidation

The circadian timing system is one of the 2 major sleep regulatory systems[41,42] (the other being a homeostatic sleep-wake process). The circadian timing system is a major determinant of the timing of sleep and sleep structure in humans, and many aspects of sleep vary markedly with circadian phase in both young and older adults.[43–46] A proper alignment between the timing of sleep and the circadian phase of sleep is important for sleep duration and quality, as demonstrated in both healthy subjects[47–49] and in some clinical conditions.[50,51] The circadian timing system has a major influence on the timing and duration of REM sleep[42] and has a smaller but still significant impact on many aspects of non-REM sleep. The

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circadian drive for wakefulness increases across the biological day, reaching its maximum in the evening hours when homeostatic sleep pressure is high, the so-called wake-maintenance zone.[52,53] The circadian drive for sleep reaches its maximum during the early morning hours just before habitual awakening time, when homeostatic sleep pressure is low.[28,54] Under ideal conditions, the circadian rhythm of sleep-wake interacts with the homeostatic sleep-wake process to allow for consolidated sleep (and wake) in humans.[55–61] Studies in young adults have demonstrated that even a small change in the circadian time of sleep can have a large impact on the ability to consolidate sleep throughout the night. Thus, age-related changes in circadian rhythms or circadian sleep regulation may underlie the sleep timing and consolidation changes seen in aging and if so may be a target for therapeutics to improve sleep.

Circadian rhythms are endogenously generated oscillations in physiology and behavior with a near-24-hour period. Human circadian period averages slightly longer than 24 hours, with a range of about 23.5 to 24.5 hours in sighted adults.[62–68] The circadian system is synchronized to the 24-hour day by signals from the environment, a process called entrainment. In humans, as in most mammals, entrainment typically occurs via light-dark exposure. Light has a phase-dependent effect on the circadian system, meaning that the effect of a given light stimulus depends on the phase (or biological time of day) at which the light exposure occurs. Light exposure in the late evening and early night shifts the timing of rhythms later (phase delay shifts), light exposure in the late night and early morning shifts the timing of rhythms earlier (phase advance shifts), whereas light exposure in the middle of the biological day produces small changes in rhythm timing.[69,70] Plots of the magnitude of the phase shift with respect to the phase at which the light exposure was given are called phase response curves (PRCs). The phase relationship between the circadian system and the entraining signal is referred to as the phase angle (or phase angle of entrainment; **Fig. 1**). Circadian period interacts with the PRC in the entrainment process, and individuals with different periods (and/or different magnitude of PRCs) have different phase angles of entrainment.[68,71]

Age-related changes in any of the structures involved in generating or entraining circadian rhythms and/or age-related changes in any of the critical features or processes involved in entrainment may therefore contribute to altered circadian rhythm timing with advancing age. The evidence for alterations in circadian rhythms with age and how these might contribute to age-related changes in sleep timing and consolidation are outlined in the following discussion.

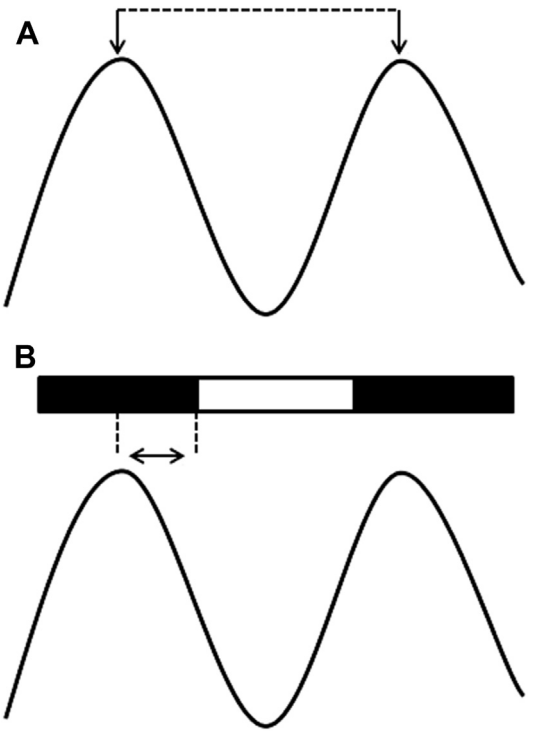

Fig. 1. Some key features of circadian rhythms. (*A*) Phase (*down arrows*) refers to a reference point in the approximately 24-hour rhythm, in this case the peak of the rhythm. The duration from the phase on one cycle to the same phase on the next cycle (*dashed line*) is the period (cycle length) of the rhythm. Period can be assessed only under controlled experimental conditions. (*B*) The near-24-hour circadian rhythms are entrained (synchronized) to the environment through periodic signals from the environment, typically light-dark exposure (*bar across the top of* [*B*]). The relationship between the entraining signal (here, lights on, *right dashed vertical line*) and the phase of the rhythm (here, the peak of the rhythm, *left dashed vertical line*) is referred to as the phase angle of entrainment (*horizontal arrow*). This phase angle depends on the period of the rhythm, the strength of the entraining signal, and the phase-dependent response to that entraining signal.

Methods for Assessing Human Circadian Rhythms

Circadian phase is typically assessed in humans by measuring one or more of the physiologic parameters that are controlled in part by the circadian timing system. The most widely used measures of circadian phase in humans are the rhythms of core body temperature and melatonin

(although many other hormones have rhythms), and each has its advantage and disadvantage. Body temperature has the advantage of being able to be collected continuously, whereas melatonin, which is typically measured in saliva or plasma, can be collected only at less frequent intervals (typically every 30–60 minutes). Body temperature can be measured using a rectal sensor or an ingestible transmitter. A major disadvantage of using body temperature as a marker of circadian timing is that the variations in temperature across the day are not only due to circadian rhythmicity but also due to factors such as posture, sleep-wake state, and activity level. Furthermore, the influence of those behavioral factors on body temperature is phase dependent, such that the change in temperature produced by the behavior is different depending on where in the circadian cycle the behavior occurs. Thus, diurnal variations in temperature, particularly the time of the nadir of the temperature cycle, may not reflect the underlying circadian variation. Melatonin has the advantage of being far less influenced by posture, sleep-wake state, and activity level than temperature, although there is some evidence that periodic changes in behavior can influence melatonin level. Melatonin is suppressed by light exposure, so ambient lighting must be strictly controlled at low levels throughout all sampling segments. One disadvantage of using melatonin as a circadian phase marker is that collection of samples during sleep may require interruption of sleep, although specialized blood collection systems used in many laboratories avoid sleep interruption. Because of this limitation, in many studies only the onset of melatonin secretion is used as a phase marker, rather than collection during the entire 24-hour rhythm. Although in many cases this dim-light melatonin onset is sufficient to determine changes in rhythm timing, it misses out on any changes in melatonin rhythm amplitude, duration, or offset timing.

The constant routine (CR) protocol was developed to assess the phase and amplitude of circadian rhythms.[72,73] The CR consists of a 24+ hour period of wakefulness in a semirecumbent posture, such that sleep-wake state, posture, and activity level are kept constant. Room temperature, humidity, and light level are similarly kept constant, and food and fluid intake are divided into small snacks that are consumed at regular intervals. In this way, many of the factors known to influence physiologic rhythms are either eliminated or are spread across day and night, allowing the underlying circadian oscillation to be observed. In studies of circadian rhythmicity in which sleep deprivation is a major concern, melatonin can be used as the sole circadian phase marker. Protocols in which 24 or more hours of data are collected under controlled conditions allow for assessment of circadian phase and amplitude, making the CR protocol ideal for such assessments.

Circadian period is typically assessed in animals by putting the animal into constant darkness and observing the rest-activity cycle over several days, whereas other methods are used to assess human circadian period. One method is the forced desynchrony (FD) protocol, in which the participant is scheduled to live on a rest-activity cycle much shorter or longer than 24 hours while continuous measurement of physiologic rhythms are collected.[62] FD data are then analyzed by accounting for the imposed periodicity resulting from the rest-activity cycle, while searching for periodicity within the circadian range. That method has been validated against period assessments from CRs and by multiple physiologic measures in the same individual showing the same periodicity.[62] Ultrashort sleep-wake cycles have been used to assess circadian period, although in most cases there has been no independent validation of this method of assessing period.

EVIDENCE FOR CIRCADIAN CHANGES IN AGING IN HUMANS

Circadian Phase

Circadian phase has been shown to move earlier, or advance, with age.[74–79] As described earlier, most rhythms controlled by the circadian system are also influenced by many external and behavioral factors, and therefore, the best evidence about circadian phase comes from studies conducted under laboratory conditions such as the CR, designed to control for effects of light exposure, posture, ambient temperature, sleep, and food intake.[73] The timing of the circadian rhythm of core body temperature has been reported to be earlier in both middle-aged and older (>60 years) adults than in young (20–30 years) adults.[1,76,80–83] The circadian phase of melatonin has also been reported to move earlier with age,[83–86] as has the timing of the cortisol rhythm.[78,79,87,88] **Fig. 2** illustrates the advanced phase observed in studies of older adults.

Phase of Entrainment

The phase relationship between a circadian rhythm of interest and the signal from the environment that entrains the rhythm (typically the light-dark cycle) is referred to as the phase angle of entrainment.[89] There is evidence from animals that the timing of the rhythm of locomotor activity

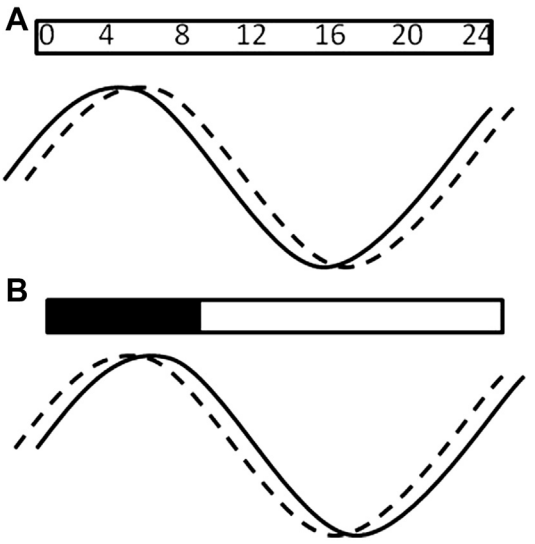

Fig. 2. Altered phase in older adults. (*A*) When compared with clock time (indicated in the bar across the *top of panel A*), the phase of both core body temperature and plasma melatonin is earlier in older adults (*solid line*) than it is in young adults (*dashed line*). (*B*) However, when compared with their usual sleep-wake and dark-light timing (sleep/dark indicated by the *horizontal black* bar, wake/light indicated by the *horizontal white* bar across the *top of panel B*), the phase of both core body temperature and plasma melatonin is later with respect to sleep/darkness in older adults (*solid line*) than it is in young adults (*dashed line*).

with respect to the timing of the light-dark cycle is altered in aging. Studies in hamsters found that activity onset is earlier with respect to lights out in older animals, and reentrainment after the light-dark cycle is shifted is faster.[90,91] However, a study in mice reported delayed activity onset and slower reentrainment.[92] Studies of phase angle in humans have either reported no difference with age[81,93–95] or found that older people show an altered phase angle, such that the timing of the phase of their rhythms of core body temperature and melatonin occur later with respect to sleep (and lights out).[1,84,85] This latter finding means that older adults are sleeping not only at an earlier clock time but also at an earlier biological time.

Circadian Amplitude

There are numerous reports of reduced circadian rhythm amplitude with aging. In animals, reduced amplitude of the rest-activity cycle[92,96–98] as well as the amplitude of multiunit electrical activity in the suprachiasmatic nucleus (SCN) have been reported.[99–102] In studies of human circadian rhythms, most reports find a reduced temperature amplitude with age,[30,76,80,103] and many but not all find reduced amplitude of the rhythms of melatonin and other hormones.[6,94,104] Although changes in the electrical activity of the SCN likely lead to alterations in output rhythm amplitude, the functional consequences of alterations in output rhythm amplitude are not well understood.

Circadian-Sleep Interaction

As outlined earlier, the circadian system interacts with a sleep-wake homeostatic process to regulate the timing and consolidation of sleep in humans. Studies using protocols such as the FD protocol have been used to separate circadian from sleep-wake-dependent influences on sleep and waking performance and to compare those influences between young and older adults. Those studies have demonstrated that the sleep of older adults is much more vulnerable to circadian misalignment than the sleep of young adults.[11,28,30,31,37,46,105] There is a much narrower range of circadian times when the end of sleep can remain consolidated in older adults compared with young adults and a corresponding reduction in the range of circadian phases at which alertness and performance is impaired in older subjects,[1,60,106,107] suggesting an age-related reduction in the circadian drive for sleep in the early morning.[11,28,30,31,37,105] Studies using ultrashort sleep-wake cycles have also reported a reduction in the circadian drive for wakefulness in the evening (the wake-maintenance zone).[37,94] Together, these findings suggest that there may be a reduction in the circadian rhythm of sleep-wake propensity that occurs in aging.

Circadian Period

It was hypothesized that a shortening of circadian period with age could explain the shift in sleep timing with age, and there was evidence from some animal studies that the period was shorter in older animals.[108–110] An initial series of FD studies in which circadian period was assessed in healthy older adults and compared with young adults found no difference in period with age,[62] and in a follow-up study of a larger group of young and older adults the authors found the same result.[68] A study of 6 blind men who each had their period estimated twice during an approximately 10-year interval found no evidence for a shortening of period with age within an individual.[111] Together, these findings suggest that an age-related shortening of circadian period does not underlie the advance in circadian rhythms and sleep timing with age in humans.

Response to Light

Light is the primary environmental signal influencing circadian rhythms and serves to synchronize the near-24-hour circadian system to the 24-hour environmental day.[62–65,89,112–114] Most humans spend little time in outdoor levels of light,[115–117] and therefore, indoor light plays a dominant role in synchronizing circadian rhythms for most people. Use of artificial illumination in the evening has been shown to partially suppress and alter the timing of the melatonin rhythm and sleep in young adults.[118–121] Thus, the pattern of exposure to light in the evening is a likely mechanism contributing to circadian timing and sleep in older adults, and there is evidence to support age-related differences in light exposure patterns in older adults living in the community.[122,123]

Whether the response to light differs between young and older adults is also relevant to sleep and circadian rhythm timing, and several studies of the circadian response to light in older versus young adults have been carried out during the past 2 decades, with mixed findings. Klerman and colleagues[124] used a bright (10,000 lux) light stimulus of 5 hours/day over 3 days in young and older adults and delivered the light stimuli across the phase delay and the phase advance regions of the PRC. They found no evidence for an age difference in phase-shifting response when light was presented in the phase delay region and a suggestion that there might be reduced responses in the older participants in the phase advance region. Benloucif and colleagues[125] used a 4-hour 3500 lux stimulus delivered in the phase delay region and also found no evidence for an age difference in phase-shifting response. Kim and colleagues[83] tested a 2-hour light stimulus of 2000 or 8000 lux delivered at a variety of different phases and did not find significant differences in phase-shifting responses between young and older participants. Duffy and colleagues[126] used a 6.5-hour light stimulus in the phase delay region and tested a wide range of stimulus intensities. They found no difference in phase delay response for low (<100 lux) or high (>1000 lux) light levels but did find evidence for a reduced responsiveness among the older subjects in the intermediate range, with a half-maximal response shifted to 263 lux compared with 119 lux in the young adults.

Although all the previous studies used polychromatic light sources, additional studies using monochromatic light stimuli have also been conducted. Herljevic and colleagues[127] used a 30-minute light stimulus of short (456 nm) wavelength light delivered in the phase delay region and found significant differences in melatonin suppression between young and older women but no age difference when a longer (548 nm) wavelength light stimulus was used. In a study of 2 hours of intermittent short- or long-wavelength monochromatic light delivered in the phase advance region, Sletten and colleagues[128] reported that phase shifting responses were slightly larger in the young participants, although the difference was not statistically significant. Najjar and colleagues[129] studied a series of nonvisual responses to monochromatic light in young and older adults and found a shift in peak sensitivity to longer wavelengths in the older participants but no change in melatonin suppression. Thus, although there are some suggestions of changes in light sensitivity with aging in humans, the differences in response to light in healthy older versus young adults are not strong, and additional research in this area is needed to better understand whether changes in light sensitivity contribute to sleep and circadian rhythm timing changes with age.

Light Transmission

The changes in circadian responses to light that have been observed in some studies may be due to age-related changes in the pathway through the eye, along the retinohypothalamic tract (RHT), and/or within the SCN.[130] There is extensive evidence for changes in the transmission of light through the crystalline lens with age.[130–132] The aging lens accumulates yellow pigmentation, which selectively reduces transmission of short-wavelength light.[129,130,132] Although the exact relevance of this for humans living freely in environments where they can control ambient polychromatic lighting is not yet clear, a study of nearly 1000 Danish adults found that the age-related increase in yellowing of the lens was associated with greater reported sleep disturbances.[133]

There are also changes in the pupil with aging, with older adults having a smaller pupil than young adults. Daneault and colleagues[134] tested whether this affects response to monochromatic light exposure. They found that, although older adults had smaller pupils at dark-adapted baseline and at all light levels tested, the reduction in pupil size in response to light was not different between young and older subjects. Thus, available evidence suggests that light transmission through the lens is altered with age, specifically reducing transmission of short-wavelength light. Age-related changes in retinal function have also been reported in humans,[135,136] and there is a report that the number of intrinsically photosensitive retinal ganglion cells (ipRGCs) declines with

age in rodless-coneless mice,[137] although the same group reported no change in responsiveness to light in the same type of older mice.[138]

Suprachiasmatic Nucleus

Although studies of human SCN function cannot be carried out, there is a general consensus based on animal studies that there are age-related changes in the SCN (reviewed, eg, in Ref.[139]). Studies carried out more than 2 decades ago demonstrated that the locomotor activity pattern of aged animals was much more consolidated after transplantation of fetal SCN, suggesting that some unknown factors that had declined with age had been reintroduced or improved.[140–143] There is strong evidence of altered patterns of electrical activity in the SCN of aged animals,[99–101] which is likely due to altered synchrony among SCN neurons, which leads to a reduced rhythm of multiunit activity.[102] Within individual SCN cells, changes in cell membrane properties that alter electrical activity of the cells have been demonstrated in older animals.[144] There is conflicting evidence about whether the size or cell number within the SCN is altered with age,[145–148] but there is general consensus that the aged SCN shows reductions in the number of cells expressing 2 major peptides, vasoactive intestinal polypeptide and arginine-vasopressin, in both animals and humans.[146–156]

Clock Gene Expression

There is some evidence from animal studies that clock gene expression is altered in aging, although not all studies are in agreement. One study found that expression of Per1 in response to an entraining light stimulus was reduced in aged hamsters, and this was associated with a significantly longer time to resynchronization.[157] That same study also found that the amplitude of Per1 and Per2 were not altered in older hamsters studied in constant darkness, but Bmal1 and Clock were altered in older hamsters. In a study of young and older mice, the amplitude of Per2 expression (but not expression of Per1, Clock, or Cry) was found to be reduced in the SCN of older mice.[158] A more comprehensive study of clock gene expression in young and older mice found age-related differences in expression of Per2, Bmal1, Rev-erbα, Dbp, and Dec1 in the SCN of the older mice.[159] Thus, even with the limited number of studies thus far, there is evidence that the molecular clockwork itself may be altered in aging, although much more research in this area remains to be done.

Circadian Rhythm Sleep-Wake Disorders

Older adults in general sleep and wake at earlier times than do young adults, and in general older adults are more likely to report advanced sleep-wake phase disorder than are young adults.[160,161] These patients report inability to stay awake in the evening and earlier than desired wake time. Delayed sleep-wake phase disorder and non-24-hour sleep-wake disorder show the reverse trend, with far fewer older adults complaining of sleep timing that is later than desired.[161] There is evidence that older adults are more prone to shift work disorder[162–167] and jet lag disorder, and this has been hypothesized to be due to a greater inability to sleep at an adverse biological time with age[11,28,30,31,46] and/or a reduced ability to phase shift with age. In addition to those circadian rhythm sleep disorders that affect community-dwelling older adults, there is evidence that institutionalized older adults and older adults with neurodegenerative diseases such as Alzheimer disease have high rates of irregular sleep-wake rhythm disorder.[168–172] This disorder is characterized by extremely irregular and fragmented sleep-wake patterns, and the disrupted sleep-wake rhythms are associated with very little bright light exposure,[173–175] which may potentially provide feedback and exacerbate the disrupted sleep patterns.[175] Interventions in which ambient lighting is increased have been tested in institutionalized settings and in some cases have been demonstrated to improve sleep-wake consolidation.[176–178]

SUMMARY

The most prominent age-related change in biological timing in humans is the shift of sleep to earlier hours. Why this occurs is still largely unknown. There is evidence for age-related changes in many aspects of circadian rhythmicity, including the transcriptional-translational feedback loops involved in circadian rhythm generation, the neuroanatomical structures, the transmission and responsiveness to light, and the timing and amplitude of output rhythms.

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