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.

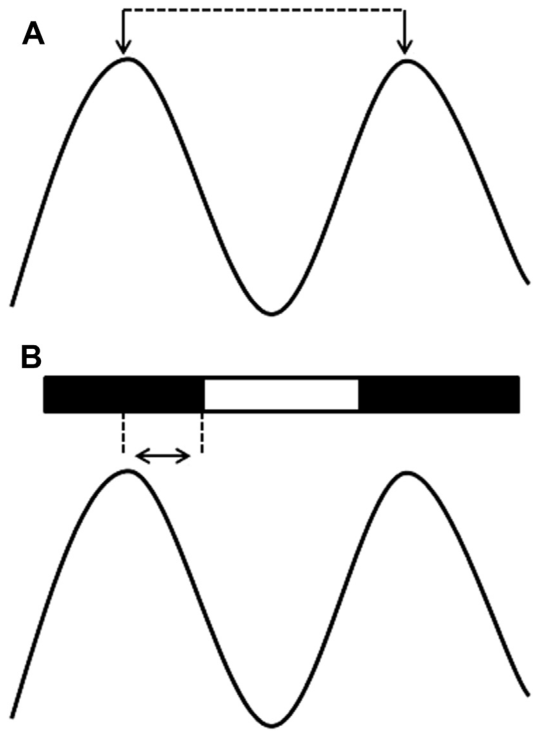

Fig. 1. Some key features of circadian rhythms. (*A*) Phase (*down arrows*) refers to a reference point in the approximately 24-hour rhythm, in this case the peak of the rhythm. The duration from the phase on one cycle to the same phase on the next cycle (*dashed line*) is the period (cycle length) of 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