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Review article

Aging and circadian rhythms

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Abstract

In many animal species including humans, numerous processes exhibit 24-hour (h) rhythms. The circadian clock regulates daily rhythms of behavior and physiology such as the sleep-wake cycle (activity/rest), autonomic nervous function, and neuroendocrine function. The mammalian master clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus incorporates environmental information and orchestrates peripheral clocks in other tissues and organs. Various characteristics of daily rhythms undergo age-dependent changes with respect to amplitude, entrained phase, free-running period (τ), and reentrainability. The mechanisms underlying aging of the circadian clock have not been fully understood. This review discusses current findings on age-related changes in daily rhythms of behavior and physiology.

Key words: human, SCN, circadian, clock, rhythm, sleep

Age-related changes in amplitude of circadian rhythm

In rodent models, age-related declines in the amplitude of circadian rhythms have been found for a diverse range of physiological functions including the activity-rest cycle, body temperature rhythm, melatonin regulation and sex hormone secretion. Among these, reduction in the amplitude of activity-rest rhythm is most remarkable. It is distinctly characterized by multiple phases and fragmentation of sleep-wake patterns, which may take the period of rest (sleep) during the active phase and activity (wake) during the rest phase (Davis and Viswanathan 1998, Labyak et al. 1998, Penev et al. 1997b, Scarbrough et al. 1997, Valentinuzzi et al. 1997, Wax 1975, Welsh et al. 1986). In humans, aging is accompanied by flattening of sleep-wake patterns, characterized by a reduction of slow-wave sleep (SWS), increased light sleep and increased napping during the day (Bliwise 1994, Copinschi and Van 1995). In the 7/13 sleep-wake paradigm, which involves ultra-short cycles of 7-min sleep and 13-min wake, diurnal changes in sleep propensity within the day among elderly subjects has been found to decline (Haimov and Lavie 1997). This is accompanied by a reduction in the amplitude of physiological rhythms such as the neuroendocrine secretion of melatonin, glucocorticoid and thyroid stimulating hormone (which participate in the induction and maintenance of the sleep-wake cycle) and body temperature regulation (Campbell et al. 1989, Czeisler et al. 1992, Moe et al. 1991, van Coevorden et al. 1991). On the other hand, for elderly subjects who have undergone a stringent health screening, it has been reported that the amplitude of circadian rhythm for their core body temperature (cBT) and melatonin secretion was the same as that of young subjects in the control group under conditions where masking effects were strictly controlled (Monk et al. 1995, Zeitzer et al. 1999). This suggests that individual variability exists in amplitude of circadian rhythm of the elderly and its age-related changes, which may arise from genetic or environmental factors.

Age-related changes in circadian phases and entrainability

As aging proceeds, entrained phases of activity-rest (sleep-wake) cycle for environmental light-dark conditions advance. In hamsters, the aged group begins activity during the dark period earlier than does the young control group. When the phase of the light-dark cycle is delayed, reentrainment speed for the activity-rest cycle and the sleep-wake cycle is slower in the aged group than in the young control group (Rosenberg et al. 1979, Zee et al. 1992). When the phase of the dark-light cycle is advanced, however, reentraiment speed is faster in the aged group. It is speculated that this results from a shortening of the free-running period (τ) due to aging in hamsters. In contrast, in mice whose τ becomes longer with age, a phase advance produces delayed reentrainment in the aged group (Valentinuzzi et al. 1997). In humans, aging causes the advanced timing of sleep-wake (Bliwise et al. 1990, Carskadon et al. 1982, Cohen et al. 1983, Drennan et al. 1991, Monk et al. 1995). There is a strong tendency among elderly people toward morning-type preference. Individual's wakefulness level begins to drop early evening, and bedtime, sleep onset and wake time all become earlier (Figure 1). Women

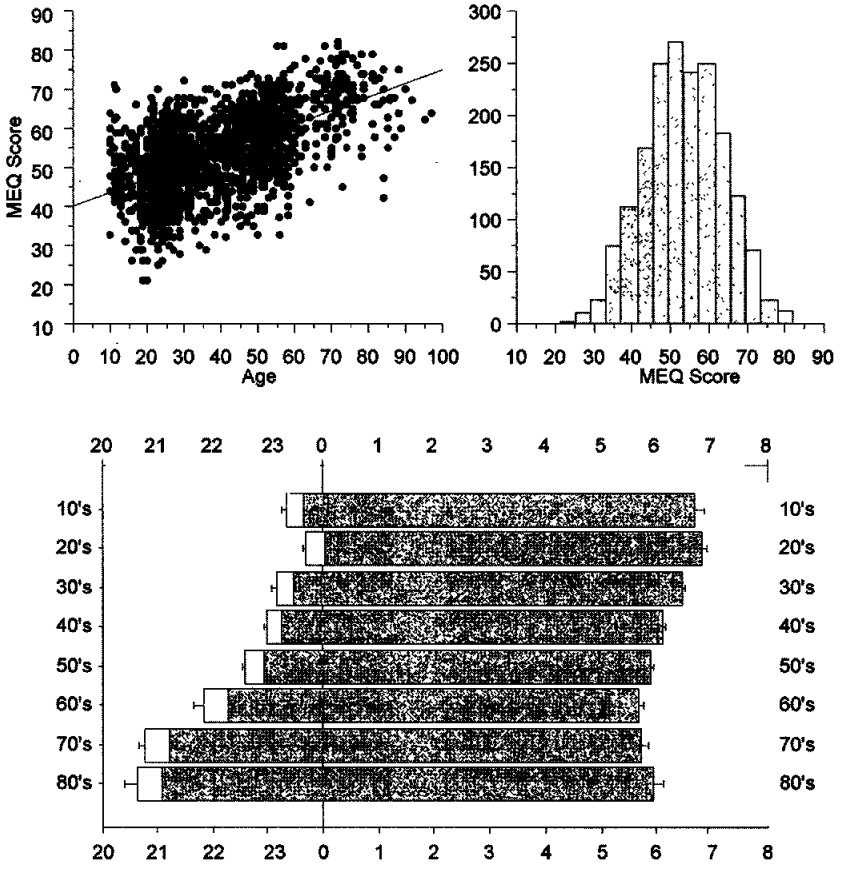

Figure 1 Diurnal preferences, sleep-wake timing and aging.
(Upper panel) Left: Age-related changes (n=1,814; mean age=39.2±16.9 (SD)) in Horne-Östberg morningness-eveningness questionnaire score (diurnal preferences, morning-type/evening-type index). Scores become higher with age, which indicates an increasing tendency toward the morning type ($F(1,1813)=941.1$; $df=1$; $p<0.001$; $r=0.585$). Right: In the scores distribution, the mean score is 53.5±10.2 (SD). (Lower panel) Average bedtime and wake time of different age groups, with actual time points as values on the x-axis. White area indicates latency to sleep onset, and gray area indicates the period between sleep onset and wake time. Subjects were the same as those in the previous figure. Although sleep timing shows phase advance as aging proceeds, bedtime becomes earlier from age 60, which greatly increases the amount of time spent in bed. (Source of data: the author)

have been found to show a stronger tendency in such behavior than do men (Campbell et al. 1989, Reyner et al. 1995). In addition, tolerance for shift work and jet lag is reduced in elderly people (Gander et al. 1993, Harma et al. 1994, Hildebrandt and Stratmann 1979, Suvanto et al. 1990). The aberrant phase relationship between sleep timing and the circadian clock have been implicated as a physiological basis for decline in an individual's ability to maintain sleep (as manifested by sleep disruption and early waking). In this hypothesis, phases of the circadian clock are advanced with aging, which causes earlier circadian phases of the various physiological functions for sleep maintenance (or wakefulness maintenance) with respect to sleep timing, and internal desynchronization. Consequently, sleep disruption occurs easily toward the latter half of sleep due to a reduced urge for sleep and an increased urge for awakening. Sleep efficiency has been thought to become low when the phase of cBT rhythm is artificially shifted forward with respect to the sleep-wake cycle by light exposure in the morning as observed in the elderly (Campbell and Dawson 1992). However, several recent studies have provided counterevidence against this assumption. These studies show that the phase advance of daily rhythm of cBT and melatonin secretion is the same as that of the sleep-wake cycle under conditions where masking effects such as sleep were minimized. It appears that there is no age-related alteration in phase angle difference between circadian clock and sleep timing (Figure 2) (Duffy et al. 2002, Tozawa et al. 2003).

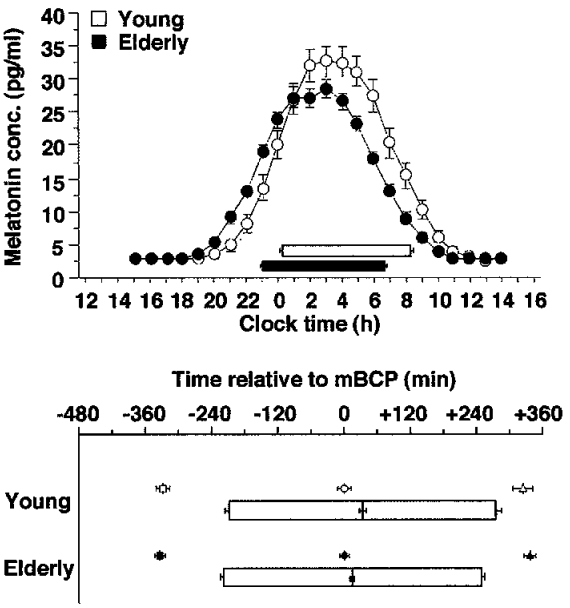

Figure 2 Sleep timing relative to circadian clock phases and its age-related changes (adapted from the literature (Tozawa et al. 2003) with modifications).
(Upper panel) 24-h variations of blood melatonin concentration and average sleep phases of young and elderly groups are shown side by side. Values on the x-axis indicate actual time points (Lower panel). The mid-point of melatonin secretion (the median value between the rising point (□■) and the falling point (△▲) of secretion under low-intensity light), using 0 as the reference point. In the elderly group, melatonin secretion phases (which serve as markers for circadian clock phases) are advanced. Sleep phases show an identical degree of advance, giving no age-related phase differences between the two rhythms.

Age-related changes of free-running period (τ)

In hamsters and rats, τ of behavioral rhythm (Davis and Menaker 1980, Morin 1988, Morin 1993, Penev et al. 1997a, Pittendrigh and Daan 1974, Rosenberg et al. 1991, Viswanathan and Davis 1995, Zee et al. 1992) and the sleep-wake cycle (Van Gool et al. 1987) become shorter with age, whereas in mice τ of activity rhythm becomes longer with age (Possidente et al. 1995, Valentinuzzi et al. 1997). However, when age-related changes are evaluated throughout the entire life span in hamsters, some studies have reported that τ does not change with age (Davis and Viswanathan 1998). In humans, age-related τ changes also remain controversial. Some groups have shown that τ shortens as a result of aging (Monk and Moline 1989, Weitzman et al. 1982), while others have denied that (Czeisler et al. 1999, Wever 1979). Based on assessment by the forced desynchrony protocol, τ is 24.18 h for both young and elderly subjects, which is very close to the 24 h daily cycle and does not suggest any significant age-related changes (Czeisler et al. 1999). In other words, even if shortening of τ occurs with age, the extent to which it shortens is likely to be very small. In that particular study, the amount of apparent changes was not significant enough to account for the forward phase shift in entrained cycles as found in the elderly subjects. In addition, it has been suggested that in elderly subjects, the phase advance of circadian clock in response to high-intensity light is weakened

(Klerman et al. 2001). At present, there is limited evidence in regard to τ or light phase response to account for the advanced phase in sleep and circadian clock among the elderly.

Age-related changes in suprachiasmatic nucleus (SCN)

It is known that the SCN undergoes age-related changes in its functions. In rodents, several characteristics associated with the aging phenotype are known, namely, low amplitude of VIP mRNA transcription in the SCN in the aged group (Kawakami et al. 1997), reduced firing rate of neurons (Satinoff et al. 1993, Watanabe et al. 1995), weakened phase response to light, and reduced induction of immediate early genes in the SCN after light exposure (Benloucif et al. 1997, Sutin et al. 1993, Zhang et al. 1996). Results from histological studies have not been consistent. It has been reported that there is a reduction in the cell count of vasopressin- and vasoactive intestinal peptide (VIP)-producing cells (Chee et al. 1988, Roozendaal et al. 1987), although the total cell number in the SCN remains unchanged in aged rats (Peng et al. 1980, Roozendaal et al. 1987). On the other hand, according to recent studies using a stereotaxic approach, in the SCN of 1- to 30-month-old Wistar rats, no changes were found in the total cell number of neurons and astrocytes or in their morphology (Madeira et al. 1995). One study on age-related cellular changes in the human SCN reported that in an elderly group aged over 80, the total cell number and vasopressin-producing cell count were reduced (Hofman et al. 1988, Swaab et al. 1985). This, however, rather suggests that in age groups up to 70 years old, no morphological changes occur in the SCN, which is consistent with various sources of evidence that no significant age-related changes can be found in τ or amplitude of circadian rhythm among the elderly.

Age-related changes in sleep structure

A meta-analysis of previous studies on age-related changes in sleep structure has been conducted (Figure 3) (Benca et al. 1992, Ohayon et al. 2004). Apart from the insights noted above, it is also found that δ wave amplitude during SWS is low, the frequency of waking during sleep increases, the number of

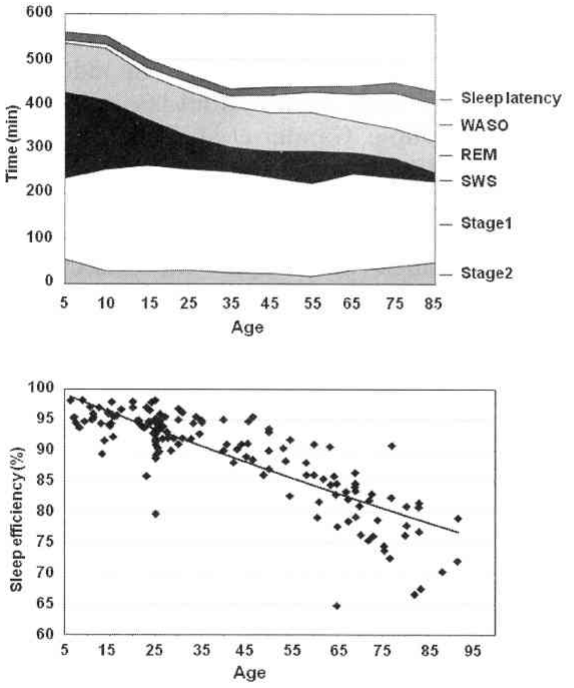

Figure 3 Age-related changes in sleep structure (adapted from the literature (Ohayon et al. 2004) with modifications).
(Upper panel) Sleep latency; WASO (wake after sleep onset); total wake time; REM (rapid eye movement sleep); SWS (slow wave sleep); stage I and stage II are light sleep stages. (Lower panel) Age-related changes in sleep efficiency (%). The plots show the data from different studies.

short waking responses as evidenced on electroencephalography (EEG) increases, and reinitiation of sleep after midnight waking becomes difficult. Sleep initiation mechanisms in the elderly are preferentially impaired compared to sleep maintenance mechanisms. It is well accepted in the sleep research that rapid eye movement (REM) sleep latency becomes shortened in aging. In healthy adults, REM sleep occurs with a cycle of 90 minutes following initial sleep phases after sleep onset. Toward the latter half of sleep, REM sleep time gradually lengthens per cycle. It is also known that in elderly people, REM sleep sustainability is reduced during the latter half of sleep, which is accompanied by an invasion of REM sleep (phase advance of REM sleep) into the initial phases of sleep. Consequently, REM sleep becomes more scattered as a component of the total sleep time. Additionally, elderly people display reduced wakefulness level from the early hours of the evening, while there is a phase advance in sleep-wake timing in terms

of their bedtime, sleep onset, and waking (Bliwise et al. 1990, Carskadon et al. 1982, Cohen et al. 1983).

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