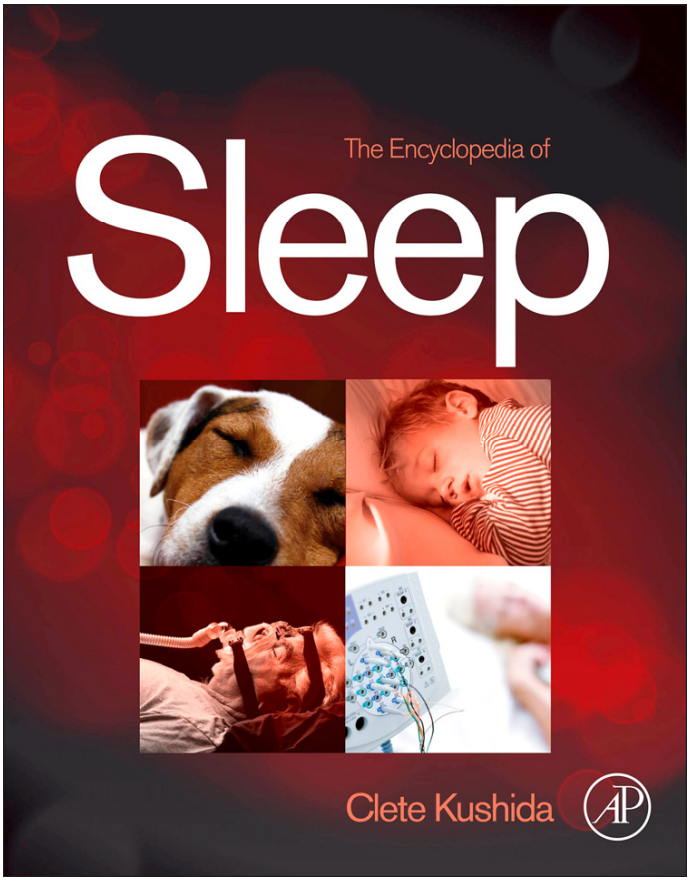




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# Age-Related Changes in Circadian Rhythms During Adulthood

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## Glossary

**Circadian challenge:** Situations in which the circadian timing system needs to adapt to changes in environmental time cues (e.g., jet lag and shift work).

**Circadian entrainment:** Circadian rhythms are endogenous, but they are sensitive to the environment. Entrainment mechanisms exist to synchronize the endogenous circadian period of about 24 h to the environmental day–night cycle of exactly 24 h. The main environmental indicator used by the biological clock to achieve this synchronization is the light–dark cycle. Light signals reach the suprachiasmatic nuclei directly through the retinohypothalamic tract. Rods, cones, and recently discovered melanopsin-expressing intrinsically photosensitive retinal ganglion cells are needed for a proper entrainment.

**Main output markers of the circadian timing system in humans:** Circadian rhythms are endogenous variations in psychological or physiological functions over a period of about 24 h ('circa diem,' about one day). In human chronobiology, two rhythms are most often used as markers of the circadian timing system: the circadian rhythm of body temperature and the circadian rhythm of the production of pineal melatonin.

**Markers of the phase of the circadian timing system in humans:** To estimate the timing of the internal biological clock (the circadian phase), the most often used markers are the time of the minimum of the rectal temperature rhythm, which occurs usually about 2 h before habitual wake time; and the time of onset of the daily episode of melatonin production, which occurs about 2 h before habitual bedtime. In addition to period and phase, circadian rhythms are also characterized by their amplitude, which is half the difference between the minimum and the maximum values of the function over the 24-h period.

**Nonvisual responses to light:** Functions other than vision (i.e., not related to image formation) regulated at least partly by light such as circadian entrainment, pupil constriction, melatonin suppression, alertness, and vigilance levels.

## Introduction

A precise interaction between the homeostatic and circadian processes is required for optimal sleep and vigilance. The homeostatic process is a regulating mechanism whereby sleep pressure accumulates with time awake and dissipates during a sleep episode. The circadian process is the rhythmic pattern of sleep–wake propensity over 24 h controlled by the circadian timing system. The primary pacemaker of the mammalian circadian system is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Entrainment mechanisms exist to synchronize the circadian timing system of about 24 h to the environmental day–night cycle of exactly 24 h. The main environmental indicator used by the biological clock to achieve this synchronization is the light–dark cycle. The SCN includes ventrolateral (the 'core') and dorsomedian (the 'shell') sections. The ventrolateral section uses mainly the vasoactive intestinal peptide (VIP) as a neurotransmitter and its main function is to receive and integrate synchronizing light signals. The dorsomedian section uses mostly the neuropeptide arginine vasopressin (AVP). It integrates the information received from the core and from other parts of the brain, and transmits the integrated rhythmic signal to the body, primarily via connections to other hypothalamic nuclei. Circadian oscillations are driven by rhythmic expression of clock genes and autoregulatory transcriptional–translational feedback loops on a period of approximately 24 h. Contrary to a longstanding belief, we now know that most tissues in the organism also have the necessary molecular clockwork to generate circadian rhythms. However, the rhythmic expression of these so-called 'peripheral' clocks depends on a proper synchronizing signal received from the master SCN clock.

In a normally entrained individual, the sleep-promoting signal sent by the circadian timing system increases during the night to reach a peak in the early morning hours, whereas the circadian wake-promoting signal increases during the day and peaks in the evening. The circadian modulation of sleep–wake pressure can be felt in jet lag and shift work situations where people try to sleep at times when the circadian system promotes wake (which leads to fragmented sleep, despite a high homeostatic sleep pressure) and try to stay awake and productive when the circadian system promotes sleep (which leads to lower alertness and attention failures, even if homeostatic sleep pressure is low). In humans, the combined action of the homeostatic and circadian processes maintains consolidated sleep episodes of about 8 h during the night and about 16 h of wakefulness during the day. Aging induces important



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changes in both of these regulatory processes. This article focuses on age-related changes in the circadian timing system.

## Age-Related Changes in Sleep Timing and Sleep Maintenance

Sleep problems among older adults is now well established. According to a recent study by Roepke and colleagues, increased prevalence of sleep complaints has been observed in elderly subjects. Multiple factors including health problems, medication side effects, and specific sleep disorders account for this age-related increase in sleep difficulties. However, drastic modifications of the sleep–wake cycle are also observed during 'optimal aging,' that is, in people who do not suffer from medical, psychiatric, or specific sleep disorders. Healthy aging is also associated with earlier bedtime and wake time, less time asleep, more frequent awakenings of longer duration, and increased rate of napping. Age-related changes in the circadian system may contribute to modifications in sleep timing and maintenance. Indeed, older people not only show sleep changes under habitual conditions, but they also appear to be more sensitive to circadian challenges. For example, older subjects report more problems adjusting to shift work than younger individuals do. They also adapt more slowly to jet lag.

## Age-Related Changes in Circadian Regulation of the Sleep–Wake Cycle

### Advance in the Timing of the Circadian Signal

It has been suggested that age-dependent changes in the timing of the sleep–wake cycle may be linked to an advanced timing of the signal from the circadian timing system. This phase advance would promote earlier initiation of sleep in the evening and earlier wake time in the morning. There are numerous reports in the literature of age-related changes in the phase of circadian rhythms. First, older people more often indicate that they are morning types than do young people. This difference can be observed as early as the middle years of life (around 40-years-old). Studies controlling for many confounding factors (such as physical activity, meals, and light exposure) have confirmed that, compared to the young, middle-aged and elderly people show a phase advance of their temperature and melatonin circadian rhythms. On average, habitual bedtime, habitual wake time, the minimum of the circadian temperature rhythm, and the onset of melatonin secretion, all occur 1–2 h earlier in older than in younger subjects.

Some authors also hypothesize that the age-related increase in the number and duration of awakenings during sleep is related to an alteration of the time relationship between the sleep/wake cycle and signals from the circadian system. According to this hypothesis, the circadian sleep/wake-promoting signal would not be in tune with the timing of the sleep–wake cycle, leading to more awakenings during sleep in older subjects than in younger ones. This interpretation has led to the suggestion that delaying the phase of the circadian rhythms (e.g., through evening bright light exposure) might alleviate sleep complaints among elderly subjects who have sleep maintenance difficulties. Studies of healthy elderly and middle-aged populations who do not complain about their sleep do not always corroborate this hypothesis since some authors have reported that young and older subjects sleep at the same circadian time.

According to human studies, there is no age-dependent modification of the length of the endogenous circadian period that could explain an early timing of the signal from the circadian timing system. Indeed, the averaged period found in older subjects does not significantly differ from the mean of 24.2 h measured in younger adults.

### Changes in the Amplitude of the Circadian Signal

In order to function properly, the circadian pacemaker should be able to generate a robust signal. It has been suggested that the age-related changes in sleep are linked to age-dependent attenuation of the signal from the circadian timing system. According to this view, there would be an age-dependent attenuation in the ability of the circadian system to create the correct internal temporal milieu for restful sleep at night and alert wakefulness during the day. Most studies have shown a reduction in the circadian modulation of many circadian markers with increasing age (melatonin, temperature, and cortisol). However, some studies suggest that a reduction in the amplitude of circadian rhythms does not necessarily accompany healthy aging. It is possible that the subjects included in these latter studies represented 'healthy survivors,' rather than the 'normal aged' and that robust, high amplitude circadian rhythms were part of the cluster of attributes that kept these people active and vital so late into life.

### Changes in the Vulnerability of the Sleep–Wake Cycle to Circadian Challenges

Sleep of older subjects seems particularly vulnerable to circadian phases of wake-promoting signals, which suggests that it is more difficult for older people to sleep at the 'wrong' circadian phase. This hypothesis might explain in part why sleep complaints related to jet lag and shift work increase with age. Forced-desynchrony studies, in which sleep episodes are initiated at all circadian phases after a constant period of wakefulness (and therefore with a fairly constant homeostatic sleep drive), have corroborated this hypothesis. Compared to when sleeping at their normal time, both younger and elderly subjects awoke more often during their sleep episode when they were required to sleep at a circadian phase of high wake-promoting signal (i.e., during the daytime). In addition, elderly subjects woke up more often during their sleep than did young subjects at all circadian phases. However, the difference between elderly and young subjects was more prominent when sleep occurred with the circadian system sending a strong wake-promoting signal. These findings support the notion that the sleep of older subjects is more vulnerable when the circadian system is not sending an optimal signal for sleep.

In a study by our group on the effects of a 25-h sleep deprivation challenge in young and middle-aged subjects, recovery sleep was initiated one hour after habitual wake time, when the biological clock sends an increasing wake-promoting signal. This experimental situation is similar to what night workers experience when they sleep during the day following their first night shift. Both age groups showed more

awakenings during their daytime recovery sleep compared to their normal nighttime sleep despite the fact that they had experienced a 25-h sleep deprivation. However, middle-aged subjects demonstrated more problems sleeping than the young, with a larger increase in awakenings during daytime sleep. These results may help to understand why people have more problems adapting to jet lag and night-shift work with increasing age.

## Age-Related Changes in Circadian Entrainment

### Light and Circadian Rhythms

Changes in the effects of light on human physiology may contribute to age-related changes in the circadian timing system. The entraining effect of the light signal depends on its intensity and duration, spectral composition, and timing of occurrence. In terms of intensity and duration, brighter and longer light exposures produce larger phase shifts than dimmer and shorter ones. Nevertheless, relatively low light levels typical of indoor lighting (rarely brighter than 500 lux) can induce very significant circadian effects. As for spectral sensitivity, it was recently demonstrated that, for a constant number of photons, short wavelength monochromatic light pulses (blue light) produce larger circadian phase shifts than long wavelength monochromatic light pulses (red or green lights). Finally, in terms of timing, the most powerful circadian effects of light can be observed during the biological night. In normally entrained individuals, the biological night occurs during the environmental night and can be delimited by the time of the daily episode of melatonin production. Light exposure delays the timing of the internal clock when applied in the early part of the biological night, and advances it when applied in the later part.

### Exposure to the Light–Dark Environmental Cycle

One early hypothesis suggested that the age-related decrease in the amplitude of circadian rhythms could be associated with lower exposure to light in older subjects. Some studies did reveal a shorter exposure to bright light in healthy elderly subjects than in younger ones, with an even shorter exposure in the institutionalized elderly. However, many reports deny any relationship between age and light exposure patterns. One recent study by Scheuermaier et al. on age-related patterns of light exposure has even shown that the healthy elderly (mean age 66-years-old) were exposed to higher light levels than young people (23-years-old) during their wake time.

Others have proposed that older individuals might be more prone to be exposed to light in the morning (due to an early wake time), which would constitute a daily phase advancing stimulus. In our study, increasing age was associated with lower relative light exposure (i.e., considering the amount of light in relation to overall light exposure during a day) in the late evening/early night and with higher relative light exposure in the morning. However, while a clear change in habitual light exposure patterns was associated with aging and with an advanced melatonin circadian rhythm in this study, it did not explain entirely the age-related advance of the melatonin circadian phase.

### Sensitivity to Light

#### *Aging of the eye*

Many age-related changes occur at the eye level leading to a reduction in the amount of light reaching the retina and the circadian timing system. A functionally important change occurring with age is a reduction in pupil size (senile miosis). As retinal illumination is proportional to pupil area, the amount of light reaching the retina is therefore decreasing with aging. In fact, the retina of a 20-year-old receives three times more light than the retina of a 60-year-old individual and six times more than the retina of an 80-year-old individual. For dark adapted eyes, the impact of age is even more severe. In this situation, the retina of a 20-year-old individual receives on average 16 times more light than the retina of an 80-year-old.

Studies using electroretinography also found a significant 50% reduction in cone response to light in elderly subjects compared to young adults (aged 15–24 years). In our lab, we observed a correlation between increasing age and decreased retinal sensitivity to light in subjects aged between 50 and 65 years but not in subjects between 20 and 49 years of age.

Senile miosis is not the only age-related phenomenon reducing the amount of light reaching the retina and affecting retinal responses to light. Age is also associated with an increase in ocular crystalline lens absorption. This increased absorption, also known as 'lens yellowing,' is mostly due to ultra violet light exposure. Since this absorption is more pronounced for the short wavelengths crucial for good entrainment of the endogenous clock, lens yellowing may contribute to a suboptimal entrainment of the circadian system.

### Nonvisual Response to Light

The phase advance of circadian rhythms with aging may result from a decrease in the phase shifting capacity of the circadian system in response to the light–dark cycle. One study by Klerman et al. showed that phase delays were not any different between young and elderly subjects except that phase advances were attenuated in the elderly. Another study by Benloucif et al. also found similar phase delays in response to bright light in young and elderly subjects. These results cannot explain the phase advance of the circadian pacemaker in the elderly. Nevertheless, some preliminary findings by Duffy et al. proposed that the circadian system of older subjects might be less able to phase delay after exposure to light of moderate intensity.

The acute suppression of melatonin by light exposure has also been investigated in different age groups. One study by Nathan et al. showed that the percentage of melatonin suppression during a 200-lux exposure from midnight to 01.00 was similar in older and younger participants. However, another study by Herljevic et al. found an age-related reduction in light-induced melatonin suppression when subjects were exposed to monochromatic blue light (456 nm), but not to monochromatic green light (548 nm). Moreover, the same research group recently reported that compared to young individuals, older subjects present a reduced effect of blue light on subjective measures of alertness, sleepiness, and mood after morning light exposure, while there were no age-related differences on these same measures with green light exposure.

In conclusion, the validity of a change in circadian light sensitivity in aging is still debated. Future studies will need to take into account the spectral composition of light in

assessments of light sensitivity in older people. Furthermore, the association of light sensitivity with pupil miosis and ocular lens yellowing will need to be thoroughly assessed.

## Molecular Mechanisms of Age-Related Changes in Circadian Rhythms

Several animal and human studies have shown significant age-related changes in molecular, cellular and neuronal states of the circadian timing system, which may contribute to sleep–wake modifications. They are briefly reviewed below.

### Implication of Clock Genes

Growing evidence from animal studies have shown that aging is associated with specific changes in clock genes expression in the SCN, the pituitary gland, and in peripheral tissues. Compared to young hamsters, old hamsters show reduced SCN *Bmal1* and *Clock* expression during the subjective night and daytime, respectively. Recently, data by Sitzmann et al. on nonhuman primates (rhesus macaque) revealed a reduction in *Per2* expression in the pituitary gland of older adults compared to juvenile animals. Moreover, at the peripheral level, a study of rodents found lower amplitudes of expression of *Per 1,2,3* in the liver, with a similar tendency in the heart, suggesting a reduction in peripheral clock gene expression with aging.

Interestingly, circadian clock gene mutations may induce 'aging-like' changes such as reduced lifespan, cataract, and greater sensitivity to circadian misalignment of simulated jet lag and shift work. *Per2* knockout mice show marked phase advance of their rest-activity cycle. In humans, a rare single base mutation in *Per2*, resulting in an increase of is degradation rate, is associated with the familial phase advance syndrome, a disorder typically found in older individuals. This rare mutation induces a phase advance abnormality in 50% of first-degree relatives of individuals with this *Per2* mutation.

Aging also influences light-induced clock gene expression. Indeed, following exposure to a constant dark condition, older rodents show a reduction in light-induced *Per1* expression compared to younger animals. Since the *Per1* gene is rapidly induced by light and is required for entrainment, these data suggest that age-related circadian changes may partly result from lower SCN sensitivity to photic stimulation. In humans, a recent study showed that compared to young subjects, older subjects show a significant reduction in light-induced *Per2* gene expression in saliva following blue but not green morning light exposure, again highlighting the importance of considering the spectral composition of light when assessing circadian sensitivity to light.

### Implication of Other Molecular and Neuronal Levels

Age-related changes in the circadian timing system may also be linked to a reduction in other SCN molecular and neuronal factors and to a reduction in the amplitude of circadian rhythms in SCN electrical activity.

#### *AVP–VIP neuronal signal*

Several animal and human studies reported an age-related decrease in the rhythmic synthesis and release of SCN VIP and AVP, which are two important neuropeptides of the circadian system. A decrease in the number of AVP-expressing neurons in the SCN neurons has also been reported in older rats. Other evidence suggested a decrease in the daily oscillations and SCN VIP mRNA expression in aged rats compared to young adults. Since VIP expression in the SCN plays an important role in photic information transmission to the circadian timing system, and since VIP-expressing neurons of ventrolateral SCN are mainly projecting to AVP-expressing neurons of the dorsomedial SCN, these age-related neuropeptides changes could contribute to a decrease in light input signals in older animals. A shift in the expression of AVP and VIP was also observed in aged nonhuman primates (i.e., mouse lemur) compared to younger animals. Evidence in humans, from post-mortem brains, also show that the diurnal oscillation of AVP expression present in young subjects (less than 50 years) is flattened in older subjects (more than 50 years). These age-related changes in AVP and VIP systems are likely to affect the precision and robustness of rhythmic information transmission by the SCN to other neural sites and could thus modify the expression of several biological rhythms.

#### *Pituitary adenylate cyclase-activating peptide and glial cells*

Animal investigations have shown age-related reduction in pituitary adenylate cyclase-activating peptide (PACAP) in the SCN. Interestingly, photic signal transduction reaching SCN passes through the release of glutamate and PACAP. Because PACAP seems to be exclusively coexpressed with melanopsin in retinal ganglion cells, age-related PACAP modifications may be associated to changes in the impact of light on circadian regulation as well as in other nonvisual responses to light.

Therefore, from a molecular and neuronal perspective, aging affects not only the master clock (SCN) but also other components of the mammalian circadian system such as peripheral oscillators and communication pathways that maintain the multioscillator circadian organization. The effects of aging on circadian organization are complex and seem to affect specific gene expression in specific tissues. More animal and human studies are needed to closely determine the differential effect of molecular and neuronal changes in healthy aging and their global effect on the circadian system.

## Concluding Remarks

Age-related changes in the sleep–wake cycle parallel significant changes in the circadian timing system. Interestingly, SCN neonatal implantation in aged hamsters increases longevity, suggesting that circadian robustness is a key element of healthy aging. Importantly, sleep–wake rhythms in aged rats can be restored with enhanced light exposure during the light period. In humans, results suggest that bright light, melatonin administration, and physical activity may have positive effects on sleep–wake regulation in healthy and institutionalized older subjects. A few recent studies investigated how light intensity, spectral composition and timing affect sleep quality in elderly subjects. However, more studies are needed to gain

a complete picture of the mechanisms involved in age-related changes at every level of the circadian timing system and to design effective preventive and therapeutic strategies for older subjects suffering from circadian disturbances.

*See also:* **Chronobiology of Sleep:** Molecular and Genetic Bases for the Circadian System; Sleep Homeostasis; The Influence of Light, Exercise, and Behavior upon Circadian Rhythms; **Features, Factors, and Characteristics of CRSD:** Circadian Rhythm Sleep Disorder: Genetic and Environmental Factors; **Intrinsic Factors Affecting Sleep Loss/Deprivation:** Homeostatic and Circadian Influences.

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