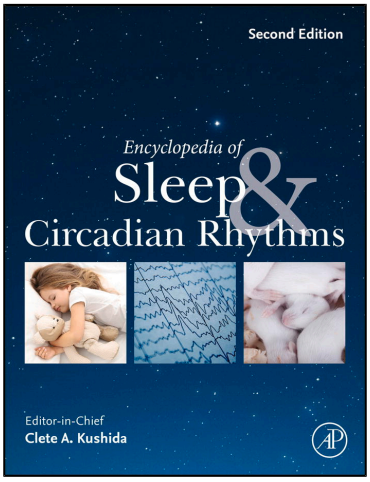

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Age-related changes in circadian rhythms and non-visual responses to light during adulthood

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Glossary

Circadian rhythms Endogenous variations in physiological, behavioral and psychological functions with a period of about 24 h ("circa diem," about one day)

Endogenous circadian period Refers to the precise length of the about 24 h rhythm in the absence of environmental synchronizers (e.g., light–dark cycle, meal), usually defined as tau

Circadian entrainment Synchronization of the endogenous circadian rhythm with the environmental 24 h cycle. The main environmental cue for circadian entrainment is the light–dark cycle

Non-visual responses to light Functions affected by light but not through image formation such as circadian entrainment, pupil constriction, melatonin suppression, modulation of alertness and vigilance levels

Post-illumination pupillary response (PIPR) Persistent pupillary constriction after light offset. This response is recognized as a direct measure of the activity of melanopsin-containing retinal ganglion cells (mRGC) including in humans

Introduction

A precise interaction between the homeostatic and circadian processes is required for optimal sleep and vigilance (Dijk and Czeisler, 1994; Maire et al., 2018; Muto et al., 2016). The homeostatic process is a regulating mechanism whereby sleep pressure accumulates with time awake and dissipates during a sleep episode (Achermann et al., 1993; Borbely et al., 2016). The circadian process is the rhythmic pattern of sleep–wake propensity over 24 h controlled by the circadian timing system (Czeisler et al., 1980). The primary

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pacemaker of the mammalian circadian system is located in the suprachiasmatic nuclei (SCN) of the hypothalamus (Ralph et al., 1990). Light signals, which are the main time cues (Zeitgeber) of the circadian system, reach directly the SCN through the retinohypothalamic tract (RHT) (Moore and Lenn, 1972; Rosenwasser and Turek, 2015). Rods, cones and melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) are the photoreceptors needed for a proper circadian entrainment (Berson et al., 2010; Hannibal and Fahrenkrug, 2006; Hattar et al., 2002). In particular, five functional ipRGCs subtypes have been described (M1-M5), with Brn3b-negative M1 ipRGCs subtype particularly engaged in photoentrainment of the circadian clock (Chen et al., 2011; Schmidt et al., 2011). Retinal light exposure leads to glutamate and pituitary adenylate cyclase-activating peptide (PACAP) release from the RHT (Hannibal et al., 2000), which in turn activate α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) postsynaptic receptors on SCN neurons (Kopp et al., 2001; Takeuchi et al., 1991). The SCN is generally divided into ventrolateral (the "core") and dorsomedial (the "shell") regions (Moore et al., 2002; Dardente et al., 2004). Neurons of the ventrolateral region mainly express the neuropeptide vasoactive intestinal peptide (VIP), and this region is recognized to receive and integrate light signals from the RHT (Moore et al., 2002; Dardente et al., 2004). Neurons of the dorsomedial region mostly express the neuropeptide arginine vasopressin (AVP) (Moore et al., 2002). This region 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 (Watanabe et al., 2000). In almost all SCN neurons, γ-aminobutyric acid (GABA) is also expressed and this main central nervous system inhibitory neurotransmitter strengthens the SCN output signal (Ono et al., 2019).

Circadian oscillations are driven by rhythmic expression of clock genes and autoregulatory transcriptional-translational feedback loops (Ospeck et al., 2009; Takahashi, 2017). Most tissues in mammals have the necessary molecular clockwork to generate circadian rhythms (Buhr and Takahashi, 2013). However, the rhythm of most of these "peripheral" clocks is dependent on proper synchronizing signal received from the master SCN clock, as well as from indirect external cues from the daily eating/fasting (e.g., nutrient consumption) and rest/activity patterns (Mistlberger and Antle, 2011; Welsh et al., 1988).

In normally entrained individuals, the circadian wake promoting signal increases during the day whereas the circadian signal promoting sleep increases during the night to reach a peak in the early morning hours (Czeisler et al., 1980; Zulley et al., 1981; Dijk and von Schantz, 2005). The circadian modulation of sleep–wake pressure can be felt during jet lag and shift work situations where people try to sleep at times when the circadian system promotes wake (which leads to fragmented sleep) and try to stay awake and productive when the circadian system promotes sleep (which leads to lower alertness and attention failures). 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 (Dijk and Czeisler, 1994, 1995). Aging induces important changes in both regulatory processes (Dijk et al., 1999). This article will focus on age-related changes in the circadian timing system. The first part of the article will cover human findings related to age-related changes on circadian rhythms. The second part will discuss animal research on cellular and molecular mechanisms underlying the effects of aging on the circadian timing system.

Age-related changes in sleep timing and sleep maintenance in humans

Sleep problems are well recognized among older adults, with 43% of people aged 50 and older complain about not getting enough sleep (Global Council on Brain Health, 2016). Multiple factors including health issues, medication side effects, and specific sleep disorders account for this age-related increase in sleep difficulties. However, important modifications of the sleep–wake cycle are also observed in healthy aging, i.e., in people who do not suffer from medical, psychiatric, or specific sleep disorders. Healthy aging is associated with earlier bedtime and wake time, less time asleep, more frequent awakenings of longer duration during the night, and increased rate of napping (Buysse et al., 1992; Gaudreau et al., 2001a; Carrier et al., 1997; Landolt et al., 1996; Webb, 1989). Advancing age is also associated with more stable yet more fragmented activity-rest rhythms (Luik et al., 2013). 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 a review see (Duffy et al., 2015)). For example, older individuals report more problems adjusting to shift work than younger individuals (Costa and di Milia, 2008). They also recover slower from jet lag (Carrier et al., 1996; Moline et al., 1992; Monk et al., 2000).

Although the effects of age on the sleep–wake cycle seem quite robust, the influence of physical activity, light environment and synaptic plasticity on the sleep–wake cycle of older individuals need to be better understood (Skeldon et al., 2016).

Age-related changes in circadian regulation of the sleep–wake cycle in humans

Age-related 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 (Duffy et al., 1999; Ishihara et al., 1992; Kawinska et al., 2005). 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 supporting the notion that older individuals show a phase advance of their circadian timing system. First, older people more often indicate that they are morning types in comparison to young people (Carrier et al., 1997; Ishihara et al., 1992; Kawinska et al., 2005). This difference can be observed as early as the middle-years of life (around 40 y.o.) (Carrier et al., 1997). Studies controlling

for many confounding factors (such as physical activity, meals, light exposure, etc.) confirmed that, compared to the young, middle-aged and elderly people show a phase advance of their core body temperature, distal skin temperature and melatonin circadian rhythms (Batinga et al., 2015; Carrier et al., 2002; Czeisler et al., 1992; Duffy et al., 1998; Kawinska et al., 2005). On average, the clock time of habitual bedtime, habitual wake time, the minimum of the circadian temperature rhythm, and the onset of melatonin secretion all occur one to 2 h earlier in older than in younger individuals.

Some authors also hypothesized 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 (Campbell and Dawson, 1992). According to this hypothesis, the circadian wake promoting signal would arrive too early during the sleep period leading to more awakenings during sleep in older individuals than in younger ones (Duffy et al., 2015). Studies of healthy elderly and middle-aged populations does not corroborate this hypothesis since some authors have reported that young and older individuals sleep over the same portion of the circadian cycle (Carrier et al., 1999; Kawinska et al., 2005) or that the phase of their circadian rhythms arrives even later during their sleep period (Duffy et al., 2002).

Although women show a 6 min shorter intrinsic circadian period as compared to men (Duffy et al., 2011), 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 (Czeisler et al., 1999). Indeed, the averaged period found in older individuals does not significantly differ from the mean of 24.2 h measured in younger ones (Czeisler et al., 1999; Duffy et al., 2011).

Age-related changes in the amplitude of the circadian signal

The circadian pacemaker needs to be able to generate a robust amplitude signal to function properly (de Nobrega et al., 2020). 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 showed reduction in the amplitude of the circadian modulation of many circadian markers with increasing age (melatonin, temperature, cortisol) (Dijk et al., 2000; Sack et al., 1986; van Cauter et al., 1996). Studies also indicate lower circadian amplitude of urine excretion and higher nocturnal ratio (i.e., night as compared to daytime amount) which may be linked to reduced sleep quality in older individuals (Duffy et al., 2016; Kirkland et al., 1983). Higher nighttime urine excretion is associated to lower circadian amplitude of hormones controlling fluid balance, including vasopressin (AVP) (Duffy et al., 2016; Kirkland et al., 1983). Interestingly, the diurnal fluctuation of cerebral proteins such as amyloid, and amyloid precursor protein measured in human CSF and blood also show a lower amplitude in older as compared to younger individuals (Dobrowolska et al., 2014; Huang et al., 2012).

Studies also indicate a lower amplitude of diurnal fluctuations of cortical excitability, cognitive functions, performance during sleep loss in older as compared to younger individuals (Blatter and Cajochen, 2007; Gaggioni et al., 2019; Raymann and van Someren, 2007; Sagaspe et al., 2012; Schmidt et al., 2012). Whether this reduction in amplitude is linked to the circadian process, the homeostatic process or their interaction is still a matter of debate. Nevertheless, using a transcranial magnetic stimulation-evoked EEG response, Gaggioni et al. observed lower excitability, but also an overall flattened circadian profile of cortical excitability in older, as compared to younger participants under sleep deprivation (Gaggioni et al., 2019). As compared to the young, older individuals show reduced response to a circadian and homeostatic misalignment on performance (Schmidt et al., 2012), with lower decline in sustained attentional task performance (e.g., psychomotor vigilance test, PVT) and smaller increase in reaction time during a sleep deprivation protocol (40 h) (Blatter and Cajochen, 2007; Sagaspe et al., 2012).

Although most studies show reduction in the amplitude of circadian rhythms in older individuals, it should be noted that some human studies suggest that a reduction in the amplitude of circadian rhythms of the core body temperature and plasma melatonin does not necessarily accompany healthy aging (Monk et al., 1995; Zeitzer et al., 1999). It is possible that the individuals 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 (Monk et al., 1995).

Age-related changes in the rigidity and vulnerability of the sleep–wake cycle to circadian challenges

Sleep of older individuals 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 (Gaudreau et al., 2001b). This hypothesis might explain in part why sleep complaints related to jet lag and shift work increase with age (Gaudreau et al., 2001b). Forced-desynchrony studies, during 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 (Dijk et al., 1999). Compared to when sleeping at their normal time, both younger and elderly individuals 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) (Dijk et al., 2001). In addition, older individuals woke more often during their sleep than did young individuals at all circadian phases (Dijk et al., 2001). However, the difference between elderly and young individuals was more prominent when sleep occurred when the circadian system sent a strong wake promoting signal. In a study by our group on the effects of a 25 h sleep deprivation challenge in young and middle-aged individuals, recovery sleep was initiated 1 h after habitual waketime, when the biological clock sends an increasing wake promoting signal (Gaudreau et al., 2001b; Lafortune et al., 2012). 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 even though they had experienced a 25 h sleep deprivation. However, middle-aged individuals demonstrated more problems sleeping than the young, with a larger increase in awakenings during daytime sleep. These findings support the notion that the sleep of older individuals is more vulnerable when the circadian system is not sending an optimal signal for sleep.

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 circadian phase shifts of core body temperature and melatonin secretion than dimmer and shorter ones (Boivin et al., 1996; Chang et al., 2012). Nevertheless, relatively low light levels typical of indoor lighting (rarely brighter than 500 lux) as well as short intermittent light pulses, can induce very significant circadian effects (Shanahan et al., 1997; Najjar and Zeitzer, 2016; Gronfier et al., 2004). As for spectral sensitivity, it was also demonstrated that, for a constant number of photons, short-wavelength monochromatic light (blue light) produce larger circadian phase shifts of melatonin and alertness, as well as greater melatonin suppression than long wavelength monochromatic light pulses (red or green lights) (Rahman et al., 2021; Brainard et al., 2001; Lockley et al., 2003). Finally, in terms of timing, the most powerful circadian effects of light can be observed during the biological night (Minors et al., 1991; Khalsa et al., 2003). 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 during aging

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 individuals (Mishima et al., 2001). Some studies have found shorter exposure to bright light in healthy elderly individuals than in younger ones, with an even shorter exposure in institutionalized elderly (Mishima et al., 2001). However, many reports do not find any relationship between age and light exposure patterns (Jean-Louis et al., 2000; Kawinska et al., 2005). One study by Scheuermaier et al. on age-related patterns of light exposure has even shown that the healthy elderly (mean age 66 y.o.) were exposed to higher light levels than young people (23 y.o.) during their wake time (Scheuermaier et al., 2010). In healthy older populations, absolute light exposure does not appear to be a major factor contributing to the age-related differences in the amplitude of circadian rhythms.

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 (van Someren et al., 2002). In one of our studies, 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 (Kawinska et al., 2005). However, whereas we found a clear change in the habitual light exposure patterns in association with aging and with an advanced melatonin circadian rhythm, this relationship did not entirely explain the age-related advance of the melatonin circadian phase.

Age-related change in the effects of light on the phase of the circadian timing system

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 (Klerman et al., 2001). One study by Klerman et al. (2001) using bright light (10,000 lux) showed that phase delays of core body temperature and melatonin did not differ between young and elderly individuals but 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 individuals (Benloucif et al., 2006). These results cannot explain the phase advance of the circadian pacemaker in the elderly. Nevertheless, some findings by Duffy et al. proposed that the circadian system of older individuals has the capacity to phase delay using moderate light intensity (270 lux) (Scheuermaier et al., 2019), but might be less able to phase delay than younger individuals after exposure to light of moderate intensity (Duffy et al., 2007).

Age-related changes in non-visual effects of light

Pupillary response and post-illumination pupillary response to light appear to persist with age (Adhikari et al., 2015; Daneault et al., 2012; Rukmini et al., 2017). 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 middle-aged and younger participants (Nathan et al., 1999). In a within-subject design study, Najjar and colleagues investigated the non-visual response (i.e., melatonin suppression) to 9 different monochromatic lights

(60 min) covering the visible spectrum (420–620 nm) in 5 young and 8 older participants. Although lens transmittance was reduced in older participants, the authors reported a shift in peak spectral non-visual sensitivity (484–494 nm) but no reduction in melatonin suppression to light in older participants compared to young (Najjar et al., 2014). These findings, suggesting age-related adaptive mechanisms in non-visual sensitivity to light, differed from earlier findings by Herljevic et al. showing an age-related reduction in melatonin suppression to 30 min of monochromatic blue light (456 nm), but not to monochromatic green light (548 nm) in elderly (Herljevic et al., 2005). In another study, the influence of blue-enriched light on melatonin, sustained attention and subjective sleepiness is also reduced in older, as compared to young individuals after 2 h of evening light exposure (Chellappa et al., 2021). Moreover, another study reported that compared to young men, older men present a reduced effect of blue light on subjective measures of alertness, sleepiness and mood after 2 h of morning light exposure, while there was no age-related differences on these same measures using green light exposure (Sletten et al., 2009). Findings indeed support that pupillary responses to light are preserved in aging, while controversial results are reported for age-related impact of light on melatonin suppression. Discrepancies between these studies may be due to differences in the timing, duration and photon density of the light exposures.

The non-visual impact of blue light on brain activity is also reported to be altered in aging in imaging and electrophysiological studies. Using fMRI protocols, we demonstrated that the older brain is less sensitive to blue light, as compared to a younger brain, while engaged in a working memory task (Daneault et al., 2018, 2014). Older individuals showed lower activations under blue light exposure in subcortical (e.g., thalamus, hippocampus and amygdala) and cortical regions (insula, frontal and occipital cortices). In another study using electroencephalographic (EEG) measurements during sleep, young individuals showed a significant reduction in frontal EEG slow-wave (2–4 Hz) activity after 2 h of blue-enriched light in the evening whereas no significant effect was found in older participants (Chellappa et al., 2021).

Overall, changes in circadian and non-visual light sensitivity in aging are observed for several functions, including alertness, subjective sleepiness, mood and the stimulating impact of blue light on brain activations and sleep-related neurophysiological correlates. On the other hand, pupillary responses to light seems to be preserved, while no consensus emerges from studies on melatonin suppression. The impact of aging varies for different light-regulated non-visual functions, which present different light sensitivities and are mediated, at least in part, by different populations of ipRGCs and brain networks (Daneault et al., 2012). More research will clarify the experimental conditions (i.e., light duration, wavelength composition, timing of exposure) under the effects of light differ between young and older populations.

Aging of the eye

Reduced non-visual light sensitivity may be linked to structural and functional age-related changes of the eye. Structural changes include a dendritic arborization degeneration of ipRGCs that begins as early as age 50 (Esquiva et al., 2017). In addition, these changes include a decreased number of ipRGCs, with a significant reduction of M1d and M3 cells in particular (Esquiva and Hannibal, 2019; Esquiva et al., 2017). Age is also associated with a reduction in pupil size (senile miosis) (Hammond et al., 2000). Since retinal illumination is proportional to pupil area, the amount of light reaching the retina decreases with aging (Charman, 2003; Hammond et al., 2000). Predominantly due to the cumulated exposure to ultra-violet light, age is also associated with a natural increase in ocular lens yellowing leading to a reduced transmittance of light (Charman, 2003; Turner et al., 2010; Kessel et al., 2010). This reduction in lens transmittance is particularly pronounced for short-wavelength lights, i.e., including blue wavelength light. Although lens yellowing may contribute to a suboptimal entrainment of the circadian system (Kessel et al., 2010; Turner and Mainster, 2008; Turner et al., 2010), to date a causal link hasn't been established between increased lens yellowing and reduced circadian entrainment with aging.

Intraocular lens (IOL) replacement for cataract surgery provides an *in vivo* model to assess the impact of lens yellowing on age-related responses to light. The yellowed crystalline lens is replaced by a clear (UV-blocking) IOL, which is more transparent than during adolescence, or by a naturally yellow-tinted lens, namely a blue-blocking (BB) IOL, which is comparable to an endogenous lens of an healthy individuals under the age of 25 (Kessel and Larsen, 2019). These BB lenses have been developed to protect the retina from potential short wavelength light exposure damage (Mainster and Turner, 2010). Studies investigating the benefits of lens replacement after cataract surgery and comparing the two IOLs report improved visual acuity, contrast sensitivity, color perception and dark adaptation after the intervention with both types of IOLs (Landers et al., 2007; Shenshen et al., 2016). However, the effects on sleep and circadian characteristics are inconsistent with some studies showing improvements in subjective sleep quality and latency (Alexander et al., 2014; Ayaki et al., 2013), whereas others did not (Brondsted et al., 2015; Zambrowski et al., 2018).

The distinction between short- and long-term effects on sleep and circadian responses is helpful to understand inconsistencies between studies. Indeed, a greater short-term improvement in sleep quality was reported in UV lens patients compared to BB lens patients at 1 month and 3–7 weeks after surgery (Feng et al., 2016; Lee et al., 2021), but no difference between IOL types was observed at 7–12 months postoperatively (Brondsted et al., 2017; Feng et al., 2016; Lee et al., 2021). One study showed greater PIPR amplitude, in comparison to pre-surgery values, in both IOL types 2 days and 3 weeks after surgery (Brondsted et al., 2015). The same group also demonstrated that the increase in PIPR amplitude persisted 1 year post-surgery, compared with baseline, but at a smaller magnitude compared with the values recorded at 3 weeks (Brondsted et al., 2017). They also reported higher melatonin amplitude 3 weeks after surgery compared to preoperative values, regardless of IOL type, with a trend for a phase advance in

melatonin rhythm in BB IOL patients only (Brondsted et al., 2015). At more chronic time points, 1 month and 1 year after surgery, no differences between pre- and post-surgery or between BB and UV IOL were observed for various melatonin parameters (e.g., onset, total amount) (Brondsted et al., 2017), except for a lower melatonin peak only in BB IOL. One small study reported greater effects of a 2 h exposure to blue-enriched polychromatic light in UV-IOL patients ($n = 5$) compared with BB-IOL ($n = 8$) on PVT performance 8 weeks after surgery (Chellappa et al., 2019).

In conclusion, circadian and light sensitivity changes observed in UV and BB IOL patients after cataract surgery generally fade over time. Next section will discuss plasticity mechanisms with may explain why the impact of cataract surgery changes over time.

Plasticity and adaptive mechanisms

Studies suggest that the non-visual system may show adaptive and plastic responses following prolonged reduced light exposure. For instance, a study conducted in young individuals showed that the wear of blue filtering orange soft contact lenses reduces light-induced melatonin suppression 30 min after the start of wearing the lens but not after 16 days of wearing the lens (Gimenez et al., 2014). These findings highlighted potential compensatory mechanisms in young individuals, preventing a reduction in non-visual sensitivity to short-wavelength light, as previously suggested by Najjar et al. (2014) in older individuals (Gimenez et al., 2014; Najjar et al., 2014). Other studies also show stronger light-induced melatonin suppression and phase shift in young individuals following prolonged exposure to low light (Chang et al., 2011; Hebert et al., 2002; Jasser et al., 2006). Our team observed similar fMRI brain responses to light in older individuals with their natural yellowed lens compared to older ones with UV and BB IOL (5-year after cataract surgery) (Daneault et al., 2018). These results indicate that natural lens yellowing in healthy older individuals does not reduce brain sensitivity to light and support the notion that adaptative and plasticity mechanisms should be considered when interpretating non-visual effects of light in aging. Nevertheless, the association between age-related changes in light sensitivity and retinal changes, pupillary miosis and ocular lens yellowing needs to continue to be thoroughly evaluated to better capture the functional impact of these changes on various behavioral rhythms.

Cellular and molecular mechanisms of age-related changes in circadian rhythms

Animal research also reports age-related changes in the circadian timing system including a decrease in the amplitude of circadian rhythms and reduced circadian responses to light in older as compared to younger animals. Indeed, rodents and nonhuman primates studies demonstrated a decrease in the amplitude of the circadian rhythms of core body temperature, melatonin secretion and locomotor activity with aging ((Aujard et al., 2006; Bruns et al., 2020; Buijink et al., 2020; Farajnia et al., 2012; Valentinuzzi et al., 1997) for a review see (Weinert, 2010)). Results also show a reduced impact of light at various intensities on the circadian rhythm of locomotor activity, with smaller phase advances and delays in older compared to younger animals (Benloucif et al., 1997; Biello et al., 2018; Zhang et al., 1996) and slower re-entrainment after a 4 h advance of the light–dark cycle (Valentinuzzi et al., 1997). Animal models also revealed that peripheral clocks are slower to entrain to a 6 h light-induced phase advance with aging (Sellix et al., 2012). A desynchrony between the master clock and the peripheral clocks/tissues has been proposed to contribute to the reduced ability of older animal to phase-shift (Hood and Amir, 2017; Sellix et al., 2012). Additional cellular and molecular mechanisms underlying age-related modifications in the circadian system have been identified in animals studies (for reviews see (Buijink and Michel, 2021; Gibson et al., 2009; Hofman and Swaab, 2006; Hood and Amir, 2017)), with some being described in more detail hereafter.

Cell density, cell shape and synaptic terminals in the circadian system

As previously mentioned, human studies identified structural changes in the eye contributing to decreased retinal sensitivity to light with age (La morgia and Sadun, 2021). An age-related reduction in the mean density of mRGC has also been reported in rats (Lax et al., 2016), and in the number of melanopsin-positive cells in the retinal ganglion cell layer in mice, including both wild-type and coneless/rodless mice (Semo et al., 2003). However, retinal thickness appears to be reduced in older in comparison to younger Per2^{luc} transgenic mice but not in wild-type mice (Goyal et al., 2021), although young and old animals were not directly compared in this study. These datasets provide support to a relationship between melanopsin cell density and circadian functioning in aging. Of note is that plasticity in the retina could also compensate for age-related alterations in melanopsin cells. For instance, an enhanced retrograde melanopsin signaling has been reported in 14-month old in comparison to 3-month old mice lacking rods and cones (Semo et al., 2016).

Several changes with age have been described in the SCN. Firstly, a lower global SCN volume was reported to be linked to older age in humans, but this relationship only reached statistical significance in women (Hofman et al., 1988). Secondly, the number of immunoreactive cells for the main SCN neuropeptides AVP and VIP was found to be decreased with aging in rodents and in men (but not in healthy women) (Chee et al., 1988; Roozendaal et al., 1987; Zhou et al., 1995). A post-mortem study in humans also showed a positive correlation between the number of VIP-immunoreactive SCN neurons in elderly (with or without Alzheimer disease) and the pre-mortem amplitude of the circadian rhythm of locomotor activity (Wang et al., 2015). Thirdly, a decreased

density of GABAergic synaptic terminals was observed in older in comparison to younger mice for both the core and shell of the SCN (Palomba et al., 2008). This change could underlie a decrease in the robustness of the main circadian pacemaker oscillation via a decreased coupling between SCN neurons. Fourthly, structural changes to non-neuronal cells of the SCN have been reported to occur with aging. In particular, a study found hypertrophy of astrocytes and microglia in the SCN in older as compared to younger mice (Deng et al., 2010). Since astrocytes are major contributors to circadian functions, notably being able to initiate and maintain stable oscillations of clock gene expression in SCN neurons (Brancaccio et al., 2019), these structural changes likely contribute to age-related alterations in the SCN output signal.

SCN firing rate and neurotransmission

Neuronal firing can be considered as a reliable index of both neuronal activity and output. Studies have reported an age-related reduction in the amplitude of the circadian rhythm of SCN neuron firing rate in rats, mice and hamsters ((Satinoff et al., 1993; Nakamura et al., 2011; Farajnia et al., 2012; Watanabe et al., 1995) see also reviews by Buijink and Michel (2021), Hood and Amir (2017)). Such an age-dependent change in the circadian rhythmicity of firing rate was also found for one of the main output region of the SCN, namely the subparaventricular zone of the hypothalamus (Nakamura et al., 2011). Furthermore, a disrupted synchrony in the activity rhythm of different neurons (i.e., lower peak phase coherence) was also specifically reported for the SCN in aged mice (Farajnia et al., 2012). This could directly contribute to amplitude reduction of the overall SCN output and accordingly, to the blunted circadian rhythms in behavior.

Another feature related to neurotransmission and found to be decreased by age in the SCN is the gene expression of the NR2B subunit of NMDA receptors (Biello et al., 2018). Given the role of NR2B in glutamatergic neurotransmission, this observation would be expected to contribute to the attenuation of circadian responses to light as aforementioned. The same group has shown an attenuated phase shift of SCN peak firing rate after NMDA application in older in comparison to younger mice, and a reduction in the light-induced phase shift of the locomotor activity rhythm under NR2B inhibition in young but not in aged mice (Biello et al., 2018). These findings thus converge to support that an impaired glutamatergic transmission in the aged SCN is contributing to an attenuation of the circadian sensitivity to light.

Neuropeptide signaling in the SCN

Alterations in SCN neuropeptide signaling with aging is supported by the age-related decrease in the number of cells expressing AVP and VIP reported above for rodents and men (Chee et al., 1988; Roozendaal et al., 1987; Zhou et al., 1995), as well as by a lower mRNA expression of VIP in aged rats and hamsters in comparison to younger ones (Duncan et al., 2001; Kallo et al., 2004; Kawakami et al., 1997). An effect of aging on SCN neuropeptides is also reinforced by the observation of a reduced amplitude of the day-night difference in the number of AVP immunoreactive cells in the SCN of older (>50 y.o.) in comparison to younger (≤50 y.o.) humans (Hofman and Swaab, 1994). Similarly, an absence of difference between the day and the night in VIP mRNA expression was found in the aged rat SCN, whereas a day-night difference is found in younger rats (Kawakami et al., 1997; Kallo et al., 2004). Since VIP expression in the SCN plays an important role in photic information transmission to the circadian timing system (Moore et al., 2002; Dardente et al., 2004), such an age-related change in the amplitude of neuropeptide expression could contribute to a decreased response to light input signals in older animals as previously suggested (Kawakami et al., 1997). In addition to these modifications in the "level" of AVP and VIP expression as well as in the amplitude of their rhythmic expression, changes in the phase of their peak expression has been reported in a nonhuman primate. Indeed, in the adult mouse lemur, AVP immunoreactivity in the SCN was shown to peak during the second part of the day, while VIP peaked during the night, whereas in the aged animals, the peaks of AVP- and VIP-immunoreactivity was observed to be shifted at the beginning of the night and at the beginning of the day, respectively (Cayetanot et al., 2005). This diversity of age-related changes in SCN AVP and VIP neuropeptides is likely to affect the precision and robustness of the rhythmic information transmission by the SCN. However, it should be noted that not all studies have reported changes in SCN AVP and VIP with aging (Buijink and Michel, 2021; Wu et al., 2007). The activity of the neuropeptide PACAP (i.e., its capacity to stimulate cAMP accumulation) was found to be reduced in the SCN of older in comparison to younger animals (Krajnak and Lillis, 2002). Photic signal transduction in the SCN is mediated by glutamate and PACAP (Moore et al., 2002; Dardente et al., 2004). Therefore, an age-related decrease in the SCN responsivity to PACAP could contribute to modifications in light processing by the SCN, and accordingly, in circadian responses to light. Interestingly, a decreased expression of melatonin receptor 1 (MT1) was also reported to occur with aging in the human SCN (Wu et al., 2007). The effects of age on the SCN thus appears to affect neuropeptide in ways that could impact SCN inputs, intra-SCN oscillations, and feedback of the circadian system on the SCN. Future research should assess the causal relationship between age-related changes in SCN neuropeptides signaling and alterations in circadian functions.

Implication of clock genes

As described in the introduction, cellular and behavioral rhythms are recognized to be driven by molecular oscillatory mechanisms involving clock genes and their protein products. Observations from animals studies have shown that aging is associated

with specific changes in the expression of clock genes in the retina, different brain regions and peripheral tissues (Claustrat et al., 2005; Buijink and Michel, 2021; de Nobrega et al., 2020; Gibson et al., 2009). This section will focus on clock gene alterations with age in the brain followed by those in peripheral tissues, and will then highlight some consequences of clock gene manipulations on aging.

Eye, SCN and beyond

In the eye, assessing rhythmic expression of PER2 in *ex vivo* tissue culture using PER2:Luciferase mice revealed age-related alterations in the retina, cornea and retinal pigment epithelium (Baba and Tosini, 2018). More precisely, the amplitude of the PER2 rhythm was reduced in all three regions, its phase was advanced in the retina and slightly delayed in the retinal pigment epithelium, and the period length was increased by 2 h in cultured retina of older in comparison to younger mice (Baba and Tosini, 2018). In the SCN, aging was also shown to affect the total and/or rhythmic expression of clock genes such as *Bmal1*, *Clock*, *Per2* and *Rev-Erbα* ((Bonaconsa et al., 2014; Kukkemane and Jagota, 2019; Kolker et al., 2003) for review see (Buijink and Michel, 2021)). For instance, old hamsters were shown to have a reduced *Bmal1* and *Clock* expression in the SCN compared to young hamsters (Kolker et al., 2003), and older rats to have a lower amplitude of rhythmic *Per2*, *Bmal1* and *Rev-erbα* expression in the SCN in comparison to younger rats (Kukkemane and Jagota, 2019). Nevertheless, there seem to be discrepancies between studies regarding the effect of age on SCN clock gene expression (Asai et al., 2001; Buijink and Michel, 2021), and the SCN was reported to be relatively resistant to the effect of aging at the level of gene expression (Buijink and Michel, 2021; Eghlidi et al., 2018; Yamazaki et al., 2002). This resistance might not apply, however, at the level of clock proteins in the SCN, which has also generally been reported to be decreased by age (e.g., for BMAL1 and PER2 (Chang and Guarente, 2013; Nakamura et al., 2015)). Other key elements regulating molecular clock mechanisms have also been shown to be sensitive to the effect of aging in the SCN. This is the case for SIRTUIN1 (SIRT1), a deacetylase notably controlling BMAL1 activity (Nakahata et al., 2008), which levels and rhythmic expression decrease with age in the SCN (Chang and Guarente, 2013; Kukkemane and Jagota, 2019), and overexpression counteracts the decline in circadian function with aging (Chang and Guarente, 2013).

In the SCN, aging was also found to affect light-induced changes in clock gene expression. Following exposure to constant darkness, older rodents show a reduction in SCN light-induced *Per1* expression (but not *Per2* expression) compared to younger animals (Asai et al., 2001; Kolker et al., 2003). Similarly, SCN *Per1* expression change in response to a shift of the light–dark cycle was shown to be altered in aged in comparison to young rats (Davidson et al., 2008). Since *Per1* in the SCN is rapidly transcribed following light exposure and is required for entrainment (Challet et al., 2003), these data suggest that age-related circadian changes may partly result from lower SCN sensitivity to photic stimulation as also supported by changes in neuropeptides in the aged SCN (see above). As suggested previously (Nakamura et al., 2015; Sellix et al., 2012), age-related clock genes expression alterations in the SCN suggest a decline in pacemaker robustness that could increase vulnerability to environmental challenges, and partly explain age-related sleep and circadian disturbances.

Age-dependent changes in clock gene expression have also been found in brain areas other than the SCN. For instance, a reduction in *Per2* expression in the pituitary gland of older adults compared to juvenile animals was observed in rhesus macaque (Sitzmann et al., 2010). In human post-mortem prefrontal cortex, aging was reported to decrease the amplitude of *PER1* expression and to shift rhythmic *PER2* expression (Chen et al., 2016). In the fruit fly, all glial cells expressing PER protein were found to show a significant age-related decline in its level (Long and Giebultowicz, 2017). On the other hand, no change in clock gene expression with age in the paraventricular nucleus and pineal area has been reported (Asai et al., 2001), which emphasizes the brain region specific effects of age on core clock molecular components.

Peripheral tissues

In peripheral tissues including the liver, heart and lungs, age-related decreases in the level and/or in the amplitude of rhythmic variations of clock genes have also been described (for review see (de Nobrega et al., 2020)). For the liver in particular, a lower amplitude of rhythmic expression was reported for *Bmal1*, *Clock*, *Rev-erbα*, *Per1*, *Per2* and *Per3* in older mice and/or rats in comparison to younger animals (Bonaconsa et al., 2014; Claustrat et al., 2005; Sato et al., 2017). In the heart, a lower amplitude of rhythmic *Bmal1*, *Per1*, *Per2* and *Per3* expression was found in aged mice and rats (Bonaconsa et al., 2014; Claustrat et al., 2005). This could specifically contribute to the attenuated time-of-day changes in cardiac electrophysiological properties reported for aged mice (Wang et al., 2020). It is important to note, however, that many between-study differences can be observed in the effect of aging on clock gene expression in peripheral tissues (de Nobrega et al., 2020). For instance, while aging was reported to attenuate the amplitude of *Rev-erbα* expression in the mouse liver in one study (Sato et al., 2017), it was reported to increase the amplitude in another (Bonaconsa et al., 2014). In addition, some tissues seems to show a relatively preserved expression (including rhythmic expression) of clock genes with aging (e.g., small intestine and colon (Paulose et al., 2019)). As indicated above, it is also highly possible that the coupling between central and peripheral clocks represents a particular challenge in aging, especially under conditions involving flexibility/adaptation of the circadian system (Sellix et al., 2012). In line with this, the response to behavioral disturbances (e.g., restraint stress, enforced exercise) by the core molecular clock in peripheral tissues was found to be altered in aging (Tahara et al., 2017). Overall, these findings emphasize the relative complexity of the manner by which aging affects the circadian system at the level of peripheral tissues.

In humans, an effect of age on clock gene expression in peripheral tissues has also been found. For instance, a lower *BMAL1* expression in peripheral blood cells was observed to significantly associate with older age in healthy women (Ando et al., 2010), and the light-dependent *PER2* expression in the oral mucosa was reported to be reduced in older as compared to young individuals (Jud et al., 2009). In human cultured fibroblasts, molecular clock properties (e.g., period length, circadian amplitude) were found to be similar between young and older individuals as assessed using a reporter construct including the *Bmal1* promoter (Pagani et al., 2011). However, when exposed to serum from young or older individuals, cultured fibroblasts expressed differences in clock properties that are better matching behavior (e.g., shorter period length driven by older serum in parallel to earlier chronotype in older individuals (Pagani et al., 2011)). This dataset highlights the importance of changing cues from the internal milieu in shaping peripheral clock functions in aging.

Clock gene manipulations and aging

Interestingly, it has been proposed that disrupting the circadian molecular clock may induce "aging-like" changes such as reduced lifespan, cataract, and greater sensitivity to circadian misalignment of simulated jet lag and shift work (de Nobrega et al., 2020). Indeed, *Per* mutant male flies have a reduced lifespan in comparison to normal male flies (Klarsfeld and Rouyer, 1998), and *Bmal1* knockout (KO) mice were reported to have a shorter lifespan, as well as characteristics reminiscent of premature aging such as sarcopenia, less subcutaneous fat, and cataracts (Kondratov et al., 2006). Similarly, mice lacking PER2 were shown to be more susceptible to the development of tumors (Fu et al., 2002), while mice lacking the CLOCK protein have a reduced lifespan, and a higher rate of cataracts and dermatitis than wild-type mice (Dubrovsky et al., 2010). Interestingly, premature aging and finding of an accelerated age-related decline in adult neurogenesis in the hippocampus was associated to an enhanced SIRT1 in *Bmal1* KO mice (Ali et al., 2015). This particular finding is in line with the above-mentioned implication of this deacetylase in aging of the SCN (see **Eye, SCN and beyond** section). This type of observation is providing support to causal relationship between molecular components of the circadian system and aging, and also highlights a bidirectional relationship between the two. These findings could also suggest that molecular clock components be considered as targets to mitigate the effect of aging on behavior and cognition.

Concluding remarks

This article reviewed findings on age-related changes in the circadian timing system that may contribute to modifications in behavioral and physiological functions in aging. Notwithstanding the complexity of age-related changes of circadian function, healthy aging should be accompanied by a variety of behaviors and habits promoting well-being, including optimized lighting environment, physical activities and feeding/fasting influences. It was indeed shown that sleep–wake rhythms in aged rats can be ameliorated with enhanced light exposure during the light period (Witting et al., 1993). 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 individuals (van Someren et al., 2002). A few studies have investigated how light intensity, spectral composition and timing affect sleep quality in elderly individuals (Figueiro et al., 2009). 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 individuals suffering from circadian disturbances.

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