Chapter 11
Pineal Gland Physiology and Aging-Related Alterations in the Circadian Timing System

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11.1 Introduction

The pineal gland (PG) is part of the epithalamus and is situated in the midline of the 3rd ventricle (i.e., the geometric center, hence "Seat of the Soul" by René Descartes) of the human brain. The circadian timing system (CTS), sleep/wake control, immunity, reproduction, cell protection, and neuroprotection are some of the examples of important functions of the pineal gland. The physiologically active proteins, peptides, and enzymes produced by the mammalian pineal body have several physiological activities in the pineal gland and help maintain the biological clock and circadian timing (Blask et al. 1983; Benson 1989; Bharti et al. 2009; Jagota and Mattam 2017). It constitutes active peptides, serotonin (5-HT), melatonin (MLT), and several other pineal indoles, which have recently been discovered to be strong regulators of a variety of physiological functions, including aging and longevity. Many researchers revealed that the blood concentrations of melatonin turn down with increasing age and are documented to be negatively associated with quite a lot of diseases together with neurodegenerative diseases (Cheng et al. 2021). As melatonin is implicated in autophagic flux, quenching of free radicals, suppressing the discharge of pro-inflammatory protein factors, and jamming apoptotic pathways, the amplitude of its rhythm during aging is crucial. Melatonin rhythm, in general, deteriorates in aged mammals and humans, the above-mentioned processes are weakened causing

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them more vulnerable to numerous disorders and diseases. The pineal gland exhibits clear age-associated deteriorations (Cheng et al. 2021). The pineal gland in humans frequently becomes calcified with age, making it a suitable imaging marker. Several studies have linked pineal calcification to a disrupted 24 h rhythm of sleep control and a reduction of melatonin synthesis during the aging process (Yoon et al. 2003).

The deficiency of melatonin is linked not just to age but also to the severity of the deficiency's impact on mental health. Extensive investigations document that nocturnal melatonin concentrations are diminished explicitly in Alzheimer's disease (AD) and that diurnal melatonin concentrations are elevated in AD patients, representing that the neurodegenerative development influences the circadian-pineal organization. Patients often report distressing sleep patterns. The absence of a daily melatonin rhythm in AD patients is inextricably linked to clinical circadian rhythm disease. These patients exhibit agitation, agitation, insomnia, and sleep dysregulation (Wu et al. 2003).

Melatonin is available without a prescription in practically every country on the planet and is available in the form of tablets, capsules, syrup, and transdermal patches (Wu et al. 2003). Nonetheless, despite its modest side effects profile and stumpy potential for misuse, there are concerns associated with the continuous usage of melatonin in the elderly. These concerns also emerge from improper administration and use in specific therapeutic situations, such as an adjuvant in benzodiazepine dose-decreasing protocols, where clinical studies are insufficient to maintain the drug's efficacy.

11.2 Neuroendocrine Perspective of Circadian Rhythm and Aging

There are various metabolic activity and cellular secretions of the hypothalamus, pituitary, pineal (SCN), adrenal, thyroid, thymus, and gonads which are associated with circadian rhythm and aging and controlled through neuroendocrine secretions. Among others, aging progressions in mammalian systems lead to major changes in the circadian clock's output rhythms, neuroendocrine disruption, compromised immunity, and loss of collagen fiber and tissue elasticity. The changes include phase shifts (usually a phase advance) and amplitude reduction. In rodents, aging causes a change in the circadian timing system and several other parameters such as regulation of body temperature, locomotor rhythm, sleep/wakefulness, drinking, and feeding rhythms (Weinert 2000). A shift in melatonin synthesis and changes in body temperature rhythms are also noted. Unlike young adults, elderly people have an earlier usual time of sleeping and awakening and sleep disturbances (Yoon et al. 2003). This has been linked to inadequate pineal secretion rhythmicities in the aged pineal gland in older adults. In older animals, this is also linked to a reduction in thyroxin, thyroxin-releasing hormone (TRH), and thymus secretion (Rezzani et al. 2020). There is a shred of evidence that pineal calcification with aging inhibits melatonin secretion

affecting immunomodulation and metabolic balance (Tan et al. 2018). Hence, it is imperative to rejuvenate the pineal gland for its normal endocrine function to control the aging process initiated due to poor melatonin and pineal secretion in the calcified gland. Melatonin regulates other cellular functions that control cell death, thereby aging, viz., mitochondrial function, free radical generation, apoptosis, anti-inflammatory function, etc. (Mattam and Jagota 2014; Hardeland 2017; Subramanian et al. 2021; Xie et al. 2021). Pineal secretions up-regulate aging suppressor sirtuin-1, which resulting better mitochondrial metabolic function and circadian rhythm.

Hence, re-normalizing the circadian clock may improve health and longevity, while disrupting the clock may cause associated medical and mental dysfunctions. So, resetting circadian clocks would help synchronization in physiology and metabolism and then increase longevity and overall health. Some studies reported resetting of circadian clocks through changing feeding regimes (Froy 2011). As a result, maintaining pineal endocrine secretions is beneficial to homeostasis and longevity.

Recently, it is stated that the pineal gland secretes neurosteroids, e.g., 7α-hydroxypregnenolone, estradiol-17β, testosterone, etc., in circadian rhythm and controls age related physiological activities (Tsutsui et al. 2018).

11.3 Changes in Sleep Pattern with Aging

Sleep is a vital physiological process that contains important curative activities necessary for optimal daytime functioning. Inadequate or poor-quality sleep has also been linked to chronic health problems and end-organ dysfunction, including an increase in mortality rates and aging (Verstraeten 2007; Punjabi et al. 2009; BaHammam and Pandi-Perumal 2010). Several physiological changes occur during normal aging. This includes sleep quality (subjective as per self reports and objective, as per polysomnographic or other diagnostic devices findings), sleep quantity, and sleep intensity. Age-associated alterations in sleep include, but are not limited to, duration of sleep and waking, the timing of sleep onset, the overall efficiency of sleep maintenance, alteration in sleep staging (a polysomnographic finding), and daytime sleep behaviors (Pandi-Perumal et al., 2010). Aging is associated with increased light (NREM Stage N1 and N2 sleep) and decreased deep (NREM Stage N3 sleep) (refer, Table 11.1). Increased frequency of unprompted arousals is also reported (Edwards et al. 2010).

The process of aging is often associated with qualitative and quantitative changes in terms of sleep/wake patterns and their robustness. The sleep period in infancy, for example, is at an all-time high, with newborn children napping for about 16 h almost every day. This need for sleep decreases throughout development eventually resulting in 7–8 h in adults. Though less widely studied, there is evidence that sleep duration decreases from young adulthood through the later years of life in humans. Other studies, however, show that sleep quantity does not change with age; rather, sleep in aging is highly fragmented and is frequently consolidated during daytime naps. Various factors, vision-related issues, including inadequate natural light exposure,

Table 11.1 Sleep changes that occur during normal aging

Sleep-related changes that occur as a result of normal aging	
i	Circadian changes, e.g., amplitude reduction, acrophase becomes labile
ii	Advanced sleep timing, i.e., early bedtime, early morning awakening
iii	Circadian dysregulation, e.g., Advanced sleep phase syndrome (ASPS)
iv	Decrease in the ability to sleep: a. Sleep fragmentation, i.e., increased a number of nocturnal awakenings b. Prolonged nocturnal awakenings (lack of consolidation)
v	Increased sleep onset latency (SOL)
vi	Increased sleep fragmentation, i.e., less consolidation, more awakening, increased arousals, and increased transition to lighter sleep stages N1 and N2
vii	Increased time spent in lighter and fragile sleep (NREM sleep stage R1 and stage R2; easily woken by external stimuli)
viii	Decreased slow-wave sleep (SWS; deep sleep or NREM Stage N3) Advanced sleep timing (going to bed too early)
ix	Reduction in overnight sleep
x	Increased daytime nap frequency
xi	Increased wake after sleep onset (time spent awake throughout the night)
xii	Decreased overall nocturnal sleep duration
xiii	Reduced and fewer NREM-REM sleep cycles and other related changes

rising health concerns, and an alteration in circadian zeitgebers, have been proposed as processes causing poor sleep quality in the aged individuals (Pandi-Perumal et al. 2010; Kun et al. 2018). Additionally, the incidence of sleep-related problems, which are becoming more common among the aged society, is a significant contributor to poor sleep quality (Figs. 11.1 and 11.2).

11.4 The Relationship Between Aging Physiology and Circadian Rhythm

Aging is typically linked with dwindling or disorganization of the circadian system. The circadian acrophase becomes highly displaced, tending to happen in advance with progressing age. The participation of clock genes in the aging physiology as they are involved in an assortment of disease processes is also noted. Current work has been giving insights into the underlying molecular pathways associated with aging physiology, with the assurance of involvement(s) to augment healthy life spans. Caloric constraint, which is constantly and recurrently connected with lengthening life in diverse animal models, is linked with amplified circadian amplitude. These data suggest the decisive significance of circadian biology in comprehending aging problems, from the circadian clock machinery coordinating metabolism to the progress up to geroprotectors (Arul and Subramanian 2014; Duffy et al. 2015). The quantitative

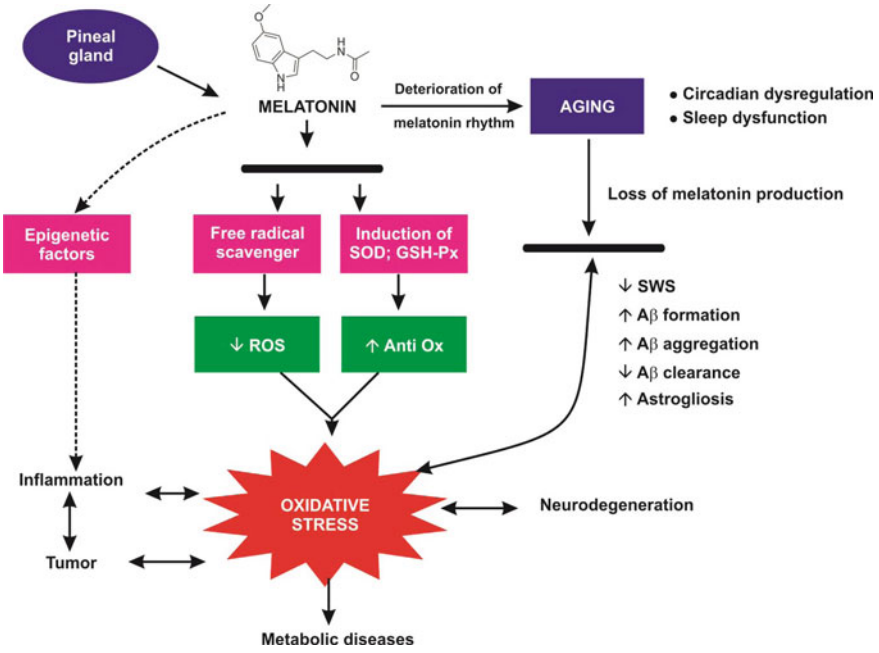

Fig. 11.1 Neuroendocrine mechanism of aging in mammals

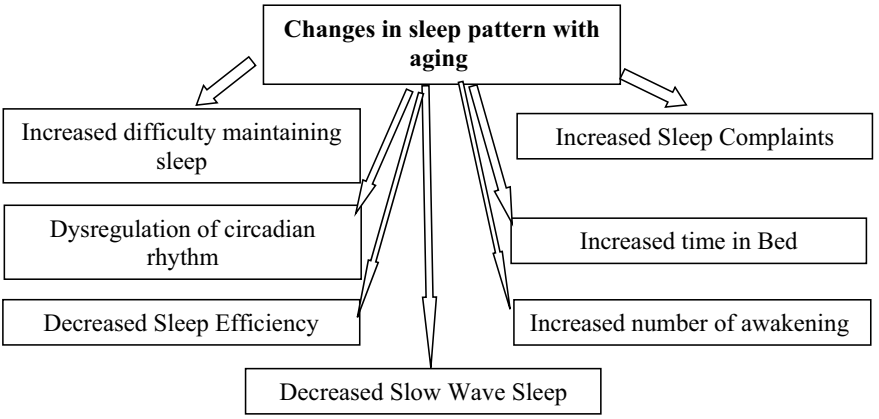

Fig. 11.2 Incidents of sleep-related problems with aging

inference of circadian rhythm hallmarks construed in light of time-dependent reference values aids in (i) distinguishing influences of normal healthy aging from those associated with disease, disorder, and disease/disorder prognosis; (ii) in identifying changes in rhythm characteristics as indicators of increased risk before the appearance of disease; and (iii) in optimizing prophylactic and/or curative intercessions

aimed at disease/disorder separately. Comprehending the alterations in amplitude and/or acrophase that may outshine any modification in normal value also shuns away depicting counterfeit interpretations resultant from data collected at a fixed clock hour. Appropriate risk recognition, along with the management optimization of the disease by timing (chronotherapy), is the objective of several ongoing widespread population-based investigations focusing on the health of the aged people, with the intention that long life is not accomplished at the outlay of an abridged quality of healthy life (Cornelissen and Otsuka 2017; Martín Giménez et al. 2022).

11.5 Aging and Circadian Rhythms

Aging has been shown to disrupt circadian rhythmicity at multiple levels of biological organization (Tabibzadeh 2021; Nathan et al. 2021; Kim et al. 2022). There is a substantial body of literature on age-related changes in the 24 h periodicity in animals. These studies documented age-associated variations in the circadian behavioral rhythms (e.g. amplitude of numerous neuronal, endocrine, and metabolic rhythms) have been documented in the literature, and discuss how the circadian clock drives these rhythms (Acosta-Rodríguez et al. 2021). However, there are still some inconsistencies (Pohl 1993). Age-associated alterations in circadian pacemakers have been investigated in both humans and other animals. Such studies include, but are not limited to morphological, behavioral, as well as electrophysiological investigations. This points to the fact that older individuals may be due to a lack of *zeitgebers* (time clues or time givers), especially if they are housebound or institutionalized.

As outlined above, the circadian clocks become weaker and often damped or phase advanced during aging. This is further evident with regular or routine adjustments in routine bedtimes and arousing times in the older individuals. These changes denote, the phase progression of the sleep–wake cycle, and these alterations could be either by a slowing or a quickening of the circadian pacemaker (suprachiasmatic nucleus, SCN). This phase moves forward phase could be linked to amplitude attenuation and phase advance in the core body temperature (cBT) rhythm. Furthermore, a reduction in endogenous period length for waking and paradoxical sleep (PS) is one of the most significant age-related changes in a temporal structure, and phase advancement or dampening of hormonal and other overt rhythms may lead to a disease state or altered physiology (Morris et al. 2016).

The phase-reversal mechanism in older animals also varies. For example, aged animals respond to a phase-reversal of the LD cycle slower than younger animals. During the day, there is a common tendency for sleep loss. Because older animals sleep less during the light phase of the LD cycle, the majority of the age-related decrease in total sleep time (TST) is due to selective sleep loss).

11.6 Modifications in Circadian Rhythms with Age

As organisms age, rhythmic processes also undergo a variety of systematic changes. While these changes may be regarded as generic representations of normal aging, it is clear that within a species, individual variations in the way aging occurs exist. As a result, many natural, distinct progressions toward disorder within circadian systems manifest themselves as increases in the standard deviations (SD) of their measured values. Several changes in overt rhythmicity appear to be linked to aging. Some of these have been linked to a loss of SCN function, while others may be the result of a decline in either entrainment mechanisms or clock-controlled systemic activities.

(a) Changes in overt circadian patterns include amplitude reduction, rhythm fragmentation, and temporal order disruption
(b) Loss of entrainment stability and sensitivity to zeitgebers. Besides, the clock-controlled process itself is likely to change. For example, changes in the volume or intensity of specific activities, the distribution of different behaviors, the amounts of circulating hormones, and the density of specific peptides, neurotransmitters, and receptors; and.
(c) Changes in period or period stability.

11.7 Amplitude and Circadian Organization

Losses in "stability" and level of rhythmic function are reflected in amplitude reductions. Numerous studies have looked at the link between rhythm abnormalities and aging. Earlier research has discovered changes in circadian hormonal rhythms. As rodents get older, many studies have found that their wheel-running activity deteriorates. Humans have also been reported to have age-related changes in locomotor activity. A decline in the amplitude of other behavioral rhythms such as feeding, drinking, and sleep/wake is also connected with aging (Hennion and Etain 2022). Aging has an impact on other physiologic rhythms in a similar way, e.g., body temperature rhythms (mice and rats), audiogenic convulsions (mice), oxygen consumption (mice), potassium excretion (humans), growth hormone (GH), testosterone, and luteinizing hormone (LH) (humans). There is a report on altered diurnal rhythms of blood cortisol, aldosterone, prolactin, and GH in older humans. The sex difference was also noted. The circadian amplitude and mesor of epinephrine and norepinephrine are decreased with age while the acrophase remained constant (Halberg 1982). There has been a decrease in the rhythm of pineal N-acetyl transferase in hamsters (Reiter et al. 1980). One of the difficult questions to answer is whether the decline in the amplitude of overt rhythms reflects a shift in circadian pacemaker activity or an age-related loss of peripheral function. When compared to young rats, Satinoff and co-workers (1993) found that the pacemaker of older rats had disrupted patterns and lower amplitude of neuronal activity, without disturbing behavioral rhythms. In response to LD transitions, Wise et al. (1987, 1988) found a reduction in glucose utilization in suprachiasmatic nucleus (SCN) tissues in aging rats.

Furthermore, there have been numerous reports of age-associated morphological and neurochemical alterations in the SCN, including alterations in cells producing vasopressin (AVP) and vasoactive intestinal polypeptide (VIP) (Roozendaal et al. 1987). Although these changes do not always correspond to explicit changes in behavior and physiology. There are adequate variations in the SCN of younger and older animals which advocate an association between dysregulation of SCN and changes in circadian patterns. Furthermore, the re-consolidation of host-driven locomotor rhythmicity in aged hamsters following transplantation of SCN demonstrates its vital role in maintaining organization and rhythmicity during the aging process (Murd and Ralph 1998).

A lack of synchronization or incorrect phase connections among rhythms is a predictable result of reduced rhythm amplitude. The major purposes of biological clocks, according to popular belief, are to elicit a time-oriented structure within rhythmic processes and to synchronize them to the geophysical environment. As a result, it's safe to assume that this organization will be jeopardized if the clock or its control mechanisms fail. Alteration in time-oriented structure (e.g., biochemical, physiology, and behavior) is a common sign of disorganization. Rhythms remain in sync with one another, yet they may have incongruent or changeable phase relationships. In humans, such a form of the disorder has been thoroughly established.

In summary, several rhythms have shown age-related changes in amplitude, including the rest/activity cycle, core body temperature (cBT), feeding, drinking, eating, and response to zeitgeber (e.g., LD cycle non-photic zeitgeber) (Mohawk et al. 2019). However, differences in the amplitude of circadian cycles could not be explained only by age-related changes in visual sensitivity. Similar to the diminished LD disparities in sleep/wake rhythms, behavioral rhythms have lower amplitudes.

11.8 Entrainment and Responsiveness to *Zeitgebers*: Influence of Aging

When compared to young adults, old persons' sleep/wake patterns become disordered and varied. A lack of organization in a light cycle could be caused by either a malfunctioning clock or a drop in sensitivity or response to *zeitgebers*. For most organisms, the environmental LD cycle serves as a pervasive and prominent zeitgeber. Other rhythmic features of the geophysical environment may also serve in this capacity (Amir and Stewart 1998). Additionally, non-photic zeitgebers will indirectly alter rhythms and serve as a potential zeitgeber (Mrosovsky and Biello 1994; Mrosovsky 1996).

Entrainment to light cycles, which is the ultimate measure of overall circadian activity, is affected by changes in the period, photoreceptor sensitivity, and circadian function. Entrainment, on the other hand, is regulated by the organism's acute light reactions, which may mask circadian gating. The most basic experiments that look at circadian reactions to external stimuli are re-entrainment and phase-shifting

paradigms. Unfortunately, while these reactions change with age, they are not consistent among species or even within experiments. Peng et al. (1980) and Peng and Kang (1984) showed no difference in the rate of re-entrainment between young and old rats. Rosenberg et al. (1979) found that older rats took longer to respond to a phase-reversal of the LD cycle than younger rats. In 1992, Zee and co-workers observed that young hamsters take longer to re-entrain to a phase advanced light cycle but take less time when the cycle is delayed, whereas Valentinuzzi et al. (1997) reported that in old mice, re-entrainment is accelerated when the cycle is advanced but unchanged when the cycle is delayed. Finally, light-induced phase delays rise in old rats but decrease in mice, and light-induced phase shifts decrease in old hamsters, but this change can be reversed by powerful light pulses (Zhang et al. 1996). The reasons for these inconsistencies are unknown, given the variety of species used and the fact that experimental conditions differ from lab to lab, this mismatch may not be surprising. Variations are more than likely related to individual differences in how animals age. Some hamsters lose their highly consolidated pattern of wheel-running activity as they get older, while others keep it (Antoniadis et al. 2000). Because activity influences circadian responsiveness to light, as well as the phase and duration of rhythms, aging may have varying effects on rhythmicity as a result of changes in wheel-running patterns. Age has an impact on non-photic cue reactions as well. Phase shifts induced by a serotonin (5-HT) agonist or the benzodiazepine (BZD), triazolam, are reduced in aged hamsters, and a prenatal SCN transplant and a melatonin agonist can restore the latter effect. Further, melatonin can also assist you in readjusting to a new light cycle (Weibel et al. 2000).

11.9 Age-Associated Changes in Circadian Dysregulation

There are numerous differences in age-related pineal secretions and physiological changes in period length to be noticed (Reiter et al. 1981). The most significant age-related changes in circadian behavioral rhythms are seen in the free-running and entrained rhythms. The amplitude of many intrinsic rhythms of metabolic and physiological indices decreases as people get older, with an apparent decrease in the rhythm's maxima, viz., body temperature cycles (mouse and rat), audiogenic convulsions (mouse), cellular oxygen utilization (mouse), excretion of potassium (humans), and secretion of growth hormone (human), testosterone (human), and luteinizing hormone (human) (Davis 1981; Sehirli et al. 2021).

Age-related defects in the circadian organization are linked to changes in the association between endogenous and ambient rhythms. Circadian rhythms are "free-run" in permanent darkness, with an intrinsic period (Tau) slightly longer or shorter than 24 h, and in humans, it is between 24.2 and 24.4 h. As the age advances, Tau gets shorter slightly. Similarly, the free-running duration in rats decreases from adolescence to old age. There are a variety of viewpoints on these changes. Several investigations found shorter periods, while others found more extended periods. On

the other hand, other researchers have claimed that no alterations have occurred (Sharma and Chandrashekaran 1998).

However, experimental, technical, and methodological variations such as age differences, exposure to earlier entrainment, and potential feedback response could skew the results. Further, experimental setup, time of the experiment, or observation time (e.g. LL vs DD) can also influence the results. Therefore, due to such a wide range of confounding factors, making any clear judgments about age-related alterations in circadian systems is not that easy. Proper caution should be exercised during the interpretation of the findings.

11.10 Conclusions

Throughout animals' and humans' lives, the pineal gland plays a critical part in the circadian timing system and maintaining homeostasis and biological clock. Melatonin levels decline with age, and in neurodegeneration, there is a marked reduction in this hormone. Melatonin has both chronobiotic and cytoprotective (antioxidant and neuroprotector) effects (Cardinali 2019). Melatonin, as a chronobiotic, can alter the phase and amplitude of biological cycles. Melatonin, as a cytoprotective molecule, prevents the low-level inflammatory damage found in aging and neurodegeneration. Administration of melatonin reset the circadian dysregulation, promotes sleep, reduces sundowning, and delays the course of cognitive deterioration in neurodegenerative disorders. Recent evidence suggests that melatonin effectively protects neuronal cells against Aβ-mediated toxicity through antioxidative defense and antiamyloid properties. Melatonin not only suppresses Aβ production, but also stops the development of amyloid fibrils through a structure-dependent interaction with Aβ. More research on the use of melatonin in the treatment of various disorders is needed, particularly at an early stage of neurodegenerative diseases.

This chapter provides and overview of some of the aspects of circadian rhythms, and its relevance to aging and neurodegeneration (Fig. 11.2. Interaction between pineal gland, aging, and sleep).

Over the years, several theories have been proposed, and recent research on pineal secretions revealed that they slow aging by reducing mitochondrial processes and physiological body defense mechanisms. For clear understanding, readers are encouraged to refer the accompanying chapters in this volume and related publications. In summary, a significant need for the study on the disruptors of the physiology of pineal, its immunomodulatory functions, and aging in variety of species should be conducted to determine their translational potential in gerontology and enhancing longevity.

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