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CIRCADIAN RHYTHMS AND SLEEP IN AGING: IMPACT ON 24-HOUR HORMONAL PROFILES

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Key words: Circadian; Sleep; Aging; ACTH; Cortisol; Glucose; Gonadotropins; Growth hormone; Insulin; Melatonin; Prolactin; Sex steroids

Keypoints

- The 24-hour temporal regulation of hormonal secretions results from the interaction of an endogenous *circadian pacemaker* and of *sleep-wake homeostasis*, a mechanism linking the timing and the intensity of sleep to the duration of prior wakefulness.
- Aging is characterized by concomitant sleep and hormonal circadian rhythms alterations, which frequently interact with each other:
 - Sleep: spectacular decrease in “restorative” sleep stage from early adulthood to mid-life, followed thereafter by sleep fragmentation and a decrease in total sleep time.
 - Hormones:
 - Reduction in rhythm amplitude
 - Phase advance of hormonal secretions.
- For a number of hormones (in particular cortisol and insulin), age-related alterations are strikingly similar to those observed in young healthy subjects submitted to sleep restriction. Thus, voluntary or not, recurrent sleep curtailment, currently experienced by an increasing number of children and adults, is likely to accelerate the senescence of endocrine and metabolic function.

Abstract

The 24-hour temporal regulation of hormonal secretions results from the interaction of an endogenous *circadian pacemaker* and of *sleep-wake homeostasis*, a mechanism linking the timing and the intensity of sleep to the duration of prior wakefulness. A prominent age-related alteration-of hormonal circadian rhythmicity is characterized by a reduction in rhythm amplitude and a phase advance. At the same time, the sleep-wake pattern undergoes major modifications, with a spectacular decrease in “restorative” sleep stage from early adulthood to mid-life, followed thereafter by sleep fragmentation and a decrease in total sleep time. Age-related sleep and endocrine-metabolic alterations frequently interact with each other.

Introduction

A prominent feature of endocrine secretion in man is its high degree of temporal organization. Hormonal variations may be observed in the ultradian range (i.e. once per 1-2 hours), in the circadian range (i.e. approximately once per 24 hours) and in the infradian range (i.e. periods longer than 24 hours, for instance the menstrual cycle). This configuration provides the endocrine system with a high and complex degree of flexibility. The temporal regulation of hormonal secretions throughout the 24-hour cycle results from the interaction, in the central nervous system, of two sophisticated time-keeping mechanisms: the so-called sleep-wake homeostasis, a mechanism linking the timing and the intensity of sleep to the duration of prior wakefulness, and the so-called circadian pacemaker (Copinschi and Challet, 2016; Oster et al., 2017).

The master circadian pacemaker – or circadian clock – is located in two bilaterally paired small nuclei in the anterior hypothalamus: the suprachiasmatic nucleus (SCN). The generation and maintenance of circadian oscillations of the master circadian pacemaker involve a series of clock genes, which interact in complex feedback loops. Secondary circadian clocks are present in other brain areas and in almost all peripheral tissues, including endocrine glands. These secondary circadian clocks are under the control of the SCN through the entrainment of the same circadian machinery at the local level. Together, the master and the secondary circadian clocks define a multi-oscillatory network generating circadian oscillations.

The SCN controls and synchronizes peripheral endocrine clocks, either directly via neural signals transmitted through the autonomous nervous system, or indirectly via the sleep-wake cycle or the rhythm of feeding. In addition, circadian variations of corticosteroids and of melatonin release – two hormones tightly controlled by the SCN – probably contribute to the transmission of temporal signals throughout the body. However, the endogenous circadian period is close to, but not exactly, 24 hours. This implies that the circadian clock has to be entrained by external agents to avoid to fall out of synchrony with the environmental day. The primary synchronizing agent is the 24-hour light-dark cycle (Copinschi and Challet, 2016; Oster et al., 2017).

The SCN not only controls the timing of most circadian rhythms, including endocrine rhythms, but also partly regulates the sleep-wake cycle. In turn, the sleep-wake cycle regulates the timing and the expression of many endocrine rhythms. Thus, the 24-hour hormonal profiles frequently result from an interaction between the circadian pacemaker, the sleep-wake homeostasis, and an ultradian, or pulsatile, pattern of release, while the 24-hour sleep-wake cycle is driven partly by the circadian clock and partly by the homeostatic regulation of sleep pressure (Copinschi and Challet, 2016; Oster et al., 2017).

Sleep and aging

Sleep involves two distinct states of brain activity that are each generated in specific brain regions and are characterized by different patterns of cerebral and peripheral activity: the rapid eye movement (REM) sleep stage and the non-REM sleep stages. Throughout the sleep period, non-REM sleep and REM sleep occur in successive cycles lasting approximately 90 minutes. Each cycle is normally initiated by the lighter non-REM stages (stages 1 + 2), followed by a deeper non-REM stage (stage 3), then by REM sleep. During stage 3 sleep, the EEG is synchronized with low-frequency high-amplitude waveforms, referred to as slow-waves (SW).

Therefore, stage 3 sleep is currently referred to as slow-wave sleep. The intensity of SW sleep, referred to as slow-wave activity (SWA), may be quantified by a spectral electroencephalogram (EEG) analysis. SW sleep is considered as the most “restorative” sleep stage. During REM sleep, EEG is similar to that of active waking, muscle tone is inhibited, and eye movements are present. Most dreams occur during REM sleep (Copinschi and Challet, 2016; Oster et al., 2017).

In young healthy adults (< 25 years), each night involves 4 to 6 successive sleep cycles. During the first cycle, the sequence normally includes an initial 10-20 minutes period of light non-REM sleep, followed by a nearly 60 minutes period of deeper non-REM sleep, then by a few minutes of REM sleep. As the night progresses, transient awakenings become longer and more frequent, non-REM sleep becomes shallower, and the duration of REM sleep periods increases. In healthy young adults, approximately 50% of a normal night is spent in light non-REM stages, 20% in SW sleep, 25% in REM sleep and 5% in wake. A typical individual sleep pattern in a healthy young man is illustrated in Fig. 1.

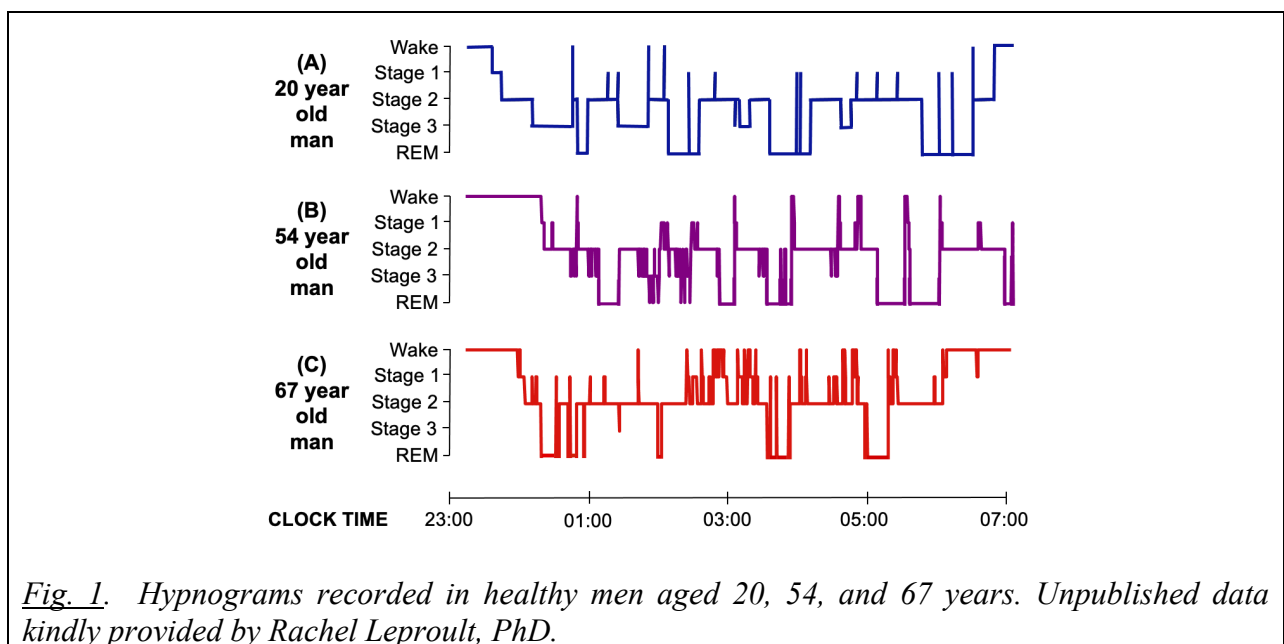
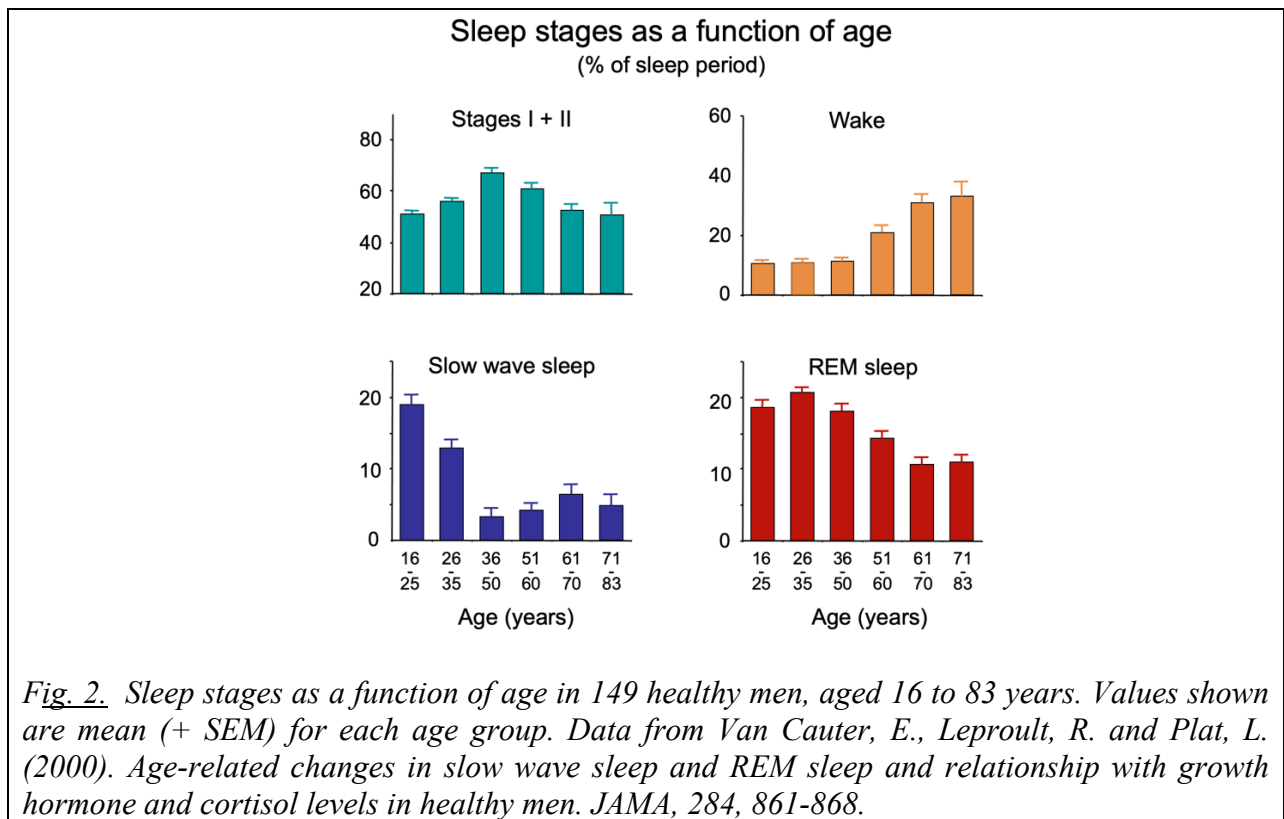


Fig. 1. Hypnograms recorded in healthy men aged 20, 54, and 67 years. Unpublished data kindly provided by Rachel Leproult, PhD.

During normal aging, this sleep-wake pattern undergoes major modifications, resulting in major alterations in sleep architecture. From early adulthood (16 to 25 years) to midlife (36 to 50 years), a spectacular decrease in SW sleep occurs, together with a compensatory increase in light non-REM sleep (stages 1 and 2). However, the duration of REM sleep and transient nocturnal awakenings remains largely unaffected, and the total sleep time stays mostly unchanged (Van Cauter et al., 2000). From mid-life to old age (51-80 years), no additional decrease in SW sleep is observed, but both REM sleep and light non-REM sleep progressively decline, associated with a mirror increase in wake time, resulting in sleep fragmentation and a decrease in total sleep time (Van Cauter et al., 2000). Moreover, there is a redistribution of REM stages across the sleep period, with a shift toward the initial part of the night. Typical individual sleep profiles in healthy 20-, 54- and 67- year-old men are illustrated in Fig. 1. The time-course of age-related modifications of sleep architecture is illustrated in Fig. 2.



Those marked alterations in sleep architecture are frequently associated with major alterations in subjective sleep quality, which are more important and more frequent in older women than in older men. During the night, healthy elderly subjects often complain of shallow sleep with frequent transient awakenings and an early final morning awakening, resulting in unwanted daytime naps (Bliwise, 1993; Prinz, 1995). Moreover, age-associated deficits in the quality of nocturnal sleep may be paralleled by decreased daytime alertness and performance, and attention and memory deficits (Ancoli-Israel, 2005).

Circadian system and aging

Age-related alterations in hormonal circadian rhythms widely differ from one hormone to another. One of the most prominent alterations is a reduction in rhythm amplitude. Many hormonal circadian rhythms are also phase-advanced, so that phase-points of the rhythms occur earlier in the elderly than in young subjects. Those alterations are likely to result from both a reduction in the strength of the circadian signal and a reduction in the homeostatic drive to sleep. Reduced outdoor activity resulting in decreased exposure to bright light, reduced professional and social constraints and decreased mobility all also contribute to disruptions in circadian rhythmicity. Daytime regular exposure to bright light and enhanced social activities may improve nighttime sleep and daytime alertness and reinforce circadian rhythms in the elderly (Copinschi and Challet, 2016; Oster et al., 2017). Conversely, nighttime light exposure in older age is associated with irregular and fragmented sleep, obesity, diabetes and hypertension (Kim et al., 2022).

The senescence process may be accelerated by conditions of circadian misalignment, such as occur in shift work or in jet lag, which induce a state of internal desynchrony between central and peripheral rhythms, with major disruptions of the internal temporal organization of a number of physiologic functions (Copinschi and Challet, 2016; Czeisler et al., 1990; Leproult et

al., 2014; Oster et al., 2017; Scheer et al., 2009). Not surprisingly, recent meta-analyses have linked shift work to increased risk of breast cancer, pregnancy complications, cardiovascular disease, and poor mental health, particularly depressive symptoms (Rivera et al., 2020; Torquati et al., 2019). In animals, prolonged circadian misalignment was found to reduce lifetime and trigger premature cellular aging (Grosbellet et al., 2015; Penev et al., 1998).

The aging-related effects on melatonin, on hormones of the hypothalamo-pituitary axis, and on glucose and insulin are reviewed in the following sections.

Melatonin

Melatonin rhythmicity is primarily dependent on the master circadian pacemaker. In addition, a pineal molecular clockwork plays a stimulatory role on the amplitude of the major melatonin circadian rise, starting between 21.00 and 23.00 h, culminating around the middle of the night, followed by a progressive decline to return by 08.00 or 09.00 h to low levels that are maintained throughout daytime until the next evening circadian rise. Melatonin rhythmicity is highly sensitive to lighting conditions, as night exposure to light exerts an immediate dose-dependent inhibition of melatonin synthesis (Copinschi and Challet, 2016; Lewy et al., 1980; Oster et al., 2017; Van Cauter et al., 1998).

Daytime low melatonin levels are similar in young and old adults. In contrast, the evening circadian elevation is markedly dampened in most, but not all, older subjects (Van Coevorden et al., 1991) (Fig. 3). This dampening may partly result from insufficient daytime environmental light since it may be reversed by midday exposure to bright light (Mishima et al., 2001).

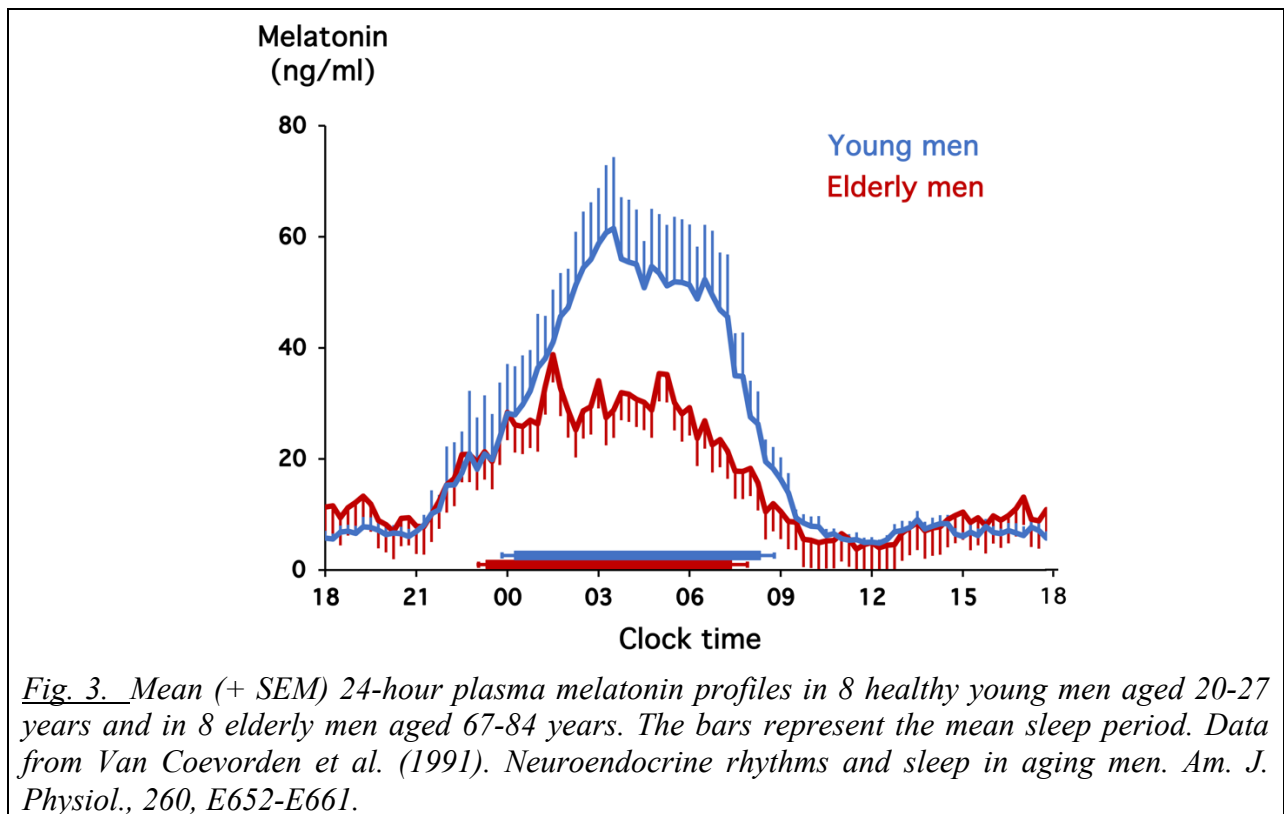


Fig. 3. Mean (+ SEM) 24-hour plasma melatonin profiles in 8 healthy young men aged 20-27 years and in 8 elderly men aged 67-84 years. The bars represent the mean sleep period. Data from Van Coevorden et al. (1991). Neuroendocrine rhythms and sleep in aging men. Am. J. Physiol., 260, E652-E661.

ACTH, cortisol, dehydroepiandrosterone

The circadian rhythms of hormones of the corticotropic axis are primarily controlled by central and adrenal circadian clocks, thanks to a flexible sophisticated machinery (Copinschi and Challet, 2016; Oster et al., 2017). Outputs from the SCN activate the circadian release of hypothalamic corticotropin-releasing hormone (CRH) that in turn stimulates circadian ACTH secretion. The 24-hour profile of adrenocortical secretion primarily depends on ACTH diurnal pattern. In addition, neuronal signals generated by the SCN are also transmitted to the adrenal cortex by a multisynaptic neural pathway (Buijs et al., 1999). The secondary adrenal circadian clock gates the adrenal response to ACTH, that is, modulates diurnal variations of the adrenal responsiveness to ACTH (Oster et al., 2006).

In young adults, the 24-hour profiles of ACTH and cortisol normally show an early morning peak, a progressive decrease toward minimal levels centered around midnight (referred to as the quiescent period), followed during the second part of the night by a sharp increase (referred to as the circadian rise) toward the early morning peak (Fig. 4). The diurnal pattern of cortisol secretion reflects a succession of secretory pulses, the magnitude of which is modulated by the circadian rhythm, without any evidence of tonic secretion. This pattern is largely unaffected by alterations of the usual sleep schedule, illustrating the strength of the circadian control. Diurnal variations parallel to those of cortisol have been evidenced for other adrenal steroids, such as dehydroepiandrosterone (DHEA) (Copinschi and Challet, 2016; Oster et al., 2017).

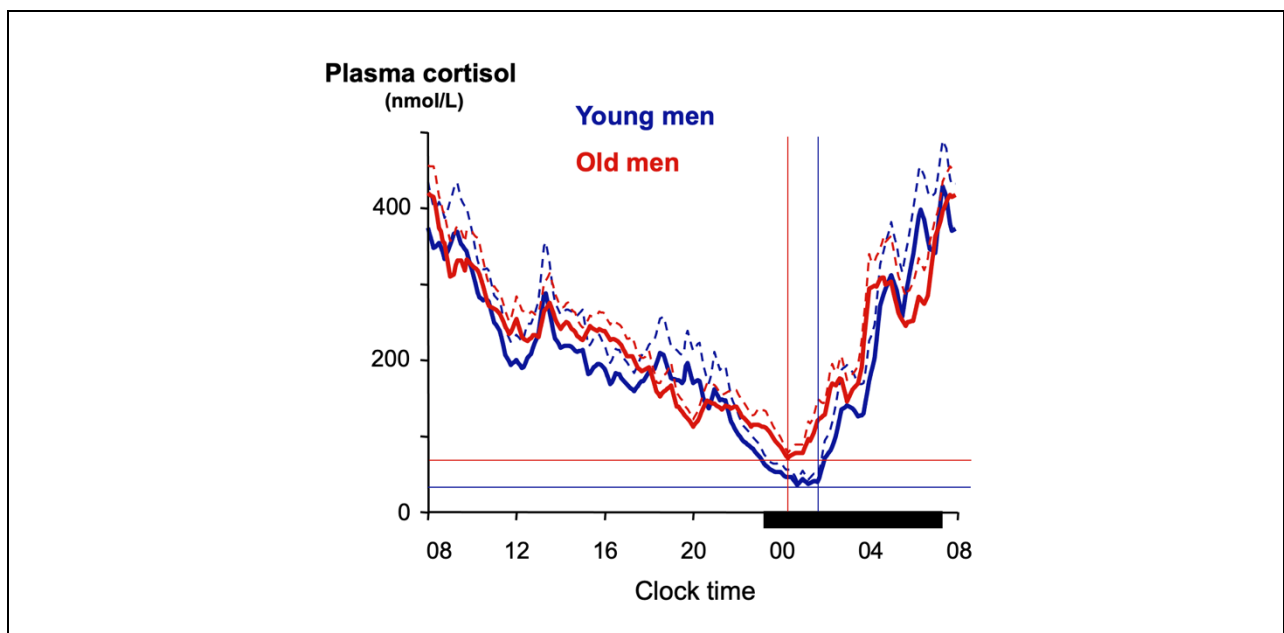


Fig. 4. Mean (+ SEM) 24-hour plasma cortisol profiles in 8 healthy young men aged 17 to 24 years and in 8 healthy old men aged 70 to 83 years matched for BMI. Dashed lines indicate SEM. The black bar represents the mean sleep period. Horizontal lines indicate the nocturnal minimum cortisol level in each group. Vertical lines indicate the timing of the circadian cortisol rise in each group. Note that in the older group, evening cortisol levels are increased, and the timing of the circadian rise is advanced. Data from Van Cauter, E., Leproult, R. and Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA*, 284, 861-868.

However, cortisol release is also modulated by the sleep-wake homeostasis. Sleep onset (and more precisely SW sleep) is consistently associated with an immediate drop in circulating cortisol levels (Caufriez et al., 2002; Copinschi and Challet, 2016; Oster et al., 2017; Van Cauter et al., 1991; Weitzman et al., 1983). This drop may be undetectable in early morning when sleep onset coincides with a peak of corticotropic activity. Conversely, all awakenings at the end of the sleep period, as well as transient awakenings during this period, consistently trigger cortisol secretory pulses (Caufriez et al., 2002; Copinschi and Challet, 2016; Oster et al., 2017; Spath-Schwalbe et al., 1991; Van Cauter et al., 1991). In an analysis of nocturnal cortisol profiles performed in healthy young men and women, all transient awakenings that interrupted sleep during 10 minutes or longer were followed within 20 minutes by significant cortisol secretory pulses (Caufriez et al., 2002). In normal sleepers, 24-hour cortisol levels were found to be positively associated with the duration of nocturnal awakenings (Vgontzas et al., 2003). Insomnia (resulting in a reduction of total sleep time) was found to be associated with elevated nocturnal cortisol levels (Vgontzas et al., 2001a).

Furthermore, in rats, intracerebral injections of CRH inhibit SW sleep (Ehlers et al., 1986), while blockade of CRH receptors reduce wakefulness (Chang and Opp, 1998). In humans, intravenous CRH injections may reduce sleep efficiency and SW sleep (Copinschi and Challet, 2016; Holsboer et al., 1988; Oster et al., 2017; Vgontzas et al., 2001b), while cortisol administration may enhance SW sleep in young and older adults (Bohlhalter et al., 1997; Born et al., 1991) presumably via negative feedback on endogenous CRH secretion. The vulnerability of sleep to stress hormones may be increased with age (Vgontzas et al., 2001b).

In healthy subjects, the circadian rhythm of cortisol persists throughout the aging process and is even present in the very elderly (Van Cauter et al., 1996; Van Coevorden et al., 1991), but, from 50 years of age onwards, evening cortisol levels progressively increase, the relative amplitude of the diurnal rhythmicity is dampened and the timing of the circadian rise is advanced (Van Cauter et al., 1996), as illustrated in Fig. 4. After 70 years of age, late evening levels are markedly higher than in young adults (Van Cauter et al., 1996). This elevation probably reflects a reduced resiliency of the corticotropic axis, resulting from age-associated alterations of hippocampal neurons (McEwen, 1998b). In older subjects, the quiescent period is markedly shortened, as it starts later, ends earlier, and is fragmented. These alterations are more pronounced in women than in men: between 25 and 65 years of age, the quiescent period shortening averages approximately 4.5 hours in women but less than 3 hours in men (Van Cauter et al., 1996). Not surprisingly, the circadian rhythm of dehydroepiandrosterone, though still present, is dampened in the elderly (Al-Turk and Al-Dujaili, 2016).

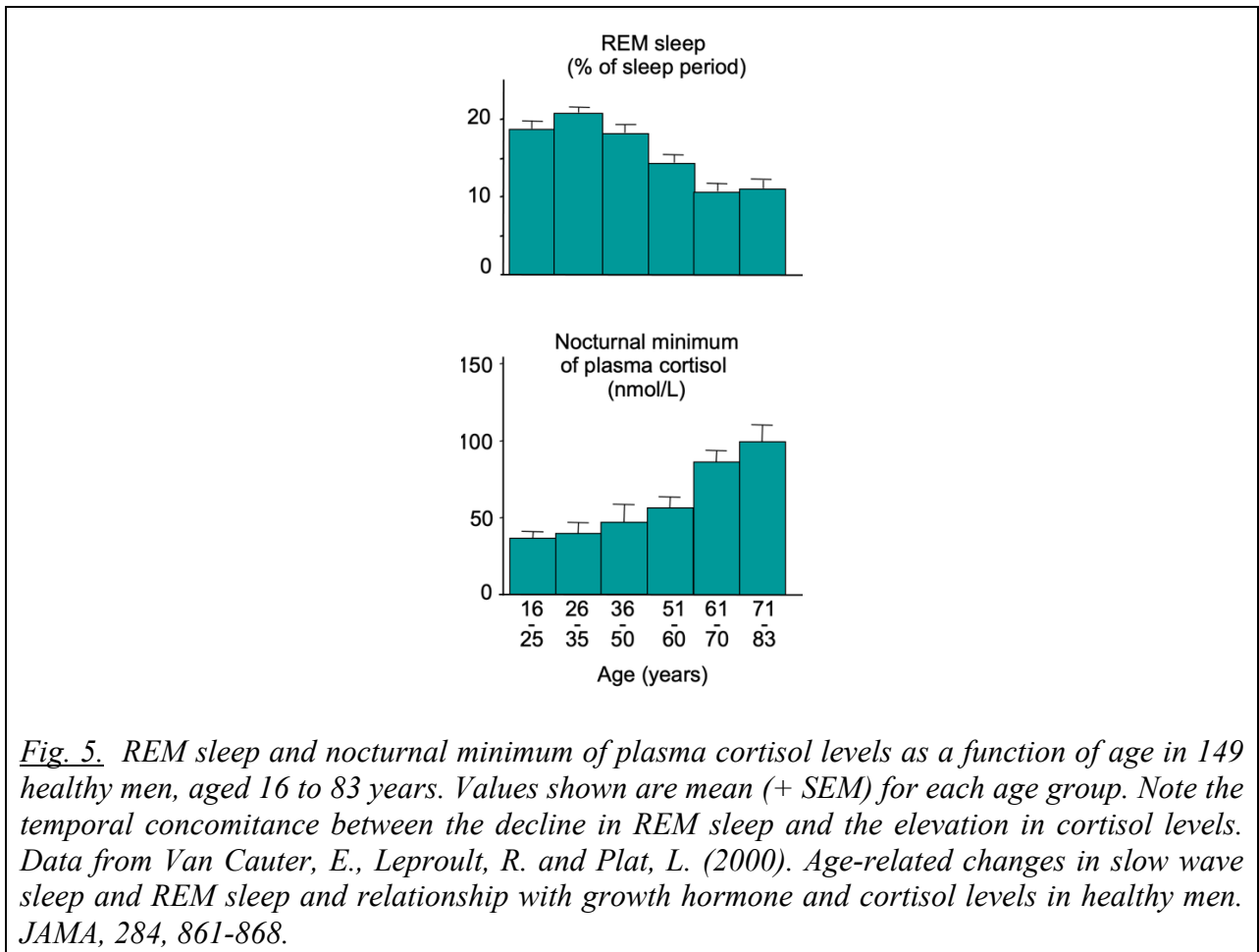
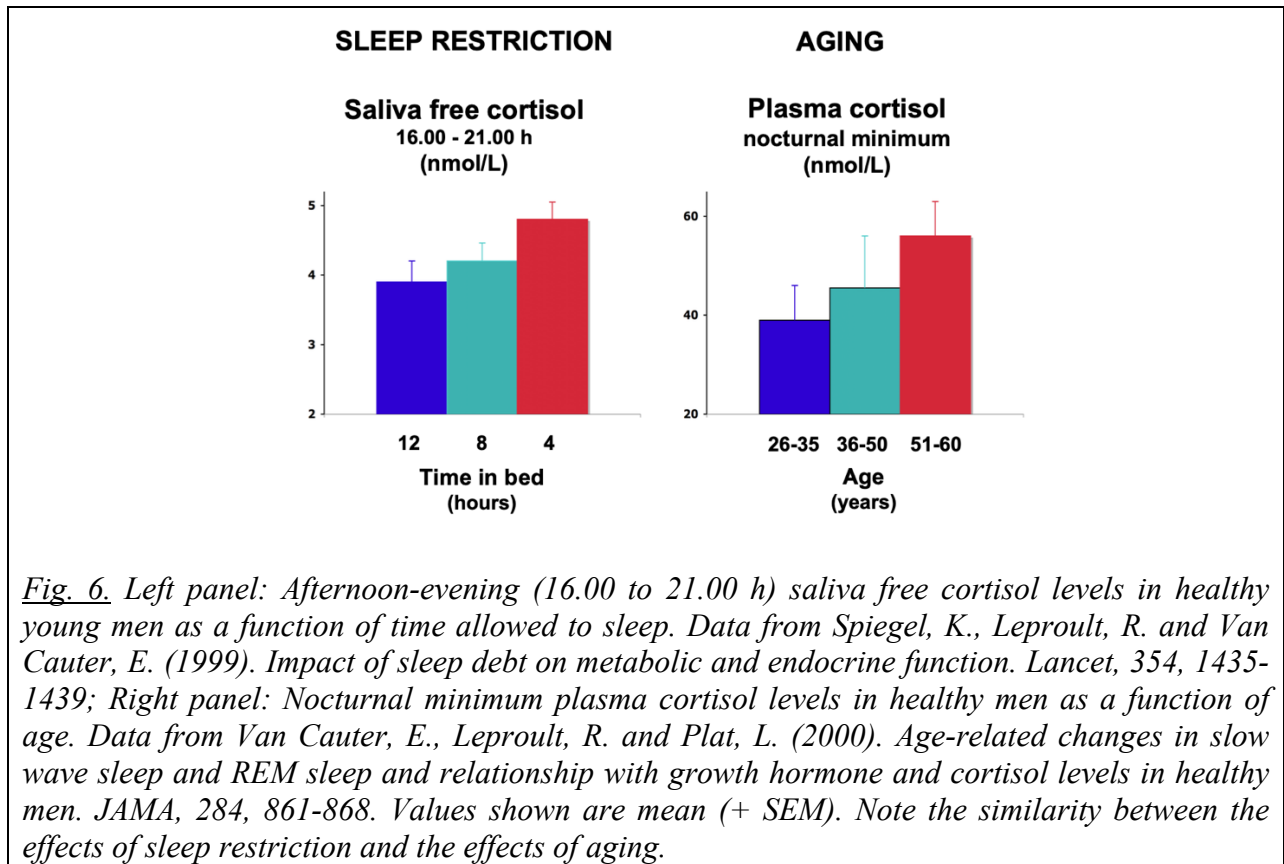


Fig. 5. REM sleep and nocturnal minimum of plasma cortisol levels as a function of age in 149 healthy men, aged 16 to 83 years. Values shown are mean (+ SEM) for each age group. Note the temporal concomitance between the decline in REM sleep and the elevation in cortisol levels. Data from Van Cauter, E., Leproult, R. and Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA, 284, 861-868.

As illustrated in Fig. 5, the age-related elevation of evening cortisol levels and the age-related decrease of REM sleep occur in mirror image (Van Cauter et al., 2000), suggesting that in the elderly, alterations of sleep quality could contribute to alterations of the corticotropic axis. This hypothesis is supported by several interventional studies. In young subjects, acute total or partial (4 hours in bed) sleep deprivation results on the following day in significant elevations of cortisol levels in late afternoon and evening (Leproult et al., 1997). Similar alterations occur if partial sleep restriction (4 hours in bed per night) is enforced during 2 to 6 consecutive days (Guyon et al., 2014; Spiegel et al., 1999). These alterations are strikingly similar to those observed in healthy elderly with normal sleep schedules (Fig. 6).

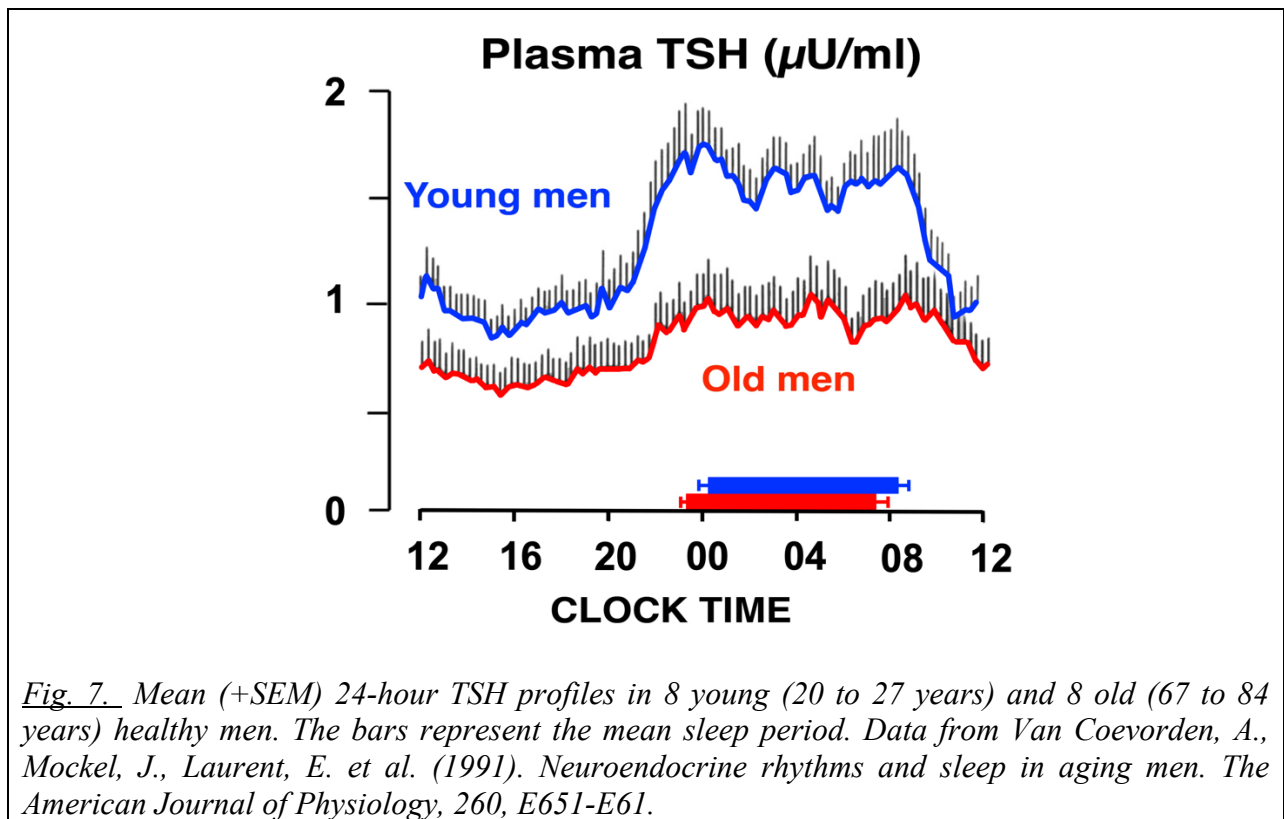


Furthermore, in a 4-year longitudinal study performed in 157 older adults, sleep duration was found to buffer long-term elevations of diurnal cortisol secretion, suggesting that long sleep protects to aging-associated increases in diurnal cortisol secretion (Rueggeberg et al., 2012). Thus, recurrent sleep curtailment is very likely to accelerate the senescence process of the corticotropic axis. Glucocorticoid excess, especially in the evening when cortisol levels should normally be low, could favor the development of central and peripheral disturbances such as insulin resistance, osteoporosis and impaired cognitive function (Copinschi and Challet, 2016; Dallman et al., 1993; Dennison et al., 1999; McEwen, 1998a; McEwen and Stellar, 1993; Oster et al., 2017; Plat et al., 1999). Moreover, offspring of nonagenarian siblings are marked by a lower activity of the corticotropic axis, as assessed by lower diurnal salivary cortisol levels (Noordam et al., 2012).

TSH and thyroid hormones

In healthy young adults, TSH levels during daytime are low and fairly stable. As illustrated in Fig. 7, they begin to rise in late afternoon or early evening, well before sleep onset. Maximal levels are reached around sleep onset. Thereafter, TSH levels progressively decrease to return to daytime low levels shortly after final morning awakening (Brabant et al., 1990). The evening elevation, referred to as the circadian rise, appears to be controlled by the circadian clock, while the subsequent decline throughout the sleep period reflects an inhibitory action of sleep on TSH secretion, as the nocturnal TSH decline is associated with SW sleep (Goichot et al., 1992). Conversely, transient nocturnal awakenings are frequently associated with TSH elevations (Hirschfeld et al., 1996). The 24-hour TSH profile is generated by amplitude and frequency modulation of TRH-driven TSH secretory pulses (Veldhuis et al., 1990). Free triiodothyronine (fT3) shows low amplitude diurnal variations that parallel TSH variations

(Russell et al., 2008). It is of interest to note that in euthyroid healthy subjects with normal and regular sleep schedules, elevated TSH levels may occasionally be observed in blood samples collected in early morning after a night of shallow sleep with frequent transient awakenings.

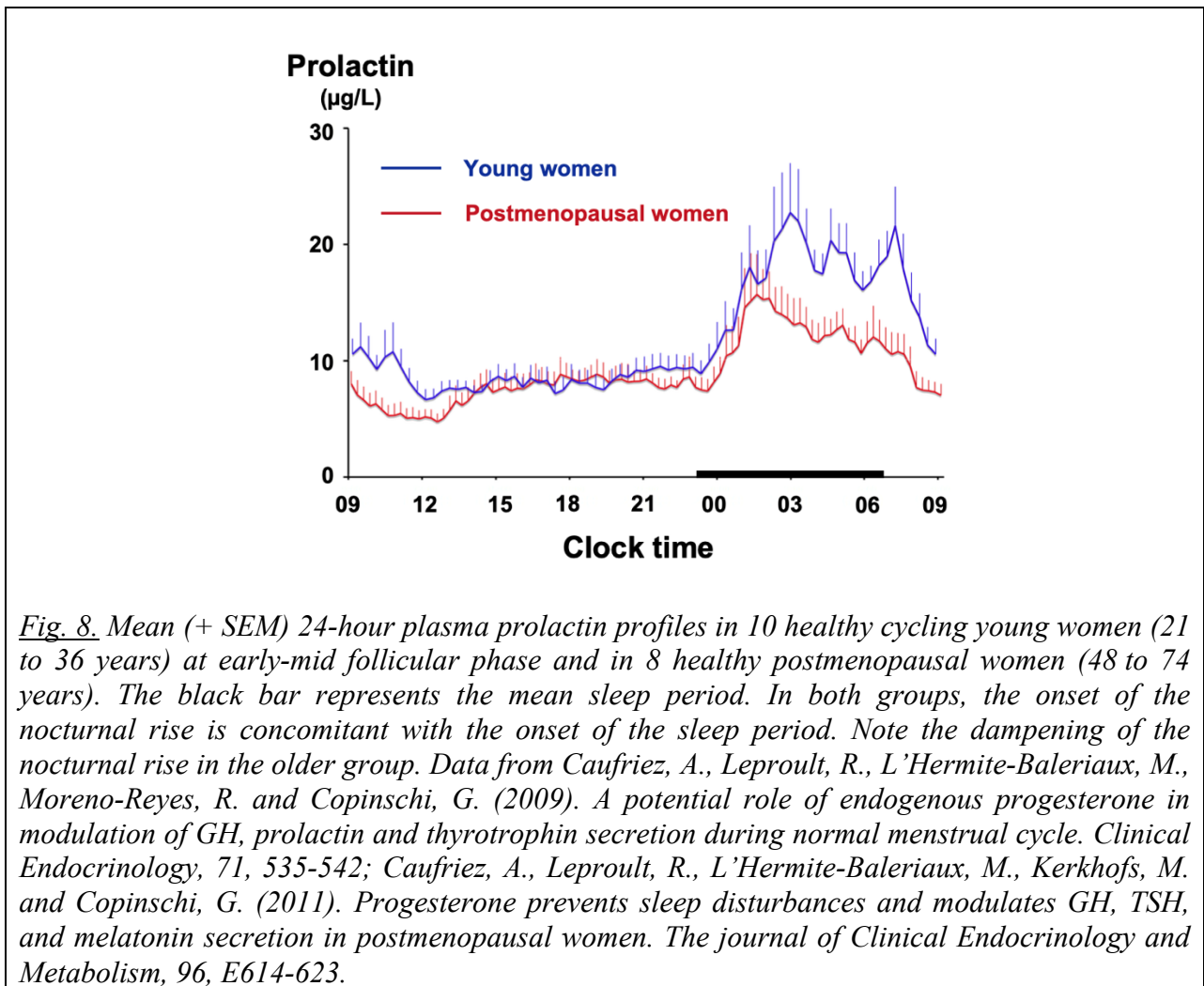


Aging is associated with an advance shifting of the timing of the circadian rise (Roelfsema et al., 2014; Van Coevorden et al., 1991) and with a progressive decrease of TSH secretion, in particular during the night, resulting in a dampening of the amplitude of the circadian elevation (Van Coevorden et al., 1991), as illustrated in Fig. 7. After 60 years of age, TSH levels in healthy subjects are lower than in young adults throughout the 24-hour span (Van Coevorden et al., 1991). This decrease might result from a diminished capacity of the hypothalamus to synthesize thyrotropin-releasing hormone (TRH) (Mariotti et al., 1995). In the elderly, thyroid hormone secretion is reduced, but circulating thyroxin levels may remain fairly unchanged since its renal clearance is also altered (Mariotti et al., 1995).

Prolactin

In healthy young subjects, minimal prolactin levels are observed around noon, followed by a modest increase in the afternoon, then by a major nocturnal elevation starting shortly after sleep onset (Fig. 8). Maximal levels are reached around mid-sleep, with an average elevation of 200% above minimum day levels (Copinschi and Challet, 2016; Oster et al., 2017; Sassin et al., 1973). The 24-hour prolactin profile is generated by diurnal variations both in tonic secretion and in amplitude of secretory pulses (Veldhuis et al., 1990). Prolactin levels are higher in cycling women than in young men or in postmenopausal women (Katznelson et al., 1998). Sleep onset (and more precisely SW sleep) is constantly associated with a rise in prolactin levels, irrespective of the time of the day, and prolonged transient awakenings during the sleep period

are associated with drops in prolactin levels (Spiegel et al., 1994; Spiegel et al., 1995). Moreover, shifts in the sleep-wake cycle are immediately followed by parallel shifts in the diurnal profile (Spiegel et al., 1994; Van Cauter and Refetoff, 1985; Waldstreicher et al., 1996).



*Fig. 8. Mean (+ SEM) 24-hour plasma prolactin profiles in 10 healthy cycling young women (21 to 36 years) at early-mid follicular phase and in 8 healthy postmenopausal women (48 to 74 years). The black bar represents the mean sleep period. In both groups, the onset of the nocturnal rise is concomitant with the onset of the sleep period. Note the dampening of the nocturnal rise in the older group. Data from Caufriez, A., Leproult, R., L’Hermite-Baleriaux, M., Moreno-Reyes, R. and Copinschi, G. (2009). A potential role of endogenous progesterone in modulation of GH, prolactin and thyrotrophin secretion during normal menstrual cycle. *Clinical Endocrinology*, 71, 535-542; Caufriez, A., Leproult, R., L’Hermite-Baleriaux, M., Kerkhofs, M. and Copinschi, G. (2011). Progesterone prevents sleep disturbances and modulates GH, TSH, and melatonin secretion in postmenopausal women. *The journal of Clinical Endocrinology and Metabolism*, 96, E614-623.*

Therefore, diurnal prolactin variations appear to be primarily dependent on the sleep-wake homeostasis. However, the amplitude of diurnal prolactin elevations may be dampened when associated with shifted daytime sleep as compared with nocturnal sleep (Van Cauter and Refetoff, 1985), and modest prolactin rises may occur during waking periods around the usual time of sleep, particularly in women (Spiegel et al., 1994; Waldstreicher et al., 1996). Thus, diurnal variations of prolactin secretion also appear to be partly modulated by circadian rhythmicity. Maximal diurnal elevations occur when the effects of sleep and of circadian rhythmicity are superimposed, that is at the usual bedtime (Désir et al., 1982; Spiegel et al., 1994; Waldstreicher et al., 1996).

Shallow and fragmented sleep is usually associated with a dampening of the nocturnal prolactin elevation. This is indeed observed in the elderly who may have a nearly 50% dampening of the nocturnal prolactin elevation usually observed in young healthy individuals (Caufriez et al., 2011; Greenspan et al., 1990; Van Coevorden et al., 1991). As illustrated in Fig. 8, there is no advance shifting of the nocturnal elevation, reflecting the fact that this elevation is associated with sleep onset and is not dependent on the circadian clock.

Growth hormone (GH)

Pituitary GH secretion is stimulated by hypothalamic GH-releasing hormone (GHRH) and by the acylated form of ghrelin (a peptide mainly produced by the stomach), and inhibited by somatostatin (Copinschi and Challet, 2016). In healthy young adults, the 24-h GH profile exhibits stable low levels abruptly interrupted by secretory pulses (Fig. 9). In baseline conditions, the most reproducible pulse occurs shortly after sleep onset, in temporal association with the first phase of SW sleep (Van Cauter and Copinschi, 1998), but other secretory episodes may be observed in later sleep and during wakefulness. In young men, this sleep-onset GH pulse is consistently the largest secretory episode over the 24-hour span (Van Cauter and Copinschi, 1998), while in normally cycling women, larger daytime pulses are frequently observed, resulting in higher 24-hour GH levels than in age-matched men (Ho et al., 1987). Daytime GH secretion was found to be higher during the luteal phase than during the follicular phase in normally cycling women (Caufriez et al., 2009).

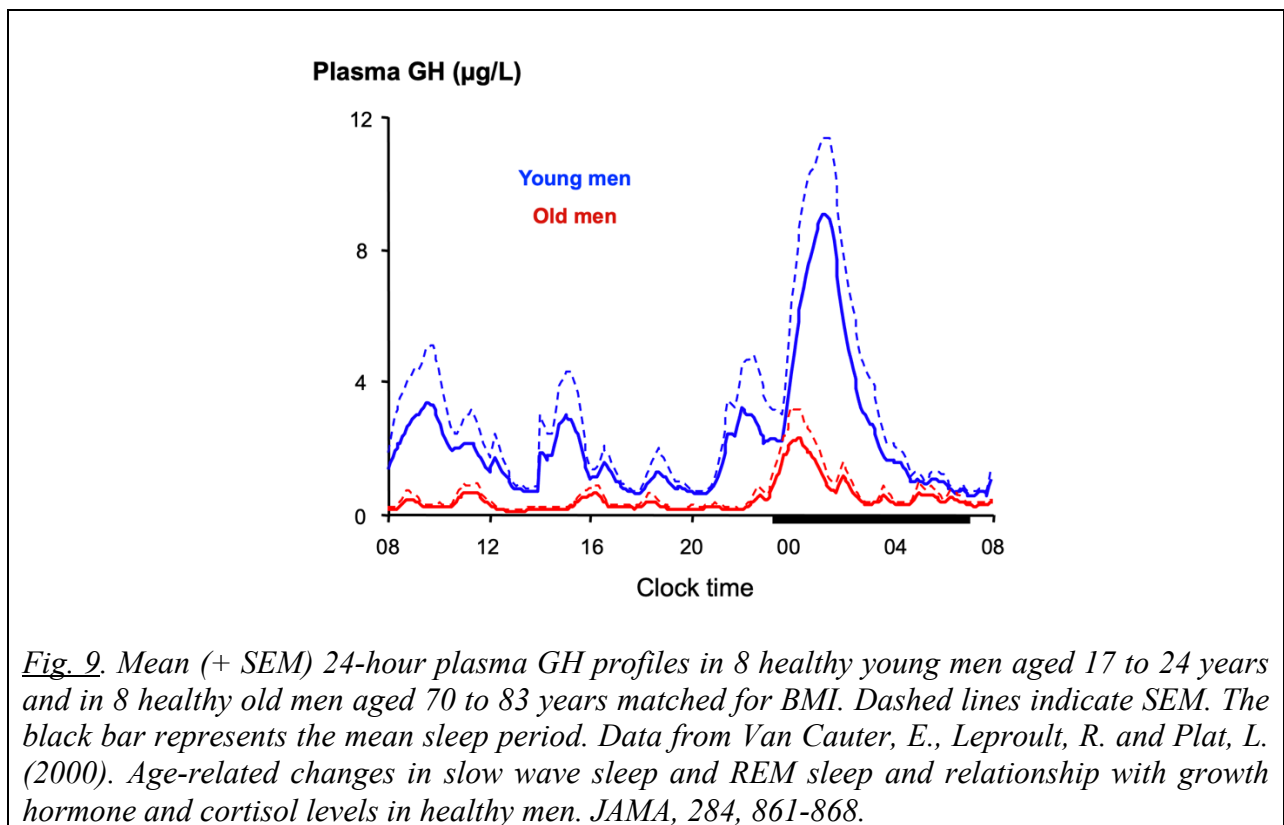


Fig. 9. Mean (+ SEM) 24-hour plasma GH profiles in 8 healthy young men aged 17 to 24 years and in 8 healthy old men aged 70 to 83 years matched for BMI. Dashed lines indicate SEM. The black bar represents the mean sleep period. Data from Van Cauter, E., Leproult, R. and Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA, 284, 861-868.

Sleep onset is closely associated, temporally and quantitatively, with a GH secretory episode, even when sleep is delayed, advanced, interrupted or fragmented (Gronfier et al., 1996; Holl et al., 1991; Van Cauter et al., 1992). Conversely, GH secretion is inhibited by transient awakenings (Gronfier et al., 1996; Holl et al., 1991; Van Cauter et al., 1992). Thus, shifts of the sleep-wake cycle are immediately followed by concomitant shifts of the GH secretory profile (Van Cauter and Copinschi, 1998).

The mechanisms underlying relationships between GH release and SW sleep probably involve synchronous activity of two or more different populations of GHRH neurons in the hypothalamus (Obal and Krueger, 2003). In animals, inhibition of endogenous GH secretion inhibits both sleep and GH secretion (Obál et al., 1988). In rodents, GHRH injections stimulate

both GH secretion and non-REM sleep in intact as well as in hypophysectomized animals (Obál et al., 1988). In healthy young adults, GHRH injections during the sleep periods may stimulate both GH release and SW sleep (Kerkhofs et al., 1993), while octreotide, a somatostatin analog, inhibits both GH release and SW sleep (Ziegenbein et al., 2004). Furthermore, stimulation of SW sleep by oral administration of low doses of gamma-hydroxybutyrate (a natural metabolite of GABA used in the treatment of narcolepsy) or of ritanserin (a selective 5HT2 antagonist) results in concomitant and correlated elevations of nocturnal GH secretion and SW sleep (Gronfier et al., 1996; Van Cauter et al., 1997a).

Thus, the temporal organization of GH secretion is clearly primarily dependent on the sleep-wake cycle. However, there is also some evidence for a circadian modulation of the occurrence and the amplitude of GH secretory pulses. The amplitude of the sleep-onset GH pulse is maximal when the surge of hypothalamic GHRH is concomitant with a period of decreased somatostatin inhibitory activity, in the evening and during the night (Van Cauter and Copinschi, 1998).

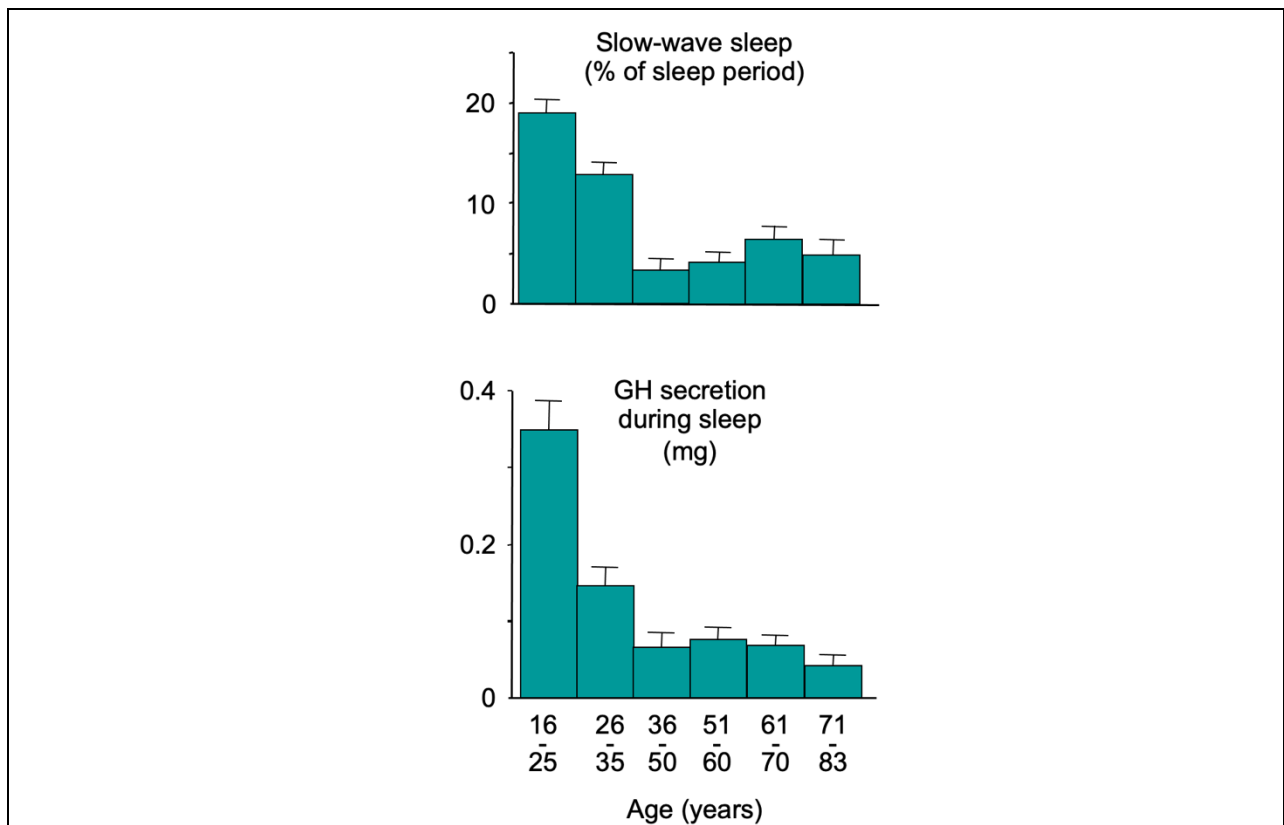


Fig. 10. SW sleep and GH secretion during sleep as a function of age in 149 healthy men, aged 16 to 83 years. Values shown are mean (+ SEM) for each age group. Note the temporal concomitance between the decline in SW sleep and the decrease in GH secretion. Data from Van Cauter, E., Leproult, R. and Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA, 284, 861-868.

GH secretion is maximal during the pubertal spurt. Thereafter, a dramatic drop of GH production occurs in an exponential fashion between young adulthood and mid-age (Ho et al., 1987; Van Cauter et al., 2000). This decrease results from a reduction in amplitude, rather than in frequency, of secretory pulses (Van Coevorden et al., 1991; Veldhuis et al., 1995; Vermeulen,

1987). At mid-age (30 to 35 years), plasma GH levels fall to values below half the levels recorded in young adults despite the persistence of high levels of sex steroids. Twenty-four-hour plasma GH profiles in young and old healthy men are illustrated in Fig. 9. The age-related decline of GH secretion follows the same chronology as the decline of SW sleep (Fig. 10) and appears to be associated with these sleep alterations (Van Cauter et al., 2000). Indeed, in a cross-sectional study performed to investigate the variance of sleep-associated GH secretion in relation to age and to SW sleep, it was shown that SW sleep and the interaction between age and SW sleep accounted for the largest part of the variance, while the effects of age *per se* were not significant (Van Cauter et al., 2000). From midlife to old age, smaller progressive decrements of GH secretion occur (Van Cauter et al., 2000), as shown in Fig. 10. In the elderly, 24-h GH profiles are largely similar in women and in men. IGF-I levels exhibit a progressive linear decrease from young adults to old age (Landin-Wilhelmsen et al., 1994).

Gonadotropins and sex steroids

Men

Rhythms in the gonadotropic axis embrace a very wide range of frequencies, from ultradian pulsatile release to menstrual cycle. Interactions of these rhythms contribute to provide a sophisticated temporal system to organize the development of the reproductive axis and its operation at the different stages of maturation

In young men, LH secretory pulses mainly reflect gonadotropin-releasing hormone (GnRH) pulsatility and exhibit an important inter-individual variability. During sleep, LH pulses appear to start preferentially during non-REM stages and to decrease during REM stages (Fehm et al., 1991). Diurnal variations of LH levels over the 24-h span are of low amplitude or even undetectable. FSH profiles show occasional secretory pulses without any detectable diurnal variation. In contrast, a clear diurnal rhythm of testosterone levels is observed in healthy young men, with peaks in the early morning and troughs in late evening (Lejeune-Lenain et al., 1987). Those diurnal testosterone variations are primarily dependent on the sleep-wake cycle, since daytime sleep, as well as nighttime sleep, is associated with significant elevations of circulating testosterone levels (Axelsson et al., 2005). However, though dampened as compared with nocturnal sleep, a progressive increase in testosterone circulating levels persists during nocturnal wakefulness (Axelsson et al., 2005), indicating the existence of a circadian component, likely to reflect adrenal testosterone secretion.

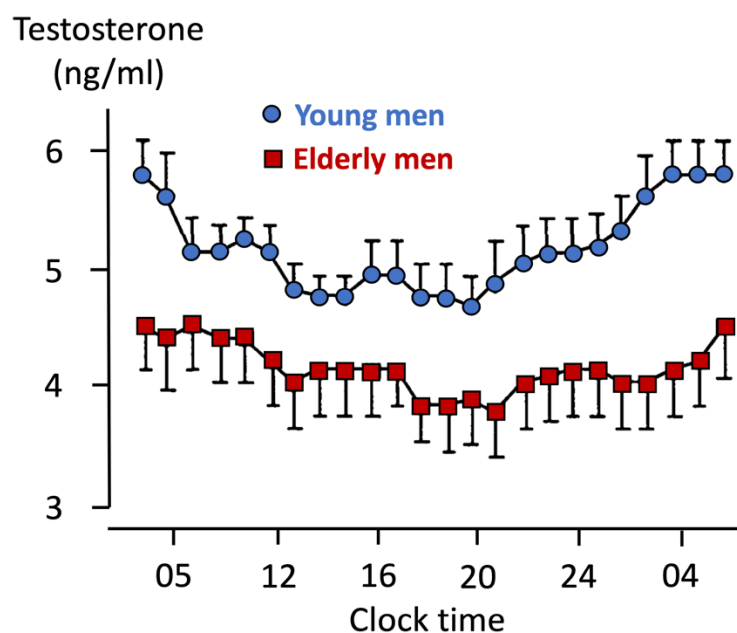


Fig. 11. Mean (and SEM) 24-hour plasma testosterone profiles in 20 young healthy men (average age 30.4 years) and in 14 healthy elderly men (average age 70.4 years). Data from Tenover, J.S. et al. (1988). The participants went to bed between 23:00 and 01:00. Age-Related Alterations in the Circadian Rhythms of Pulsatile Luteinizing Hormone and Testosterone Secretion in Healthy Men. Journal of Gerontology, 43, M163–M169.

Aging is associated with a progressive decrease in circulating testosterone levels, by 1 to 2 % per year from 30 years of age onwards (Kaufman and Vermeulen, 2005). This decline contrasts with a simultaneous increase in sex hormone binding globulin, so that the fall in bioavailable testosterone is more marked than the fall in total testosterone. Though dampened, diurnal variations persist in the elderly but LH diurnal variations are no longer detectable (Tenover et al., 1988) (Fig. 11).

This decline in testosterone levels has a mixed etiology. On the one hand, primary functional alterations of testicular Leydig cells. On the other hand, altered neuroendocrine regulation of pituitary LH secretion (Kaufman and Vermeulen, 2005). In addition, the testosterone decline may also be modulated by age-related sleep disturbances. In older men, the duration of nocturnal sleep was found to be an independent predictor of morning free and total testosterone (Penev, 2007). Consistent with this finding, sleep restriction (5 hours in bed per night for one week) was associated in young healthy men with significant decreases in daytime testosterone levels (Leproult and Van Cauter, 2011).

Women

In healthy adult menstruating women, no circadian rhythm of FSH and LH can be evidenced in constant routine conditions, indicating that the circadian pacemaker plays no role in their diurnal variations (Klingman et al., 2011). Circulating FSH, LH, estradiol and progesterone profiles show episodic pulses throughout the 24-hour span (Backstrom et al., 1982). Frequency and amplitude of gonadotropin pulses are modulated by estrogen levels and therefore vary markedly throughout the menstrual cycle (Caufriez et al., 2009; Filicori et al., 1986). In addition, they are also modulated by sleep. In early follicular phase, LH pulse frequency is diminished

during nocturnal sleep as well as during daytime sleep, but not during nighttime wakefulness (Caufriez et al., 2009; Filicori et al., 1986; Hall et al., 2005). During the sleep period, LH pulses preferentially occur in association with transient awakenings (Hall et al., 2005). Therefore, sleep alterations (fragmentation and shortening of the sleep period) commonly observed in night and shift workers are likely to favor alterations of the menstrual function. Conversely, potential effects of the menstrual cycle on sleep architecture have also been evidenced. Awakenings are less frequent in the early luteal phase, when both estrogen and progesterone levels are increasing, and more frequent in late luteal phase when both hormone levels are decreasing.

Ovarian steroid secretions fall markedly at menopause. In postmenopausal women, estradiol, progesterone and testosterone circulating levels are very low, resulting in major gonadotropin elevations, principally of FSH. Gonadotropin levels and LH pulse frequency are already higher in normally cycling women beyond 40 years of age than in younger women (Reame et al., 1996).

At the same time, postmenopausal women frequently complain of sleep problems, especially of more nocturnal transient awakenings. The origin of those troubles is likely to be multifactorial, including both the effects of menopause associated hormonal alterations and the effects of aging per se, but the underlying mechanisms remain largely hypothetical. Sleep disturbances have been associated with decreases in estradiol and increases in FSH levels, but polysomnographic studies provided inconsistent results (Baker et al., 2018). On the other hand, a recent study suggests that the effects of aging from mid-life into early old age may have been overstated (Matthews et al., 2020). Awakenings may occur independently of vasomotor symptoms (hot flushes), but nocturnal flushes are consistently associated with concomitant awakenings (Manber and Armitage, 1999). Hot flushes and concomitant sleep disruptions mostly occur around 04.00-05.00 h, i.e. in temporal association with enhanced cortisol secretion, suggesting a possible involvement of the corticotropic axis.

Studies in postmenopausal women concerning possible effects of hormonal replacement therapy on sleep quality have yielded inconsistent results, most likely because the protocol design varied widely from one study to another. Two carefully designed studies performed in ovariectomized female rats indicated that REM sleep was modulated by estradiol in a time-of-day dependent manner (Schwartz and Mong, 2011; Schwartz and Mong, 2013). In healthy postmenopausal women, oral administration of progesterone, an active neurosteroid, was found to restore normal sleep when sleep was disturbed by environmental conditions, improving both sleep duration and sleep quality with an increase in SW sleep (Caufriez et al., 2011). Those results suggest that progesterone and estradiol might contribute to physiological sleep regulation by reinforcing the actions of the sleep-wake homeostasis and of the circadian clock, respectively (Copinschi and Caufriez, 2022).

Glucose and insulin

Glucose homeostasis is primarily dependent on the balance between glucose production by the liver and glucose consumption by insulin dependent tissues (such as muscle, adipose tissue) and non-insulin dependent tissues (such as brain). But in healthy subjects, glucose utilization varies throughout the 24-hour span. In normal young subjects, fasting during daytime wakefulness is associated with a clear fall in circulating glucose levels. Conversely, during nocturnal sleep, glucose levels remain stable or decline only minimally despite relatively prolonged fasting. On the other hand, in case of prolonged fasting during nighttime wakefulness, glucose levels decrease, while they remain stable during daytime sleep, indicating that sleep

associated mechanisms are operative to prevent inappropriate hypoglycemia (Van Cauter et al., 1991; Van Cauter et al., 1997b).

Experimental investigations involving constant intravenous glucose infusion or constant enteral nutrition have shown that glucose tolerance deteriorates during the first part of nighttime sleep to reach a minimum around the middle of the night, and improves thereafter to progressively return to morning levels (Scheen et al., 1996; Van Cauter et al., 1991; Van Cauter et al., 1997b). This sleep-associated decline in glucose tolerance results from a reduction in both peripheral and cerebral glucose utilization (Boyle et al., 1994). Positron emission tomography studies have evidenced that during SW sleep (a dominant stage during the first half of the normal sleep period), cerebral glucose utilization is markedly lower than during REM sleep or during wake (Maquet, 2000). This is physiologically important since cerebral glucose utilization is estimated to represent at least 20% of total body glucose utilization (DeFronzo, 2004). In addition, glucose uptake by insulin-dependent tissues is probably inhibited by the sleep-onset associated GH release (Møller et al., 1990). It appears therefore that sleep-wake homeostasis exerts significant modulatory effects on glucose regulation.

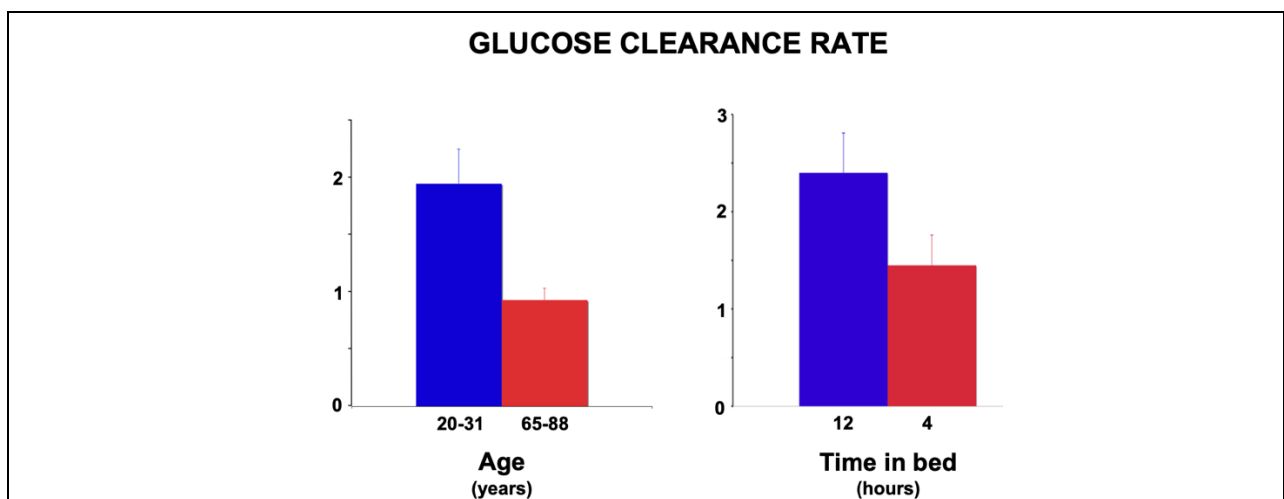


Fig. 12. *Left panel:* glucose clearance rate following intravenous glucose injection (IVGTT) in 11 healthy old subjects (65 to 88 years) as compared to 11 healthy young subjects (20-31 years) Data from Palmer, J.P. and Ensinnck, J.W. (1975). Acute-phase insulin secretion and glucose tolerance in young and aged normal men and diabetic patients. *The journal of Clinical Endocrinology and Metabolism*, 41, 498-503. *Right panel:* glucose clearance rate following intravenous glucose injection (IVGTT) in 11 healthy young subjects (18 to 27 years) in a sleep-debt condition as compared to fully rested condition. Data from Spiegel, K., Leproult, R. and Van Cauter, E. (1999) Impact of sleep debt on metabolic and endocrine function. *Lancet*, 354, 1435-1439. Values shown are mean (+ SEM). Note the similarity between the effects of aging and the effects of sleep restriction.

Aging is associated with a decrease in both insulin secretion and insulin activity, resulting in a decrease in glucose tolerance (Chen et al., 1985). Interestingly, following an intravenous glucose tolerance test (IVGTT), the magnitude of the reduction of glucose clearance rate in healthy older subjects beyond 65 years as compared with young controls, is fairly similar to the reduction observed in healthy young subjects submitted to partial sleep restriction as compared to a fully rested condition (Palmer and Ensinnck, 1975; Spiegel et al., 1999), as illustrated in Fig. 12. Indeed, well-controlled laboratory studies have consistently shown that partial sleep deprivation for 1–7 days may result in increased insulin resistance in men and in pre- and postmenopausal women (Buxton et al., 2010; Singh et al., 2023; Spiegel et al., 1999). In healthy

adults who are chronically sleep restricted, behavioral sleep extension is feasible and is associated with improvements in insulin sensitivity (Kothari et al., 2021; Singh et al., 2023). Even alterations in sleep quality (all-night selective suppression of SW sleep), without reduction in total sleep duration, were found to induce a reduction in glucose tolerance (Tasali et al., 2008). Moreover, these observations are consistent with data recorded in numerous epidemiologic studies showing that short sleep duration is significantly associated with an increased risk of developing prediabetes and diabetes, particularly in the elderly (Knutson and Van Cauter, 2008; Lu et al., 2021; Yan et al., 2018). Interestingly, this association persists even among participants who follow a healthy diet (Noga et al., 2024). This bunch of data strongly suggests that sleep curtailment might accelerate age-associated alterations of glucose metabolism.

Conclusions

Though the respective roles of sleep and of the circadian clock in the regulation of endocrine function widely differ from one hormone to another, age-related sleep and endocrine-metabolic alterations frequently interact with each other. Most prominent age-related alterations of hormonal circadian rhythms are a phase-advance and a reduction in diurnal amplitude, which are likely to result from both a reduction in the strength of the circadian signal and a reduction in the homeostatic drive to sleep.

For a number of hormones, age-related alterations are strikingly similar to those observed in young healthy subjects submitted to sleep restriction. Thus, voluntary or not, recurrent sleep curtailment, currently experienced by an increasing number of children and adults, is likely to accelerate the senescence of endocrine and metabolic function.

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