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CLINICAL REVIEW

Sleep and the GH/IGF-1 axis: Consequences and countermeasures of sleep loss/disorders

Mounir Chennaoui [a, b, *], Damien Léger [b, c], Danielle Gomez-Merino [a, b, **]

[a] Institut de Recherche Biomédicale des Armées (IRBA), Brétigny-sur-Orge, France
[b] Université de Paris, Equipe d'accueil VIgilance FAtigue SOMmeil (VIFASOM), EA 7330, Paris, France
[c] APHP, APHP-5, Hôtel Dieu, Centre du Sommeil et de la Vigilance, Paris, France

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SUMMARY

This article presents an up-to-date review of the state-of-the-art knowledge regarding the effect of sleep on the anabolic growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis. This axis is involved in learning and memory and neuroprotection at the central level, and in the crosstalk between sleep and the immune system, with respect to its anti-inflammatory properties. We also aim to provide insight into the consequences of sleep loss on cognitive capacities in healthy individuals and patients with obstructive sleep apnea (OSA), regarding the mechanistic association with the GH/IGF-1 axis. Finally, this review examines the inflammatory/endocrine pathways that are affected by sleep loss, and which may consequently interact with the GH/IGF-1 axis.

The deleterious effects of sleep loss include fatigue, and can cause several adverse age-dependent health outcomes. It is therefore important to improve our understanding of the fundamental physiology underlying these effects in order to better apply non-pharmacological countermeasures (e.g., sleep strategies, exercise training, continuous positive airway pressure therapy) as well as pharmacological solutions, so as to limit the deleterious consequences of sleep loss/disorders.

Introduction

Sleep is a basic physiological need that is crucial for human life. In most individuals, sleep occupies between 20 and 40% of a 24-h day, and serves multiple restorative functions in the body and the brain. Indeed, sleep improves memory recall, regulates metabolism, and reduces mental fatigue, while also playing important roles in tissue repair, synaptic homeostasis, and immune-inflammatory control [1–3].

The adverse effects of insufficient sleep and/or sleep disorders include decreased cognitive abilities, dizziness, fatigue, mood disorders, stress, psychiatric symptoms, accidents and injuries, and mortality [4–7]. Impaired physical capacities in daily tasks have also been described, and are sometimes associated with a decrease in muscular strength [8]. Several sleep transformations that occur throughout life are now well-recognized, such as changes in the amount of time spent in different sleep stages, a phase-advance in the timing of circadian rhythms occurring in the elderly, and the observation that insomnia increases with age [9].

Sleep and its different stages are characterized by a specific neurochemical milieu of neurotransmitters and hormones, and a pattern of considerable activity in various endocrine systems that has been studied by both observational and experimental research, indicating that sleep loss results in changes in hormone secretion. Sleep is accompanied by a marked increase in growth hormone (GH), prolactin, and melatonin release, as well as the down-regulation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) [10–12]. Consequently, there is a nocturnal decrease in plasma cortisol, epinephrine and norepinephrine levels. A rapid increase in plasma thyroid-stimulating hormone (TSH) levels is also observed in the early evening, beginning 4–5 h before the habitual bedtime [13]. Sleep deprivation and sleep restriction have been shown to clearly disturb endocrine secretions including increased evening concentrations of cortisol, and decreased concentrations of the anabolic hormones testosterone, GH, and the GH-related growth factor IGF-1 [14–16]. Perturbations to endocrine secretions may influence

* Corresponding author. IRBA and Université de Paris, Equipe d'accueil Vigilance, Fatigue, SOMmeil (VIFASOM), EA 7330, Paris, France.
** Corresponding author. IRBA and Université de Paris, Equipe d'accueil Vigilance, Fatigue, SOMmeil (VIFASOM), EA 7330, Paris, France.
E-mail addresses: mounirchennaoui@gmail.com (M. Chennaoui), dangomez51@gmail.com (D. Gomez-Merino).

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Abbreviations

AHI	apnea-hypopnea index
BDNF	brain-derived neurotrophic factor
BMI	body mass index
cAMP	cyclic adenosine monophosphate
CNS	central nervous system
CPAP	continuous positive airway pressure
CREB	cAMP response element binding protein
EPO	erythropoietin
GH	growth hormone
GHRH	growth hormone-releasing hormone
HPA	hypothalamic pituitary adrenal
IH	intermittent hypoxemia
IL	interleukin
IGF-1	insulin-like growth factor 1
IGFBP	insulin-like binding protein
LRP1	lipoprotein-related receptor 1
MMP-9	matrix metalloproteinase-9
OAHI	obstructive apnea hypopnea index
OSA	obstructive sleep apnea
PKA	protein kinase A
PWS	Prader-Willi syndrome
REM	rapid eye movement
SNS	sympathetic nervous system
SR	chronic sleep restriction
SWS	slow-wave sleep
TNF	tumor necrosis factor
TSD	total sleep deprivation
TSH	thyroid stimulating hormone
TST	total sleep time

cognitive functions, and some of these hormones specifically contribute to memory consolidation [17,18]. The functionality of the immune system is additionally altered by acute and chronic sleep loss, resulting in the sub-clinical production of inflammatory cytokines that are known to be associated with cognitive impairments in healthy, asymptomatic individuals [19].

The effects of sleep and the GH/IGF-1 axis on cognition

Sleep regulation of the GH axis

Growth hormone (GH) plays an essential role in maintaining the homogeneity of tissues and organs during the normal development of the human body, or after injury. Its effects on growth during childhood and puberty are partly direct and partly mediated by insulin-like growth factor I (IGF-1), a polypeptide hormone with endocrine, paracrine, and autocrine effects that shares structural homology with insulin. In turn, the IGF-1 transcription factor, which occurs independently of GH in many tissues, is dependent on adequate GH secretion. IGF-1 is primarily secreted by the liver and is transported to other tissues, thus acting as an endocrine hormone, but it is also produced in most (if not all) tissues (including skeletal muscle and the brain) and acts locally as a paracrine hormone [20,21]. GH and IGF-1 both play essential roles in controlling somatic growth (including the stimulation of tissue growth and protein anabolism) and in regulating multiple physiological processes in humans and other species. IGF-1 travels in the blood as a complex with insulin-like binding protein 3 (IGFBP-3) and an “acid labile subunit” chaperone, which regulates IGF-1 availability to target tissues by coordinating its release. Neuronal activity drives IGF-1 transport into the Central Nervous System (CNS) through the stimulation of matrix metalloproteinase-9 (MMP-9), resulting in the cleavage of IGFBP-3 (which liberates IGF-1) and interaction with the membrane cargo protein transporter lipoprotein-related receptor 1 (LRP1) [22].

The secretion of GH from the anterior pituitary gland is regulated by complex homeostatic interactions that are mediated by neural and peripheral influences. GH synthesis and secretion are under the control of hypothalamic peptides, with stimulation by growth hormone-releasing hormone (GHRH) and inhibition by somatostatin [23]. Furthermore, IGF-1 produced in the liver in response to GH results, via long-loop feedback, in the suppression of GH release through the stimulation of somatostatin release, as well as the inhibition of GH and GHRH release. Another stimulus of GH release is ghrelin, which is mainly secreted by the stomach [24]. Other hormonal regulators of the GH axis include glucocorticoids, gonadal sex hormones, and thyroid hormone. GH secretion is pulsatile in all species, with a similar pattern in humans and male rodents. Notably, the 24-h pattern of spontaneous GH release changes with age, and the biological roles of GH vary greatly with age and reproductive status. Throughout puberty, an increase in GH secretion occurs alongside an increase in circulating IGF-1 levels [25]. Then, starting at 18–25 y of age, there is an exponential decline in mean 24-h GH concentrations in men and women, accompanied by a gradual fall in IGF-1 circulating levels, all of which occur regardless of sex hormone levels [23]. In addition, age and body mass index (BMI) are distinct and specific correlates of individual attributes of GH secretion and clearance in men [26]. Finally, strong physiologic stimuli of GH secretion are sleep and exercise. Exercise is a proven stimulus of GH release and an acute bout of exercise stimulates a significant GH pulse [27].

The GH secretion is observed preferentially during slow-wave sleep (SWS) [10], and GH secretion during the beginning of sleep appears primarily regulated by GHRH stimulation occurring during a period of relative somatostatin withdrawal [28]. However it remains difficult to define precisely mechanisms whether sleep modulates GH secretion. A bidirectional interaction also exists between the activity of the GH/IGF-1 axis and sleep regulation [12,28,29]. Indeed, GHRH represents an important sleep-promoting substance, and it is well-documented that this hormone is essentially controlled by the sleep-wake homeostasis [29]. The impact of hormones of the somatotropic axis on sleep has been thoroughly described and is outside of the focus of this review. In normal adults, the maximal GH secretory burst occurs within minutes after the first period of slow-wave sleep (SWS) [10,30,31]. When the sleep cycle is delayed or advanced, GH secretion is consequently delayed or advanced to coincide with the first episode of sleep, as well as during repetitive three-hour sleep-wake cycles for 10 d [32,33]. The nocturnal release of GH is minimal or altogether absent during a night of sleep deprivation, while a robust increase is observed during the recovery night, and SWS is positively correlated with GH levels both pre- and post-sleep deprivation [34,35]. Brandenberger et al. [34] observed that the GH pulses were more equally distributed throughout the 24 h of sleep deprivation compared to a night-time sleep condition, with large individual pulses occurred during the day. Vgontzas et al. [35] found that deep sleep enhances the activity of the GH axis and has an inhibitory effect on cortisol levels. During the night of sleep recovery that

follows total sleep deprivation, SWS has been shown to increase [36] as well as GH secretion during the first half of the night, and levels were elevated in the total night after sleep deprivation in comparison to the baseline night [37]. In contrast, during the first night of sleep recovery following chronic sleep restriction (4 h in bed during seven days), SWS increased [16] while 24-h GH levels were no higher than at the baseline (5.5 h *vs.* 8.5 h bedtimes during 14 d) [38]. Also, after one night of sleep restriction (mild sleep restriction), basal and hypoglycemia-stimulated concentrations of the counterregulatory GH were unchanged [39]. During aging, the amount of GH secretion and the duration of SWS markedly decrease in the same proportion [28]. In male volunteers aged 20–92 y, the nocturnal GH peak values exponentially decreased with age, while the lowest point for cortisol increased linearly as a function of age [40]. In this study, age-related changes in the sleep-dependent secretion of GH and cortisol correlated significantly with an age-dependent decrease in SWS. The authors suggested that during aging, changes in GH and cortisol secretion may act together to reduce anabolic functions of sleep.

Finally, it should be noted that sleep and the GH/IGF-1 axis may interact in memory, neuroprotection, neurogenesis and neuroplasticity, and neurodegenerative diseases [41].

The effects of sleep and the GH/IGF-1 axis on cognitive capacities: possible mechanistic interactions

Sleep and cognition: the pathways

Cognition refers to a range of mental processes relating to the acquisition, storage, manipulation, and retrieval of information. It underpins many daily activities, in health and disease, across the age span. Cognition can be separated into multiple distinct functions, dependent on particular brain circuits and neuromodulators. Cognitive assessment refers to the objective measurement of distinct cognitive abilities, such as working memory, inhibition, cognitive flexibility, psychomotor speed and sustained attention.

A body of literature suggests that an important function of sleep is to maintain or enhance cognitive capacities, particularly learning and memory [18]. Sleep optimizes memory consolidation, improving the strength and stability of new memories acquired before sleep [42]. This has been particularly demonstrated in experimental human sleep deprivation protocols, revealing the negative consequences on attention and working memory [4]. Moreover, studies have identified positive effects of additional sleep in the form of daytime naps, even as short as six min, on learning and declarative memory in non-sleep-deprived subjects [43,44].

Apart from its beneficial effects on the consolidation of previously learned memories, sleep also benefits the subsequent acquisition of new learning memories [45]. The sleep–memory relationship is also influenced by factors such as age [46], gender and hormonal status [47], and mental health [48].

Emerging evidence suggests a possible role for sleep in the regulation of adult neurogenesis in relation to brain plasticity, as well as hippocampus-dependent cognitive functions such as learning and memory [for review, see: 49,50]. A change in neurogenesis could affect these hippocampus-dependent functions. For example, there is experimental evidence linking decreased neurogenesis to impaired learning, particularly regarding the spatial domain and decreased memory retention [51]. While only a few studies have shown that periods of increased sleep are associated with increased cell proliferation or survival, there is strong evidence that chronic restriction of sleep inhibits hippocampal cell proliferation and in some cases neurogenesis [for review see 52]. Sleep restriction may impair synaptic plasticity and memory processes through attenuations of intracellular cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling which may lead to alterations in cAMP response element binding protein (CREB)-mediated gene transcription, neurotrophic signaling, and glutamate receptor expression [52].

In rodents, prolonged sleep deprivation reduces hippocampal cell proliferation and inhibits adult neurogenesis, although this is not associated with elevated adrenal glucocorticoid rates [53,54]. In this case, eight hours of recovery sleep cannot normalize the reduced cell proliferation associated with prolonged sleep deprivation [55]. In humans, reduced hippocampal activation and lower memory performance have been revealed after 35 h of sleep deprivation or mild sleep disruption [45,56]. Several reviews have suggested that sleep might not be capable of promoting cell proliferation and maturation directly, although it is essential for the normal functioning of other processes and systems that, in turn, regulate neurogenesis [49,50]. This is particularly important for health as recent data support the persistence of adult hippocampal neurogenesis in the adult human dentate gyrus until the ninth decade of life [57].

Finally, several endogenous factors have been suggested to impair synaptic plasticity and reduce neurogenesis following sleep deprivation, including the GH/IGF-1 trophic axis, BDNF (brain-derived neurotrophic factor), hormones, cytokines, and a range of neurotransmitters and neuromodulators such as adenosine [50,52].

The implication of sleep-GH/IGF-1 and cognition in clinical issues

The effects of GH and its mediator IGF-1 on brain function have been evaluated in many clinical and preclinical laboratories. Both are implicated in cognition and neuroprotection, regeneration, and functional plasticity in the adult brain [for review, see: [41,58–60]]. The GH receptors expressed in the hippocampus and frontal cortex might mediate significant aspects of memory and cognition. The neuroprotective actions of IGF-1 are tacitly assumed to operate in response to altered brain homeostasis. Neurons, glia, endothelia, epithelia, and perivascular cells are all targets of IGF-1 actions and key cellular processes in the brain that are affected by IGF-1. This is illustrated by decreased circulating levels of GH and IGF-1 in the elderly, and their association with cognitive impairment [61,62].

IGF-1 has therefore emerged as a promising restorative molecule for increasing hippocampal neurogenesis and memory accuracy in aged individuals [63]. There are multiple possibilities for direct actions of peripherally derived or locally produced GH, as well as endocrine or autocrine/paracrine effects of IGF-1 on the CNS. Both GH and IGF-1 can penetrate the blood–brain barrier and induce profound effects on various CNS-related behaviors [for review, see: 58,59]. GH administration has profound effects on memory and cognitive capacity in experimental animals as well as humans with impaired GH production [64,65]. In addition, increased IGF-1 gene expression in the hippocampus was found in two-month-old intact male Wistar rats treated with GH in association with a significant positive effect of GH on memory functions [66]. Exogenous GH administration has been shown to increase IGF-1 hippocampal gene expression, and it also attenuates hypoxia-induced cognitive deficits and hippocampal injury (i.e., increased cleaved caspase-3 expression as a marker of neuronal apoptosis) [67]. IGF-1 also plays an important role in brain development, as well as neuroplasticity and neurocognitive functions in adults [20,41,60]. For instance, peripheral infusion of IGF-1 selectively induces neurogenesis in the adult rat hippocampus [68]. Serum IGF-1 has also been shown to be an important determinant of exercise-induced increases in hippocampal neurogenesis [69]. These authors reported that many (but not all) of the beneficial effects of exercise on brain function depend on circulating IGF-1 and are associated with increased hippocampal neurogenesis in

adult mice, including improved cognition and reduced anxiety. One previous electrophysiological study [70] indicated that liver-derived circulating IGF-1 affects learning and synaptic plasticity through its trophic effects on central glutamatergic synapses. A myriad of potential ways may explain how GH and IGF-1 mediate neuroplasticity, including effects on glutamate receptors, excitation/inhibition balance in neuronal circuitry, calcium channels, synaptic proteins, and interactions with other neurotrophic factors [for review see 60]. IGF-I also modulates synaptic strength by controlling the synthesis and release of diverse neurotransmitters such as acetylcholine or dopamine [for review see [71]]. Interestingly, it was recently discovered that dopamine neuron-derived IGF-1 controls dopamine neuron firing, skill learning, and exploration [72].

Sleep and cognition: the interaction of sex hormones and inflammation

Another point to consider is that endogenous factors related to sleep and cognitive function may interact with GH/IGF-1, sex hormones and inflammatory mediators. Sex hormones may play a role in the regulation of adult hippocampal neurogenesis, in addition to modulating forms of hippocampus-dependent and prefrontal cortex-dependent learning and memory in adult rodents and humans [73]. Chronic peripheral inflammation is associated with behavioral disturbances linked to disrupted adult hippocampal neurogenesis, such as cognitive impairment, and deficits in learning and memory [74]. Normal aging involves the decline of anabolic sex hormones as well as GH and IGF-1, and creates a state of chronic peripheral inflammation that can occur at the onset of cognitive impairment [14,74].

The effects of sleep loss and the GH/IGF-1 axis on cognition

The magnitude of sleep loss in the population

Sleep loss may result from total sleep deprivation (in night-shift workers), chronic sleep restriction (due to work, medical conditions or lifestyle, or even training, practice, and travel schedules for athletes), or sleep fragmentation/disruption (such as age-related sleep impairments, or sleep disorders such as sleep apnea) [for review see 75]. Acute total sleep deprivation refers to wake periods that extend beyond the typical 16–18 h, whereas sleep restriction refers to not getting enough sleep per 24 h for one or multiple nights.

Sleep deprivation is indeed often found chronically associated with night work with an averaged one-hour loss per day compared to day workers [76] and the metabolic impact of sleep debt in night workers is well demonstrated [77,78]. Conversely, insomnia, the most prevalent sleep disorder, is not always synonymous of short sleep and sleep deprivation in adults or even adolescents [79,80]. However, subjects with insomnia who reported chronic short sleep may have a higher risk of obesity [81].

Unlike total sleep deprivation, restricted sleep is pervasive in most modern societies, whether it is found in adults, school-aged children, or adolescents (26%), and is characterized by lower reported sleep durations than the age-recommended amount [82]. Total sleep time was shown to be severely diminished in a French cross-national study, concerning 16.0% of 11-year-old children and 40.5% of 15-year-old children [83]. In many athletic populations (including elite adolescent athletes), reduced sleep quantity and/or poor sleep quality appear to exist, although this may be specific to athletic training and competition [84]. Similarly, in a military environment, the three components of good sleeping (timing, duration, and quality) are challenged, and the self-reported sleep duration has been reported to range from 5.8 to 6.5 h per night, irrespective of deployment status, fatigue, depression, post-traumatic stress disorder, or pain syndromes [85].

Sleep loss and cognitive capacities in the lab

The cognitive, behavioral, and psychophysiological effects of acute total sleep deprivation (TSD) and chronic sleep restriction (SR) are well-documented in laboratory protocols, showing that the largest performance decrements occur for measures of sustained attention and working memory, while more complex tasks are comparatively affected to a lesser degree [75,86–88]. A recent meta-analysis (comprising 71 different study populations and 1688 participants) on the neurocognitive consequences of SR demonstrated negative effects on neurocognitive functioning, particularly for measures of sustained attention and executive function, as well as attentional lapses and behavioral inhibition within these domains [88]. This analysis considered the duration and severity of the sleep restriction protocols, and the age and sex distribution of the participants. The results indicate that: 1) the magnitude of the effect increases with age but without any significant effect on the older adult population; 2) the effect progressively increases over subsequent days of restricted sleep; and 3) the effect is directly modulated via sleep deficit severity. Finally, several studies have reported on the negative effects of restricted sleep duration on several aspects of emotional and cognitive functioning in children and adolescents [for review, see: [89]]. The negative effects of sleep loss on athletic performance have been repeatedly examined, mainly showing an altered mood state that affects motivation and the athlete's precompetitive mood states [90], as well as decreased motor performance at submaximal intensity [91,92]. In the military environment, the sleep loss-related impairment of specific cognitive abilities during continuous operations has been previously described [93]. In all cases, a number of studies have repeatably revealed that systematic interindividual differences exist in the resistance and vulnerability to the neurocognitive effects of acute TSD and chronic SR [94], with prior research suggesting an underlying genetic component [for review, see [95]].

Sleep loss and cognition, and their relationship to the GH/IGF-1 axis, sex hormones, and inflammation

Acute TSD and chronic SR modulate synaptic plasticity and neurogenesis-related molecules implicated in cognitive functioning, including GH/IGF-1, BDNF trophic factors, cytokines, hormones, and a range of neuromodulators and neurotransmitters (Fig. 1). GH administration has been shown to strongly promote cell proliferation in the adult rat brain and also protect the hippocampal neuronal processes against the deleterious effect of sleep loss [96]. Several animal studies have also shown the detrimental effects of restricted sleep on memory processes (i.e., spatial memory and vigilance) concomitantly with mechanistic factors that could account for neuroplastic changes and putative brain mechanisms [for review, see [97]]. Sleep deprivation (96 h) has also been shown to reduce hippocampal neurogenesis in adult rats [98]. In addition, TSD has been found to reduce circulating levels of IGF-1, both in rats and in healthy young men [15,99–101].

The hippocampal expression level of the BDNF trophic factor is reduced after restricted sleep, while brain inflammatory cytokines are elevated [102]. However, human studies have identified some questions concerning the exclusive role of BDNF in sleep deprivation-related cognitive impairments [103,104], whereas the implication of IGF-1 and inflammatory cytokines appear to be strengthened. Declarative memory was impaired after TSD in healthy young adults while BDNF levels were increased; furthermore, performance was normal regarding attention, response

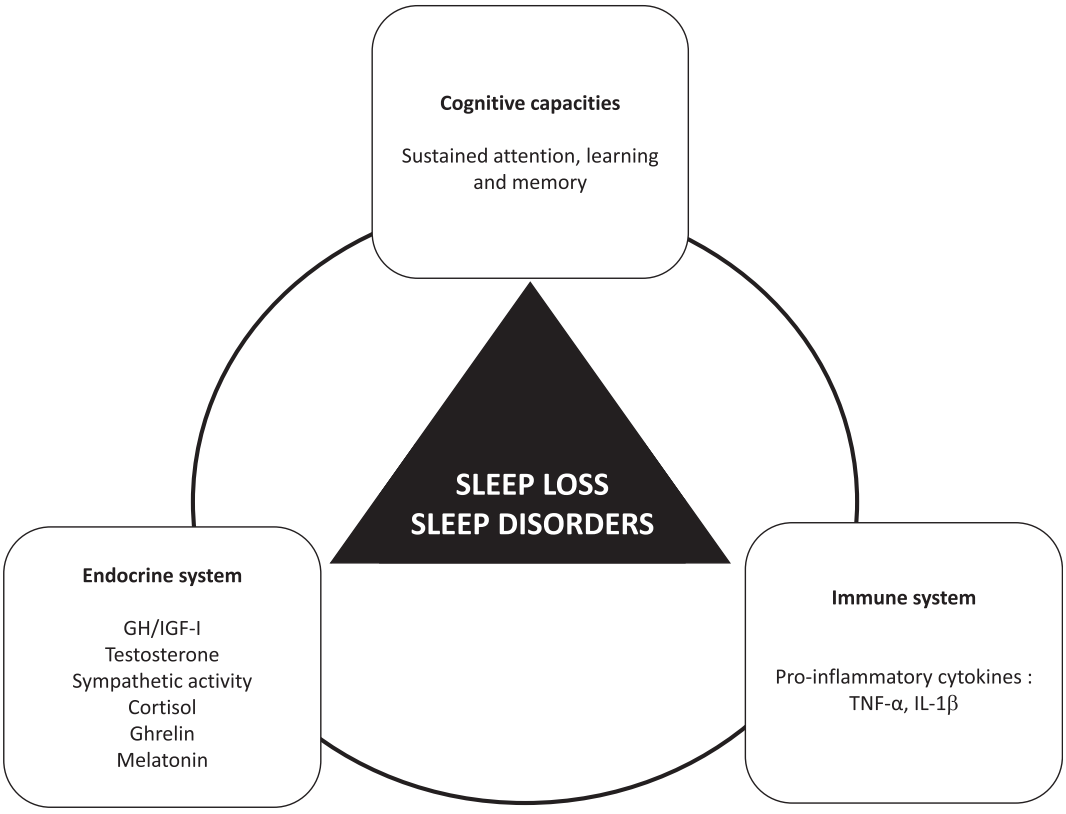

Fig. 1. Sleep loss/sleep disorders and cognitive capacities: the endocrine and pro-inflammatory cytokines responses.

inhibition capacity, and working memory [104]. TSD was also found to impair sustained attention [87] in association with decreased IGF-1 levels [15] in young healthy adults, whereas seven days of sleep extension (one hour per night) limited these deleterious effects and increased IGF-1 [103].

Peripheral and central inflammation related to sleep loss may also play a role in cognitive impairments. TSD and SR have been shown to impair sustained attention [16,19,87] in association with increased TNF-α serum levels [19,36] and increased TNF-α gene expression (but not protein levels), with as little as two days of SR [105]. In rats, TSD and chronic SR induce increased levels of IL-1β and TNF-α in the circulation and in the brain at gene expression and protein levels [102,106].

Sex hormones have also been identified among the various factors that may potentially interact with the GH/IGF-1 axis, regarding the relationship between sleep loss and cognitive impairments. Along these lines, anabolic testosterone levels have been repeatedly observed to decrease after TSD and SR, although they are readily corrected following sleep recovery [99,105,107].

In summary, the mechanisms by which sleep loss affect cognitive capacities may involve a complex and interacting set of factors that mediate changes in adult synaptic plasticity and neurogenesis, associated with learning and memory. Here, we have reviewed the results underlying the potential roles played by molecular factors such as the trophic GH/IGF-1 axis, the pro-inflammatory cytokines TNF-α and IL-1β, and sex hormones.

OSA and the roles of the GH/IGF-1 axis and cognition

Obstructive sleep apnea (OSA) is the only sleep disorder that may be considered as being possibly associated with the GH/IGF-1 axis and cognition. No specific association has been found between insomnia, the most frequent sleep disorder, and this axis. Indeed, the GH/IGF-1 axis has been poorly implicated in type one narcolepsy, along with the related deficiency in the hypothalamic hypocretin system.

The reciprocal association between OSA and obesity (a multifactorial disease) is well-established, and the incidence of OSA is 12- to 30-fold higher in morbidly obese patients than in the general population; conversely, OSA may predispose individuals to worsening obesity due to sleep deprivation, daytime sleepiness, and disrupted metabolism [108]. In non-diabetic obese patients with OSA, previous research has found that nocturnal GH secretion, and IGF-1 concentrations were decreased, along with impaired peripheral sensitivity to GH [109]. Izumi et al. [110] assessed IGF-1 levels in a group of 74 overweight and obese men who were recorded by polysomnography (PSG) for OSA screening. The authors classically differentiated three groups: 11 subjects with no OSA (<5/h), eight subjects with mild OSA ($5 \leq x < 15$/h), and 28 subjects with moderate-severe OSA ($\geq$15/h). They concluded that OSA is significantly associated with a reduction in IGF-I. Interestingly, IGF-1 levels were negatively correlated with BMI, waist circumference, the apnea-hypopnea index (AHI), and the sleep duration with oxygen saturation under 90% as independent variables. Conversely, IGF-1 was positively correlated with the average and the minimum O_2 saturation as independent variables. These results show that hypoxemia is associated with reduced IGF-1 [110].

The mechanisms underlying how OSA affects the secretion of GH and IGF-1 are not yet clearly understood, independently of the impact of obesity by itself. However, several studies have shown that OSA contributes to the development of the metabolic syndrome and diabetes [111], which may by themselves reduce the secretion of GH and IGF-1. Conversely, obesity by itself is generally

not found to have a significant influence on the level of IGF-1 in OSA patients [112]. In this latter study, plasma IGF-1 levels, as well as free and total testosterone, were significantly lower in relation to the severity of sleep apnea.

Other studies have proposed that OSA may impact GH secretion, via the percentage of SWS [113]. GH is indeed secreted during SWS, mainly within the first part of the night [31], which is often fragmented by OSA. The association found by Izumi et al. [110] between AHI and the IGF-1 index should be in favor of such a fragmentation role. Moreover, Gianotti et al. [114] conducted a survey that observed 13 adult male patients with OSA (mean age: 52.6 y) as well as 15 weight-matched patients with simple obesity and 10 normal lean male subjects, concluding that OSA more markedly impairs the maximal secretory capacity of somatotroph cells, together with reduced IGF-1 sensitivity to GHRH stimulation. This suggests that OSA concomitantly impairs GH secretion and sensitivity. However, contradictory results have been found in elderly subjects (mean age: 77 y) [115]. These authors studied 1233 participants in the Cardiovascular Health Study, and found no significant linear association between SWS (objectively measured by PSG) and IGF-1, IGFBP-1, or IGFBP-3 levels after adjusting for age, sex, race, BMI, diabetes, estrogen use, progestin use, and physical activity. The authors therefore postulated that aging appears to dilute the adverse influence of sleep-disordered breathing on the GH/IGF-1 axis system.

Hypoxemia by itself is also believed to reduce IGF-1 levels. In mice, treatment with a selective GHRH agonist reduced markers of oxidative stress in the cortex and hippocampus, promoted an enhanced expression of the neuroprotective genes IGF-1 and EPO, and markedly attenuated intermittent hypoxia (IH)-induced cognitive and behavioral deficits [116]. In men with OSA [110], IGF-1 levels were independently correlated with the average desaturation and oxygen desaturation index.

All deleterious mechanisms previously discussed in this review may also affect those cognitive disorders that are classically associated with OSA [117] (Fig. 1). Both desaturation and fragmented sleep may contribute to this altered cognition, which may also be affected by the cognitive reserve of each individual. There are certainly other less documented yet important factors at work such as cerebral blood flow, the blood–brain barrier, systemic inflammation, and metabolic dysfunction, all of which we described here, as well as any genetic predisposal to susceptibility [117]. In addition, sleepiness, a cardinal symptom of OSA, is strongly associated with attention dysfunction and may possibly impact short-term memory without affecting working memories or recovery domains [118]. Here, due to the contributions of SWS and REM sleep to different memory function processes [119], sleep disruption associated with OSA may be able to explain altered cognition in patients, depending on the severity and the duration of the disease.

Finally, the cognitive effect of OSA can certainly be attributed to the oxidative and inflammatory processes that we have described here, which are associated with the adaptive or maladaptive responses to repetitive hypoxemia and oxygenation on brain cells [110,116]. One survey in children has been illustrative in showing that IGF-1 levels are higher in children with OSA, particularly those who do not manifest any neurocognitive deficits, suggesting that the magnitude of the IGF-1 response elicited by OSA may play a significant protective role against the neurocognitive dysfunction associated with OSA [120].

On a reciprocal point of view, it is also of interest to enquire how GH-IGF-1 specific disorders like acromegaly or Prader–Willi syndrome (PWS) may affect by themselves sleep and OSA or cognition [121–123]. It may be found indeed it paradoxical that patient with acromegaly (due to an excess secretion of GH and IGF-1) had also an excess rate of OSA. By one side, the modified craniofacial appearances of patients with acromegaly may explain the pathophysiology of the excess of OSA comorbidity in these patients [121]. A vertical growth of the mandible leads to a dorsocaudal rotation, which promotes the pharyngeal obstruction. The treatment of acromegaly either with medical (which act on the soft tissue but not on the bone) and by surgical reduction of hyperplastic bone may or not improve OSA with contradictory results [121,124,125]. Besides OSA, central sleep apnea events were also reported, in relation with the specific cardiomyopathy with concentric biventricular dystrophy, which results to the excess of GH and IGF-1. This pathological issue has not been taken into account, in our knowledge, to understand the neuroprotective effect of OSA in acromegaly versus control patients.

The children with Prader–Willi syndrome (PWS) having a hypopituitarism syndrome with an insufficient secretion of GH had a high rate of OSA (between 38 and 100%) depending of studies [126,127]. Among youths with OSA, 53.07% had mild OSA, 22.35% moderate OSA, and 24.58% severe OSA [127]. The treatment by GH is not associated systematically with an improvement of OSA severity and the surgical treatment may sometimes increase the risk of velopharyngeal insufficiency with no OSA index improvement [128]. Adenotonsillectomy was associated with improvement in OSA for most children with PWS. However, residual OSA was present in the majority of cases post-surgery [128].

Sleep loss and OSA: the impact of countermeasures on the GH/IGF-1 axis

Limiting of sleep loss-related impairments to cognitive capacities in healthy subjects

Sleep extension

Several countermeasures are useful for limiting cognitive impairments related to sleep loss, particularly in adolescents and relatively young populations such as athletes and enlisted military personnel. In athletes, sleep is suggested to be the best strategy for recovery [129]. Sleep promotion may be approached via behavioral interventions such as sleep hygiene, nighttime sleep extension, daytime napping, or even the use of sleep-promoting compounds (e.g., melatonin). In normal-sleeping college students (and even in short-sleeping workers), sleep extension has been shown to produce favorable effects on alertness and performance during the first day of the following week, although these benefits dissipate soon afterwards [130]. Subsequently, a study on sleep extension and athletic performance revealed that actively competing athletes have significant improvements in specific indices, reaction times, daytime sleepiness, and mood, after 5–7 wk of sleep extension [131]. In chronically sleep-deprived obese individuals, sleep extension (468 ± 88 d) via lifestyle modifications was shown to improve cognitive function and attention [132]. Two laboratory studies found beneficial effects of sleep extension on cognitive performance in healthy young adults under TSD and SR conditions [87,133]. Seven days of sleep extension before one week of SR (3 h/night) and before TSD have been shown to influence the rate of degradation in cognitive performance and alertness, both during sleep restriction and in subsequent recovery periods. Because of the importance of the GH/IGF-1 axis on cognition and adult neurogenesis, the upregulation of the neurotrophic IGF-1 has been suggested to represent a possible physiological mechanism for such cognitive benefits [87] (Fig. 2). Specifically, seven days of sleep extension (72 min per night) increased circulating levels of total and free IGF-1 in young healthy adults during a TSD experimental protocol [103]. In rats, IGF-1 levels were significantly higher in the frontal cortex, plasma,

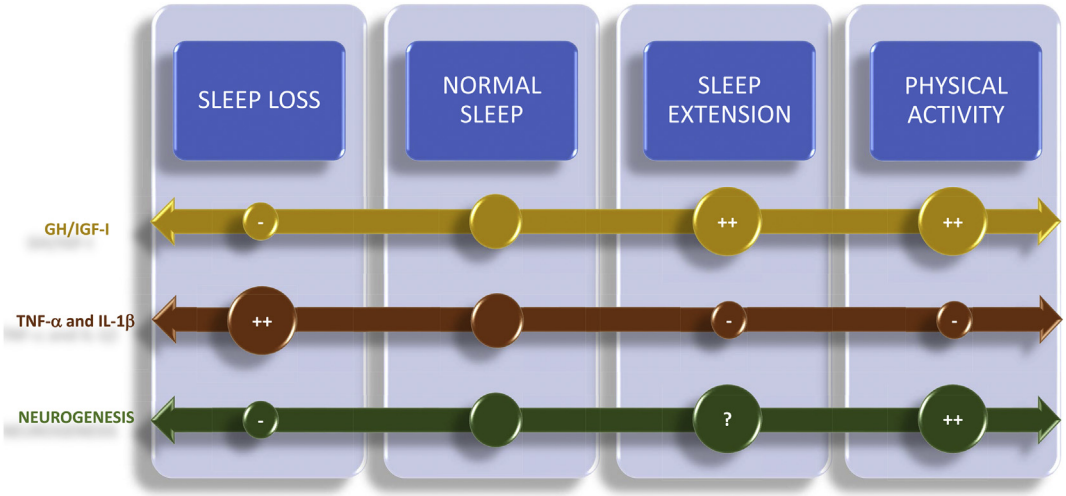

Fig. 2. Modulation of neurogenesis by sleep and physical activity: Impact of the GH/IGF-I axis and inflammation.

and skeletal muscle after fourteen days of sleep extension, while levels of testosterone were not influenced [134].

Exercise training

Recent evidence indicates that physical activity enhances SWS and improves memory performance, particularly in the elderly (after an activity program of 14 continuous days of exposure to structured social and physical activities) [135]. The benefits of physical activity (particularly aerobic exercise) on cognitive function (especially in cognitive domains dependent on the hippocampus) have been well-established in animal models, and also more recently using neuroimaging approaches throughout the human lifespan [for review, see [136,137]]. In healthy young men, seven weeks of combined moderate- and high-intensity exercise interval training was recently shown to have a significant but relatively small beneficial effect on the vigilance/sustained attention deficits during total sleep deprivation, without effects on inhibition and working memory capacities [138]. Exercise training has also been shown to increase the size of the hippocampus and to improve memory in older adults [139].

Concerning molecular mechanisms, exercise exerts beneficial effects on learning and memory via modulation of the key growth factors IGF-1 and BDNF. Exercise increases GH release, as well as BDNF and IGF-1 gene expression and protein levels, in the periphery and in several brain regions. Acute (i.e., brief, high-intensity) exercise-induced GH responses have been found to be significantly increased in sleep-deprived individuals [140]. One report has suggested that peripheral IGF-1 and possibly centrally derived IGF-1 mediate the induction of hippocampal BDNF with exercise, subsequently enhancing learning [141]. These authors postulated that exercise develops brain health and cognition through growth factor cascades, and also anti-inflammatory peripheral and central effects. Exercise training also reduces hippocampal IL-1β and TNF-α related to TSD in rats [106]. Furthermore, exercise-reduced levels of hippocampal IL-1β have been found to improve memory in aging rats [142]. The possibility that sleep extension may promote effects similar to exercise on growth factors (particularly IGF-1) and cognition was recently established in healthy men and adult rats (discussed above) [87,103,134]. In summary, the beneficial effects of sleep extension or exercise interventions on cognitive performance may be due to anti-inflammatory effects and upregulation of anabolic IGF-1 levels in the brain and the periphery.

Limiting the consequences of OSA on cognitive capacities

Therapeutic approaches that target sleep disturbances in order to normalize circadian rhythms and sleep homeostasis may represent a novel strategy to preserve or enhance neuroprotection in subjects afflicted by fragmented sleep or OSA sleep disorder.

Administration of GH in patients with OSA

By studying rats with intermittent hypoxemia (IH), several teams have shown that exogenous GH administration has anti-apoptotic and neuroprotective effects in the context of IH-induced neuronal injury, and that the physical activity associated with these neuroprotective effects mediates, at least in part, endogenous IGF-1 expression [67,143]. Administration of a GHRH agonist has been proven to attenuate IH-induced neurocognitive deficits, anxiety, and depression in mice, along with a reduction in associated stress markers and an increase in IGF-1 markers [116]. Furthermore, the authors suggest that these results may be associated with an improvement in oxidative stress on the CNS attributed to IH.

The impact of continuous positive airway pressure (CPAP) therapy

The gold standard for OSA treatment is CPAP therapy. Recently, Hoyos et al. [144] clearly demonstrated the positive impact of treating OSA with CPAP on GH and IGF-1 parameters. These authors conducted a randomized 12-wk long sham-controlled study to examine the effects of CPAP therapy on pulsatile GH secretion, IGF-1, IGFBP-3 and IGFBP-1. Additionally, the authors measured overnight GH secretion and pulsatility with frequent overnight blood sampling using gold-standard deconvolution analyses in a subset of participants. They also used correlation to assess whether these changes were driven by changes in SWS or hypoxemia, since both typify OSA. The authors concluded that twelve (but not six) weeks of CPAP therapy increases IGF-1, with a further increase occurring after 24 wk. Total and pulsatile GH secretion, secretory burst mass, and pulse frequency were also increased by 12 wk of treatment. These results indicate that CPAP therapy improves specific elements of the GH/IGF-1 axis in a time-dependent manner.

The fact that CPAP restores altered cognition in patients with OSA and reduces daytime sleepiness and mood problems associated with the disease has been widely reported in meta-analyses [118]. Therefore, it is not easy to objectively assess

this improvement, since cognition is not systematically included as a main criterion in clinical trials using CPAP [118]. However, patients with Alzheimer's disease and OSA have a slower cognitive decline when they are treated by CPAP [145,146]. CPAP also partly reversed the damage to hippocampal regions by improving neurocognitive deficits in 17 patients that were treatment-naive to sleep apnea, in comparison to 15 age-matched healthy control subjects [147]. Moreover, one recent review postulates that CPAP therapy is needed at least four hours per night to improve executive function at two months [148]. Nevertheless, six hours (or more) of therapy may provide additional neurocognitive improvement for vulnerable populations characterized by a decreased neurocognitive reserve and associated diseases. Genetic profiles may also help to predict the neurocognitive effects of CPAP.

Conclusion and perspectives

Sufficient sleep on a regular basis is highly recommended for good health in children and adults. In this review, we have described the interactions between sleep cognition and the GH/IGF-1 axis in order to highlight how sleep is also important for maintaining cognitive function in healthy individuals during sleep loss conditions.

Our review also emphasizes the importance of sleep for youth, athletes and the military in particular, since performance in the latter group relies heavily on sleep, especially when critical management decisions are at stake, as well as well-being and health. Indeed, it has become essential in modern societies to implement sleep hygiene practices, since this is an inexpensive approach for optimizing cognitive and physical capabilities at all ages.

It is important to note that we lack information on the relative contribution of genetic factors to individual responses within the context of the GH/IGF-1 axis, since there are interindividual differences to sleep loss responses in healthy individuals. Research in the 1990s suggested the influence of genetic factors and lifestyle, due to observed differences in the magnitude of the GH response to GHRH administration in a homogeneous group of healthy young men [28]. In addition, several other studies have proposed the importance of genetic factors on the variability of circulating levels of IGF-1 (and its main binding protein IGFBP-3) within normal populations [149]. Future research will need to more extensively explore the relationship between the anabolic IGF-1 axis, sleep, and sleep loss consequences.

Practice points

1 Sleep regulates the anabolic GH/IGF-1 axis; cognitive capacities are intertwined with both systems of the axis
2 Sleep loss impairs the cognitive capacities of healthy individuals and influences GH/IGF-1 responses
3 OSA impairs GH secretion and IGF-1 sensitivity, which may contribute to cognitive impairment
4 Sex hormones and inflammation are likely to be involved in the clinical consequences of sleep loss/OSA sleep disorder that affect cognition
5 Sleep loss and OSA-related cognitive deficits may be lessened by sleep extension, physical activity or CPAP therapy, by acting through the upregulation of the anabolic GH/IGF-1 axis and downregulation of inflammation

Research agenda

1 More studies are required to examine the mechanistic and neurophysiological links between sleep loss/disorders and the anabolic GH/IGF-1 axis
2 Future research will be needed to examine whether auditory closed-loop slow sleep oscillations can influence the anabolic GH/IGF-1 axis

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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