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Review

Sleep regulation and sex hormones exposure in men and women across adulthood

Régulation du sommeil et hormones sexuelles chez les hommes et les femmes au cours de la vie adulte

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ABSTRACT

This review aims to discuss how endogenous and exogenous testosterone exposures in men and estrogens/progesterone exposures in women interact with sleep regulation. In young men, testosterone secretion peaks during sleep and is linked to sleep architecture. Animal and human studies support the notion that sleep loss suppresses testosterone secretion. Testosterone levels decline slowly throughout the aging process, but relatively few studies investigate its impact on age-related sleep modifications. Results suggest that poorer sleep quality is associated with lower testosterone concentrations and that sleep loss may have a more prominent effect on testosterone levels in older individuals. In women, sex steroid levels are characterized by a marked monthly cycle and reproductive milestones such as pregnancy and menopause. Animal models indicate that estrogens and progesterone influence sleep. Most studies do not show any clear effects of the menstrual cycle on sleep, but sample sizes are too low, and research designs often inhibit definitive conclusions. The effects of hormonal contraceptives on sleep are currently unknown. Pregnancy and the postpartum period are associated with increased sleep disturbances, but their relation to the hormonal milieu still needs to be determined. Finally, studies suggest that menopausal transition and the hormonal changes associated with it are linked to lower subjective sleep quality, but results concerning objective sleep measures are less conclusive. More research is necessary to unravel the effects of vasomotor symptoms on sleep. Hormone therapy seems to induce positive effects on sleep, but key concerns are still unresolved, including the long-term effects and efficacy of different hormonal regimens.

Mots clés :
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RÉSUMÉ

L'objectif de cette revue est d'évaluer les effets de l'exposition exogène et endogène à la testostérone chez l'homme et aux estrogènes et à la progestérone chez la femme sur le sommeil. Les niveaux de testostérone sont maximaux lors du sommeil et la privation de sommeil supprime la testostérone. Peu d'études ont évalué les effets de la diminution de la testostérone avec l'âge sur les modifications de sommeil associées au vieillissement. Lors du vieillissement, les niveaux plus bas de testostérone seraient associés à une qualité moindre de sommeil et les effets de la privation de sommeil sur la testostérone seraient plus prononcés. Chez les femmes, les niveaux d'hormones sexuelles fluctuent lors du cycle menstruel et des étapes de la vie reproductive. Les modèles animaux indiquent que les estrogènes et la

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progestérone influencent le sommeil. La plupart des études ne montrent pas d'effet marqué du cycle menstruel sur le sommeil mais souvent avec un échantillon très petit ou un design expérimental non optimal. La grossesse et la période postpartum sont associées à des difficultés de sommeil mais leurs liens avec le milieu hormonal reste à déterminer. Finalement, la transition vers la ménopause s'accompagne d'une diminution de la qualité subjective du sommeil mais les études sur les variables objectives restent non concluantes. Le rôle des symptômes vasomoteurs dans la détérioration du sommeil lors de la ménopause devra également être déterminé. L'hormonothérapie semble améliorer le sommeil mais des questions cruciales restent à éclaircir, notamment les effets à long terme et l'efficacité des types offerts.

1. Introduction

Although sex hormones have received considerable attention in research, our knowledge of their relation to sleep is still limited. The objective of this review is to bring together results that demonstrate the link between sleep and the regulation of sex hormones over the lifespan of men and women. The review will focus mainly on the major sex hormones, namely testosterone in men and estrogens and progesterone in women, and describe how endogenous and exogenous exposures to these hormones interacts with sleep regulation throughout adulthood.

2. Factors contributing to endogenous sex steroid exposure

In women, biosynthesis in the gonads is stimulated by a cascade of hormonal events initiated in the brain at puberty and terminated at menopause, whereas in men, it is a lifelong process following puberty. In brief, the series of events begins in the hypothalamus, which releases gonadotropin-releasing hormones (GnRH) in a pulsatile fashion and stimulates the anterior pituitary to secrete two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn stimulate the secretion of gonadal hormones (estrogens and progesterone in women and testosterone in men). In women, sex steroids have positive and negative feedback effects on the secretion of LH and FSH. These closed-loop feedback systems create the cyclical process of the menstrual cycle with varying sex steroid levels depending on the phase of the cycle [1–3]. In men, sex steroids levels decline slowly and in a linear fashion with aging across adulthood [4,5]. On the other hand, female sex steroid levels are characterized during adulthood by a marked monthly cycle in addition to reproductive milestones such as menarche, pregnancy, breast-feeding, and menopause, all of which have a profound influence on endogenous sex steroid exposure.

3. Sleep and testosterone exposure in males

3.1. Sleep and testosterone in young men

It is widely accepted that testosterone secretion fluctuates throughout the day with blood concentrations peaking around wake time and falling during the day [6–8]. This circadian rhythm is accompanied by a shorter ultradian rhythm in which blood testosterone concentration oscillates every 90 minutes, reflecting its pulsatile secretory pattern [9]. However, results from one study suggest that the diurnal testosterone rhythm might be a sleep-related rather than a circadian-driven phenomenon [10]. Research from this study reported that in healthy young men, testosterone levels increased and reached peak concentrations during sleep, regardless of whether subjects slept during the day or night. In addition, testosterone levels decreased after waking from both daytime and nighttime sleep. In a series of studies, Luboshitzky et al. evaluated whether the rise of testosterone levels across the night was correlated with sleep architecture. The authors found that in young men, nocturnal testosterone rise begins at sleep onset, peaks around the time of the first REM-sleep episode, and remains heightened throughout the rest of the night [11,12]. They also showed that REM latency correlates with the slope of this testosterone rise (i.e. the rise was smoother when the REM latency was longer) [11].

Sleep restriction studies in animals and humans indicate that sleep disturbances induce changes in the gonadal endocrine axis, resulting in reduced levels of circulating testosterone. Recently, Wu et al. evaluated serum testosterone levels in adult male rats after 24 or 48 hours of total sleep deprivation (SD). Compared to control and sham groups, the sleep-deprived rats secreted significantly less testosterone regardless of the duration of SD [13]. These results also support findings from studies using selective REM-sleep deprivation in male rats, in which testosterone levels show a linear time-dependent decrease during a period of up to 7 days of REM-sleep deprivation [14,15]. Interestingly, an equivalent period of recovery sleep following REM-sleep deprivation does not necessarily restore testosterone to its baseline levels, which suggests that long periods of SD may lead to lasting adverse effects on sexual hormone regulation [14]. However, it is well-documented that SD induces stress response by increasing hypothalamus-pituitary-adrenal (HPA) axis activity, which has been shown to reduce testosterone production [16]. Therefore, the possibility that the testosterone reduction following SD might be related to an increase of HPA axis-related hormones, especially corticosterone in rodents, cannot be dismissed [14].

In humans, results from SD studies are, to some extent, in line with animal studies. In a recent study, the sleep of 10 healthy young men was restricted to 5 hours during 8 consecutive days, a condition experienced by at least 15% of the U.S. working population [17]. One week of sleep restriction led to a 10 to 15% decrease in daytime testosterone levels when compared with the levels found after a normal night of sleep [17]. A recent study also reported that compared with a normal sleep episode, daytime testosterone levels were lower after one night of total SD or after a 4.5-hour sleep episode restricted to the first half of the night [18]. However, the results also showed that daytime testosterone levels were not affected by two consecutive 4-hour sleep episodes restricted to the second half of the night, which is heavier in REM-sleep [18]. These data are supported by another study that observed no change in daytime testosterone levels after 5 nights of sleep restricted to the latter part of the night [19]. Taken together, research suggests that the timing, rather than the severity of sleep restriction, plays a pivotal role in daytime testosterone concentrations [18]. Nevertheless, extending sleep duration and avoiding SD should be further explored as behavioural modifications that may prevent sex hormone alterations in men. It is worth noting, however, that even though it is believed that testosterone