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CLINICAL REVIEW

The effects of testosterone on sleep and sleep-disordered breathing in men: Its bidirectional interaction with erectile function

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Summary As a major androgen with a key role in developing and maintaining male sexual characteristics, testosterone exerts a broad range of actions regulating several systems throughout human life. This article reviews data on the role of sleep in modulating endocrine release, as well as data on the effects of testosterone and androgen-replacement therapy on sleep architecture and breathing. This review also discusses the interaction of testosterone and sleep, with a particular emphasis on bilateral effects. Changes in nocturnal testosterone are sleep-related, with levels rising during sleep and falling on waking, whereas circadian effects are apparently marginal. Peak testosterone levels coincide with rapid-eye movement (REM) sleep onset. The decreasing sleep efficiency and numbers of REM sleep episodes with altered REM sleep latency observed in older men are associated with lower concentrations of circulating testosterone. The well-established male preponderance of sleep apnea suggests that sex hormones are involved in the pathogenesis of this breathing disorder. In addition, androgens are most certainly key players in the central and peripheral modulation of erectile function. Among other effects, sleep curtailment has been shown to lead to reduced levels of circulating androgens in healthy men and male rodents, and this highlights the biological significance of sleep homeostasis for endocrine regulation.

Abbreviations: ANS, autonomic nervous system; CNS, central nervous system; CPAP, continuous positive airway pressure; DHEA, dehydroepiandrosterone; EEG, electroencephalogram; FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; LPOA, lateral preoptic area; NREM, non-rapid-eye movement; OSA, obstructive sleep apnea; PRL, prolactin; REM, rapid-eye movement; SD, sleep deprivation; SHBG, sex hormone-binding globulin; SRE, sleep-related erections; SWS, slow wave sleep.

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Introduction

Androgens play a key role in the development of male secondary sexual characteristics. The three steroids of primary importance to male reproductive function are testosterone, dihydrotestosterone, and estradiol. From a quantitative standpoint, the most important androgen is testosterone, which was first characterized as the male sex hormone in the mid-1930s and is a major androgen crucial to the development and maintenance of male sexual characteristics. Over 95% of testosterone is secreted by the testicular Leydig cells. The testes also secrete small amounts of the potent androgen dihydrotestosterone and the weak androgens dehydroepiandrosterone (DHEA) and androstenedione. Researchers have described a number of biologic effects of androgens in males that are essential for appropriate differentiation of the internal and external male genital system during fetal development. Puberty involves androgen-mediated growth of the scrotum, epididymis, vas deferens, seminal vesicles, prostate, and penis, all of which require androgens in order to become fully functional.

Reproductive functions are regulated mainly by the hypothalamus, anterior pituitary, gonads, and reproductive tract. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which, on reaching the anterior pituitary, binds to the gonadotrophs and stimulates the release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH) into the bloodstream. In males, FSH induces spermatogenesis in the seminiferous tubules of the testes, and LH stimulates testosterone secretion by the interstitial Leydig cells. Testosterone promotes development of the male reproductive organs and elicits feedback from the hypothalamo-pituitary system inhibiting gonadotropin release. At puberty, most growth in testicular size is due to seminiferous tubular development in response to stimulation by FSH, with a smaller fraction of the growth due to Leydig cell stimulation by LH.

Variation in testosterone concentrations

In regulating various physiological systems throughout life, sex hormones exert a wide range of effects.[1] Testosterone concentrations change as a function of age. Major changes in the levels of reproductive hormones occur during puberty[2] as serum gonadal steroid concentrations gradually increase. In the course of aging, circulating testosterone concentrations in healthy men fall an average of 1–2% per year starting from the third decade of life.[3] Nevertheless, some octogenarians maintain androgen concentrations at the levels normally found in young adults.[4] The variability in hormone concentrations not only during a single individual's lifespan, but also between individuals, makes it difficult to distinguish between normal change (e.g., age-related deterioration) and abnormal change (e.g., accelerated decline).[1]

Aging is characterized by a progressive decline of virtually all physiological functions, including the secretory capacity of the endocrine glands.[5] After the age of 50, the overall testosterone concentration in men decreases at the rate of approximately 1% per year. Biochemical hypogonadism is observed in only about 7% of men under the age of 60, but is evident in over 20% of men over the age of 60.[6] Though this decrease in testosterone with age is well documented, men may not necessarily show symptoms of andropause.[1] A study of middle-aged men (40–62 yr) found that about 25% demonstrated low bioavailability of testosterone, and the figure was even higher in older men.[7] A detailed study by Pirke et al.[8] reported that testosterone and its precursors decreased in testicular tissue of elderly men. Overall, this research shows that the hormonal system undergoes profound changes with aging.

A better understanding of how the hypothalamo-pituitary-testicular axis evolves with age is of utmost importance from a scientific perspective, in order to elucidate the physiology of reproductive capacity. It is also important from a clinical perspective, in order to properly assess complaints such as loss of libido or diminished reproductive performance.[9,10] Androgen deficiency (or andropause) in aging males is a syndrome characterized primarily by six key clinical alterations[1]: diminishing sexual desire and erectile quality; loss of intellectual capacity; decreased lean body mass; alterations in body hair and skin; decreased bone mineral density; and increased visceral fat. Notably, testosterone is currently believed to be most responsible for all six alterations.

Testosterone and sleep

As a complex behavioral state occupying one-third of human life, sleep is often thought of as a passive condition, but it is in fact a highly active and dynamic process. Electrophysiological studies in the 1950s uncovered two main states of sleep, non-rapid-eye movement (NREM) and rapid-eye movement (REM) sleep. The lighter stages of NREM sleep (phases 1 and 2) come first and often

alternate with brief waking episodes before deeper NREM sleep stages set in. The deeper stages of NREM sleep (phases 3 and 4) predominate early in the night, but REM sleep appears at intervals of approximately 90 min. There are usually 4–6 of these sleep cycles each night, with REM sleep episodes becoming longer and NREM sleep shorter and lighter over the course of the night. NREM sleep is recognizable by its low frequency and high amplitude waves, as well as by the presence of sleep spindles on an electroencephalogram (EEG) and hypotonia on an electromyogram (EMG). During REM sleep, information acquired during waking hours seems to be reprocessed and integrated into existing neural templates.[11] The electrophysiological features of REM sleep include a wide range of un-synchronized EEG frequencies, the loss of EMG activity, and rapid-eye movement. The EEG shows intense cerebral cortical activity, and this distinguishes REM from NREM sleep; in fact, the similarity between EEG patterns during REM sleep and EEG patterns during wakefulness has led some to call the former ''paradoxical'' sleep.

Until recently, sleep was believed to be important primarily for restoring brain function, but there is increasing evidence that it also modulates metabolic and endocrine regulation, immune functions, and cardiovascular activities. In particular, sleep exerts important modulatory effects on most components of the endocrine system, not only on those of the hypothalamic-pituitary axis, but also on those controlling carbohydrate metabolism, appetite, and water and electrolyte balance.[12] The central nervous system (CNS), primarily via anterior and posterior pituitary hormones, is well established as a major factor in controlling endocrine regulation. The pituitary hormones show pulsatile, episodic secretion patterns that follow prominent circadian rhythms in several cases. In addition, their secretion patterns can be altered by neurochemical intervention from the CNS, such as in cases of stress. These relationships point out the importance of the CNS and of sleep in regulating endocrine function.[13] The impact of hormones on sleep has been studied extensively in humans, perhaps because methods such as frequent-interval blood sampling, sensitive assays of blood elements, and polysomnographic recordings can be more readily used with humans than with laboratory animals.

In healthy adults, reproducible alterations of essentially all hormonal and metabolic variables occur during sleep and at wake–sleep transitions.[11] Hence, understanding the influence of sex hormones on sleep is crucial for developing and testing theories of how sleep is regulated. Receptors for sex steroids, such as estrogens, progestins and androgens, have been identified in the brain of several species, including fish, birds, reptiles, and mammals.[14] Male–female differences in sleep characteristics may be partly explained by different concentrations of their sex hormones.

The aim of the present article is to review circadian testosterone changes, their specific role in normal sleep and breathing, and the effects of disrupted sleep on hormonal levels. Testosterone has been the focus of several research and review studies in males, but few have addressed its interaction with sleep. Further knowledge of this relationship is not only important for understanding the basic physiology of sleep, but it may also shed light on the causes of certain health problems associated with sleep disorders, aging, and shift work.[15]

Nocturnal sleep is characterized by a specific pattern of hormonal secretion,[16] and although a great deal has been learned about the secretion patterns of hormones, very little is understood about the physiological and metabolic significance of their pulsatile, episodic release, their unique circadian and ultradian rhythms, or their relationship to sleep–wake cycles and to the different stages of sleep.[13] The diurnal rhythm of testosterone can already be identified in 4–5-yr olds.[17] Healthy adult men show a different pattern, with testosterone concentrations peaking around waking time and falling during the day.[18] This pattern is often referred to as a circadian rhythm, despite the fact that disturbed sleep reduces or blunts the nocturnal rise of testosterone.[19,20] For instance, the overall diurnal rhythm of testosterone peaks around 08:00 h and enters a trough around 20:00 h.[21,22] Most study protocols have investigated relatively short periods, few of them extending more than 12 h, and consequently we have little knowledge of the relative weights of sleep and circadian regulation. Recent research[15] has sought to determine whether testosterone is driven by a circadian rhythm-independent sleep effect. Seven healthy young men had their sleep period acutely shifted to daytime and were subjected to a 24-h sampling regimen. Results showed that 24-h mean testosterone concentrations did not differ between night-sleep and day-sleep conditions, but did vary over time. Furthermore, maximum hormone concentrations always occurred during sleep, regardless of the individual or the experimental conditions. This study reported that testosterone in young men rises during daytime sleep as it does during nighttime sleep, but the level falls on waking, thus confirming that

sleep, rather than a circadian rhythm, is critical for testosterone regulation.[23] Healthy young men show comparable blood testosterone levels during sleep regardless of when they choose to sleep during the day, as long as they manage to sleep for the same duration.[15]

Several studies have indicated a relationship between testosterone releases and sleep stages, although the data are conflicting. Nocturnal testosterone rhythm is related to deep sleep[24] and REM/NREM cycles.[23] Peak testosterone levels coincide with the onset of REM sleep.[25,26] Indeed, the sleep-related rise in testosterone levels in young men is associated with the start of the first REM sleep episode of the night.[19] In 1971, Evans et al.[25] reported that while REM sleep does not trigger the production of testosterone, there is likely to be a link between the neurophysiological state underlying REM sleep and the mechanism regulating the production of testosterone. However, baseline concentrations of testosterone have been shown to be highest in the later hours of the sleep period, when the overall amount of REM sleep is maximal.[13,19] Similarly, Luboshitzky et al. found that the rise in testosterone in normal young men during continuous nocturnal sleep began at sleep onset and reached a plateau around the time of the first REM sleep episode 90 min later.[19,27] Hourly testosterone concentrations were lower when subjects were awake (19:00—22:00 h) than when they were asleep (23:00—07:00 h). Furthermore, the testosterone curve during the initial sleep period closely correlated with REM sleep latency, but not with other sleep stages.[27]

What hormone could link REM sleep and testosterone levels? LH is considered to be the pituitary hormone that stimulates testosterone release by the testis, but its secretion during sleep bears little or no relation to REM sleep. Therefore studies have sought to identify the hormone(s) controlling testosterone release in healthy men. Several factors may influence the normal diurnal rhythm of testosterone secretion. Recently, Walton et al.[28] examined the 24-h hormone profile of healthy men (testosterone, inhibin B, LH, FSH, and cortisol) under control conditions or during administration of testosterone together with etonogestrel to suppress gonadotrophin secretion. The results showed a diurnal variation in serum testosterone in normal subjects, with a mean peak in the morning at 07:00 h and in LH at 05:00 h. Inhibin B concentrations showed marked periodicity and synchronized diurnal variation with a mean peak in the early afternoon in the treated group but not the control group. As observed by the authors, these data suggest that even without LH stimulation there is a diurnal variation in testicular steroidogenesis, and that under both normal and suppressed states there is a diurnal variation in Sertoli cell function. Other studies reported that mean LH concentrations did not vary over the 24 h period in either young or elderly men,[29] whereas testosterone rhythm was positively correlated with serum inhibin B rhythm, with the levels of both being higher in the early morning and lower in the evening.[30] In pubertal boys, sleep-related LH elevations are common[31,32] but only 15% of adult men have sleep-related LH elevation,[32] and so there is no clear circadian rhythm.[31] These data indicate that at best, LH may only partially control the robustly secretion rhythm of testosterone.[19,33]

Rubin et al. conducted a series of studies on the interrelations of plasma LH, FSH, prolactin (PRL), and testosterone during sleep in normal young adult men.[13,34] Baseline LH and FSH concentrations did not change during the night, whereas PRL and testosterone did show similar patterns of increasing concentrations over the course of the night. These findings suggest that LH and PRL, more so than FSH, are both relevant for the nocturnal synthesis and release of testosterone.[13]

Other major factors that have been implicated in the amplitude of rhythmic testosterone release include increasing saturation of the binding proteins following a surge in testosterone production and changes in protein concentration related to postural changes.[35] The findings suggest that the rise in cortisol concentrations in the early morning due to competition with testosterone for albumin-binding sites might be responsible for the diurnal testosterone rhythm.

While diurnal variation of testosterone in young men is generally accepted, the concept of seasonal variations remains controversial.[36—38] For instance, hormone concentrations were reported to be lower in summer than in winter in Tromsø, located at a latitude of 69.65°N.[38] The likeliest explanation is that at this latitude, sleep is shorter in summer,[39] often resulting in a longer wake span before samples are taken.[40] Indeed, reduced testosterone concentrations after waking indicate that time spent awake is as relevant a factor as time of day. According to Axelsson et al.[15] sleep duration, sleep quality, and time between waking and sampling should be measured when determining testosterone concentrations.

An interesting example is Ramadan, when Muslims refrain from eating and drinking from sunrise until sunset. With intake restricted to nighttime, sleep onset is later, sleep duration is reduced, and there are alterations in behavioral

and social habits that may result in phase delays in many biological rhythms. Researchers found that Ramadan did not modify the 24-h mean concentration of testosterone, but did delay the onset of the increase.[41,42]

It is well documented that androgen production in men declines with age,[4] resulting in decreased concentrations of both total and bioavailable testosterone.[43] A number of symptoms are associated with decreasing androgen concentrations. Not all of these are directly related to decreased androgens; some may be the result of decreased levels of products derived from androgens. Testosterone levels vary significantly between individuals.[44] Hence, the broad range of available testosterone preparations should not be used indiscriminately, but they should be applied to specific patients, taking into account their normal levels.[45]

Circadian rhythms of serum testosterone concentrations observed in young men were attenuated in elderly men, and their mean testosterone concentrations over a 24-h period were lower.[33,46] For instance, Liu et al.[33] examined testosterone secretion in older and young men in response to near-physiological LH stimulation, and found that healthy older men fail to achieve their younger counterparts' testosterone concentrations when exposed to pulsatile LH stimulation and concomitant suppression of LH secretion with a selective GnRH receptor antagonist. Various studies have investigated nocturnal LH—testosterone rhythms in elderly men by measuring hormone concentrations over a 24-h period.[46] A central mechanistic issue in human male reproductive aging is whether low-amplitude and disorderly pulsatile LH secretion in older men is an intrinsic neuroregulatory anomaly or a secondary neuroendocrine response to partial androgen deficiency. Further clinical investigation is needed to address this important question and to link it to testosterone levels.

The process of aging commonly affects sleep architecture, which becomes increasingly fragmented by arousals and awakening episodes, sometimes leading to poor sleep maintenance and consolidation, and shorter overall sleep time.[4,47] These effects are similar to those observed with lower testosterone concentrations, which are associated with a decrease in sleep efficiency, a lower number of REM sleep episodes, and altered REM sleep latency.[23] As recently stated by Penev,[4] a precise understanding of the biological significance and clinical implications of variable androgen decline in older men[48] may therefore benefit from studies into how sleep and aging relate to this process.

Testosterone was one of the first drugs to be marketed, and it has been in clinical use for decades primarily as a safe and effective replacement therapy for androgen-deficient men. Moreover, testosterone and synthetic androgens have long been used pharmacologically to obtain specific anabolic or other effects in non-androgen-deficient men with chronic disease.[49] Research on patients with relevant clinical syndromes has examined the effects of gonadal steroids on circadian regulation and on the sleep—wake cycle, but interpreting the results has not been straightforward because of difficulties in determining causality, the variability of gonadal steroid concentrations, and the use of nonrepresentative test subject populations.[50]

We have recently seen a dramatic increase in androgen abuse, with illicit self-administration of massive doses for non-medical purposes in power sports and body building. This procedure has been associated with a range of symptoms, including sleep disorders, and it constitutes a significant public health problem. Reductions in total sleep time, sleep efficiency, percentage of NREM sleep, and increased stage 2 sleep have been reported.[51]

Genetic or acquired disorders of the hypothalamus, pituitary, or testis resulting in androgen deficiency are a principal clinical indication for androgen-replacement therapy.[49] Testicular testosterone production may be reduced by gonadotrophin deficiency or Leydig cell dysfunction. In androgen-replacement therapy, testosterone is used at doses designed to reproduce endogenous blood testosterone concentrations and physiological exposure of tissues to androgen.[49] There is substantial interest in using such androgen supplements to improve body composition, muscle and bone strength, and physical function in older men.[29,51,52] Many testosterone products with widely varying pharmacological features are now available to provide effective androgen-replacement therapy.[44] In a randomized, double-blind study, Liu et al.[51] recruited 17 healthy men over the age of 60 and administered three injections of high-dose intramuscular testosterone esters or matching oil-based placebo at weekly intervals, followed by an 8-week washout, and then switched to the other treatment. The results indicated that at supraphysiological doses, testosterone therapy can shorten time slept. Even though previous studies have been inconsistent on the effects of testosterone therapy on sleep patterns,[50] this study raises safety questions about the use of these preparations for older men trying to reverse or remediate clinical symptoms most probably associated with the hypogonadism of aging.

Testosterone treatment should only be administered after carefully evaluating the potential risks and benefits specific to the patient.[1] Both the risks and benefits of testosterone treatment in older men with only age-related functional decreases in blood testosterone differ considerably from those pertaining to younger men with gonadal disorders.[49]

As mentioned previously, testosterone concentrations start to rise with sleep onset and then reach a plateau at REM sleep onset approximately 90 min later. This pattern in serum concentration is similar to that of melatonin.[53] In fact, it has been suggested that melatonin exerts its antigonadal effects at least partly by directly inhibiting testosterone production.[54] The interaction between melatonin and testosterone in normal and hypogonadal men has been studied with polysomnography,[55,56] and researchers found that hypogonadism alters melatonin secretion in males. In hypogonadism associated with an excess of GnRH, melatonin concentrations are lower than in age-matched controls, while hypogonadal males associated with deficient GnRH exhibit high melatonin levels.[57] Interestingly, testosterone replacement normalizes both situations.[55,56]

Testosterone and sleep breathing disorders

Respiration as a vital function is not regulated by specific hormones, but is influenced by a wide range of hormones.[58] Current evidence suggests that hormones work through several mechanisms to help regulate breathing: some, such as testosterone, may stimulate breathing directly at the level of the CNS or peripheral chemoreceptors, while others indirectly affect breathing by altering the metabolic rate.[58] The observed links between sex hormones and sleep-related breathing supports the notion that even when present within normal ranges, these hormones play an important role in sleep disorders.[59]

The main breathing disorders associated with sleep are obstructive sleep apnea (OSA), central sleep apnea, and hypoventilation. OSA is an upper airway respiratory disorder of varying severity affecting approximately 5—7% of the adult male population.[60] In fact, this common disorder, which affects the vital functions of respiration and circulation, has major consequences for the endocrine system. For example, much research interest has focused on the relationship between OSA and sexual dysfunction.[61]

Testosterone is reported to increase the ventilatory response to hypoxia in hypogonadal men, which may cause or exacerbate sleep apnea by driving CO_2 below the apnea threshold.[62] However, androgen blockade does not affect sleep apnea or chemosensitivity.[63] Few studies have examined the influence of testosterone on upper airway resistance during sleep, or the impact of nocturnal apneic events on the reproductive system.

The well-established male preponderance of OSA suggests that gonadal hormones are involved in the pathogenesis of this breathing disorder.[64,65] For instance, decreased morning testosterone concentrations were reported in male apneics,[66,67] though this result may also have been related to the subjects' abdominal (visceral) obesity.[5] Although other studies indicate an association between sleep apnea and decreased testosterone release in the absence of complications,[67] it is clear that in obese patients suffering from OSA, the severity of hypoxia may be an additional factor in the reduction of testosterone levels, regardless of body mass index and abdominal fat distribution.[68] This suggests that both OSA and coexisting comorbidities contribute to low testosterone concentrations.

Testosterone may inhibit breathing via several mechanisms, since upper airway patency is determined by many structural and neuromuscular factors controlling pharyngeal airway size and collapsibility.[51] In 1994, Cistulli et al.[69] demonstrated that testosterone was associated with an increase in upper airway collapsibility during sleep, and that this may be the mechanism by which testosterone induces or exacerbates OSA. A number of mechanisms have been proposed to explain this effect. It has been postulated that the anabolic effects of testosterone may reduce the dimensions of the upper airway, making it more vulnerable to closure during sleep.[69] Other studies have not supported this hypothesis, although an increase in supraglottic resistance was reported in one case of a woman receiving testosterone.[70] It therefore seems unlikely that a reduction in airway dimensions is the dominant mechanism involved. Cistulli et al.'s study[69] suggested an influence on neuromuscular control of upper airway patency during sleep.

Apneic males with severe desaturation exhibited delayed peak testosterone concentrations.[71] Men with severe OSA show significantly reduced serum concentrations of free and total testosterone and of sex hormone-binding globulin (SHBG), though their LH levels are normal.[67] This endocrine abnormality was reversed after 3 months of continuous positive airway pressure (CPAP) therapy.[67] However, in another study, normal concentrations of testosterone were reported in patients with moderate to severe sleep

apnea, and these remained unchanged over 7 months of CPAP treatment.[72] The discrepancies between these findings may be related to the degree of severity of OSA, to the unchanged SHBG levels that could explain the unchanged testosterone levels,[72] or to the inconsistent duration of CPAP treatments.

Altogether, these data suggest that OSA in middle-aged men is associated with reduced androgen secretion. This is jointly caused by obesity and aging, with hypoxia and sleep fragmentation as additional contributing factors in decreasing pulsatile testosterone concentrations in these patients.[73]

A marked reduction in time slept after testosterone administration was observed by Liu et al.[51] Furthermore, testosterone raises the nocturnal metabolic rate,[74] which can impair sleep quality.[75] The fact is that both high and low circulating testosterone concentrations may be associated with sleep disturbances. It is therefore appropriate to keep in mind the work of Saaresranta and Polo[58] on the interactions between hormones and breathing, which provides new perspectives on novel pharmacological therapies for breathing disorders, and which challenges us to intensify research investigating how the endocrine system influences breathing control in health and disease.

Testosterone changes after sleep deprivation (SD)/sleep restriction

The hectic lifestyles humans have been obliged to follow in recent decades have affected sleep quality, causing an increase in sleep disorders. In industrialized societies, regular exposure to artificial light and the availability of social activities at all hours of the day, coupled with social and economic pressures, result in less time spent asleep, which lies at the heart of the plethora of sleep-related disorders. Indeed, chronic sleep loss is increasingly common in industrialized societies and it affects about 45% of adults.[75] Normal average sleep duration has decreased from 8.0 to 8.9 h per night in 1960[76] to about 6.9—7.0 h in 2000—2002.[77] This sleep impairment may result from various common sleep disturbances, such as insomnia and apnea, and can lead to striking alterations in metabolic, endocrine, and immune functions.[78,79]

The most commonly observed pattern of irregular sleep—wake schedules is to shorten sleep time during a working week, accumulate a sleep debt, and then compensate for the deficit by sleeping longer on weekends. During these ''catch up'' nights there is high sleep efficiency, short sleep latency, and an increased duration of stage 3 and 4 NREM sleep. But waking at a later time in the morning causes a phase delay the following day, which is often followed by an earlier wake up time at the start of the work week. Thus, sleep duration is substantially less, and SD resumes.

The concept that modern society is chronically sleep deprived has recently received wider acceptance. Many researchers have begun to look at the repercussions of sleep loss across broad physiological and systemic mechanisms. Despite the growing literature on the topic, much remains to be understood about the chain of physiological events underlying SD.[80] For instance, sleep loss is considered to be a health risk factor that contributes to several disease processes,[81] reduces longevity,[76] and leads to behavioral[82—87] and hormonal[78,88—90] alterations.

The endocrine system integrates the physiology of multiple organs through the actions of the endocrine axis. Hormonal effects are determined not only by the levels of hormones in circulation, but also by when a specific organ is exposed to a specific hormone. Studies have shown that SD induces changes in the endocrine axis. It causes a reduction in circulating androgens in healthy men[92] and in healthy medical interns.[93] In our laboratory, we have consistently observed decreased concentrations of testosterone in sleep-deprived male rats. For instance, SD induced decreased estrone levels and increased levels of progesterone, PRL, corticosterone, and catecholamines after 4 days of SD in male rats.[94] Because SD induces such profound changes in secretory patterns in distinct endocrine axes, the investigation of hormone secretion could provide some insight into the physiological and metabolic events related to SD.[91]

There is consistent evidence that shift work, or night work, heightens the risk of developing both psychological[95] and physiological[96] health problems. Axelsson et al.[97] compared major anabolic and catabolic hormones in shift workers, and found that dissatisfied shift workers had lower morning testosterone levels than satisfied ones. Furthermore, low testosterone concentrations were associated with greater sleep need, disturbed sleep/wakefulness, and an increased need for recovery after the work period. In fact, the need for recovery proved to be the best predictor of testosterone levels.

During military operations involving prolonged physical and psychological stress, SD lasts several days and androgen levels fall by 70—90%.[98] An androgen decrease of this magnitude cannot be

explained solely by a halt in testicular secretion, since the testis releases only a fraction of the DHEA, androstenedione, and 17a-hydroxyprogesterone circulating in the blood. Rather, it would appear that a halt in both testicular and adrenal androgen secretion is the cause.

More recently, it has been suggested that accumulated SD may be a major contributor to adverse changes in the levels of hormones including testosterone in overtrained recruits.[99] In addition, data indicate that experimental fragmentation of sleep *per se* in young adults disrupts the usual rise of blood testosterone levels during the night.[19] These endocrine changes may have negative effects on health, since in the event of sustained physical exertion and caloric and sleep restriction, it is the endocrine system that acts to maintain the metabolic processes needed for tissue repair, regeneration, and recovery.[100]

On its own or in conjunction with exercise or stress, SD alters circulating androgen levels. This highlights the biological significance of sleep homeostasis for normal endocrine regulation. A rapidly growing body of evidence suggests that chronic partial sleep loss has become increasingly prevalent during the last few decades[101] and has led to endocrine dysregulation in many people. Such sleep disturbances may have long-term adverse effects on overall health,[102] particularly on the metabolic and cardiovascular systems.[103]

Sleep-related erections (SRE)

Several studies have provided evidence for a critical role of androgens in maintaining the erectile response in mammals. However, stimulated erections in wakefulness occur by different mechanisms from spontaneous erections during sleep. The CNS oversees sleep transitions and coordinates sleep-associated neurogenic reflexes in men, such as sleep penile tumescence. As early as 1944, almost a decade before the classic description of REM sleep, Ohlmeyer et al.[104] noted the occurrence of penile erection cycles during sleep in adult males.[105] These SRE appeared at 85-min intervals and had an average duration of 25 min.[104] Oswald[106] noted that erections accompanied some REM sleep periods, but subsequent work by Fisher et al.[107] and Karacan et al.[108] demonstrated a strong temporal association between the occurrence of erection and REM sleep. Fisher et al. found erectile episodes to be present in over 95% of REM sleep periods but absent entirely from NREM sleep, except immediately before and after REM sleep periods.[107] Similarly, Karacan et al.[108] reported that 80% of REM sleep periods conformed to this pattern, but they observed occasional erections during NREM sleep.

Penile tumescence cycles in sleep occur in all normal healthy males from birth through adulthood and into old age,[109–111] regardless of dream content.[112] For instance, by studying males from 3 to 79 yr of age, Karacan et al.[113] determined that there is a rapid decrease in total sleeping time throughout the teen years, with no significant change from 20 to 50 years of age. Total REM sleep time decreases throughout the preteen and teen years and remains stable in subsequent years at approximately 100 min per night. Total penile tumescence time decreases from age 13 through age 79. Tumescence time during these years is approximately 90 min per night, or 20 percent of total sleep time. The increase in total penile tumescence time during the prepubertal and very early pubertal years is associated with an increase in NREM-related tumescence as REM sleep decreases. In addition, there is a steady albeit slight decline in REM-related erections from age 20 to 70 with an associated increase in NREM-related erections. In the 20- to 29-yr-old population, the average length of an SRE episode is 38 min, whereas the average length of the SRE episode is 27 min in the 61- to 67-yr-old population. Not all SRE[a] episodes are associated with a full erection, and in fact the incidence of partial erections increases during SRE with advancing age.[114]

The consistency and persistence of this involuntary phenomenon in healthy males, despite ontogenetic changes, together with the autonomic nature of penile tumescence in sleep, led researchers to begin monitoring and recording SRE as the first and probably still one of the best methods for assessing organic impairment of erectile capacity.[115,116] Since SRE alterations may reflect abnormalities in the vascular, neurological, or hormonal systems, monitoring is a useful diagnostic tool for patients complaining of erectile disorders[116] and has been used as a clinical tool to differentiate ''psychogenic'' from ''organic'' impotence.

Monitoring of sleep-related erections

The notion that erections during REM sleep provide insight into the pathophysiology of the erectile

[a] Sleep-related erections (SRE) are also commonly referred to as nocturnal penile tumescence, but the inclusion of ''nocturnal'' in this term is misleading since these erections may occur during daytime naps.[117]

system makes a number of assumptions: (1) potent men should have an SRE pattern within a certain range, as measured by penile erection PE number, duration, and relation to sleep stages[118]; (2) a group of impotent men with a pathophysiology that might be expected to impair potency (e.g., diabetes), should have fewer SRE than normal men[119]; (3) impotent men with abnormal SRE should benefit from correcting identifiable contributory physiological deficits, e.g., revascularization[120]; (4) impotent men with normal SRE should have distinct psychological profiles[121] and respond to behavioral or psychiatric treatment for impotence; and (5) psychological factors should not produce impaired SRE patterns similar to those seen in organic impotence if sleep patterns remain intact.[122,123]

SRE monitoring has been used for decades as a first means of differential diagnosis, based on the premise that if men had normal SRE, then erectile physiology could be assumed to function normally, and failure to have an erection with a sexual partner could generally be assumed to be psychogenic. However, the occurrence of normal SRE only demonstrated the erectability of the penile corpora and the normality of proerectile function in the related peripheral nerves and spinal cord.[117] From the evidence reviewed above, there may well be organic dysfunction in various areas of the brain that could affect erection in some contexts while leaving SRE undisturbed.[117]

Although more than half a century has past since the discovery of penile erections cycles during sleep, their neural mechanisms largely remain unexplored. Elucidation of both sleep-related and waking-state erectile mechanisms is essential for diagnosis and treatment of the etiologies of impotence.

Mechanisms of sleep-related erections

Much has been speculated about erectile control during REM sleep since its discovery. In 1972, Karacan et al.[110] suggested that the neural mechanisms of both REM sleep and REM-related erections are not completely interdependent, given the variable onset of tumescence relative to REM sleep and the occasional occurrence of erection during NREM or slow wave sleep (SWS). While investigating penile erection events during sleep in rats, Schmidt et al.[124] also speculated that REM sleep mechanisms are not always linked functionally to neural systems controlling tumescence because erections were observed in only 30% of REM sleep episodes in rats, but in 80—95% of REM sleep episodes in humans.[107,108] This contrasts with other tonic and phasic events such as muscle atonia and REMs, which occur during every REM sleep episode.

The role of the autonomic nervous system (ANS) in SRE control has also been investigated, since the pattern of ANS activity during REM sleep changes with respect to SWS and wakefulness. Relative to SWS, REM sleep is associated with a general increase in parasympathetic activity and a decrease in sympathetic tone.[125] It has thus long been assumed that tumescence during REM sleep is the result of these associated autonomic changes.[112] The function of the ANS in erectile control during REM sleep, however, is unknown and understanding it is complicated by the fact that the two autonomic divisions show highly variable activity within and across species, and by the fact that autonomic activity during REM sleep can show changes in phase, which may have variable effects (parasympathetic vs. sympathetic) depending on the effector organ involved.[125]

It is commonly assumed that REM-related erections result from a decrease in descending erectile inhibition.[124,126] Reflex activation of local spinal erectile mechanisms is thought to be associated with this disinhibition. This assumption may have arisen historically because of the clinical appeal of SRE testing, in which ''psychogenic'' impotence is detectable as normally occurring erections during sleep, when psychological inhibitory influences are minimized. Although it is well established that the spinal generator controlling erections is under a tonic descending inhibition during wakefulness,[127] the level of inhibitory control during sleep remains to be explored. Finally, it is not known whether merely removing a descending inhibition suffices to produce erections. Many structures extending from the brainstem reticular core to the cortex become active during REM sleep, and several studies have suggested that SRE control may also involve a descending activation or excitation.[112]

New animal models for SRE research have contributed to our understanding of SRE neurophysiology. The new technique of chronic erectile recording in rats proposed by Schmidt et al.[124] provided the first opportunity to examine SRE mechanisms and answer fundamental questions regarding REM-erectile control. These researchers performed neural transections to elucidate the effects of paraplegia on REM-related erection and to determine the brain level at which mechanisms underlying REM-erectile activity are generated. They found that mesencephalic transections disrupt REM-erectile activity even though REM sleep remains otherwise qualitatively intact,[124]

thus suggesting that forebrain structures rostral to the trans-section are required to produce REM-related erections. As an extension of these findings, the same group investigated the role of the preoptic area since it is implicated in both sleep generation and copulatory mechanisms, suggesting that it may be a primary candidate for REM-erectile control. Lesion analysis revealed that the candidate structures for REM-erectile control include both the lateral preoptic area (LPOA) and ventral division of the bed nucleus of the stria terminalis; however, LPOA lesions were the most effective in disrupting REM-erectile activity and resulted in long-lasting insomnia, characterized by a significant increase in wakefulness and a decrease in SWS.[128] REM sleep architecture and waking-state erections remained unchanged after the lesion. These data identify LPOA as essential in both REM-related erectile mechanisms and SWS generation. Moreover, erectile mechanisms appear to be context-specific because LPOA lesioning selectively disrupted REM-related erections but left waking-state erections intact.

Finally, the function of penile tumescence in sleep remains an enigma. One may speculate that repetitive nocturnal erections from infancy to old age potentially play a role in both the development and maintenance of erectile neural circuitry from the end organ to supraspinal levels, as well as perhaps in the daily activity of skeletal perineal muscles essential for penile rigidity. Given the unpredictable nature of mating opportunities for many species, it is tempting to hypothesize that daily SRE activity from birth would confer a reproductive advantage in generating an erection relative to a competing male who may have never produced a erection before his first sexual encounter.[129] These are some of the factors that make SRE one of the more fascinating and enduring areas of sleep research.

Sleep-related erections and testosterone

As mentioned previously, peak testosterone concentrations coincide with REM sleep onset.[25,26,130] This makes it particularly attractive to study the association between testosterone levels and SRE.

Diminished SRE and rigidity are found in androgen-deficient hypogonadal men, whereas testosterone replacement leads to significant SRE improvement,[131–133] indicating that SREs are androgen-dependent.[134] In fact, exogenous testosterone significantly increases the frequency of masturbation and sexual activity and enhances the rigidity of SRE in normal men and in hypogonadal men.[135] It also increases the number of SREs but does not modify responses to audiovisual sexual stimulation.[133] Androgens like testosterone are not the only determinants of SRE, however. While androgen reduction does adversely affect SRE, it does not eliminate SRE even after a 12-week trial in healthy young men, supporting the assumption that androgens play a relevant, but not all-determining role in SRE.[26]

Granata et al.[134] proposed to identify a possible threshold for a serum testosterone level below which SRE are impaired. They studied 201 men, including hypogonadal and eugonadal subjects. The group of individuals with higher testosterone showed higher values for erectile parameters than the subjects with lower testosterone levels, without any significant difference within the group having normal testosterone levels. These results are in agreement with those of Buena et al.[136] who found no significant differences in sexual behavior or SRE between individuals with serum testosterone at either the low or high ends of the normal male range. Together, these studies confirm previous reports suggesting an important role for androgens in SRE.

Recently, Montorsi and Oettel[137] reviewed the effects of testosterone on SRE. They concluded that erectile response to tactile or visual erotic stimuli in wakefulness is almost independent of androgen, although it may be influenced by androgen-sensitive mechanisms to some degree. Androgens are most certainly key players in the physiology of nocturnal erections, and the widespread use of testosterone should stimulate further investigations in this field.[137]

Studies involving oral drugs for erectile dysfunction may also be used to examine the control of central erectile pathways and their putative role in other aspects of sexual response. Foresta et al.[138] examined the possible influence of circulating androgen and apomorphine or sildenafil on the regulation of sexual function. Administering 3 mg of apomorphine and 50 mg of sildenafil had no effect on erectile function of men with severe hypogonadism, whereas long-term testosterone treatment brought SRE and other penile parameters back into the normal range. These findings suggest that testosterone plays a key role in the central and peripheral modulation of erectile function, although the precise threshold for testosterone concentrations that may affect these processes remains to be elucidated.[110] More recently, the administration of sildenafil in hypogonadal men with very low testosterone levels improved SRE, suggesting that nitric oxide pathways can be pharmacologically enhanced even at low testosterone concentrations.[139]

Finally, SRE is not significantly affected by external factors (e.g., embarrassment, anxiety, psychological correlates), which may interfere with erections when studied in awake subjects.[140] Because they are the most androgen-dependent type of erection in men, SRE provide a ''gold standard'' for examining the effects of sildenafil and testosterone on penile function.[134] However, caution should be exercised, since a 50 mg dose of sildenafil in apneic patients at bedtime exacerbates respiratory and desaturation events,[141] which in turn contributes to erectile dysfunction.

Concluding remarks

Testosterone is the major circulating androgen in the male. In addition to regulating male sexual function, it plays a role in many other processes in the body. The pulsatile secretion patterns of certain hormones like testosterone suggest that the CNS helps to regulate sleep through the endocrine system. Studies have shown that testosterone levels rise during sleep and fall during waking, whereas circadian effects appear to be marginal. Furthermore, rising nocturnal testosterone levels coincide with the onset of REM sleep.

The mystique of testosterone as a sex hormone encoding the virile properties of masculinity attracts male drug users. As a therapeutic drug, testosterone is widely used; sales have risen 20-fold in the US since 1990.[142] It can be both overused and underused; in both cases, sleep is affected, and in particular, waking time increases. Illicit use of massive doses of testosterone also disrupts sleep architecture. Furthermore, male preponderance of OSA, coupled with reports that testosterone administration can lead to OSA, suggests that androgens play a role in the pathogenesis of this sleep-related breathing disorder.

The noticeable reduction in average sleep time in the general population over the last few decades has had adverse effects. SD results in a constellation of generalized symptoms leading to alterations in catecholamine, hormone levels, and behaviors. In particular, sleep loss has been associated with altered regulation of the hypothalamic-pituitary-adrenal axis, and it impairs gonadal function by producing a marked reduction in testosterone concentration. Subnormal testosterone concentrations may contribute to sexual inadequacy in humans, which may affect established or desired sexual relations. Although progress has been made in our understanding of interactions between the endocrine system and sleep, further studies are required to examine the bidirectional effect of testosterone on sleep in different age-groups, and the role of sleep or SD on androgen function. This review has sought to outline the different actions of testosterone on sleep.

Practice points

Testosterone is a hormone involved in different behaviors and physiologic processes such as erectile quality and sleep. Recently, findings have suggested that there is a bidirectional relationship between testosterone and sleep disorders:

1. There is a relationship between testosterone release and progression through sleep stages: androgen abuse has been reported to lead to reductions in total sleep time, in sleep efficiency, and in percentage of NREM sleep, as well as to an increase in stage 2 sleep.
2. Sleep deprivation induces alterations in the endocrine axis, reducing circulating androgens in men. It has also been suggested that accumulated sleep loss may be a major contributor to adverse hormonal changes.
3. The male preponderance of sleep apnea and its exacerbation by androgen treatment suggest the involvement of testosterone.
4. Androgens play a key role in sleep-related erections.

Research agenda

1. Better comprehension of the crucial relationship between the regulation of testosterone and sleep should provide a much needed basis for future investigation. In-depth knowledge of this interaction is not only of theoretical interest, but may also contribute to our understanding of the underlying causes of certain health problems associated with sleep disorders, aging, and shift work.
2. Research conducted on new animal models and the development of techniques to record sleep-related erections have contributed to our understanding of fundamental questions regarding the neurophysiology of REM-erectile control.

3. Additional studies of the role of sleep and of age-related changes in older men may contribute to our understanding of the biological significance and clinical implications of variable androgen decline.
4. The decrease in testosterone concentrations observed in apneic men points to another alarming consequence of sleep apnea. Reversal of this effect through CPAP treatment should be highlighted.
5. Though androgens are already widely investigated for their role in controlling male sexual behavior, their role in sleep-related erections should be studied in well-controlled clinical trials.

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References

1. Heaton JPW. Hormone treatments and preventive strategies in the aging male: whom and when to treat? *Rev Urol* 2003;**5**:S16—21.
2. Turek FW. Gender (sex) and sleep: shh…not in front of the children. *Sleep* 2006;**29**:21—2.
3. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachussets male aging study. *J Clin Endocrinol Metab* 2002; **87**:589—98.
*4. Penev PD. Association between sleep and morning testosterone levels in older men. *Sleep* 2007;**30**:427—32.
5. Gooren L. Androgen deficiency in the aging male: benefits and risks of androgen supplementation. *J Steroid Biochem Mol Biol* 2003;**85**:349—55.
6. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapuetics implications. *Endocr Rev* 2005;**26**:833—76.
7. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 2000;**49**:1239—42.
8. Pirke KM, Sintermann R, Vogt HJ. Testosterone and testosterone precursors in the spermatic vein and in the testicular tissue of old men. Reduced oxygen supply may explain the relative increase of testicular progesterone and 17 alpha-hydroxyprogesterone content and production in old age. *Gerontology* 1980;**26**:221—30.
9. Pincus SM, Mulligan T, Iranmanesh A, Gheorghiu S, Godschalk M, Veldhuis JD. Older males secrete luteinizing hormone and testosterone more irregularly, and jointly more asynchronously, than younger males. *Proc Natl Acad Sci USA* 1996;**93**:14100—5.
10. Veldhius JD. Recent neuroendocrine facts of male reproductive aging. *Exp Gerontol* 2000;**35**:1281—308.
11. Jouvet M. Paradoxical sleep as a programming system. *J Sleep Res* 1998;**7**:1—5.
12. Van Cauter EV. Endocrine physiology. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 4th ed. New York: WB Saunders Co.; 2005. p. 266.
13. Rubin RT, Poland RE. Synchronies between sleep and endocrine rhythms in man and their statistical evaluation. *Psychoneuroendocrinology* 1976;**1**:281—90.
14. Pfaff DW, McEwen BS. Actions of estrogens and progestins on nerve cells. *Science* 1983;**219**:808—14.
*15. Axelsson J, Ingre M, Akerstedt T, Holmback U. Effects of acutely sleep on testosterone. *J Clin Endocrinol Metab* 2005;**90**:4530—5.
16. Kern W, Perras B, Wodick R, Fehm HL, Born J. Hormonal secretion during nighttime sleep indicating stress of daytime exercise. *J Appl Physiol* 1995;**79**:1461—8.
17. Mitamura R, Yano K, Suzuki N, Ito Y, Makita Y, Okuno A. Diurnal rhythms of luteinizing hormone, follicule-stimulating hormone and testosterone secretion before the onset of male puberty. *J Clin Endocrinol Metabol* 1999; **84**:29—37.
*18. Boyar RM, Rosenfeld RS, Kapen S, Finkelstein JW, Roffwarg HP, Weitzman ED, et al. Simultaneous augmented secretion of luteinizing hormone and testosterone during sleep. *J Clin Invest* 1974;**54**:609—18.
19. Luboshitzky R, Zabari Z, Shen-Orr Z, Herer P, Lavie P. Disruption of the nocturnal testosterone rhythm by sleep fragmentation in normal men. *J Clin Endocrinol Metab* 2001;**86**:1134—9.
20. Luboshitzky R, Zabari Z, Shen-Orr Z, Herer P, Lavie P. decreased pituitary-gonadal secretion in men with obstructive sleep apnea. *J Clin Endocrinol Metab* 2002; **87**:3394—8.
*21. Resko JA, Eik-Nes KB. Diurnal testosterone levels in peripheral plasma of human male subjects. *J Clin Endocrinol* 1966;**26**:573—6.
22. Plymate SR, Tenover JS, Bremner WJ. Circadian variation in testosterone, sex hormone-binding globulin, and calculated non-sex hormone-binding globulin bound testosterone in healthy young and elderly men. *J Androl* 1989;**10**:366—71.
23. Schiavi RC, White D, Mandeli J. Pituitary-gonadal function during sleep in healthy aging men. *Psychoneuroendocrinology* 1992;**17**:599—609.
24. Veldhuis JD. Older men manifest multifold synchrony disruption of reproductive neurohormone outflow. *J Clin Endocrinol Metab* 2000;**85**:1477—86.
*25. Evans JI, MacLean AW, Ismail AAA, Love D. Concentrations of plasma testosterone in normal men during sleep. *Nature* 1971;**229**:261—2.
*26. Hirshkowitz M, Moore CA, O'Connor S, Bellamy M, Cunningham GR. Androgen and sleep-related erections. *J Psychosom Res* 1997;**42**:541—6.
*27. Luboshitzky R, Herer P, Levi M, Shen-Orr Z, Lavie P. Relationship between rapid eye movement sleep and testosterone secretion in normal men. *J Androl* 1999;**20**: 731—7.
28. Walton MJ, Anderson RA, Kicman AT, Elton RA, Ossowska K, Baird DT. A diurnal variation in testicular hormone production is maintained following gonadotrophin suppression in normal men. *Clin Endocrinol* 2007;**66**:123—9.

* The most important references are denoted by an asterisk.

29. Tenover JS. Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab* 1992;**75**:1092—8.
30. Carlsen E, Olsson C, Petersen JH, Andersson AM, Skakkebaek NE. Diurnal rhythm in serum levels of inhibin B in normal men: relation to testicular steroids and gonadotropins. *J Clin Endocrinol Metab* 1999;**84**:1664—9.
*31. Miyatake A, Morimoto Y, Oishi T, Hanasaki N, Sugita Y, Iijima S, et al. Circadian rhythm of serum testosterone and its relation to sleep: comparison with the variation in serum luteinizing hormone, prolactin, and cortisol in normal men. *J Clin Endocrinol Metab* 1980;**51**:1365—71.
32. Reyes-Fuentes A, Chavarria ME, Carrera A, Aguilera G, Rosado A, Samojlik E, et al. Alterations in pulsatile luteinizing hormone and follicle-stimulating hormone secretion in idiopathic oligoasthenospermic men: assessment by deconvolution analysis—a clinical research center study. *J Clin Endocrinol Metab* 1996;**81**:524—9.
33. Liu PY, Takahashi PY, Roebuck PD, Iranmanesh A, Veldhuis JD. Aging in healthy men impairs recombinant human luteinizing hormone (LH)-stimulated testosterone secretion monitored under a two-day intravenous pulsatile LH clamp. *J Clin Endocrinol Metab* 2005;**90**:5544—50.
34. Rubin RT, Gouin PR, Lubin A, Poland RE, Pirke KM. Nocturnal increase of plasma testosterone in men: relation to gonadotropins and prolactin. *J Clin Endocrinol Metab* 1975;**40**:1027—33.
35. Cooke RR, McIntosh JE, McIntosh RP. Circadian variation in serum free and non-SHBG-bound testosterone in normal men: measurements, and simulation using a mass action model. *Clin Endocrinol* 1993;**39**:163—71.
36. Smals AG, Kloppenborg PW, Benraad TJ. Circannual cycle in plasma testosterone levels in man. *J Clin Endocrinol Metab* 1976;**42**:979—82.
37. Dabbs Jr JM. Age and seasonal variation in serum testosterone concentration among men. *Chronobiol Int* 1990;**7**: 245—9.
38. Svartberg J, Jorde R, Sundsfjord J, Bonaa KH, Barrett-Connor E. Seasonal variation of testosterone and waist to hip ratio in men: the Tromso study. *J Clin Endocrinol Metabol* 2003;**88**:3099—104.
39. Kolmodin-Hedman B, Swensson A. Problems related to shift work. A field study of Swedish railroad workers with irregular work hours. *Scand J Work Environ Health* 1975;**1**:254—62.
40. Svartberg J, Barrett-Connor E. Could seasonal variation in testosterone levels in men be related to sleep? *Aging male* 2004;**7**:205—10.
41. Bogdan A, Bouchareb B, Touitou Y. Ramadan fasting alters endocrine and neuroendocrine circadian patterns. Meal-time as a synchronizer in humans? *Life Sci* 2001;**68**:1607—15.
42. El-Migdadi F, Shotar A, El-Akawi Z, Banihani I, Abudhese R. Effect of fasting during the month of Ramadan on serum levels of luteinizing hormone and testosterone in people living in the below sea level environment in the Jordan Valley. *Neuroendocrinol Lett* 2004;**25**:75—7.
43. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts male Aging Study. *J Clin Endocrinol Metab* 1991;**73**:1016—25.
44. Kelleher S, Conway AJ, Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. *J Clin Endocrinol Metab* 2004;**89**:3813—7.
45. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. *Clin Endocrinol* 2006;**65**: 275—81.
46. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab* 1983;**56**:1278—81.
47. Penev P, Spiegel K, L'Hermite-Baleriaux M, Schneider R, Van Cauter E. Relationship between REM sleep and testosterone secretion in older men. *Ann Endocrinol* 2003;**64**:157—8.
48. McLachlan RI, Allan CA. Defining the prevalence and incidence of androgen deficiency in aging men: where are the goal posts? *J Clin Endocrinol Metab* 2004;**89**:5916—9.
49. Handelsman DJ. Testosterone: use, misuse and abuse. *Med J Aust* 2006;**185**:436—9.
50. Leibenluft E, Schmidt PJ, Turner EH, Danaceau MA, Ashman SB, Wehr TA, et al. Effects of leuprolide-induced hypogonadism and testosterone replacement on sleep, melatonin, and prolactin secretion in men. *J Clin Endocrinol Metab* 1997;**82**:3203—7.
51. Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG, Grunstein RR, et al. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. *J Clin Endocrinol Metab* 2003;**88**:3605—13.
52. Ferrando AA, Sheffied-Moore M, Yeckel CW, Gilkinson C, Jiang J, Achacosa A, et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. *Am J Physiol Endocrinol Metab* 2002;**282**:E601—5.
53. Luboshitzky R, Lavi S, Lavie P. The association between melatonin and sleep stages in normal adults and hypogonadal men. *Sleep* 1999;**22**:867—74.
54. Sirotkin AV, Schaeffer HJ. Direct regulation of mammalian reproductive organs by serotonin and melatonin. *J Endocrinol* 1997;**154**:1—5.
55. Luboshitzky R, Lavi S, Thuma I, Lavie P. Testosterone treatment alters melatonin concentrations in male patients with gonadotropin-releasing hormone deficiency. *J Clin Endocrinol Metab* 1996;**81**:770—4.
56. Luboshitzky R, Wagner O, Lavi S, Herer P, Lavie P. Abnormal melatonin secretion in hypogonadal men: the effect of testosterone treatment. *Clin Endocrinol* 1997; **47**:463—9.
57. Stillman MJ. Testosterone replacement therapy for treatment refractory cluster headache. *Headache* 2006; **46**:925—33.
58. Saaresranta T, Polo O. Hormones and breathing. *Chest* 2002;**122**:2165—82.
59. Vidal AH, Vaughn BV. Testosterone levels in sleep related breathing disorders. *Sleep* 2001;**24**:A297—8.
60. Meston N, Davies RJ, Mullins R, Jenkinson C, Wass JA, Stradling JR. Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea. *J Intern Med* 2003;**254**:447—54.
61. Guilleminault C, Simmons FB, Motta J, Cummiskey J, Rosekind M, Schroeder JS, et al. Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. *Arch Intern Med* 1981;**141**:985—8.
62. Dempsey JA, Skatrud JB. A sleep-induced apneic threshold and its consequences. *Am Rev Respir Dis* 1986; **133**:1163—70.
63. Stewart DA, Grustein RR, Berthon-Jones M, Handelsman DJ, Sullivan CE. Androgen blockade does not affect sleep-disordered breathing or chemosensitivity in men with obstructive sleep apnea. *Am Rev Respir Dis* 1992;**146**:1369—93.
64. Young TP, Skatrud JMD, Peppard PEP. Risk factors for obstructive sleep apnea in adults. *JAMA* 2004;**291**:2013—6.
65. Liu PY, Yee BJ, Phillips CL, Grunstein RR. Sleep apnea and neuroendocrine function. *Sleep Med Clin* 2007;**2**:225—36.

66. Santamaria JD, Prior JC, Fleetham JA. Reversible reproductive dysfunction in men with obstructive sleep apnoea. *Clin Endocrinol* 1988;**28**:461—70.
67. Grunstein RR, Handelsman DJ, Lawrence SJ, et al. Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. *J Clin Endocrinol Metab* 1989;**68**:352—358.
68. Gambineri A, Pelusi C, Pasquali R. Testosterone levels in obese male patients with obstructive sleep apnea syndrome: relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. *J Endocrinol Invest* 2003;**26**:493—8.
69. Cistulli PA, Grustein RR, Sullivan CE. Effect of testosterone administration on upper airway collapsibility during sleep. *Am J Respir Crit Care Med* 1994;**149**:530—2.
70. Johnson MW, Anch AM, Rmeers JE. Induction of the obstructive sleep apnea syndrome in a woman by exogenous androgen administration. *Am Rev Respir Dis* 1984; **129**:1023—5.
71. Kouchiyama S, Honda Y, Kuriyama T. Influence of nocturnal oxygen desaturation on circadian rhythm of testosterone secretion. *Respiration* 1990;**57**:359—63.
72. Bratel T, Wennlund A, Carlstrom K. Pituitary reactivity, androgens and catecholamines in obstructive sleep apnoea: effects of continuous positive airway pressure treatment (CPAP). *Respir Med* 1999;**93**:1—7.
73. Luboshitzky R, Lavie L, Shen-Orr Z, Herer P. Altered luteinizing hormone and testosterone secretion in middle-aged obese men with obstructive sleep apnea. *Obes Res* 2005;**13**:780—6.
74. White DP, Schneider BK, Santen RJ, McDermott M, Pickett CK, Zwillich CW, et al. Influence of testosterone on ventilation and chemosensitivity in male subjects. *J Appl Physiol* 1985;**59**:1452—7.
75. Bonnet MH, Arand DL. 24-Hour metabolic rate in insomniacs and matched normal sleepers. *Sleep* 1995;**18**: 581—8.
76. Kripke DF, Simons RN, Garfinkel L, Hammond EC. Short and long sleep and sleeping pills. Is increased mortality associated? *Arch Gen Psychiat* 1979;**36**:103—16.
77. National Sleep Foundation. Sleep in America Poll, 2001—2002. Washington, DC: National Sleep Foundation.
78. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;**354**: 1435—9.
79. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007;**11**:163—78.
80. Leibowitz SM, Lopes MC, Andersen ML, Kushida CA. Sleep deprivation and sleepiness caused by sleep loss. *Sleep Med Clin* 2006;**1**:31—45.
81. Miller NE, Bartus RT. Sleep, sleep pathology, and psychopathology in later life: a new research frontier. *Neurobiol Aging* 1982;**3**:283—6.
82. Tufik S, Lindsey CJ, Carlini EA. Does REM sleep deprivation induce a supersensitivity of dopaminergic receptors in the rat brain? *Pharmacology* 1978;**16**:95—108.
83. Frussa-Filho R, Goncalves MT, Andersen ML, de Araujo NP, Chinen CC, Tufik S. Paradoxical sleep deprivation potentiates amphetamine-induced behavioural sensitization by increasing its conditioned component. *Brain Res* 2004; **1003**:188—93.
84. Andersen ML, Bignotto M, Tufik S. The effect of apomorphine on genital reflexes in male rats deprived of paradoxical sleep. *Physiol Behav* 2003;**80**:211—5.
85. Andersen ML, Bignotto M, Papale LA, Tufik S. Age-related effects on genital reflexes induced by paradoxical sleep deprivation and cocaine in rats. *Exp Gerontol* 2004;**39**: 233—7.
86. Andersen ML, Bignotto M, Tufik S. Facilitation of ejaculation after methamphetamine administration in paradoxical sleep deprived rats. *Brain Res* 2003;**978**: 31—7.
87. Andersen ML, Perry JC, Tufik S. Acute cocaine effects in paradoxical sleep deprived male rats. *Prog Neuropsychopharmacol Biol Psychiat* 2005;**29**:245—51.
88. Andersen ML, Bignotto M, Machado RB, Tufik S. Does paradoxical sleep deprivation and cocaine induce penile erection and ejaculation in old rats? *Addict Biol* 2002;**7**: 285—90.
89. Andersen ML, Bignotto M, Tufik S. Hormone treatment facilitates penile erection in castrated rats after sleep deprivation and cocaine. *J Neuroendocrinol* 2004;**16**: 154—9.
90. Andersen ML, Tufik S. Does male sexual behavior require progesterone? *Brain Res Rev* 2006;**51**:136—43.
91. Baumgartner A, Graf KJ, Kurten I, Meinhold H, Scholz P. Neuroendocrinological investigations during sleep deprivation in depression. *Biol Psychiat* 1990;**28**:556—68.
92. Cortes-Gallegos V, Castaneda G, Alonso R, Sojo I, Carranco A, Cervantes C, et al. Sleep deprivation reduces circulating androgens in healthy men. *Arch Androl* 1983; **10**:33—7.
93. Singer F, Zumoff B. Subnormal serum testosterone levels in male internal medicine residents. *Steroids* 1992;**57**: 86—9.
94. Andersen ML, Martins PJ, D'Almeida V, Bignotto M, Tufik S. Endocrinological and catecholaminergic alterations during sleep deprivation and recovery in male rats. *J Sleep Res* 2005;**14**:83—90.
95. Bohle P, Tilley AJ. The impact of night work on psychological well-being. *Ergonomics* 1989;**32**:1089—99.
96. Harma MI, Ilmarinen J, Knauth P. Physical fitness and other individual factors relating to the shiftwork tolerance of women. *Chronobiol Int* 1988;**5**:417—24.
97. Axelsson J, Akerstedt T, Kecklund G, Lindqvist A, Attefors R. Hormonal changes in satisfied and dissatisfied shift workers across a shift cycle. *J Appl Physiol* 2003;**95**:2099—105.
98. Opstad PK. Androgenic hormones during prolonged physical stress, sleep, and energy deficiency. *J Clin Endocrinol Metab* 1992;**74**:1176—83.
99. Booth CK, Probert B, Forbes-Ewan C, Coad RA. Australian army recruits in training display symptoms of overtraining. *Mil Med* 2006;**171**:1059—64.
100. Nindl BC, Rarick KR, Castellani JW, Tuckow AP, Patton JF, Young AJ, et al. Altered secretion of growth hormone and luteinizing hormone after 84 h of sustained physical exertion superimposed on caloric and sleep restriction. *J Appl Physiol* 2006;**100**:120—8.
101. Van Cauter E, Holmback U, Knutson K, Leproult R, Miller A, Nedeltcheva A, et al. Impact of sleep and sleep loss on neuroendocrine and metabolic function. *Horm Res* 2007;**67**:2—9.
102. Martins RCS, Andersen ML, Tufik S. The reciprocal interaction between sleep and Type 2 diabetes mellitus. Braz J Med Biol Res 2008, in press.
103. Trenell MI, Marshall NS, Rogers NL. Sleep and metabolic control: waking to a problem? *Clin Exp Pharmacol Physiol* 2007;**34**:1—9.
104. Ohlmeyer P, Brilmayer H, Hüllstrung H. Periodische Vorgänge im schlaf. *Pflugers Arch* 1944;**248**:559—60.
105. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science* 1953;**118**:273—4.

106. Oswald I. *Sleeping and waking*. Amsterdam: Elsevier; 1962.
107. Fisher C, Gross J, Zuch J. Cycles of penile erection synchronous with dreaming (REM) sleep. *Arch Gen Psychiat* 1965;**12**:29—45.
108. Karacan I, Goodenough DR, Shapiro A. Erection cycle during sleep in relation to dream anxiety. *Arch Gen Psychiat* 1966;**15**:183—9.
109. Karacan I, Hursch CJ, Williams RL, Littlell RC. Some characteristics of nocturnal penile tumescence during puberty. *Pediatr Res* 1972;**6**:529—37.
110. Karacan I, Hursch CJ, Williams RL, Thornby JI. Some characteristics of nocturnal penile tumescence in young adults. *Arch Gen Psychiat* 1972;**26**:351—6.
111. Schmidt MH, Schmidt HS. Sleep-related erections: neural mechanisms and clinical significance. *Curr Neurol Neurosci Rep* 2004;**4**:170—8.
112. Hirshkowitz M, Moore CA. Sleep-related erectile activity. *Neurol Clin* 1996;**14**:721—37.
113. Karacan I, Salis PJ, Williams RL. The role of the sleep laboratory in the diagnosis and treatment of impotence. In: Williams RL, Karacan I, Frazier SH, editors. *Sleep disorders: diagnosis and treatment*. New York: Wiley; 1978. p. 353.
114. Kessler WO. Nocturnal penile tumescence. *Urol Clin North Am* 1988;**15**:81—6.
115. Schiavi RC. The role of the sleep laboratory in the evaluation of male erectile dysfunction. *The Mount Sinai J Med* 1994;**61**:161—5.
116. Ware JC, Hirshkowitz M, Thornby J, Salis P, Karacan I. Sleep-related erections: absence of change following presleep sexual arousal. *J Psychosom Res* 1997;**42**:547—53.
117. Sachs BD. Contextual approaches to the physiology and classification of erectile function, erectile dysfunction, and sexual arousal. *Neurosci Biobehav Rev* 2000;**24**:541—60.
118. Karacan I, Salis PJ, Thornby JI, Williams RL. The ontogeny of nocturnal penile tumescence. *Waking Sleeping* 1976;**1**: 27—44.
119. Karacan I, Salis PJ, Ware JC, Dervent B, Williams RL, Scott FB, et al. Nocturnal penile tumescence and diagnosis in diabetic impotence. *Am J Psychiat* 1978;**135**:191—7.
120. Michael V, Kramar R, Pospichal J, Hejhal L. Arterial epigastricocavernous anastomosis for the treatment of sexual impotence. *World J Surg* 1977;**1**:515—20.
121. Beutler LE, Karacan I, Anch AM, Salis PJ, Scott FB, Williams RL. MMPI and MIT discriminators of biogenic and psychogenic impotence. *J Consult Clin Psychol* 1975;**43**: 899—903.
122. Karacan I, Scott FB, Hartse K, Williams RL, Aslan C, Takanami M, et al. Prevalence of erectile dysfunction in the sleep disorders center. In: Guilleminault C, Lugaresi E, editors. *Sleep/wake disorders: natural history, epidemiology, and long-term evolution*. New York: Raven Press; 1983. p. 261—73.
123. Ware JC. Penile erection during sleep. Their use in the differential diagnosis of impotence. *Alabama J Med Sci* 1986;**23**:398—401.
124. Schmidt MH, Valatx JL, Schmidt HS, Wauquier A, Jouvet M. Experimental evidence of penile erections during paradoxical sleep in the rat. *Neuroreport* 1994;**5**:561—4.
125. Parmeggiani PL. The autonomic nervous system in sleep. In: Kryger MH, Roth R, Dement WC, editors. *Principles and practice of sleep medicine*. Philadelphia: WB Saunders; 1994. p. 194.
126. Giuliano F, Rampin O, Bernabé J, Rousseau J-P. Neural control of penile erection in the rat. *J Autonom Nerv Syst* 1995;**55**:36—44.
127. Sachs BD, Bitran D. Spinal block reveals roles for brain and spinal cord in the mediation of reflexive penile erection in rats. *Brain Res* 1990;**528**:99—108.
128. Schmidt MH, Valatx JL, Sakai K, Fort P, Jouvet M. Role of the lateral preoptic area in sleep-related erectile mechanisms and sleep generation in the rat. *J Neurosci* 2000; **20**:6640—7.
129. Schmidt MH. Sleep-related penile erections. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 3rd ed. Philadelphia: WB Saunders Company; 2000. p. 305.
*130. Roffwarg HP, Sachar EJ, Halpern F, Hellman L. Plasma testosterone and sleep: relationship to sleep stage variables. *Psychosom Med* 1982;**44**:73—84.
131. O'Carroll R, Shapiro C, Bancroft J. Androgens, behaviour and nocturnal erection in hypogonadal men: the effects of varying the replacement dose. *Clin Endocrinol* 1985; **23**:527—38.
132. Cunningham GR, Hirshkowitz M, Korenman SG, Karacan I. Testosterone replacement therapy and sleep-related erections in hypogonadal men. *J Clin Endocrinol Metab* 1990;**70**:792—7.
133. Carani C, Scuteri A, Marrama P, Bancroft J. The effects of testosterone administration and visual erotic stimuli on nocturnal penile tumescence in normal men. *Horm Behav* 1990;**24**:435—41.
134. Granata AR, Rochira V, Lerchl A, Marrama P, Carani C. Relationship between sleep-related erections and testosterone levels in men. *J Androl* 1997;**18**:522—7.
135. Schiavi RC. Androgens and sexual function in men. In: Oddens BJ, Vermeulen A, editors. *Androgens and the aging male*. New York: The Parthenon Publishing Group; 1996. p. 111—25.
136. Buena F, Swerdloff RS, Steiner BS, Lutchmansingh P, Peterson MA, Pandian MR, et al. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. *Fertil Steril* 1993;**59**:1118—23.
*137. Montorsi F, Oettel M. Testosterone and sleep-related erections: an overview. *J Sex Med* 2005;**2**:771—84.
138. Foresta C, Caretta N, Rossato M, Garolla A, Ferlin A. Role of androgens in erectile function. *J Urol* 2004;**171**:2358—62.
139. Rochira V, Balestrieri A, Madeo B, Granata AR, Carani C. Sildenafil improves sleep-related erections in hypogonadal men: evidence from a randomized, placebo-controlled, crossover study of a synergic role for both testosterone and sildenafil on penile erections. *J Androl* 2006;**27**:165—75.
140. Granata A, Bancroft J, Del Rio G. Stress and the erectile response to intracavernosal prostaglandin E1 in men with erectile dysfunction. *Psychosom Med* 1995;**57**:336—44.
141. Roizenblatt S, Guilleminault C, Poyares D, Cintra F, Kauati A, Tufik S. A double-blind, placebo-controlled, crossover study of sildenafil in obstructive sleep apnea. *Arch Intern Med* 2006;**166**:1763—7.
142. Bhasin S, Singh AB, Mac RP, Carter B, Lee MI, Cunningham GR. Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. *J Androl* 2003;**24**:299—311.