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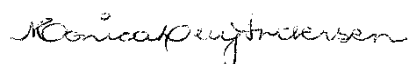
Abstract: Testosterone has been the focus of several investigations and review studies in males, but few have addressed its effects on sleep and sexual function despite the evidence of androgenic effects on circadian activity in both sexes. Studies have been conducted to understand how sleeping increases and waking decreases testosterone levels and how this rhythm can be related to sexual function. This review addresses the inter-relationships among testosterone, sexual function and sleep, including sleep-disordered breathing in both sexes, specifically the effects related to sleep deprivation. In addition, hormonal changes in testosterone that occur in the gonadal and adrenal axis with obstructive sleep apnea and other conditions of chronic sleep deprivation, which consequently affect sexual life, have also been explored. Nevertheless, hormone-associated sleep disruptions occur across a lifetime, particularly in women. The association between endogenous testosterone and sex, sleep and sleep disturbances is discussed, including results of clinical trials as well as animal model studies. Evidence of possible pathophysiological mechanisms underlying this relationship is also described. Unraveling the associations of sex steroid hormone concentrations to sleep and sexual function may have clinical implications, as sleep loss reduce testosterone levels in males, and low sex steroid hormone concentrations have been associated with sexual dysfunction.

February 16, 2011

Dear Prof. Irwin B. Levitran, Editor in Chief,

It is certainly an honor to receive this invitation. In response, we would like to submit a review article for consideration in Brain Research Reviews entitled ***“The association of testosterone, sleep, and sexual function in men and women”***. This article is part of a consolidated line of research that focuses on the effects of sleep deprivation on testosterone levels and sexual behavior to better understand the associations between sex steroid hormone concentrations, sleep, and sexual function. Recently, we have reviewed the influence of sleep deprivation/restriction on testosterone in males (Sleep Med Rev, 2008) and the neurobiological role of progesterone in sexual function (Brain Res Rev, 2006). The global population has been exposed to conditions that result in sleep deficits; these conditions are especially prominent in industrialized countries. The chronic sleep-restriction environment is usually associated with more demanding work-related activities, an intense social life, long periods of internet usage, late-night shift work, and other sleep disturbances that collectively compromise normal circadian sleep in many people. As life expectancy has progressively increased for both men and women, it can be expected that more people will prolong their sexual activities. However, it is not surprising that an increase in sexual complaints might also accompany this substantial increase in lifespan. This review provides a comprehensive summary of the interaction between testosterone and sexual function, depicting how sleep loss can influence levels of testosterone in both sexes and the resulting effects on sexual behavior. Finally, we also review the literature of how testosterone is related to varying health outcomes (e.g., erectile dysfunction) associated with sleep disturbances. The present review highlights recent contributions in the fields of sexual behavior and sleep toward understanding the role of testosterone in the framework of neurobiology of sleep related to sexual function.

Thank you in advance for your consideration,



Monica L. Andersen

June 28, 2011

Dear Editor,

Please find enclosed the revised manuscript by BRES-D-11-00294 entitled "*The association of testosterone, sleep, and sexual function in men and women*". We would like to thank the Reviewer who raised very relevant points that helped us to improve the overall quality of the manuscript. Our revision was guided by the pertinent critiques. All of the remarks made by the Reviewer were accepted and included in the new version of the manuscript, as detailed below in a point-by-point reply to the comments.

Reviewer: 2

This is a clearly written article that should provide useful background about testosterone, sleep and sexual function in women and men. A few modifications will make this paper more useful for the readership of this journal.

1. Searching the literature a bit more carefully regarding papers related to the menopausal transition and both sleep and sexual desire will yield a few more useful citations, e.g. Dennerstein's work.

We would like to thank the Reviewer for this comment. We have included additional paragraphs in the text to address this relevant topic. In summary, female sexuality is a complex and multifactorial condition. Testosterone replacement appears to be more effective at increasing sexual response when the individual's serum level of testosterone is low (see Alexander et al., 2004, 2006), as low desire usually occurs in parallel with low levels of testosterone. An example of the complexity of female sexual dysfunction is the finding that a placebo can also provide benefits, as psychological issues are also present. In general, testosterone is indicated to improve hypoactive sexual desire disorder in postmenopausal women when estrogen treatment has been already prescribed and testosterone levels are low. However, the long-term effects of testosterone treatment in women are still unknown. Considering different assessment instruments of female sexual function, both estrogen therapy alone and the combination of estrogen and testosterone can improve female sexual function

(Alexander et al., 2004, 2006). Of note, the evaluation of female sexuality is limited, not only because every woman responds in a different way, but also because each woman has a distinct responses to hormone therapy. Finally, the multifactorial condition of female sexual dysfunction has to be considered; the condition involves physical changes, hormonal, psychological, mood, and sleep quality, among others, all of which are aggravated after menopause.

2. Figures will be useful to readers and guide their understanding of the text.

We appreciate this remark. In fact, two figures are included in this review. These figures depict the neuropathways of hormonal secretion.

3. There are a few papers on androgen profiles over the lifespan in men and I would recommend referencing these in the citations, e.g. studies of both adrenal androgens as well as testosterone.

We thank the Reviewer for this important observation. We have now included a topic in section 2, "Adrenal androgens", where additional citations have been included.

4. p 16, last line of text ... do you mean DURING CPAP TREATMENT?

The study of Cistulli et al. (1994) demonstrated that testosterone was associated with an increase in upper airway collapsibility during sleep, and these authors hypothesized that this feature may be the mechanism by which testosterone induces or exacerbates OSA. Moreover, nocturnal testosterone was reported to be partially corrected during the CPAP treatment (Luboshitzky et al., 2003).

p 18 + use of "during menopause" is not really very descriptive. Do you mean the Final Menstrual Period (FMP)? do you mean during the menopausal transition? early postmenopause? See the STRAW criteria by Soules et al, 1991 for further information about using this terminology precisely.

We have clarified the segments mentioned.

5. p. 19, line 2 decrease in estrogen levels is ... is there a word missing in this sentence?

We have corrected this sentence.

6. Discussion of the Paul 2006 work and later reference to diestrus phase: is this relevant to progesterone? testosterone? what significance do these phases have with respect to hormone levels? and for what are they markers?

We apologize if we have not made ourselves completely clear. We have restructured the text on pages 20 and 21, and we hope that this point is more appropriate now.

p. 22, p. 3 series of studies HAS

p. 24 last line -- not as simple AS WHAT?

p. 7. Is andropause REAL?

p. 28 Sexual NEITHER mood ...???

p. 29. Please check Jan Shifren's clinical trial of testosterone effects they are opposite some of the studies you cite and hers is a well-designed study

We thank the Reviewer for these comments. All points above have been corrected. In addition, we have cited Shifren et al. (2006), who used a testosterone patch in naturally menopausal women on page 30.

p. 30 for studies of sexual desire and menopausal transition and hormone effects: see work by Woods and also by Dennerstein which emphasizes importance of estrogen, not only testosterone.

We appreciate this suggestion. Studies of Woods, Dennerstein, and others have been included in the revised version of the text.

p. 34. re animal studies: the social context, e.g. safety, history of social interaction in different cage situations is also important here.

We have expanded the text to address this remark.

p. 38 testosterone and estrogen and sexual desire.... see Woods et al, 2009 as well as Dennerstein more recent citations

As mentioned above, more studies have been included, as suggested.

p. 43 ejaculatory latency, and decreases? the length of the inter-intromission interval?

We have added new citations, as suggested, and also rewrote some sentences on the inter-intromission interval to provide additional information (page 45).

Need a stronger conclusion and recommendations for where this work should go

On the basis of the scientific evidence, it is possible to state that good sleep quality directly reflects the activity of the neuroendocrine reproductive control, allowing optimal regulation of the hormonal homeostasis. Thus, increasing the duration and quality of sleep can be an additional approach to improving sexual satisfaction by reducing the negative effects mediated by sleep deprivation/sleep restriction in both men and women. This sentence has been added to the text.

We thank the Reviewers for their helpful input and for giving us the opportunity to significantly improve the clarity of this text. We hope that you will find this revised manuscript suitable and ready for publication in *Brain Research Reviews*.

Thank you for your attention,

Monica L. Andersen and colleagues

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The association of testosterone, sleep, and sexual function in men and women

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Abbreviations: PSD, paradoxical sleep deprivation; HT, hormonal therapy; NO, nitric oxide; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; SHBG, sex hormone-binding globulin; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; NREM, non-rapid-eye movement sleep; REM, rapid-eye movement sleep; SWS, slow wave sleep; 5-HIAA, 5-hydroxyindoleacetic acid; CNS, central nervous system; DHT, dihydrotestosterone; SWS, slow wave sleep; TRT, testosterone replacement therapy. **DHEA, dehydroepiandrosterone; III, inter-intromission interval.**

Abstract

Testosterone has been the focus of several investigations and review studies in males, but few have addressed its effects on sleep and sexual function, despite evidence of its androgenic effects on circadian activity in both sexes. Studies have been conducted to understand how sleeping increases (and how waking decreases) testosterone levels and how this rhythm can be related to sexual function. This review addresses the inter-relationships among testosterone, sexual function and sleep, including sleep-disordered breathing in both sexes, specifically its effects related to sleep deprivation. In addition, hormonal changes in testosterone that occur in the gonadal and adrenal axis with obstructive sleep apnea and other conditions of chronic sleep deprivation, and which consequently affect sexual life, have also been explored. Nevertheless, hormone-associated sleep disruptions occur across a lifetime, particularly in women. The association between endogenous testosterone and sex, sleep and sleep disturbances is discussed, including the results of clinical trials as well as animal model studies. Evidence of possible pathophysiological mechanisms underlying this relationship is also described. Unraveling the associations of sex steroid hormone concentrations with sleep and sexual function may have clinical implications, as sleep loss reduces testosterone levels in males, and low sex steroid hormone concentrations have been associated with sexual dysfunction.

Keywords: Testosterone, sleep, sexual function, men, women, climacteric, androgen, sleep deprivation, erection.

1. Introduction

The machinery of reproduction is elaborate, involving a well-orchestrated sequence of events. The biology of sexual function is an integral part of life satisfaction. In men and women, androgens appear to play an important role in sexual function and development. Testosterone, although defined as a male hormone, is essential to both sexes and is directly involved in several physiological effects, including the sense of well-being, motivation, muscle mass and strength, and cognition and memory.

As life expectancy has progressively increased at the turn of the 20th century for both men and women, it can be expected that more people will prolong their sexual activities. Thus, quality of life and general well-being are underlined by high expectations. However, it is not surprising that an increase in sexual complaints might also be accompanied by this substantial increase in lifespan. Indeed, impairment in sexual life due to age or medical illness may seriously hinder extended life satisfaction.

In addition to aging, the current global population works and lives under a 24/7 lifestyle that imposes less sleep and increases physical activities. Sleep deprivation has many consequences in humans, especially on the hormonal profile and possibly on sexual life. In addition, the search for sexual satisfaction has accelerated with wide-spread mainstream media coverage. The influence of testosterone on sexual behavior, mainly in males, has been documented for decades, but our knowledge about its interaction with sleep and the effects that sleep loss has on its concentrations is still limited. Moreover, the majority of hormone-associated sleep alterations occur mainly in women, because their reproductive lives include **menstrual cycles, pregnancy and menopause transition**, among other dynamic physiological conditions.

The main objective of the present review is to provide a comprehensive summary of the interaction between testosterone and sexual function, depicting how sleep loss and common lifestyle conditions of many societies can influence testosterone levels in both sexes

and the effects on sexual behavior. Finally, we also review the literature of how this hormone is related to various health outcomes (e.g., erectile dysfunction (ED)) associated with sleep disturbances.

2. Testosterone

The three steroids of primary importance to male reproductive function are testosterone, dihydrotestosterone (DHT), and estradiol. However, in recent years, adrenal androgens, as dehydroepiandrosterone (DHEA), are gaining prominence in reproductive control. It can be assumed from a quantitative standpoint that the most important androgen is testosterone, as it is the major androgen crucial to the development and maintenance of male sexual characteristics.

-Synthesis and secretion of testosterone

The reproductive system exhibits complex neurohumoral regulation that involves central nervous system (CNS) structures (limbic system, hypothalamus and pituitary) and peripheral structures (autonomic sympathetic and parasympathetic systems) in addition to the reproductive organs.

Testosterone is a steroidal hormone produced by the process of steroidogenesis. This synthetic pathway is active mainly in the testicular interstitial cells (Leydig cells) and ovarian theca cells of males and females, respectively (Sttoco and McPahual, 2006; Couse et al., 2006). Cholesterol is the substrate for testosterone synthesis. Another important site of androgen synthesis is the adrenal cortex of both sexes (Miller, 2009; Auchus, 2009).

Physicians usually measure total testosterone levels, unless they suspect that it would be inappropriate to measure total testosterone levels due to a decrease or increase in sex hormone-binding globulin (SHBG), in which case the free form of testosterone is measured instead (for review, see Zarrouf et al., 2009). Approximately all of the testosterone circulating

in the blood is bound to SHBG or albumin; only 1-2% of circulating testosterone is free (Zarrouf et al., 2009).

After puberty, gonadotropin releasing hormone (GnRH) is synthesized and secreted in the medial basal hypothalamus and preoptic area in a pulsatile way (Plant and Witchel, 2006). This protein hormone reaches the hypophyseal-portal system, and from there, it contacts the anterior pituitary, stimulating gonadotrophs to synthesize and secrete gonadotropins (luteinizing hormone (LH), and follicle stimulating hormone (FSH)). These hormones then reach the bloodstream and arrive at the gonads (Santen and Bardin, 1973; Veldhuis, 1987).

In men, endocrine control over spermatogenesis is exerted mainly by LH, FSH, and testosterone. In fact, testosterone's effects are mediated by LH. FSH (and perhaps testosterone) is necessary for the initiation of spermatogenesis at puberty; testosterone can maintain this process throughout maturity as well as restore spermatogenesis when a suppression event occurs (O'Donnell et al., 2006). Testosterone, or DHT, acts via the androgen receptor, which is mostly confined to Leydig cells, peritubular cells and Sertoli cells. It affects a few stages of the spermatogenic cycle directly, but it can also interfere in the processes mediated by other testicular cells. Testosterone is the main testicular steroid, but significant aromatase activity in the testis and peripheral tissues also results in the production of estradiol. Testosterone, DHT and estradiol are steroid hormones that act to inhibit the hypothalamic-pituitary axis (Figure 1).

Recently, kisspeptin, a peptide that is expressed in the arcuate, periventricular, and anteroventral periventricular nuclei, has been associated with negative feedback of testosterone and estradiol on GnRH secretion. Kisspeptin stimulates GnRH secretion (Kotani et al., 2001; Muir et al., 2001). Testosterone and estradiol clearly inhibit kisspeptin transcription and consequently GnRH secretion (Navarro et al., 2004; Smith et al., 2005). Chronic administration of kisspeptin lowered serum LH levels in non-human primates

(Seminara et al., 2006). Estradiol is also important in this process, as it decreases LH production (Finkelstein et al., 1991). In the negative feedback loop, another important component is inhibin B, a dimeric molecule from the TGF- β family that is synthesized by Sertoli and granulosa cells (Rajkovic et al., 2006). Inhibin B promotes an inhibitory effect on FSH secretion by the pituitary gland.

- Role of testosterone in men

As reviewed by Zarrouf et al. (2009), the effects of testosterone begin in the prenatal period when it stimulates the differentiation and development of the testes, penis, epididymis, seminal vesicles, and prostate. Testosterone continues to affect these tissues during the pubertal period and in adult life (Mooradian et al., 1987; Santulli et al., 1990). In males, the testes are the major site of testosterone production, and the adrenal glands are a minor site.

The testis develops through different maturational phases exhibiting specific morphological and functional changes in different testicular compartments during its ontogeny (for review, see Rey et al., 2009). Once differentiated, two typical compartments can be distinguished in the fetal testis: the seminiferous cords (Sertoli and germ cells) and the interstitial tissue (Leydig cells and connective tissue). Both Sertoli and Leydig cells have endocrine functions that are essential to fetal sex differentiation (Rey et al., 2009).

Testosterone concentrations change as a function of age. Major changes in the levels of reproductive hormones occur during puberty (Turek, 2006) as serum gonadal steroid concentrations gradually increase. LH drives Leydig cell maturation, resulting in active steroidogenesis and an elevation of intratesticular androgen concentration (Rey et al., 2009). In the course of aging, circulating testosterone concentrations in healthy men decline an average of 1-2% per year, starting at the third decade of life (Feldman et al., 2002). With aging, the decrease in bioavailable testosterone appears to be greater than the decline in total testosterone due to an age-related increase in SHBG (Rubens et al., 1974). To advance

our understanding of the involvement of aging processes with the hypothalamic-pituitary-testicular axis on reproductive capacity, further studies should be conducted to assess the association of aging and sexual complaints.

Testosterone affects almost every organ in the body (see Zarrouf et al., 2009). Functions of testosterone include promoting spermatogenesis, maintenance of the accessory organs, muscle growth, secondary sexual characteristic development, and feedback to the hypothalamus-pituitary.

- Testosterone and ontogeny phases in women

Androgen production in women occurs in three organs of the body: the ovary, adrenals, and peripheral tissues. Most testosterone production occurs in the theca cells of the ovary, and this production is considered a marker of ovarian androgen production (Lobo, 2001; Figure 2). This production is mainly regulated by LH and insulin. The peripheral compartment involves the interconversion of androgens as well as the conversion of androgen to estrogen (via aromatase activity; for review, see Lobo, 2001). This conversion is essential to the physiological ovulatory process. In women, at least one-third of circulating testosterone is derived from precursors from the adrenal gland. However, the physiology of normal androgen production in women is still not completely understood.

Testosterone fluctuations during the menstrual cycle have been reported (Goebelsmann et al., 1974). However, a previous study found that testosterone showed a mid-cycle peak coincident with the LH surge, although testosterone levels remain constant during the menstrual cycle (Abraham, 1974). Recently, the cyclical testosterone pattern was reported not to vary among three different menstrual cycle phases studied: mid-follicular, late follicular and luteal phases (Nobrega et al., 2009).

Over a woman's lifetime, 50% of circulating testosterone is derived from the peripheral conversion of androstenedione in the premenopausal period (Luu-The et al., 2001; Al-Azzawi

and Palacios, 2009). The other half of production occurs in the ovaries and adrenal glands. As reviewed by Al-Azzawi and Palacios (2009), at 35 years of age, women start a gradual process of ovarian senescence until menopause occurring at approximately 51 years of age.

Controversy surrounds the issue of the decline in testosterone levels at menopause, especially because natural menopause does not result in an abrupt decline in testosterone production (Lobo, 2001). Indeed, a recent study demonstrated that postmenopausal ovaries remain active with respect to androgen production, contributing significant amounts of testosterone even into late menopause (Fogle et al., 2007). However, androgen deficiency may develop as a result of low androgen synthesis or low bioavailability due to elevated SHBG levels (Al-Azzawi and Palacios, 2009). In their review, these authors indicated that androgen production declines with age from its peak levels in the third decade of life.

- Adrenal androgens

The biosynthesis of all sex steroids in humans depends on the DHEA that is secreted by the adrenal cortex. This secretion changes over the human lifespan. In contrast to cortisol, DHEA peaks in adulthood and start to decline at 70-80 years of age (see Genazzani et al., 2007). This androgen acts directly as a neurosteroid (Williams et al., 1991), or indirectly on peripheral target tissues by its conversion to androgen or estrogens, or both (Martel et al., 1994). In men, one-third to one-half of DHEA production is estimated to occur in peripheral organs. In pre- or post-menopausal women, this fraction is higher; about 50 to 100% of DHEA synthesis occurs in peripheral tissue (Genazzani et al., 2007).

In women, DHEA acts on the reproductive system to promote a reduction in menopause's genitourinary (Diamond et al., 1996) and thermoregulatory disturbances (Stomati et al., 2000; Genazzani et al., 2003). Androgens produced by DHEA in vaginal tissues are involved in increased lubrication and the neurovascular smooth muscle response (Basson, 2002). The DHEA plasma reduction in women at menopause explains the

fact that both estrogen and androgen levels are decreased in this phase of a woman's life (Labrie et al., 1997).

In men with adrenal insufficiency and hypogonadism without androgen replacement associated with total androgens depletion, DHEA promotes significant elevation of androgens circulating, but these hormones do not reach normal values (Artl, 2004). Overall, and similar to testosterone, DHEA is an important androgen that is produced in the adrenal cortex and is involved in reproductive activities, particularly in women.

3. Testosterone and sleep

-Clinical findings in men

As pointed out by Axelsson and colleagues (2005), a better understanding of the relationship between sleep and testosterone is not just of theoretical interest. This research may also contribute to a better comprehension of the mechanisms behind certain health problems associated with sleep disturbances, aging, and shift work. Indeed, over the last 50 years, there has been a substantial increase in lifespan for most populations, and sleep disorders are quite common in many societies (Tufik et al., 2010). Alterations in hormonal levels, such as testosterone, are to be expected.

Sleep is a complex behavioral state that occupies one-third of the human lifespan. Although viewed as a passive condition, sleep is in fact a highly active and dynamic process. Until recently, sleep was believed to be important primarily for restoring brain function. However, increasing evidence suggests that sleep also modulates the metabolic, endocrine and cardiovascular systems. Pioneer studies conducted by Kleitman, Aserinsky and Dement 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. Phases 3 and 4 are considered the deeper stages of NREM sleep and occur predominantly

early in the night, whereas REM sleep appears at intervals of approximately every 90 minutes. Usually four to six of these sleep cycles occur each night, with REM sleep episodes becoming longer and NREM sleep episodes becoming shorter and lighter over the course of the night.

Sleep is well documented to exert important modulatory effects on most components of the endocrine system. These relationships indicate the importance of the CNS and of sleep in regulating endocrine function (Rubin and Poland, 1976; Leproult and Van Cauter, 2010). Indeed, sex steroid hormone concentrations are significantly associated with several lifestyle factors, including sleep (Goh et al., 2007). The impact of hormones on sleep can be more readily investigated in humans than in animals, probably because of well-established methods such as frequent blood sampling, sensitive assays of blood elements, and complete polysomnographic recordings (Van Cauter, 2005).

Testosterone shows both circadian and ultradian rhythms, as pointed out by Borst and Mullingan (2007). The circadian rhythm results in peak testosterone levels during the early morning period that then fall during the day (Boyar et al., 1974, Luboshitzky et al., 2001, 2002). The overall diurnal rhythm of testosterone peaks around 08:00 h and enters a trough around 20:00 h (Resko and Eik-Nes, 1966; Plymate et al., 1989). The ultradian rhythm has a cycle whereby the testosterone concentration oscillates approximately every 90 minutes. This ultradian rhythm represents the burst-like secretory pattern of testosterone, which is superimposed on testosterone's basal or tonic secretion (Borst and Mullingan, 2007).

Testosterone concentrations start to rise with sleep onset and then reach a plateau at REM sleep onset approximately 90 minutes later (Evans et al., 1971; Hirshkowitz et al., 1997). 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 (Luboshitzky et al., 2001). For instance, Liu et al. (2003) observed shorter sleep time with decreases in both NREM and REM sleep in

older men after high-dose testosterone treatment. For review, see Andersen and Tufik (2008).

Nocturnal testosterone rhythm is related to deep sleep (Veldhuis et al., 2000) and REM/NREM cycles (Schiavi et al., 1992). In 1971, Evans et al. reported that testosterone concentrations were increasing prior to the second REM sleep episode, and a peak occurred at the onset of the third REM episode. There was a decrease when the subject returned to sleep. The authors concluded that REM sleep did not trigger the production of testosterone; however, there seems to be a link between the neurophysiological state involved in REM sleep and the regulatory mechanisms involved in testosterone synthesis.

In a series of studies, Luboshitzky and colleagues investigated whether reproductive hormone levels are correlated with sleep architecture. For this purpose, they determined the nocturnal serum levels of testosterone, LH and FSH in men. Specifically, testosterone levels were lowest when the subjects were awake and were highest during the first REM sleep episode. Moreover, correlation analyses indicated that the longer the REM sleep latency, the slower the rise in testosterone (Luboshitzky et al., 1999, 2001). The authors discussed how the circadian rhythm of testosterone could be under the control of LH and circadian fluctuations in other hormones, diurnal changes in Leydig cell response to LH, or sleep-associated variations in testicular blood flow (see Luboshitzky et al., 1999 and references therein). To this point, it is important to note that some authors associate the testosterone increase during REM sleep with the frequent erections in this phase.

A more recent study reported that testosterone levels in young men rise during daytime sleep just as in nighttime sleep, but the levels fall upon waking (Axelsson et al., 2005), thus confirming that sleep, rather than a circadian rhythm, is critical for testosterone regulation (Schiavi et al., 1992). Healthy young men showed comparable blood testosterone levels during sleep regardless of when they chose to sleep during the day, as long as they managed to sleep for the same duration (Axelsson et al., 2005).

To address the age-specific changes in the regulation of LH-dependent testosterone secretion, Liu and colleagues assessed responsiveness to varying endogenous gonadotropin outputs in normal men. For instance, Liu et al. (2005) reported that healthy older men fail to achieve testosterone concentrations equivalent to those in young men in response to pulsatile LH stimulation. Importantly, it has been documented that pulsatile, and thus total, testosterone secretion declines in older men, although the reasons for this decrease are not fully understood. Mean testosterone concentrations over a 24 h period were also lower in the elderly (Bremner et al., 1983; Liu et al., 2005).

Several studies have indicated a relationship between testosterone release and sleep stages in men, although further studies are warranted to fully elucidate this bidirectional relationship (Penev, 2007; Andersen and Tufik, 2008). In particular, Barrett-Connor et al. (2008) reported that lower testosterone levels were associated with less consolidated sleep (decreased sleep efficiency and increased awakenings) in elderly men. Moreover, both high and low circulating testosterone concentrations may be associated with sleep disturbances. A marked reduction in sleep time was observed after testosterone administration (Liu et al., 2003), whereas testosterone raises the nocturnal metabolic rate (White et al., 1985), which can impair sleep patterns and, consequently, the quality of sleep.

In 2009, Goh and Tong observed that men tend to sleep for shorter durations as they age. Moreover, total testosterone levels were highest in men who slept between 6 to 8 hours or more. Further clinical investigations are needed to address sleep regulation and testosterone levels at several time-points in male life, as well the interplay between sleep and androgen levels. According to Axelsson et al. (2005), sleep duration, sleep quality, and time awake during sampling should be measured when determining testosterone concentrations.

-Clinical findings in women

It is known that sleep affects the episodic secretion of gonadotropin hormones (Hall et al., 2005). In addition, alterations in the endocrine profile can lead to direct influences on sleep-wake cycles. Women in particular are exposed to several hormonal changes over their lifetime. Moreover, women may also present with hormone imbalances that affect sleep duration and quality. **Adult women of all ages report more sleep problems, including inadequate sleep time and insomnia than do their male counterparts** (Bixler et al., 2002; Collop et al., 2004; Zhang and Wing, 2006; Silva et al., 2008; Bittencourt et al., 2009). Moreover, women report nightmares twice as frequently as do men (Ohayon et al., 1997). The reasons for such gender discrepancies are attributed to hormonal fluctuations over menstrual or estrous cycles, a factor that has been associated with sleep variations in both humans and rats (Hachul et al., 2006, 2010, 2011; Antunes et al., 2006, 2007).

Although both estrogen and progesterone are necessary in the female cycle and although their influence on sleep has been investigated, few studies have focused on the effect of testosterone on sleep in women, despite an extensive body of literature that describes the effects of testosterone on sleep in men. Among those few studies, they usually are limited to women with sleep disorders.

Sowers et al. (2008) examined the relationship of testosterone and sleep in women. Their results indicated that lower baseline levels of testosterone were modestly but significantly associated with increased wake after sleep onset. No other associations of sleep measures with menopause status were observed in models that included testosterone before or after adjusting for other variables. The authors pointed out that selected aspects of sleep in women may also be sensitive to variations in testosterone levels. The Seattle Midlife Women's Health Study reported no association between sleep disruption and testosterone, although a negative trend was observed (Woods et al., 2007). Studies describing the effects of testosterone in women are rare and demonstrate inconsistent findings, probably because

of the complexity of measuring hormonal androgen levels across the menstrual cycle and many other confounding factors, such as the use of birth control pills, normal versus abnormal cycles, and baseline testosterone levels.

- Sleep disturbances and androgen levels

Several factors may influence the normal diurnal rhythm of testosterone secretion. More recently, sleep has been considered a variable with marked influence on androgen levels. However, as pointed out by Barrett-Connor et al. (2008), limited attention has been paid to the potential association of sleep disturbances with testosterone levels and an association with endogenous testosterone levels.

The average sleep duration has decreased over the last several decades. This sleep impairment may result from various common sleep disturbances, such as insomnia and obstructive sleep apnea (OSA), and may lead to striking alterations in metabolic and endocrine functions (Spiegel et al., 1999). In particular, OSA is one of the most common sleep disorders and is characterized by an airflow interruption despite persistent respiratory efforts, thus causing chronic sleep deprivation due to frequent awakenings at the termination of apneic episodes. Furthermore, long-term sleep loss may represent a novel risk factor for several outcomes, such as weight gain, insulin resistance, and Type-2 diabetes. The diurnal variation disturbances of testosterone when routine sleep-wake cycles were disorganized (Nieschlag and Ismail, 1970) led Evans et al. (1971) to suggest that overnight concentrations of testosterone are linked to sleep.

Sleep and breathing disorders are now seen as major public health problems. The main breathing disorders associated with sleep are OSA, central sleep apnea, and hypoventilation. Androgen levels may stimulate breathing directly at the level of the CNS or via peripheral chemoreceptors, whereas others indirectly affect breathing by altering metabolic rate (Saaresranta and Polo, 2002). Interaction among sex hormones and sleep-

related breathing supports the notion that these hormones play an important role in sleep disorders (Vidal and Vaughn, 2001; Andersen and Tufik, 2008). For instance, habitual snoring was the most common complaint, reported by about 20% of interviewees in a large survey (Pires et al., 2007). Moreover, a large Brazilian community-based survey study demonstrated a high 32.9% prevalence of sleep apnea (Tufik et al., 2010). In fact, this common disorder that affects the vital functions of respiration and circulation has a major influence on the endocrine system.

-Men

Testosterone may inhibit breathing via several mechanisms, because upper airway patency is determined by many structural and neuromuscular factors controlling pharyngeal airway size and collapsibility (Liu et al., 2003). Testosterone has been reported to be associated with increased ventilatory response to hypoxia in hypogonadal men, which may cause or exacerbate sleep apnea by driving CO₂ levels below the apnea threshold (Dempsey and Skatrud, 1986). However, testosterone blockade did not affect sleep apnea or chemosensitivity (Stewart et al., 1992). A limited number of studies have investigated the influence of this hormone on upper airway resistance during sleep or the influence of nocturnal apneic events on the reproductive system.

The well-established male preponderance of OSA led to the hypothesis that gonadal hormones were involved in the pathological mechanism of this sleep-breathing disorder (Young et al., 2004; Liu et al., 2007). Indeed, decreased morning testosterone concentrations have been reported in apneic men (Santamaria et al., 1988; Grustein et al., 1989), whereas induction of OSA or symptom exacerbation have been described after testosterone supplementation in hypogonadal males (Saaresranta and Polo, 2002; Liu et al., 2003). Cistulli et al. (1994) demonstrated that testosterone was associated with an increase in upper

airway collapsibility during sleep and that this increase may be the mechanism by which testosterone induces or exacerbates OSA.

Several lines of evidence suggest that both OSA and coexisting comorbidities contribute to low testosterone concentrations. For example, the severity of hypoxia may be an additional factor in the lower testosterone levels, regardless of body mass index and abdominal fat distribution (Gambineri et al., 2003). Obesity and aging, in conjunction with hypoxia and sleep fragmentation, have also been indicated as additional contributing factors in the decreased pulsatile testosterone concentrations in OSA subjects (Luboshitzky et al., 2005). In particular, Luboshitzky et al. (2002) performed an investigation that clearly demonstrated that both LH and testosterone were significantly lower in OSA men compared with controls free of any breathing disorder during sleep, independent of age and degree of obesity. The authors' conclusion suggests that sleep fragmentation and, to a lesser extent, hypoxia (in addition to the degree of obesity and aging) may be responsible for the central suppression of testosterone in OSA patients.

There is an overall decline in levels of testosterone with age. Not many studies have addressed age-associated changes in male sex hormones and sleep. Liu and colleagues (2003), in a randomized placebo-controlled study, clearly demonstrated the adverse effects of testosterone therapy on sleep and breathing, particularly in older men. The results showed that testosterone injections shortened sleep, worsened sleep apnea, and increased the duration of hypoxemia.

Endocrine abnormalities on androgen levels in men with OSA have been shown to be reversed after continuous positive airway pressure (CPAP) therapy (Santamaria et al., 1988; Grunstein et al., 1989). The effect of chronic CPAP treatment **on nocturnal testosterone** in OSA patients reported to be partially corrected during the CPAP treatment (Luboshitzky et al., 2003).

In summary, several factors such as aging, obesity, hypoxia, and sleep fragmentation may account for the reduced testosterone levels observed in OSA patients. However, the complete integrated mechanisms involved in this highly prevalent sleep disorder still needs further research. An overlapping vicious cycle can be initiated by the decreased levels of testosterone caused by OSA mainly due to hypoxia or fragmented/disrupted sleep. Therapy with CPAP reverses the negative effect of OSA on testosterone levels. It is therefore appropriate to consider the complex interactions among hormones and breathing, which challenge us to intensify research on how the endocrine system influences breathing.

-Women

The menstrual cycle is well known to be characterized by fluctuating progesterone levels (Zelevnik and Pohl, 2006), and progesterone has a modulating influence on sleep (for review, see Andersen et al., 2006). However, sleep data on the effects of testosterone in women are still scarce. For instance, polycystic ovarian syndrome is known to be directly associated with elevated androgen levels. Women suffering from this condition have a higher apnea-hypopnea index than do healthy females (Fogel et al., 2001).

Ovaries are a major source of androgen, which modulates sleep. Because there is senescence in ovarian function with age, it can be expected that changes in sleep pattern will also occur in women over their lifetime. Indeed, **ovarian hormones have been reported to be** implicated in the regulation of sleep and waking (Lindberg et al., 1997). Nevertheless, exogenous administration of testosterone in women induces sleep apnea (Johnson et al., 1984). Moreover, testosterone increases baseline ventilation during wakefulness, altering the apneic threshold and increasing ventilator sensitivity to CO₂ during sleep in healthy women (Zhou et al., 2003; Ahuja et al., 2007; see Behan and Wenninger, 2008 for review).

Women experience considerably more sleep problems than do men (Lindberg et al., 1997, Ohayon et al., 1997; Bixler et al., 2002; Collop et al., 2004; Zhang and Wing, 2006;

Silva et al., 2008; Bittencourt et al., 2009) with resulting decreases in waking functions. This area is one of significant concern that has not, to date, been adequately addressed (Trenell et al., 2007). Furthermore, sleep disturbances worsen during the transition to menopause (see Hachul et al., 2010), and symptoms vary according to the stage of reproductive aging workshop (STRAW) menopause transition (Soules et al., 2001). This period involves a progressive decline in ovarian follicular populations and reduced steroidogenic capacity by the ovarian stroma. As reviewed by Lobo (2001), testosterone is efficiently aromatized in many tissues, including in the brain; thus, the effects attributed to testosterone may be due to estrogen, and thus, estrogen replacement alone may be sufficient (Roselli et al., 1993).

Given the large number of women experiencing sleep disturbances and consequent decreases in waking function during menopause, the “estrogen protective” phase has been proposed during the reproductive years in OSA disorders. In a large representative random sample survey, Bixler et al. (2001) reported that the prevalence of sleep apnea was quite low in premenopausal and postmenopausal women with hormone therapy (HT). However, postmenopausal women with no hormone treatment had a significantly higher prevalence of sleep apnea than did premenopausal women with HT. Further studies with a large sample of women also observed that menopause increased the likelihood of sleep-disordered breathing (Young et al., 2003) and that HT reduced sleep-disordered breathing (Shahar et al., 2003).

More recently, Hachul et al. (2009) using the STRAW recommendations, reported that although early menopause is associated with several symptoms, sleep complaints were higher in the late post-menopausal group. However, polysomnographic findings reveal no significant differences between early and late postmenopausal women. The same group previously found that objective sleep was not significantly improved after estrogen and/or progesterone treatment, although there was a trend toward improvement in objective sleep quality with hormonal treatment (Hachul et al., 2008). In females, the increase in endogenous testosterone levels may be hypothesized to coincide with the decrease in estrogen levels is

associated with peri- and menopausal phases. These findings may also contribute to the increased prevalence of sleep-disorder breathing after menopause (Young et al., 2003 and for review, Trenell et al., 2007). To test whether the administration of testosterone increases the apneic threshold in premenopausal women, Zhou et al. (2003) examined the effects of transdermal testosterone on NREM sleep in healthy, non-snoring, premenopausal women. The results of an amplified apneic threshold in these women led the authors to suggest that increased breathing instability during sleep in men is related to the presence of testosterone.

More research is required to understand the complex relationship between sleep apnea and hormonal function. In women, although HT showed beneficial effects on OSA, the risks and benefits should be evaluated for this treatment in postmenopausal women.

-Pre-clinical findings

Animal models provide an excellent research source to investigate how reproductive hormones modulate sleep-wake cycles. For example, Karatsoreos et al. (2007), using a transgenic mouse strain, reported that the suprachiasmatic nucleus regulates circadian rhythms in gonadal hormone secretion, and in turn, androgens act on their receptors within this nucleus to alter circadian function.

To investigate whether androgen replacement in males and estrogen replacement in females alters sleep pattern and sleep rebound after sleep deprivation, Paul et al. (2009) performed an experimental study in inbred mice. The results showed that gonadectomy suppressed their previous findings of sex differences during baseline sleep recording (Paul et al., 2006). Moreover, females treated with estradiol showed a decrease in sleep (dark phase). Conversely, testosterone replacement in males induced an increase in sleep time, even in the dark phase. After 6 hours of sleep deprivation, hormone-treated animals of both sexes exhibited similar amounts of recovery sleep, although hormone-treated males exhibited slightly more sleep than did those in the control group. The authors concluded that

androgens and estrogens are primarily responsible for sex differences in baseline sleep-wake cycles; however, they do not have marked effects on homeostatic sleep rebound after sleep deprivation.

In rats, alterations in sleep patterns occur during the estrus cycle (Kleinlogel, 1975; Schwierin et al., 1998). This cycle in rodents is divided into four phases: proestrus, estrus, metestrus and diestrus. Each phase has different physiological and cytological characteristics. The length of different estrus cycle phases is based on vaginal smear analyses. Proestrus lasts for 12 to 14 hours; estrus, 25 to 27 hours; metestrus, 6 to 8 hours; and diestrus, 55 to 57 hours (Freeman, 2006). **Of note, there is hormonal oscillation during the estrus cycle. There are 2 phases of progesterone secretion, one occurring in the diestrus phase. This peak probably arises from the newly formed corpora lutea. The other appears during the late afternoon of proestrus (Freeman, 2006). In contrast, testosterone and androstenedione have secretion patterns similar to that of estradiol. In the diestrus, the plasma concentration begins to rise and continues to do so during this phase. In early proestrus, the values reach their peak, whereas the plateau occurs in mid-proestrus (Freeman, 2006).**

In the 1990s, Fang and Fishbein (1996) reported no alterations in slow wave sleep (SWS) during the estrus cycle. However, in the proestrus phase, there is a reduction in the amount of NREM and REM sleep in the dark phase as well as a reduction SWS activity in NREM sleep when compared with other estrus cycle phases (Colvin et al., 1968; Zhang et al., 1995; Schwierin et al., 1998). Moreover, marked reductions in REM sleep compared with other days of the estrous cycle have been reported in proestrus (high estradiol-level) females (Hadjimarkou et al., 2008). These authors suggest that hormones in females play a major role in the regulation of sleep and arousal via the activation of neurons in key sleep and arousal centers. Because of these arousing properties, females with higher levels of estrogens have an increased awake time compared with females with low or absent gonadal

hormones (Colvin et al., 1968; Kleinlogel, 1990; Zhang et al., 1995; Fang and Fishbein, 1996; Schwierin et al., 1998; Paul et al., 2006). Recently, Andersen et al. (2008) demonstrated that the estrus cycle had an undetectable influence on sleep patterns during baseline recording in female rats. However, females in the diestrus phase of the estrus cycle showed a significant increase in SWS compared with males. In response to sleep deprivation, females demonstrated marked alterations in the rebound period compared with males.

In rats, it is common to use an experimental model called paradoxical sleep deprivation (PSD). This model is based on a platform technique and involves numerous awakenings that predominantly affect the paradoxical stage of sleep. Thus, the PSD model mimics sleep fragmentation due to repeated awakenings and is a useful tool to investigate the effects of sleep loss on sleep patterns (Andersen et al., 2008; for review, see Tufik et al., 2009). In females, PSD provokes a significant increase in paradoxical sleep on the first day of the rebound dark period in all groups (proestrus, estrus, and anestrus). These results differ from females in diestrus and males who maintained this increase until the second day of the rebound dark period. It is possible to infer that the marked alterations in hormonal concentrations in anestrus rats (Antunes et al., 2006) influence their sleep architecture by prolonging the recovery effects of sleep loss. In agreement with previous findings reporting that diestrus females present with a disruption of cycle when submitted to PSD, these recent data indicate that these females also have marked sleep changes.

In response to sleep deprivation, women show a more dramatic increase in slow wave activity after 40 hours of total sleep deprivation than do age-matched men, demonstrating a greater response to sleep loss in women (Armitage et al., 2001). Because of the lack of studies, further investigations are warranted to address the questions of how sleep is differentially regulated between genders and the magnitude of the consequences of sleep loss in both males and females.

Studies utilizing sleep deprivation have been conducted to comprehend the mechanisms involved in the regulation of sleep. Additionally, this methodology has been used to investigate the overall consequences caused by sleep loss in humans due to spontaneous sleep curtailment or induced sleep disturbances. For instance, Luboshitzky et al. (2002) pointed out in their study that, under the sleep fragmentation paradigm, sleep was repeatedly interrupted for much longer periods than the brief arousal that characterizes the apneic patient. Similarities do exist between these two conditions of sleep deprivation, as both lead to sleep fragmentation due to an increased number of awakenings.

Our group has consistently documented that sleep deprivation methods in experimental animals result in a constellation of behavioral (Tufik et al., 1978; Frussa-Filho et al., 2004; Andersen et al., 2003a, 2007; Fukushiro et al., 2007; Alvarenga et al., 2009; Patti et al., 2010) and hormonal changes in both young (Andersen et al., 2003b) and adult and old rats (Andersen et al., 2004a, 2005).

Testosterone is a hormone particularly affected by sleep deprivation in rats. A series of studies has demonstrated the drastic effects that PSD has on androgen levels. Decreased concentrations of testosterone in sleep-deprived male rats have consistently been observed (Andersen et al., 2003b, 2004b, 2007). Furthermore, selective sleep loss induced decreased levels of estrone and increased levels of progesterone, prolactin, corticosterone, and catecholamines after four days of sleep deprivation in male rats (Andersen et al., 2005). Testosterone has shown to drop by 30% in adult sleep-deprived males compared with a control group (Andersen et al., 2002).

Interestingly, the assessment of testosterone levels across the estrus cycle in female rats demonstrates that this hormone is lower in rats in diestrus than in those in proestrus. When female rats were exposed to sleep deprivation, a significant reduction was noted in estrus compared with in the proestrus and diestrus groups. Testosterone levels did not differ significantly among PSD and the respective normal sleep group for each estrus phase

(Antunes et al., 2006). Although studies in laboratory animals can provide evidence of the mechanisms by which testosterone can modify respiratory parameters, only limited studies have focused on the effects of testosterone on ventilation in animals. For instance, acute testosterone administration in neutered male cats increased hypoxic and hypercapnic ventilatory responsiveness and as well as hypoxic sensitivity of the carotid body (Tatsumi et al., 1994).

As hypoxia and sleep fragmentation are common events in OSA patients, the development of an animal model for hypoxia is of great interest in order to mimic sleep apnea and to address the mechanisms involved in this pathological condition. Intermittent hypoxia models in both rats and mice that parallel hypoxia seen in humans have been used consistently by several groups. Chronic sustained hypoxia increases wakefulness, reduces paradoxical sleep and induces fragmented sleep (Laszy and Sarkadi, 1990), whereas milder intermittent hypoxic insults have proven to be less disruptive to sleep architecture (Gozal et al., 2001). Following the proposal that hypoxia and sleep fragmentation are implicated in cardiovascular risk associated with OSA, Perry and Decker (2010) pointed out that animal models have revealed that intermittent hypoxia is the critical stimulus underlying the development of increased sympathetic activity and hypertension.

As OSA has been linked to intermittent hypoxia and studies of the interaction between hypoxia and reproductive systems are limited and inconclusive, it is relevant to conduct studies utilizing an intermittent hypoxia model in laboratory animals. Indeed, lower testosterone levels have been reported in patients following hypoxia administration (Semple et al., 1984). Accordingly, Hwang et al. (2010) have recently shown, using a rat model, that testosterone levels of plasma and Leydig cell culture medium are increased following intermittent hypoxia, in contrast to human data (Luboshitzky et al., 2002, 2003, 2005). So far, the description of the mechanisms related to testosterone in the OSA/hypoxia experiments is incomplete.

4. Testosterone and sexual behavior

Because the field of neuroendocrinology has largely focused on the dominant role of testosterone in sexual behavior, most studies mainly involved males. It is well documented that testosterone influences the behavior and sexual function of men (Nóbrega et al., 2009). Thus, it can be stated that androgens play an integral role in the sexual behavior in other animals as well as in humans. For instance, many studies have found that testosterone plays a role in sexual desire, sexual thoughts, intensity of sexual feelings, and sexual activity (Davidson et al., 1982; Bagatell et al., 1994). Of note, inconsistencies in the effects of testosterone on sexual behavior have also been reported. Studies with women are confounded by low concentration levels of this hormone and difficulties in measurement. However, not all studies investigating exogenous administration of testosterone in women measure serum levels. In concert, these facts indicate a significant need to study the role of testosterone in the sexual behavior of women.

-Effects in men

Erectile function is a neurovascular process that depends on the health of the central and peripheral nervous systems, the vascular health of the erectile tissue, and the endocrine milieu (Traish et al., 2007; see Traish, 2009 for review).

According to Goh and Tong (2009), androgens may have a limited effect on sexual motivation in men. As noted in the present study, sexual functions were associated with age and other sex steroids; hence, some of the differences noted in various studies might have arisen, in part when age and other factors were not taken into consideration for the analysis. For instance, Schiavi et al. (1997) pointed out that androgen administration to eugonadal men with ED may activate their sexual behavior without enhancing erectile capacity and without effects on mood or psychological symptoms. Androgen deficit does not present a homogenous picture in aging men, and its diagnosis is not as simple (Gooren, 2003).

With respect to illicit androgen abuse, although some men report increased sexual arousal, sexual complaints such as potency and ejaculatory problems are also commonly described (Eklof et al., 2003). Thus, the negative consequences of illicit androgen abuse should be widely disseminated to the general population, especially to adolescents.

-Androgen replacement therapy

Male hypogonadism can be defined as failure of the testes to produce normal concentrations of testosterone, combined with signs and symptoms of androgen deficiency. In men, in addition to the decline of androgen levels due to aging (andropause), different factors can alter androgen levels. For instance, OSA patients present with several important outcomes, such as obesity, hormonal changes, sexual dysfunction, and metabolic and cardiovascular alterations. Several studies have shown obesity, when associated with OSA, **to be a main factor leading to** impaired reproductive function (Hammoud et al., 2007, 2008). In fact, some hormones are known to be responsible for the development and maintenance of reproductive function. Dysfunctional hormonal changes could be associated with the relationship between OSA and erectile function (Zhuravlev et al., 2009; Andersen et al., 2011), suggesting that sleep apnea itself may result in changes to male fertility.

As reported, total and free testosterone levels progressively decrease with increasing body weight, and this decline is associated with a progressive decrease in SHBG concentrations in the obese males (Pasquali, 2006). Androstenedione and DHT are usually normal or slightly reduced. Changes in testosterone metabolism through 5 α -reductase activity may also occur in obesity, although this process is still not fully elucidated (Pasquali, 2006). Abdominal fat distribution may also have a negative influence on testosterone concentrations in men (Wajchenberg, 2000; Pasquali, 2006). However, the increased estradiol found in obese men is associated with significant gene expression of aromatase

(CYP19) in adipose tissues, leading to impairment of the reproductive system (de Boer et al., 2005).

Testosterone therapy (TT) has been widely used for many years in cases of hypogonadism and infertility. The first historical evidence that testosterone contributed to virility came from early experiments by Berthold in 1849 when he transplanted testes from roosters to the abdomen of capons (castrated roosters) and observed that animals with transplanted testes behaved like normal roosters (see Simmer, 1961). Over time, several experimental manipulations were performed to elucidate the processes involved in the supplement of testosterone. Transdermal testosterone gels have been used in the US since 2000. These compounds have emerged as a favored mode of testosterone substitution. Testosterone reaches a steady-state in the first 24 hours of application and remains in the normal range for the duration of the application. Recently, Lakshman and Basaria (2009) reported that this pharmacokinetic profile was comparable to that of the testosterone patch but superior to injectable testosterone esters, which are associated with peaks and troughs with each dose. Despite advisory statements involving TT in OSA that emerge frequently in the TT guidelines and literature, Hanafy (2007) did not demonstrate consistent evidence that TT causes and/or aggravates OSA. Thus, this is still an area of controversy and requires more attention from clinicians and researchers.

-Anabolic-androgenic steroid abuse

Initially, anabolic-androgenic steroid abuse was confined to athletes seeking enhancement of their strength and endurance. Recently, the general population has been widely using these compounds for several reasons (for review, see Talih et al., 2007). Anabolic-androgenic steroids are made by modifying the testosterone molecule.

As glucose intolerance and lipid and neuroendocrine abnormalities are consequences of anabolic-androgenic steroid use, changes in sleep regulation can be expected. Indeed,

some studies have reported several sleep disorders in anabolic-androgenic steroid users (Eklof et al. 2003; Parkinson and Evans, 2006). Generally, the main sleep disturbances are insomnia and decreased sleep time. Venancio et al. (2008) found, in addition to reduced sleep efficiency, a higher number of awakenings after sleep onset in the steroid user group.

Recently, Daly et al. (2010) examined the effects of methyltestosterone administration on the levels of monoamine metabolites, neurohormones, and neuropeptides in the cerebrospinal fluid of healthy men. The results showed that short-term anabolic-androgenic steroid use affects brain neurochemistry, increasing cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA). These changes were correlated with increases in “activation” symptoms (energy, sexual arousal, and diminished sleep). The alterations found in the serotonergic system (serotonin is related to sleep-wake mechanisms) suggest that serotonin is a key factor in sleep disorders caused by the use of anabolic-androgenic steroids.

Illicit androgen abuse has become an epidemic over the last few decades. To boost appearance and enhance sports performance, elite athletes and bodybuilders have denied the serious and long-lasting consequences of their misuse. Physicians should be alerted to the signs and symptoms of steroid abuse. Early recognition and intervention may prevent adverse and potentially irreversible consequences (Talih et al., 2007).

-Role in women

In this section, we will review some of the articles reporting the influence of androgens in women during the reproductive stage of life. The role of testosterone during postmenopausal years will also be discussed. In addition to the effects of androgen in men, testosterone also modulates sexual behaviors in women. In the latter half of the 1970s, Persky et al. (1978) studied plasma testosterone levels and the sexual behavior of couples. During 3 menstrual cycles, the initiation score was significantly correlated with the wives' responsivity (degree of sexual gratification). The husband's plasma testosterone levels were

significantly correlated with the initiation-responsivity data. Self-rated gratification scores obtained from the wives were also significantly correlated with female testosterone levels. The study showed a dichotomous profile among wives. They found a high baseline testosterone level in some women and a low baseline level in others. The high baseline correlated with high self-rated gratification and an ability to establish good interpersonal relationships. Thus, in the 1980s, androgens, not estrogens, were associated more with libido (Persky et al., 1982). Testosterone levels were associated with an increase in the frequency of intercourse. Another interesting result is the female ratio of androgen/estradiol, which peaks on the first day of the menstrual cycle (Persky et al., 1982).

In women, circulating androgens derive mainly from the adrenal cortex. Androstenedione, DHT and dehydroepiandrosterone are synthesized by the adrenal cortex and supply 50-90% of the circulatory stock (Persky et al., 1982). Interestingly, a classic study conducted by Waxenberg et al. (1959) showed that women submitting to adrenalectomy during treatment for metastatic breast carcinoma presented with a marked reduction in sexual behavior compared with women submitting to oophorectomy under the same clinical conditions. This result pointed to the possibility that female libido is androgen- rather than estrogen-dependent. Another situation involving androgens is a physiologic condition present during the climacteric phase as explored by Persky et al. (1982). Young women showed markedly higher levels of androgens than did postmenopausal women. However, this endocrine profile was not supported by an adrenopause condition in postmenopausal women, because there was no significant difference among cortisol levels or in dexamethasone-suppression tests (Abraham et al., 1974).

Evidence in women is limited by the lack of normative data for androgen levels, and much controversy exists over the types of treatment. Neither sexual nor mood questionnaires have been used consistently; thus, comparisons between androgen secretion patterns and

possible behavioral changes during the menstrual cycle are not available (Nobrega et al., 2009).

In terms of sexual function, testosterone and free testosterone have been correlated with decreased sexual frequency and desire (Bixo et al., 1995; Dow et al., 1983; Lobo, 2001). Symptoms of decreased sexual arousal and function have also been found to be more prevalent in women with reduced testosterone levels (Bachmann and Leiblum, 1991). Indeed, controlled trials have showed an improvement in parameters of sexual function and well-being with testosterone replacement over the use of estrogen alone (Lobo, 2001). Controversy exists as to whether the improvements, which have been observed in prospective studies, are due to the pharmacological or the physiological effects of testosterone replacement. Indeed, the data suggest that a level of testosterone above the physiological range is necessary for significant improvement (Lobo, 2001).

Recent studies have speculated that testosterone influences mate choice, sexual behavior, and parenting, which could improve mating success among non-mothers compared with mothers that present with lower waking testosterone (Harris et al., 1996; Grant and France, 2001; Braunstein et al., 2005; Buster et al., 2005; van Anders et al., 2007; Davis et al., 2008). As pointed out by Schwenkhagen (2007), studies with women involving testosterone treatment were based on androgen effects on sexual functioning and psychological well-being. Since the 1980s, several studies have suggested that including testosterone with HT would have a beneficial effect on sexual function in postmenopausal women. A growing body of data has demonstrated that exogenous testosterone improves many facets of sexual function, including arousability, desire, fantasy, orgasm, and overall satisfaction (Meston et al., 2004; Abdullah and Simon, 2007). Randomized controlled trials demonstrate the efficacy of testosterone therapy in correcting sexual desire disorders in postmenopausal women (Simon et al., 2005; Hubayter and Simon, 2008). A single dose of testosterone sublingually administered to sexually functional women was able to promote

increased genital and subjective sexual arousal (Tuiten et al., 2000). In this context, Shifren et al. (2006) designed a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial testing the testosterone patch in naturally menopausal women diagnostic with hypoactive sexual desire disorder. The short-term treatment with the testosterone patch significantly increased sexual desire and activity, and personal distress in naturally menopausal women was reduced in comparison with the group receiving placebo patches for in the same experimental period.

Considering all of these aspects, testosterone is an important steroidal hormone involved in female sexual control. Thus, during ovarian failure or in some female sexual disorders, it is important to consider a request for testosterone replacement to help these women acquire a more desirable sexual status of well-being.

4- Animal model investigations

Copulation is probably the most natural and most frequently examined behavior in laboratory tests of sexual function, and there are obvious homologies between human copulatory behavior and that of many animal species (Pfaus, 1996). However, the conditions of testing copulatory animal behavior vary from the usual highly restricted space in which a male-female pair is observed to a more natural space, which gives the female greater control over the pacing of copulation and in which multi-male, multi-female groups may permit competition between mates (McClintock, 1984). Indeed, the use of animal models is of great relevance to elucidate the possible mechanisms involved in sexual behavior.

Numerous studies demonstrate the influence of hormonal factors that determine the overall expression of copulatory activity. The expression of sexual behavior in mammals is modulated by the action of androgens, especially testosterone. Thus, changes in the concentration of circulating hormones may lead to alterations in sexual behavior. A look into the history of behavioral neuroendocrinology teaches us how transcendental discoveries

regarding brain-hormone interactions were conducted in different species, including roosters, rabbits, guinea pigs, hamsters, rats and even large-animal species such as pigs, lambs and goats. Currently, the rat is the species most used in behavioral neuroendocrine studies, although other small species are also studied.

In particular, the use of rats in the study of behavioral neuroendocrinology is due to not only their availability and ease of handling but also their sexual behavior patterns, which are characterized by stereotypical motor patterns that are easily identifiable and readily manipulated by hormones. Both male and female rats have a peculiar sexual behavior pattern for which it is relatively easy to analyze the influence of gonadal hormones and their interactions with neurotransmitter systems. In this review, we discuss the basics of rat sexual behavior and its use as a tool in understanding the neuroendocrine mechanisms underlying this phenomenon. Among gonadal hormones, testosterone is considered the main candidate for modulating sexual function in male rats. Furthermore, its level can be modified by sexual experience.

The rat is a nocturnal mammal, meaning that most of its activity occurs during the dark phase of the 24-hour cycle. Therefore, the common conditions used to record rat behavior include a room with an inverted light-dark cycle. Sexual behavior is recorded under a dim red light, which is undetectable to the rat but allows the researcher to clearly observe the events. The rats are placed inside a Plexiglas cage with sawdust on the floor of the cylinder. Usually the male rat is first placed into the arena for a 5-minute habituation period, and the female is subsequently placed in the arena with the male. Assessment of male sexual behavior requires the participation of a receptive female, which will be the stimulus.

Sexual behavior is directed by a sophisticated interplay of steroid hormone actions in the brain. Among the steroid hormones, testosterone is considered the main candidate for modulating sexual function in male rats. Testosterone secreted by the fetal testes plays a key role in the permanent organization of the developing CNS toward masculine patterns.

Importantly, the brain, especially the hypothalamus, expresses the enzymes that transform testosterone into compounds which amplify (DHT) or differentiate (estrogens) its actions; these enzymatic systems include 5 α -reductase and aromatase, respectively.

Testosterone is involved in the activation of male rat mating behavior, is secreted by Leydig cells and is metabolized in target cells to either E₂ (by aromatization) or DHT (by 5 α -reduction). Krey and McGinnis (1990) demonstrated that, in castrated rats, plasma testosterone levels were undetectable within 24 h of castration. However, copulatory ability decreased gradually over days or weeks. Five to 10 days of testosterone was usually required to reacquire mating behavior (McGinnis et al., 1989; Hull and Dominguez, 2007). Adult male rats stressed during the prenatal phase have reduced testosterone levels and, consequently, reduced copulatory activity (Gerardin et al., 2005). However, Pereira et al. (2006) demonstrated that neonatal administration of testosterone was able to inhibit the changes in sexual behavior during adulthood caused by prenatal stress.

Androgens regulate sexual arousal and the experience of sexual rewards that give rise to expectations of competent sexual activity, sexual desire, arousal and performance. Edinger and Frye (2007) reported that sexually experienced rats had increased testosterone levels compared with animals that were never exposed to sexual stimuli. Furthermore, testosterone was also significantly reduced in animals with low/no sexual performance compared with animals with excellent/adequate performance (Alvarenga et al., 2010). In addition to testosterone, estrogen and LH have also been consistently reported to be associated with sexual experience in male rats (Tenk et al., 2009; Wu and Gore, 2009).

Although testosterone is necessary for normal development of male sexual behavior, if an intact male is treated neonatally with testosterone (hyper-androgen condition), male sexual behavior in adulthood is disrupted (Henley et al., 2010). There is a possibility that the hyper-androgen treatment suppresses male sexual behavior by altering the male's partner

preference and by thereby reducing his motivation to approach the female (Diamond et al., 1973; Pollak and Sachs, 1975; Zadina et al., 1979; Piacsek and Hostetter, 1984).

The sexual behavior of male rats is characterized by repeated approaches and mounts upon the female. Mount and intromission latencies are defined as the time elapsed from the introduction of the female until the presentation of the first mount or the first intromission. When the first event is an intromission, then mount latency is equal to intromission latency. Ejaculatory latency is defined as the time elapsed from the first intromission to ejaculation. The number of mounts and intromissions preceding an ejaculation are also physiologically important parameters. In addition, some physiologically relevant indices can be obtained. The inter-intromission interval is the mean time elapsed between intromissions. The inter-copulatory interval is the mean time elapsed between any event, mount or intromission. The hit rate is obtained by dividing the number of intromissions by the sum of intromissions and mounts.

Male sexual behavior can be assessed by observing only one ejaculatory series, regardless of the duration. However, sexual behavior can also be observed for 30 minutes, recording all of the events that take place during that time. In the second scenario, if the male rat does not display any activity for 15 minutes, the test ends. In addition, sexual exhaustion can be assessed by allowing the male to freely copulate for several hours. Two behavioral criteria are applied to determine sexual exhaustion: the male rat spends more than 30 minutes without displaying any sexual activity or the male rat spends more than 90 minutes without having an ejaculation.

It has been reported that copulatory experience can alter sexual performance in male rats and that some rats display low sexual activity in the presence of a receptive female (Dahlof and Larsson, 1978; Frankel, 1981; Meisel and Sachs, 1994; Pfau and Wilkins, 1995; Bialy et al., 2000; Sura et al., 2001). Because copulatory experience can alter sexual performance in male rats, it is necessary to submit the male to sexual behavior training. We

have recently proposed a training protocol for acquiring sexual experience that consists of exposing the male rat to a receptive female for 15 minutes every other day for 9 days (Alvarenga et al., 2010). Testing was stopped if the male rat did not display any activity for 15 minutes. If the rats expressed intromission behavior, the timer was restarted for fifteen more minutes until ejaculation. Maximum latency was recorded for animals that did not exhibit any ejaculation. Thus, a 9-day training period was not sufficient for some male rats to acquire a good level of sexual performance. Whereas 42.5% of the rats displayed excellent sexual performance during the training sessions, 17.5% showed adequate performance, 7.5% had low sexual activity, and 32.5% of the rats did not display any sexual behavior whatsoever. Additionally, after 4 days of training, rats with excellent/adequate performance showed a significant decrease in ejaculation latency relative to the first day of training. Moreover, testosterone was significantly reduced in animals with low/no sexual performance compared with the excellent/adequate sexual performers. Hence, the training to acquire sexual experience is an important tool to standardize sexual activity as well the hormonal profile involved in this context. In summary, male sexual behavior is the result of complex interactions between neurotransmitters and hormones, which must interact in a harmonious sequence to express the desire and ability to mate. A number of manipulations can alter the proper development of this behavior. Thus, animal models are a reliable and powerful tool to analyze sexual behavior.

5. Association of testosterone, sleep and sexual function

The global population, especially those individuals living in industrialized countries, has been exposed to sleep deficit conditions. The chronic sleep restriction environment is usually associated with more demanding work-related activities, intense social life, long periods of internet usage, late-night shift work and sleep disturbances that collectively compromise normal circadian sleep in many people. For instance, in 1995, 27.6% (1.7

million) of Sao Paulo inhabitants complained of difficulty staying asleep (Pires et al., 2007). In addition to lifestyle changes that involve sleep curtailment, other factors, including obesity and several other prevalent diseases, have substantially exacerbated this problem. These alterations can be directly linked to complaints about sexual life. Although acute sleep deprivation (2 nights) has been associated with heightened sexual interest in male subjects (Zarcone et al., 1974) and patients with psychogenic impotence showed an increase in penile tumescence and rigidity after being sleep deprived for 24 h under an audiovisual stimulation condition (Ferini-Strampi et al., 1996), current sleep deprivation practices imposed on individuals in society today promote a chronic extension of sleep loss with long-lasting consequences. In particular, sleep restriction over long periods has been shown to have deleterious effects on the reproductive system, especially on sexual function.

-Men

Serum testosterone levels decline with age. Indeed, as recently pointed out by Goh and Tong (2009), age is a major determinant of many of the physiological changes in men with regard to sleep, sex steroid hormones levels and sexual activity. Their results showed that men with acute sleep restriction (<4 h daily) and those with moderate sleep restriction (4 to 6 h daily) had significantly lower androgen concentrations than did those who slept over 8 hours. Their study demonstrates a positive association between sleep duration and androgen concentrations in men living in society rather than men studied under experimental laboratory or military exercise settings, as reported in earlier studies (Opstad, 1992; Penev, 2007).

With aging, significant declines in sleep duration, bioavailability of testosterone and dehydroepiandrosterone sulfate (DHEAS) concentrations, coital frequency, engagement in masturbation, and frequency of masturbation were noted (Goh and Tong, 2009). Independent of age, sleep duration was positively associated with testosterone levels. In this fashion, some of the age-related changes in muscle mass, bone mineral density, fat mass,

and sexual and cognitive functions resemble those observed in young, hypogonadal men (Gray et al., 2005). With respect to how these functions affect testosterone, according to Axelsson et al. (2005), the log-linear increase with sleep suggests that sleep length is crucial for testosterone levels; short sleep reduces testosterone, and long sleep has the opposite effect.

Other significant components that change sexual life are androgen levels and sleep patterns in men with OSA. In fact, apnea-related hypoxic episodes lead to several awakenings during the night at the termination of each obstructive event. Consequences include long-term severe intermittent hypoxia and sleep fragmentation. Sleep fragmentation, in turn, disrupts diurnal testosterone rhythm, resulting in a considerable attenuation of the nocturnal rise (Luboshitzky et al., 2001). Moreover, nocturnal testosterone rise was significantly suppressed compared with that in control men of similar ages, and morning testosterone levels were measured in the hypogonadal range in 40% of the apneic patients (Luboshitzky et al., 2002).

Because of the interaction between androgens and sexual function, research interest has focused on the relationship between OSA and sexual dysfunction frequently reported by decreased libido in male patients with OSA. In their pioneer report, Guilleminault et al. (1977) demonstrated that 48% of sleep apneic men report ED, ejaculatory problems, and/or diminished libido. Subsequently, several other studies have reported similar findings.

The impact of sleep disturbances, in particular OSA, on erectile function have been recently reviewed (Hirshkowitz and Schmidt, 2005; Jankowski et al., 2008). Several mechanisms have been proposed to explain the link between ED and sleep disorders (Hirshkowitz et al., 1989; Goncalves et al., 2005). Hormonal, neural and endothelial mechanisms have been implicated in linking sleep disorders with ED. Recently, Jankowski et al. (2008) suggested a possible pathway for the development of ED in OSA through hypertension and diabetes, both of which are known to exhibit relatively strong associations

with sleep apnea, even if subclinical. The association between OSA and sexual complaints can be attributed, at least in part, to risk factors including older age, male gender, obesity, diabetes mellitus and endothelial dysfunction (Liu et al., 2007; Bradley and Floras, 2009). In this context, Liu's group and others have hypothesized that OSA and ED may be linked distinctly through endothelial dysfunction that aggravates the cardiovascular condition. Indeed, ED has been claimed to be a silent marker for vascular disease, particularly cardiovascular diseases in asymptomatic men (for review, see Jackson, 2008).

Recently, in a survey of 467 men from 20 to 80 years old at the time of their enrollment in the Epidemiologic Sleep Study (EPISONO), we demonstrated that the prevalence of ED complaints reached 17.08% overall in the city of Sao Paulo. For instance, the survey showed that ED complaints increased from 7.3% in younger men (20 to 29 y) to 63.25% in older individuals (>60 y) (Andersen et al., 2010). The logistic regression model showed that reduced time spent in REM sleep and fragmented sleep had a significant effect on ED complaint risk factors. Obesity, low testosterone levels, low quality of life, an apnea-hypopnea index over 15 and OSA were associated with a higher risk of ED complaints. Thus, adequate sleep patterns and normal testosterone concentrations, a marker for sexual motivation, may be protective against ED.

To treat OSA and its comorbidities, CPAP has been proposed with successful results. Similarly, data from impotent apneic men have shown improvement in erectile function with CPAP (Karacan and Karacan, 1995; Goncalvez et al., 2005; Margel et al., 2005; Perimenis et al., 2007). Indeed, CPAP therapy should be considered in these cases because our group has demonstrated that sildenafil worsens respiratory and desaturation events in patients with severe OSA (Roizenblatt et al., 2007). The therapeutic value of CPAP can further lead to additional cardiovascular, cognitive and neurophysiological benefits.

Although there are reports that gonadal hormones influence the physiology of sleep as well as sleep disturbances, the underlying mechanisms by which these hormones influence

sleep are still unknown. Moreover, the relationship between cause (pathology) and effect (erectile dysfunction) seems quite evident, but the factors that contribute most to sexual dysfunction are not yet fully understood. Future studies should focus on how the hormonal profile is related to OSA and the mechanisms behind these sleep-breathing disorders that can lead to the manifestation of ED in some men. Moreover, the influence of the treatment of mechanical CPAP on hormone and sexual life also remains to be elucidated.

-Women

Testosterone and estrogen are reported to play key roles in influencing sexual desire in women, whereas progesterone has been implicated in enhancing receptivity (for review, see Dennerstein et al., 2001, 2002, 2007). A growing body of data has demonstrated that exogenous testosterone improves many facets of sexual function, including arousability, desire, fantasy, orgasm, and overall satisfaction (Bancroft et al., 2006; for review see [Dennerstein et al., 2002](#)). Sexual disorders in females represent a complex topic. There are difficulties in managing this disorder in women, especially because of underreporting by the patient as well as inadequate assessment by clinicians.

In addition to biological and psychosocial changes that occur during the menopausal transition, the development of concurrent and subsequent sexual dysfunction provides a foundation for important research with regard to both epidemiology and the treatment of the individual patient (reviewed by Graziottin and Leiblum, 2005). It is possible to describe broad changes in biological structure and function, as well as in manifested symptoms, that are driven by hormonal influences during the menopausal transition. Among these changes, sleep and sexual function are frequent topics for complaints. Studies in women are also needed to understand the influence of androgens on sexual function as related to sleep. Few researchers have addressed this question.

As a decline in androgen levels is a normal consequence of the aging process (Davis, 2002), alterations in sexual behavior are expected to be even worse in menopausal women, in which sleep disturbances are a common factor (Hachul et al., 2008, 2009). Indeed, women with female androgen insufficiency may have alterations in sexual motivation, sexual fantasies, sexual enjoyment, sexual arousal, vaginal lubrication, vasocongestion, pubic hair, bone mass, muscle mass, and quality of life (Bachmann et al., 2002; see Schwenkhagen, 2007 and references therein). Moreover, the menopausal transition has been reported to adversely affect sexual functioning, with significant decreases in responsivity, frequency of sexual activity and libido, and significant increases in dyspareunia and partner problems (Dennerstein et al., 2001). For instance, Hayles (2011) pointed out that these data indicate the prevalence of low desire increasing with age whilst the proportion of women affected decreases. Such findings led the authors to state that these findings could explain why there is often no association between hypoactive sexual desire disorder and age reported in the scientific literature. Thus, further studies should stratify the data by age and examine sexual desire and distress separately when investigating hypoactive sexual desire disorder (Hayles, 2011).

Female sexuality is a complex and multifactorial condition. Testosterone replacement appears to be more effective at increasing the sexual response when its serum level is low (see Alexander et al., 2004, 2006), as low desire usually corresponds to low levels of testosterone. An example of the complex nature of female sexual dysfunction is the finding that a placebo can also provide benefits, as psychological issues are also present. In general, testosterone is indicated to improve hypoactive sexual desire disorder in postmenopausal women when estrogen treatment has been already prescribed and when testosterone levels are low. However, the long-term effects of testosterone treatment are still unknown. Considering different assessment instruments of female sexual function, both estrogen therapy alone and the combination of estrogen and testosterone can

improve female sexual function (Alexander et al., 2004, 2006). Of note, the evaluation of female sexuality is limited, not only because every woman responds in a different way, but also because each woman has distinct response to HT. Finally, the multifactorial nature of female sexual dysfunction has to be considered; these factors include physical, hormonal, psychological, mood, and sleep quality changes, among others, that are aggravated during the post-menopause period.

To facilitate a complete understanding of the role of androgens in menopause, it is necessary to assess what is known regarding the production/metabolism of these hormones and the role of the ovaries (Schwenkhagen, 2007). Furthermore, additional investigations should combine levels of testosterone in women across their menstrual phases and associate the oscillation with sexual motivation and sleep patterns. Unfortunately, the literature concerning these connections is still limited.

-Animal models

The scientific debate over the consequences of chronic sleep restriction has centered on theoretical concepts such as sleep deficit and core sleep versus optional sleep. Controversial studies in different species have shown that sexual behavior is either limited to SWS or that it has no effect on sleep. According to this notion, Boland and Dewsbury (1971) assessed the sleep patterns of male rats immediately after they attained sexual satiety and after a period during which they were undisturbed. The results showed that the rats slept significantly more following sexual activity compared with following either wheel running or no disturbance. The pattern of sleep following sexual activity was characterized by no increase in the number of sleep episodes or periods but a large increase in their average length as well as an increase in the time spent in SWS and in the shorter latency to the first SWS. Following wheel running, there were generally more episodes or periods of sleep, but they were shorter than those following sexual activity. According to the authors, the prevalence of

sleep following sexual satiety was consistent with the proposal of Beach and Whalen (1959), that satiety is attributable to general fatigue. However, it may also be consistent with the view of McGill (1965) that if one assumes sexual activity does indeed produce fatigue, termination of copulatory activity is governed by some other more specific mechanism that is essentially independent of fatigue. The increased sleep following sexual activity could be more the result of prolonged autonomic stimulation or other processes of the sort, frequently referred to under the categories of stress or emotion (Oswald, 1962), rather than of fatigue.

Recently, Velazquez-Moctezuma's group has expanded the investigation of the effect of masculine sexual activity on sleep in rats and hamsters. Within this context, the rats were exposed to the presence of an ovariectomized (or intact non-receptive) female and a receptive female until 1 or 3 ejaculations were reached. In addition, after 10 days, males were randomly exposed to one of the following copulatory conditions: remain in the presence of an ovariectomized rat; remain in the presence of a non-receptive female; and remain with a receptive female until sexual satiety was reached. The sleep recording obtained immediately after the experimental testing in the 3-ejaculations group in the first experiment and the satiety group in the second experiment showed enhanced time spent in SWS-II and a shorter latency to the first sleep episode compared with baseline conditions (Vazquez-Palacios et al., 2002). In addition, neither the presence of a non-receptive or an ovariectomized female nor sexual behavior until 1 ejaculation was reached had any effect on sleep stages. These findings suggest that the increase in SWS-II induced both by 3 ejaculations and sexual satiety may be governed by some specific mechanisms that are virtually independent of physical exercise or stress. Still, copulatory activity might be the source of neurohormonal processes that induce sleep and may involve the participation of neurotransmitters and other endogenous regulators of sleep and wakefulness.

Considering that each species may require different physical efforts to perform copulatory activity, Golden hamsters seem to be a suitable model to analyze the effect of a

peculiar pattern of copulatory behavior on sleep. The speed of mount, intromission, and ejaculation in this rodent is faster than in rats; they can also perform almost 10 ejaculations in approximately 30 minutes (Beach and Rabedeau, 1959; Bunell et al., 1976) and do not exhibit common motor inhibition seen in other species (Arteaga and Morali, 1997). The hamsters were allowed to copulate for 30 and 60 minutes, and locomotor activity was also assessed. The results showed that male sexual behavior induced a significant increase in SWS-II with a reduction in wakefulness. No effect was observed on paradoxical sleep when the effects on sleep architecture of the 2 different sexual activities were compared. The effect of locomotor activity produced an increase of SWS-I and only a slight nonsignificant decrease of both SWS-II and paradoxical sleep (Jiménez-Anguiano et al., 2003). This result suggests that sleep pattern is differentially modified by sexual behavior and locomotor activity and that regardless of the features of any specific copulatory pattern, the effects of sexual activity on sleep architecture are more reflected by SWS.

Of course, the crucial question is whether sexual interaction increased SWS in these studies simply because it involved partial sleep deprivation or whether sexual interaction increased SWS beyond what one would observe after a similar period of wakefulness without sexual activity. In other words, if the animals had been kept awake for the exact same amount of time in the mildest possible way without inducing sexual arousal and satiety, they might have shown the exact same increase in SWS. The findings of Meerlo and Turek (2001), which included a sleep deprivation control group, suggested that sexual interaction did not result in an increase in SWS beyond the level one sees after normal wakefulness (Meerlo and Turek, 2001; Meerlo, 2003).

Dement has reported the effect of sleep deprivation on sexual behavior in both humans and animals. First, he studied 12 male cats deprived of sleep for 30 days or longer. The results revealed that 6 animals showed a marked increase in sexual behavior, whereas a control group of cats demonstrated no sexual behavior (Dement, 1965). Similarly, another

study also verified that PSD over 8 days induced hypersexuality in cats (Vimont-Vicary et al., 1966). Years later, Fergunson and Dement (1969) demonstrated that sexual behavior was observed in PSD male rats following the administration of amphetamine, reflected by mounts that often showed no regard for orientation (front to tail or even sideways). It must be pointed out that sexual behavior was not the main target in the studies mentioned above.

In the 1980s, Velazquez-Moctezuma's group resumed work in this research field by studying the effect of PSD on the sexual behavior of rats, focusing on the action of gonadal steroids. For this purpose, gonadectomized male rats were submitted to PSD for 120 hours, and their hetero- and homo-typical sexual response to estradiol benzoate was tested because PSD facilitates the induction of lordosis behavior in female rats treated with this hormone (Velazquez-Moctezuma et al., 1984). This study was also grounded in the fact that testosterone propionate and progesterone can elicit a feminine sexual response in males (Davidson and Levine, 1969; Sodersten and Larsson, 1975), and testosterone conversion in estradiol might play an important role in the induction of lordosis behavior in male rats (Beyer et al., 1976), as it is documented that stressful conditions change aromatase activity in the hypothalamus (Farabollini et al., 1978). The findings demonstrated that PSD itself did not produce a lordosis response; however, a marked positive effect of PSD was verified after estrogen treatment on feminine sexual behavior compared with that in non-PSD groups (Canchola et al., 1986).

Shortly thereafter, Velazquez-Moctezuma et al. (1989) explored the possibility that PSD induces changes in the action of yet another gonadal steroid, testosterone, in terms of its ability to elicit masculine sexual behavior in castrated adult male rats. Testosterone treatment in subjects after seven days of PSD required only half as much time to achieve a response in 50% of subjects compared with that in the control group, suggesting that PSD facilitates the effects of testosterone on masculine sexual behavior, just as it facilitates the effects of estrogen on feminine sexual behavior.

Although the studies mentioned earlier focus somewhat on sexual behavior and involve different sleep deprivation methodologies, male sexual copulatory behavior in the presence of females tested at the end of a 72- to 96-hour PSD period in rats was previously described. Morden et al. (1968) reported that hypersexual male rats showed an increase in copulatory rate after PSD. According to Verma et al. (1989), PSD resulted in an increase of sexual behavior in rats verified by an increase in intromission frequency, a decrease in ejaculatory latency, and reduction in the inter-intromission interval. The inter-intromission interval is an indicator of the intensity of copulatory behavior (Agmo, 1997). It has been reported that female rats tend to prefer longer intervals between intromissions than those imposed under male control during sexual behavior experiments. Thus, females use the temporal patterning of intravaginal stimulation as one criterion for ending mating with a particular male (Huck et al., 1988). Furthermore, Erskine (1989) suggested that the ability to discriminate among varying intensities of coital stimulation and the active patterning of approach/withdrawal that controls receipt of that stimulation are two types of pacing behavior. Thus, it can be stated that there is an intricate relationship between male and female sexual behavior regarding successful reproduction.

Although prolonged sleep deprivation has been performed in laboratory animals in an attempt to shed light on this issue, it was Velazquez-Moctezuma et al. (1996) who initially focused on this subject relating to sexual behavior. Male rats underwent PSD for 24 or 16 hours daily for 20 days. A decrease was reported in the percentage of 24-h PSD rats presenting mount, intromission and ejaculation when compared with either the partial PSD or the control group. The animals under partial PSD (16 hours daily) were sexually active during the experimental period evaluated, and no changes in sexual performance were observed compared with the control group. These data indicate that the extent of the sleep loss period interferes with the mechanisms that regulate male sexual behavior and that participation of the stress condition should be considered to be a factor relevant to this effect.

The pathways underlying the relationship between sleep deprivation and behavioral alterations are likely to involve multiple physiological systems such as the endocrine system. In fact, recent evidence indicates that disorders of sleep disrupt the endocrine system (Borthel, 2002). On the cellular and tissue levels, hormones are the key players. Homeostasis of the body and its systems are interrelated; when one or more of these hormone systems suffer dysfunction, the entire body is affected.

Because sexual behavior is under hormonal control, especially by testosterone in males, we performed a series of studies to investigate the effects of selective sleep loss (i.e., PSD) on erectile function as well as on sexual behavior. In modern life, most sleep deprivation affects the paradoxical sleep/REM phase of sleep that occurs in the last half of the night; therefore, our studies focus on PSD.

Our initial studies revealed that, although somewhat unexpected because testosterone is known to exert motivational effects necessary for the display of male sexual behavior, testosterone concentrations were significantly reduced after 96 hours of PSD in contrast to the marked increase in genital reflexes displayed by the sleep-deprived adult rats (Andersen et al., 2002, 2003a, 2007; Alvarenga et al., 2009). This marked effect on androgen levels promoted by sleep deprivation also occurs in young (30-day-old; Andersen et al., 2003b) as well as old rats (over 22-months-old rats; Andersen et al., 2002, 2004a).

If 96 hours of PSD changes testosterone, what would happen after a prolonged sleep deprivation period? The hormone analysis revealed that the concentrations of testosterone were still significantly reduced compared with those in the home-cage control group; however, after 3 periods of 96 hours of PSD with resting intervals (mimicking weekdays/weekends), the concentrations increased compared with the single 96 h PSD period. According to the findings mentioned above, it seems that if sleep is essential for health and life, then sleep deprivation is a biological stressor. It is important to note that whereas some hormones recover to their normal concentrations rather rapidly, others remain

altered, indicating that sleep normalization (i.e., recovery) is not the sole factor that leads to the recovery of homeostasis. For instance, testosterone levels in PSD male rats did not return to a normal concentration range in a 96-hour sleep recovery period (Andersen et al., 2005).

Because genital reflexes are observed in PSD animals even when testosterone concentrations are reduced, we designed a set of experiments to test whether testosterone supplementation during the sleep deprivation period would recover erectile events seen in intact-PSD rats. As testosterone effects on sexual behavior could be mediated by the aromatization of testosterone to estradiol, raising the likelihood that estradiol could also influence erection, we also tested estradiol treatment in addition to progesterone. Throughout the 96 hours of PSD, distinct groups of rats were administered daily doses of testosterone, progesterone or estradiol. Interestingly, the only group that displayed erections was the one treated with progesterone. Only 30% of the PSD rats showed erections in the testosterone-treated group (Andersen et al., 2004b).

Because most adults have experienced sleep deprivation at some stage of their lives, research using preclinical models can provide a framework to determine how sleep loss might affect female sexual behavior. We previously demonstrated that PSD disrupts the estrous cycle in rats by influencing hormonal profiles (including testosterone) (Antunes, 2006). We therefore hypothesized that female rats deprived of sleep would present a reduced sexual response because of altered hormonal concentrations (Andersen and Alvarenga et al., 2009). To the best of our knowledge, this study is the first to investigate whether PSD can affect receptivity (acceptance) and proceptivity (solicitation) behaviors in female rats. PSD produced a distinct response in the hormonal profile that was consistent with the phase of the estrus cycle. The results show that PSD enhanced the sexual response in proestrus PSD rats, as manifested by greater adoption of the lordosis posture. In contrast, PSD in the diestrus group produced behaviors characterized by boxing, fighting, and prone

defensiveness. Thus, sleep loss can be assumed to affect sexual motivation and might lead to important clinical implications, including alterations in female physiology and reproductive abnormalities. Collectively, the sequence of these studies indicates the strong effects of sleep deprivation, and more specifically, PSD, on testosterone levels and sexual function. Although these studies indicate a facilitating role for PSD on erections, such findings are in agreement with studies of short-term sleep loss in humans (Zarcone et al., 1974; Ferini-Strampi et al., 1996). However, given the chronic sleep disruption in modern societies, long-term sleep deprivation should be more intensely investigated in animal models.

To this end, Gozal's group conducted a well-designed study in which they were able to determine whether intermittent hypoxia during sleep affected ED in mice (Soukhova-O'Hare et al., 2008). This study was the first to address how chronic intermittent hypoxia, one of the hallmarks of OSA, could mediate ED in rodents. Using different behavioral contexts (spontaneous erections, sexual activity during mating, and noncontact tests) after 5 weeks of chronic intermittent hypoxia and treatment with tadalafil, the authors assessed the animals. Plasma testosterone levels were also measured at 2 time points for the experiment. The results showed that, although plasma testosterone levels were not affected, relatively short periods of chronic intermittent hypoxia (one of the key components of OSA) are associated with significant effects on sexual activity and erectile function in mice. Furthermore, chronic intermittent hypoxia-related effects were not testosterone-dependent and did not appear to be associated with disruption of testicular anatomy, including the number and appearance of Leydig and Sertoli cells. This study reports the occurrence of ED in a murine model of OSA, leading the authors to raise the implications of a multifactorial role for chronic intermittent hypoxia in the complex impairments of erectile function that have been reported in patients with OSA.

A comparison of the relevant animal and human literature reveals a striking difference in the conceptualization of pharmacological mechanisms involved in such behavioral effects.

In the animal literature, the evolution of sophisticated methods for defining and testing the various components of sexual responsiveness, in addition to the opportunity to use invasive techniques that permit localization of the effects of the drug within the brain, have led to impressive advances in our understanding of the neurobiology of sexual behavior (Everitt and Bancroft, 1991).

7. Final considerations

Hormones play an important role in homeostasis. Androgens are crucial factors for the normal development of both male and female gonadal function, especially for male reproductive functions. Studies focusing on the variations in androgen levels, or on its pulsatility, can contribute to the understanding and management of some conditions related to androgen action, such as ED in males and mood and sexual behavior in women experiencing androgen insufficiency syndrome. In addition to improving sexual function, there are well-documented beneficial effects of androgens on many organ systems, including the brain. Potential therapeutic possibilities have been reported for both men and women.

This review emphasized the research that demonstrated the effects of androgens on sexual function in the context of sleep. Although testosterone itself has been the target of a great deal of research, few studies have examined its effects on sexual behavior related to sleep in both sexes. Critical studies that link the components of sexual behavior and sleep deprivation via androgen levels may be fruitful from a clinical perspective.

Currently, sleep-related problems are envisaged not only as a medical issue but also as a topic of social and economic interest. To solve these problems and to better understand sleep and sleep disorders, multidisciplinary approaches are required. In this context, emphasis is placed not only on behavioral approaches but also on neuroendocrine, biochemical and molecular biological methods of answering these questions. Collectively, studies so far have predicted the biological significance of sleep homeostasis for normal

endocrine regulation and a satisfied sexual life. These lines of evidence reinforce the idea that sleep disturbances may have long-term adverse effects on overall health, especially on reproductive and sexual function and, consequently, quality of life. ED in men and sexual disorders in women are multifaceted issues, and assessment of sleep pattern and quality, especially in older men and postmenopausal women, should be considered in clinical practice. Thus, adequate and high-quality sleep is important for good health in all individuals, regardless of sex, to restore energy lost during the previous day's activities and due to a demanding schedule. The maintenance of good nightly sleep quality enhances alertness, performance and physical capacities and might also improve sexual satisfaction.

Although sleep deprivation has a dramatic impact on multiple physiological processes, modern society has been exposed to an accumulation of several stressful factors that increase the number and variety of activities during wakefulness, which, consequently, curtails the time available for sleep. In addition to voluntary sleep restrictions, there has been an increase in general knowledge regarding the pervasiveness and consequence of sleep disorders. As sleep plays a vital role in overall health and well-being, sleep disruption compromises biological processes necessary for cognitive function and physical health. The ways in which the body is affected by sleep loss are not fully understood.

Males and females have different mechanisms to cope with stress (inherent factor involved in sleep deprivation), and their recovery from sleep loss is also distinct. Thus, it is necessary to conduct further studies to examine gender biological determinants on the neurobiology of sleep as well as to address the influence of reproductive hormones, such as testosterone, that can interfere with the ability to recover from sleep deprivation. This ability may be further aggravated in women due to additional child care and home tasks. In summary, the full constellation of consequences caused by sleep restriction, which is well-documented and established for males, remains to be demonstrated in females.

The sex hormone testosterone affects sleep duration and sleep quality. However, sleep deprivation in male rats and sleep restriction in men is associated with reduced androgen concentrations and, consequently, may affect androgen-dependent functions. Deficiencies in androgen levels might promote significant negative impacts on health, especially on sleep quality and sexual satisfaction, which ultimately affect quality of life. Goh and Tong (2009) recently proposed that promoting better sleep hygiene may represent a **non-pharmacologic method for improving androgen concentrations in hypogonadal men that have poor sleep habits**. Additionally, study data strongly indicate a marked association of sleep with androgen levels, suggesting that sleep might be a contributing factor in the etiology of **low concentrations of androgens**.

One of the major scientific advances in recent decades has been the discovery that sleep is essential for overall well-being and health. Interdisciplinary studies are necessary to elucidate the full impact of sleep on androgen levels and to understand how poor-quality sleep can affect sexual life. These future studies will provide comprehensive documentation of the physiological and pathological mechanisms underlying the relationships between sleep and sexual function mediated by testosterone.

On the basis of the scientific evidence, it is possible to state that good sleep quality has a direct effect on the activity of the neuroendocrine reproductive control, allowing the optimal regulation of the hormonal homeostasis. Thus, increasing the duration and quality of sleep can be an additional approach for improving sexual satisfaction by reducing the negative effects mediated by sleep deprivation/sleep restriction in both men and women.

Legend

Figure 1 - Kisspeptin, a hypothalamic neuropeptide, stimulates GnRH (gonadotrophin release hormone) secretion. GnRH causes the release of LH (luteinizing hormone) and FSH (follicle stimulant hormone) from the anterior pituitary. LH acts on Leydig cells in testes to produce testosterone. FSH acts on Sertoli cells in seminiferous tubules to maintain spermatogenesis as well as produce sex-hormone binding globulin (SHBG). FSH stimulates the production of inhibin B, which has a negative feedback effect on the pituitary. Testosterone is converted to estradiol by aromatase and to dihydrotestosterone (DHT) by 5α -reductase. These hormones contribute to negative feedback on the pituitary gland.

Figure 2 - Normal ovarian function is controlled primarily by the gonadotrophins LH (luteinizing hormone) and FSH (follicle-stimulating hormone) secreted by the anterior pituitary gland. This secretion is regulated by the hypothalamic hormone, gonadotrophin releasing hormone (GnRH). In females, GnRH is secreted in a cyclical pattern that maintains the menstrual cycle. LH acts on the ovarian follicle to induce ovulation and maintain the corpus luteum. FSH causes development of the ovarian follicle and stimulates secretion of estradiol and progesterone. These steroidal hormones inhibit GnRH release and, subsequently, LH and FSH release via a negative feedback loop. However, estradiol in sustained high levels causes an LH surge that is associated with ovulation. The effects of leptin (a hormone emanating from fat cells) and insulin from the pancreas alter the bioavailability of estradiol and testosterone by affecting production of sex hormone-binding globulin (SHBG) from the liver. Insulin can also function directly on the ovary.

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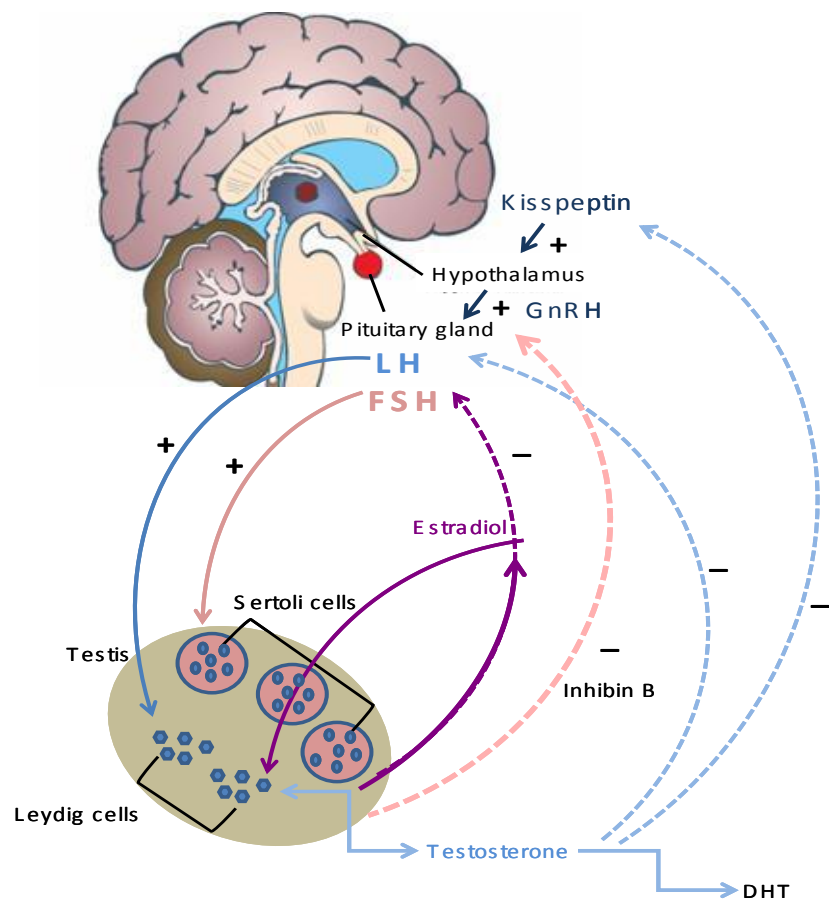
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