Psychiatr. Pol. 2014; 48(4): 701–714
PL ISSN 0033-2674
www.psychiatriapolska.pl

Androgens – a common biological marker of sleep disorders and selected sexual dysfunctions?

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Summary

The relationship between sleep disturbances and sexual dysfunctions still remains unclear. The links which indicate the importance of central nervous system and sleep mechanisms in regulations of the endocrine system seem to have bilateral character; the nature of such associations is not fully understood. The aim of the paper is to describe the influence of androgens on the relations between sexual functioning and sleep functions in patients of both sexes. The physiological role of the androgens is described with the emphasis put on the specific action of these hormones in sleep regulation, as well as the mutual relations between the regu- latory role of sleep on the sexual apparatus. The newest data suggest that the androgenic hormonal profile is linked to the sleep rhythm, but not to the chronobiological diurnal rhythm in male patients. This may constitute the purpose for further research on the role of androgens in the connections between sexual and sleep disturbances. Up to date there is little known about androgens' role in sleep regulation in women. The influence of sexual activity disturbances as behavioral factors influencing the severity and the persistence of insomnia as well as their position among other factors important for the triggering of insomnia requires further scientific exploration.

Key words: androgens, sleep disorders, sexual disorders

Introduction

The relationship between sexual life, sleep quality and neurotic symptoms has been already pointed out by ancient physicians such as Hippocrates, who in the fourth century BC recommended for "hysterical" girls marriage and pregnancy. The phenomenon of 'hysteria' widespread among women was often discussed in the literature of the nineteenth century. According to those publications hysteria could be manifested in a wide range of symptoms and among them "weakness, nervousness, excessive sexual desire, insomnia, shortness of breath, lack of appetite and a decreased libido," [1].

Furthermore, among the symptoms, in the form of which hysteria could be manifested one could find both: symptoms of sleep disorders and sexual dysfunction. Author of the psychoanalysis Sigmund Freud in the early years of the twentieth century, in his work "Interpretation of Dreams" suggested a close relationship between sexual dysfunctions and sleep disorders. He pointed that the attenuation of the physiological manifestations of libidinal energy, can cause neurotic reactions, and among them, disturbed sleeping, or insomnia. [2] Despite more than two hundred years of scientific debate linking sleep disorders and sexual dysfunctions, it is still little understood how sleep and sexual functioning influence each other.

Although sleep, from the point of view of evolutionary psychology and behavioral physiology is considered as a passive state, the currently available scientific data clearly show that the sleep fulfills several important physiological functions through the modulation of the endocrine, metabolic and cardiovascular system [3] and indirectly sexual and procreative functions. The role of the central nervous system activity and the processes of sleep in regulation of the endocrine system is of great importance [4], and the relationships between all these processes appears to have bilateral character. However. the nature of these links still leaves a lot of ambiguity.

In modern neurophysiological studies the relationship between the physiological sexual responses, and the various stages of sleep were confirmed. It was found that during REM sleep the brain bioelectric activity (electroencephalographic activity – EEG) is no longer dominated by slow waves and EEG resembles the EEG of active wakefulness. During REM sleep tachypnea, irregular breathing, increased heart rate and rapid eye movements under closed eyelids are observed. In addition during REM sleep signs of sexual arousal (respectively penis erection in men and increased vaginal lubrication in women) are observed. Sexual arousal during REM sleep has no connection to the sexual or lack of the sexual content of dreams. Studies of rhythmic sexual responses in a sleep were conducted beginning from the 70's of last century. They were concentrated on searching for the links between sleep stages determined by EEG and erections of the penis or clitoris, detecting the variety of vegetative functions changes in sleep.

In modern studies, the physiological reactions of the body during sleep are recorded by means of phallography (in women – clitorography and colpography),electroencephalography, electrocardiography, electrooculography, electromyography, respirography, electrodermatography. The most important fact from the pioneering research of Fisher et al was that spontaneous erections occurring during sleep begin and end in close temporal association with the stages of sleep [6], and the fact that their severity and frequency were not dependent on the frequency of prior sexual contacts, or the duration of the period of sexual abstinence prior to polysomnographic recording.

The morning erections observed in men reflect the arousal corresponding to the last stage of REM sleep. This phenomenon coincides with the peak of the circadian rhythm

of secretion of androgens. The serum concentration of androgens is highest in the morning, and the lowest in the evening, with a difference of about 30% [7]. In studies that started in the 70's of last century, and were confirmed recently, the infradian rhythm of testosterone secretion with the length of the cycle of 20-28 days depending on the author of the study was demonstrated [89]. Rhythmic physiological changes in genital reactivity occurring during the nocturnal sleep correspond to the rhythmic electrophysiological changes and reflect the rhythm of hormonal cycle.

The androgen levels and circadian rhythm of testosterone secretion are considered as the most important endocrine marker related to sexual functioning of both sexes [10]. The appropriate level of testosterone determines the proper sexual excitability.

In extreme cases the abnormalities in the control of sexual behavior during sleep manifest in sexual activity in the form of masturbation or sexual activity directed towards others. The disorder first described in 1996 has been classified as a NREM parasomnia [11], or sexomnia. Sexomnias are very rare, however, in contrast to a very high prevalence of sexual dysfunctions associated with certain sleep disorders such as sleep apnea syndrome (See below). All rare forms of abnormal sexual behavior associated with sleep have been described by Schenck et al, and their discussion is beyond the scope of this work [12].

Among a number of disorders co-occurring with sleep disturbances, sexual dysfunction in this context seems to be the least understood, despite the fact that the co-existence of both these disorders is very common. Even less known is the role of androgens as a common marker of sleep disorders and sexual dysfunction, despite the fact that for both: sleep medicine and sexology, the role of the androgens in the pathogenesis of diseases specific to each of these areas is evident. The purpose of this paper is therefore to discuss bimodal relations concerning the effects of androgens on sexual function and sleep functions in both sexes.

Androgens- basic biological functions

Main steroid hormones, the most important for reproductive function and sexual functions of both sexes are: testosterone (TTE), dihydrotestosterone (DHT) and estradiol (secreted by the gonads) and adrenal androgen dehydroepiandrosterone. Androgens are synthesized from cholesterol by steroidogenesis and secreted in a dimorphic way – in men by testicular Leydig cells, whereas in women, by the ovaries and the adrenal cortex [13, 3]. There is evidence that steroid hormones may also be synthesized by adipose tissue, skin, and what is most surprising – in the central nervous system [10]. About 99% of testosterone in serum is bound to SHBG (Sex hormone binding globulin) or albumin, and only 1-2% of circulating testosterone remains in the bloodstream in the free form.

In the ontogeny of both women and men two main peaks of androgens are observed, although basal levels of testosterone and growth hormone concentrations are significantly lower in women than in men. The first peak in testosterone level occurs in utero, during the second trimester of pregnancy (with dramatic decline after birth), and another – in adolescence, with a gradual decrease beginning from about 40 years of age. In the male the additional rapid increase in androgen levels within several months after birth is observed, but the physiological function of this phenomenon has not been fully elucidated up till now.

The physiological function of exposure to high levels of androgens in utero and during puberty, probably plays an important role in the sexually dimorphic brain organization, regulating properties of some of the cognitive and behavioral characteristic of a particular sex. A number of studies have shown a significant modulatory effect of testosterone to neuronal activity, the formation and loss of synaptic connections, the growth and migration of nerve cells, apoptosis and metabolism of neurotransmitters [13].

The prenatal exposure to androgens influence the development of internal and external genitalia, and in adolescence – a maturation of sexual organs and initiation of sexual and reproductive functions by the genitalia.

The concentration of testosterone in serum of adult women is typically ten times lower than in men. Women, however, are more sensitive to androgens. The homeostatic negative feedback of the hypothalamic-pituitary-gonadal system is the main regulatory system of secretion of sex steroid hormones in both sexes where any increase in the concentration of sex steroids causes the consequent decrease in the release of the luteinizing hormone (LH) and follicle stimulating hormone (FSH). Only recently it was proven that the negative feedback of hypothalamic-pituitary-gonadal system is also involved the peptide kisspeptin, that is expressed in the arcuate nuclei, the periventricular nuclei and anteroventral periventricular nuclei.

Androgen and estrogen receptors are not expressed by luteinizing hormone releasing hormone (L HRH) neurons, and alpha estrogen and androgen receptors are present on kisspeptin neurons [14, 13]. Kisspeptin stimulates the secretion of gonadotropin releasing hormone (GnRH), while both testosterone and estradiol inhibit the kisspeptin transcription and GnRH secretion [3].

Nowadays it is considered that androgens play a very important role for both male and female sexuality but also influencing the level of desire, arousal and the number of sexual fantasies experienced per day.

Androgens exert not gender related effects in peripheral tissues. They exhibit miotrophic and proteoanabolic action. They cause the sodium, potassium, chloride, calcium and water retention. Stimulate erythropoiesis, activate the function of sebaceus and sweat glands, affect the gender-specific distribution of hair. Accelerate bone maturation and ossification of long bones. What is very important for some pathologies

associated with sleep – androgens cause lengthening and thickening of the vocal cords [15], and may affect the overall increase in laxity of the upper respiratory tract [16], increasing the risk of severity of sleep apnea syndrome.

The anabolic effects of androgens are well known and have been in detail described in the literature. Apart from the basic anabolic function androgens affect the number of body function in the sexually dimorphic way. They influence the sex-specific distribution of body fat and hair. During puberty androgens cause the eventual morphological and functional development of male genitalia and prostate along with the development of the secondary male sexual features. In women adequate androgen levels is necessary for the maturation of the female reproductive organs and clitoris. In mature male androgens are responsible for the proper spermatogenesis process, the secretory activity of the prostate and seminal vesicles. However, in mature women administering of the exogenous androgens can cause hypertrophy and increase of clitoral sensitivity [10].

A number of studies has been already conducted on the topic how testosterone affects the target tissue and modifies the final phenotype [13]. On the other hand there are more and more data concerning the internal and external factors affecting the changes of levels of testosterone. Androgens affect not only the autonomic functions of sexual response, but also in the dimorphic way regulate emotional, motivational and cognitive aspects of sexual behavior [13]. It has been proven that even the fantasizing about sexual activity increases the level of testosterone in the serum of the women [17]. In men the concentration of testosterone increases during both the observation of sexual activities undertaken by others, and as a result real sexual activity [18]. Changes in levels of testosterone are also observed in subjects in love, wherein the concentration of testosterone of men falling in love is lower, and of women is higher than in an emotionally neutral state. These differences, however, equalize in the course of duration of love relationship [19].

In addition, changes in androgen levels in both women and men have a direct impact on the assessment of the attractiveness of the opposite sex. In women, increase in androgens accompanying the ovulation influence the level of visual attention directed to attractive men [20], while in men high level of testosterone influences the stronger physical attraction to femininity in women's faces [21].

Androgens' impact on sexual function

Although there have been a number of studies on the effects of androgens on the sexual functioning of both sexes, as well as concerning the relationship of sleep disturbances and endocrine dysfunction (especially in the context of co-occurrence of sleep disorders, metabolic syndrome, and hypoandrogenism), a few studies have focused on the effects of androgen hormones for the coexistence of sexual dysfunction in conjunction with the quality of sleep. Proper hormonal environment is a fundamental

role in the regular and satisfactory sexual functioning. Hypogonadism in animals result in a marked decline in libido and severe dysfunction of smooth muscles and corpus cavernosum, leading to erectile dysfunction, which can be inverted using testosterone supplementation [22].

For both men and women hormones with androgenic effect are responsible for the manifestation of sexual interest in sexual objects and for sexual excitability. In men who passed through puberty and have not entered into a period of aging, the appropriate level of testosterone determines the proper mechanisms of desire, arousal and genital response [10], affecting both the central and peripheral receptors for testosterone.

In studies of men diagnosed with late-onset hypogonadism who were supplemented with testosterone in a crossover, double-blind manner, it is known that since the third week, after withdrawal of testosterone supplementation the level of desire and arousal decreased and in the consecutive weeks the dysfunction of ejaculation has joined. In this kind of studies, there was no significant placebo effect on improvement of the different phases of male sexual response, and the improvement of these functions followed soon after returning to testosterone supplementation [10].

In women, testosterone also plays a major role in their sexuality, although the physiology of gonadal hormones in women is much more complicated than in men by the enormous complexity of the female endocrine reproductive system [10]. Women also tend to be more diverse than men in terms of their physiological response to testosterone levels. Thus, women response to significantly lower concentrations, or more subtle declines in testosterone, than those that men react. In addition, correlative studies on testosterone levels and certain other steroid hormones in women presenting for sexologic consultation because of the low level of desire did not yield conclusive results [23-25]. Both Stewart [23] and Schreiner-Engel [24] have not found in their studies evidence that the women with low levels of testosterone differ in the level of sexual desire from women in the control group. However, in Stewart's study [25] that was performed with a slightly different methodology in the field of determined endocrine markers, it was shown a lower rate of free androgen (FAI-free androgen index) in women presenting with complaints of persistent lifelong very low levels of libido, compared with women from the control group. It should be noted at this point that the conceptualization of the phenomenon of female desire in the last few years underwent a clear evolution. Today, attention is paid to the circularity rather than linearity in the women's responses to sexual stimuli [26], where the different phases of sexual response does not pass in a linear fashion from desire, through the arousal, plateau and orgasm until relaxation (as on the Masters, Johnson and Kaplan model).

In the circular multivariate model desire is not a necessary condition for sexual activity and arousal can develop during sexual activity with its cognitive and physical

components. The sexual satisfaction cannot be connected directly with the experience or lack of the experience of orgasm [26]. The population study also shows that even more than 30% of sexually active women do not feel sexual desire, or do not experience sexual fantasies, and even 97% of women over 25 years of age undertake sexual behavior without the sexual desire [27]. In the interpretation of the results of the these studies [23-25] there was used a linear model of Masters, Johnson and Kaplan, not the circular Basson model, which could affect the interpretation of the decreased sexual desire reported by women eligible for correlative study of endocrine markers of sexual functions.

Based on the results of research on the effects of exogenous testosterone supplementation it is evident that apart from constitutionally conditioned activity of dopaminergic, noradrenergic and oxytocinergic pathways [10] and physiological changes in estrogen levels on a menstrual cycle, in a woman's life cycle i.e. puberty, maturity and menopause, androgens play a key regulatory role to the level of desire exerted by women. There is increasing evidence for the fact that exogenous testosterone improves several aspects of sexual function in women (including the level of desire, the amount of sexual fantasies, orgasm and overall sexual satisfaction) [10].

However, age-related physiological decline in androgen levels is reflected by the deterioration in sexual functioning, clearly seen in menopause and it also correlates with the occurrence of severe sleep disorders present in this period [28].

Androgens and sleep

One of the first studies on the coexistence of sleep disorders and sexual disorders showed that as many as 48% of men diagnosed with sleep apnea reported complaints of erectile dysfunction, disturbed ejaculation or libido [29]. However, the results of the more modern epidemiological study called EPISONO, which focused on the prevalence of erectile dysfunction in correlation with sleep disorders showed that complaints of erectile dysfunction were quite prevalent in the male population of Sao Paulo, especially among older men. The role of the protective factor against the occurrence of erectile dysfunction in this population were regular sleep patterns (adequate sleep patterns), and normal or high levels of testosterone [30]. The study also showed that the prevalence of sleep apnea had a negative impact on erectile function and sexual activity. The role of androgens for sleep disorders and sexual dysfunction in older men with late-onset hypogonadism has not yet been fully elucidated. It is known, however, that in mature eugonadal males testosterone levels is higher than that which is sufficient to maintain sexual arousal, suggesting that for the peripheral effects testosterone levels must be higher than for the central effects. On the other hand, changes in sleep architecture occurring with aging, overlay the period of late hypogonadism and a decline in androgen levels suggest that worsening with age re-

duction in androgens levels may act unfavorable for the control of central inhibition and stimulation processes.

Even less known are relationships of sleep disorders and sexual dysfunction in women. The physiological relationship between the degree of sexual dysfunction and sleep disorders has been confirmed for the menopausal period of female population, but much less is known about these processes in relation to groups of other age.

In the 80's of last century, the relationship between experimental sleep deprivation and various endocrine markers were explored. One of the earliest studies in this field shows that sleep deprivation decreases the levels of androgens in male subjects. [31]. However, this study did not include the impact of sleep deprivation-induced reduction of androgens on the patients' sexual functioning.

Another small study conducted in 8 healthy males showed that the 72-hour sleep deprivation led to significant adaptive changes in the hypothalamic-pituitary-gonadal and a temporary drop in the level of gonadal hormones (testosterone, androstenedione, estradiol, dihydrotestosterone) [32]. The physiological significance of this phenomenon or the relationship between sleep and sexual disorders in correlation to the hypothalamic-pituitary-gonadal dysfunction remains unclear. This line of research did not evaluated, apart from already evident clinical circumstances associated with an increased risk of erectile dysfunction and sleep apnea in hypogonadal men with symptoms of metabolic syndrome.

Already well known increased risk of male gender to sleep apnea syndrome has given rise to the hypothesis, according to which the pathogenesis of respiratory disturbances during sleep can be connected with the gonadal secretory function and correlate with the level of androgens. Testosterone can affect the respiratory disorder in the upper respiratory tract by a variety of mechanisms, associated with a very complicated structure of the respiratory tract. It has been proven that testosterone may have the effect of flaccidity of the upper respiratory tract, which may be a pathological mechanism in which testosterone influences exacerbation of sleep apnea syndrome [16]. These correlations show a bilateral nature, as it has been proven that in males suffering from the sleep apnea syndrome testosterone levels are reduced compared to the control group, unrelated to age or degree of obesity [33].

Androgens and sleep in men

The few existing studies suggest that androgens affect both sleep duration and the quality of sleep. The secretion of testosterone has a circadian rhythm, which reflects the increase in the concentration of testosterone in the early-morning hours (around 8:00 am) and a decrease in the day to the lowest concentrations of approximately 8 p.m. [34,35]. In men the night rhythm of testosterone secretion is associated with the cycles of NREM / REM sleep [36]. According to different authors, sleep-related

increase in the concentration of testosterone in men to the start of the first period of REM sleep [34] or the introduction to the second period of REM sleep and with the highest concentration at the beginning of the third period of REM sleep [37]. Clinical studies have shown a reduction of the total amount of sleep with the reduction both REM sleep and NREM sleep duration in older men, taking for reasons of late hypogonadism high doses of testosterone [38].

Correlation studies also indicated that lower levels of testosterone are connected to worse sleep consolidation in the form of reduced performance, and increased frequency of awakenings in the group of older men [39]. It is also known that men with age sleep shorter. The research has shown that in group composed of aging men the highest concentration of testosterone is observed in those of the respondents who sleep more than 6-8 hours [40]. Diurnal rhythm of testosterone secretion in men for many years was linked with circadian regulatory chronobiological processes, the nature of which has long been described in detail, while not entirely clear still remains their physiological significance.

The research of Axelsson et al [41], as well as previous studies of Boyar et al [42] provided very interesting conclusions which allowed for formulating hypotheses regarding the regulatory function of sleep to endocrine procreative and sexual functions in young men. The study of Axelsson revealed that in men aged 22-32, sleep during the day similarly to night sleep influenced the concentration of testosterone [41]. That led to a gradual increase in testosterone levels during the consequent hours of sleep with a peak just before waking up and the decrease just after waking up [41]. These studies revealed new aspect of the regulatory functions of sleep on the concentration of androgen levels. Still, however, it is necessary to clarify the physiological role of this phenomenon.

Androgens and sleep in woman

Despite the fact that the relationship between androgen levels and sleep architecture is well known in men, the same question with regard to women is still completely unclear. Adult women often report more sleep problems (especially insomnia) than men [43], but also twice more nightmares compared to men [44]. Sex steroid hormones appear to play a very important role in the regulation of sleep in women. It has been shown that the administration of testosterone in men as well as in women results in the formation of the symptoms of sleep apnea. [45] In one of the few studies on the correlation relationship between testosterone levels and quality of sleep in women suggests that the initial low testosterone level was associated with an increased wake after sleep onset [46]. In Seattle Midlife Women's Health Study the trend toward lower levels of testosterone in correlation with poor sleep quality was observed [47].

Summary and conclusions

Changes in the concentration of steroid hormones, including androgens are linked to a number of lifestyle factors [40] and they are sensitive to a number of factors associated with the presence of sexual activity or lack of sexual activity. The studies of androgen levels in relation to sexual dysfunction and the quantity and quality of sleep presented and analyzed in this article revealed number of correlations between the analyzed phenomenon that were confirmed by the various research teams. New light on the physiological regulatory role of sleep for the procreative and sexual functions shed Axelsson's studies that have shown links of androgenic hormone profile with the rhythm of sleep and not with the chronobiological circadian rhythm.

This may have encouraged further exploration of the role of androgens in sleep disorders, especially that relatively little data have been collected so far on the role of androgens in the regulation of sleep in women. Studies concerning the female population have focused mostly on female sex hormones and the phenomena associated with menopause as a clinical model of hormonal environment that promotes sleep disorders.

Correlation studies in the field of behavioral endocrinology and physiology bring more and more data on bilateral relations concerning the role of androgens for lifestyle and sexual behavior associated with the length and function of sleep in the modern population. These studies, however, contain a number of limitations in their structure resulting from the fact that the direction of the relationship between the analyzed phenomena often remains unclear. The first describer of behavioral endocrinology Frank Beach already in 1975 noted that hormones can cause behavioral changes, but also a number of behaviors can cause changes in the hormonal profile [48]. Thus, on the basis of such research often becomes difficult to determine the direction of causality of these processes.

A number of social changes that modulate social behavior such as the level of stress, social status, experience of successes or failures (such as social awards or reproductive success), poor sleep hygiene resulting from the pace of modern life, as well as irregularities of sexual activity (lack or excess) may be factors interfering with the various dimensions of a complex endocrine functions. Little is yet known about the effects of disorders of sexual activity as a behavioral factor, the severity and persistence of insomnia, and the location of this factor among other variables taken into account in Spielman's three- factor insomnia model [49]. According to this model, the development of insomnia must meet constitutional factors related to biological susceptibility of physiological system regulating activity and sleep and factors triggering and stabilizing the insomnia. Among them the attempts to compensate for shortages of sleep, such as: sleeping during the day, cautious way of life and limitation of physical activity. The authors of the model did not take the level of sexual activity

among the factors which strengthen insomnia. On the other hand, there are a number of hypotheses concerning the role of sex in promotion of sleep [50].

Assuming the constitutional increased sympathetic nervous system activity in patients suffering from insomnia, successful sexual intercourse can result in predominance of the parasympathetic discharge that results in psychological and physical relaxation, promoting sleep. From the physiological studies it is known that the experience of full cycle of sexual response (especially in men) is completed with the refraction phase combined with relaxation, or the persistent excitation of the sympathetic nervous system with the sense of discomfort, if the sexual contact is not completed with orgasm (especially in women). For this reason, it can be assumed that some factors concerning sexual behavior or some sexual dysfunctions may also be classified as factors stabilizing insomnia. Considering the high prevalence of sleep disorders and sexual dysfunction the prevention of the problems associated with inadequate sleep hygiene and the promotion of satisfactory quality of sexual life seems to be not only a medical problem, but belong to important category of public health of modern societies.

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