Steroid Hormones and Sleep Regulation

G. Terán-Pérez, Y. Arana-Lechuga, E. Esqueda-León, R. Santana-Miranda, J.Á. Rojas-Zamorano and J. Velázquez Moctezuma*

Sleep Disorders Clinic, Universidad Autónoma Metropolitana-Iztapalapa, México, D.F., México

Abtsract: In the search of the sleep substance, many studies have been addressed for different hormones, responsible for sleep-wake cycle regulation. In this article we mentioned the participation of steroid hormones, besides its role regulating sexual behavior, they influence importantly in the sleep process. One of the clearest relationships are that estrogen and progesterone have, that causing changes in sleep patterns associated with the hormonal cycles of women throughout life, from puberty to menopause and specific periods such as pregnancy and the menstrual cycle, including being responsible for some sleep disorders such as hypersomnia and insomnia. Another studied hormone is cortisol, a hormone released in stressful situations, when an individual must react to an extraordinary demand that threatens their survival, but also known as the hormone of awakening because the release peak occurs in the morning, although this may be altered in some sleep disorders like insomnia and mood disorders. Furthermore neurosteroids such as pregnanolone, allopregnanolone and pregnenolone are involved in the generation of slow wave sleep, the effect has been demonstrated in experimental animal studies. Thus we see that the sleep and the endocrine system saved a bidirectional relationship in which depends on each other to regulate different physiological processes including sleep.

Keywords: Sleep, steroid hormones, endocrine system, cortisol, neurosteroids.

INTRODUCTION

One of the most conspicuous non-sexual action of steroid hormones is their influence on sleep regulation. Solid evidence has been generated in the last decades indicating that the sleep-wakefulness cycle is markedly disturbed in physiological or pathological conditions that are underlined by steroid hormone disturbances. This phenomenon is particularly noticeable in women throughout their reproductive life and even within the menstrual cycle. Although in men hormonal changes are not as marked as in women, they do exist and also can influence sleep regulation [1].

Pioneering studies in animals during the late 60's, showed that sleep, in general, and sleep stages, in particular, could be affected by hormonal conditions. The group of Dr. Charles Sawyer, one of the most influential behavioral endocrinologists, reported that the sleep pattern in female rats showed significant variations during the estrous cycle. These effects were linked to steroid hormones after they observed the changes in the sleep pattern in ovariectomized rats, which were subsequently reverted by hormonal replacement [2].

After those studies, several reports involved the relationship between hormones and sleep, using mainly two approaches: one was the assessment of hormonal levels during sleep and the other, was recorded the impact on the sleep pattern of hormonal variations, generated both endogenous and exogenously.

*Address correspondence to this author at the Departamento de Biología de la Reproducción, Universidad Autónoma Metropolitana-Iztapalapa, C.P. 09340 Iztapalapa, D.F. México, México; Tel: (+52 55)- 58044701; Fax: 58044704;
E-mail: jvm@xanum.uam.mx

To analyze this issue, clinical conditions of hormonal unbalance in humans represent the natural model to study these relationships. In the present chapter, we revisit the influence of the main steroid hormones on sleep, emphasizing on physiological or pathological conditions in which hormones show acute oscillations.

ESTROGENS

The influence of sexual steroid hormones on regulatory sleep mechanisms in mammals has been recently reviewed [3]. Concerning women, the specific interaction of estrogens and sleep regulation can be analyzed in several conditions in which hormones display a particular pattern. Throughout their life, women experience drastic physiological changes that are accompanied by huge variations in hormone concentrations. At the end of childhood, girls have a few months to cope with a tremendous transformation from a child to a potentially reproductive woman. Steroid hormone oscillations are the major factor in this transformation. From the very first menstrual cycle women experience changes in sleep durring the menstruation period. Thereafter, pregnancy, delivery, lactation and menopause are the incidences when women might display sleep disturbances mainly due to hormone oscillations.

The relationship between hormonal status and sleep patterns has been analyzed by both basic and clinical researchers. As sleep medicine evolved, gyneco-obstetric conditions have been taken into account as risk factors for sleep disturbances. Also, hormone replacement therapy has been a rich source of information regarding steroid control of sleep [4].

1875-5607/12 $58.00+.00

Puberty

Among the dramatic physical and emotional changes associated with puberty, sleep is not an exemption. However, as the physical changes are associated also with cognitive and behavioral alterations, it has been difficult to determine the influence on sleep changes of extrinsic and intrinsic factors. Some studies have recently focused on this issue.

Menstrual Cycle

The menstrual cycle is a complex event in which both proteic and steroidal hormones are involved. Hypothalamic factors regulate the participation of hypophysiary hormones some of which, when acting in the periphery, induce the release of both adrenal and gonadal steroids. A number of studies have reported that most of the hypothalamic-hypophysiary hormones exert an effect on sleep mainly, though not exclusively, increasing the amount of slow wave sleep.

However, when sleep patterns are analyzed throughout the menstrual cycle, the results reported are often contradictory. Solid evidence showed that sleep patterns display most of their disturbances during the luteal phase of the cycle. These changes are characterized by an increase of sleep latency, a decrease in sleep efficiency and a significant increase of diurnal somnolence [5]. Nevertheless, subjective alterations of sleep were mainly reported in association with the premenstrual period, during which no objective changes in the sleep pattern have been detected (Fig. **1**).

Endocrine and emotional alterations days before menstruation are a common condition known as the premenstrual syndrome. Women affected by this condition report a variety of sleep alterations such as insomniac or hypersomniac periods, and nightmares. These changes are associated with a decrease in physical capabilities and cognitive alterations. These changes are characterized by the fact that all of them are relieved during menstruation [6].

PREGNANCY AND DELIVERY

Pregnant women commonly complain about sleep disturbances. As pregnancy progresses, sleep disturbances worsen. During the first trimester, the increase of estrogens and progesterone is associated with neurovegetative symptomatology. It has been suggested that the estrogen increase results in a shortening of REM sleep periods, mainly by increasing noradrnaline turnover in the brain stem [7]. In addition, it has been reported that light sleep increases progressively in accordance with a decrease of slow wave sleep [8]. During the second and third trimesters of pregnancy, the main sleep complaints have to do with the development of the fetus. The increase in size and weight of the fetus results in a progressive unpleasant sensation with an increase of nocturnal awakenings and an increase of diurnal somnolence and more frequent naps [9]. Women with symptomatology compatible with restless leg syndrome and periodic leg movements, show high concentrations of plasma estradiol. The picture is often totally reverted after delivery [10].

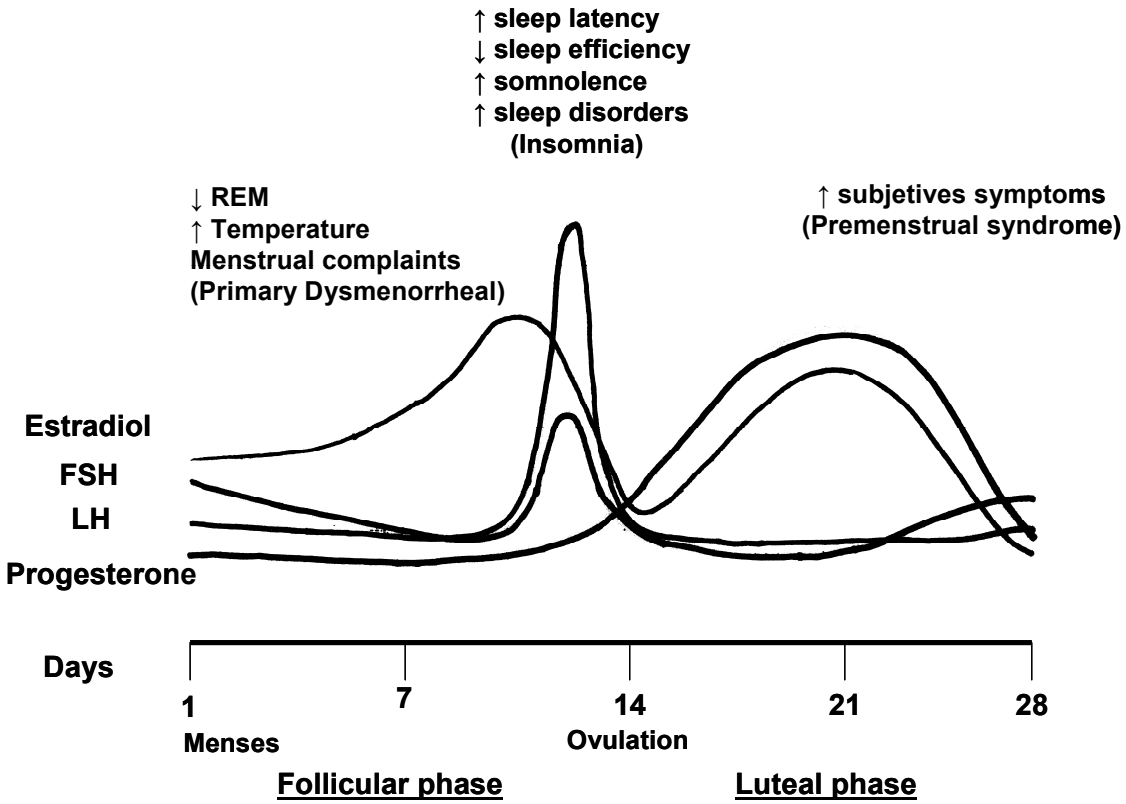

Fig. (1). Menstrual cycle and sleep disorders relations. This figure shows the changes in sleep patterns for the different phases of the menstrual cycle. It appears that in the ovulatory period are most sleep disorders.

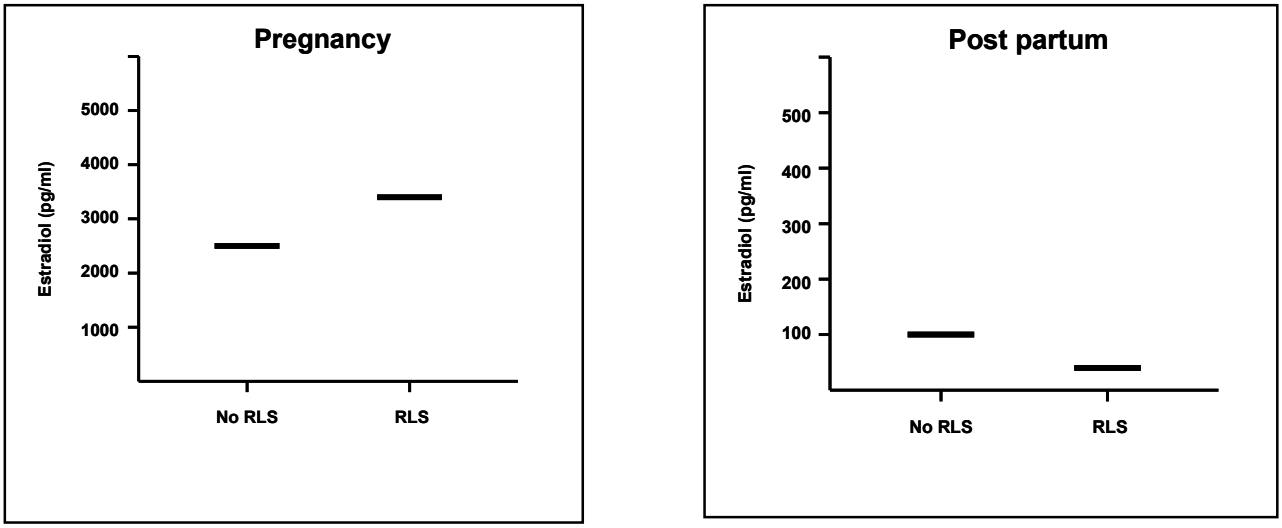

Fig. (2). Significant higher levels of estradiol are observed in RLS patients but not in healthy women during pregnancy. This difference disappears after delivery. (Modified from Dzaja A, Wehrle R, Lancel M, *et al*. Elevated estradiol plasma levels in women with restless legs during pregnancy. Sleep. 2009 Feb 1; 32(2):169-74).

On the other hand, sleep respiratory alterations during pregnancy are receiving increasing attention because of their association with hypertension. It has been suggested that sleep respiratory alterations during sleep are the main reason for hypertension during pregnancy and with delay in fetal growth [11].

After delivery, the main source of sleep alterations is the sudden decrease of hormone concentration, the irregular sleep pattern of the newborn baby and the parents anxiety due to the lack of experience in parenthood [12] (Fig. **2**).

MENOPAUSE

As in puberty, menopause is a period characterized by drastic hormonal and emotional changes, often resulting in sleep alterations. Among other hormonal changes during menopause, estradiol levels decrease, although the proteic gonadotrophins (LH and FSH) increase. Insomnia is the prevalent sleep disturbance during this stage of life although it is not the only one. A number of sleep alterations can arise during this stage, although there is no single one with a particular high frequency [13]. The presence of hot flashes emotional disturbances and respiratory alterations are the main cause of sleep fragmentation. A high percentage (83) of menopausal women with a complaint of insomnia also has an associated sleep respiratory [14].

HORMONAL REPLACEMENT THERAPY

In a recent study, Deurveilher and cols [15] reported that ovariectomized rats receiving hormonal treatment with estrogens, progesterone or both, showed an increase of REM and non-REM sleep. In addition, a high concentration of estradiol facilitates REM sleep with a corresponding decrease of non-REM sleep.

Women suffering alterations in the onset or in the maintenance of sleep, showed a significant recovery after hormonal replacement therapy with estrogens plus progesterone [16]. In addition, there is a notable recovery in the subjective symptomatology derived from respiratory alterations, such as snoring [17] and other sleep alterations, such as periodic limb movements, microawakenings, bruxism and excessive diurnal somnolence [18].

TESTOSTERONE

During sleep, most physiological functions undergo a sort of restorative process. Thus, several metabolic pathways experience this kind of adjustment during sleep. This phenomenon is mainly mediated by the endocrine system, through the synthesis and release of hormones, which in turn, exert a reciprocal influence on sleep. Furthermore, some aspects of the endocrine function are sexually dimorphic. This gender difference could explain the existence of sleep alterations mainly in one sex. In the analysis of this issue, the effects of sexual hormones on sleep are quite relevant, and testosterone, in particular, has been a useful tool in the effort to elucidate the source of gender differences in sleep disturbances. The relationship between testosterone and sleep has been an interesting subject, mainly due to the clear circadian release rhythm of the hormone that is readily detectable from four years of age [19]. In 2005, Axelsson [20], suggested that the circadian rhythm of testosterone is also dependant on the sleep cycle. The daily rise of testosterone starts together with the onset of sleep, reaching a steady level just before the first episode of rapid eye movements [21] (Fig. **3**).

On the other hand, there is a clear correlation between testosterone levels throughout life and some characteristic of the sleep pattern. In elder men, testosterone shows a drastic decrease that has been associated with the decrease of the number of REM sleep episodes as well as with the amount of slow wave sleep [22]. However, some results are still controversial. In 1980, Miyatake [23] analyzed the

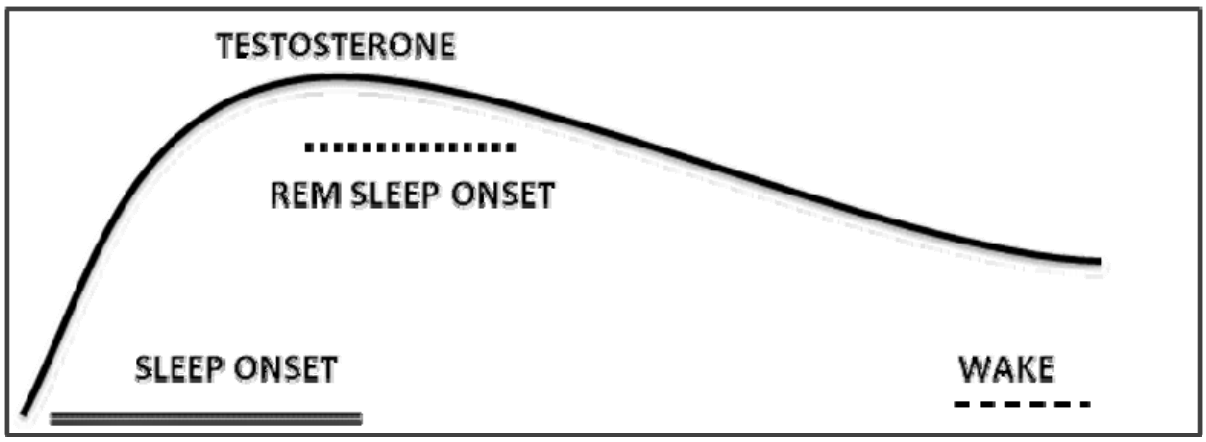

Fig. (3). Testosterone level changes associated with sleep cycle. Nocturnal testosterone rising begins on the period of falling asleep and reaches a pleateu at the first REM episode.

correlation between plasma levels of testosterone and the number of both REM and non-REM sleep episodes. The author reported that no significant correlation was detected. Nevertheless, a more recent study indicates that plasma testosterone levels display a significant positive correlation with sleep efficiency, latency to REM sleep and the total number of REM sleep episodes [21] (Fig. **4**).

One of the main components of REM sleep stage are penile erections, however, the relationship between the levels of testosterone and penile erections is also controversial. It is well known that testosterone release is promoted by the hypothalamic protein known as Lutenizing Hormone Releasing Hormone (LHRH). Despite this relation, it has been reported that chronic administration of LHRH agonists decreases the frequency of penile erections during REM sleep [24]. On the other hand, patients suffering from hypogonadism and absence of nocturnal erections, showed no significant differences regarding plasma testosterone levels when compared to healthy controls [25, 26]. Experiments performed in rats have revealed interesting information concerning the role of testosterone in sleep regulation. From the pioneering experiments of Rampin *et al.,* [27] it is well known that stressful situations modify sleep patterns, particularly by increasing the amount of REM sleep. However, these changes seem to be gender dependent and males showed a more intense effect than females [28]. Some researchers have focused on this issue, and in recent articles, a clear influence of gonadal hormones on sleep changes induced by stress, has been reported. Gonadectomized animals of both sexes and submitted to stress showed no gender differences concerning changes in the sleep pattern [29].

As sleep medicine has progressed, it has become clear that respiratory alterations play a major role in sleep disturbances. In addition, it is well known that several hormones are involved in respiratory regulation. It has been

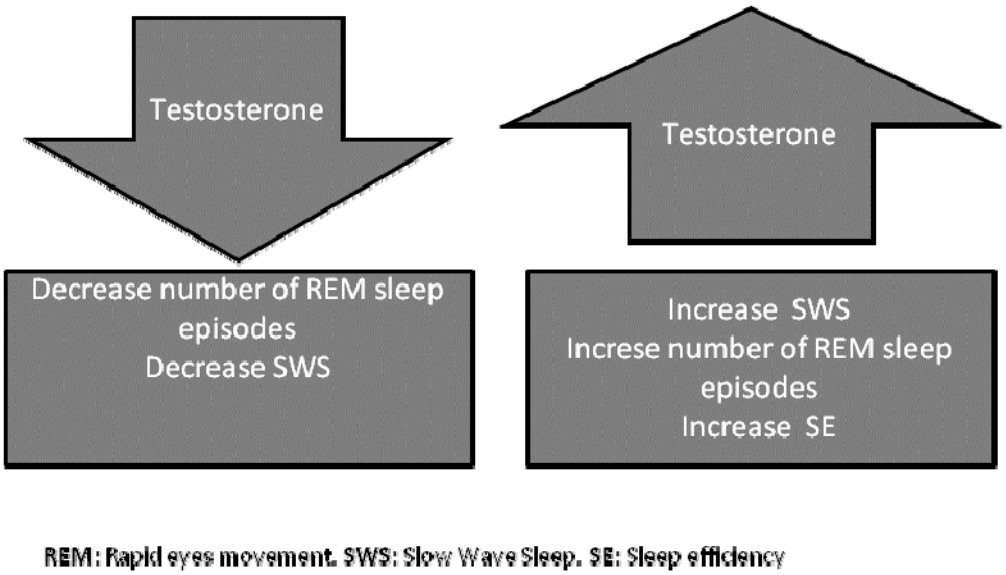

Fig. (4). Sleep architecture changes associated to serum testosterone levels.

suggested that testosterone is an important respiratory stimulant at the central nervous system level [30]. Taking these data into account, some studies have analyzed plasma levels of testosterone during sleep in patients affected by sleep respiratory diseases. Reports indicate that patients suffering from sleep apnea showed a significant decrease of testosterone levels during the early hours of the morning [31]. The exact mechanisms by which testosterone is involved in respiratory alterations during sleep are still unknown, but effects in both obstructive and central level apnea are in consideration.

Finally, as testosterone seems to have a clear influence on sleep, the other way around also seems true. Sleep seems to have an influence on testosterone release. It has been reported that sleep fragmentation induces significant disturbances in the circadian release of testosterone [32].

CORTISOL

Sleep is mainly regulated by two powerful influences: the circadian rhythm and the homeostatic process. Homeostasis in the system has a marked influence on the characteristics of sleep and is also influenced by sleep. On the other hand, the circadian rhythm of sleep depends on several synchronization factors that influence the suprachiasmatic nucleus, which is also known as the biological clock. One of the major influences on this nucleus is the variation of the light-dark cycle. In addition, the homeostatic and the circadian mechanisms also influence endocrine regulation. The suprachiasmatic nucleus regulates the circadian oscillations that most hormones display. The biological clock regulates the activity of most of the hormonal axes including, of course, the hypothalamic-hypophysiary-adrenal (HHA) axis which is the main mechanism activated during the stress response [33].

Although the stress response is a generalized reaction that involves the whole body, some major components can be defined. Most of the known stressors cause the activation of the noradrenergic system, the opioidergic system and the already mentioned HHA axis. The activation of this axis involves the participation of the corticotrophin releasing factor (CRF) from the hypothalamus, which acts on the hypophysis. In turn, the adrenocorticotrophic hormone (ACTH) is released from the hypophysis into the blood stream to reach the adrenal glands. Once in the adrenal glands, ACTH induces the release of several glucocorticoids, including cortisol. Receptors of cortisol are widely distributed in the body, thus, its effects are quite diverse [34]. Thereafter, cortisol is able to regulate its own secretion through a feedback mechanism that acts at several levels, including the adrenals themselves or the hypothalamus (Fig. **5**).

As mentioned, cortisol receptors are widely distributed throughout the body. Thus, the hormone can influence the endocrine and immune systems, among others. In the central nervous system, cortisol receptors are located mainly in the limbic system, especially in the hippocampus, amygdala and also, in the prefrontal cortex [35].

Cortisol has a clear circadian rhythm closely infuenced by sleep. Lower levels are present at the onset of sleep, while towards the end of the sleep period, there is a rise that reaches its highest peak minutes before the subject wakes up. This rhythm is established between three and six months of age in close relationship with the sleep wakefulness cycle. Before that age, new born babies show two peaks of cortisol every 24 hours without a clear correlation to daytime hours [36].

These data, among other results, support the idea that cortisol plays a major role in the onset of wakefulness [37]. From the time of the initial rise of cortisol, in approximately 20 to 30 minutes subjects reach a state of full alertness, in which cortical and subcortical structures are rapidly activated. This general activation is quite similar to that

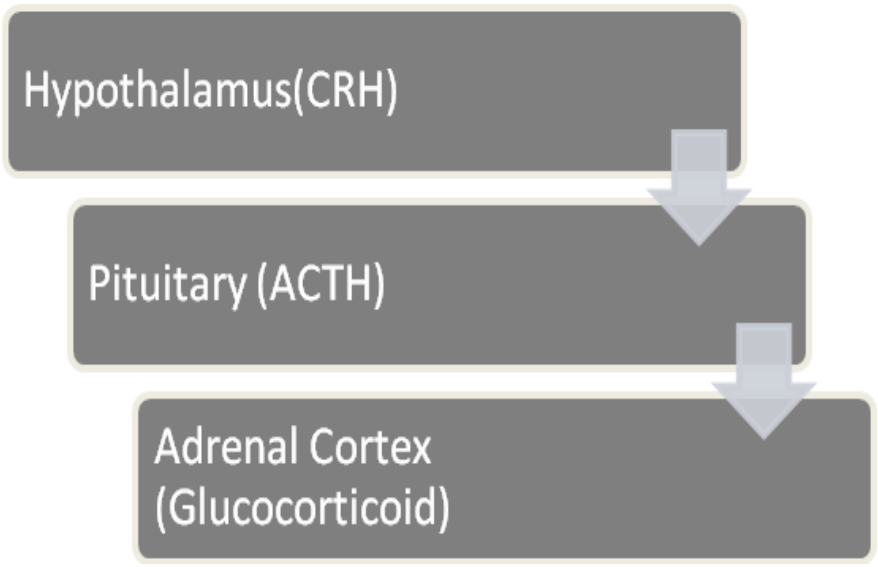

Fig. (5). Hypothalmus-Pituitary-Adrenal HPA axis.

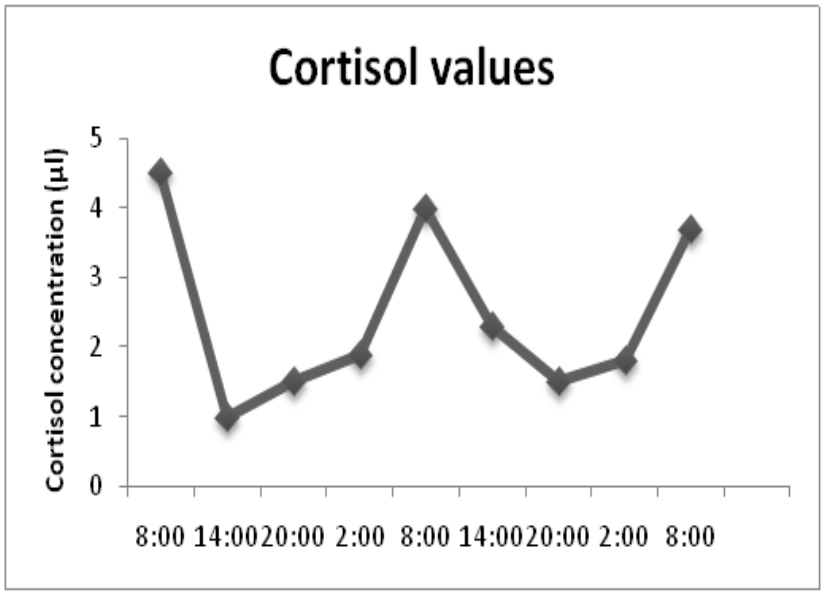

Fig. (6). Cortisol levels in a period of 48 hours.

observed when the brain switches from one sleep stage to another. In addition, the participation of the reticular formation in the awakening response is well known, and it has been suggested that cortisol exerts its action also at this level [35]. Pharmacological experiments in rats have corroborated the alerting effect of cortisol [38] (Fig. **6**).

On the other hand, as it was mentioned before, cortisol plays a major role in the stress response. The final expression of HHA activation is the release of cortisol, which will act together with other released factors to induce a rapid alertness. It must be mentioned that not all stressors induce the same stimulation of cortisol. The rise of cortisol will depend, not only on the nature of the stressor, but also on other factors such as the rat's strain, the time of day and the particular moment of the light-dark cycle, among other factors [39]. As part of the stress response, the HHA axis is activated and, therefore some proteic hormones are released. CRF and ACTH release are the previous events needed for cortisol release, but these proteic hormones also have an effect on sleep regulation. Pharmacological studies indicate that CRF induces wakefulness, while ACTH promotes slow wave sleep [40]. In turn, slow wave sleep exerts an inhibitory effect on the activation of the HHA axis [37].

While the relationship between sleep and cortisol is reciprocal, it must be mentioned that alterations of the sleep pattern will affect the circadian secretion of cortisol. Patients with severe sleep restriction or with insomnia display a significant increase of cortisol during the evening [41].

Nowadays, life in modern urban societies very often involves a situation in which sleep is severely restricted due to social or working conditions. Since the availability of computers and the internet, a high percentage of the population decides on a daily basis to spend the night hours exploring the internet, instead of sleeping. The impact on health of this drastic sleep restriction has not been yet fully elucidated, however, the participation of cortisol in some of the already reported alterations seems to be beyond any doubt. Sleep restriction is accompanied by a significant rise of cortisol, quite similar to that observed after severe stress. Sleep restriction has been correlated with the increase of hypertension, obesity, diabetes and psychiatric alterations [41].

Cortisol has been recently associated with mood changes in a relationship that seems to be reciprocal. Some recent reports have indicated that cortisol shows some alterations in correlation with mood changes. Feelings of loneliness, sadness or fear are associated with an increase in cortisol levels the next morning. Low levels of cortisol predict situations of fatigue or physical unpleasantness. Thus, it is clear that cortisol plays a major role in daily awakening, but events during the day will determine the levels of cortisol the following day [42].

NEUROSTEROIDS

Most steroidal hormones come from the gonads or from the adrenal gland. However, there is a group of steroids that are synthesized in the brain. This group of steroids is known as neurosteroids and their action on brain mechanisms is still far from being fully understood.

From the pioneering studies of Baulieu and cols., the quantity of results concerning the actions of this group of steroids has been constantly growing. Neurosteroids alopregnanolone (ALO), pregnanolona (PNA) and pregnenolone (PNE) are synthesized in glial cells using cholesterol as their precursor [43] (Fig. **7**).

After a number of studies, it has become clear that neurosteroids act on the nervous system through the modulation of GABA-A receptors with an alosteric interaction [44, 45]. Two of them, ALO and PNA, act in the membrane by increasing the conductance of chloride channels linked to the GABA receptor. Thus, the mechanism of action of neurosteroids on the GABA-A receptor is quite different from the mechanism that has been described for barbiturates and benzodiazepines [46]. Experimental

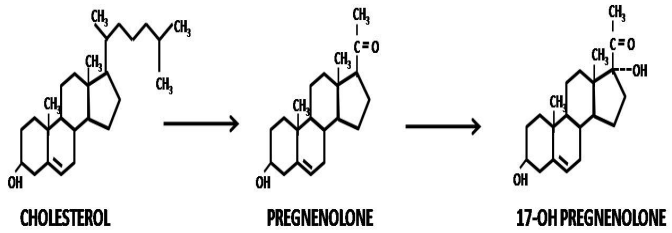

Fig. (7). Biosynthesis of pregnanes in the brain.

	SWS	REM	WAKE
ALO	↑	↓	↓
PNA	↑		
PNE		↑	

Fig. (8). Effects of pregnanes on the sleep architecture.

evidence indicates that neurosteroids are involved in a number of organic functions such as learning and memory, feeding, and also have an effect on sleep [47].

The effect of neurosteroids on sleep has been described mainly in pharmacological research on animals. The administration of ALO in rats induces electroencephalographic synchronization similar to that induced by barbiturates, although according to the authors, ALO induces slow wave sleep [48]. Recently, it has been reported that ALO administration modifies the sleep pattern by decreasing the latency to sleep and by increasing total time of slow wave sleep and a decrease of REM sleep and the duration of wakefulness [49]. Furthermore, when ALO was administered directly into the nucleus basalis there was an increase of slow wave sleep and a decrease in REM sleep time. It must be mentioned that this nucleus is cholinergic and has been involved in the regulation of sleep and wakefulness, particularly, with REM sleep [47]. More detailed studies reported that ALO administration not only increases slow wave sleep time, but also increases the transitional phase between slow wave sleep and REM sleep known as pre-REM [49]. In addition, some reports indicate that PNA administration increases slow wave sleep in an effect quite similar to that observed after ALO administration [50]. The similar action of both ALO and PNA on sleep may be due to the similar mechanisms of action. Both neurosteroids act as stimulants of the GABA-A receptor. On the other hand, PNE is also a neurosteroid but it has a different mechanism of action. PNE is an antagonist of the GABA-A receptor. When PNE is administered directly into cholinergic nuclei that regulate sleep, such as the nucleus basalis and the pedunculopontine tegmental nucleus, a significant increase of REM sleep is observed [51]. From these results, it has been suggested that the cholinergic system acts in close correlation with PNE in the regulation of REM sleep [52, 53]. In humans, however, administration of PNE, induces an effect quite similar to that observed after administration of benzodiazepine compounds, with an important increase in the percentage of slow waves seen in the electroencephalogram [54, 55] (Fig. **8**).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT

Declared none.

REFERENCES

[1] Colvin, G.B.; Whitmoyer, D.I.; Lisk, R.D.; Walter, D.O.; Sawyer, C.H. Changes in sleep-wakefulness in female rats during circadian and estrous cycles. *Brain Res*., **1968**, *7*(2), 173-81.

[2] Colvin, G.B.; Whitmoyer, D.I.; Sawyer, C.H. Circadian sleep-wakefulness patterns in rats after ovariectomy and treatment with estrogen. *Exp. Neurol.,* **1969**, *25*(4), 616-25.

[3] Paul, K.N.; Turek, F.W.; Kryger, M.H. Influence of sex on sleep regulatory mechanisms. *J. Womens Health (Larchmt),* **2008**, *17*(7), 1201-8.

[4] Sadeh, A.; Dahl, R.E.; Shahar, G.; Rosenblant-Stein, S. Sleep and Transition to adolescence: A longitudinal Study. *Sleep,* **2009**, *32*(12), 1602-1609.

[5] Mamber, R.; Bootzin, R.R. Sleep and the menstrual cycle. *Health Psychol*., **1997**, *16*, 209-14.

[6] Mauri, M. Sleep and the reproductive cycle: a review. *Health Care Women Int.,* **1990**, *11,* 409-21.

[7] Heritage, A.S.; Sumpf, W.E.; Sar, M.; Grant, L.D. Brainstem catecholamine neurons are target sites for sex steroid hormones. *Science,* **1980**, *207*, 1377-9.

[8] Lee, K.A.; Zaffke, M.E. Longitudinal changes in fatigue and energy during pregnancy and the postpartum period. *J. Obsted. Gynecol. Neonatal. Nurs.,* **1999**, *88*, 183-91.

[9] Mindell, J.A.; Jacobson, B.J. Sleep disturbances during pregnancy. *J. Obstet. Gynecol. Neonatal. Nurs.,* **2000**, *29*, 590-7.

[10] Dzaja, A.; Wehrle, R.; Lancel, M.; Pollmächer, T. Elevated estradiol plasma levels in women with restless legs during pregnancy. *Sleep,* **2009**, *32*(2), 169-74.

[11] Franklin, K.A.; Homgren, P.A.; Jonsson, F.; Poromaa, N.; Stenlund, H.; Svanborg, E. Snoring, pregnancy-inducted hipertensión, and growth retardation of the fetus. *Chest,* **2000**, 117, 137-41.

[12] Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. *Obstet. Gynecol.,* **2000**, *95*, 14-8.

[13] Pien, G.W.; Sammel, M.D.; Freeman, E.W.; Lin, H.; De Blasis, T.L. Predictors of sleep quality in women in the menopausal transition. *Sleep*, **2008**, *31*(7), 991-9.

[14] Guilleminault, C.; Palombini, L.; Poyares, D.; Chowdhuri, S. Chronic insomnia postmenopausal women, and sleep disordered breathing: part 1. Frequency of sleep disordered breathing in a a cohort. *J. Psichosom. Res.,* **2002**, 53(1), 611-5.

[15] Deurveilher, S.; Rusak, B.; Semba, K. Estradiol and progesterone modulate spontaneous sleep patterns and recovery from sleep deprivation in ovariectomized rats. *Sleep*, **2009**, *32*(7), 865-77.

[16] MacLennan, A.; Lester, S., Moore, V. Oral estrogen replacement therapy versus placebo for hot flushes: A systematic review. *Climateric.,* **2001**, *4*, 58-74.

[17] Campos, H.H.; Bittencourt, L.R.A.;, Haidar, M.A.; Tufik, S.; Baracat, E.C. Prevalência de distúrbios do sono na pós-menopausa. *Rev. Bras. Ginecol. Obastet*., **2005**, *27*(12), 731-6.

[18] Hachul, H.; Bittencourt, L.;R.; Andersen, M.L.; Haidar, M.A,; Baracat, E.C. Tufik S. Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women. *Int J. Gynaecol. Obstet.,* **2008**, *103*(3), 207-12. Epub.

[19] Bremner, W.J.; Vitiello, M.V.; Prinz, P.N. Loss of circadian rhytmicity in blood testosterone levels with aging in normal men. *J. Clin. Endocrinol. Metab*., **1983**, *56*, 1278-1281.

[20] Axelsson, J.; Ingre, M.; Akerstedt, T.; Holmback, U.; Effects of acutely sleep on testosterone. *J. Clin. Endocrinol. Metab.,* **2005**, *90*, 4530e5.

[21] Luboshitzky, R.; Herer, P.; Levi, M.; Shen-Orr, Z.; Lavie P. Relationship between rapid eye movement sleep and testosterone secretion in normal men. *J. Androl.,* **1999**, *20*(6).

[22] Schiavi, R.C.; White, D.; Mandeli, I. Pituitary-gonadal function during sleep in healthy aging men. *Psychoneuroendocrinology,* **1993***, 17,* 599-609.

[23] Miyatake, A.; Morimoto, Y.; Oishi, T.; Hanasaki, N.; Sugita, Y.; Itjima, S.; Teshima, Y.; Hishikawa, Y.; Yamamura, 1. Circadian rhythm of serum testosterone and its relation to sleep: comparison with the variation in serum luteinizing hormone, prolactin and cortisol in normal men. *J. Clin. Endocrinol. Metab.,* **1980***, 51,* 1365-1371.

[24] Hirschkowitz, M.; Moore, C.A.; O'Conner, S.; Bellamy, M.; Cunningham, G.R. Androgen and sleep-related erections. *J. Psychosomat. Res.,* **1997**, *42,* 541-54-6.

[25] Kwan, M.; Greenlead, W.J.; Mann, J.; Crapo, L.; Davidson, J.H. The nature of androgen action on male sexuality-a combined laboratory self-report study in hypogonadal men. *J. Clin. Endocrinol. Metab.,* **1983***, 57*, 557-562.

[26] Granata, A.R.; Rochira, V.; Lerchl, A.; Marrama, P.; Carani, C. Relationship between sleep-related erections and testosterone levels in men. *J. Androl.,* **1997**, *18*, 522e7.

[27] Rampin, R.; Cespuglio, N.; Chastrette. Jouvet, M. Immobilisation stress induces a paradoxical sleep rebound in rat. *Neurosci. Lett.,* **1991**, *126*, 113-118.

[28] Koehl, M.; Battle, S.; Meerlo, P. Sex differences in sleep: the response to sleep deprivation and restraint stress in mice. *Sleep,* **2006**, *29*(9), 1224-31.

[29] Paul, K.N.; Losee-Olson, S.; Pinckney, L.; Turek, F.W. The ability of stress to alter sleep in mice is sensitive to reproductive hormones. *Brain Res*., **2009**.

[30] Saaresranta, T.; Polo, O. Hormones and breathing. *Chest,* **2002**, *122*(6), 2165-82.

[31] Grunstein, R.R.; Handelsman, D.J.; Lawrence, S.J. Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. *J. Clin. Endocrinol. Metab.,* **1989***, 68*, 352e358.

[32] Luboshitzky, R.; Zabari, Z.; Shen-Orr, Z.; Herer, P.; Lavie, P. Disruption of the nocturnal testosterone rhythm by sleep fragmentation in normal men. *The J. Clin. Endocrinol. Metabol.,* **2000***, 86*(3).

[33] Dedovic, K.; Duchesne, A.; Andrews, J.; Engert, V.; Pruessner, J.C. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *Neuroimage,* **2009**, *47*(3), 864-71.

[34] Hellhammer, D.H.; Wüst, S.; Kudielka, B.M. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology,* **2009***, 34*(2), 163-71. Dec 18. Review

[35] Clow, A.; Hucklebridge, F.; Stalder, T.; Evans, P.; Thorn, L. The cortisol awakening response: More than a measure of HPA axis function. *Neurosci Biobehav.,* **2009**, Rev. Dec 22.

[36] Scher, A.; Hall, W.A.; Zaidman-Zait, A.; Weinberg, J. Sleep quality, cortisol levels, and behavioral regulation in toddlers. *Dev Psychobiol.,* **2010**, *52*(1), 44-53.

[37] Dahlgren, A.; Kecklund, G.; Theorell, T.; Kerstedt, T. Day-to-day variation in saliva cortisol—Relation with sleep, stress and self-rated health. *Biological Psychology*. **2009**, 82, 149-155.

[38] Vazquez-Palacios, G.; Velazquez-Moctezuma, J. Effect of electric foot shocks, immobilization, and corticosterone administration on the sleep-wake pattern in the rat. *Physiol. Behav.,* **2000***, 71*(1-2), 23-8.

[39] Rojas-Zamorano, J.A.; Esqueda-Leon, E.; Jimenez-Anguiano, A.; Cintra-McGlone, L.; Mendoza-Melendez, M.A.; Velazquez-Moctezuma, J. The H1 histamine receptor blocker, chlorpheniramine, completely prevents the increase in REM sleep induced by immobilization stress in rats. *Pharmacol. Biochem. Behav.,* **2009***, 91*(3), 291-4

[40] Steiger, A. Sleep and the hypothalamo-pituitary-adrenocortical system. *Sleep Med. Rev.,* **2002**, *6*(2), 125-38.

[41] Wu, H.; Zhao, Z.; Stone, W.S.; Huang, L.; Zhuang, J.; He, B.; Zhang, P.; Li, Y. Effects of sleep restriction periods on serum cortisol levels in healthy men. *Brain Research Bulletin,* **2008***, 77* (241-245).

[42] Adam, E.K.; Hawkley, L.C.; Kudielka, B.; Cacioppo, J. Day to day dynamics of experience-cortisol associations in a population-based sampleof older adults. *Proceedings of the National Academy of Sciences, **2006**, 103 (45), 17058-17063*.

[43] Baulieu, E. Neuroesteroids: of the nervous system, by the nervous system, for the nervous system. *Recent. Prog. Horm. Res.,* **1997***, 52:1-32*.

[44] Majewska, M.D. Neurosteroids: Endogenous bimodal modulators of the GABAA receptor: Mechanism of action and physiological significance. *Prog. Neurobiol.,* **1992***, 38,* 379-395.

[45] Rupprecht, R.; Holsboer, F. Neuroactive steroids: mechanism of action and neuropsychopharmacological perspectives. *Trend Neurosci.,* **1999**, *22*, 410-416.

[46] Paul, S.; Purdy, R. Neuroactive Steroids. *Faseb J.,* **1992***, 6*, 2311-2322.

[47] Darnaudéry, M.; Pallarés, M.; Bouyer, J.; Le Moal, M.; Mayo, W. The promnesic neuroesteroid pregnenolone sulfate increases paradoxical sleep in rats. *Brain Research,* **1999-A**, *818*, 492-498.

[48] Mendelson, W. Human sleep: research and clinical care. *New York: Plenum Publishing,* **1987-A**, 129-179.

[49] Damianisch, K.; Rupprecht, R.; Lancel, M. The Influence of subchronic administration of the neuroesteroid allopregnanolone on sleep in the rat. *Neuropsychopharmacology,* **2001***, 24*(4), 576-584.

[50] Dale, M.;, Wesley, F.;, Seidel, K.;, Lan, N.G.; Xia, H.; Hawkinson, J.;, Wieland, S.; Carter, R.; Wood,. P. An orally bioavailable analog of the endogenous neuroactive steroid, pregnanolone, demostrates potent sedative hypnotic actions in the rat. *J. Pharmachol. Exp. Ther.,* **1997**, *282*, 420-429.

[51] Darbra, S.; George, O.; Bouyer, J. J.; Piazza, P. V.; Le Moal, M.; Mayo, W. Sleep-wake states and cortical synchronization control by pregnenolone sulfate into the pedunculopontine nucleus. *J. Neurosci. Res.,* **2004***, 76*, 742-747.

[52] Darnaudéry, M.; Pallarés, M.; Bouyer, J.; Le Moal, M.; Mayo, W. Infusion of neuroesteroids into the rat nucleus bassalis affects paradoxical sleep in accordance with their memory modulating properties. *Neuroscience,* **1999-B**, *2*, 583-588.

[53] Marrosu, F.; Portas, C.; Mascia, M.S.; Casu, M. A.; Fa, M.; Giagheddu, M.; Imperato, A.; Gessa, G. L. Microdialysis measurement of cortical and hippocampal acetylcholine release

during sleep-wake cycle in freely moving cats. *Brain Res.,* **1995**, *671*, 329-332.

[54] Steiger, A.; Trachsel, L.; Guldner, J.; Hemmeter, U.; Rothe, B.; Rupprecht, R.; Vedder, H.; Holsboer, F. Neurosteroid pregnenolone induces sleep-EEG changes in man compatible with inverse agonistic GABAa-receptor modulation. *Brain Res.,* **1993**, *615*, 267-274.

[55] Lancel, M.; Cronlein, T.; Muller-Preuss, P.; Holsboer, F. Pregnenolone enhances EEG delta activity during non- rapid eye movement sleep in the rat, in contrast to midazolam. *Brain Res.,* **1992**, *575*, 63-68.

Received: May 02, 2011 Revised: May 13, 2011 Accepted: August 17, 2011