

БИОЛОГИЯ И МЕДИЦИНСКАЯ БИОЛОГИЯ BIOLOGY AND MEDICAL BIOLOGY

DOI: 10.29413/ABS.2018-3.5.2

УДК 616.8-009.836:618.173:612-018.2

Semenova N.V., Madaeva I.M., Kolesnikova L.I.

Insomnia and Circadian Rhythms of Melatonin in Menopausal Women *

Scientific Centre for Family Health and Human Reproduction Problems
(ul. Timiryazeva 16, Irkutsk 664003, Russian Federation)

The aim of the review is to analyze literature data about sleep homeostasis and the role of the one of circadian system key elements – melatonin – in the regulation of the sleep-wake cycle in women in menopause. It was shown that the prevalence and structure of sleep disorders depends on the menopausal phase. It was revealed that the melatonin content in the body, determined in various biological media (blood, saliva, urine), depends on age, sex, race, and chronotype. It was shown that morning melatonin can be used as a biological marker for determining the chronotype. Most studies indicated a decrease in melatonin level with aging. Moreover, women have lower melatonin level than men. In case of insomnia, lower melatonin level was found, although the results of the studies are ambiguous. The shift in the peak of hormone secretion in the early morning hours was described in menopausal women. Also, the dependence of melatonin circadian rhythm on the menopausal phase was revealed, which determines different approaches to insomnia therapy. We revealed the association of melatonin secretion circadian rhythms with Clock 3111T/C gene polymorphism in Caucasian patients with insomnia, which allows considering 3111T allele as risky in the formation of melatonin circadian rhythm disturbances in these patients.

Key words: circadian rhythms, melatonin, menopause, insomnia

For citation: Semenova N.V., Madaeva I.M., Kolesnikova L.I. Insomnia and circadian rhythms of melatonin in menopausal women. Acta biomedica scientifica, 3 (5), 16-21, DOI 10.29413/ABS.2018-3.5.2.

Инсомния и циркадные ритмы мелатонина у женщин в менопаузе

Семёнова Н.В., Мадаева И.М., Колесникова Л.И.

ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека»
(664003, г. Иркутск, ул. Тимирязева, 16, Россия)

Обзор литературы посвящён анализу полученных к настоящему времени данных относительно гомеостаза сна и роли гормона мелатонина, являющегося одним из ключевых элементов циркадной системы организма, в регуляции цикла «сон-бодрствование» у женщин в менопаузе. Содержание мелатонина определяют в различных биологических средах, таких как моча, кровь, слюна, и исследованиями последних лет показана зависимость уровня данного гормона от пола, возраста, хронотипа, а также расовой принадлежности. Так, более низкий уровень мелатонина отмечен у женщин, представительниц азиатской расы, с возрастом. Более того, мелатонин в 9.00 ч. может быть использован в качестве биологического маркера определения хронотипа человека. Результаты исследований хронобиологических ритмов мелатонина у женщин в менопаузе неоднозначны, однако большинство результатов свидетельствуют о более низком содержании гормона при нарушениях сна. При этом выявлен факт смещения пиков секреции мелатонина, ассоциированного с наличием инсомнических расстройств в перименопаузе и отсутствием данной взаимосвязи в постменопаузе, на ранние утренние часы. Показано, что данная зависимость определяется носительством мажорного аллеля полиморфного варианта гена Clock только у представительниц европеоидной расы.

Ключевые слова: циркадные ритмы, мелатонин, менопауза, инсомния

Для цитирования: Семёнова Н.В., Мадаева И.М., Колесникова Л.И. Инсомния и циркадные ритмы мелатонина у женщин в менопаузе. Acta biomedica scientifica, 3 (5), 16-21, DOI 10.29413/ABS.2018-3.5.2.

Sleep is a periodically occurring, natural physiological condition characterized by cyclicality, a significant restriction of motor activity, a decrease in muscle tone and in response to stimuli. People spend about a third of their life sleeping, and the wholesomeness of sleep determines the overall level of health and quality of life measured in terms of social, mental, emotional and physical well-

being. At present, sleep is considered as an active state, a complex functional and chronobiological process. Normally, sleep includes a succession of four stages of non-rapid eye movement sleep (NREM) and a phase of rapid eye movement sleep (REM), which is a complete cycle repeated 4–6 times during the entire period of night sleep. The cycle time in a healthy people is relatively stable

* Статья опубликована на основании доклада на III Всероссийской научно-практической конференции молодых учёных «Фундаментальные и прикладные аспекты в медицине и биологии» (Иркутск, октябрь, 2018).

and equals to 90–100 minutes. The function of non-rapid eye movement sleep is to restore brain homeostasis and to optimize control of internal organs, and the main function of REM-sleep is that of mental adaptation [11].

MENOPAUSE AS A RISK FACTOR OF SLEEP DISORDERS

Menopause is a biopsychosocial process of transition from the reproductive phase to its full decline. During this period women experience physiological changes under the influence of various ethnic, psychological, social and cultural factors. Signs of menopause are depletion of the ovarian follicular apparatus, a decrease in its functional activity, changes in the relations between hormone levels, a decrease of the estrogen level, and anovulation [20].

Given the hormonal and metabolic changes in women during and after menopause, the incidence of sleep problems in this age group increases in comparison with the reproductive phase and is 16–42 % in perimenopausal and 35–60 % in postmenopausal women [50]. A number of studies have shown that perimenopausal women are more likely to complain about sleep disorders than postmenopausal ones [5]. The oxidative stress formed during postmenopause plays a significant role in the formation of insomnia in postmenopausal women [38]. Despite the fact that postmenopause creates independent risks for the development of sleep disorders compared with perimenopause [18], studies on Asian [12] and Hispanic [7] women have not revealed any differences in the frequency characteristics of sleep disorders depending on the climacteric phase. The work of G.W. Pien et al. (2008) which included Caucasian and African American women have shown a greater risk of developing sleep disorders in perimenopausal women [36]. The various results obtained may be due to ethnicity – thus, Asian women have a lesser manifestation of vasomotor symptoms compared with Caucasians [16].

One of the most common sleep disorders in menopausal women is insomnia [2]. The incidence of insomnia in the population is 9–15 %, and this pathology is more often detected in women. Moreover, gender differences in the frequency of sleep disorders are becoming increasingly important with age [26].

The basic model of insomnia pathogenesis considers three groups of factors influencing the development of this pathology – predisposing, provoking and supportive. The predisposing factors include:

- biological factors reflecting the hyperactivity of stress body systems (decrease in activity of inhibitory neurotransmitter systems, desynchronization of EEG rhythms with an increase in the beta spectrum activity and a decrease in the activity of delta and gamma waves, increased tone of the sympathetic nervous system, changes in the hormone secretion profile, increased metabolism during the day, increased heart rate with a decrease in heart rate variability);
- psychological factors (increased anxiety, emotionality, hypochondria);
- social factors (shift and night work, frequent change of time zones, low socioeconomic status, family history);
- behavioral factors (lack of sleep hygiene, alcohol, smoking, low physical activity level).

A provoking factor in the development of insomnia can be any stressful event, accompanied by emotional hyperactivation. In the presence of predisposing factors or of high intensity or duration of stress, supporting factors manifest themselves as somatic and cortical hyperactivation (predominance of the tone of the sympathetic nervous system, imbalance of inhibitory and activating systems of the brain) [42].

At the onset of menopause, hormonal and metabolic changes stressful for women are the causes of insomnia. According to B. Phillips et al. (2005), the main symptom of insomnia in postmenopausal women (physiological or surgical) is difficulty falling asleep [35], while the results of another study have indicated a greater frequency of night awakenings in postmenopause with no difference in relation to the difficulty of falling asleep and to morning and afternoon fatigue between the climacteric phases [24]. The results of L. Kolesnikova et al. (2017) have shown that perimenopausal women have more frequency of the difficulty falling asleep and postmenopausal ones have more the number of nocturnal awakenings [32]. Various works were devoted to the role of vasomotor symptoms in menopausal women in the pathogenesis of insomnia [24, 46]. The presence of vasomotor symptoms in postmenopause makes the risk of night awakenings 1.85 times higher [46]. A correlation has been found between the frequency of night hot flashes and the number of awakenings [48]. In postmenopause, even a slight frequency of night sweats occurrence leads to awakenings, while in perimenopause only frequent bouts of night sweats are associated with these disorders [24]. According to polysomnographic monitoring in women with different menopausal status and pronounced vasomotor reactions, a decrease in sleep efficiency, a change in its 'architecture' and a longer waking time during the night are revealed, although not all the studies confirm this [15]. Violation of the sleep-wake cycle is part of a general disturbance in the vegetative balance regulation and sleep organization in menopausal women. This is confirmed, on the one hand, by the studies showing the association of poor sleep quality with a decrease in estradiol levels and an increase in luteinizing hormone levels in menopausal women [31], and, on the other hand, by clinical studies confirming the positive effect of hormone replacement therapy on the process of maintaining sleep, its duration and efficiency [23].

Another significant factor in the development of insomnia in menopausal women is depressive disorders in the pathogenesis of which a key role belongs to the disruption of the serotonergic brain systems (lack of serotonin in the brain and in receptor sites, the inability of serotonin to reach receptor sites, and a decreased level of tryptophan) [41]. A greater predisposition to depression in women is due to a lower serotonin content in the brain, a decrease in the functional activity of serotonin 5-HT₂ receptors in the frontal, parietal, temporal and cingulate cortices [37]. Deficiency of female sex hormones at the onset of menopause has a major role in the pathogenesis of depression in connection with their neuroprotective role, their effect on synthesis and metabolism of all monoamines, mostly of serotonin, and their participation in the development of many brain functions [28]. In postmenopausal women, depression is associated not only with difficulties of falling

asleep and early morning awakenings [46], but also with night awakenings [48].

The consequences of insomnia can be both social (increased risk of road accidents, decreased productivity), and medical. Insomnia increases the risk of further development of mental disorders, alcoholism and drug dependence. At present, data have shown that insomnia also is interlinked with obesity, cardiovascular diseases, oncology, bronchial asthma, impaired carbohydrate metabolism, pain and mortality [8].

MELATONIN IS THE ONE OF THE KEY ELEMENTS OF THE SLEEP-WAKE CYCLE

A large array of physiological and metabolic processes in the body, such as temperature, sleep-wake cycle, glucose level, cortisol production, blood pressure, heart rate, oxidative stress are controlled by a circadian system consisting of central clocks located in the suprachiasmatic nuclei of the hypothalamus (SCN) and a number of peripheral oscillators such as the liver, lungs, adrenal glands, fibroblasts and other tissues that are synchronized daily with the help of nervous or humoral signals. When the work of the biological clock is disrupted, either the connections between local oscillators in different tissues or between the central oscillator and the rest of the body are torn, which underlies the further malfunction of neuroendocrine rhythms and behavior. At present, it is known that any changes in the circadian system increase the risk of developing pathological conditions such as sleep disorders, affective disorders, diabetes, oncology, obesity, cardiovascular diseases, and reproductive disorders [14].

The one of the key elements of the circadian mechanism is the hormone melatonin produced by the pineal gland [45]. However, in the literature there are substantial data on the study of melatonin after pinealectomy in patients of reproductive age, when the hormone level in the evening decreased, yet the sleep-wake cycle persisted [40]. It was established that the pineal gland is not the only organ capable of synthesizing melatonin. Cells producing this hormone have been found in the retina, gastrointestinal tract, bone marrow, respiratory tract, adrenal gland, thyroid gland, thymus, cerebellum, genitourinary system, placenta, etc. In addition, mast cells, natural killer cells, eosinophilic leukocytes, platelets and endotheliocytes were also proved to synthesize melatonin [1].

The rhythm of melatonin secretion has a clearly expressed circadian character. In healthy people the melatonin level begins to rise in the evening, coinciding with a decrease in illuminance and reaching a maximum in the middle of the night (02.00–03.00 h), progressively decreasing by morning [4]. In this case, the pineal gland acts as a universal mediator of the light information passing through the SCN neurons through the thoracic spine and the sympathetic neurons of the superior cervical ganglion. The synthesis of melatonin is carried out from tryptophan which enters the pinealocytes from the vascular bed and through 5-hydroxytryptophan is converted into serotonin. During the dark phase of the day, the electrical signals coming from the SCN cause an increase in the synthesis and release of norepinephrine from the sympathetic nerve endings, which in turn activates in pinealocytes the arylalkylamine-N-acetyltransferase and

hydroxyindole-O-methyltransferase – the ferments taking part in the conversion of melatonin from serotonin [21].

In many studies, a decrease in the night peak of melatonin concentration with age was noted, which is a consequence of functional changes in the pineal gland and other links of the circadian system of the body during physiological aging [33, 44]. When searching for gender differences in the melatonin level in people aged 60 years and older, a lower melatonin level in women is revealed [32], although in the reproductive age the opposite results were noted [10]. The age-related decrease in melatonin secretion in the female body signals a disorder of the pineal and pituitary control over the ovarian cycle and the progressive decline of the fertile function [43]. E. Toffol et al. (2014) in their study of melatonin effect on mood, sleep, vasomotor symptoms and quality of life in women depending on the menopausal phase have shown that postmenopausal women have lower melatonin concentrations in the serum at night than perimenopausal women. The duration of melatonin secretion was shorter in postmenopausal women, whereas the peak time does not differ [44]. The results of another study showed that the night secretion of melatonin in women aged 17 to 45 years decreased gradually and had a sharp rise at 46 to 50 years. In postmenopause, a sharp, age-related decrease in night melatonin secretion was detected within 15 years after the onset of menopause [33]. E. Waleca-Kapic et al. (2015) not only have confirmed a decrease in urine 6-sulfatoxymelatonin in postmenopausal women, but also have found a negative correlation between its excretion and body mass index, which confirms the melatonin effect on metabolism [47].

Data on the racial differences in the melatonin content are of interest. Studies in this area are few and the results have indicated lower hormone levels in the Asian representatives compared with Caucasians, which can be due to both ethnic characteristics and a darker eye pigment [22].

To date, data have been obtained confirming the relationship between the melatonin level and the sleep-wake cycle. Thus, a number of studies revealed that evening sleepiness and the onset of sleep usually occurs 2 hours after the onset of the endogenous melatonin formation [6]. According to several authors, the role of melatonin is rather to open the so-called 'sleep gate', to create a 'predisposition to sleep', to inhibit the mechanisms of wakefulness than to directly impact the somnogenic structures. The opening of the 'sleep gate' is preceded by a period of increased human activation – the 'forbidden period' for sleep, sharply replaced by the 'opening of the gate'. There is some evidence in favor of the assumption that this 'forbidden period' of sleep is the peak of the daily wake cycle, since it is combined with the daily peak of body temperature. The beginning of the nightly increase in melatonin secretion usually occurs in the middle of the 'forbidden period', and when a certain concentration in the blood corresponding to about half of the maximum nighttime level occurs, the 'sleep pressure' sharply increases, facilitating the transition from wakefulness to sleep [25].

There are several scientific works comparing the melatonin level at certain times between representatives of different chronotypes. Thus, the study by M. Gibertini et al. (1999) where blood was sampled every hour from

00.00 until 07.00 showed no differences in the content of this hormone [17]. A.L. Morera-Fumero et al. (2013) in their study comparing serum melatonin level at three time points (9.00, 12.00 and 00.00) depending on the chronotype revealed a significant increase in the hormone level by almost 2 times in representatives of the 'night owl' chronotype at 9.00; in connection with this the researchers have suggested considering morning melatonin as a biological marker for determining the human chronotype [30]. The results of study by H.J. Burgess et al. (2008) demonstrated that the earlier the subject wakes up, the earlier melatonin secretion begins [9]. When studying the circadian rhythm of melatonin in patients with delayed sleep phase syndrome (a disorder of diurnal rhythms where the onset of a normal sleep pattern is delayed by 2 or more hours compared to most people and is characteristic of the 'night owl' chronotype), the shift in the hormone secretion peak was by 3–5 hours compared to the control group [29].

Studies carried out to date have shown that people with insomnia have a lower melatonin level [49]; moreover, the peak of the hormone secretion is shifted, which was demonstrated in the work on the association of melatonin, menopausal depression and sleep time. A delay in the peak of hormone secretion before morning was revealed in women with menopausal depression, which, according to researchers, may be caused by longer sleep duration as a compensation for insomnia in these women [34]. Similar results were obtained in another study where the shift in the peak of melatonin secretion in the early morning hours in women with sleep disorders in perimenopause was shown. In postmenopause, the morning peak of melatonin was also noted, regardless of the presence of sleep disorders [27]. The present study further revealed the association of melatonin secretion circadian rhythms with Clock 3111T/C gene polymorphism in Caucasian patients with insomnia, consisting of an increased hormone level in early morning hours in carriers of the TT-genotype, which allows considering 3111T allele as risky in the formation of melatonin circadian rhythm disturbances in these patients. Moreover, differences in the circadian rhythms of melatonin in the Asian women with insomnia, depending on the genotype of the Clock 3111T/C polymorphism, were not found [39].

The undoubted influence of the hormone on the sleep-wake cycle was also confirmed by current clinical experiments demonstrating the effectiveness of the use of exogenous melatonin in the treatment of sleep disorders in different groups of patients [6]. Exogenous melatonin acts similarly to endogenous, affecting the MT1 and MT2 receptors located in the SCN, hypothalamus, hippocampus, cerebral cortex, cerebellum, retina and other tissues. The interaction of melatonin with these types of receptors leads to the activation of various cell signaling systems, to the synthesis of secondary messenger - cyclic adenosine monophosphate and to a change in the concentration of calcium ions. By binding to cytosolic calmodulin, the hormone can directly affect calcium signals by interacting with enzymes such as adenylate cyclase and phosphodiesterase, as well as with structural proteins [3]. Experimental studies showed that blocking the MT1 receptor in mice increases the length NREM, while

blocking the MT2 receptor reduces it, i.e., in the process of sleep the receptors perform the opposite roles [13].

CONCLUSION

Given the multiple biological functions of melatonin (biorhythmological, immunomodulating, antioxidant, antistress, thermoregulation, sleep induction, sexual development regulation), the disruption of its production, both quantitatively and rhythmically, can be the trigger mechanism for desynchronization at the initial stages and then to the onset of organic pathology [19]. Considering the menopausal syndrome as disadaptation of the female organism under conditions that require an increased activity of the adaptive system, the study of the melatonin role as an adaptogen of the female reproductive system is now extremely important. Moreover, given the high prevalence of insomnia among menopausal women, the consequences of these disorders, as well as the relationship of this pathology with obesity, disorders of carbohydrate metabolism, cardiovascular diseases, etc., studying one of the main sleep-wake cycle regulators will allow identifying personalized approaches to developing methods for correcting sleep disorders, which will significantly improve the patients' quality of life. Taking into account the ambiguity of the results presented in the literature sources on this issue, as well as the dependence of melatonin level on factors such as sex and ethnicity, studies on the genetic aspects of the circadian system are, indeed, highly promising.

Declaration of interest statement

The authors report no conflicts of interest.

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Information about the authors

Semenova Natalya Viktorovna – Candidate of Biological Sciences, Senior Research Officer, Scientific Centre for Family Health and Human Reproduction Problems (664003, Irkutsk, ul. Timiryazeva, 16, e-mail: natkor_84@mail.ru)

Madaeva Irina Mikhailovna – Doctor of Medical Sciences, Head of Somnological Centre, Scientific Centre for Family Health and Human Reproduction Problems (e-mail: nightchild@mail.ru)

Kolesnikova Lyubov Ilynichna – Doctor of Medical Sciences, Professor, Academician of RAS, Scientific Advisor, Scientific Centre for Family Health and Human Reproduction Problems (e-mail: iphr@sbamsr.irk.ru)