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Chapter

Role of Pineal Hormone Melatonin in a Woman's Life: From Conception to Decline of Life

Elena N. Usoltseva and Marina V. Danilova

Abstract

In the presented article, we cover the issues concerning physiology of secretion of pineal hormone melatonin and its role in the vital processes of a body. Focus is given to melatonin effect on the female reproductive system, its participation in the aging process, and formation of pathological menopause. The article also presents research data on the effectiveness of the melatonin drug when tackling climacteric syndrome. It is revealed that according to the available literature up to date there is no information about the standards of secretion of melatonin for women of different age groups, and the lack of secretion of melatonin can be judged by clinical manifestations and also when compared with groups of healthy women. The issues of the melatonin drug application at various complications of pregnancy and gynecological diseases remain unclear. Long-term intake of melatonin to treat pathologic menopause is still to be discussed.

Keywords: women, pineal gland, melatonin, 6-sulfatoxymelatonin

Key points

1. Melatonin functions in the human body are very diverse, and its normal secretion is extremely important for the preservation of somatic health.

2. The important role of melatonin in the formation of the reproductive function of women, the formation of a two-phase cycle, high-quality ovulation and fertilization, prevention of violations of a number of gynecological and obstetric pathologies.

Currently there are convincing data on the role of melatonin in the onset of menopause, the formation of climacteric syndrome, depression, osteoporosis, dyslipidemia, menopausal metabolic syndrome and cardiovascular diseases, and breast cancer in women in perimenopausal and postmenopausal women.

1. Introduction

Melatonin is a principal hormone produced by pineal cells in the pineal gland located in the cerebrum center behind the third ventricle (**Figure 1**). This endocrine gland consists of two cell types: pineal cells (which dominate and produce indolamines, mainly represented by melatonin, and peptides, such as arginine vasotocin) and neuroglia cells. The information received from neurons and modified by means

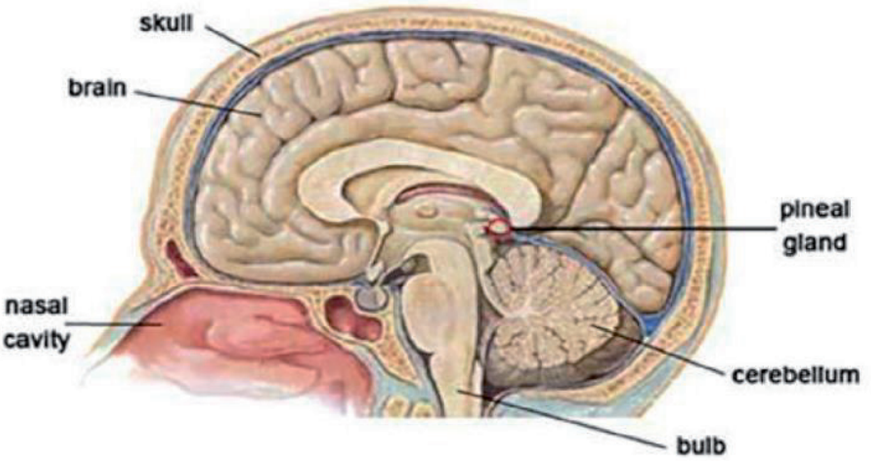

Figure 1.
Anatomical location for pineal body.

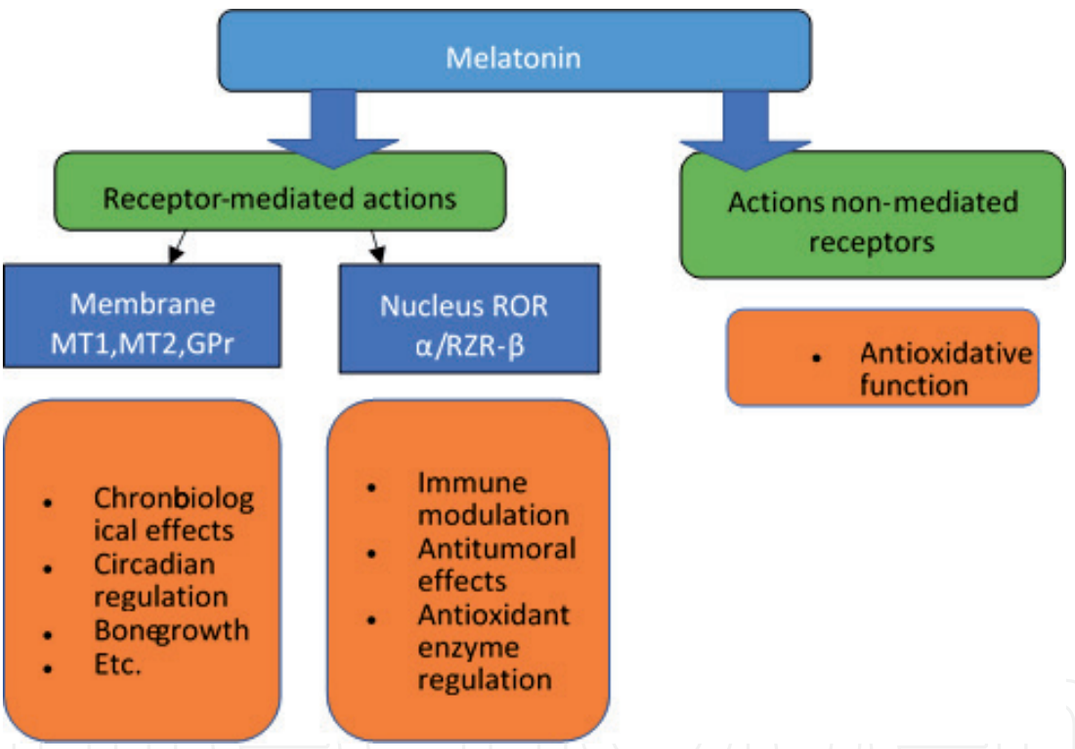

Figure 2.
Melatonin mechanisms of action.

of night and daylight intensity transforms in the pineal gland into chemical signals. Receiving the information about luminosity the pineal gland turns it into endocrine response by producing melatonin, which is a biogenic amine pertaining to the indole class, based on its chemical structure. Melatonin is a derivant of biogenic amine serotonin, which in its turn is synthesized from the amino acid tryptophan, received with food. Activity of ferments participating in serotonin transformation into melatonin is suppressed by lighting—that is why this hormone can be produced only during hours of darkness [1].

Melatonin is mainly released to the cerebrospinal fluid (liquor), getting from there to the blood flow and afterwards easily allocating itself in various organs and tissues due to good lipophilic properties [2]. Key effects of melatonin are connected with the action on membrane receptors—*MT*1 and *MT*2. They relate to a group of receptors

connected with G-protein. These receptors are responsible for chronobiological effects and regulation of circadian rhythm and are widely distributed in different organs and tissues. Melatonin receptor presentation in the reproductive organs and receptors to sexual hormones in the epiphysis enables drawing the conclusion that melatonin plays an important role in regulation of reproductive aspect (**Figure 2**).

In the same way, the nuclear receptors of melatonin *ROR*-α/*RZR*-β have been discovered. It is evident that many immune-stimulating and antitumoral effects are mediated by them.

Antioxidative function of melatonin is based on the receptor action, but this hormone is able to directly withdraw free radicals without receptor actuation [3].

Russian scientists discovered that apart from epiphyseal melatonin, there is an extrapineal one that is formed in different gastrointestinal tracts and other organs: liver, kidneys, supramental capsules, gall bladder, ovaries, endometrium, placenta, thymus, white blood cells, thrombocytes, and endothelium. Biologic action of the extrapineal melatonin is carried out right where it is synthesized [1].

2. Melatonin main physiological functions and its role in maintaining human health

During the recent years, new data on the mechanisms providing for the integral interaction among the nervous, immune, and endocrine systems have been received. Presumably, pineal gland is an integrator of such interaction, while its main hormone, melatonin, takes part in regulation of the activity of central and vegetative nervous systems, endocrine organs, and immune system. The performed investigations have demonstrated that melatonin fulfills an extremely wide range of physiological functions: biorhythmic and immunomodulatory processes, thermal control and sleep onset, and antioxidative and anti-stress effects [3]. Hormone secretion starts on the third month of infant development and reaches its peak during the first years (not later than at the age of 5). Before puberty, melatonin synthesis remains at a constantly high level [4]. During the age of 11–14, due to the fact that the pineal gland reduces melatonin production, the hormone mechanisms of sexual development are launched. The next significant reduction in activity occurs simultaneously with menopause onset—at the age of 45–60. With the aging progression, along with decrease in basal level, melatonin secretion peaks are getting lower [1]. During daytime melatonin concentration in the blood serum remains low (10–20 pg/ml), while during the night hours it grows considerably (80,120 pg/ml) and reaches its maximum value between midnight and 3–5 a.m. Melatonin secretion usually starts at 9 p.m. and terminates at 7–9 a.m. Melatonin metabolites are found in urine: 6-sulfatoxymelatonin (80–90%) and 6-hydroxyglucuronide (10–20%) corresponding to the circadian rhythm that is very close to the rhythm of melatonin secretion [5].

A new science, biorhythmology, introduced the notion of desynchronosis—clinically very important—that means ill-being or pathological syndrome, which is connected with the unbalance of circadian rhythms. A degree of desynchronosis is defined by the quantity and rhythm of melatonin production during the day and night. It has been determined that when a somatic disease goes hard or aggravates, melatonin production is getting worse, and its night indicator is getting closer to the day value [6]. Disturbed melatonin secretion finds its clinical manifestation in tiredness, indisposition, sleep disorder, and sometimes aggravation of a chronic disease or even appearance of a new one. Desynchronosis condition is exemplified by jet lag syndrome caused by rapid long-distance transmeridian travel [7].

It is generally known that melatonin has an antidepressant function. However, foreign colleagues stated disturbed circadian rhythm of melatonin secretion

experienced by patients with depression during a menopause along with its increase during the morning hours as compared with women in good health that also has impact on sleep, level of follicle-stimulating hormone, and body mass index [8]. A connection was established between sleep disorder and melatonin reduction in female saliva during perimenopause without registering such pattern among women in postmenopause [9].

Therefore, melatonin functions in a human body are quite diversified, and its normal secretion is highly important for maintaining human health in a contemporary world.

3. Melatonin involvement into hormonal regulation of female reproductive system functions and its aging

In 1963 R.J. Wurtman et al. reported for the first time that exogenic intake of melatonin causes weight reduction in female rat ovaries. Since those times many evidences that pineal gland and its main hormone, melatonin, influence reproductive function have been received. Studies showed that neurons in preoptic and mediobasal areas of hypothalamus and hypophysis represented the main points, through which melatonin produced its reproductive action. The main physiological effect of melatonin lies in the slowdown of gonadotrophin secretion, with greater suppression of the lutenizing hormone (LH) by melatonin rather than the follicle-stimulating one. Negative correlation is registered between melatonin level at night and lutenizing hormone concentration. In addition, secretion of other tropic hormones of hypophysis anterior lobe (such as corticotrophin, thyrotropin, somatotropin) is reduced, though to a lesser extent. Melatonin can be called a universal inhibitor of endocrine function in a female body [10].

Melatonin takes part in regulation of many vital physiological processes, such as puberty and genital formation, menstrual cycle, and aging of reproductive system. High level of nocturnal melatonin was found in children with delayed puberty, while among children having accelerated puberty, a decrease in melatonin secretion at night was noted. High levels of melatonin among children produce a dominating effect on pulsatile gonadotropin secretion, ovary function, and puberty [4].

Abnormal levels of melatonin in blood are connected with a number of malfunctions in the system "hypothalamus—hypophysis—ovaries." This gives boost to precocious puberty or its delay and formation of hypothalamic or hypergonadotropic amenorrhea. Therefore, melatonin may have indirect influence on the function of reproductive glands through its intervention into the secretion of gonadotropin-releasing hormone and/or secretion of gonadotrophins. Some data demonstrate that melatonin can also be synthesized in reproductive glands. Decreased melatonin secretion in summer coincides with higher fertility among women living in the Northern Hemisphere [11].

Based on these data, it was presupposed that melatonin could be a part of events preceding activation of hypothalamus-ovary axis during a puberty period [12]. Non-serial MRI of female head region helped register a reliable decrease in pineal gland volume during the ovulatory phase as well as while perimenopause. It indicates pineal gland involvement into "turning off" female reproductive function [13].

Melatonin may also produce direct influence on ovaries. High level of melatonin was found in preovulatory follicular fluid with triple concentration as compared to blood. Connecting areas of iodine melatonin were identified in human cells of granulosis and preovulatory follicles.

Antioxidative effect of melatonin is considered to be the most prominent one. It has been determined that melatonin ties free radicals of oxygen and at the same time stimulates enzymatic systems and SOD and possesses protective properties in relation to free-radical damage of DNA [14].

It's generally known that macrofags, neutrophils, and vascular endothelium cells located in follicles produce AOS during ovulation. Despite the fact that AOS (active oxygen species) participate in breaking follicles, potentially they may damage an ovum and granulosis lutein cells. AOS inhibit progesterone production by lutein cells due to inhibition of steroidogenesis enzymes and transport intracellular protein. Melatonin is an important antioxidant in ovary follicles and enables progesterone synthesis by luteal cells [15]. Research outcomes have shown that melatonin intake leads to increased concentration of this hormone in follicular fluid and reduced oxidative damage inside follicles, thus raising a chance of fertilization and pregnancy [16, 17]. Melatonin intake also improved progesterone synthesis among women with infertility issues caused by insufficiency of the cycle luteal phase [18].

Pregnancy and acts of delivery are characterized by deep alterations in the endocrine profile of a female body as well as in pineal gland operation. In the case of physiological pregnancy, increased melatonin excretion with urine is marked, while just before an act of delivery its level plummets.

Decreased melatonin level is noted in the case of threatening miscarriage [4].

At the same time, many scientists speak about the great importance of melatonin in the body aging process. It is also pointed out that from the age of 45, melatonin starts to decline steadily till the end of human life. Numerous studies have demonstrated the correlation between melatonin synthesis and menopause onset [19]. The second decrease in melatonin level may be related to involutory processes in pineal gland [13].

In a placebo-controlled clinical study, it was established that there was a connection between decreased content of nocturnal melatonin in saliva and menopause onset, while intake of 3 mg of melatonin by female patients during perimenopause on a daily basis for 6 months eliminates hormonal and neurovegetative disorders and recovers menstruation cycle and thyroid function [20].

Women in postmenopause had lower concentration of melatonin in blood serum as compared to women in perimenopause, with a shorter duration of melatonin secretion in postmenopause as a rule, while melatonin synthesis peak time (acrophase) was almost the same. A pattern was determined that as melatonin secretion peak occurs later among women in perimenopause, anxiety level gets higher ($p = 0.022$), and as melatonin secretion continues for a longer period, the quality of life among patients gets better ($p < 0.001$) [21].

Some scientists suggest using melatonin drugs at the first stage of climacteric disorder treatment even before the start of hormonal therapy of menopause [4]. Moreover, in a double-blind placebo-controlled clinical study, it was determined that prescription of menopause hormonal therapy to postmenopausal women shifts melatonin secretion peak time without changing the melatonin level in the blood serum, which requires further research [21]. Other authors did not found in their research analyses devoted to alternative therapy for climacteric disorders any convincing data on hot flash arresting by melatonin drug [22].

4. Melatonin lipid metabolism

A growing number of evidences are emerging, which point to melatonin involvement into lipid metabolism. The study of H. Tamura was devoted to melatonin influence on lipid metabolism among women in perimenopause and

postmenopause. A negative correlation was established between nocturnal melatonin and total cholesterol level, low-density lipoprotein, and positive correlation with high-density lipoprotein. No correlation was found between nocturnal melatonin and triglyceride level in blood. These findings show that melatonin drug prescription may represent a new approach to the correction of lipid metabolism and prevention of cardiovascular diseases during perimenopause and postmenopause [23]. Other scientists determined that melatonin improves lipid profile (leads to a reduced level of low-density lipoprotein) and fulfills antioxidant protection [24].

Under a study led by L.I. Maltseva [25], scientists analyzed melatonin role in the development of climacteric syndrome and its effectiveness for treating pathological climacterium. Russian scientists established that the level of 6-sulfatoxymelatonin in a 24-h urine among patients with severe climacteric syndrome amounts to 35.09 ± 3.5 ng/ml, medium severity (44.01 ± 7.92 ng/ml), and mild climacteric syndrome (45.91 ± 12.42 ng/ml) (1.7 times lower as compared to women in good health). Accordingly, secretory function of hypophysis is altered in various ways. Women with low level of 6-sulfatoxymelatonin in a 24-h urine show significant growth of both gonadotropic hormones—follicle-stimulating and luteinizing hormones—in a proportional way. A research showed that women had a high level of catecholamines (adrenaline and noradrenaline) with its degree being dependent on climacteric syndrome severity. It was also determined that women in perimenopausal age have increased the level of atherogenic fractions of blood lipids on the background of lower melatonin level.

Scientists came to the conclusion that melatonin acts as a modifier of alterations which occur with the development of climacteric disorders and influence hormonal, mediating, and biochemical indicators of the female body. Women with mild climacteric syndrome taking 3 mg of melatonin per day as monotherapy demonstrated during the repeated evaluation of clinical, hormonal, and biochemical indicators after 1 month a positive dynamics of all indicators. The blood hormone level was close to reference values, follicle-stimulating hormone level dropped by 2.29 times, luteinizing hormone level by 2.1 times. Values of melatonin sulfate in a 24-h urine grew by 2.64 times and were close as never to the reference values 27.95 ± 7.92…73.95 ± 24.85 ng/ml. However more significant alterations were noted for the severe climacteric syndrome without any side effects when melatonin treatment and menopause hormonal therapy were used together [25].

5. Menopause and sleep disturbance

Japanese scientists stated that estradiol level was firmly higher among women that worked night shifts and went to sleep later than 1 a.m. as compared to women that slept at night, with the level of serum testosterone and DHEA-sulfate unaffected, while 6-sulfatoxymelatonin concentration in urine was lower among the first group patients. Similar hormonal disruptions among postmenopausal women experiencing sleep disorder represent serious risk factors of breast cancer [26]. Singapore Chinese Health Study (2008) also showed that among women in postmenopause, the risk of breast cancer gets lower when sleep duration increases ($p = 0.047$). When sleep duration exceeds 9 h, a relative risk equals to 0.67 (95% confidence interval 0.4–1.1) as compared to women with a sleep duration of 6 h or less. At that, melatonin level was higher by 42% when sleep duration was 9 h or more. Such pattern was registered for women with normal weight (body mass index of 23.2 kg/m), $p = 0.024$ [27]. American scientists proved through a largescale

prospective analysis that among women with 6-sulfatoxymelatonin content within the upper quartile, there were fewer with invasive breast cancer than among those whose values were within the bottom quartile [28]. It was established that the increased concentration of 6-sulfatoxymelatonin in the morning urine portion was statistically related to a lower risk of breast cancer (ratio of chances for upper and lower quartiles of 6-sulfatoxymelatonin level 0.62; 95% confidence interval 0.41–0.95; $p = 0.004$) [29].

C.G. Harrod and his colleagues made an assumption that a growing risk of cerebrovascular disease registered among menopausal women can be to some extent explained by changes in the level of circulating melatonin and estrogens and their modulating influence on biologic activity of endothelial cells, including vascular tone regulation, leukocytes adhesion, and angiogenesis. This hypothesis is confirmed by numerous studies demonstrating the braking effect of melatonin and estrogens on vessel tone, neuroprotection, and expression of receptors [30].

Increased melatonin secretion in the morning is more typical for menopausal patients with depression than women in good health. Moreover, menopause duration, level of the follicle-stimulating hormone, sleep end time, and body mass index may lead to alterations in melatonin secretion when suffering from depression during a menopause [8].

6. Melatonin effects on bone metabolism

At present a relation between melatonin and skeleton is known. Melatonin may produce an effect on bone tissue which manifests itself in bone tissue formation with osteoblasts and/or hindering bone resorption with osteoclasts. The study of K. Satomura et al. [31] confirms the melatonin (*Mel1*) receptor expression in human osteoblasts and tendency of its level reduction with aging. It is also demonstrated that melatonin can have a boosting effect on proliferation and differentiation of human osteoblasts [32]. Through a controlled randomized trial (2012), exogenous melatonin effect on bone tissue density was revealed. Bone tissue condition was controlled in two ways—bone tissue density estimation and bone marker determination. There was no considerable improvement noted in terms of bone tissue density in T points or as compared with placebo. An average change in the activity of bone resorption marker, N-telopeptide (NTX), in this study did not differ much inside and between the groups. Similarly, the average change in the activity of bone formation marker, osteocalcin, did not show any remarkable differences either inside a group or between groups. However, NTX to osteocalcin ratio followed a downward trend among the women who took melatonin as compared to placebo. It is quite important because among menopausal women, this ratio is known to increase so that osteoclasts activity outstrips osteoblast activity, which leads to a loss of bone mass. Probably, decreased level of nocturnal melatonin that occurs during a menopause causes hormonal unbalance and perimenopause symptoms, including the loss in bone mass. These data prove that melatonin intake may enable the balancing of bone resorption and formation processes, potentially preventing fast loss of bone mass attributed to a menopausal period [33].

Melatonin inhibits resorption activity by reducing RANKL-mediated osteoclastogenesis and therefore decreases bone resorption. Melatonin also protects from losing bone mass induced by free radicals, which occurs in the case of extreme bone resorption, due to its powerful antioxidative properties [34, 35]. In addition to its direct effect on the bone tissue, melatonin can produce an indirect influence on bone metabolism through the hypothalamus-pituitary axis, by suppressing levels of

follicle-stimulating hormone and estrogen and increasing the level of progesterone. In contrast to the follicle-stimulating hormone, melatonin has positive correlation with progesterone level. Progesterone is known to influence on the mineral density of bone tissue, especially on osteoblast differentiation [36]. Reduced level of progesterone during a perimenopause may lead to the decreasing of bone tissue density because of osteoblasts loss.

7. Conclusion

Therefore, melatonin role in a female body is quite significant from the moment of birth till the last breath. It is revealed that up to the present time according to the literature data there is no information about the standards of secretion of melatonin for women of different age groups, and the lack of secretion of melatonin can be judged by clinical manifestations, and also when compared with groups of healthy women. The issues of using melatonin treatment for different cases of pregnancy complications and gynecological disorders remain unclear. Long-term intake of melatonin to treat pathological menopause is still to be discussed.

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