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CASE REPORT

Endocrine regulation of the course of menopause by oral melatonin: first case report

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Abstract

Objective: The pineal gland, through its hormone melatonin, is involved in the mechanisms that regulate the aging process involved in the onset of menopause. Considering the melatonin changes reported during pre-, peri-, and postmenopause, an influence of melatonin on the hormonal changes associated with menopause transition could be expected.

Design: We report the first longitudinal case study, covering a 7.5-year period, on the effects of melatonin administration on the reproductive hormones luteinizing hormone, follicle-stimulating hormone, and 17β-estradiol during that period of the reproductive life.

Results and Conclusion: The data obtained in this case report show that melatonin administration was able to delay the characteristic endocrine changes that occur during the course of menopause.

Key Words: Melatonin – Menopause – Luteinizing hormone – Follicle-stimulating hormone – Estradiol.

It has been established that the pineal gland and its principal hormone, melatonin, are involved in the central master clock mechanisms that regulate reproduction and trigger the aging processes involved in the onset of menopause.[1-4] The effect of melatonin seems to be related largely to the regulation of high-affinity melatonin receptors. A neurobiological basis for a role of melatonin in the regulation of reproduction has been provided by the localization of melatonin receptor MT1 in both the human hypothalamus and pituitary.[5] In the human ovary, specific melatonin receptors have also been described in the granulosa cells responsible for estrogen production.[6]

Decreasing levels of endogenous estrogens during the perimenopausal period have been related to a temporal increase in pineal melatonin synthesis during that period in female rats[7] as well as in premenopausal women.[8] A progressive reduction in nocturnal serum melatonin concentrations has been observed in healthy aging humans.[9,10] Mean melatonin concentrations were found to be negatively correlated with age in females.[11] To date only one study, using 6 months of treatment, has been published on the effects of oral melatonin on reproductive hormones in perimenopausal and menopausal women.[12] To characterize the entire transitional period to menopause, it was considered that studies have to begin more than 5 years before menopause occurs.[13] Historically, menopause, the end of reproductive life, was considered to have occurred at bleeding cessation.[14] The World Health Organization,[15] however, has defined that perimenopause commences when the first features of approaching menopause begin until at least 1 year after the final menstrual period (FMP). Postmenopause is defined as occurring after 1 year of amenorrhea in association with a persistent elevation of gonadotropin output.[16] Considering the decrease in melatonin during the aging process and the changes reported during pre-, peri-, and postmenopause,[17] we attempted to investigate the effect of nighttime administration of melatonin on the onset of menopause.

CASE REPORT

When this study began the participant was 48 years old; she had a high educational level and no known illnesses; was taking no drugs, hormones, or herbal preparations; was a nonsmoker; did not drink alcohol; and was conducting a normal and safe lifestyle with regular sleep habits and no insomnia. She was well aware of the aims of the research since she was an investigator of the study (B.D.L.). The study comprised a longitudinal 7.5-year period from June 1999 to January 2007. Serum reproductive hormones such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2) were measured to assess whether oral melatonin influenced their pattern of secretion during the course of menopause. The participant's hormonal pattern was

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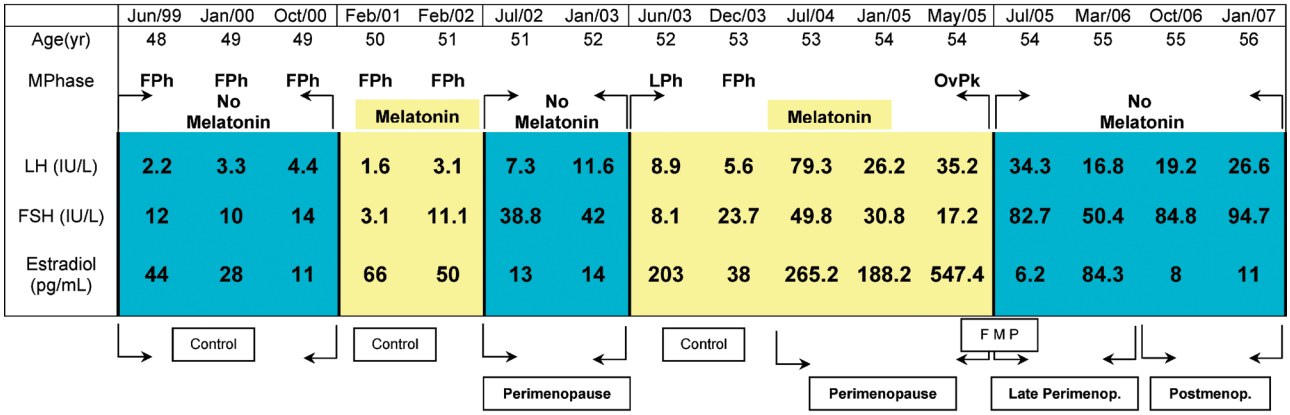
MPhase, Menstrual phase; FPh, Follicular Phase; LPh, Luteal Phase; OvPk, Ovulatory Peak; FMP, Final Menstrual Period.



Hormone standard values of the menstrual phases				
	Follicular Phase	Ovulatory Peak	Luteal Phase	Menopause
LH (IU/L)	1.9-12	17-81	0.8-18	3.2-34
FSH (IU/L)	3.6-14	8.2-23	2.3-11	15-139
Estradiol (pg/mL)	30-50	150-450	150-230	< 25

FIG. 1. Hormonal developmental pattern during the menopause course, influence of melatonin.

compared with patterns described in the scientific literature. Oral melatonin (1.5 mg) as a tablet (Schiff Products, Salt Lake City, UT) was taken every night, 10 minutes before bedtime (11:30 PM-12:30 AM) over two different time periods. The first melatonin intake period began on December 2000 and was maintained until February 2002. At this time, due to a polymenorrhea process associated with menorrhagia, the intake of melatonin was discontinued until January 2003. The second melatonin administration period lasted from January 2003 to May 2005.

Fasting blood samples were obtained between 9:00 and 10:00 AM by venipuncture on the days shown in Figure 1. Blood was refrigerated 1 to 2 hours after phlebotomy, and then, after centrifugation, the serum was aliquoted and frozen until assayed at the Clinical Biochemistry Service, Asturias Central University Hospital, Oviedo, Spain. LH, FSH, and E_2 concentrations were determined by radioimmunoassay.

Hormone determinations

From 1999 to 2002, the determinations of LH and FSH were performed using radioisotopic kits from Nichols Institute Diagnostic, San Juan Capistrano, CA. During 2003, LH and FSH levels were determined by Immunometric Assay (Immulite 2000 DPC kits, Los Angeles, CA). From 1999 to 2003, serum E_2 was determined by a double-bound antibody radioimmunoassay using Clinical Assays Dia Sorin kits (Dia Sorin, Saluggia, Italy). From 2004 to 2007, LH, FSH, and E_2 were determined by electrochemiluminescence immunoassay using Elecsys 1010/2010 and Modular Analytics E 170 (Elecsys module) immunoassay analyzers (Roche Diagnostic GmbH, Mannheim, Germany).

Hormone patterns

During the study five different stages could be differentiated (Fig. 1). The first stage (June 1999), before commencing melatonin, showed a normal reproductive period with menses occurring every 28 to 30 days and hormone concentrations representative of the follicular phase. From January 2000 to October 2000, the hormonal pattern was not clearly different from that of the earlier year except that the E_2 values were slightly decreased. This period has been classified as a control period, indicating a reproductive hormonal stage without any symptoms of approaching menopause. The second stage started on December 2000, ended in February 2002, and coincided with the first melatonin intake period. During this period, FSH levels were low (3.1 and 11.1 IU/L), and E_2 levels increased, reaching concentrations between 66 and 50 pg/mL. The third stage, during melatonin withdrawal, extended from the end of February 2002 to January 2003. The first data collected at this stage on July 2002 showed an increase in FSH levels (38.8 IU/L) and decreased E_2 levels (13 pg/mL). The second data set collected during this stage was very similar, again confirming the diagnosis of perimenopause. The fourth stage, from the end of January 2003 to May 2005, represented the second period of melatonin intake. The first measurements during this stage in June 2003 showed an endocrinological situation completely different from before, with lower gonadotropin concentrations and higher E_2 levels than 6 months earlier. Another set of determinations 6 months later (December 2003) again showed lower gonadotropin concentrations and higher E_2 levels (38 pg/mL). LH levels remained in the normal range up to this time point, when the woman was 53 years old, with values of 5.6 IU/L. After this age LH levels showed higher values. Seven months later, in July 2004, the levels of LH and FSH (79.3 and 49.8 IU/L, respectively) showed a significant increase because they increased from values characteristic of the reproductive age to values characteristic of the menopause transition. However, at this time the E_2 levels were high (265.2 pg/mL), which could preserve the patient's overall health, including vascular and bone function. In January 2005, both LH and FSH showed a

slow decrease in secretion, and E_2 levels remained elevated (188.2 pg/mL). Four months later (May 2005), both gonadotropins were within the limits of the preovulatory peak, and this was confirmed by menstrual bleeding 2 weeks later. This was the FMP. In May 2005, E_2 levels were 547.4 pg/mL. Because of this hyperestrogenism, the intake of melatonin was stopped, and gynecological probes were requested to rule out possible organic pathology or possible side effects of melatonin. Pap smear testing was normal. Sonography described a uterus in an intermediate position, regular with measures of 120 × 52 × 50 mm, endometrium stripe of 3 mm, right ovary of 26 × 28 mm, and left ovary of 25 × 20 mm with some follicles inside.

The fifth stage of the study, namely, melatonin withdrawal, extended from the end of May 2005 to January 2007. The hormone determinations of this last block showed a significant increase in FSH levels (82.7, 84.8, and 94.7 IU/L) and a decrease in E_2 levels (6.2, 8, and 11 pg/mL). The high E_2 levels of 84.3 pg/mL observed in March 2006 could represent irregular maturation of residual ovarian follicles with the hypothalamopituitary-ovarian regulatory feedback system not operative, as deduced by the FSH levels. Different data support this result. After menopause the endocrine activity of the ovary may remain for some time, and E_2 levels do not drop abruptly, as in the case of castration.[18,19] The perimenopause includes the year after menopause, partly because during that year there is evidence of variable and not consistently low estrogens levels.[20]

In addition to the hormonal pattern, hot flashes and/or sleep disturbances can be considered indicators of the course of menopause. The participant in the present case report occasionally experienced some of these symptoms, but only during late perimenopause and postmenopause.

DISCUSSION

Menopause, an aging process in women, is known to be associated with characteristic changes in the secretion of gonadotropins and sex steroids. Longitudinal data provided by 100 women over a period of 3 to 12 years on the progression from pre- to peri- to postmenopause, as proposed by the Stages of Reproductive Aging Workshop model, described 8 to more than 20 different perimenopausal stage patterns.[13]

There is little information about the interaction between melatonin and neuroendocrine reproductive hormones during the reproductive aging process. During 6 months of melatonin treatment at bedtime, a significant decrease in LH was observed in younger women (43-49 y old), whereas no effect was seen in older women (50-62 y old). In addition, a decrease in FSH was observed in melatonin-treated women with low basal melatonin levels.[12] The developmental pattern of serum FSH concentrations observed in the present case report showed the first increased serum FSH concentrations (38.8 and 42 IU/L) at the age of 51 to 52 years, coinciding with the melatonin withdrawal period. This represents a delayed increase in FSH compared with other data from the literature. FSH concentrations in a similar range were recorded at the age of 49.5 to 50 years in the longitudinal Study of Women's Health Across the Nation, which included a multiethnic population of 3,257 women. The women provided blood for determinations of serum FSH and E_2 in the early follicular phase during three consecutive annual visits. Similar patterns in the decline of E_2 and in the increase in FSH with age were found across ethnic groups. Serum E_2 concentrations decreased significantly with age, with a steeper decline at older ages (52-54 y).[21]

Prospective menstrual calendar and annual serum FSH data were collected from two population-based cohorts aged 42 to 57 years. Women (N = 193) from the Melbourne Women's Health Project and the Study of Women's Health Across the Nation (N = 2,223) contributed to the study with 10 or more menstrual cycles and at least one annual serum FSH value. FSH values for the late transition to menopause were similar across both studies. An annual serum FSH concentration of 40 IU/L was incorporated, in conjunction with bleeding markers, into the Stages of Reproductive Aging Workshop paradigm of markers for the late menopausal transition.[22] In women older than the age of 45 years with continuing regular menstrual cycles, FSH levels in the follicular phase increase without an accompanying change in LH. In women from 21 to 49 years of age, the mean follicular phase levels of immunoreactive inhibin were significantly lower in the 45- to 49-year age group than in the younger age groups, whereas FSH levels were significantly higher in the 45- to 49-year age group.[23] These studies have demonstrated that elevated FSH in women of advanced reproductive age may represent a primary neuroendocrine change associated with reproductive aging.

In the present case study the first oral dose of melatonin was taken exactly 1 day before the participant's 50th birthday, and dosing lasted for 15 months. During the first period of oral melatonin intake, the FSH values were within the range of standard values (3.1-11.1 IU/L). The second period of oral melatonin administration began at 52 years of age and lasted for 26 months. During the first year of this period, FSH concentrations were again within the standard range and lower than the former period at melatonin withdrawal. Afterward, at the age of 53 to 54 years, FSH concentrations started to increase simultaneously with E_2 levels, which were very high. This developmental pattern is representative of the recruitment of the follicular pool in the ovary in response to high FSH levels during aging and of the consequent decrease in the negative feedback from inhibin A and/or inhibin B, which may explain the increase in FSH. The decrease in inhibin B precedes the decrease in inhibin A and occurs concomitantly with an increase in E_2, suggesting that the inhibin B negative feedback is the most important factor controlling the earliest marker of the decrease in follicle number during reproductive aging.[24]

A direct action of melatonin during reproductive aging on human ovary granulosa and luteal cells has been described.[25] The E_2 levels recorded in the present case study in the last assay during oral melatonin intake (May 2005) showed hyperestrogenism (547.4 pg/mL). This value corresponds to

a preovulatory peak because 15 days later the FMP occurred, at the age of 54 years 8 months. According to data relating to the most frequent menopausal age, namely, 50 years,[26,27] menopause was delayed for more than 4 years in the study participant. It cannot be ascertained whether this delay was solely due to melatonin or whether the delayed onset of menopause is a particular characteristic of the woman studied. From the longitudinal study carried out in this participant, it can be concluded that when the hormonal pattern was indicative of the perimenopausal stage, oral melatonin was able to reverse and delay the process. The most relevant effects resulting from the two oral melatonin intake periods were the higher E_2 levels, indicative of improved ovarian function, and a delay in the FSH increase. The monotropic FSH increase is a cardinal endocrine feature of perimenopause.[21,22] After ovulation ceased (FMP) in June 2005, the average LH and FSH concentrations in the blood increased and remained elevated throughout the remainder of the year (late perimenopause). Hormone determinations performed later in October 2006 and January 2007 confirmed the postmenopausal condition.

The relationship between the pineal gland and endocrine parameters of the hypothalamopituitary-ovarian axis has been investigated in women during the fertile stage, the perimenopausal and postmenopausal periods.[28] The postmenopausal period comprised 40 healthy women, aged 46 to 51 years, in whom regular menses had disappeared at least 3 to 4 years before. Serum melatonin decreased with age, attaining minimum levels during menopause. In postmenopause, as during the follicular phase, melatonin and FSH were negatively correlated.[28] The action of melatonin secreted in small amounts during senescence was investigated in a cross-sectional study in pre- and postmenopausal females, with special attention to women of approximately 50 years of age, the mean menopausal age. Nocturnal urinary excretion of melatonin was found to decline significantly from premenopause to postmenopause. In the age group 40 to 44 years, melatonin secretion declined by 41%. The second significant decline took place between the age groups 50 to 54 years and 55 to 59 years. Serum FSH increased sharply to higher levels before the age of 50 years and remained elevated thereafter. The inverse changes in melatonin and FSH secretion during the perimenopausal years, with the sharpest decrease in nocturnal secretion of melatonin, may be related to the initiation of menopause.[17]

The present results show that by maintaining higher levels of melatonin, the onset of menopause can be delayed for some time. In the case described, irregular cycles of more than 45 days were observed at age 54 to 55 years. Similarly long cycles occurred throughout perimenopause, but the largest increase in mean cycle length did not occur until the final year before menopause.[29]

The effects produced by melatonin administration in the present case are in agreement with the reported data about reproductive aging in animal models, which have been used to better understand the complex interactions between melatonin and the onset of menopause. In middle-aged rats, the patterns and synchrony of multiple neurochemical events that are critical for the preovulatory gonadotropin-releasing hormone surge undergo subtle changes. The lack of precision in the coordination of the output of neural signals leads to a delay and attenuation of the LH surge, which in turn leads to irregular estrous cyclicity and, ultimately, to the cessation of reproductive cycles.[30] In this respect we have investigated the possible role of melatonin in the reproductive system of female rats during aging and in middle-aged rats, showing an irregular duration of the estrous cycle. Plasma LH, FSH, and prolactin concentrations were significantly increased in the afternoon of the day of proestrus after melatonin (150 μg/100 g body weight) treatment for 2 months compared with control rats. Similarly, E_2 concentrations were significantly higher in the morning of proestrus in melatonin-treated rats compared with control animals. Melatonin administration for 2 months also enhanced the amount of LH released during the surge and may have improved synchronization. The effect of melatonin on the gonadotropin response to gonadotropin-releasing hormone showed a stimulatory effect, as melatonin-treated rats had greater LH secretion and a higher amplitude FSH surge than control rats.[1]

Exogenous melatonin improved the pituitary responsiveness to a bolus of gonadotropin-releasing hormone (50 ng/100 g body weight) in old acyclic female rats. Melatonin treatment reduced the enhanced response observed in old acyclic rats and produced a pituitary responsiveness similar to that of young cycling rats. The chronological pattern of gonadotropins indicated that in 23- to 25-month-old rats, the gonadotropin levels increased and then significantly decreased to levels similar to those observed in young rats after melatonin treatment for 2 months.[31]

CONCLUSIONS

The present results demonstrate for the first time that melatonin can induce a delay in endocrine parameters associated with menopause onset in the specific woman under study. In this case oral melatonin was given in two different periods of reproductive aging. During the first melatonin intake period, FSH levels were lower and E_2 levels higher than in the months before. During the second period of oral melatonin administration, FSH concentrations were again within the range of the standard values for another year, and E_2 levels remained elevated. However, it will now be necessary to study a large number of women receiving melatonin before melatonin treatment can be recommended as a possible method to postpone the onset of menopause.

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