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The effect of hormone therapy on serum melatonin concentrations in premenopausal and postmenopausal women: A randomized, double-blind, placebo-controlled study

Elena Toffol[a,*], Nea Kalleinen[b,c], Jari Haukka[a,d], Olli Vakkuri[e], Timo Partonen[a], Päivi Polo-Kantola[b,f]

[a] Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare (THL), Mannerheimintie 170, Helsinki, Finland
[b] Sleep Research Unit, Department of Physiology, University of Turku, Lemminkäisenkatu 14-18A, 5th Floor, Turku, Finland
[c] Heart Center, Turku University Hospital and University of Turku, PL 52, Turku, Finland
[d] Department of Public Health, Hjelt Institute, University of Helsinki, Mannerheimintie 172, Helsinki, Finland
[e] Department of Physiology, University of Oulu, Aapistie 7, Oulu, Finland
[f] Department of Obstetrics and Gynaecology, Turku University Central Hospital and University of Turku, PL 52, Turku, Finland

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ABSTRACT

Objectives: Melatonin levels decrease physiologically with age, and possibly with the transition to menopause. The plausible influence of hormone therapy (HT) on melatonin is poorly understood. The aim of this randomized, placebo-controlled, double-blind trial was to investigate the effect of HT administration on serum melatonin concentrations in late premenopausal and postmenopausal women.
Study design: Analyses were carried out among 17 late premenopausal and 18 postmenopausal healthy women who participated in a prospective HT study in Finland. Serum melatonin was sampled at 20-min (21:00–24:00 h; 06:00–09:00 h) and 1-h (24:00–06:00 h) intervals at baseline and after 6 months with HT or placebo.
Main outcome measures: Melatonin levels and secretion profile after 6 months of HT compared to placebo.
Results: Mean melatonin levels, mean melatonin exposure level (area under curve, AUC) and mean duration of melatonin secretion did not differ after 6 months with HT vs. placebo, irrespectively of the reproductive state. However, in postmenopausal women the melatonin peak time (acrophase) was delayed by 2.4 h (2 h 21 min) on average after 6 months with HT vs. placebo ($p < 0.05$). No interaction between time and group was detected when melatonin level was modelled before or after treatment.
Conclusions: Administration of HT to postmenopausal women alters melatonin peak time, but not melatonin levels. Further research on larger clinical samples is needed to better understand the effects of HT on melatonin profile.

1. Introduction

Melatonin is a hormone produced by the pineal gland and, in smaller amounts, in peripheral sites including the retina, skin and the gastrointestinal tract [1]. Its synthesis starts from the serotonin precursor, tryptophan, and is strongly regulated by the light-dark transitions, with light having an inhibitory effect [2]. Specifically, melatonin production and secretion follow a circadian rhythm, increasing about 2 h before the sleep onset, peaking during the night and decreasing in the early morning.

Although with conflicting results, animal and human studies suggest that female gonadal hormones contribute to the modulation of melatonin production [3,4]. Specifically, several animal studies have found a reduced melatonin synthesis and secretion in association with high oestrogen levels [5–9], while others have reported an oestrogen-mediated stimulation of melatonin receptor activation in rats and hamsters [10,11], and a stimulation of melatonin synthesis and release in rat pinealocytes following oestrogen exposure [4]. Similarly, high levels of progesterone (either endogenous, during the luteal phase of the menstrual cycle, or exogenous as in combined oral contraceptives) were associated with high melatonin levels in women [12,13]. In general melatonin levels seem to vary in connection with reproductive events. For example,

* Corresponding author at: Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare (THL), Mannerheimintie 170, P.O. Box 30, FI-00271 Helsinki, Finland. Tel.: +358 29 524 8736; fax: +358 29 524 6101.
E-mail address: elena.toffol@thl.fi (E. Toffol).

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despite inconsistencies regarding the associations with menstrual cycle phases [12,14–20], healthy pregnant women were found with higher melatonin levels than postpartum women [21]. Probably as a consequence of higher gonadal hormone levels, melatonin exposure levels increased with the number of weeks during pregnancy [21] and, contrary to the duration of secretion and the offset timing, positively correlated with oestrogen and progesterone levels [22]. As opposite associations were found in depressed pregnant women, the authors suggested that the sensitivity to the modulating effects of oestradiol on melatonin receptors may be impaired in depression [21,22].

Further indirect support to the hypothesis of potential associations between melatonin and reproductive hormones comes from research on the modulation of circadian rhythms by gonadal steroids [23]. In fact, melatonin can be considered one of the best measures of circadian clock functions in humans [24]. On the basis of these studies, oestrogens are deemed to advance circadian rhythms (reflected in the timing of sleep onset) and shorten circadian periods [25–27], while progesterone may phase-delay [28] circadian rhythms. In this context, it would be plausible to hypothesize that in conditions of relatively high levels of gonadal steroids (such as in the premenopause), melatonin rhythms would be more phase-advanced, whereas in conditions, such as postmenopause, where there is a decline in gonadal steroids, rhythms would be more phase-delayed. However, as age is as such associated with a decreased hypothalamic sensitivity to oestrogens [29], it is possible that ageing causes a reduced phase-shift response to gonadal steroids. In addition, peak levels, as well as the total amount of melatonin, are known to decrease physiologically with age [30,31]. Partly as a consequence of this, melatonin levels are lower in postmenopausal women when compared with both premenopausal and perimenopausal women [32,33]. It is likely that the menopause-related hormonal changes, alone or in combination with age, contribute to this decline. With this respect, a transient increase in melatonin levels has been described in connection with the transition to menopause, whether natural or surgical [34]. However, melatonin levels have been observed to subsequently decline after the beginning of menopause [34].

We have previously shown that the mean overnight melatonin concentration and exposure level (AUC, i.e. area under nocturnal melatonin curve), as well as the duration of secretion, are lower in postmenopausal than in perimenopausal women [33]. Administration of hormone therapy (HT) after the menopause is known to restore the female gonadal hormone levels and is commonly used to alleviate climacteric symptoms in peri- and postmenopausal women; additionally, it is also effective in controlling early symptoms in premenopausal women. Nevertheless, to date only a few studies have addressed the question whether HT, either as unopposed oestrogen treatment (ET) or combined oestrogen-progesterone treatment (EPT), may also influence serum melatonin levels. Even with some inconsistencies [35], their main findings have been those of a reduction in nocturnal [34] or diurnal [36] melatonin levels after oestrogen or progesterone [5] administration in postmenopausal women.

The aim of this prospective, randomized, placebo-controlled, double-blind study was therefore to investigate the effect of HT (specifically EPT, which is the most commonly used form in clinical practice) on melatonin levels and secretion profile in late premenopausal and postmenopausal women. As gonadal steroids are known to influence the levels and secretion profile of melatonin, and as the menopausal-related reduction of gonadal hormones may be associated with a reduction in melatonin levels in postmenopause, we hypothesized that 6-month treatment with HT could restore serum melatonin levels of postmenopausal women to late premenopausal levels.

2. Methods

2.1. Subjects

Seventeen late premenopausal (mean age = 47.7 years; SD = 2.2; range = 43–51 years) and 18 postmenopausal (mean age = 63.4 years; SD = 3.6; range = 58–71 years) women were recruited to participate in a prospective study aimed to evaluate the effects of ageing and HT on sleep and cognition as well as on melatonin secretion. The recruitment procedure consisted of advertisements in the local newspapers in the area of Turku, Finland. The reproductive state was defined as late premenopausal, if serum FSH levels were lower than 23 IU/ml and the subject had ongoing regular or irregular menstrual cycle, whereas postmenopausal women were defined by age (≥58 years) and chronic amenorrhea more than one year. Women having a mental, cardiovascular (except drug-treated balanced hypertension), endocrine (except drug-treated balanced hyperlipidaemia), pulmonary, neurological or specific sleep disorder (like sleep apnoea or restless legs); malignancies; or other conditions possibly affecting sleep (e.g. fibromyalgia, anaemia) were excluded. Alcohol abuse, smoking, excessive caffeine intake (>5 cups per day) and use of other substances that affect the central nervous system were additional exclusion criteria. The subjects kept a sleep diary in the three weeks before and one week after the study to verify their sleep–wake schedules; all women had regular sleep–wake schedules (22:00–23:00 h to 6:00–7:00 h). Women were ensured to have normal levels of blood haemoglobin, leucocytes, thrombocytes and serum thyrotropin before enrolment on the study. One late premenopausal woman and 13 postmenopausal women had previously used HT. A washout period of at least 12 months was required. More details about the data collection and study design have already been described elsewhere [37]. After receiving oral and written information, all women gave written informed consent. The study was registered as a European Research Project (QLK6-CT-2000-00499) and approved by the Ethics Committee of Turku University Hospital and the University of Turku, Finland. The study was carried out in accordance with the Declaration of Helsinki.

2.2. Study design

The randomized, placebo-controlled, double-blind study consisted of a baseline phase followed by a 6-month follow-up assessment. At baseline, the women spent three nights (one adaptation night from 19:30 h to 8:00 h, and two sleep-recording nights, the first one from 19:30 h to 12:00 h and the second one from 19:30 h to 21:00 on the next day) in the sleep laboratory at the University of Turku, Sleep Research Unit. The women went to bed (lights-off) at 23:00 h, and were woken up (lights-on) at 7:00 h. During the night only red light was allowed for illumination if needed. During the third evening an intravenous catheter was inserted into the forearm and blood was drawn every 20 min for 24 h, starting at 21:00 h. At night (21:00 h to 7:00 h.) the catheter was connected to a plastic tube extending into an adjacent room to allow repeated blood sampling with minimal disturbance of the subject's sleep. Between 21:00 h and midnight as well as between 6:00 h to 9:00 h melatonin measurements were available from 20-min interval samples, and between midnight and 6:00 h from 1-h interval samples. The blood samples were drawn into EDTA tubes, placed in the refrigerator for 20 min, centrifuged, frozen immediately and stored at −70 °C until assayed. Samples were assayed for melatonin by radioimmunoassay with an iodinated melatonin tracer and a melatonin-specific antiserum [38]. The lowest detectable concentration by the method was 1.3 pg/ml (5.7 pmol/l), and the intra-assay and inter-assay coefficients of variation were from 6.7 to 9.5% and from 9.8 to 12.5%, respectively.