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Original Article

The temporal relationship between growth hormone and slow wave sleep is weaker after menopause

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ABSTRACT

Objective: To study the temporal association between growth hormone (GH) and slow wave sleep (SWS) in middle-aged women.
Methods: Seventeen premenopausal and 18 postmenopausal women were studied using all-night polygraphic sleep recordings and blood sampling at 20-min intervals. The postmenopausal women were re-studied after six months on hormone therapy (HT) according to a randomized, double-blind, placebo-controlled protocol.
Results: The total sleep time (premenopausal 361.9 ± 81.5 min, postmenopausal 358 ± 67.7 min) and the percentages of the sleep stages did not differ between pre- and postmenopausal women. In postmenopausal women the first GH peak after sleep onset occurred later and with a more variable time interval compared to premenopausal women. The percentage of SWS was highest 40–20 min prior to the first GH peak after sleep onset in both groups with a higher SWS proportion in premenopausal women ($p = 0.048$), although the total SWS percent for night did not differ. HT did not affect the distribution of SWS in postmenopausal women.
Conclusions: The temporal relationship between GH and SWS in premenopausal women is less robust after menopause and is not improved with HT.

1. Introduction

Most studies show that subjective sleep quality worsens at menopause [1,2], but objective measures of sleep quality do not confirm this [2,3]. In a large longitudinal population-based study (The Wisconsin Sleep Cohort Study) postmenopausal women slept better than premenopausal women according to objectively recorded sleep, but their subjectively reported sleep was worse [2]. Sleep quality is related to female sex hormones since menopausal hormone therapy (HT, including both unopposed estrogen and combined estrogen–progestogen) reduces sleep complaints [2,4–7]. However, the mechanisms of action behind the HT effect are not known.

Growth hormone (GH) is strongly related to sleep and especially to slow wave sleep (SWS) [8–11]. Repetitive hourly administrations of GH-releasing hormone (GHRH) increase GH as well as non-REM (NREM) sleep with decreased awakenings in men but has the opposite, and sleep impairing, effect in women [12]. GH levels [11,13,14] as well as SWS [11,14] decrease with increasing age both in men and women. Women have higher GH levels than men of the same age, but this difference disappears after menopause [13,15]. Compared to men, women show pre-sleep GH surges more often, and additional GH pulses later during the night [16]. We have previously shown that GH is reduced in postmenopause compared to premenopause, and that HT reverses this change [17]. Despite higher GH levels and better preserved SWS [18], sleep complaints are more common in women than in men [19,20]. The temporal association between GH and SWS is less known in women because of sparse data, but it is suggested to be weaker than in men [15,21,22].

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One possible mechanism behind the beneficial sleep effects of HT could be that the same mechanisms increasing GH also increase SWS. However, polygraphic sleep recording studies have not shown increased SWS [2,3,23,24] with HT. In our earlier studies we found that HT increased GH in postmenopausal women [17] but had no effect on objective sleep quality [23]. Changes in the total amount of SWS or in the levels and peaks of GH may be too broad as parameters to show differences in sleep quality across menopause. We hypothesized that temporal association between GH and SWS would be weaker in postmenopausal women compared to premenopausal women. Furthermore, we have hypothesized that HT could strengthen and thus restore this association after menopause, which could partly explain the beneficial effect of HT in subjective sleep quality. We examined SWS and concomitant GH levels in middle-aged premenopausal women compared to postmenopausal women before and after six months of HT.

2. Methods

2.1. Subjects

Eighteen healthy postmenopausal women (mean age 62.8 ± 2.9 years) and 17 healthy premenopausal women (mean age 47.9 ± 1.7 years) were included in the study from the Turku city area, Finland, after thorough interview and physical examination including gynecological examination, transvaginal ultrasound, and blood samples. Menopausal status was defined as premenopausal if serum follicle stimulating hormone (FSH) levels were lower than 23 IU/mL (mean 11.4 ± 4.7 IU/mL) and the subject had ongoing menstrual cycle whereas postmenopausal women were defined by age and amenorrhea. The mean ± standard deviation body mass index (BMI) was 24.3 ± 2.4 kg/m^2 for premenopausal and 27.6 ± 4.9 kg/m^2 for postmenopausal women. Women with abnormalities in serum thyroid stimulating hormone, blood hemoglobin, leucocyte, and thrombocyte levels were excluded and a urine drug screen was performed. Women were excluded from participation if they were smokers; currently used HT; had pre-existing neurological, cardiovascular (apart from treated hypertension), endocrinological (apart from treated hyperlipidemia), or mental disease; had malignancies; abused alcohol or medications; or had excessive consumption of caffeine. The washout time for any use of medication with CNS effects or antioxidants was three months minimum. One premenopausal woman had used estrogen treatment for three months but had discontinued use 12 months before the study. In the postmenopausal group, 13 women had used HT previously: the average time of use was 74 months (range 3–156) and the average washout period was 51 months (range 12–147). All subjects provided informed written consent. The experimental protocol was approved by the Ethical Committee of Turku University Central Hospital. The women were asked to keep a regular sleep-wake schedule (bedtimes 10–11 pm to 6–7 am) that was monitored via sleep diaries for three weeks before and one week after the sleep studies. During the sleep studies, and for one week prior, a caffeine free diet was followed and the use of alcohol as well as traveling across time zones was prohibited.

2.2. Protocol

All-night polygraphic sleep recordings were conducted on three consecutive nights. The first two nights were habituation nights to the laboratory environment and the equipment. The results of the second night sleep variables have been published earlier [23]. The subjects spent the time allotted for sleep (11 pm–7 am, lights off–lights on) recumbent in bed in a dark room where only red light was allowed for illumination if needed. Daytime naps were not allowed. During the second evening a catheter was inserted into a forearm vein two hours before the commencement of the blood sampling. Blood samples were collected at 20 min intervals for 24 h, starting at 9 pm. To avoid disturbing the subject at night the catheter was connected to tubing extending to an adjacent room. While in bed, the forearm of the subject was loosely attached to the bed supporting the extension of the forearm to ensure successful sampling throughout the night. The premenopausal women had their sleep studies and blood sampling during the follicular phase of the menstrual cycle. After blood sampling, postmenopausal subjects were randomized for the treatment or placebo period of six months in six-person blocks.

Postmenopausal women received continuous HT (2 mg estradiol valerate + 0.7 mg noretisterone Merigest: Novartis, Basel, Switzerland) or placebo. Randomization was performed at the pharmacy of the Turku University Central Hospital where randomization codes were kept until data analyses were completed. Nine women received HT and nine women received placebo. After three months of treatment they were interviewed to ensure compliance and serum estradiol (E_2) and FSH levels were measured (data not shown). At the end of the six-month treatment period, the sleep studies and blood sampling was repeated in an identical manner to the procedures at baseline. For four women in the HT group and in two subjects in the placebo group the duration of the treatment was 3–5 months, mainly due to side-effects. During the sleep study periods, food was provided by the laboratory with the same timing and composition during both study periods.

2.3. Sleep recording and analysis

Polygraphic sleep recordings consisted of continuous monitoring of four electroencephalograms (EEG; C3/A2, C4/A1, O1/A2 and O2/A1), two electro-oculograms (EOG), a mandibular electromyogram (EMG), and an electrocardiogram (ECG, two channels) (Embla, Medcare Flaga hf. Medical devices, Reykjavik, Iceland). The recordings were visually scored at 30-s intervals in stages 1 (S1), 2 (S2), and slow wave sleep (SWS) (stage 3 and 4), rapid eye movement sleep (REM), and wake time after sleep onset (WASO) using the original Rechtschaffen and Kales standardized criteria [25]. Sleep onset was defined as the time to the occurrence of three consecutive epochs of stage 1 or the first epoch of any other sleep stage. The total duration of each stage was expressed as a percentage of the time in bed (from lights off to lights on).

Spectral analysis was used to quantify the slow wave activity (SWA, 0.75–4 Hz) during NREM sleep episodes. Sleep cycles were defined according to the rules of Feinberg and Floyd [26] excluding the requirement for the minimum duration of the first REM sleep episode. Only full NREM/REM cycles were included. The first NREM sleep episode was defined as the sleep period from sleep onset to the beginning of the first REM sleep episode. The following NREM sleep episodes then began from the end of each REM sleep episode lasting to the beginning of the next. The time course of SWA was normalized by calculating the SWA power per 30 s in each NREM sleep episode. The power spectrum was calculated from the C3-A2- or C4-A1 derivation in 4-s epochs using 256-point fast Fourier transform with 50% overlapping. EEG artifacts (movements, eye movements) and event triggered slow waves with increased muscle tone were visually identified and excluded [27]. To preserve continuity, power spectrum samples that contained manually marked artifacts were classified as missing data. Comparisons were carried out on the first four NREM sleep episodes.

2.4. Hormone assays

Serum GH levels were measured with the AutoDELFIA assays (PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku,