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Effect of hormone replacement therapy on the auditory brainstem response of postmenopausal women

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Abstract

Objective: To investigate whether hormone replacement therapy modifies the auditory brainstem response in postmenopausal women. **Methods:** Nineteen postmenopausal women received hormone replacement therapy (study group) and 25 received no treatment nor placebo (control group). In both groups, age ranged from 45 to 60 years and pure-tone sensitivity was 25 dB or better at frequencies between 500 and 2000 Hz. Auditory brainstem response was evaluated before and after 3 months of hormone use in the study group. The control group was also evaluated at the same periods. The following auditory brainstem response parameters were compared between the two groups: latencies of waves I, III, and V; I-III, III-V, and I-V interpeak intervals. **Results:** Mean age did not differ between groups (study group: 51.5 ± 0.7 years; control: 52.9 ± 0.6 years). No significant differences in wave latencies, or interpeak intervals were observed between the two groups ($p > 0.05$).

Keywords: estradiol, hormone replacement therapy, postmenopause, progesterone.

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INTRODUCTION

Estrogen is classically known to influence the growth, differentiation and function of the female and male reproductive tract[1]. Moreover, it exerts a wide range of biological effects throughout different organs and systems, like immune[2], cardiovascular[2], skeletal[3], central nervous systems[4] and mammary gland[5] by interacting either directly or indirectly with estrogen receptors alpha (ERα) and beta (ERβ)[6]. Both ERα and ERβ are present in the inner ear of humans and animals[1,7] and both subtypes seem to be active in the hearing process[8]. In the brain, estrogens affect both the activity and the connectivity of specific neuronal populations and thereby modulate physiological parameters that are important for the regulation of animal reproduction, but also of non-reproductive events such as learning and memory[9]. Recent studies indicate that the lack of ERβ in animals leads to the degeneration of cortical neurons in the brain which increases with age[10].

There is no visible nuclear staining of progesterone receptors (PR's) in the stria vascularis, organ of Corti or spiral ganglion in either of human or rat inner ears, indicating that progesterone could not have a direct effect on the hearing modulation in the inner ear via its nuclear receptors. However, PR's have been shown in both osteoblasts and osteoclasts in the bone of humans, rats, and mice. These findings lead us to conclude that there is no direct effect of progesterone on hearing, but possibly indirect effects via other signaling pathways[11,12].

The functional role of estrogen and receptors in hearing physiology and pathophysiology is beginning to be elucidated[1,6,13].

A number of studies have shown that estrogen (E) and progesterone (P) can alter hearing thresholds[14-16] and auditory brainstem response (ABR) latencies[17-19]. There are also case reports of irreversible[20] or reversible[21] sudden hearing loss after the use of the contraceptive pill or hormone replacement therapy (HRT)[22].

Elkind-Hirsh et al.[17] observed no significant changes in ABR latencies in women using oral contraceptives. In contrast, Caruso et al.[19] suggested that steroids present in oral contraceptives affect ABR. Swanson and Dengerink[14], Petiot and Parrot[15] and Cox[16] reported that 4 kHz thresholds were worse during the menstrual phase, when both estrogen and progesterone levels were lowest. Better thresholds were found during the postovulatory phase, when progesterone is highest. Caruso et al.[19], Serra et al.[23] and Elkind-Hirsh et al.[17] showed that the increased neural conduction time of the ABR coincides with ovulation, when estrogen levels are highest. Dehan and Jerger[24] reported a decrease in wave V latency at the luteal phase during progesterone peak. On the other hand, Fagan and Church[18] observed no changes in wave V during the menstrual cycle.

Bittar et al.[25] studied 17 guinea-pigs with normal ABR that used 1.5 mg of conjugated estrogens daily by intramuscular administration for 30 days. The results showed thresholds elevation at the ABR in 47% of animals, with severe hearing loss in two of them, and increase of the amplitudes (mean) of the waves I, II, III and V. These findings are compatible with an ototoxic action. On the other hand, it was also observed a decrease of the latencies (mean) of the five waves of ABR, and this fact suggest a possible facilitatory action in the conductibility of the sensory auditory pathway, in contrast with the above exposed observations.

Women tend to hear better than men throughout life but during menopause the hearing thresholds deteriorate at more rapid space[26]. But little is known about the effect of lack of sex hormones and their replacement on the hearing of women before, during, or after menopause. Several HRT studies have been performed, but the results are still controversial. Because of the widespread prescription of hormone replacement therapy (HRT), it is critical to determine the effects of HRT on sensory systems in postmenopausal females[27].

The ABR has become an important objective measure of hearing since its first description by Jewett and Williston in 1971[28]. The measurement of ABR is part of a battery of routine tests used to evaluate peripheral auditory sensitivity and neural integrity of the auditory central nervous system.

The term climactery is defined as the transition from reproductive years to a non-reproductive stage of life. Menopause indicates the last menstruation. The years after menopause are defined as the postmenopausal period of life[29].

The objective of the present study was to evaluate the effect of combined HRT (estrogen plus progestin [synthetic progesterone]) on the ABR of postmenopausal women after three months of continuous use.

MATERIALS AND METHODS

A prospective clinical study was conducted between January 2009 and March 2012 and involved 44 postmenopausal women (88 ears) who were recruited by the Gynecology Department of the Hospital do Gama, Brasília, DF, Brazil and sent to the Otolaryngology Department of Hospital de Base, Distrito Federal. The study was approved by the Ethics Committee of the Government Health Department of the Federal District and informed consent was obtained from all subjects (Permit nº 363/08). The study was conducted in accordance with the Declaration of Helsinki.

Postmenopausal women were recruited according to the following criteria: age between 45 and 60 years; audiometry with pure-tone thresholds of 25 dB or better in the 500 to 2.000-Hz range; normal type A tympanometric

curve, presence of ipsilateral and contralateral stapedial reflex; amenorrhea for at least 1 year, presence of uterus and ovaries, no systemic or local HRT use for the past 6 months and no major abnormalities of serum glucose, lipids, liver enzymes or thyroid hormones. Exclusion criteria were undiagnosed genital bleeding, known or suspected malignant or premalignant disease, neurological diseases, metabolic problems, vascular diseases, any previous otologic disease detected in the patient's history, acoustic trauma, a history of ototoxic drug use, middle ear disease, previous ear surgery, a history of vestibular problems, and recent aspirin intake.

The 44 postmenopausal women (88 ears) was divided into two groups: a study group consisting of 19 (38 ears) women who used HRT (Suprelle - 17β-estradiol 1 mg + norethisterone acetate 0.5 mg) for 12 weeks, and a control group consisting of 25 postmenopausal women (50 ears) who did not use HRT or placebo. Postmenopausal women of the study group were experiencing moderate to severe menopausal symptoms (Kupperman index ≥ 20[29,30]) and had no absolute contraindications to HRT use. Climacteric symptoms were hot flushes, night sweating, sleep problems, vaginal dryness, and tiredness. Postmenopausal women of the control group had mild menopausal symptoms (Kupperman index < 20) or fear of HRT use based on the side-effects and risks of it[31]. Absolute contraindications to HRT use included thromboembolic disease, breast cancer, uncontrolled hypertension, undiagnosed genital bleeding, coagulopathies, or liver disease.

Both groups were submitted to a detailed physical examination involving complete otolaryngological and gynecological examination and complete blood count. The audiologic tests used were a conventional audiometry (AC 40 Clinical Audiometer -Interacoustics, Assens, Denmark), standard earphones (Telephonics TDH-39P, Denmark), impedance audiometry (AT 235H - Interacoustics, Assens, Denmark) and ABR (Chartr EP - GN Otometrics, USA). All patients were evaluated by the same investigator who was unaware whether the subjects used HRT or not. The ABR recordings were obtained over the first 15 milliseconds after onset of an auditory stimulus, with the patient in a supine position in a silent electrically shielded room. We used two earphones (ICS Medical, 300 Ω, USA) and four surface electrodes (GN Otometrics, USA) that were assigned as follows: the active electrode was fixed on the forehead, the reference electrodes were positioned on the mastoids, and the ground electrode was placed near the active electrode (impedance < 5 kΩ). The following parameters were evaluated: absolute latency of waves I, III and V; intervals between the different waves (I-III, III-V and I-V interpeak latencies). The normal pattern described by Gorga et al.[32] was used as a reference and modified for our population by the audiologic clinic of the hospital. The prevalence of normal and abnormal results of each parameter was calculated for each patient group, before and after 12 weeks. The ABR results were analyzed by two independent persons and no significant difference between them was observed ($p > 0.05$).

Statistical analysis was performed considering the results obtained for the number of ears (n = 88) instead of the number of patients, since the results of the right and left ears in the same individual are independent. A commercial software (PASW Statistics, v.18.0) was used. Mean age was compared between groups using the *t* test for independent measures. The χ^2 test was used to evaluate possible associations between HRT and ABR results. The correction of the level of statistical significance in all 2 x 2 contingency tables was performed using Fisher's exact test. The ABR results were analyzed using a mixed model ANOVA that included the variables 'group' (control and HRT), 'time' (beginning and end), and 'ear' (right and left). The Greenhouse-Geisser method was used for correction of the degrees of freedom. The statistical significance of multiple comparisons was corrected using the Bonferroni test. The results are reported as the mean and standard error of the mean (SEM). The mean of each parameter of ABR was compared between right and left ear using the paired *t* test. A level of significance of $p < 0.05$ was adopted.

RESULTS

The study group (SG) consisted of 38 ears from 19 patients. The control group (CG) consisted of 50 ears from 25 patients. Age ranged from 45 and 60 years in the two groups. The mean age did not differ between groups (SG: 51.5 ± 0.7 years; CG: 52.9 ± 0.6 years; $p = 0.147$). The patients were considered to have abnormal results when they had at least one parameter of ABR that was not normal according to the adopted values.

In the control group, ABR were abnormal in 5 (20%) patients at baseline and in 3 (12%) after 3 months. In the study group, ABR were abnormal in 5 (26.3%) patients at baseline and in 6 (31.6%) after 3 months of HRT. These results did not differ between groups ($p > 0.05$) (Tables 1 and 2).

Table 1. Results of auditory brainstem responses in the study and control groups at baseline.

Group	Baseline auditory brainstem response		Total	*p*-value*
	Altered	Normal		
Control group	3 (12.0%)	22 (88.0%)	25 (100%)	
Study group	5 (26.3%)	14 (73.7%)	19 (100%)	0.262
Total	8 (18.2%)	36 (81.8%)	44 (100%)	

* χ^2 test.

Table 2. Results of auditory brainstem responses in the study and control groups after 3 months.

Group	Final auditory brainstem response		Total	*p*-value*
	Altered	Normal		
Control group	3 (12.0%)	22 (88.0%)	25 (100%)	
Study group	6 (31.6%)	13 (68.4%)	19 (100%)	0.144
Total	9 (20.5%)	35 (79.5%)	44 (100%)	

* χ^2 test.

The mean (SEM) absolute latencies of waves I, III and V, I-III, III-V and I-V interpeak intervals obtained for the study and control groups are shown in Tables 3 and 4. No significant prolongation in the latencies of waves I, III or V and I-III, III-V, I-V interpeak intervals were observed in the study group when compared to control at baseline or after 3 months ($p > 0.05$).

Table 3. Comparison of parameters of the auditory brainstem response between the study and control groups at baseline.

Parameter (ms)	Normal Values	Control group	Study group	*p*-value*
Wave (n = 88)				
I	1.32-1.85	1.58 (0.04)	1.60 (0.02)	0.650
III	3.32-3.97	3.75 (0.02)	3.76 (0.03)	0.957
V	5.02-6.02	5.54 (0.03)	5.47 (0.04)	0.169
Interpeak (n = 88)				
I-V	3.37-4.51	3.92 (0.03)	3.88 (0.03)	0.404
I-III	1.71-2.43	2.14 (0.02)	2.16 (0.03)	0.654
III-V	1.48-2.28	1.78 (0.02)	1.71 (0.03)	0.089

* ANOVA; Results are reported as mean (standard error); ms: Milliseconds; n: Number of ears.

Table 4. Comparison of parameters of the auditory brainstem response between the study and control groups after 3 months.

Parameter (ms)	Normal Values	Control group	Study group	*P*-value*
Wave (n = 88)				
I	1.32-1.85	1.63 (0.02)	1.58 (0.02)	0.134
III	3.32-3.97	3.74 (0.02)	3.75 (0.03)	0.787
V	5.02-6.02	5.55 (0.03)	5.52 (0.04)	0.516
Interpeak (n = 88)				
I-V	3.37-4.51	3.94 (0.03)	3.94 (0.04)	0.971
I-III	1.71-2.43	2.11 (0.02)	2.16 (0.03)	0.184
III-V	1.48-2.28	1.81 (0.02)	1.77 (0.03)	0.236

* ANOVA; Results are reported as mean (standard error); ms: Milliseconds; n: Number of ears.

The analyzes of the results of ABR showed no significant effects of the factor 'ear' on all the evaluated measures between the control group and study group ($p > 0.05$).

The mean of each parameter of ABR of the groups was compared between right and left ear at baseline and after 3 months and the results are shown in Table 5. There were no statistically significant differences between the means of the parameters of right and left ears ($p > 0.05$).

DISCUSSION

The effects of estrogen and progesterone on hearing have been extensively investigated and the results are contradictory. Changes in auditory function have been demonstrated in postmenopausal women, which were attributed in part to lower levels of ovarian hormones[33]. Some clinical and experimental studies have shown positive effects of gonadal hormones on the maintenance of normal hearing in young and middle-aged women, whereas a negative or no effect on hearing has been reported by others[34-41]. The previous reports are based on papers dealing with different HRT and sometimes not well controlled. We decided to perform this controlled study in order to evaluate the effect of combined HRT (estradiol plus progestin - E + P) on the ABR in postmenopausal women during three months. We chose three months of study once it is the minimum period required for observation of clinical symptoms due to hormone therapy[25].

Sensory function declines with age. Age-related hearing loss is one of the top three chronic medical conditions of elderly persons and makes verbal communication difficult[39]. The actions of estrogen and progestin have been linked to sensory and central nervous system processes and disorders such as cognition, memory and dementia[40]. It has been suggested by many studies that HRT given at the time of menopause, especially during the menopausal transition, is effective in the prevention of some diseases, including neurodegenerative diseases, cardiovascular diseases and osteoporosis[2-4,31]. But the effects of HRT on hearing are controversial and there are need for more investigations as to whether HRT is actually beneficial or detrimental to sensory functioning in postmenopausal women[39]. On the other hand, HRT has some known side effects[31], and new studies investigating these possible beneficial improvements on hearing should be attempted.

Table 5. Comparison of parameters of the auditory brainstem response between right and left ears at baseline and after 3 months.

Session	Parameter (ms)	Normal Values	Right ear	Left ear	*P*-value *
Baseline	Wave (n = 88)				
	I	1.32-1.85	1.59 (0.02)	1.56 (0.04)	0.314
	III	3.32-3.97	3.76 (0.02)	3.76 (0.02)	0.683
	V	5.02-6.02	5.51 (0.02)	5.51 (0.03)	0.883
	Interpeak (n = 88)				
	I-V	3.37-4.51	3.9 (0.02)	3.92 (0.03)	0.185
	I-III	1.71-2.43	2.15 (0.02)	2.16 (0.02)	0.633
	III-V	1.48-2.28	1.75 (0.02)	1.75 (0.02)	0.900
After 3 months	Wave (n = 88)				
	I	1.32-1.85	1.61 (0.01)	1.61 (0.02)	0.963
	III	3.32-3.97	3.74 (0.02)	3.75 (0.02)	0.610
	V	5.02-6.02	5.54 (0.03)	5.54 (0.04)	0.867
	Interpeak (n = 88)				
	I-V	3.37-4.51	3.94 (0.02)	3.94 (0.03)	0.458
	I-III	1.71-2.43	2.14 (0.02)	2.14 (0.03)	0.496
	III-V	1.48-2.28	1.79 (0.02)	1.79 (0.02)	0.813

* *t* test; Results are reported as mean (standard error); ms: Milliseconds; n: Number of ears.

We found no significant differences ($p > 0.05$) in the latencies of waves I, III and V, interpeak intervals or hearing between the group receiving HRT and the control group before or after 3 months of therapy.

Hedestierna et al.[35] observed better thresholds in pre-, peri- and postmenopausal women using HRT when compared to postmenopausal women not receiving HRT. However, the authors did not report the type or dose of HRT used by the groups. Caruso et al.[36] showed shorter latencies of ABR waves and interpeak intervals after 3 months of estrogen therapy when compared to baseline. No control group was included in that study and the authors compared ABR between two groups receiving two different doses of estradiol (transdermal gel and transdermal patches). These biases were avoided in the present study since only one type and dose of HRT was used. Moreover, the study group was compared to a control group.

Guimaraes et al.[27] investigated the auditory system of postmenopausal women receiving combined hormone treatment (E + P) and compared this group to a group treated only with estrogen (E) and to a control group (CG). The results of pure-tone audiometry, tympanometry, distortion-product otoacoustic emissions, transient otoacoustic emissions, and the hearing in noise test showed worse performance for the E + P group when compared to E and CG. These findings suggest a protective effect of estradiol on the female auditory system and that the addition of progestin seems to have a negative influence on the peripheral and central auditory system. The length of hormonal treatment varied from 5 to 35 years. We can observe that the long period of HRT use maybe is a factor that can influence the effect of hormone therapy.

Kilicdag et al.[34] reported that pure tone thresholds of postmenopausal women using E were better than pure tone thresholds of those on E + P and in CG. The authors studied 109 patients who received the same HRT regimen as in the present study, but with a double dose of estrogen and progestin (17β-estradiol - 2 mg + norethisterone acetate - 1 mg) and for a longer period (E + P for 4.13 ± 2.41 years; E for 3.35 ± 2.20 years). These findings suggest that adding progesterone to estrogen therapy may attenuate the positive effects of estrogen on hearing. A higher dose of HRT used by these authors compared to our study perhaps is the second factor that could enhanced the positive effects of estrogen. The longer period of HRT use (more than 3 years) can be considered the third factor of HRT influence on the auditory system.

In contrast to Guimaraes et al.[27] and Kilicdag et al.[34], Khaliq et al.[37] evaluated separately the effects of E and E + P after 6 months of HRT use and found no difference in ABR values between the two groups (E + P [n = 32] *versus* E [n = 15]. No control group was included in the study and the authors concluded that progestin does not antagonize or potentiate the effects of estrogen. A shorter period of time of HRT use and a small number of patients could maybe explain the lack of effects of hormone therapy.

In most studies, authors had been used results of both ears combined. Köşüş et al.[38,39] compared

audiometry results of right and left ears separetly in menopausal women before and 6 months after tibolone treatment. Tibolone is a syntetic steroid hormone used frequently in treatment of menopausal symptoms and has estrogenic, gestagenic and weak adrogenic effects on different target organs. They found that improvement at low frequencies was more prominent on the right side. The reason of better improvement on the right side is not known. The authors postulated that there might be some other factor modifying the condition or effect of the drug such as laterality. There might be hearing lateralization in menopausal women. Especially significant improvement on right ear might be explained by differences in distribution of estrogen receptor (ER) in the ear. Another possible reason might be difference in bone mineral density of sides of body which is lower on the right side. In our study we analysed the results of both ears (Table 5), but in contrast to Köşüş et al.[38,39] we did not find differences between the ears.

Sator et al.[40] in a first prospective randomized study observed good response with the administration of tibolone. They showed a significant decrease in ABR latencies of the waves II, III and V with administration of tibolone for 3 months in 12 healthy postmenopausal women compared to 12 postmenopausal women who received placebo. In this study, even with the use of HRT for a short period of time and with a small number of patients, they observed positive differences on ABR latencies with HRT use.

In a recent study, Köşüş et al.[41] found worse thresholds in postmenopausal women with or without tibolone therapy when compared to premenopausal women of the same age, suggesting that intrinsic estrogen at physiological levels might slow down hearing loss in aging women. Tibolone used for at least 1 year had no negative effect on hearing function when they compared the tibolone group (n = 33) with the non-tibolone group (n = 50).

Similar to Köşüş et al.[41] and Kaliq et al.[37], our study showed that HRT had no negative nor positive effect when compared to the control group. But as we can see, the results of the influences of HRT on the auditory system do not have a consensus. Broadly, estrogen seems to have more positive than negative effects to the auditory system. On the other hand, progestin seems to have more negative than positive effect on the auditory system. Proposed mechanisms for progesterone's negative effects on hearing are diverse. One possible mechanism centers on progesterone's ability to down regulate estrogen receptors in breast and uterine tissue, balancing the effects of estrogen or possible irreversible receptor damage[6]. However, more studies are warranted in order to prove the hypothesis of patients with E reposition having a better hearing performance than the ones with E + P and to help in the designing of selective estrogen agonists in order to avoid negative side-effects, such as breast cancer.

In our study we did not find positive or negative effects of estrogen and progesterone, but we had a limited sample. Maybe a larger sample could allow different results. Further studies using a much larger sample are therefore needed to settle this issue.

CONCLUSION

The present results suggest that HRT consisting of estradiol and progestin has no positive nor negative effect on ABR latencies in postmenopausal women when given for three months.

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