Effects of Selective Serotonin Reuptake İnhibitors on Auditory Brainstem Responses in Patients with Depressive Disorder

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ÖZET:

Depresif bozukluğu olan hastalarda selektif serotonin geri alım inhibitörlerinin işitsel beyin sapı yanıtları üzerine etkileri

Amaç: Selektif serotonin reuptake inhibitörlerinin (SSRI) serotonerjik sistemdeki etkisinin spesifik bir bölgede olmadığı iyi bilinmektedir. Bu çalışmada, depresif bozukluğu bulunan hastalarda SSRI'ların işitsel beyin sapı yanıtları üzerine olan etkisini değerlendirmeyi amaçladık.
Yöntem: DSM-IV kriterlerine göre depresif bozukluk tanısı olan hastalara işitsel beyin sapı yanıtları (ABR), Beck Depresyon Envanteri ve Klinik Global İzlenim-Şiddet ölçeği tedavi öncesi (n=51), tedaviden 2 hafta sonra (n=51) ve tedaviden 2 ay sonra (n=32) yapıldı. Sonuçlar, yaş ve demografik özellikler açısından çalışma grubuna benzeyen 34 sağlıklı gönüllüden oluşan kontrol grubuyla karşılaştırıldı.
Bulgular: Hastaların, Beck Depresyon ölçeği skorları tedavi öncesi 33.5±5.1, tedaviden 2 hafta sonra 30.6±4.6 ve tedaviden 2 ay sonra 13.0±3.5 olarak saptandı. Klinik Global İzlenim-Şiddet ölçeği skorları tedaviden önce 5.0±0.7, tedaviden 2 hafta sonra 4.2±0.8 ve tedaviden 2 ay sonra ise 1.2±0.7 olarak bulundu. Tedavi öncesi ve tedaviden 2 ay sonraki kontrol grubu ABR dalga mutlak latans ve interpik latans değerleri ile hasta grubu değerleri arasında her iki kulak için anlamlı fark saptanmadı (p>0.05). Hastaların tedaviden 2 hafta sonraki sağ kulak I-V ve III-V interpik latans değerleri ile sol kulak I-III interpik latans değerleri kontrol grubuna göre anlamlı olarak daha uzamış saptandı (p<0.05). Hastaların tedaviden 2 hafta sonraki sağ kulak III-V interpik latans değerleri hastaların tedavi öncesi sağ kulak değerlerine göre anlamlı olarak uzamış bulunurken (p<0.05), hastaların tedavi öncesi, tedaviden 2 hafta sonra ve tedaviden 2 ay sonraki diğer tüm mutlak ve interpik latans değerleri arasında anlamlı fark saptanmadı.
Sonuç: SSRI'ların işitsel beyin sapı yanıtları üzerine olan etkilerini tedavinin 2. haftası sonunda gösterdiğini ve bu etkilerin tedaviden 2 ay sonra kaybolduğunu saptadık.

Anahtar sözcükler: Selektif serotonin reuptake inhibitörleri, işitsel beyin sapı yanıtları, depresif bozukluk

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ABSTRACT:

Effects of selective serotonin reuptake inhibitors on auditory brainstem responses in patients with depressive disorder

Objectives: It is well known that the action of selective serotonin reuptake inhibitors (SSRIs) on the serotonergic system is not regionally specific. We aimed to evaluate the effects of SSRIs on auditory brainstem responses in patients with depressive disorder.
Material and Methods: Measurement of auditory brainstem response (ABR), Beck Depression Inventory (BDI) and Clinical Global Impressions-Severity of Illness Scale (CGI) were performed to the patients who have depressive disorder diagnosis based on DSM-IV criteria, before SSRI treatment (n=51) and after completing the 2nd week (n=51) and 2nd month (n=32) of the treatment. The result were compared to the results of control group, which included 34 healthy volunteers similar to the study group in terms of age and sociodemographic characteristics.
Results: The BDI scores of the patients were 33.5±5.1, 30.6±4.6 and 13.0±3.5 before the treatment, after the 2nd week and 2nd month of the treatment, respectively. CGI scores of the patients were 5.0±0.7, 4.2±0.8, 1.2±0.7 before the treatment, after the 2nd week and 2nd month of the treatment respectively. There was no significant difference in terms of absolute latency and interpeak latencies of ABR on both right and left ears between the control and patient groups before the treatment and after 2nd month of the treatment (p>0.05 for all statistical). I-V and III-V interpeak latencies of the right ears and I-III interpeak latencies of the left ears of the patients after the 2nd week of treatment were determined significantly longer than the control group (p<0.05). While III-V interpeak latencies of the right ears of the patients after the 2nd week of the treatment were found to be statistically prolonged compared with pretreatment measurements (p<0.05), there was no statistically significant difference according to the other absolute latencies and interpeak latencies among the visits.
Conclusions: According to the results of our study the effects of SSRIs on ABR were demonstrated at the 2nd week of treatment, but disappeared at the 2nd month visit.

Key words: Selective serotonin reuptake inhibitor, auditory brainstem responses, depressive disorder

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INTRODUCTION

Serotonin (5-hydroxytryptamine or 5-HT) is derived from the amino acid tryptophan. In brain, serotonin is profoundly localized in the dorsal and medial raphe nuclear complex and is also found in the cerebellum, pons, medulla, thalamus, hypothalamus and substantia nigra. Serotonin plays an important role in many behavioral and mood functions as a central nervous system (CNS) neurotransmitter or neuromodulator (1,2). It is also known that serotonin is found in many structures of the central auditory pathway, constituting one of the most important neuromodulatory circuits in hearing processing (3).

It has been suggested that the central serotonergic system is involved in the pathophysiology of various psychiatric disorders such as depression, schizophrenia, anxiety disorders, and obsessive compulsive disorder (4,5). Pharmacological intervention in order to balance the actions of serotonergic neurotransmission is central to many therapeutic approaches. Selective serotonin reuptake inhibitors (SSRIs) are antidepressants, known for their effectiveness in the enhancement of serotonin available in the synaptic cleft by blocking the re-uptake mechanism. This allows higher amounts of serotonin to target the receptors in the next neuron (6).

The action of SSRIs on the serotonergic system is not regionally specific and it increases the serotonin levels in some regions of the CNS and peripheral nervous system leading to the side effects (7). The most common adverse reactions of the SSRIs are neuropsychiatric symptoms, particularly headache, insomnia, anxiety and tremor, sexual dysfunction such as anorgasmia, decreased libido and delayed ejaculation, and gastrointestinal symptoms, specifically nausea (6, 8-10). Regarding to the side effects of SSRIs, only few studies reported cochleovestibular side effects such as tinnitus and hearing loss (11,12). Most of the common side effects may present at any time during treatment but are most common in the initial two weeks and often go away within time, in contrast to most therapeutic effects which are delayed and are enhanced over time (13).

Auditory brainstem response (ABR) is a neurological test of auditory brainstem function in response to auditory (click) stimuli. ABR audiometry is the most common application of auditory evoked responses. It provides information regarding auditory function and hearing sensitivity. The ABR test is reliable, objective, noninvasive and painless. There are some studies about the effects of SSRIs usage for a long time on the auditory brainstem responses (14,15). However, we could not find any about the effects of SSRI usage on the auditory brainstem responses during the early treatment period, when the side effects are often seen. Therefore we aimed to determine the auditory effects of SSRIs usage during the early (2nd week) and late period (2nd month) in depressive patients by ABR.

MATERIAL and METHODS

Fifty-one (female: 33 and male: 18) outpatients, who applied to Psychiatry Department of Afyon Kocatepe University, Medical School who had Depressive Disorder diagnosis based on The Diagnostic and Statistical Manuel of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994) (16) criteria, were included in the study. The patients were either drug naive or have not been using any psychotropic drugs at least till one month prior to study. Thirty-four healthy subjects, women (n=20) and men (n=14) served as control group. The in addition, providing criteria for the study, patient and control groups were matched in terms of age and gender.

Exclusion criteria for the patients included the followings: being younger than 18 years old, having a chronic organic disease or an active infectious disease, ototoxic drug use, alcohol and substance abuse and dependence, having significant difficulties in communication because of socio-cultural, education, or language problems. Exclusion criteria for the controls were: having individual or familial psychiatric disease story; stressful life circumstances, any medical treatment within last three months. Additionally, all the patients underwent otorhinolaryngological examination. The pure-tone audiometry (AD229e model of diagnostic audiometer, Interacoustic, Denmark), tympanograms, and acoustic reflex thresholds (MI 34 model of automatic empedancemeter, Maico, USA) were obtained from each ear, and the patients who showed pathologic results were excluded from the study.

After a brief initial interview, if the subjects appeared suitable for the study, they were given standard information about details of study. The written informed consent to participate in the study was obtained from the subjects. The Local Ethics Committee in accordance with the Declaration of Helsinki approved the research protocol.

Each patient underwent a detailed diagnostic evaluation the psychiatrist in training (O.G.) by using The Structured Clinical Interview for DSM-IV and they have filled a sociodemographic data form. The patients have been received paroxetine (n=15, 20 mg/day), fluoxetine (n=10, 20 mg/day), sertraline (n=10, 50 mg/day), escitalopram (n=10, 10 mg/day), fluvoxamine (n=6, 50 mg/day) as initial doses. Out of 51 patients, 12 patients needed additional treatment and 9 of them were not able to be reached, therefore only 32 patients (9 paroxetine, 7 sertraline, 6 fluoxetine, 7 escitalopram and 3 fluvoxamine patients) were assessed at the 2nd month tests.

Assessments were performed at baseline and after and upon completion of 2nd week and 2nd month of treatment with SSRI. All subjects were evaluated by based on a semi-structured questionnaire form, which was arranged by us in accordance with clinical experience and complated from available information sources before treatment, Beck Depression Inventory (BDI) (17), and Clinical Global Impressions-Severity of Illness scale (CGI) at besiline before treatment, and on 2nd week and 2nd month of treatment. Likewise, ABR was obtained on three times. The same tests were performed only once on the control group.

ABR was obtained in a silent room using a device (Evostar 2/x + Evoselect, Germany) and disposable eartips (ER-3A, Indianapolis, IN). It has been reported that the latencies obtained with ER-3A eartips are delayed 0.9ms when compared to TDH-39 eartips (25). Alternating click stimuli were obtained and also masking was performed. We used a positive electrode placed on the midline on the forehead, a negative electrode on one mastoid tip and a ground electrode on the other one for measurements. Each trace was obtained as the mean of over 2000 stimuli and the test was repeated twice to ensure that we got the correct results. Surface disc electrodes were used and electrode impedance was maintained below 5000 Ohms. ABR was recorded at intensity levels presented at 80 dB threshold (dB nSL). The absolute latencies of I, III and V waves and interpeak latencies of I-III, III-V and I-V waves were recorded.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS/PC 11.5 version). Chi-square test (Fisher Exact test) was used to compare nominal values while the Student-t test was used to compare numeric values. Paired Samples Test was used to compare the BDE and CGI scores, and the measurement of absolute and inter-peak latencies of the ABR waves at among each visit, the baseline, 2nd week and 2nd month of the treatment. Two-tailed forms were used. Differences were considered significant at $p<0.05$ for all tests.

RESULTS

The mean age of the patients was 35.9±11.7 year. While BDI scores of the patients were 33.5±5.1 at baseline, BDI scores in the 2nd week and 2nd month of the treatment

Table 1: Beck Depression Inventory and Clinical Global Impressions scores of the patients before and after the treatment.

	Beck Depression Inventory	Clinical Global Impressions
Depressive Disorder		
I. Baseline (n=51)	33.5±5.1	5.0±0.7
II.15. days (n=51)	30.6±4.6	4.2±0.8
III. 60 days(n=32)	13±3.5	1.2±0.7
Control group (n=34)	7.1±4.3	

Table 2: Absolute latencies and interpeak latencies of ABR waves of the right ear before and after the treatment.

	Wave I latency (msec)	Wave III latency (msec)	Wave V latency (msec)	I-III Interpeak latency (msec)	I-V Interpeak latency (msec)	III-V Interpeak latency (msec)
Depressive Disorder						
I. Baseline (n=51)	2.7080±0.2063	4.7116±0.2886	6.5394±0.2985	2.0080±0.2417	3.8373±0.2349	1.8282±0.1481
II.15. days (n=51)	2.6598±0.2137	4.6586±0.2453	6.5639±0.2906	2.0047±0.2056	3.9098±0.2806	1.9059±0.1896
III. 60 days(n=32)	2.7431±0.2118	4.7397±0.2738	6.5862±0.2925	1.9966±0.1860	3.8441±0.1933	1.8456±0.1280
Control group (n=34)	2.7029±0.1835	4.6915±0.2150	6.4829±0.2425	1.9853±0.1466	3.7891±0.1914	1.8003±0.1573
Statistical data						
I-IV	t=0.12, p=0.91	t=0.12, p=0.73	t=0.12, p=0.37	t=0.5, p=0.61	t=1.0, p=0.31	t=0.82, p=0.40
II-IV	t=-1.10, p=0.30	t=-0.7, p=0.50	t=1.30, p=0.20	t=0.48, p=0.62	t=2.20, p=0.03	t=2.69, p=0.01
III-IV	t=0.81, p=0.41	t=0.80, p=0.43	t=1.57, p=0.12	t=0.27, p=0.79	t= 0.17, p=0.25	t=1.28, p=0.21
I-II	t=1.75, p=0.09	t=1.76, p=0.09	t=-0.72, p=0.48	t=0.11, p=0.92	t=-1.85, p=0.07	t=-2.31, p=0.025
I-III	t=-0.43, p=0.67	t=-0.15, p=0.99	t=-0.60, p=0.55	t=0.34, p=0.74	t=-0.14, p=0.90	t=-0.66, p=0.52
II-III	t=-1.70, p=0.1	t=-1.68, p=0.10	t=-0.23, p=0.83	t=0.31, p=0.76	t=1.49, p=0.15	t=1.48, p=0.15

Table 3: Absolute latencies and interpeak latencies of ABR waves of the left ear before and after the treatment.

	Wave I latency (msec)	Wave III latency (msec)	Wave V latency (msec)	I-III Interpeak latency (msec)	I-V Interpeak latency (msec)	III-V Interpeak latency (msec)
Depressive Disorder						
I. Baseline (n=51)	2.6786±0.2781	4.7063±0.3229	6.5973±0.3704	2.0178±0.2191	3.9088±0.2986	1.8908±0.0320
II.15. days (n=51)	2.6598±0.1568	4.7478±0.2687	6.5845±0.3470	2.0875±0.2224	3.9245±0.3167	1.8363±0.2237
III. 60 days(n=32)	2.6547±0.2585	4.7247±0.2728	6.5812±0.3555	2.0566±0.2337	3.9256±0.3217	1.8559±0.1983
Control group (n=34)	2.6968±0.1619	4.6615±0.2130	6.4859±0.2727	1.9635±0.1702	3.8644±0.2179	1.8268±0.1775
Statistical data						
I-IV	t=-0.35, p=0.73	t=0.71, p=0.48	t=1.50, p=0.14	t=1.22, p=0.23	t=0.74, p=0.46	t=1.38, p=0.17
II-IV	t=-1.05, p=0.30	t=1.56, p=0.12	t=1.40, p=0.17	t=2.76, p=0.01	t=0.96, p=0.34	t=0.20, p=0.84
III-IV	t=-0.80, p=0.43	t=1.06, p=0.30	t=1.23, p=0.22	t=1.86, p=0.07	t=0.91, p=0.37	t=0.63, p=0.53
I-II	t=0.58, p=0.57	t=-1.14 p=0.26	t=0.32, p=0.75	t=-1.84, p=0.07	t=0.71, p=0.74	t=1.46, p=0.15
I-III	t=-0.50, p=0.97	t=-0.47, p=0.65	t=0.60, p=0.56	t=-0.23, p=0.83	t=0.38, p=0.49	t=1.23, p=0.23
II-III	t=0.19, p=0.85	t=0.43, p=0.68	t=0.52, p=0.61	t=0.53, p=0.60	t=0.39, p=0.70	t=0.21, p=0.84

were 30.6±4.6 and 13.0±3.5, respectively. Additionally, CGI scores of the patients were 5.0±0.7, 4.2±0.8, 1.2±0.7 before the treatment at baseline, after the 2nd week and 2nd month of the treatment, respectively (Table 1).

The absolute and interpeak latencies of ABR waves of the right and left ears of the patients that were measured before and after the treatment are shown in Table 2 and Table 3, respectively.

There was no significant difference in terms of the absolute latencies and interpeak latencies of ABR on the both right and left ears between the control and patient groups before treatment and after 2nd month of the treatment ($p>0.05$ for all statistical). While I-V and III-V interpeak latencies of the right ears and I-III interpeak latencies of the left ears of the patients after the 2nd week of treatment were determined significantly longer than the control group ($p<0.05$), there was no statistically significant difference between the other absolute latencies and inter-peak latencies ($p>0.05$).

No statistically significant difference was determined in terms of the absolute latencies and interpeak latencies of ABR in the patients among before the treatment and after the 2nd month of treatment ($p>0.05$). While III-V interpeak latencies of the right ears of the patients at the 2nd week of the treatment were found to be statistically prolonged compared with pretreatment measurements ($p<0.05$), there was no statistically significant difference according to the other latencies and interpeak latencies among the visits. Moreover, the absolute latencies and interpeak latencies of the patients did not differ significantly among the 2nd week and 2nd month of the SSRI treatment.

DISCUSSION

To our knowledge, this was the first study focused on the effects of SSRIs during the early treatment period on the latency and interpeak latencies of ABR. The main finding of the present study was that some interpeak latencies of ABR were prolonged in the first two weeks of the treatment, but this effect disappeared in the second month.

It has been shown that serotonergic pathways interface with the auditory system, although the exact role of serotonin in the auditory system is not well recognized. Serotonergic fibers originating in midline raphe regions of the brain have been found to terminate in several auditory structures including the cochlea, the eighth nerve, cochlear nucleus, superior olivary complex, lateral lemniscus and inferior colliculus (18-20,15). The presence of serotonin in inner ear can show a probable modulatory role in hearing and balance (21). It is found that serotonin may regulate the function of stria vascularis and may involve cochlear microcirculation dysfunction (22). Recently, serotonin containing fibers have been found accompanying the olivocochlear efferent system. Serotonin may function as a neuromodulator of the efferent cholinergic and GABA innervation of this efferent system. These fibers form glomerulus-like structures under the inner hair cells and send collaterals to the first row of the outer hair cells (1,19,23).

Efferent fibers originating from the brainstem modulate neurotransmission of inner hair cells either postsynaptically through synapses with afferent dendrites

of primary auditory and vestibular neurons or presynaptically through synapses with the hair cells. In the cochlea, efferent fibers are theorized to play a significant role in the shifting of sound level functions and the protection and regulation of sensory hair cells (24). Efferent fibers release the inhibitory neurotransmitter acetylcholine, which is believed to be modulated by serotonin (23,20).

The effects of SSRIs on the auditory system were performed especially with ABR amplitudes in the previous studies (14). Three basic criteria are considered when determining ABR; absolute and interpeak latencies, amplitudes and morphologies of the waves. Morphology of the waves is important, but it is a subjective criterion as it is affected by many factors. Since amplitude of the waves shows a wide variability among healthy individuals, we had to be prudent while interpreting the ABR. The most reliable and frequently used criteria of ABR analysis is the latencies, such as absolute, inter-peak and interaural latencies (25).

In terms of ABR, Gopal et al. (14) showed no significant differences in absolute or interpeak latencies, however, they showed significant differences in amplitude growth between non-depressed individuals and unmedicated clinically depressed individuals. They also reported that the amplitude growth which was abnormally large in the unmedicated session returned to levels closer to the healthy group with medication in the depressed patients (15). This observation has not been supported by some authors, who have suggested no exaggerated or augmented amplitude growth with low serotonin levels (26,27).

The previous studies focused on the long term effects of treatment. In contrast we evaluated short term effects of the SSRI treatment and demonstrated that ABR latencies were affected by the short term treatment of SSRI in the present study. Another important finding was that the prolonged interpeak latencies of ABR on 2nd week of the treatment disappeared in the second month visit. Activation of 5- HT1A autoreceptors results in the feedback inhibition of the raphe nucleus, with downregulation of autoreceptors and a subsequent increase in serotonergic neurotransmission in the short term of the treatment. The delay in autoreceptor down-regulation coincides with the usual "therapeutic lag" of 2 to 3 weeks (28). The changes in the interpeak latencies of ABR in the short term of the treatment may be due to the aforementioned serotonergic metabolism. We also suggest that the changes of ABR interpeak latencies, which are so susceptible to the cochlear ischemia, are due to the impairment of the modulatory role of serotonergic pathways in the olivocochlear efferent system on the cochlear microcirculation. These results also confirm the previous data that most of the common side effects may present in the initial two weeks and often abate go away with time (13).

As our sample size was small, we did not evaluate men and women separately. This is one of the limitations of the our study.

In the present study, prolongation of the different interpeak latencies between the right (III-V and I-V) and left (I-III) ears may be due to the peripheral asymmetries in the auditory system (29).

Consequently, in the present study, we determined that interpeak latencies of ABR were prolonged at the 2nd week of the SSRI treatment and this effect has not been detected shown at the 2nd month of the SSRI treatment. We believe that further studies are needed to clarify the auditory effects of SSRIs, which is related to the olivocochlear efferent system, in depressed patients.

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References:

1. Tadros SF, D'Souza M, Zettel ML, Zhu X, Lynch-Erhardt M, Frisina RD. Serotonin 2B receptor: upregulated with age and hearing loss in mouse auditory system. Neurobiol Aging 2007; 28:1112-1123.

2. Wilkinson LO, Dourish CT. Serotonin and animal behavior. In: Serotonin receptor subtypes: basic and clinical aspects, Peroutka SJ (editors), New York: Wiley-Liss, 1991:147-210.

3. Cruz OLM, Kase CA, Sanchez M, Barbosa F, Barros FA. Serotonin reuptake inhibitors in auditory processing disorders in elderly patients: preliminary results. The Laryngoscope 2004; 114:1656-1659.

4. Heninger GR, Delgado PL, Charney DS. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry 1996; 29:2-11.

5. Debener S, Strobel A, Kürschner K, Kranczioch C, Hebenstreit J, Maercker A, Beauducel A, Brocke B. Is auditory evoked potential augmenting/reducing affected by acute tryptophan depletion? Biol Psychol 2002; 59:121-133.

6. Schatzberg AF, Nemeroff CB. Klinik Psikofarmakolojinin Esasları. Çeviri editörleri: Ceylan ME, Ger C, Arısoy Ö. 1. baskı,. Esin Ofset Matbaa ve Reklamcılık A.Ş, 2005; 29-45.

7. Carrasco JL, Sandner C. Clinical effects of pharmacologic variations in selective serotonin reuptake inhibitors: an overview. Int J Clin Pract 2005;59:1428-1434.

8. Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. Drugs 1999; 57:507-513.

9. Kuloğlu M, Atmaca M, Geçici Ö, Nülüfer Kılıç N,Tezcan AT. The side-effects of antidepressants on sexual functıon. Bull Clin Psychopharmacol 2000; 10:97-102 (In Turkish).

10. Atmaca M, Kuloğlu M, Geçici Ö, Tezcan AE. Sildenafil use in antidepressant drugs induced erectile dysfunction. Bull Clin Psychopharmacol 2001;11:106-110 (In Turkish).

11. Gündoğar D, Dereköy S, Yılmaz D. Hearıng impairment and tinnitus during fluvoxamine treatment: case report. 39th The National Congress of Psychiatry, 14-19 October 2003, Antalya, Turkey. (In Turkish).

12. Cunningham M, Cunningham K, Lydiard RB. Eye tics and subjective hearing impairment during fluoxetine therapy (Letter to the Editor). American Journal of Psychiatry 1990; 147: 947-948.

13. Stahl SM. Essential Psychopharmacology The Prescriber's Guide. First publilished, Canada: Cambridge University Press, 2005: 195-200.

14. Gopal KV, Bishop CE, Carney L. Auditory measures in clinically depressed individuals. II. Auditory evoked potentials and behavioral speech tests. Int J Audiol 2004; 43: 499-505.

15. Gopal KV, Briley KA, Goodale ES, Hendea OM. Selective serotonin reuptake inhibitors treatment effects on auditory measures in depressed female subjects. Eur J Pharmacol 2005 27;520:59-69.

16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington DC, 1994.

17. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:53-63.

18. Gil-Loyzaga MP, Bartolome MV, Vicente-Torres MA. Serotonergic innervation of the organ of Corti of the cat cochlea. NeuroReport 1997; 8:3519-3522.

19. Gil-Loyzaga P, Bartolomé V, Vicente-Torres A, Carricondo F. Serotonergic innervation of the organ of Corti. Acta Otolaryngol 2000;120:128-132.

20. Thompson GC, Thompson AM, Garrett KM, Britton BH. Serotonin and serotonin receptors in the central auditory system. Otolaryngol Head Neck Surg 1994;110:93-102.

21. Vicente-Torres A, Bartolome MV, Carricondo F, Esquifino A, Gil Loyzaga P. HPLC detection of serotonin within the rat cochlea. Neuroreport 1998;9:3699-3701.

22. Luo ZQ, Kong WJ. The influence of serotonin on cochlear microcirculation. J Clin Otorhinolaryngol 2000; 14:81-82.

23. Gil-Loyzaga P, Vicente-Torres MA, Garcia-Bonacho M, Esquifino A. Presence of catecholamines and serotonin in the rat vestibule. Brain Res 1997; 746:265-268.

24. Schrott-Fischer A, Kammen-Jolly K, Scholtz A, Rask-Andersen H, Glueckert R, Eybalin M. Efferent neurotransmitters in the human cochlea and vestibule. Acta Otolaryngol 2007; 127:13-19.

25. Muş N, Özdamar Ö. Auditory brainstem responses. Ankara, 1996 (In Turkish).

26. Debener S, Strobel A, Kürschner K, Kranczioch C, Hebenstreit J, Maercker A,Beauducel A, Brocke B. Is auditory evoked potential augmenting/reducing affected by acute tryptophan depletion? Biol Psychol 2002; 59:121-33.

27. Dierks T, Barta S, Demisch L, Schmeck K, Englert E, Kewitz A, Maurer K, Poustka F. Intensity dependence of auditory evoked potentials (AEPs) as biological marker for cerebral serotonin levels: effects of tryptophan depletion in healthy subjects. Psychopharmacology 1999; 146:101-107.

28. Bezchlibnyk-Butler K, Aleksic I, Kennedy SH. Citalopram a review of pharmacological and clinical effects. J Psychiatry Neurosci 2000; 25:241-254.

29. Khalfa S, Collet L. Functional asymmetry of medial olivocochlear system in humans. Towards aperipheral auditory lateralization. Neuroreport 1996; 7:993-996.