Araştırma Makalesi/Original Article
Makale Dili "İngilizce"/Article Language "English"

Türk Hijyen ve Deneysel Biyoloji Dergisi

# Effect of postnatal thiamine deficiency on central auditory processing during adulthood

## Postnatal tiamin eksikliğinin yetişkinlik döneminde merkezi işitsel işlemlemeye etkisi

**Deniz KANTAR[1] (ID), Betül DANIŞMAN[1] (ID), Nevreste Didem SONBAY YILMAZ[2] (ID)**

### ABSTRACT

**Objective:** Thiamine deficiency (TD) during the developmental period is a very rare condition in the developed countries but it is becoming more frequent worldwide because of worsened socioeconomic status in some communities. Thiamine has many metabolic and structural functions in the brain especially in the developmental period. Postnatal TD may cause long-lasting effects in the brain. Chronic TD causes hearning deficit but the effects of postnatal TD to the central auditory processing during adulthood have not been investigated sufficiently. The loudness dependence of auditory evoked potentials (LDAEP) provides a well established marker of the central serotonin activity. Besides, paired-click responses (PRs) are associated with glutamatergic/GABAergic transmission. İnvestigating these responses and underlying oscillations that reflect the neuronal correlate of auditory processing provides important information about auditory changes due to TD condition.

**Methods:** Rats were divided into two groups as follows; Control whose dams fed with normal diet (C), thiamine deficient whose dams fed with thiamine_deficient diet during postnatal period (TD). In adulthood, we recorded AEPs and PRs and analyzed LDAEP, components and

### ÖZET

**Amaç:** Gelişim döneminde tiamin eksikliği (TD) gelişmiş ülkelerde çok nadir görülen bir durumdur, ancak bazı topluluklarda kötüleşen sosyoekonomik durum nedeniyle dünya çapında daha yaygın hale gelmiştir. Tiaminin beyinde özellikle gelişim döneminde birçok metabolik ve yapısal işlevi vardır. Doğum sonrası TD, beyinde uzun süreli etkilere neden olabilir. Kronik TD işitme kaybına neden olur, ancak doğum sonrası TD'nin yetişkinlikte merkezi işitsel işlemlere etkileri yeterince araştırılmamıştır. İşitsel uyarılmış potansiyellerin şiddet bağımlılığı (İUPŞB) merkezi serotonin aktivitesinin iyi bilinen bir belirtecidir. Çift-klik (ÇK) yanıtları ise glutamaterjik/GABAerjik ileti ile ilişkidir. İşitsel süreçlerin nöronal eşdeğerini yansıtan bu yanıtların ve altta yatan osilasyonların incelenmesi TD'ye bağlı işitsel değişimler hakkında önemli bilgiler sağlayacaktır.

**Yöntem:** Bu çalışmada sıçanlar aşağıdaki gibi iki gruba ayrıldı; Anneleri normal diyet ile beslenen grup (C), anneleri doğum sonrası tiamin yetersiz diyetle beslenen grup (TD). Yetişkinlik döneminde üç aylık sıçanlardan İUP ve ÇK yanıtları kaydedildi ve İUP'lerin ses şiddeti bağımlılığı, bileşenleri ve spektral

[1]Akdeniz University, Faculty of Medicine, Department of Biophysics, Antalya
[2]Antalya Training and Research Hospital, Department of Otolaryngology, Antalya

İletişim / Corresponding Author : Deniz KANTAR
Akdeniz Üniversitesi, Tıp Fakültesi, Dekanlık Binası, B Blok 2. Kat. Biyofizik AD., Antalya - Türkiye
E-posta / E-mail : dkantar@akdeniz.edu.tr

Geliş Tarihi / Received : 27.01.2021
Kabul Tarihi / Accepted : 24.05.2021

DOI ID : 10.5505/TurkHijyen.2022.68466

Kantar D, Danışman B, Sonbay Yılmaz ND. Effect of postnatal thiamine deficiency on central auditory processing during adulthood. Turk Hij Den Biyol Derg, 2022; 79(3): 385 - 396

spectral changes to unravel the network alterations.

**Results:** The N1/P2 responses for two loadest stimulus were significantly increased in the TD group versus the C group. In parallel, higher LDAEP value was obtained in the TD group. As gamma level was significantly attenuated in the TD group, elevated theta/alpha response was observed in the TD group compared with the C group. For PRs, higher N1 response to second stimuli and lower suppression rate detected in the TD group. Concomitant increment of theta responses to second stimuli was observed in the TD group.

**Conclusion:** Postnatal TD causes degenerative changes with long-term implications observed in auditory network dynamics which could be partly explained by altered serotonergic and glutamatergic/GABAergic transmission.

**Key Words:** Thiamine deficiency, loadness dependence of auditory evoked potentials, pair-click response

değişiklikler analiz edilerek ağ değişiklikleri incelendi.

**Bulgular:** En şiddetli iki uyaran için N1/P2 yanıtlarının TD grubunda C grubuna kıyasla önemli ölçüde arttığı bulundu. Buna paralel olarak TD grubunda daha yüksek İUPŞB değeri elde edildi. TD grubunda gama yanıtlarında anlamlı düzeyde zayıflama ve C grubuna göre artan teta/alfa yanıtları gözlendi. ÇK yanıtları için, TD grubunda ikinci uyarana daha yüksek N1 yanıtı ve daha düşük baskılama oranı tespit edildi. TD grubunda ikinci uyaranlara karşı teta yanıtlarının da eşzamanlı olarak arttığı gözlendi.

**Sonuç:** Postnatal TD'nin işitsel ağ dinamiklerinde gözlenen uzun vadeli etkileri olan dejeneratif değişikliklere neden olduğu saptanmıştır. Bu etkilerin serotonerjik ve glutamaterjik/GABAerjik ileti değişimiyle ilişkili olduğu düşünülmektedir.

**Anahtar Kelimeler:** Tiamin eksikliği, işitsel uyarılmış potansiyel şiddet bağımlılığı, çift-klik yanıtları

## INTRODUCTION

Thiamine deficiency (TD) has occurred frequently in refugees and low socioeconomic populations depend on malnutrition (1,2). Although the frank deficiency is rare nowadays, subclinical deficiency has seen in large segments of the world's population due to the limited intakes of thiamine riched foods (3). Especially, pregnant women are at higher risk because of increased body demands in both pre and postnatal periods. Thiamine has many obligatory functions in the brain biochemistry and membrane structure (4,5). It is essential for the enzymes involved in energy metabolism, synthesis of neurotransmitters and antioxidant defense system (4,6,7). Also, thiamine has many structural roles in axoplasmic and synaptosomal membranes which is necessary for proper synaptic transmission (4). It has been shown that thiamine facilitates synaptic transmission by enhancing synaptosome release (8) and deficiency causes neural circuit defects for example in GABAergic and glutamatergic circuits (6,9,10). Previous studies also reported serotonergic abnormalities due to TD conditions (6,11). Serotonergic system dysfunction occurs in mice fed with a TD diet (12). So, postnatal thiamine deficiency may cause long-term consequences at multiple brain processes as well as neural circuit changes. But those effects of TD diet on central auditory processing are not known.

Brain circuits can be examined by recording evoked potentials and analyzing spectral changes of brain oscillations. These oscillatory patterns are defined as the brain's fingerprints and reflect neural circuit dynamics (13). Previous studies showed that thiamine deficiency caused abnormalities in the wave shape, amplitude and latencies of auditory brainstem response (ABR) (14,15). The results showed that

infantile TD leads to auditory neuropathy of brainstem origin which was determined with ABR abnormalities at later periods up to seven years old (15).

However, to date, there has been no detailed study investigating the effects of postnatal thiamine deficiency on neural circuit dynamics of the central auditory system during adulthood. Therefore, we recorded loudness dependent auditory evoked potentials and pair click responses in order to examine the different auditory processes from postnatally TD rats during their adulthood period. Loudness dependence of AEPs (LDAEP) is generally used to investigate the serotonergic system as a marker and LDAEP is inversely correlated with the level of serotonergic transmission (16,17). Besides, paired-click responses (PRs) reflect sensory gating mechanisms and glutamatergic/GABAergic systems have been implicated in sensory gating (18-20). In addition to evoked amplitudes, spectral characteristics evolved to unravel the oscillatory changes underline evoked responses. So, the aim of the present study is to determine the developmental effects of thiamine deficiency on central auditory processing during the adulthood period.

## MATERIAL and METHOD

### Animals

All experiments were approved by the Akdeniz University Animal Care and Use Committee and were performed in accordance with the European Community directive. Sixteen Wistar rats, aged three months, were used. All rats were kept in steel cages with a 12-hour light/dark cycle at a mean temperature of 25˚C. The thiamine-deficient diet used in the study was purchased from Test-Diet® company. The experiments were performed between 9:00 and 17:00. Rats were randomly divided into two groups (n=8 for each): Group 1: the group dams received a normal diet before birth and after birth; Group 2: the group dams received a normal diet before birth and a thiamin-deficient diet after birth for 21 days. Throughout the pregnancy, all the rats were fed with normal diet. Rats gave birth at mean 23 days (range, 20-28 days). During the postnatal lactation period, nutrition was continued as per the protocol for each group. All experimental protocols were conducted on 3 months old rats.

### AEPs recordings

AEPs were recorded between 09:00 am and 02:00 pm. Rats aged 3 months were anesthetized (24 g/100 ml) with intraperitoneal injections of urethane (1.2 g/kg, Sigma-Aldrich, St Louis, MO, USA). The head of the anesthetized animal was attached to the standard stereotaxic frame and four small holes (1.5 mm diameter) were drilled for the placement of the stainless steel electrodes. Recording electrodes were placed laterally on auditory cortex (AP: -5.0 mm, ML: +6.5) and reference, ground electrodes were placed on cerebellar skull. The rats were confirmed to have normal external auditory canal and tympanic membranes. The anesthetized animal was moved into a sound-attenuated recording room. Mean background noise level of the recording room measured 46 dB with a sound level meter (Testo 816 Sound Level Meter, Germany). The EEG signal was amplified (Brainamp EEG/EP Amplifier, Brain Products, Munich, Germany), band-pass filtered (0.1-300 Hz) and digitized at a 1000 Hz sampling rate (Brainvision Recorder, Brain Products, Munich, Germany).

AEPs were recorded using randomized sinus tones of 4 ms duration and 2000 Hz frequency. Tones were presented in four different intensities: 87, 96, 104 and 111 dB. Each tone was used 70 times with a 1.5-2.0 s ISI in a random order. For auditory sensory gating measure, two equal tones at 2500 Hz, 80 dB were used as pair click stimulation. The duration of the tones was 4 ms with an ISI of 300 ms. The tones were presented through a loudspeaker at a distance of 15 cm from the ear.

### Data Analysis

All analyses were performed by using BrainVision Analyzer (Brain Products GmBH). AEPs were processed in 100 ms anterior to stimulus and 300 ms poststimulus

epochs. All data were corrected for technical and other artifacts by visual analysis of the single sweeps. Data were filtered (0.1–150 Hz) and baseline corrected. AEPs responses were averaged for each rat. Subsequently, amplitudes of the components were determined as highest positive or negative values in the latency Windows as follows: P1, 10–30 ms; N1, 41–80 ms; P2, 80–130 ms; N2, 130–200 ms. The loudness dependence of each component was calculated as the median slope of all possible straight lines connecting the different amplitude values to each intensity level. The mean slope indicates the amplitude change due to increasing stimulus intensity. Then, spectral amplitudes of oscillatory activity in the time-frequency domain were calculated by the means of complex Morlet´s wavelet transform, with wavelets of about 5 and 7 cycles between 0.5-20 Hz and 30-90 Hz, respectively in 0.5 Hz steps. Gamma, alpha, and theta spectral changes were averaged over the trials of each subject, separately for each condition.

### Statistical analysis

The statistical analysis of the obtained data was performed by SPSS (SPSS 18.0, SPSS Inc., Chicago, IL) software for Windows. Statistical comparisons were performed by using the repeated measures ANOVA with stimulus as the within-subject factor, and groups as the between-subject factors. Post-hoc Bonferroni test was performed. Student-t test was performed for 2 independent means.

This study was approved by the Akdeniz University Animal Experiment Local Ethics Committee (Date:29.08.2016 and No: 71).

## RESULTS

No significant difference could be observed in the body weight change among different experimental groups (data not shown).

P1, N1, P2, N2 components of AEPs for experimental groups are presented in Figure 1. Mean ± SEM of AEP components (P1/N1, N1/P2 and P2/N2) are shown in Table 1. There was a main group effect in N1/P2 amplitudes for S3/S4 stimulus [$F(1,10)=10.13$, $p<0.05$]. Also, analysis revealed significant stimulus [$F(3,30)=58.56$, $p<0.001$] and group x stimulus [$F(3,30)=9.56$, $p<0.001$] effects for N1/P2 amplitude. Post-hoc comparisons showed that N1/P2 responses were higher in the TD group in comparison with the control group for S3/S4 stimulus at both electrode regions ($p<0.05$). For P1/N1 [$F(1,10)=4.96$, $p>.05$] and P2/N2 [$F(1,10)=1.88$, $p>.05$] components, no such effect was observed.

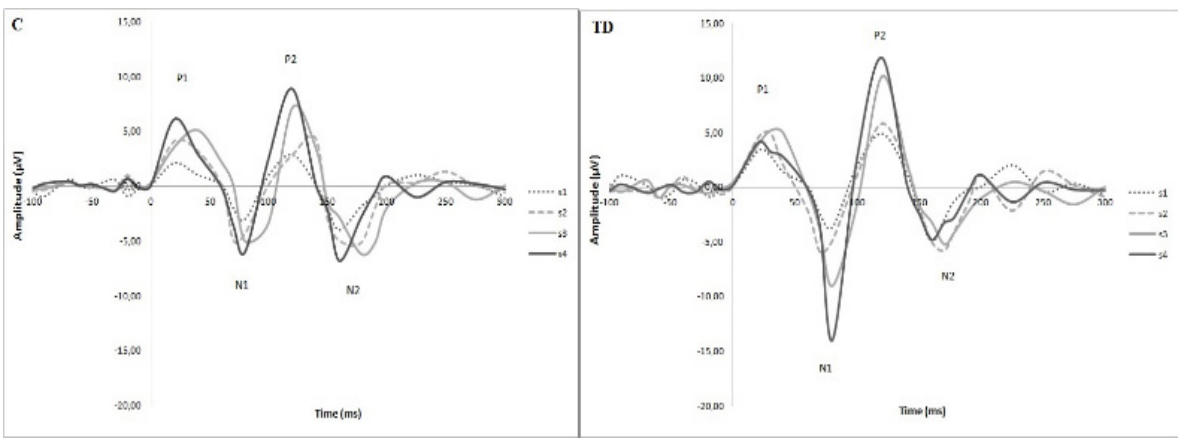


**Figure 1.** Representative AEPs in response to increasing stimulus intensity level for all groups (S1=87, S2=96, S3=104 and S4=111 dB). Two positive (P1,P2) and two negative (N1,N2) peaks were presented.

**Table 1.** The mean and standard errors of peak-to-peak amplitudes (μV) of AEP components in response to four stimulus with increasing loudness level in all experimental groups

| Aux | Stim | Control | TD |
|---|---|---|---|
| P1/N1 | S1 | 5,16±1,14 | 6,11±0,41 |
| | S2 | 9,37±0,75 | 12,66±1,12 |
| | S3 | 10,44±1,12 | 14,01±2,13 |
| | S4 | 12,11±1,29 | 15,98±0,99 |
| N1/P2 | S1 | 6,55±1,50 | 8,60±0,83 |
| | S2 | 9,38±1,37 | 12,15±2,58 |
| | S3 | 11,58±1,61 | **20,34±2,40*** |
| | S4 | 14,90±1,76 | **25,31±2,64*** |
| P2/N2 | S1 | 7,57±1,04 | 8,74±0,67 |
| | S2 | 9,73±0,56 | 12,62±0,91 |
| | S3 | 12,46±1,13 | 13,79±1,06 |
| | S4 | 14,93±1,54 | 14,04±1,81 |

*: Significant difference versus control group

The LDAEP values were presented in Table 2. The AEPs of all rats showed a clear loudness dependence. In the TD group we found a significant increase in LDAEP of the N1/P2 component versus the control group [$t(10)=2.97$, $p<0.05$].

Auditory evoked gamma band spectrograms for S4 stimulus were presented in Figure 2. The ERSP values in the gamma band were presented in Table 3. There was no group difference in terms of gamma ERSP values [$F(1.10)=0.294$, $p>0.05$]. However, repeated ANOVA indicated a significant stimulus effect [$F(1.10)=318.92$, $p<0.001$]. Post-hoc test showed that auditory evoked gamma ERSP values decreased in the TD group versus the control group for S4 stimulus ($p<0.01$).

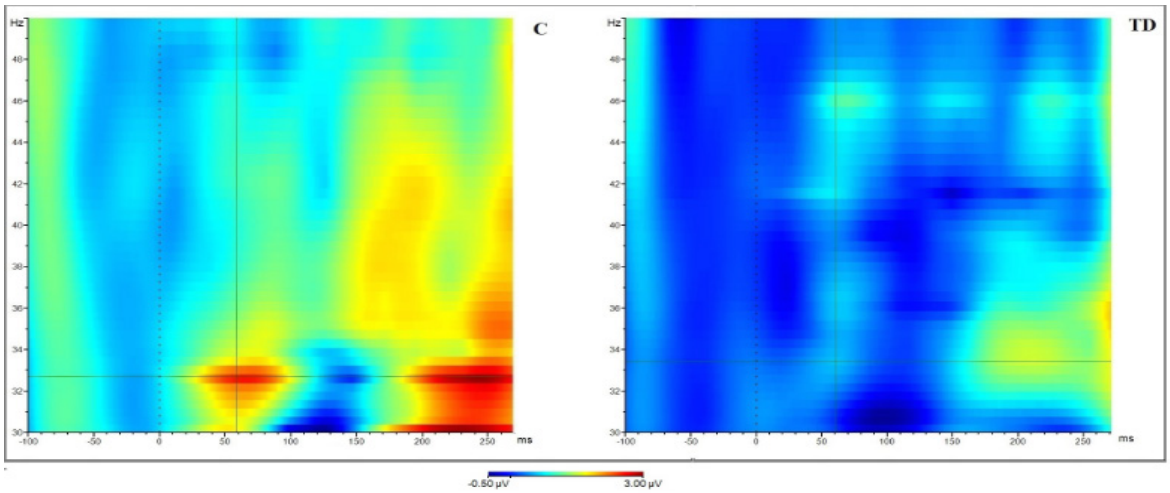


**Figure 2.** Auditory evoked spectral changes in gamma band activity during the loudest stimuli (S4 =111 dB) for all groups. Time-frequency plots illustrate the spectral changes upon stimulus onset.

**Table 2.** The mean and standard errors of LDAEP values in all experimental groups

| | Group | Mean |
|---|---|---|
| LDAEP | Control | 2,78±0,29 |
| | TD | **5,57±1,08*** |

*: Significant difference versus control group

**Table 3.** The mean and standard errors of gamma spectral values (μV) of AEPs in response to four stimulus with increasing loudness level in all experimental groups.

| Aux | Stim | Control | TD |
|---|---|---|---|
| Gamma | S1 | 1,24±0,07 | 1,132±0,44 |
| | S2 | 1,48±0,33 | 1,33±0,21 |
| | S3 | 2,24±0,23 | 1,82±0,25 |
| | S4 | 2,91±0,30 | **2,10±0,13*** |

*: Significant difference versus control group

Auditory evoked theta/alpha band spectrograms for S4 stimulus were presented in Figure 3. The ERSP values in the theta/alpha band was presented in Table 4. In the theta frequency band, analysis revealed no significant group [$F(1.10)=0.28$, $p>0.05$] or stimulus effect [$F(3.30)=0.364$, $p>0.05$]. Besides, there was a significant group x stimulus effect for theta band [$F(1.10)=9.27$, $p<0.05$]. Theta/alpha ERSP evoked by S4 was more prominent in TD group compared to control group ($p<0.01$).

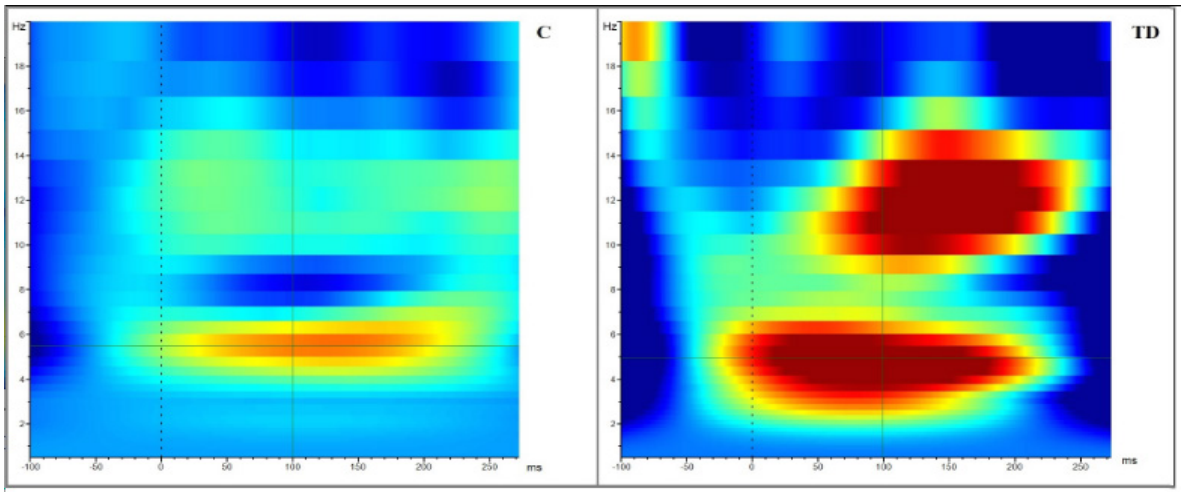


**Figure 3.** Auditory evoked spectral changes in theta/alpha band activity during the loudest stimuli (S4 =111 dB) for all groups. Time-frequency plots illustrate the spectral changes upon stimulus onset.

**Table 4.** The mean and standard errors of theta/alpha spectral values (μV) of AEPs in response to four stimulus with increasing loudness level in all experimental groups

| Aux | Stim | Control | TD |
|---|---|---|---|
| Alpha | S1 | 8,66±2,90 | 13,67±5,37 |
| | S2 | 11,40±3,13 | 12,20±2,92 |
| | S3 | 10,40±1,25 | 13,76±3,07 |
| | S4 | 14,37±2,88 | **16,83±2,15*** |
| Theta | S1 | 12,03±3,07 | 13,70±2,15 |
| | S2 | 11,42±3,69 | 12,57±3,57 |
| | S3 | 13,91±3,60 | 17,30±3,01 |
| | S4 | 15,37±1,77 | **19,73±2,17*** |

*: Significant difference versus control group

P1, N1 components of AEPs to PRs for experimental groups are presented in Figure 4. Peak amplitudes of mid-latency auditory AEP components (P1 and N1) and suppression and difference values are shown in Table 5. Repeated ANOVA indicated significant stimulus effect for P1 [F(1,10)=122.95, $p$<.001] and N1 [F(1,10)=13.24, $p$<.01] amplitudes. There was no significant group [F(1,10)=0.007, $p$>0.05] and group x stimulus [F(1,10)=1.78, $p$>0.05] effects in P1 amplitude. There was a main group effect in N1 amplitude [F(1,10)=5.88, $p$<0.05]. Post hoc comparisons showed that N1 amplitudes were higher in controls than in TD group at both electrode region ($p$<0.05).

There was a significant difference between groups for N1 difference (S1-S2) [t(10)=7.72, $p$<0.001] and N1 ratio [t(10)=2.72, p<.05]. N1 difference and ratio were significantly reduced in TD group versus the control group (difference: $p$<0.01, ratio score: $p$<0.05).

The ERSP values in the gamma band were presented in Table 6. The auditory evoked ERSP was clearly present after the first click and less prominent after the second click in the gamma frequency band in both groups. Repeated ANOVA analysis indicated a significant stimulus effect for gamma ERSP values [F(1.10)=13,50, $p$<0.01]. There was no significant group [F(1.10)=0,01, $p$>0.05] or group x stimulus [F(1.10)=0,03, $p$>0.05] effect.

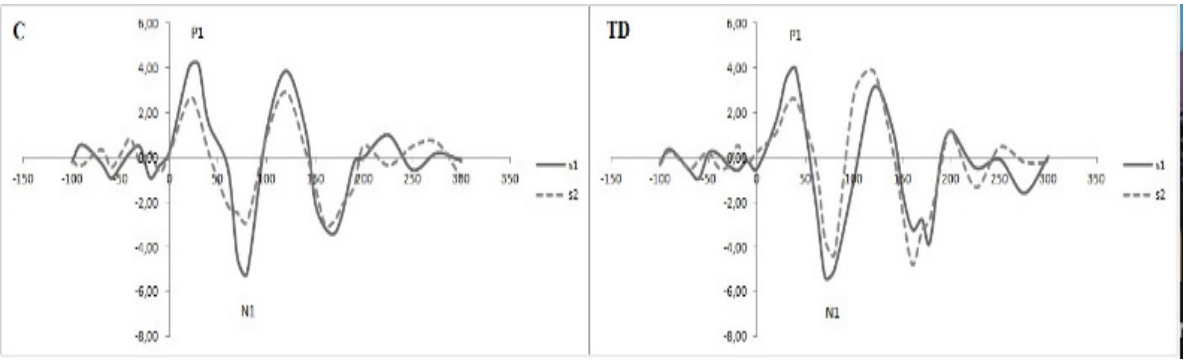


**Figure 4.** Representative PRs for all groups (S1=first, S2=second stimulus). Two positive (P1,P2) and two negative (N1,N2) peaks were presented.

**Table 5.** The mean and standard errors of peak amplitudes (μV) of AEP components in response to pair-click stimulus in all experimental groups.

| Aux | Stim | Control | TD |
|---|---|---|---|
| P1 | S1 | 4,37±1,05 | 3,95±0,62 |
| | S2 | 1,62±0,60 | 1.93±0,38 |
| | %Sup | 31,82±2,24 | 28,03±2,17 |
| | Dif | 3,76±0,55 | 3,68±2,78 |
| N1 | S1 | 5,75±2,47 | 5,36±1,18 |
| | S2 | 2,36±0,69 | **4,28±1,30*** |
| | Sup | 45,87±3,34 | **21,52±2,68*** |
| | Dif | 8,89±0,75 | **4,28±0,34*** |

*: Significant difference versus control group

**Table 6.** The mean and standard errors of gamma/theta spectral values (μV) of AEPs in response to pair-click stimulus in all experimental groups.

| | Condition | Control | TD |
|---|---|---|---|
| Gamma | S1 | 2,72±0,32 | 2,46±0,42 |
| | S2 | 1,65±0,28 | 1,89±0,83 |
| Theta | S1 | 12,70±1,53 | 15,43±2,02 |
| | S2 | 7,91±1,30 | **12,20±4,49*** |

*: Significant difference versus control group

Auditory evoked theta band spectrograms for S4 stimulus were presented in Figure 5. The ERSP values in the theta band were presented in Table 6. Repeated ANOVA analysis revealed a borderline significant group effect for theta ERSP values [F(1.10)=5.09, $p$=0.05]. But there was a significant group x stimulus effect. In the theta frequency band, ERSP evoked by S2 was more prominent in TD group versus the control group ($p$<0.01) and this theta difference was not observed for the S1 stimulus.

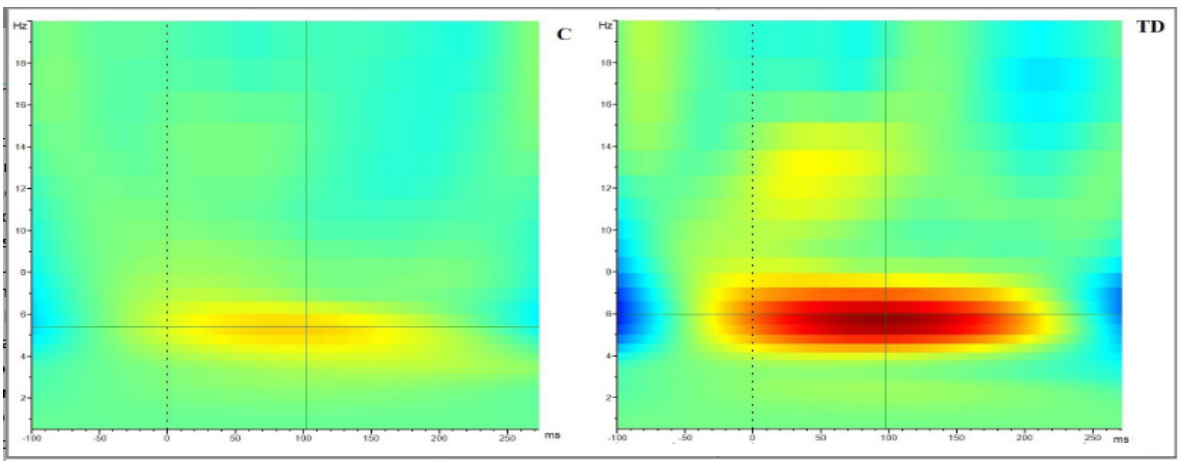


**Figure 5.** Spectral changes in theta band activity during the second stimuli (S2) of PRs for all groups. Time-frequency plots illustrate the spectral changes upon stimulus onset.

## DISCUSSION

The present study was designed to investigate the effects of postnatal thiamine deficiency on auditory neuronal processing estimated by the LDAEP and sensory gating. In order to investigate neurophysiological correlates of information processing, evoked and event-related potentials have been widely used in the previous studies (21,22). So, two different paradigm were used to analyze auditory processing at postnatal TD condition. LDAEP represents an increase in the neuronal response in the auditory cortex with an increase in sound intensity. This means a variation in amplitude which reflects the increament the amount of reactivity of the neuronal networks. This increament ratio is not linear and attenuates to protect the brain from overstimulation (23,24). Although glutamate/GABA transmission has a role in generating the AEPs (25,26), LDAEP is most likely a consequence of different levels in the serotonergic transmission (16,27,28). Previos studies showed that a strong LDAEP reflects a low serotonergic activity and a weak LDAEP reflects a high serotonergic activity (28,29). Thiamine deficient group showed stronger LDAEP than the control group. This result indicates that postnatal TD causes an alteration in serotonergic neurotransmission at adulthood and decreases serotonergic activitiy at the auditory cortex. This is in accordance with the previous studies showing that TD leads selective serotonergic fiber loss, serotonin uptake decreament and certain behavioral alterations related with serotonergic system (6, 1,12). In the spectral analyses, decreased gamma responses were observed in the TD group versus the control group for the loudest stimuli (S4). This finding indicates an alteration at network dynamics. It is known that TD causes regionally selective changes at multiple neurotransmitter functions (6). In addition to serotonergic deficit, glutamatergic/GABAerjic deficit might be involved in postnatal TD related pathophysiological changes. In accordance with this notion, decreament of cerebral glutamate, GABA levels and glial abnormalities have been reported as a consequences of TD (30,31). This may inturn influence gamma oscillatory dynamics at loadness dependent responses due to the role of GABAergic and glutamatergic network at gamma generation (32,33). In parallel to amplitude changes, theta/alpha responses were higher in the deficieny condition for S4 stimulus. Auditory stimuli typically elicits theta/alpha compound responses mainly related to primary sensory processing (34). Increment of these compound responses reflects the TD related disinhibition of over-stimuluation. Theta/alpha response has the same increment trend as the late N1/P2 component in the TD group. It is reasonable to suggest that impaired serotonergic transmission may partly contribute to the theta/alpha increament at TD group. However we can not ruled out the possible effects of other neurotransmitter systems.

In TD condition, examining the disturbances of mid-latency auditory ERP components are interesting because they reflect mostly preattentive aspects of the sensory information processing. As LDAEP selectively reflects serotonergic neurotransmission at auditory system, both glutamat and GABA transmission has regulatory role at auditory sensory gating (18-20). Supression of P1 and N1 responses showed a different pattern in the TD group. The reduction of N1 response after second stimuli was more prominent in controls than in TD group. In paralel, both supression and difference values for N1 response were significantly attenuated in the TD group. However, no significant difference was observed between groups for P1 amplitude, supression and difference values. In parallel, theta response after second stimuli increased in the TD group versus the control group. This finding indicates a sensory gating deficit at the later component in TD group. Our results on theta response correspond to our amplitude results as the N1 amplitude showed the same pattern with a reduced decreament after S2 in the TD group versus the control group. This pattern of N1 and theta frequency changes can be interpreted

as correlate of a deficient habituation in auditory information processing especially in the later components. In addition, the gamma ERSP values for both stimulus did not differ between group similar to the P1 response. While TD cause a disturbance at late component of AEP, sensory gating mechanism was intact at early P1 component. Although gamma values and early P1 response was not affected, N1 difference in the TD group can be partly related with changes in GABAerjik transmission. It should be noted that reduction of excitatory physiology might also contribute this result in addition to GABAergic dysfunction because of the known glutamatergic alterations caused by TD (31,35). These results suggest that gamma frequency do not contribute to the deficiency in auditory habituation and early auditory information processing is intact in the TD group. Postnatal TD affects selectively the neural network related with the late components of auditory processing. Although observed changes at sensory gating responses are partly related to glutamate/GABA system, other modulatory neurotransmitter systems can be involved. In addition to neurotransmitter systems, TD leads to both metabolic consequences such as disturbance of energy metabolism, glial dysfuction, oxidative damage, cellular deficit and structural consequences such as membrane damage, altered synaptic transmission and synapse formation in the devoloping brain (4,6,7). Structural alterations constitute the main effects of postnatal TD accompanied with biochemical modifications result in neuronal cell loss. Previous studies revealed that thiamine interferes with the membrane structure and function, acts against agents-induced cytotoxicity by binding on biological membranes (4). Taken together, all these factor may influence the development of central auditory network with long-term implications through the adulthood period.

## ETHICS COMITTEE APPROVAL

* This study was approved by the Akdeniz University Animal Experiment Local Ethics Committee (Date:29.08.2016 and No: 71).

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## REFERENCES

1. World Health Organization. Thiamine deficiency and its prevention and control in major emergencies. 1999; WHO/NHD/99.13.

2. McGready R, Simpson JA, Cho T, Dubowitz L, Changbumrung S, Böhm V, et al. Postpartum thiamine deficiency in a Karen displaced population. Am J Clin Nutr, 2001; 74: 808-13.

3. Butterworth RF. Maternal thiamine deficiency: still a problem in some world communities, Am J Clin Nutr, 2001; 74: 712-3.

4. Ba A. Metabolic and structural ole of thiamine in nervous tissues, Cell Mol Neurobiol, 2008; 28: 923-31.

5. Hazell AS., Butterworth RF. Update of cell damage mechanisms in thiamine deficiency: Focus on oxidative stress, excitotoxicity and inflammation, Alcohol Alcoholism, 2009; 44: 141-7.

6. Butterworth RF. Neurotransmitter function in thiamine-deficiency encephalopathy. Neurochem Int, 1982; 4: 449-64.

7. Gibson GE., Zhang H. Interactions of oxidative stress with thiamine homeostasis promote neurodegeneration. Neurochem Int, 2002; 40: 493-504.

8. Haas RH. Thiamin and the brain. Annu Rev Nutr, 1988; 8: 483-515.

9. Page MG, Ankoma-Sey V, Coulson WF, Bender DA. Brain glutamate and gamma-aminobutyrate (GABA) metabolism in thiamin-deficient rats. Br J Nutr, 1989; 62: 245-53.

10. Dodd PR, Thomas GJ, McCloskey A, Crane DI, Smith ID. The neurochemical pathology of thiamine deficiency: GABAA and glutamateNMDA receptor binding sites in a goat model. Metab Brain Dis, 1996; 11 :39-54.

11. Murata A, Nakagawasai O, Yamadera F, Oba A, Wakui K, Arai Y, et al. Dysfunction of serotonergic systems in thiamine-deficient diet fed mice: effects of SSRI on abnormality induced by thiamine deficiency. Jpn J Psychopharmacol, 2004; 24: 93-9.

12. Chan-Palay V, Plaitakis A, Nicklas W, Berl S. Autoradiographic demonstration of loss of labeled indoleamine axons of the cerebellum in chronic diet-induced thiamine deficiency. Brain Res, 1977; 138: 380-4.

13. Basar E, Guntekin B. Darwin's evolution theory, brain oscillations, and complex brain function in a new "Cartesian view". Int J Psychophysiol, 2009; 71 :2-8.

14. Chan YW, Mcleod JG, Tuck RR, Feary PA. Brain-stem auditory evoked-responses in chronic-alcoholics. J Neurol Neurosur Ps, 1985; 48: 1107-12.

15. Attias J, Raveh E, Aizer-Dannon A, Bloch-Mimouni A, Fattal-Valevski A. Auditory system dysfunction due to infantile thiamine deficiency: Long-term auditory sequelae. Audiol Neuro-Otol, 2012; 17: 309-20.

16. Wutzler A, Winter C, Kitzrow W, Uhl I, Wolf RJ, Heinz A, et al. Loudness Dependence of Auditory Evoked Potentials as Indicator of Central Serotonergic Neurotransmission: Simultaneous Electrophysiological Recordings and In Vivo Microdialysis in the Rat Primary Auditory Cortex. Neuropsychopharmacol, 2008; 33: 3176-81.

17. Wyss C, Hitz K, Hengartner MP, Theodoridou A, Obermann C, Uhl I, et al. The loudness dependence of auditory evoked potentials (LDAEP) as an indicator of serotonergic dysfunction in patients with predominant schizophrenic negative symptoms. PloS one, 2013; 12: 8-7.

18. Swerdlow NR, Geyer MA, Shoemaker JM, Light GA, Braff DL, Stevens KE, et al. Convergence and divergence in the neurochemical regulation of prepulse inhibition of startle and N40 suppression in rats. Neuropsychopharmacol, 2006; 31: 506-15.

19. Ma JY, Leung LS. GABA(B) receptor blockade in the hippocampus affects sensory and sensorimotor gating in Long-Evans rats. Psychopharmacology, 2011; 217: 167-76.

20. Rowland LM, Edden RAE, Kontson K, Zhu H, Barker PB, Hong LE. GABA predicts inhibition of frequency-specific oscillations in schizophrenia. J Neuropsych Clin N, 2013; 25: 83-7.

21. Basar E. A review of alpha activity in integrative brain function: Fundamental physiology, sensory coding, cognition and pathology. Int J Psychophysiol, 2012; 86: 1-24.

22. Basar E, Duzgun A. The brain as a working syncytium and memory as a continuum in a hyper timespace: Oscillations lead to a new model. Int J Psychophysiol, 2016; 103: 199-214.

23. Buchsbaum M. Individual differences in stimulus intensity response. Psychophysiology, 1971; 8: 600-11.

24. Juckel G, Csepe V, Molnar M, Hegerl U, Karmos G. Intensity dependence of auditory evoked potentials in behaving cats. Electroencephalogr Clin Neurophysiol, 1996; 100: 527-37.

25. Javitt DC, Schroeder CE, Steinschneider M, Arezzo JC, Ritter W, Vaughan HG. Cognitive event-related potentials in human and non-human primates: Implications for the PCP/NMDA model of schizophrenia. Electroencephalogr Clin Neurophysiol, 1995; 44: 161-75.

26. Zheng J, Wu X, Li L. Metabotropic glutamate receptors subtype 5 are necessary for the enhancement of auditory evoked potentials in the lateral nucleus of the amygdala by tetanic stimulation of the auditory thalamus. Neuroscience, 2008; 152: 254-64.

27. Juckel G., Molnar M., Hegerl U., Csepe V., Karmos G. Auditory-evoked potentials as indicator of brain serotonergic activity-First evidence in behaving cats, Biol Psychiatry, 1997; 41: 1181-95.

28. Juckel G, Hegerl U, Molnar M, Csepe V, Karmos G. Auditory evoked potentials reflect serotonergic neuronal activity - A study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacol, 1999; 21: 710-6.

29. Hegerl U, Juckel G. Intensity dependence of auditory evoked-potentials as an indicator of central serotonergic neurotransmission- a new hypothesis. Biol Psychiatry, 1993; 33: 173-87.

30. Robertson DM, Wasan SM, Skinner DB. Ultrastructural features of early brain stem lesions of thiamine-deficient rats, Am J Pathol, 1968; 52 :1081-97.

31. Le O, Heroux M, Butterworth RF. Pyrithiamine-induced thiamine-deficiency results in decreased Ca2+-dependent release of hlutamate from rat hippocampal slices. Metab Brain Dis, 1991; 6: 125-32.

32. Brunel N, Wang XJ. What determines the frequency of fast network oscillations with irregular neural discharges? I. Synaptic dynamics and excitation-inhibition balance, J Neurophysiol, 2003; 90: 415-30.

33. Wang XJ. Neurophysiological and computational principles of cortical rhythms in cognition. Physiol Rev, 2010; 90: 1195-268.

34. Schurmann M, Basar E. Topography of alpha-oscillatory and theta-oscillatory responses upon auditory and visual-stimuli in Humans. Biol Cybern, 1994; 72: 161-74.

35. Carvalho FM, Pereira SRC, Pires RGW, Ferraz VP, Romano-Silva MA, Oliveira-Silva IF, et al. Thiamine deficiency decreases glutamate uptake in the prefrontal cortex and impairs spatial memory performance in a water maze test. Pharmacol Biochem Be, 2006; 83: 481-9.