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ORIGINAL ARTICLE

Effect of perinatal and postnatal thiamine deficiency on auditory pathway of the Wistar-Albino rats

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HIGHLIGHTS

- Thiamine is very important for both pregnancy and the continuation of pregnancy.
- Even though ABR is normal, degeneration occurs in IHC even if the thiamine deficiency is compensated with thiamine supplementation in the postnatal period.
- If the thiamine deficiency continues in the perinatal period also in the postnatal period, significant deterioration in ABR and significant degeneration in IHC occur.
- If there is no deficiency in the perinatal period, but thiamine deficiency occurs in the postnatal period, there is no degeneration in the hair cells.
- However, more studies are needed to support this issue

KEYWORDS
Thiamine deficiency;
DPOAE;
ABR;
Auditory pathway

Abstract
Objective: In this study, we created an animal model to demonstrate the effects of thiamine on the hearing pathways of new-borns during pregnancy and lactation by inducing a dietary thiamine deficiency in the mother.
Methods: The study included 16 female Wistar albino rats. The animals were separated into four groups and provided the appropriate amounts of dietary thiamine according to their groups during pre-pregnancy, pregnancy, and lactation periods. Three pups from each mother were included in the study, and 12 pups were selected from each group. On the fortieth day after birth, the auditory pathways of 48 pups in the 4 groups were examined electro physiologically and ultra-structurally.

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Results: In Group N-N, morphology of hair cells stereocilia degeneration was not obtained in all turns of cochlea. In Group N-T, Inner Hair Cells (IHCs) and Outher Hair Cells (OHCs) stereocilia didn't show degeneration in all turns of cochlea but had rupture inrows of HCs stereocilia. In group T-N IHCs stereocilia less degeneration was observed in all turns of cochlea. OHC stereocilia partial loss was observed only in basal turn of cochlea. In Group T-T IHCs stereocilia was observed less degeneration and rupture in all turns of cochlea.
Conclusion: Thiamine is vital for the development of cochlear hair cells during both prenatal and postnatal periods. Even partial deficiency of thiamine causes significant degeneration to the auditory pathway.
Level of evidence: The level of evidence of this article is 5. This article is an experimental animal and laboratory study.

Introduction

Thiamine (vitamin B1) is a water-soluble essential vitamin B that is not stored in the body.[1,2] Thiamine Pyrophosphate (TPP), the active form of thiamine, is a cofactor of pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and the transketolase enzyme involved in carbohydrate metabolism.[3,4] The energy needs of the Central Nervous System (CNS) are met solely through carbohydrate metabolism. Hence, the CNS is most affected by thiamine deficiency[5] because the thiamine level in the body is closely related to carbohydrate intake.[1]

Thiamine is plentifully available in consumed foods; however, the synthesis of thiamine by intestinal microorganisms is negligible, and thiamine storage in the body is minimal. Hence, symptoms of dietary deprivation of thiamine (e.g., beriberi) manifest rapidly[4] – subjective symptoms are visible as early as 2–3 weeks in adults.[2,6]

Thiamine deficiency remains an important health-care issue world-wide among all populations.[7] Thiamine deficiency commonly occurs due to the intake of inadequate diet, consumption of foods containing thiaminases or antithiamine compounds (such as betel nut, fermented tea leaves, and fish paste), prolonged cooking of foods, and clinical disorders such as chronic alcoholism, HIV-AIDS, and gastrointestinal disorders.[7,8] Specifically, during pregnancy and lactation, thiamine replacement may be required if the need for thiamine increases.

Studies have shown that maternal thiamine deficiency is actually transmitted to the foetus.[8,9] Indeed, maternal thiamine deficiency provokes cell death and atrophy in the foetal brain, which that persists in adulthood. The developing brain is particularly especially vulnerable to thiamine deficiency.[6,10] Because If thiamine deficiency occurring during this period early stage of development, the reduction of thiamine-dependent enzymes activities causes impairment in the myelinisation of neurons.[8]

The effects of thiamine deficiency on the auditory pathway are not fully understood. Temporary or permanent, unilateral or bilateral, stable or progressive hearing loss can be observed due to thiamine deficiency.[2] Recently, thiamine deficiency has been linked with auditory neuropathy;[1,2] however, few studies have explored this issue.

In this study, we created an animal model to explore factors influencing the hearing pathways of new-borns during pregnancy and lactation by inducing a maternal dietary thiamine deficiency.

Methods

Animals and procedure

Approval for the study was granted by the Experimental Animal Research Local Ethics Committee of Akdeniz University. The study was conducted in Akdeniz University Experimental Animals Laboratory in accordance with the principles of the Helsinki Declaration.

The study included 16 female and 4 male Wistar albino rats aged 6 months, and each weighing 250–300 g. The rats were housed in steel cages with a 12-h light/dark cycle at a mean temperature of 25 °C. The thiamine-deficient diet used in this study was purchased from Test-Diet®.

The animals were separated into 4 groups with 4 females in each group:

Group N-N: The animals in this group received a normal diet before birth and during lactation.

Group N-T: The animals in this group received a normal diet before birth and a thiamine-deficient diet during lactation.

Group T-N: The animals in this group received a thiamine-deficient diet before birth and a normal diet during lactation.

Group T-T: The animals in this group received a thiamine-deficient diet both before birth and during lactation.

In each group, one male rat was placed in a cage with two female rats for three days for mating. After pregnancy was confirmed using smear tests, the male rats were removed from the cages, and each female rat was placed in a separate cage and fed the assigned diet.

After birth, the date of delivery and litter size were recorded. Each female gave birth to an average of 6–8 offspring (range, 4–13), and the respective prenatal diets were continued postpartum. On day 40, three pups were randomly

selected from each litter. A total of 12 pups were selected from each group for further studies.

Initially, original plan it was decided to use thiamine-free diet rather than thiamine-deficient diet was provided to the rats in all the research groups. However, this diet prevented conception in the T-N and T-T group animals except for the normal diet group (2 mg/kg thiamine), the rats in the other 3 groups could not complete the breastfeeding or lactation period with a thiamine free diet. None of the Group T-N and Group T-T mothers that were fed with thiamine-free diet during pregnancy could become pregnant. Therefore, the rats were switched to a low-thiamine diet. Firstly and 0.2 mg/kg, then 0.4 mg/kg thiamine was added into the diets. This was later increased to 0.4 mg/kg. However, this diet failed to support pregnancy conception in all but failed. Even if pregnancy occurred in two mother rats' females, it could not be completed, and which ended in miscarriage occurred. Therefore Hence 0.5 mg/kg thiamine was added to the pre-natal diets. Postnatally, except for the rats in the normal diet group (2 mg/kg thiamine), the rats in the other 3 groups could not complete the breastfeeding or lactation period with a thiamine free diet. Since The mothers' females fed with that resumed the thiamine- free diet again after birth in group N-T cannibalized all their offspring's. Hence, 0.5 mg/kg thiamine was added to the diets the mothers in for the groups N-T and T-T during the lactation period. As a result, it was decided to finally, provide a thiamine-deficient diet (0.5 mg/kg thiamine) was provided to the animals in the T-T, N-T, and T-N groups, which contained 0.5 mg/kg thiamine.

The initial weight of the rats was determined at the start of the study. Throughout pregnancy, rats were fed according to the diet stipulated for the group, and the same amount of thiamine was administered during the entire duration of the study. All rats gave birth at a mean gestation period of 26 days (range, 22–30 days). During the postnatal lactation period, nutrition was provided according to the protocol for each group. Forty days after birth, the mothers were separated from their offspring, which were included in the study.

Anesthesia and electrophysiological evaluation

All rattling's in all research groups were weighed. Intraperitoneal anesthesia was applied of 50 mg/kg ketamine and 6 mg/kg xylazine. The anesthetic effect was checked by examining the absence of tail, foot and ear reflexes.[11] Following anesthesia, all the animals passed otoscopic examination. If debris was determined in the outer ear pathway during the examination, it was cleaned. After anesthesia and examination of the rats, they were transferred to a quiet room. DPOAE and ABR were applied using an EchoLab OAE device Labat software. Each rat was positioned horizontally on the floor and measurements were taken from the right ear.

In the evaluation of the DPOAE results, f2 values were selected as 3000, 4000, 6000, 8000 and 10,000 Hz and the signal/noise ratios at these frequencies were taken for evaluation. Each measurement lasted mean 1 min.

During the ABR recording, the body temperature of the rats was maintained at 37 °C. A stainless steel needle electrode was used for the recording. The reference electrodes were placed as active electrodes on the vertex of the rat, and on the mastoid of the right ear and the earth electrode on the tail. After placement of the electrodes, it was checked that impedance was <5 Kohm.

A Medelec Insert Earphone Dual 54455/A probe was used for the stimulus. The probe was placed in the outer ear, then potentials filtered in the range of 300–3000 Hz band were created with acoustic stimuli at 8–16 kHz and varying severity and mean 500 responses were obtained and recorded. At 60 dB, 1–3 Interpeak Latency Duration (IPL1-3) and 1–5 Interpeak Latency Duration (IPL1-5) were recorded and evaluated. We have observed that the location of the 3rd wave was not clear in 2 offspring in the N-N and T-T groups, and in 1 offspring in the T-N group when we re-evaluated the ABR tests for statistical analysis. As the ABR values of these 5 rattling's might corrupt the statistical analysis, these rattling's were excluded from the analysis.

Ultrastructural evaluation: electron microscopy

After the completion of electrophysiological measurements, rats were sacrificed to remove the cochleae for ultrastructural examination. The surface topography of the organ of Corti was examined and photographed with a Scanning Electron Microscope (SEM). Relevant changes (site of degeneration) were evaluated 1.2 as normal IHCs and OHCs with intact V- or W-shaped stereocilia bundles and abnormal IHCs and OHCs with damaged stereocilia or loss of the normal V- or W-shaped stereocilia while total absence of stereocilia and rupture of the cuticular plate were considered as absent IHC and OHCs.[12,13]

Statistical analysis

The recorded DPOAE and ABR findings were analyzed statistically using IBM SPSS Statistics for Windows v 23.0 software (IBM Corp, Armonk, NY, USA). The normality assumptions were controlled by the Shapiro-Wilk test. Kruskal Wallis test was used for comparison of non-parametric variables between groups and Bonferroni-Dunn test was used as a post-hoc test for significant cases while One-Way ANOVA with post-hoc Tukey HSD test was used for parametric variables. The results were expressed as mean ± SD and median (minimum–maximum) values. A value of $p < 0.05$ was accepted as statistically significant.

Results

The results of the comparisons of the Distortion-Product Otoacoustic Emissions (DPOAE) values between the groups are shown in Table 1. The latency periods of the 8 kHz Auditory Brainstem Response (ABR) waves are shown in Table 2.

No statistically significant difference was found between the four groups with respect to the IPL1-3 durations in the 8 kHz ABR values ($p = 0.202$). The IPL1-5 durations were determined to be significantly longer in the N-T, T-N, and T-T groups than in the N-N group ($p = 0.001$) (Table 3). The latency periods in the 16 kHz ABR values are shown in Table 4. The IPL1-3 durations were determined to be sig-

Table 1 DPOAE Data. Data are presented as median (min–max).

	N-N (n = 12)	N-T (n = 12)	T-N (n = 11)	T-T (n = 12)	p
3000 Hz	−1.5 (−8 to 5)	−1 (−10 to 15)	−4 (−7 to 7)	−2.5 (−14 to 7)	0.775
4000 Hz	0 (−7 to 6)	3.5 (−1 to 20)	1 (−8 to 8)	−0.5 (−6 to 22)	0.076
6000 Hz	1 (−6 to 16)	7 (−10 to 16)	3 (−6 to 62)	5.5 (−1 to 13)	0.332
8000 Hz	4 (−9 to 27)	12.5 (−2 to 33)	4 (−6 to 18)	6.5 (−10 to 19)	0.059
10,000 Hz	−2.5 (−17 to 34)[a]	4 (−5 to 26)[a,b]	3 (−3 to 8)[a]	16.5 (−2 to 37)[b]	**0.013**

Kruskal Wallis test with Bonferroni-Dunn post-hoc test. Significant differences were presented with different lowercases).

Table 2 Comparisons of the latency of ABR waves at 8 kHz. Data are presented as mean ±SD and median (min–max).

	N-N (n = 10)	N-T (n = 12)	T-N (n = 11)	T-T (n = 10)	p
Wave 1	1.64 ± 0.29[a]	2.07 ± 0.13[b]	2.25 ± 0.12[b]	2.8 ± 0.34[c]	<0.001
Wave 2	2.47 (2.2–2.88)[a]	2.95 (2.74–3.4)[b]	3.14 (2.94–3.42)[b,c]	3.82 (2.85–4.21)[c]	<0.001
Wave 3	3.46 ± 0.27[a]	3.69 ± 0.18[a,b]	3.91 ± 0.17[b]	4.45 ± 0.69[c]	<0.001
Wave 4	4.37 ± 0.28[a]	4.74 ± 0.3[a,b]	5.13 ± 0.33[b,c]	5.46 ± 0.61[c]	<0.001
Wave 5	5.25 (5.02–5.9)[a]	6.55 (5.38–6.8)[b]	6.86 (6.14–7.22)[b]	6.97 (5.22–7.69)[c]	<0.001

ANOVA with Tukey HSD post-hoc test, Kruskal Wallis test with Bonferroni-Dunn post-hoc test. Significant differences were presented with different lowercases.

Table 3 Comparisons of the IPL 1–3 and IPL 1–5 values at 8 kHz. Data are presented as mean ± SD and median (min–max).

	N-N (n = 10)	N-T (n = 12)	T-N (n = 11)	T-T (n = 10)	*p*
IPL1-3	1.62 ± 0.26	1.82 ± 0.09	1.97 ± 0.11	2,17 ± 0.38	0.202
IPL1-5	3.82 (3.22–4.06)[a,c]	4.46 (3.42–4.72)[b,c]	4.5 (3.92–5.06)[b]	4.55 (2.97–4.84)[b]	**0.001**

ANOVA with Tukey HSD post-hoc test, Kruskal Wallis test with Bonferroni-Dunn post-hoc test. Significant differences were presented with different lowercases.

Table 4 Comparisons of the latency of ABR waves at 16 Hz. Data are presented as mean ± SD and median (min–max).

	N-N (n = 10)	N-T (n = 12)	T-N (n = 11)	T-T (n = 10)	p
Wave 1	1.93 ± 0.44[a]	2.34 ± 0.21[b]	2.55 ± 0.2[b]	3.18 ± 0.31[c]	**<0.001**
Wave 2	2.73 ± 0.39[a]	3.36 ± 0.2[b]	3.69 ± 0.33[b]	4.35 ± 0.48[c]	**<0.001**
Wave 3	3.7 (3.04–4.02)[a]	3.89 (3.4–4.86)[a,b]	4.2 (3.78–5.29)[b,c]	5.3 (4.67–5.98)[c]	**<0.001**
Wave 4	4.55 (4.24–4.96)[a]	5.16 (4.46–5.46)[a,b]	5.54 (5.12–6.12)[b,c]	6.18 (5.1–6.67)[c]	**<0.001**
Wave 5	5.43 (5.1–6.1)[a]	6.29 (5.66–7.26)[a,b]	6.8 (6.1–7.74)[b,c]	7.35 (6.22–7.67)[c]	**<0.001**

ANOVA with Tukey HSD post-hoc test, Kruskal Wallis test with Bonferroni-Dunn post-hoc test. Significant differences were presented with different lowercases.

nificantly longer in the T-T group than in the N-T group ($p < 0.001$). In the N-N group, the IPL1-5 durations were significantly shorter than those of the T-N and T-T groups ($p = 0.009$). In our study, we evaluated stereocilia degeneration in the surface anatomy of the organ of Corti for loss of Hair Cells (HCs) in the experimental and control groups (Figs. 1–4).

Discussion

That thiamine requirements increase during pregnancy and breastfeeding is well known.[1] The increased thiamine requirements in the third trimester of pregnancy are generally thought to be the result of sequestration of vitamins by the foetus and placenta. During this period, foods containing high concentrations of thiaminases or anti-thiamine compounds, such as betel nut, fermented tea leaves, or fish paste, may further exacerbate thiamine deficiency.[8,9] Even when the mother is on a thiamine-deficient diet, the mother's thiamine reserve is reported to pass into the umbilical cord blood during pregnancy and later into breast milk after birth.[9] However, the effects on the cochlea when the mother's thiamine reserves are exhausted is unknown.

Other studies on thiamine deficiency have defined the effect it has on the CNS as Wernicke encephalopathy.[10] In human beings, both adults and infants with thiamine deficiency have revealed a clear pattern of selective damage to subcortical areas of the brain, specifically the thalamus and mammillary bodies, midbrain inferior colliculus, and brain stem structures, including the vestibular nuclei and

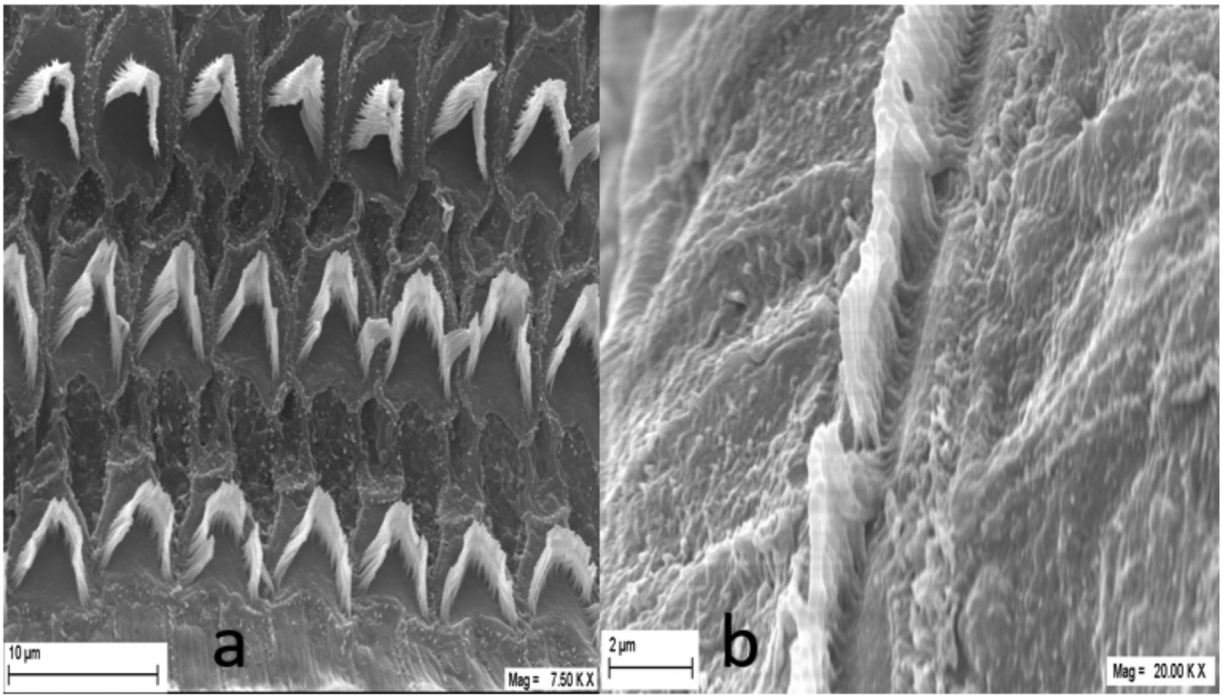

Figure 1 The surface of the organ of Corti in the group N-N: (a) Intact rows of OHCs stereocilia in the basal turn; (b) Intact rows of IHCs stereocilia in the basal turn.

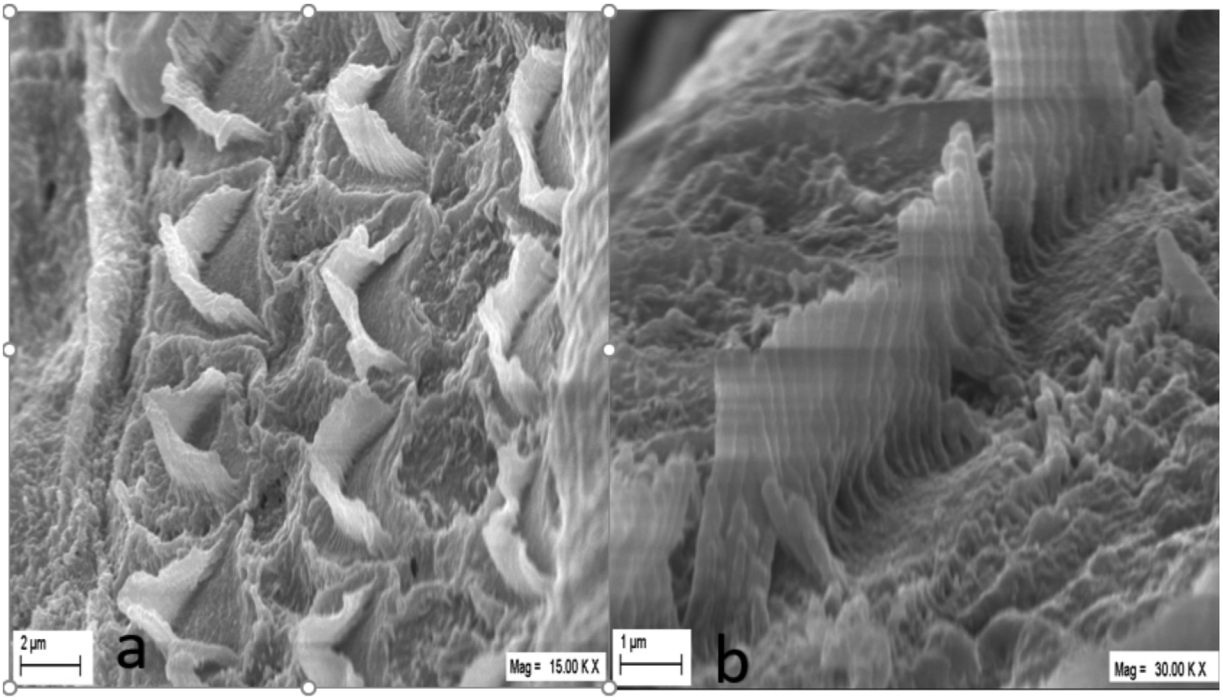

Figure 2 SEM micrograph in the group N-T: IHCs and OHCs had rupture in the rows of (a) OHCs stereocilia, (b) IHCs sterocilia.

the olivary complex.[3,10] However, the effects of thiamine deficiency on the auditory pathway are not yet fully understood.

The most conclusive evidence of the correlation between thiamine and hearing loss was demonstrated in 2003 in a study in Israel that involved children bottle-fed an infant formula completely deficient in thiamine due to manufacturing defects.[2] Although 600–1000 infants all over the country were fed this defective formula, only 20 infants developed Wernicke encephalopathy, and only 11 infants were diagnosed with hearing loss during long-term follow-up. This hearing loss was in the form of sensory neural hearing

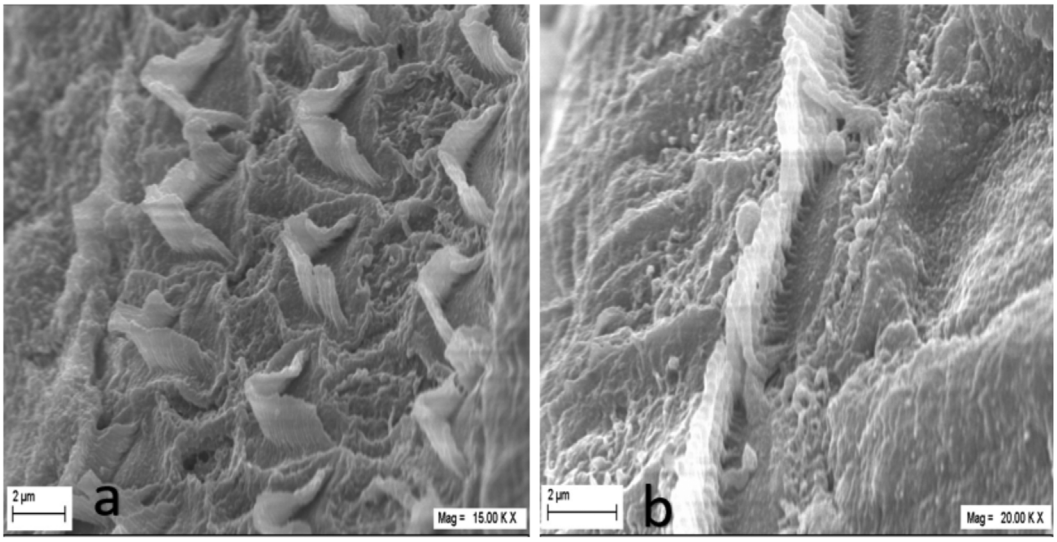

Figure 3 SEM micrograph in the group T-N: (a) Partial loss of OHCs stereocilia; (b) Mild degeneration was observed in IHCs stereocilia.

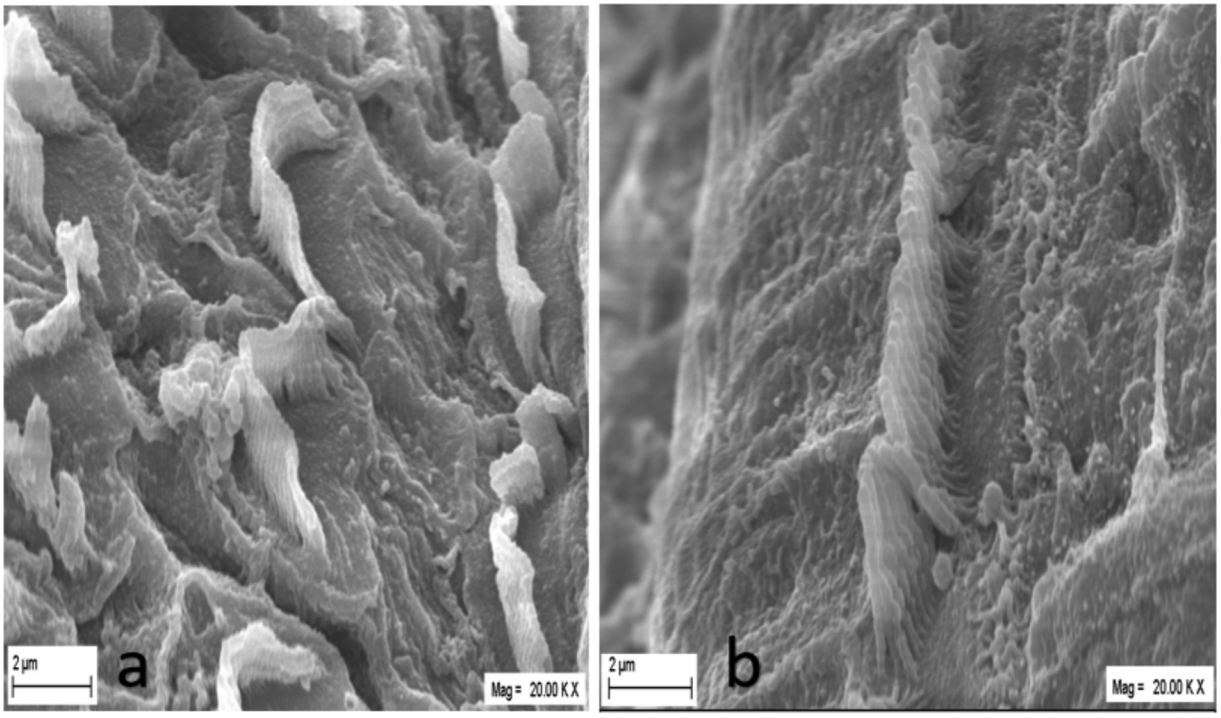

Figure 4 SEM micrograph in the group T-T: (a) Partial loss in OHCs stereocilia; (b) Mild degeneration and rupture in IHCs stereocilia.

loss or auditory neuropathy spectrum disorder. This study strongly suggests a connection between thiamine deficiency and auditory neuropathy. Even though cochlear hearing loss improved with thiamine replacement therapy, thiamine replacement after the development of auditory neuropathy did not improve the condition; in fact, it continued to worsen in some babies. What is more interestingly, in this study, is that all infants with impaired language development and decreased hearing loss due to a being diagnosed is of with auditory neuropathy or cochlear hearing loss have impaired language development and decreased hearing loss showed improvements in the first year due to thiamine replacement improves in the first one year. This suggests that thiamine has a pronounced effect on hearing pathways, especially in the perinatal and early postnatal periods. Again, in the related sub-group of the study, all children fed with this formula were followed-up; and delayed development of expression and recipient expressive and receptive language was observed in 20 patients who were considered asymptomatic because they had no due to absence of neu-

rological symptoms.[5] These results highlight the importance vitality of thiamine as an essential nutrient component for normal speech and language development in the first year of life.

However, the effects of thiamine deficiency on HCs of the inner ear remain unknown. To clarify this issue, studies have been carried out on Thiamine-Responsible Megaloblastic Anaemia (TRMA), which results due to a mutation in the SLC19A2 gene that encodes a thiamine transporter. TRMA progresses to diabetes mellitus, cochlear hearing loss, and thiamine-sensitive megaloblastic anemia.[9] Unlike dietary thiamine deficiency, this hearing loss is progressive and does not respond to replacement therapy. Liberman et al.,[4] in their study in adult mice with a deletion mutation on SLC19A2, showed that no significant deterioration in ABR thresholds occurred due to thiamine deficiency and that all mice had normal or near-normal outer hair cell function, whereas a significant loss was observed in IHCs. They also showed that the high-affinity thiamine transporter was better expressed in the Inner Hair Cells (IHCs) than in the Outer Hair Cells (OHCs) in the cochlea.[4] Therefore, selective IHC loss and hearing loss occurs in TRMA. Although this selective loss of IHCs suggests that IHCs are more susceptible to thiamine deficiency, there is no conclusive evidence of selective IHC loss.

Thiamine deficiency causes neural cell energy deficiency that can be attributed to either mitochondrial dysfunction or glutamate-mediated neurotoxicity or both.[2] Prolonged stimulation of glutamate receptors leads to generation of Reactive Oxygen Species (ROS). ROS are responsible for direct cellular damage to lipids, proteins, and DNA, triggering apoptosis or necrosis.[13] Although OHC is the first to be affected by ROS, IHC could be vulnerable to further damage in addition to that incurred due to thiamine deficiency. However, damage due to ROS was not limited to the IHCs alone but extended to spiral ganglion cell loss and mild degeneration of central neurons.[2]

In our study, we obtained clear ABR waves in all groups. However, it should be noted that we were unable to provide a 100% thiamine-free diet. The reasons for this are non-occurrence of pregnancy, loss of pregnancy, or rejection and termination of the offspring by the mother after birth. Therefore, we were able to induce only partial thiamine deprivation. However, we found that even partial thiamine deficiency caused prolongation of all ABR waves. Although a prolongation in IPL1-3 at 8 kHz was observed, this difference was not statistically significant. IPL1-5 showed a statistically significant prolongation in all three groups compared with that of the normal group. In contrast, at 16 kHz, the prolongation in IPL1-3 was statistically significant, whereas the prolongation in IPL1-3 was not significant. This indicates that thiamine deficiency rather than myelinization has a greater adverse effect on HC in the prenatal and postnatal periods, and IHCs are affected earlier at high frequencies.

Although we presumed in our study that OHCs were unaffected by thiamine deficiency, we found impairment in DPOAE only at 10,000 Hz. In our opinion, the degree of susceptibility of HCs depends on the duration and extent of thiamine withdrawal. Therefore, despite only the IHCs being initially affected due to thiamine deficiency, prolonging the duration of the deficiency (from pregnancy until breastfeeding) cause degeneration to the OHCs similar to that detected in the IHCs, especially at high frequencies.

In addition, no degeneration was observed in IHCs and OHCs in the N-T group, whereas partial degeneration was observed in IHCs in the T-N group, suggesting that the inner ear is more sensitive to thiamine deficiency during the prenatal period when cell proliferation is rapid, rather than in the postnatal period. Prenatal thiamine deficiency interferes with the stages of cellular proliferation and migration. Perinatal thiamine deficiency interferes with the period of cellular differentiation. Postnatal thiamine deficiency interferes with the stages of synapse formation, axonal growth, myelinogenesis, and the onset of physiological functions. A critical period called ''the development window'' has been identified during the stages of cell proliferation and differentiation. During this period the effects of vitamin deficiencies become pronounced; however, supplementing the deficient vitamins during this period alleviates the symptoms, and failure to do so makes the symptoms permanent. Whereas the development window is 3–4 weeks in the case of biotin deficiency, it is 1–2 weeks in the case of thiamine deficiency.[11] This explains the reason for increased degeneration in the T-T group than in the T-N group; the normal thiamine intake during lactation in the T-N group must have halted the progression of the degeneration induced by dietary thiamine deficiency during pregnancy without requiring thiamine replacement.

Conclusion

The effects of thiamine deficiency on the auditory pathway have not been fully elucidated. In this study, four main results were obtained. Thiamine is especially important for both pregnancy and the continuation of pregnancy. Although ABR is normal, degeneration occurs in IHCs even if thiamine deficiency is compensated for by thiamine supplementation in the postnatal period. If thiamine deficiency continues from the prenatal to the postnatal period, significant deterioration in ABR and degeneration in IHC occur. In the case of absence of thiamine deficiency in the prenatal period but occurrence of deficiency in the postnatal period, no degeneration was observed in the HCs. However, further studies are required to address this issue.

Funding

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Ethical approval

Approval for the study was granted by the Experimental Animal Research Local Ethics Committee of Akdeniz University. The study was conducted in Akdeniz University Experimental Animals Laboratory in accordance with the principles of the Helsinki Declaration.

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

Conflicts of interest

The authors declare no conflicts of interest.

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