



RESEARCH

THE PROTECTIVE ROLE OF TRIMETAZIDINE ON OXIDATIVE SYSTEM AND TEOAEs IN RABBITS EXPOSED TO NOISE*

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SUMMARY

Objective: Trimetazidine (TMZ) is an antianginal drug, which has potent antioxidant activity on various tissue. The aims of this study were to uncover the effects of noise exposure on oxidative status and hearing thresholds and to investigate possible protective role of drug TMZ on oxidative system and hearing thresholds. **Materials and Methods:** Two groups of rabbits were used in this study and each group had eight rabbits. Eight rabbits in the first group (control group) were not given any treatment whereas TMZ (20 mg/kg p.o, tid, 7 days) was given to the other eight rabbits in the second group. TEOAE's were recorded in all animals before and after noise exposure. As oxidative stress parameters plasma MDA levels as well erythrocyte GSH, GP and GR enzyme activities were measured in all rabbits. All the rabbits were exposed to noise (100 dB SPL, 1000 Hz, 1 h) and then TEOAEs were recorded again. **Results:** In the first group, after noise exposure plasma MDA levels were found to be increased (p<0,05) whereas erythrocyte GSH, erythrocyte GP, erythrocyte GR levels were found to be decreased (p<0,05). In the second group which was given trimetazidine plasma MDA levels were found to be increased (p<0,05) but erythrocyte GSH, erythrocyte GP, erythrocyte GR levels did not changed (p>0,05). TEOAEs after noise exposure were weaker in both groups, but reproducibility and signal noise ratio levels were higher in the second group (p<0.05). **Conclusions:** It was shown in this study that cochlear damage due to noise exposure detected by OAE changes was prevented by TMZ in rabbits and this effect of TMZ is possibly mediated via its antioxidant properties. In our opinion, this drug which is used for treatment of ischemic heart diseases and episodic vertigo can play a role in prevention of noise induced hearing loss in people working in hazardous areas.

Keywords: Cochlea, hearing loss, noise induced, trimetazidine, antioxidant

TRIMETAZİDİNİN OKSİDATİF SİSTEM VE TEOAE'LER ÜZERİNE OLASI KORUYUCU ETKİSİNİN GÜRÜLTÜYE MARUZ BIRAKILAN TAVŞANLARDA ARAŞTIRILMASI

ÖZET

Amaç: Trimetazidine bir çok dokuda antioksidan etkilere sahip olan antianginal bir ilaçtır. Bu çalışmanın amacı gürültünün oksidatif sistem ve işitmeye olan etkisini araştırmak ve trimetazidinin bu sistemler üzerine olası sitoprotektif etkisini araştırmaktır.

Gereçler ve Yöntem: Bu çalışmada her biri 8 tavşandan oluşan 2 grup hayvan kullanıldı. İlk gruptaki (kontrol grubu) hayvanlara hiçbir madde uygulanmazken 2. gruptaki hayvanlara trimetazidine (TMZ) (20 mg/kg p.o, tid, 7 gün) verildi. Daha sonra Her iki gruptaki tüm hayvanlar gürültüye maruz bırakıldı. (100 dB SPL, 1000 Hz, 1 h) Gürültü öncesinde ve sonrasında hayvanların TEOAE'leri kaydedildi ve oksidatif stres parametreleri için kanları alındı. Bulgular: İlk grupta gürültü sonrası, plazma MDA seviyelerinin arttığı (p<0,05) ve eritrosit GSH, GP, GR seviyelerinin düştüğü gözlemlendi. (p<0,05). Trimetazidine verilen 2. grupta ise yine plazma MDA seviyelerinin arttığı (p<0,05) fakat eritrosit GSH, GP, GR seviyelerinin değişmediği gözlemlendi (p>0,05). Gürültü sonrası TEOAE ölçümleri her iki grupta da zayıftı fakat , reproducibility ve sinyal/gürültü oran seviyeleri 2. grupta daha yüksek bulundu (p<0.05). **Sonuçlar:** Bu çalışmada gürültünün tavşanlarda OAE ile tespit edilen koklear hasara yol açtığı ve bu hasarın TMZ tarafından kısmen önlendiği saptanmıştır. TMZ'nin bu koruyucu etkisi büyük olasılıkla ilacın antioksidan özelliklerine bağlıdır. Kanımızca, iskemik kalp hastalıkları ve episodik vertigo tedavisinde yaygın biçimde kullanılan TMZ gürültü riski taşıyan bölgelerde çalışan kişilerde gürültüye bağlı oluşan işitme kayıplarının önlenmesinde önemli rol oynayabilir.

Anahtar Sözcükler: Koklea, işitme kaybı, gürültü, trimetazidin, antioksidan

INTRODUCTION

Trimetazidine (TMZ) is an antianginal drug, which has potent antioxidant activity on various tissue¹. It has been used as an active drug in ischemic heart diseases, hepatic ischemia and nephrotoxicity induced by cyclosporine^{2,3,4}

Clinical studies have shown that TMZ also reduces duration and frequency of vertigo, improves cochleo-vestibular disorders associated with Meniere's disease (tinnitus, deafness and vertigo) and with ischemia. It was also shown to be effective on isolated tinnitus and has beneficial effects on sudden sensorineural hearing loss^{5,6,7,8}. The mechanism of action of TMZ has been studied on different tissues. TMZ inhibits the excessive release of oxygen free radicals and reduces the release of inorganic phosphate and efflux of phosphocreatine. TMZ also protects ATP stores, reduces membrane lipid peroxidation and induces preferential utilization of

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exogenous glucose¹. Additionally, TMZ preserves the physiological activity of isolated cardiac cells submitted to hypoxia⁹. Moreover, TMZ probably acts on the control of the intracellular pH and, consequently, modulates ionic fluxes (Na⁺/H⁺, Na⁺/Ca²⁺, Na⁺/K⁺-ATPase, etc.)^{10,11}. TMZ most probably prevents intracellular swelling by inhibition of an excessive intracellular Na⁺/Ca²⁺ store, and preventing the loss of intracellular K⁺.¹²

The precise mechanism leading to tissue damage in noise trauma is not known. Noise-induced hearing loss (NIHL) is a sensorineural deafness which appears classically as a notch at 3,4 or 6 kHz in a pure-tone audiogram¹³. The initial response to hazardous noise is the decreased microcirculation due to vasoconstriction and localized edema with vascular permeability increase¹⁴. Lipid peroxidation and free radical species (FRS) generated after prolonged hypoxia and ischemia periods were found to be responsible for damages to inner and outer hair cells^{15,16}. The presence malondialdehyde (MDA) which is a byproduct of lipid peroxidation indicates that membrane lipids have been subjected to oxidative damage^{17,18}. Erythrocyte glutathione (GSH), erythrocyte glutathione peroxidase (GP) and erythrocyte glutathione reductase (GR) are mainly intracellular antioxidants protecting the cells against free radical damage¹⁹.

Transient evoked otoacoustic emissions (TEOAEs) test is widely used in the diagnosis of cochlear disease like noise-induced hearing loss²⁰. The aims of this study were to uncover the effects of noise exposure on oxidative status and hearing thresholds and to investigate possible protective role of drug trimetazidine on oxidative system and hearing thresholds.

MATERIAL and METHODS

Sixteen rabbits (New Zealand strain, 1.80-1.95 kg) were used in this study. The experimental protocol was approved by the Animal Ethic Committee at Afyon Kocatepe University. The rabbits were divided into two groups 8 rabbits each. The rabbits in the first group were not given any treatment whereas a total dose of 20 mg/kg/day TMZ was given per orally tid for 7 days to each rabbit in the second group. On the 8th day attempts to record TEOAEs in the animals were made first without anesthesia, i.e. all the rabbits were alert during the whole study (Homoth T-OAE diagnostic system, Hamburg). Left ears were used for hearing tests and right ears were used to obtain blood specimens. During the hearing measurements, a 24-mm probe was inserted deeply into the ear canal while the

animal was placed in a small wooden box open at the top in a sound-proofed booth. After recording the TEOAEs, 2 ml peripheral blood was obtained from each rabbits to measure oxidative parameters. Then all the rabbits were exposed to noise (100 dB SPL, 1000 Hz, 1h) in a sound exposure cage of dimensions 1.5x0.75x0.75 m which were used for generation of narrow band noise (1000 Hz) presenting free-field from loudspeakers (Interacoustics AD 229 audiometer). The sound was calibrated and measured in the cage to ensure uniformity of the stimulus using a sound level meter (Testo 816, Germany). Immediately after noise exposure, the rabbits were removed from the cage and within 30 min TEOAEs were recorded again. Finally within 1 h of exposure, blood samples were taken from the animals for biochemical measurements.

Biochemical Methods: Blood samples were drawn into heparinized tubes. After 10 min centrifugation at 2500 rpm and +4°C, plasma and buffy coat were removed. Erythrocytes were washed three times with ice-cold physiologic saline. All chemicals were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Plasma MDA levels were determined using a method of Ohkawa et al.²¹. Erythrocyte GSH levels were determined according to Beutler et al.²². Erythrocyte GPx and GR activities were measured with a Hitachi 917 autoanalyzer using commercial kits obtained from Randox Laboratories (Randox Laboratories Ltd. Antrim, UK.).

Data were statistically evaluated by SPSS for windows (SPSS Inc., Chicago, IL, USA). Mann-Whitney U test was used for the comparison of the oxidative parameters and TOAE's between two groups. Wilcoxon signed rank test was used for the comparison of pre and postoperative data within each group.

RESULTS

When oxidative parameters before noise exposure were compared, no difference was detected between 1st (control) and 2nd (trimetazidine) group ($p>0,05$) (Table 1). In the first group, after noise exposure plasma MDA levels were found to be increased ($p<0,05$) whereas erythrocyte GSH, erythrocyte GP and erythrocyte GR levels were found to be decreased ($p<0,05$) (Table 1). In the second group which was given trimetazidine plasma MDA levels were found to be increased ($p<0,05$) but no statistically significant change was detected in erythrocyte GSH, erythrocyte GP and erythrocyte GR levels ($p>0,05$) (Table 1).

When oxidative parameters after noise exposure were compared between 1st (control) and



2nd (trimetazidine) group MDA levels were found to be lower ($p<0,05$) whereas eGSH, eGP eGR levels were found to be higher ($p<0,05$) in the second group (Table 1).

TEOAEs after noise exposure were weaker in both groups ($p<0.05$), but reproducibility and signal noise ratio levels were significantly higher in the second group ($p<0.05$) (Table 2).

N=16		Plasma MDA (umol/L)	Mean		Erythrocyte-GSH (U/g Hb)
			Erythrocyte-Glutathion peroxidase (U/g Hb)	Erythrocyte-Glutathion reductase (U/g Hb)	
1 st (control) group	Before noise	0,27± 0,05	4,02±0,89	9,49±1,07	146,5±32,20
	After noise	1,99 ± 0,59	2,01± 0,92	7,27 ±1,08	112,8± 13,26
	Before noise	0,32± 0,08	3,91 ± 0,54	9,53 ±1,19	144,8± 2,00
2 nd group (Trimetazidine)	After noise	0,78 ± 0,24	3,44± 0,57	8,99 ±0,84	134,5±15,12

Table 1. The mean levels of oxidative parameters in both groups

N=16		Mean	
		Reproducibility(%)	SNR (db)
1 st (control) group	Before noise	66,9± 5,69	6,0 ±1,24
	After noise	37,8±12,22	0,6±2,68
2 nd (Trimetazidine) group	Before noise	65,4±7,74	6,4±1,03
	After noise	55,4±7,42	4,8±0,99

Table 2. The mean levels of OAE parameters in both groups

DISCUSSION

It is shown in the previous studies that acoustic trauma causes free radical formation in inner ear^{19,23,24,25}. Noise exposure also causes oxidative stress for all the body and this condition is not limited to cochlear tissue¹⁹. According to some authors these free radical species are responsible for noise or drug induced hearing loss and antioxidants may play a protective role^{19,26,27}.

The destructive effects of oxygen free radicals on cochlea can be attributed to:

1. Impairment of mitochondrial energy production in basolateral membrane of cochlea causing a decrease in rate of endolymph secretion¹
2. Loss of intracellular K⁺ due to membrane lipid peroxidation which causes a passive K⁺ permeability of the cell membrane¹
3. Impairment of evoked release of neurotransmitters from the hair cells due to modification of synthesis and release of these neurotransmitters. This deleterious action can be ascribed to the ability of oxygen free radicals to induce protein breakdown and reduction of enzymic metabolism¹

Quirk et al reported¹⁵ that lazaroid, U74389F, a lipid peroxidation inhibitor provides partial protection from noise-induced temporary threshold shifts. The study of Seidman et al.²⁸ demonstrated that SOG-polyethylene glycol and allopurinol

attenuate noise-induced temporary threshold shifts. It was suggested that brief antioxidant loading with pharmacological doses can reduce high energy noise induced oxidative stress²⁹. Application of ascorbic acid before the noise exposure resulted in a lower or no loss of hair cells within cochlea³⁰. Kaygusuz et al. demonstrated that melatonin prevents increase of MDA and decrease of erythrocyte GP levels thus protects hearing thresholds³¹.

In the present study plasma MDA levels were increased significantly in both the control and the TMZ group after noise exposure. But when we compare the post-noise MDA levels. It is obviously seen that MDA levels in TMZ group were significantly lower than the saline group. Additionally, no significant change was detected after noise exposure in GSH, erythrocyte GP and erythrocyte GR levels in TMZ group in contrast to control group. These results show that TMZ avoided consumption of free radical scavenging molecules in plasma.

Lamm and Arnold³² reported that exposure to broad band noise induces cochlear hypoxia and ischemia and TMZ was shown to prevent free radical formation in ischemic conditions during reoxygenation period in rat heart cells³³. In light of these data we think that TMZ similarly avoids free radical formation in cochlea like it does in heart cells.

It has recently been shown that TMZ is capable of increasing membrane phospholipid turnover which could account for the cytoprotective



effect observed in cardiac cells^{34,35}. This action of TMZ may have some role especially on restoring membrane lipid composition of cochlear cells after lipid peroxidation avoiding passive K⁺ permeability.

Aubert et al.¹ in their study concluded that TMZ has beneficial action on bioelectrical potential generation when the semicircular canal was exposed to phenazine methosulphate (a substance which is a generator of free radicals) on frog model. According to Gil-Loyzaga et al.³⁶ TMZ prevents cochlear damage after intraperitoneal and perilymphatic administration of kainic acid.

In this study, after noise exposure the percentage reproducibility and SNR levels as parameters of TEOAEs test showed significant decrease in both of two rabbit groups. Xu et al.³⁷ have demonstrated that with increasing hearing loss, percentage reproducibility becomes much weaker. However reproducibility and SNR levels in the rabbits treated by TMZ were found to be higher than the control group. This result shows that TMZ attenuates noise-induced hearing threshold shifts and it appears to play a protective role for cochlea to some extent. Regarding our results it can be suggested that, protective role of TMZ is related to its capacity to prevent oxygen free radical formation.

In conclusion, it is shown for the first time that trimetazidine prevents noise induced cochlear damage by avoiding free radical formation in rabbits. In our opinion, TMZ which is used in ENT practice for treatment of episodic vertigo and tinnitus may play a role in prevention of noise induced hearing loss in people working in hazardous areas. For this reason it will be useful to conduct further clinical studies in human subjects testing the efficacy of TMZ to protect against noise induced cochlear damage.

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