Inner ear barotrauma (IEB) is a disorder caused by acute pressure changes such as those occurring during scuba diving, aviation, or simply blowing one’s nose (1). Acute changes in pressure are among the greatest risks facing scuba divers, as they can cause IEB, which may lead to permanent sensorineural hearing loss (SNHL). However, the precise mechanism remains unknown. In our previous study of IEB, we suggested that disturbance of cochlear blood flow produced by intense pressure loading leads to lipid peroxidation of cochlear tissue and that outer hair cell (OHC) loss was seen 28 days after intense pressure loading (2).

The neurotrophic compound 1-{3-[2-(1-benzothiophen-5-yl)ethoxy]propyl}azetidin-3-ol maleate (T-817MA), a neurotrophic compound newly synthesized for the treatment of Alzheimer’s disease, has been found to reduce oxidative stress and exert neuroprotective effects. By assessing the auditory functioning and observing the cochlear sensory epithelia, we investigated whether T-817MA protects the cochlea from inner ear barotrauma in guinea pigs treated with rapidly intense pressure change. Sustained oral administration of T-817MA significantly reduced the extent of auditory threshold shifts and outer hair cell loss, indicating that T-817MA attenuates the intense pressure–induced cochlear damage that accompanies inner ear barotrauma via antioxidative activity.

Keywords: T-817MA, inner ear barotrauma, free radical

Received February 17, 2011; Accepted July 21, 2011
after (day 0), and at 3, 7, 14, and 35 days after pressure loading by measurement of auditory brainstem response (ABR) thresholds at frequencies of 4, 8, 12, 16, and 20 kHz. The ABR threshold was determined by measurement of wave III or IV, which reflect the neural activity of the cochlear nucleus and the superior olivary complex in response to sound stimulation, respectively. In our previous study, we found that the threshold shift remains nearly unchanged 35 days after pressure loading in cases of IEB (2). For histological assessment, 9 animals were randomly assigned to 1 of 3 groups (n = 3/group): T-817MA–treated group (T-817MA concentration, 0.2 mg/mL), non-treated (distilled water) control group, and normal group. The T-817MA–treated and non-treated control animals were decapitated 4 weeks after pressure loading. The cochleae were locally perfused with 4% paraformaldehyde and allowed to remain in the fixative overnight. The organ of Corti was stained with 1% rhodamine–phalloidin (Invitrogen, Carlsbad, CA, USA) and processed for surface preparation. The sections were examined with a fluorescence microscope and the number of the missing OHCs was counted. To clarify if T-817MA attenuates oxidative stress, 6 animals were randomly assigned to 1 of the 3 groups (n = 2/group) described before. The T-817MA–treated and non-treated control animals were decapitated 1 h after pressure loading, and the expression of 8-hydroxy-2 deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, was examined immunohistochemically. This method precisely follows that described in a previous report (2).
The Baseline ABR thresholds did not differ significantly among the groups. As can be observed in Fig. 1, C – G, the threshold shifts of both groups of T-817MA–treated animals significantly decreased at 12 kHz at 14 days; at 16 kHz at 7, 14, and 35 days; and at 20 kHz at 7, 14, and 35 days after pressure loading (*P < 0.05, **P < 0.01, Mann–Whitney U-test). Although OHC loss was significantly reduced in the T-817MA–treated group in the basal turn compared with the non-treated control group, no significant difference was observed between the untreated and treated groups in the middle and apical turns (Fig. 2: A – L; P < 0.05, Mann–Whitney U-test). In the immunohistochemistry for 8-OHdG, the animals were decapitated 1 h after pressure loading and the cochleae were removed. Strong immunoreactivity was observed in the OHC nuclei of the non-treated control group, whereas weak immunoreactivity was observed in the normal group. Lesser amounts of immunoreactivity were observed in the same region of the T-817MA–treated group as compared with that observed in the non-treated control group (Fig. 3: A – C).

We previously reported that oxidative stress is produced in the cochlea in response to acute pressure change

![Image](image-url)
and that 3-methyl 1-phenyl-2-pyrazolin-5-one (edaravone), a potent free radical scavenger, has a therapeutic effect on IEB-induced SNHL. We also suggested that intense pressure loading induced circulatory disturbances and produces reactive oxygen species (6), which leads to biochemical damage of cochlear cells and functional damage in hearing. Because T-817MA suppresses a decrease of glutathione (7) and reduces hydrogen peroxide–induced neuronal death (8), we hypothesized that T-817MA could be effective for treating neurodegenerative disorders associated with oxidative stress such as IEB.

In the present study, administration of T-817MA reduced the oxidative stress in the cochlear cells, especially in the basal turn, which is associated with high-frequency hearing. The tendency that the basal turn is more severely injured than the other turns is similar to that in noise-induced hearing loss (9). The difference in vulnerability could be due to not only the anatomical but also the biochemical gradient through the turns. Although the precise mechanism of the neuroprotective effect of T-817MA remains unknown, several studies have reported it. T-817MA promotes neurogenesis in cultured neuronal cells (8) and functions as a neurotrophic factor, such as insulin-like growth factor-1, which protects the cochlear tissue from oxidative stress (10). T-817MA could act as a neurotrophic factor in the cochlea. Furthermore, we have shown that the neuroprotective effect of T-817MA is related to the protein kinase C (PKC) pathway because translocation of PKCε was observed in T-817MA–treated neuronal cultured cells (11). Translocation of PKC isoforms was observed in the phorbol 12-myristate 13-acetate–stimulated OHCs in the cochlea (12); thus, T-817MA might demonstrate a protective effect through activation of PKC in the cochlea. Although the pharmacological details remain to be elucidated, the findings in the present study indicate that T-817MA could be a new candidate drug for the protection or treatment of acute SNHL.

References