Local Dexamethasone Therapy Conserves Hearing in an Animal Model of Electrode Insertion Trauma-Induced Hearing Loss

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Hypothesis: The progressive loss of hearing that develops after electrode insertion trauma (EIT) can be attenuated by local dexamethasone (DXM) therapy.

Background: Hearing loss (HL) that develops after cochlear implant EIT occurs in two stages in laboratory animals, that is, an immediate loss followed by a progressive loss. Direct infusion of DXM into the guinea pig cochlea can attenuate both ototoxic- and noise-induced HL.

Materials and Methods: Auditory-evoked brainstem responses (ABRs) of guinea pigs were measured for 4 frequencies (i.e., 0.5, 1, 4, and 16 kHz) before, immediately after, and more than 30 days post-EIT for experimental (EIT, EIT + artificial perilymph, and EIT + DXM) and for the contralateral unoperated cochlea of each group. An electrode analog of 0.14-mm diameter was inserted through a basal turn cochleostomy for a depth of 3 mm and withdrawn. DXM in artificial perilymph was delivered immediately post-EIT into the scala tympani via a miniosmotic pump for 8 days.

Results: The ABR thresholds of EIT animals increased progressively post-EIT. Contralateral unoperated cochleae had no significant changes in ABR thresholds. Immediately post-EIT, that is, Day 0, the DXM-treated animals exhibited a significant HL at 1, 4, and 16 kHz, but this HL was no longer significant by Day 30 compared with contralateral control ears.

Conclusion: The results from immediate local treatment of the cochlea with DXM in an animal model of EIT-induced HL suggest a novel therapeutic strategy for hearing conservation by attenuating the progressive HL that can result from the process of electrode array insertion during cochlear implantation.

Key Words: Cochlear implantation—Oxidative stress—Conservation of hearing—Electrode trauma—Initiated hair cell and hearing loss—Corticosteroids—Dexamethasone.


With the trend toward extending cochlear implant surgery to patients with significant residual low-frequency hearing and the use of hybrid devices that combine acoustic and electrical stimulation of these patients (1), the need to conserve a presurgery level of functional hearing during and after cochlear implantation has become essential (2,3).

We have investigated the effect of electrode insertion trauma (EIT) in both fresh human temporal bone preparations (4) and in laboratory animals (5). EIT causes both macroscopic trauma to cochlear structures (e.g., rupture of basilar membrane or fracture of osseous spiral ligament) and changes at the molecular level that can cause a loss of hair cells via either necrosis, necrosis-like programmed cell death, apoptosis, or any combination of these mechanisms that end in the death of these affected organ of Corti sensory cells (6). Prevention of the macroscopic trauma to cochlear structures is currently being achieved by the design of less traumatic implant electrodes (e.g., short electrodes) and through the modification of surgical techniques (1,2,7). Prevention of unwanted effects of electrode array insertion on a

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molecular level will require that we identify candidate drugs and determine if they can conserve hearing and hair cell integrity both during and after implant surgery.

Glucocorticoids have been demonstrated through animal experimentation to reduce cochlear damage and loss of hearing that result after insults from exposure to 1) ototoxic drugs, 2) ischemia/reperfusion, 3) mechanical trauma, and 4) noise exposure (8–12). High-dose systemic steroids have been successfully used for many years to treat sudden idiopathic sensorineural hearing loss (HL); there is at present an increase of intratympanic delivery of steroids into the middle ear cavity to reach the inner ear's scala tympani via the round window membrane, especially in patients who have failed to receive benefit from systemic steroid therapy (13,14). Therefore, it is important to determine if local delivery of dexamethasone (DXM) has the potential to conserve residual hearing after cochlear implantation surgery.

We recently described the pattern of HL that occurs in a rat model of cochlear implant EIT (5). We observed an initial loss of hearing immediately after EIT, that is, Day 0, that was followed by a progressive loss of hearing that develops post-EIT, that is, Days 3, 5, and 7. The same pattern of HL was observed in a guinea pig model of EIT (6). Surface preparations of the middle turns of the organ of Corti from EIT guinea pigs have demonstrated changes in the nuclear staining of the auditory hair cells that is consistent with apoptosis (i.e., condensation of nuclear DNA and formation of apoptotic bodies). This observation of hair cell apoptosis after EIT is supported by terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick end–labeling (TUNEL) labeling of organ of Corti surface preparations from EIT–damaged cochleae that showed a progressive increase in TUNEL–labeled hair cell nuclei compared with no TUNEL labeling of unoperated control cochleae (6).

The present study tests the efficacy of local treatment of the cochlea's scala tympani with high-dose DXM in artificial perilymph (AP) for the conservation of hearing after trauma in a guinea pig model of EIT–induced HL.

MATERIALS AND METHODS

Experimental Animals and Surgical Procedures

Twenty-eight guinea pigs were randomly assigned to 1 of 3 experimental groups: 1) guinea pigs who received EIT followed by closure of the cochleostomy immediately after EIT (n = 8); 2) those who underwent EIT followed by scala tympani perfusion with AP for 8 days (EIT + AP, n = 8); and 3) guinea pigs given EIT followed by scala tympani perfusion with DXM (100 µg/ml) in AP for 8 days (EIT + DXM, n = 12).

One cochlea from each guinea pig was randomly chosen as the experimental ear, with the contralateral cochlea serving as the unoperated control ear. Both cochleae of each guinea pig were evaluated for hearing thresholds (i.e., auditory-evoked brainstem responses [ABRs]) in response to pure-tone stimuli before surgery and post-EIT. All surgeries were performed by the same surgeon (J.H.) under general anesthesia, that is, intramuscular injection of ketamine (90 mg/kg) mixed with xylazine (10 mg/kg). This study was performed in accordance with the University of Miami Miller School of Medicine Internal Animal Care and Use Committee and in compliance with United States Department of Agriculture and National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animals.

Osmotic Pump Preparation

AP was freshly prepared on the day before use in live animals, via pyrogen-free, sterile, double distilled water with the following salt and buffer concentrations: NaCl, 145 mmol/L; KCl, 2.7 mmol/L; MgSO4, 2 mmol/L, CaCl2, 1.2 mmol/L; and HEPES, 5 mmol/L that yielded a pH of 6.84. AP was filtered through a 0.45-µm sterile filter (Corning, Corning, NY, USA) and then loaded into Alzet 2001 miniosmotic pumps. Both AP control and DXM (100 µg/ml) in AP–filled miniosmotic pumps were primed overnight at 37°C in a beaker filled with the same AP or AP plus DXM solution outside the pump that is within the pump.

EIT–Only Group

Eight guinea pigs comprised the EIT–only group. Under general anesthesia, the experimental ear was identified, and a retroauricular incision was made. Once the bulla was located, a scalp was used to gently open it and identify the round window membrane niche and the promontory. Using a straight surgical pick, a cochleostomy was performed in the basal turn of the experimental animal's cochlea. A steel electrode analog of 0.14-mm diameter was then inserted through the cochleostomy for a depth of 3 mm into the scala tympani and then carefully withdrawn. The cochleostomy site was sealed immediately after trauma with a temporalis muscle graft (6).

EIT Plus AP Group

Eight guinea pigs were randomly assigned to the EIT plus AP perfusion group. The same electrode insertion and withdrawal procedure was performed on the experimental cochlea of these guinea pigs; however, instead of clamping the cochleostomy site with a muscle graft, these guinea pig cochleae had a specially constructed microcatheter inserted into their cochleostomy that delivered AP at a rate of 1 µL/h for 8 days. The catheter was held in place within the cochleostomy by packing with fascia. Dental cement was used to secure the catheter within the bulla and the miniosmotic pump was held in place by a pocket created under the skin of the back of the scapulae. The bulla was sealed, and the skin wound was closed with sutures. The EIT of all guinea pig cochleae was performed by the same investigator (J.H.).

EIT Plus DXM in AP Group

Twelve guinea pigs were randomly assigned to this group. The randomly assigned experimental cochlea of each guinea pig underwent the same cochleostomy surgery as the other groups. After the electrode analog was inserted for 3 mm and carefully withdrawn, a catheter was inserted into the cochleostomy just as in the EIT plus AP group. This catheter delivered 100 µg/ml of DXM in AP solution at a rate of 1 µL/h for 8 days. The catheter and miniosmotic pump were secured to the bulla and between the scapulae, with the skin closed in the same manner as described previously.

ABR Recording

The hearing of both ears of all guinea pigs was measured by ABR responses to pure-tone stimuli (0.5–16 kHz) at Otology & Neurotology, Vol. 28, No. 6, 2007

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presurgery and on post-EIT on Days 0, 3, 5, 7, 14, and 30 as previously described (15). Intelligent Hearing Systems (IHS, Miami, FL, USA) hardware and software were used to record ABR responses to pure-tone stimuli of 0.5, 1, 4, and 16 kHz. The ABRs were obtained using recording electrodes placed in the superior postauricular area (−) and in the vertex (+) of the guinea pig’s scalp. The ground electrode was inserted in a deep muscle of the left leg. Tone bursts of 0.5, 1, 4, and 16 kHz were delivered at a rate of 29 Hz to the cochlea being tested. The responses were amplified using an Opti-Amp bioamplifier from Intelligent Hearing Systems that was connected to a Smart EP system. The intensity of stimulation was decreased by 10-dB decrements until no ABR response was identifiable by visual inspection of the responses by 2 of the investigators (J.H. and A.A.E.).

Statistical Analysis
Auditory test data were compared using frequency, time, and group as the test variables. Statistical analyses were performed using the Statistical Package for the Social Sciences version 15 software. Within groups, experimental and unoperated control ears were compared using the nonparametric Mann-Whitney U test. The p value for statistical significance was set at a value of p < 0.05.

RESULTS

EIT-Only Group
Before surgery and EIT, there were no significant differences in median ABR thresholds between control and experimental cochleae across all frequencies (Fig. 1;

![Graph showing ABR thresholds across different days and frequencies]

**FIG. 1.** EIT-only group (n = 8). Box-Whisker plots displaying median ABR threshold trends of control and experimental ears. Each box runs from the 25th percentile to the 75th percentile, and the area contained within it is the Interquartile range. The horizontal line at the lower end of each box represents the lower quartile (25th percentile), whereas the bar at the upper end represents the upper quartile (75th percentile). The horizontal bar in between the lower and upper quartiles depicts the median ABR threshold response. The ends of the vertical lines ("Whiskers") that appear below and above each box represent the 9th and 91st percentiles, respectively. Outliers that are greater than 1.5 times the Interquartile range are marked with a circle. Outliers that are greater than 3.5 times the Interquartile range are indicated with a star. These plots show an increasing loss of ABR thresholds post-EIT that continues to worsen with time post-EIT. SPL, sound pressure level.
Immediately after EIT (i.e., Day 0), the experimental cochlea exhibited a significantly higher median ABR threshold only at 16 kHz ($p = 0.001$) compared with this response in contralateral control cochlea. This value remained significant from Day 3 through Day 30 ($p = 0.000-0.046$). At 4 kHz, the experimental cochlea had a significantly higher median ABR threshold from Days 3 to 30 ($p = 0.001-0.050$) compared with their contralateral control cochlea. For the remaining frequencies (i.e., 0.5 and 1 kHz), the experimental animals had a significantly higher median ABR threshold only on Day 7 ($p = 0.005$ at 0.5 kHz and $p = 0.016$ at 1 kHz) compared with control cochlea.

**EIT Plus AP Group**

There was no significant presurgery difference in median ABR thresholds between experimental and contralateral control cochlea (Fig. 2; $p > 0.05$). As with the EIT group, there was a significantly higher median ABR threshold in the experimental cochlea on Days 0 to 30 at 16 kHz ($p = 0.001-0.026$). At 4 kHz, the experimental cochlea had a significantly higher median ABR threshold on Day 14 only. There were no significant differences between experimental and control cochlea at 0.5 and 1.0 kHz stimulation frequencies for their median ABR responses across the length of the experiment.

**FIG. 2.** EIT plus AP group ($n = 8$). Box-Whisker plots displaying ABR threshold trends of control and experimental ears. Each box runs from the 25th percentile to the 75th percentile, and the area contained within it is the interquartile range. The horizontal line at the lower end of each box represents the lower quartile (25th percentile), whereas the bar at the upper end represents the upper quartile (75th percentile). The horizontal bar in between the lower and upper quartiles depicts the median ABR threshold response. The ends of the vertical lines ("whiskers") that appear below and above each box represent the 5th and 95th percentiles, respectively. Outliers that are greater than 1.5 times the interquartile range are marked with a circle. Outliers that are greater than 2.5 times the interquartile range are indicated with a star. These plots show an increasing loss of ABR thresholds post-EIT that seems to become stable at around 14 days post-EIT. SPL, sound pressure level.

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EIT Plus DXM Group

The control and experimental cochleae showed no significant difference in median ABR thresholds presurgery across all frequencies tested (Fig. 3). Immediately after surgery and EIT, the experimental cochlea had a significantly higher median ABR threshold in response to 1, 4, and 16 kHz pure-tone stimuli ($p = 0.002, 0.003$, and $0.000$, respectively). At 16 kHz, significant differences between the ABR thresholds of experimental and control cochleae continued up to and including Day 14 ($p = 0.000-0.010$). However, at 30 days post-EIT, there was no significant difference in the median ABR threshold value at 16 kHz between experimental and control animals ($p > 0.05$). There was also no significant difference in median ABR thresholds at 4 kHz for Days 3 to 30 post-EIT ($p > 0.05$). At 4 kHz, the experimental cochlea exhibited a significantly higher median ABR threshold again on testing Day 14 ($p = 0.044$), but not on post-EIT Days 3, 7, and 30 ($p > 0.05$) when compared with contralateral control values. During the entire course of the experiment, there were no significant differences found in the ABR responses to a 0.5-kHz pure-tone stimulus between experimental and control cochleae ($p > 0.05$).

The median values for the ABR tests performed for the contralateral unoperated control cochleae (Table 1A) from all 3 groups and the experimental cochleae (Table 1B) of these 3 groups (i.e., EIT, EIT + AP, EIT + DXM) are presented in Table 1 for each of

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**FIG. 3.** EIT plus DXM group (n = 12). Box-Whisker plots displaying ABR threshold trends of control and experimental ears. Each box runs from the 25th percentile to the 75th percentile, and the area contained within it is the interquartile range. The horizontal line at the lower end of each box represents the lower quartile (25th percentile), whereas the bar at the upper end represents the upper quartile (75th percentile). The horizontal bar in between the lower and upper quartiles depicts the median ABR threshold response. The ends of the vertical lines ("whiskers") that appear below and above each box represent the 5th and 95th percentiles, respectively. Outliers that are greater than 1.5 times the interquartile range are marked with a circle. Outliers that are greater than 2.5 times the interquartile range are indicated with a star. These plots show an initial loss of the ABR thresholds immediately post-EIT (Day 0) that seems to recover toward normal pre-EIT threshold values by Day 30 post-EIT. SPL, sound pressure level.

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TABLE I. Median ABR thresholds from unoperated control ears and experimental ears from EIT (n = 8), EIT plus AP (n = 8), and EIT plus DXM (n = 12) groups of guinea pigs

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ABR, auditory-evoked brainstem response; EIT, electrode insertion trauma; DXM, dexamethasone; Presurgery, presurgery data; 0, data obtained immediately after EIT; and Days 3, 7, 14, and 30 all represent post-EIT data.

The results of this study show that this local administration of DXM into the scala tympani immediately after EIT provides a significant level of protection against EIT-induced HL that was stable at 30 days post-EIT (see Figs. 1–3; Table 1). This finding of hearing conservation in our animal model of cochlear implantation trauma is in agreement with other animal studies that have demonstrated a protective effect of corticosteroid treatment against development of a permanent HL induced by sound trauma (8,9) and protection against noise-induced temporary threshold shifts (10). In further support of our results are the findings that DXM treatment attenuates HL caused by aminoglycoside ototoxicity (11) and ischemia-reperfusion injury to outer hair cells (12), and protects isolated outer hair cells against the cytotoxicity of two aminoglycosides that are contained in otic drop preparations (18).

A complete understanding of the molecular mechanism(s) involved in the protective effect of corticosteroids on hearing is not fully understood. It is presumed that they act within the cochlea by their potent immunosuppressive and anti-inflammatory functions (e.g., nuclear transcription factor-κB [NF-κB]), in support of an anti-inflammatory action are studies that report the induction of inflammatory cytokine production within cochlear tissues as a response to trauma (19) and the protective action of the corticosteroids against acoustic trauma, which is mediated through the GRs (20). Animal studies of noise- and vibration-induced permanent HLs show an upregulation of proinflammatory cytokine production by cochlear tissues (e.g., tumor necrosis factor-α [TNF-α]), and in the case of vibration-induced HL, there is also an upregulation of TNF-α receptors (19,21). The results of an acoustic trauma study where mice were exposed to a moderate level of damaging noise indicate that either inhibition of glucocorticoid synthesis, or blocking of GRs, or the inhibition of NF-κB can all increase the HL caused by this noise exposure, and that treatment of the animals with DXM before this noise exposure attenuates the HL (20). Another series of studies demonstrate that restraint stress–induced protection of hearing from acoustic trauma is mediated through the action of the glucocorticoid response system (22–24).

Results obtained from studies in other systems confirm that the potentially beneficial effects of glucocorticoids are mediated through their anti-inflammatory action due, in part, to blocking the transcription of proinflammatory molecules through the inhibition of NF-κB and activator protein 1 (AP-1), recruitment of transcription factors that encode anti-inflammatory factors, and inhibition of leukocyte migration (25,26). An in vitro study demonstrates that a 100-nmol/L dose of DXM blocks 80 to 90% of TNF-α–induced apoptosis in cultures of MCF-7 cells, and that DXM also blocks TNF-α–initiated downregulation of an antiapoptosis protein (i.e., inhibitor of apoptosis [IAP]) (27).

Another possible mechanism of action of glucocorticoids in the inner ear is through the direct inhibition of...
cell death signal cascades such as the mitogen-activated protein kinase (MAPK)/c-Jun N-terminal kinase (JNK) signal cascade (28). A recent electrode trauma-induced HL study shows that blocking the MAPK/JNK cell death signal cascade in the cochlea by local delivery of a JNK binding protein (i.e., D-form of JNK inhibitory peptide [D-JNKI-1]) prevents the progression of EIT-induced HL (6). This ability of DXM to interfere with the MAPK/JNK signaling is an important action when considering possible protective mechanism(s) of action for DXM therapy. Another recently defined protective action of DXM within the inner ear to consider is its ability to enhance the rate of synthesis of glutathione (a naturally occurring antioxidant) by spiral ganglion cells in mice after DXM treatment (29).

Cochlear implant insertion trauma–induced HL is currently under intense investigation. Insertion of an electrode array into a fresh unfixed cochlea of a cadaver can damage the basilar membrane, spiral ligament, and osseous spiral lamina (4,30). In response to this damage, it is presumed that the body produces an inflammatory response in an attempt to reduce the amount of damage done to the inner ear and to aid in the repair process within the cochlea (31). If this inflammatory response becomes too robust, then it can result in the production of an excess of free radicals, leading to additional oxidative stress damage, with this cycle eventually leading to the loss of damaged cells via programmed cell death.

The validity of in vitro experiments and animal studies depends on their analogy to a clinical setting, multiple testing of the hearing immediately after cochlear implant surgery to define the pattern of HL after electrode insertion is complicated by the limitations that are inherent to clinical studies. Complete loss of residual hearing immediately after surgery has been documented (32,33). However, there are also clinical studies that document preservation of pure-tone audiometric hearing at 2 years postimplantation (33,34). And studies where both partial preservation of residual hearing (HL, 15–40 dB) and delayed loss of residual hearing were documented in prospective clinical studies (33,35).

The guinea pig cochlear implant trauma model (6) used in the present study is a normal-hearing animal before EIT. Therefore, it is not the same as implanting a partial hearing animal with residual low-frequency hearing as is being done during implantation of a candidate for bimodal stimulation of high-frequency area with the implant and any surviving low-frequency hearing with acoustic energy for a modified hearing aid (36). It is our experience that an EIT-lesioned normal-hearing animal provides a more reproducible pattern of both initial and progressive loss of hearing (6) than does EIT-lesioning of a partially deafened animal (Van De Water and Eshraghi, unpublished data). This reproducible pattern of HL after EIT allows for a more precise assessment of HL with or without DXM local therapy. The withdrawal of the electrode analog after the initial EIT avoids a foreign body reaction and therefore allows assessment of only the effect of the trauma on the pattern of HL.

We did not perform masking of the contralateral normal ear during our ABR testing but did verify these results with the pattern of change of the amplitudes of distortion product otoacoustic emissions (DPOAEs) (not reported) observed in the same ear; this allows us to confirm that the thresholds found were truly those of the tested ear. The slightly higher ABR thresholds at presurgery in the EIT plus DXM group of guinea pigs was controlled for by internal comparison between experimental and unoperated control cochleae by nonparametric analysis (see "Materials and Methods" section).

DXM was chosen as the experimental corticosteroid because it is known to decrease inflammation and because receptors for it have been localized within the tissues of the cochleae (13,14,17). Artificial perilymph perfusion was used as a treatment control because it was the carrier solution to deliver the DXM therapy and because we wanted to rule out the possibility of hearing preservation secondary to a washout of inflammatory mediators (e.g., TNF-α) or free radicals. The AP perfusion did not have a significant effect on attenuating the EIT-induced HL at 16 kHz, but did at 4 kHz (p > 0.05), whereas the overall pattern of HL, although not significantly affected, there was less of a HL that developed post-EIT than was observed in the EIT-only animals. This suggests mild attenuation of the EIT-induced HL by AP perfusion, which suggests that there was some washout effect. This result of a small, but overall not significant, protective effect by AP perfusion suggests a possible mechanism for the EIT-induced HL. TNF-α is a potent mediator of the inflammatory process, and it exists in two forms within a cell undergoing an inflammatory reaction, that is, a membrane-bound form and a soluble form (37). The conversion of membrane-bound TNF-α to the soluble form of this cytokine is accomplished by the activity of TNF-α converting enzyme, and blocking of TNF-α converting enzyme has suggested that this formation of soluble TNF-α is critical for the expression its tissue toxicity (38). Given these facts, it can be hypothesized that perfusion of the scala tympani with AP after EIT has a moderating effect on the levels of soluble TNF-α within the cochlea, and this would explain the moderating effect of AP perfusion on the level of EIT-induced HL. At this point, this suggestion of a TNF-α mechanism for EIT-induced HL is entirely theoretical and must be proven experimentally; however, the results from skull vibration trauma experiments (21) and sound trauma experiments (19) support this hypothesis as does the fact that TNF-α can induce JNK signaling (28), and inhibition of JNK signaling can prevent the progression of EIT-induced HL (39).

More investigations are required to identify and characterize the molecular mechanism(s) involved in the otoprotective effect of DXM therapy for the reduction of HL in this guinea pig model of cochlear implantation.
CONCLUSION

EIT causes both an immediate and a progressive threshold shift that becomes a permanent HL. Perfusion of the scala tympani with AP does not prevent either the immediate or the progressive HL that is caused by EIT but does have a moderating effect on the extent of the HL. Perfusion of the scala tympani with high-dose DXM (i.e., 100 μg/ml) in AP immediately after EIT conserves the animals' hearing against EIT-induced HL affecting both the initial and the progressive components of the EIT-induced HL. The conservation of hearing against EIT-induced HL by local DXM therapy to the cochlea is stable at 1-month post-EIT.

REFERENCES


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