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The effect of systemic lipoic acid on hearing preservation after cochlear implantation via the round window approach: A guinea pig model

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ABSTRACT

The present study aimed to evaluate the effects of systemic lipoic acid on hearing preservation after cochlear implantation. Twelve Dunkin-Hartley guinea pigs were randomly divided into two groups: the control group and the lipoic acid group. Animals in the lipoic acid group received lipoic acid intraperitoneally for 4 weeks. A sterilised silicone electrode-dummy was inserted through the round window to a depth of approximately 5 mm. The hearing level was measured using auditory brainstem responses (ABRs) prior to electrode-dummy insertion, and at 4 days and 1, 2, 3 and 4 weeks after electrode-dummy insertion. The threshold shift was defined as the difference between the pre-operative threshold and each of the post-operative thresholds. The cochleae were examined histologically 4 weeks after electrode-dummy insertion. Threshold shifts changed with frequency but not time. At 2 kHz, ABR threshold shifts were statistically significantly lower in the lipoic acid group than the control group. At 8, 16 and 32 kHz, there was no significant difference in the ABR threshold shift between the two groups. Histologic review revealed less intracochlear fibrosis along the electrode-dummy insertion site in the lipoic acid group than in the control group. The spiral ganglion cell densities of the basal, middle and apical turns were significantly higher in the lipoic acid group compared with the control group. Therefore, systemic lipoic acid administration appears to effectively preserve hearing at low frequencies in patients undergoing cochlear implantation. These effects may be attributed to the protection of spiral ganglion cells and prevention of intracochlear fibrosis.

1. Introduction

The cochlear implant is a neural prosthesis that transduces acoustic signals into electric signals, enabling individuals with profound hearing loss to hear sound. Since the first cochlear implant was approved by the US Food and Drug Administration in 1984, the device has achieved successful hearing rehabilitation and become the standard treatment for individuals with profound hearing loss. With the progress of cochlear implant systems, the indications for cochlear implantation have broadened. In recent years, cochlear implantation has been performed in cases with not only profound hearing loss but also residual hearing at lower frequencies (Havenith et al., 2013). Electroacoustic stimulation (EAS) is a new method of hearing rehabilitation that uses a cochlear implant aided by an ipsilateral hearing aid. It uses both electrical and acoustical stimulation simultaneously based on the preserved residual hearing. EAS has demonstrated auditory benefits over a conventional cochlear implant, such as increased sound resolution and localisation, speech recognition in a noisy environment, and music recognition (Podskarbi-Fayette et al., 2010). Hearing preservation at low frequencies has been the meaningful issue of cochlear implantation.

The suspected aetiologies of hearing loss after cochlear implanta-

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tion include mechanical damage during electrode insertion, oxidative stress, inflammation caused by a foreign body reaction, and surgical stress (Lee et al., 2013). Several studies support roles of oxidative stress and inflammation in hearing loss, especially delayed hearing loss after cochlear implantation and hearing loss at regions apical to the actual position of the electrode (Gantz et al., 2009; Gantz et al., 2005). Glucocorticosteroids are one of the most widely used medications in hearing loss. Several studies have shown their otoprotective effects (Connolly et al., 2011; Dinh et al., 2008; Eastwood et al., 2010; Eshraghi et al., 2011; Haake et al., 2009). However, systemic glucocorticosteroids have numerous adverse effects, including hyperglycaemia, opportunistic infections, osteoporosis, and osteonecrosis. Furthermore, delayed hearing loss (more than 1 month) after cochlear implantation has been reported (Gantz et al., 2009). The ideal medication for hearing loss would have no adverse effects even with long-term administration.

We investigated lipoic acid as a treatment for hearing loss due to its antioxidant and anti-inflammatory properties. Lipoic acid is an over-the-counter drug that has been commonly prescribed in Germany for decades. The adverse reaction rate of lipoic acid has been reported to be low (Rathmann et al., 1998). Lipoic acid has been shown to have neuroprotective effects in animal models (Abdin and Sarhan, 2011). Furthermore, several studies have shown that lipoic acid can mitigate oxidative stress and inflammation (Bae et al., 2009; Cui et al., 2012; Di Pierro and Settembre, 2013; Trivedi and Jena, 2013).

The current study used a guinea pig model to evaluate the effects of lipoic acid for hearing preservation after cochlear implantation. The electrode-dummy was inserted more deeply than in previous studies to mimic the clinical situation appropriately (Connolly et al., 2011; Lee et al., 2013). Lipoic acid was administered intraperitoneally for 4 weeks.

2. Materials and methods

2.1. Experimental Design

This study was approved by the Institutional Animal Care and Use Committee of Boramae Medical Center (2015-0010). All surgical procedures and auditory brainstem response (ABR) recordings were performed after anaesthesia with intramuscular administration of ketamine (40 mg/kg) and xylazine (4 mg/kg). Seven-week-old male Dunkin-Hartley guinea pigs weighing from 410 to 450 g were used for this study. Twelve guinea pigs were randomly divided into two experimental groups: the control group (n = 6) and the lipoic acid group that received 30 mg/kg lipoic acid (n = 6). We used lipoic acid (Bukwang Pharm, Seoul, South Korea) that is on the market for human medical use. It was diluted with normal saline to stock concentrations of 3 mg/ml and injected intraperitoneally three times per week for 4 weeks.

2.2. Auditory Brainstem Response Recordings

The hearing level of both ears of all animals was measured using ABRs before surgery. Tone pips of 2, 8, 16, and 32 kHz were used as the sound stimuli (5-ms duration, cos shaping, 21 Hz). Subdermal needle electrodes were located below the ears and at the vertex. The Intelligent Hearing System (IHS Inc., Miami, FL, USA), employing IHS high-frequency transducers (HFT9911–20–0035) and IHS high-frequency software (ver. 2.33), was used to record ABRs. The responses were amplified (100,000×), band pass-filtered (100–1,500 Hz), and then averaged over stimulus repetitions. Two researchers, blinded to the study protocol, recorded responses by decreasing stimuli intensity in 5 dB decrements. The lowest stimulus level that induced recognisable responses was determined as the threshold. Electrode-dummy insertion was then performed. Further ABR thresholds were measured at 4 days and 1, 2, 3 and 4 weeks after electrode-dummy insertion. The threshold shift was defined as a value obtained by subtracting the preoperative threshold from each of the postoperative thresholds. A positive value for the threshold shift indicated hearing loss.

2.3. Electrode-dummy Insertion

All animals underwent electrode-dummy insertion on the left side. For analgesia, meloxicam (0.2 mg/kg) was administered to all animals before and after surgery. A 4-mm chisel and rongeur were used to open the bulla and expose the round window under an operating microscope. An incision was made on the round window membrane. A sterilised silicone electrode-dummy (shaft diameter, 0.75 mm; tip diameter, 0.30 mm) was inserted through the round window to a depth of approx. 5 mm and left in situ. A small amount of subcutaneous tissue behind the external auditory canal was harvested and packed around the electrode-dummy to prevent electrode-dummy migration and perilymph leakage.

2.4. Histological Preparation of the Inner Ear

After the last ABR recording, all animals were deeply anaesthetised with ketamine (90 mg/kg) and xylazine (10 mg/kg) and perfused intracardially with PBS then 4% paraformaldehyde (PFA). The left cochleae were harvested and fixed at 4 °C overnight. The 12 cochleae were washed and decalcified in 10% (w/v) EDTA (Santa Cruz Biotechnology, Santa Cruz, CA, USA) in PBS for 3 weeks. The cochleae were then trimmed, after which the electrode-dummies were carefully removed and then embedded in paraffin in the plane of the modiolus. Five 4-μm-thick sections were collected every 200 μm. At the edge of the cochlea, three sections were taken every 200 μm. They were stained with either hematoxylin & eosin (H & E) or a trichrome kit (Abcam, Cambridge, UK).

Histological analyses of the basal, middle and apical turns of the cochlea were performed under light microscopy (CX31; Olympus, Tokyo, Japan). The tissue responses, including intracochlear fibrosis, ossification, and spiral ganglion cell density were evaluated using the results of H & E staining. Microscopic images of five sequential sections around the area with the most apparent tissue responses were taken and converted to JPEG files. The area of the scala tympani, and of the tissue responses surrounding it, were measured using Image J software (National Institutes of Health, Bethesda, MD, USA). The percentage of the area occupied by tissue responses in the scala tympani was calculated in each section and a mean percentage was obtained for each animal. To measure the spiral ganglion cell densities, five sequential sections around the mid-modiolar region were examined. The basal, middle and apical turns of each section were evaluated using Image J software. The number of type I cells with a clear nucleus in Rosenthal's canal was counted and divided by the canal area to calculate the mean spiral ganglion cell density for each animal.

2.5. Statistical Analyses

SPSS software (ver. 21.0; IBM Corp., Armonk, NY, USA) was used for statistical analyses. The success of treatment over 4 weeks was assessed using a repeated measures ANOVA with ABR threshold shifts across time as a repeated measure (at 4 days and at 1, 2, 3 and 4 weeks) with treatment group and stimulus frequency as fixed factors. After identification of the effects of time and frequency, linear mixed models were used to evaluate the effects of treatment. Post hoc testing used the Bonferroni procedure and the mean difference (M), standard error of the mean (S.E.M) and probability (*P*) were reported. Histological analyses were performed using the t-test. The mean (M), standard error of the mean (S.E.M) and probability (*P*) were again reported. Pearson's correlation analysis was performed between ABR threshold shifts at 4 weeks after electrode-dummy insertion and histological factors.