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Research paper

A cool approach to reducing electrode-induced trauma: Localized therapeutic hypothermia conserves residual hearing in cochlear implantation

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ABSTRACT

Objective: The trauma caused during cochlear implant insertion can lead to cell death and a loss of residual hair cells in the cochlea. Various therapeutic approaches have been studied to prevent cochlear implant-induced residual hearing loss with limited success. In the present study, we show the efficacy of mild to moderate therapeutic hypothermia of 4 to 6 °C applied to the cochlea in reducing residual hearing loss associated with the electrode insertion trauma.

Approach: Rats were randomly distributed in three groups: control contralateral cochleae, normothermic implanted cochleae and hypothermic implanted cochleae. Localized hypothermia was delivered to the middle turn of the cochlea for 20 min before and after implantation using a custom-designed probe perfused with cooled fluorocarbon. Auditory brainstem responses (ABRs) were recorded to assess the hearing function prior to and post-cochlear implantation at various time points up to 30 days. At the conclusion of the trials, inner ears were harvested for histology and cell count. The approach was extended to cadaver temporal bones to study the potential surgical approach and efficacy of our device. In this case, the hypothermia probe was placed next to the round window niche via the facial recess or a myringotomy.

Main results: A significant loss of residual hearing was observed in the normothermic implant group. Comparatively, the residual hearing in the cochleae receiving therapeutic hypothermia was significantly conserved. Histology confirmed a significant loss of outer hair cells in normothermic cochleae receiving the surgical trauma when compared to the hypothermia treated group. In human temporal bones, a controlled and effective cooling of the cochlea was achieved using our approach.

Significance: Collectively, these results suggest that therapeutic hypothermia during cochlear implantation may reduce traumatic effects of electrode insertion and improve conservation of residual hearing.

1. Introduction

Conservation of residual hearing by reducing cochlear trauma has always been an important goal during inner ear surgeries, especially during cochlear implantation (CI). Patients with residual hearing are now being implanted to take advantage of bimodal electroacoustic stimulation (EAS) (Irving et al., 2014). The Food and Drug Administration (FDA)-approved indications for CI now allow bilateral implants in young children (Carlson et al., 2015; Ching et al., 2014), in whom residual hearing levels may be difficult to ascertain (Tharpe and Sladen, 2008). Furthermore, in recent years, novel CI electrode designs have improved efficiency and performance by locating stimulation sites closer to spiral ganglion neurons and deeper into the scala tympani. As a result, in the future, the number of CI/EAS recipients with some degree of usable hearing is likely to increase. Depending upon the insertion depth and

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the intracochlear electrode position, however, CI can result in inflammation and oxidative stress leading to neural degeneration, hair cell loss and loss of residual hearing (Eshraghi et al., 2005; Wardrop et al., 2005). The nature of cochlear electrode insertion trauma has been characterized both in animal models and in temporal bone studies. Previous research has demonstrated the relationship between device-specific CI electrodes and surgical techniques with cochlear trauma (Adunka et al., 2005; Ahmad et al., 2012; Briggs et al., 2001). Auditory brainstem response (ABR) studies in animal models have observed significant increase in hearing thresholds within 7 days of implantation trauma (Balkany et al., 2005) and can be a result of both the intrinsic and extrinsic cell death signaling pathways (Bas et al., 2015). The loss of residual hearing due to electrode-induced trauma (EIT) can negatively impact the learning ability and speech recognition in younger patients. As such the importance of protecting residual hearing during and after implantation has grown proportionately. To reduce trauma-associated cellular response, refinements in surgical techniques and neuroprotective drug-eluting electrodes are being investigated (Dinh et al., 2008; Friedland and Runge-Samuelson, 2009; James et al., 2008; Jolly et al., 2010; Van De Water et al., 2010; Vivero et al., 2008). While surgical techniques and electrode designs have been advanced, residual hearing is still lost in many cochlear implant patients (Balkany et al., 2006; Kiefer et al., 2004).

The present study tested the hypothesis that localized therapeutic hypothermia applied to the cochlea prior to implantation can protect hair cells (HC) and neurons and hence may preserve residual hearing. Mild to moderate hypothermia is a promising neuroprotective intervention when induced during or after a central nervous system injury (Cappuccino et al., 2010; Dietrich et al., 2009; Kawai et al., 2000; Levi et al., 2010; Matsui et al., 2006). When localized and administered prior to trauma, these effects may be enhanced with little adverse effects on other biological phenomena or immune response (Purdy et al., 2013; Tzen et al., 2013). Mild therapeutic hypothermia, defined as a temperature decrease of 4–6 °C below body temperature, has the potential to reduce or prevent oxidative stress (Balkany et al., 2005; Henry and Chole, 1984; Shintani et al., 2010). Prior literature, both from animal studies and clinical trials, has shown protective effects of therapeutic hypothermia on ischemic and traumatic injuries to neurons (Levi et al., 2010; Ohta et al., 2007; Shintani et al., 2010; Yanamoto et al., 1999; Yokobori et al., 2011) in cases of mild traumatic brain injury (mTBI), seizures (Atkins et al., 2010), ischemia and inflammatory response (Cappuccino et al., 2010; Kawai et al., 2000; Levi et al., 2010; Matsui et al., 2006) after cardiac arrest, and related to spinal cord injuries (Cappuccino et al., 2010; Dietrich et al., 2009). Unfortunately, systemic hypothermia has multiple side effects on functioning of organs and organ systems including impairment to immune response, higher infection, altered effects of other drugs and compromising vascular function. These adverse effects restrict its use in clinical setting, and make it challenging to utilize hypothermia for preserving sensory functions of the inner ear.

That temperature is an important parameter and influences cochlear responses has been long known (Brown et al., 1983; Liberman and Dodds, 1984; Ohlemiller and Siegel, 1992, 1994) with demonstrated benefit of applied hypothermia (Henry and Chole, 1984; Watanabe et al., 2001). To test the beneficial effects of localized hypothermia in otoprotection, we designed a custom device to cool the cochlea that does not require any modifications to the current CI surgical approach. Direct comparisons were made between hearing thresholds post-surgery in normothermic and hypothermic-treated cochleae in normal hearing rats subjected to EIT. We also carried out a detailed histological study at the end of the long-term implantation and observed significant otoprotection with hypothermia.

2. Methods

2.1. Animal preparation and surgical approach

The use of Brown Norway rats with normal hearing in this study was approved by the University of Miami Animal Care and Use Committee and was in compliance with USDA and NIH Guidelines for the Care and Use of Laboratory Animals. The animals were anesthetized with an initial intraperitoneal injection of Ketamine and Xylazine (22–60 and 5–10 mg/kg respectively) and maintained with supplemental doses. Lidocaine HCl 1% was used for local analgesia prior to surgical incision. Withdrawal reflex was measured by extension of one leg and pinching the web of skin between the toes or pinching the ear. A positive reflex was indicated by flexion of the limb with toe, paw pinch or movement of the head or whiskers with ear pinch. Once anesthetized, a bland, sterile ophthalmic base ointment was applied to corneas to prevent eye dryness. The skin over the skull and behind the ears was shaved, and prepped with Betadine scrub. All surgical procedures were performed under aseptic conditions. For the approach to the inner ear organs, a post-auricular incision was made extending from the dorsal skin defect down behind the ear to terminate approximately over the posterior edge of the mandible. The soft tissues were dissected to expose the temporal bone over the bulla. A small defect in the bone of the bulla was created using the tip of a scalpel blade or a hand-held micro-drill to expose both the round window membrane niche and the lateral bony wall of the cochlea adjacent to the niche. Electrode trauma to the cochlea was accomplished by the insertion of an electrode analog into the scala tympani via the round window to a depth of 5 mm. The electrode analog was 0.28 mm monofilament as described previously (Bas et al., 2012, 2015) to allow for insertion in the smaller scala tympani of the rat. The site around the electrode was secured by packing with a graft of fascia obtained locally from the site of the surgical approach to the bulla. Once the placement and stability of the electrode analog were established, the defect in the ventro-lateral wall of the temporal bone bulla was covered with carboxylate cement, with care taken not to allow the cement to enter into the bulla. A subcuticular closure was made using vicryl absorbable sterile sutures and the skin was closed with vicryl absorbable sutures. A topical antibiotic silver sulfadiazine 1% or Bacitracin Zinc was applied to the wound sites. To prevent post-op dehydration the animals received IP or SC injection of sterile Ringer's solution (up to 1 mL). To prevent post-operative pain, buprenorphine (Buprenex, 0.05 mg/kg) was given once at the time of surgery and sequential dosages were provided for 48 h to aid recovery. To prevent hypothermia post-op, the animal holding/recovery cages where placed on water-circulating heating pads. There were three experimental groups: in the first group, the left ear was implanted under normothermic condition and in the second group, therapeutic hypothermia (cooling by 3–6 °C measured at the round window) was provided using the newly developed hypothermia device. The right contralateral ear always served as the intra-animal control.

2.2. Delivery of therapeutic hypothermia

A novel copper hypothermia probe attached to a custom thermoelectric Peltier device was placed in the middle ear adjacent to the cochlea under direct visualization. Fluorocarbon cooled by the Peltier system was used as the refrigerant, and circulated through the metal probe. In acute experiments ($n = 7$), the temperatures at the apex and the basal turn of the cochlea were measured using (QTI Sensing Solutions' T320/E320) microthermistors over time. The temperature of the cochlea was reduced by a 5–6 °C with our device (Fig. 1) and cooling was maintained within ±0.3 °C over the