EXPERIMENTAL ANIMAL MODEL OF INTRACOCHLEAR OSSIFICATION IN RELATION TO COCHLEAR IMPLANTATION

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INTRODUCTION

Histopathologic examinations of the temporal bones of implanted human patients and experimental animals have demonstrated various degrees of abnormal fibrous tissue or new bone formation within the cochlea; in some cases, extensive new bone formation was reported. The presence of new
bone following cochlear implantation is undesirable, since it may adversely affect current distributions in the electrically stimulated cochlea. The pathogenesis of intracochlear osteoneogenesis as a direct result of cochlear implantation is unclear.

The aim of this study is to use an experimental animal model to investigate some of the factors underlying the formation of new bone and fibrous tissue within the implanted cochlea, especially the role of insertion trauma and bone chips, and also a possible way of inhibiting such a process using an anticalcific agent of the diphosphonate family, disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP). The local release of EHDP from a polydimethylsiloxane (Silastic silicone rubber, Dow Corning Corp) controlled delivery system has been shown effective in the context of bioprosthetic heart valve. Its application within the cochlea has not been documented, to our knowledge.

MATERIALS AND METHODS

Experimental Setup. Ten cats, all with otoscopically nor-
mal tympanic membranes, were implanted with an electrode array in each cochlea, with or without bone chips and deliberate trauma. These electrodes were made of Silastic silicone rubber (Dow Corning Corp), with EHDP incorporated in the fabrication process in a range of concentrations: 0%, 2%, 6%, 10%, 15%, 20%, and 30% w/w. The Table shows the insertion parameters of the 20 cochleas, including implant durations. Electrical stimulation was not applied as a variable in this study, since previous safety studies have established safe charge densities that are not associated with abnormal intracochlear osteoneogenesis.5

**Auditory Brain Stem Evoked Response Measurements.** Immediately following premedication and just prior to implant surgery, a baseline measurement of auditory brain stem evoked response (ABR) thresholds was made for each ear for the pure tone frequencies 1, 2, 4, 8, 16, and 32 kHz by means of standard ABR equipment in the department. This procedure was repeated immediately prior to sacrifice of the cats. The differences in ABR thresholds, between preimplantation and pretermination measurements, were averaged across the frequency range for each cochlea to yield their individual mean rise in ABR threshold.

**Surgery.** Due approval of the experimental protocol was obtained from the Royal Victorian Eye and Ear Hospital Animal Ethics Committee prior to commencement of implant surgery. All cats were premedicated with subcutaneous atropine sulfate (0.04 mg/kg) and acepromazine (0.04 mg/kg). Once ABR measurements were made, anesthesia was induced with intravenous Saffan (10 mg/kg) and maintained with halothane and methoxyflurane administered via an endotracheal tube. The round window membrane was accessed via a postauricular incision followed by opening of the bulla cavity. Where indicated, intentional trauma was applied by gently scraping the endosteum with the bent tip of a 23-gauge needle just inside of the round window for a distance of 2 mm. A drop of blood was then withdrawn from a neighboring blood vessel and placed over 2 mg of bone dust that had previously been autoclaved. The mixture was stirred to form a semisolid bone pâté that was introduced through the round window incision into the scala tympani. The appropriate electrode array was then inserted a distance of 6 mm along the scala tympani, with the electrode lead wire being fixed with a silk suture to the bulla wall. Routine daily postoperative care followed.

**Morphologic Analyses.** The cats were painlessly sacrificed with an overdose of pentobarbitone administered intramuscularly. The temporal bones were removed and trimmed and the bulla was opened. The cochlea was trimmed and decalcified in about 4 weeks with 14% ethylenediaminetetraacetic acid in neutral buffered formalin. The cochlea was then embedded in Spurr's resin and sectioned in the paramodiolar plane at a thickness of 3 μm. All histologic sections were examined for evidence of tissue growth, trauma, infection, and survival of neurosensory structures. A computer software package developed at the Department of Otolaryngology, University of Melbourne, affords an accurate analysis of images projected via a video camera from slides mounted on a standard microscope. This is carried out by delineating and recording the borders of specified histologic features on contiguous sections, and allowing the automatic sorting of such data to produce a three-dimensional screen display of these features, as well as a calculation of their area and volume (Fig 1). The quantified features permit statistical comparisons to be made between different cochleas to which differing parameters have been applied.

**RESULTS**

Two of the four cochleas in group A, which consisted of cochleas to which neither bone pâté nor trauma was intentionally applied, showed no new bone growth and minimal fibrous tissue reaction (cochleas 675L and 692R); one (692L) displayed evidence of unintentional trauma and new bone and fibrous tissue growth, while the remaining cochlea (675R) contained extensive new bone and dense fibrous tissue formation due to an unknown cause.

All the remaining 16 cochleas (group B) that received trauma, intentional or otherwise, and/or bone pâté displayed certain degrees of intracochlear new bone and fibrous tissue
formation. The commonest sites of osteoneogenesis appeared to be 1) along the outer wall of the scala tympani, usually extending from the region of the round window membrane, 2) beneath the osseous spiral lamina (Fig 2), and 3) within the fibrous tissue surrounding the electrode tract.

The total volumes of new bone and fibrous tissue in the scala tympani of each cochlea are shown in the Table. The Mann-Whitney U test applied to the histologic data demonstrated the presence of a significant overall correlation between the presence of bone pate and/or trauma and the intracochlear growth of new bone (p = .01). However, there did not appear to be a significant correlation with fibrous tissue formation (p = .19).

Multiple regression confirmed a significant correlation between the volume of new bone in the scala tympani of a cochlea and the mean change in ABR threshold of that cochlea. This relationship, however, did not appear to hold true for the growth of fibrous tissue. Using the same nonparametric tests and selecting individual cochleas with specific insertion parameters for statistical comparison, it was possible to show that in the presence of both endosteal trauma and bone chips, there was no significant difference in the amount of intracochlear new bone (p = .25) and fibrous tissue (p = .46) between cochleas that had been implanted with electrodes containing no EHDP and those that had been implanted with EHDP electrodes. Furthermore, in the presence of bone chips, endosteal trauma, whether intentional or not, exerted no significant influence on the amount of intracochlear osteoneogenesis and fibrous tissue formation, no matter whether EHDP was present or not. Finally, in the absence of demonstrable trauma and in the presence of EHDP, the introduction of bone chips made no significant difference to the amount of new bone (p = .36) or fibrous tissue (p = .17) that subsequently formed.

**DISCUSSION**

The present study demonstrates in the experimental animal the ease with which new bone and fibrous tissue can form within the scala tympani in response to the implantation of an electrode array, and that such tissue growth is associated with an elevation of ABR threshold for the cochlea. In addition, endosteal trauma and bone chips are both associated with an increased risk of intracochlear osteoneogenesis. However, once new bone and/or fibrous tissue form, the actual amount of tissue growth is not predictable, and the relative roles of trauma and bone chips may not easily be separated. This implies that other factors are involved in the pathogenesis of intracochlear new bone growth, for instance, the local cochlear microenvironment and host factors such as infection, causing biologic variation between cochleas of different animals. In addition, EHDP did not appear to have made any significant difference to the extent of new bone and fibrous tissue growth within the cochlea. The finding of a highly significant correlation between the extent of intracochlear new bone growth and elevation of ABR thresholds in this study indicates that intracochlear osteoneogenesis may be associated with a significant deterioration in the hearing function of a subject.

**CONCLUSION**

Intracochlear osteoneogenesis and fibrous tissue growth represent a real pathologic complication of cochlear implantation, for which no effective therapeutic or prophylactic measure is presently available, apart from the adoption of a general cautious surgical approach minimizing the risks of endosteal trauma and introduction of minute bone chips into the scala tympani. The mechanism of intracochlear osteoneogenesis is complicated and is likely to be multifactorial.

**REFERENCES**


