Histopathology Following Electrode Insertion and Chronic Electrical Stimulation


Department of Otolaryngology, University of Melbourne, Parkville, Victoria, 3052; and *C.S.I.R.O., Division of Manufacturing Technology, Fitzroy, Victoria, 3052, Australia

Abstract

We have examined a number of safety issues associated with cochlear implants. This work has been primarily designed to evaluate the histopathological effects of intracochlear electrode implantation and chronic electrical stimulation. The results of these studies may be summarized as follows: 1) The insertion of the banded free-fit scala tympani array into human cadaver temporal bones produces minimal damage, occurring primarily to a localized region of the spiral ligament. This damage would not result in significant neural degeneration and thus, would not compromise the efficacy of the multiple channel device; 2) chronic intracochlear electrical stimulation for continuous periods of 500 to 2000 hours, using charge balanced biphasic current pulses developing charge densities of 18-32 μC/cm² geom./phase, does not adversely affect the spiral ganglion cell population; 3) labyrinthine infection severely reduces the viable spiral ganglion cell population; 4) the formation of new bone -- present in approximately half of the animals we have implanted -- is not associated with electrical stimulation per se; 5) scanning electron microscope studies of electrodes subjected to long periods of intracochlear electrical stimulation reveals minimal platinum dissolution when compared with unstimulated control electrodes, and electrodes that have been stimulated for similar periods in inorganic saline.

Introduction

There are a number of safety issues that must be addressed prior to the clinical application of cochlear implants. These safety considerations include; the degree of trauma associated with electrode insertion, and the histopathological consequences of chronic electrode implantation and electrical stimulation.

The development of cochlear implants has inevitably resulted in a number of design approaches. Such variations in design, which include; size and rigidity of the electrode array, size and type of stimulating electrode(s), electrode insertion technique, implant encapsulant, and stimulation regime, may result in significant variations in the histopathological response. It is therefore apparent that the pre-clinical development of each device must include a rigorous assessment of these safety issues.

The purpose of this paper is to review a number of studies we have performed as part of the evaluation of the safety and efficacy of the Australian multiple channel cochlear prosthesis.
An Evaluation of Electrode Insertion Trauma in Human Temporal Bones

It is essential that the surgical placement of an electrode array does not compromise the residual spiral ganglion cell population. Animal studies have consistently demonstrated that tears along the basilar membrane or fractures of the osseous spiral lamina will result in severe neural degeneration localized to the site of damage (6, 16, 17, 21, 23). Therefore, it is particularly important to evaluate insertion trauma in multiple channel devices as their operational strategies are based on the selective stimulation of specific spiral ganglion cell populations.

This study was designed to evaluate the trauma associated with the insertion of the banded scala tympani electrode array. The electrodes were inserted into fresh human cadaver temporal bones and the damage was assessed histologically.

Methods

Nine human temporal bones were used in this study. They were obtained at post-mortem, stored in cold saline and were inserted with an electrode array within 24 hours of death. The surgical preparation and insertion of the electrode array followed our surgical protocol for this procedure (7). Figure 1 shows a diagram of the free-fit banded scala tympani array used in this study. Each array was inserted to 25mm or the point of first resistance, and a new array was used for each temporal bone. Following insertion, the array was withdrawn and the insertion distance measured. The temporal bone was placed in fixative and the cochlea prepared for histological evaluation. Damage to the osseous spiral lamina, basilar membrane, spiral ligament, and Reissner's membrane were recorded, and located along the cochlear spiral.

![Diagram of the banded scala tympani array used in this study. All dimensions are in millimeters (Nucleus, Ltd, by permission).](image)

Results

The electrode insertion distance varied from 15.5mm to 27mm (mean 18.6mm; SD = 3.5mm). Figure 2 summarizes the results of this study. In this figure, the aggregate trauma for each damage mode is indicated as a percentage of the aggregate insertion distance for the nine cochleas. Three of these cochleas showed no evidence of trauma as a result of the electrode insertion.

The most common form of trauma was a tear in the spiral ligament...
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Figure 2: Aggregate insertion trauma in millimeters or as a percentage of the aggregate distance of 167mm.

lining the outer wall of the scala tympani. An example of this form of damage is shown in Figure 3. Trauma of this kind occurred in five cochleas and was generally restricted to a region of approximately 7-11mm from the round window. Tears in Reissner's membrane were frequently associated with this trauma; presumably as a result of tension following damage to the spiral ligament.

Figure 3: Photomicrograph of a tear in the spiral ligament of the scala tympani (arrow), approximately 10mm from the round window. (x58).
Three cochleas had localized tears in the basilar membrane as a result of the electrode insertion. In one cochlea, the tip of the electrode array deviated from its course along the scala tympani, penetrated the basilar and Reissner's membrane, resulting in a 1mm tear in the basilar membrane 15mm from the round window. It is worth noting that during the insertion procedure, the surgeon reported resistance to insertion at approximately 17mm from the round window, after which no further insertion was attempted. A second cochlea had a 3mm tear in the basilar membrane associated with a severe tear in the spiral ligament. Like the trauma to Reissner's membrane, it is felt that this damage is a result of excess tension, following distortion of the spiral ligament by the electrode array. A third cochlea had a tear in the basilar membrane localized to a 1mm fracture of the osseous spiral lamina. This fracture occurred approximately 5mm from the round window and was the only example of osseous spiral lamina damage resulting from electrode insertion. The fracture was attributed to the electrode array buckling in the basal turn.

Discussion

These results must be evaluated in terms of their probable histopathological consequences.

Damage to the osseous spiral lamina and basilar membrane were restricted to a few small locations in three of the nine cochleas. This damage was thought to be due to the array buckling in the basal turn, and attempts to force the array past a point of significant resistance. Both forms of trauma have been well documented in animal studies, resulting in severe, localized neural degeneration (6, 18, 19, 20, 21, 23). Furthermore, all studies have shown new bone growth associated with damage to the osseous spiral lamina.

Tears along the spiral ligament typically occurred in a 7-11mm region from the round window. Presumably, this is a region where the array would first come in contact with the outer bony wall of the scala tympani following a round window insertion. Similar damage was reported to have occurred in the right cochlea of a patient who had received bilateral cochlear implants (9). Although little data is available on the histopathological consequences of this trauma, we would not expect resultant neural degeneration unless the damage included the basilar membrane. A soft tissue reaction would however be expected. Indeed, Johnsson et al. (9) reported a very small fibrosis without associated new bone. However, the possibility of osteogenesis cannot be ruled out as it has been reported to be associated with endosteal trauma (17).

Reissner's membrane is a delicate structure and is most susceptible to histological artifact. It is therefore difficult to be sure of the extent of trauma to this membrane attributable to electrode insertion. There are few experimental studies that have examined neural degeneration as a consequence of this form of trauma; however, results from two studies would indicate that the amount of neural degeneration is insignificant providing the fistula can close (6, 8).

Considering the extent and type of trauma experienced in the present study, we would conclude that the insertion of the banded free-fit scala tympani array would not result in significant neural degeneration, and therefore would not affect the operational efficacy of the multiple channel cochlear implant. Moreover, the present study clearly highlights the care required for the surgical placement of this type of array.
Allowing the array to buckle, or forcing the array past a point of first resistance, could result in localized neural degeneration; these findings should therefore ensure even less electrode insertion trauma.

Perhaps the most common histological reaction experienced following the insertion of this type of electrode array would be fibrosis in response to tears along the spiral ligament. Fibrosis may make the replacement of an electrode array difficult, and highlights the need to incorporate a connector in the implant design. This would allow the replacement of a faulty implant package without the need to remove the electrode array.

An Evaluation of Chronic Intra cochlear Electrical Stimulation

The effect of chronic electrical stimulation on cochlear structures is fundamental to an evaluation of the safety and efficacy of cochlear implants.

The development of biologically safe means of electrically stimulating neural tissue is currently receiving considerable attention from a number of investigators. Direct and radio frequency currents are known to result in destruction of tissue; however, non-destructive electrical stimulation can be achieved by the use of biphasic pulsatile stimuli (10, 13). Although maximum biologically safe stimulation regimes have yet to be clearly defined, the evidence from a number of investigators suggests that the charge density per phase (\( \mu \text{C/cm}^2 \text{ geom./phase} \)) and the charge injected per phase (\( \mu \text{C/phase} \)) are important parameters when establishing biologically safe stimulating levels (2, 4, 14). In addition, a maximum electrochemically safe stimulation regime for platinum electrodes has been determined, thus ensuring minimal electrochemical reactions at the electrode tissue interface (5). This stimulation regime consists of balanced biphasic pulses at a maximum charge density of 300 \( \mu \text{C/cm}^2 \text{ geom./phase} \).

This study was designed to examine the histopathological and physiological effects of chronic intracochlear electrical stimulation in cats, using a stimulation regime and electrode array developed for the Australian multiple channel cochlear prosthesis. The stimulation regimes were within the upper operating range of the Australian device, although well below the maximum electrochemically safe level (5). The status of the auditory nerve was monitored periodically throughout the stimulation program using electrically Evoked Auditory Brainstem Responses (EABRs), and the cochleas were histopathologically evaluated under light microscope.

Methods

Using sterile conditions, a banded bipolar electrode array was inserted 5mm into the scala tympani via the round window of ten normal-hearing adult cats. Both cochleas of each animal were implanted; one side served as a control. Allowing ten days for recovery, each animal commenced a continuous electrical stimulation program. The stimulus regime consisted of biphasic constant current pulses with a pulse width of 0.2 ms per phase and a repetition rate of 500 pulses per second. The phases were charge balanced to within 0.01-0.1%. Mid-dynamic range stimulus currents were used and they varied from 0.5-0.9 mA, thus developing charge densities of 18-32 \( \mu \text{C/cm}^2 \text{ geom./phase} \). EABRs were recorded periodically for each animal; these data provide a non-invasive means of establishing the status of the auditory nerve, as the EABR growth response is monotonically related to the number of neural fibres being stimulated (12).
Following completion of the stimulation program, each animal was sacrificed and their cochleas prepared for histology. Each cochlea was evaluated for its histopathological reaction, and spiral ganglion cell densities (cell/mm²) were determined for cell populations within 1 mm of the bipolar electrodes. This is a region within the electrically excited field for mid-dynamic range currents. The inflammatory reaction for each cochlea was graded from I to V on the basis of the number of polymorphonuclear and mononuclear leukocytes, and the degree of fibrous tissue. The mean spiral ganglion cell densities for stimulated and control cochleas were statistically evaluated; they were also statistically compared with the degree of acute inflammation.

Following sacrifice, the control and stimulated electrode arrays were removed from the cochleas, ultrasonically cleaned, and prepared for examination under a Scanning Electron Microscope (SEM). These in vivo electrodes were compared with identical arrays stimulated in inorganic saline for comparable periods using the same stimulation regime. The SEM evaluation included inspection of both the Silastic carrier and the metal electrode surface, with particular attention given to areas of possible metal corrosion.

Results

The animals in the present study were continuously stimulated for periods ranging from 424 to 2029 hours, with implantation periods of 32 to 113 days.

Cochlear Histopathology:

Five of the 20 cochleas in the present study had moderate-to-severe inflammatory reactions (grades III to V). The degree of inflammation reaction was not associated with the degree of electrical stimulation, as two of the five cochleas were non-stimulated controls. Mild inflammation did not generally result in extensive hair cell loss or atrophy of the organ of Corti (Figure 4a). The presence of viable hair cells adjacent to the bipolar electrode, in a cochlea stimulated for 2029 hours, suggests that electrical stimulation per se has little adverse effect on hair cells. An eosinophilic exudate was occasionally present in cochleas with a mild inflammatory reaction, and was generally restricted to the basal portion of the scala tympani. A number of cochleas showed no apparent inflammation reaction (Figure 5a).

Cochleas with moderate-to-severe inflammation reactions had significant increases in the number of polymorphonuclear and mononuclear leukocytes, and more pronounced and widespread exudate (Figure 6a). These reactions were also associated with more extensive hair cell loss and atrophy of the organ of Corti. Loss of dendrites were closely associated with atrophy of the organ of Corti.
Figure 4a: Basal turn of a cochlea stimulated for 1011 hours. This cochlea had a grade II acute inflammation. Inner and outer hair cells and spiral ganglion cells appeared normal throughout all turns. e, electrode tract. (x30)

b: Spiral ganglion cells adjacent to the bipolar electrode. (x350)

c: EAHR growth responses (recording days are indicated as days post-surgery. (From Shepherd et al., Acta Otolaryngol. (1983b) by permission) (19).
Figure 5a: Basal turn of a cochlea stimulated for 568 hours. This cochlea showed no inflammatory reaction to the presence of the electrode array; however, inner and outer hair cells were missing in all turns. (x30).

b: Spiral ganglion cells adjacent to the bipolar electrode. (x350).

Figure 6a: Basal turn of a cochlea stimulated for 1189 hours. The electrode array had fractured the osseous spiral lamina resulting in new bone (n). This cochlea had a grade III acute inflammation; polymorphs were present in the scala tympani, and a pronounced exudate had spread through all turns of the cochlea (ex). Hair cells and the organ of Corti were absent throughout the cochlea, and the dendrite population was severely reduced. (e) electrode tract. (x30).

b: Residual spiral ganglion cells in the basal turn. (x120).

c: EABR growth responses. Note the loss of the low-gradient response and the reduction in the slope of the high-gradient response. (From Shepherd et al., Acta Otolaryngol. (1983b) by permission (19).
Electrode insertion trauma was observed in two of the 20 implanted cochleas. In both cases the osseous spiral lamina had been fractured, resulting in localized moderate-to-severe spiral ganglion cell loss and new bone growth (Figure 6a).

The implanted array evoked a fibrous tissue reaction in 18 cochleas; these reactions varied from fine tissue capsules surrounding the array, to generalized reactions occupying the entire scala tympani and extending to the middle turn. The degree of fibrous tissue reaction was not related to the degree of electrical stimulation. New bone occupied small regions of the scala tympani in nine cochleas, and appeared to originate from the endosteal lining in association with fibrous tissue. The extent of new bone growth did not, however, show any correlation with the extent of fibrous tissue within the scala tympani or the degree of acute inflammation. Moreover, its formation did not appear to be related to intracochlear electrical stimulation - four of the nine cochleas containing new bone were controls.

Spiral Ganglion Cell Histopathology:

Spiral ganglion cell densities were not adversely affected by chronic electrical stimulation. Analysis of spiral ganglion cell densities for both control and stimulated cochleas showed no statistically significant difference. However, the correlation between spiral ganglion cell density and the degree of acute inflammation was highly significant (p<0.01, multiple linear regression analysis).

Histological examination of cochleas with little or no acute inflammation revealed normal spiral ganglion cells (Figures 4b, 5b). Although cochleas with moderate-to-severe inflammatory reactions showed significant and widespread spiral ganglion cell loss, the majority of remaining cells appeared normal (Figure 6b).

Electrically Evoked Auditory Brainstem Responses:

The biocompatible nature of the stimulation regime was confirmed by the EABR growth response data. This is illustrated by the growth responses from an animal continuously stimulated for 1728 hours over 92 days (Figure 7). The reproducible nature of the responses throughout the stimulation program indicates that the stimulation regime did not adversely affect the spiral ganglion cell population. This was confirmed histologically.

The two gradient response of the EABR growth response curve is a result of two different physiological responses to the electrical stimulus (3). The low-gradient (large dynamic range) response is electrophonic in origin and, consequently, can be masked with low intensity broad band noise. The high-gradient (small dynamic range) response is due to direct electrical excitation of peripheral auditory neurones. From this finding, it was possible to obtain good correlation between EABR growth responses and cochlear histopathology. During the course of the electrical stimulation program, three distinct trends in EABR growth responses became apparent. First, a group of four animals showed little variation in the growth response throughout the stimulation program (Figures 4c, 7). Histological evaluation of these cochleas revealed near normal hair cell
populations and normal spiral ganglion cell populations. Second, a group of three animals showed progressively elevated thresholds and a loss of the low-gradient electrophonic limb, with little change in the high-gradient limb (Figure 5c). These cochleas showed widespread hair cell loss with normal spiral ganglion cell populations. Third, a group of three animals showed a greater increase in threshold compared with the second group of animals, a complete loss of the low-gradient limb and a significant reduction in the high-gradient limb (Figure 6c). Histologically, these cochleas showed total hair cell loss together with extensive spiral ganglion cell loss and moderate-to-severe acute inflammation.

Scanning Electron Microscopy of Platinum Electrodes:

Evaluation of the surface of in vitro stimulated platinum electrodes revealed surface pitting corrosion, the extent of which depended on the charge density and, to a lesser extent, on aggregate charge (Figure 8). In contrast, however, the stimulated in vivo electrodes did not show this correlation although they had been stimulated for as long as 2029 hours (Figure 9). Indeed, there was no apparent difference between the surfaces of in vivo stimulated and control electrodes. Small amounts of pitting were, however, occasionally seen on both stimulated and control in vivo electrodes, and appeared localized to extensively worked regions of the electrode surface, such as weld zones. There was no sign of degradation of the Silastic barrier in either in vitro or in vivo arrays. Fibrous tissue was frequently attached to the platinum electrode surface. This attachment was quite effective considering the electrode array had been removed from the cochlea, and ultrasonically cleaned. No fibrous tissue was seen attached to the Silastic carrier.
Discussion

The results of the present study have important implications for cochlear prostheses. These results clearly indicate that chronic intracochlear electrode implantation and electrical stimulation - using a carefully controlled charge balanced biphasic stimulation regime - has little adverse effect on the cochlea in general, and the primary auditory neurones in particular. Furthermore, the results of the SEM analysis of in vivo electrodes indicate that the stimulation regime does not affect the corrosion properties of the platinum electrode to any significant extent. The adverse effects of infection, however, emphasize the need to ensure that both implant designs and surgical protocols are produced with the aim of minimizing this risk.

Experimental studies in animals have demonstrated the inability of an implanted cochlea to tolerate infection (6, 21). With this in mind, we evaluated a number of round window sealing techniques by inoculating the bullae of implanted cats with Staphylococcus aureus or Beta Haemolytic Streptococcus. Although preliminary, the results indicate little difference in the inflammatory reactions of inoculated cochleas when compared with implanted control cochleas, and suggest that infection, if present, is most likely to spread into the cochlea during, or shortly after, surgery, prior to the formation of an effective round window seal. Our clinical experience has not demonstrated a problem with infection; however, there is a need to ensure the effectiveness of round window seals, especially if children are to be considered as implant candidates.
Although a maximum biologically safe charge density has yet to be defined for any neural stimulation site, results from a number of studies suggest that such a charge density is significantly less than the electrochemically safe limit of 300 μC/cm² geom./phase. (1, 2, 14). Walsh and Leake-Jones (24) monitored EABR thresholds and growth responses during chronic intracochlear electrical stimulation in cats, and concluded that stimulus induced damage of the auditory nerve occurred at charge densities of 100-200 μC/cm²/phase, with no stimulus damage at 20-40 μC/cm²/phase. The results of the present study confirm the biocompatible nature of stimulus regimes operating with charge densities in the order of 40 μC/cm² geom./phase. Experience with our cochlear implant patients indicates normal comfortable levels are in the range of 20-30 μC/cm² geom./phase, although there is some variation with patients. It is important to note that these studies used controlled stimulation regimes, i.e., the charge densities were known and the pulses were carefully charge balanced. Some cochlear prostheses use analogue stimulation regimes derived from speech signals, thus providing little control over the instantaneous charge densities developed. It is conceivable that these stimulation regimes would not be as well tolerated by the biological environment.

The correlation between EABR growth responses and cochlear histopathology demonstrated in the present study has been reported by other investigators (22). These authors used a round window electrode and stimulated using a monopolar regime; they were able to correlate the slope of the electrical EABR growth response with residual spiral ganglion cell populations. Although the results of the present study could not...
demonstrate such a quantitative correlation, they nevertheless indicate the suitability of the technique for clinical assessment of patients. Indeed, Smith and Simmons (22) propose to use the technique to assess neural populations in candidate implant patients. In addition, this technique should prove a useful research tool for the non-invasive assessment of the status of the auditory nerve in implant patients.

The presence of a low threshold large dynamic range electrophonic response, evoked from animals with normal hearing, as demonstrated in the present study, indicates that physiological or psychophysical data from implanted, normal hearing animals, must be interpreted with caution. Clearly, deaf animals would provide better animal models.

In seven of the nine cochleas containing new bone, there was no obvious sign of trauma to the endosteum or the osseous spiral lamina. Moreover, the mechanism of new bone formation in these cochleas appeared to be associated with a loose fibrous tissue reaction adjacent to the endosteum. Unlike a similar study that found new bone growth associated with electrical stimulation (24), the results of the present study did not find such a correlation. This variation in results may be due to variations in stimulation regimes, as one study adopted a protocol that included deliberate over-stimulation and charge asymmetry for a number of animals (24).

SEM analysis of the in vivo and in vitro electrodes agreed with electrochemical studies investigating dissolution of platinum stimulating electrodes (11, 15) and illustrated the ability of the protein-rich biological environment to inhibit platinum dissolution. In addition, the small amounts of pitting associated with extensively worked regions of the platinum ring emphasizes the need to develop simple electrode fabrication techniques with minimum cold metal working.

Conclusion

We have addressed a number of safety issues associated with cochlear implants. Our results may be summarized as follows: 1) The insertion of the banded free-fit scala tympani array produces minimal damage that would result in neural degeneration. The limited extent of this damage would not reduce the efficacy of the multiple channel prosthesis; 2) The electrode array should not be allowed to buckle during the insertion procedure, as this is likely to result in a fracture of the osseous spiral lamina; 3) The array should not be inserted past the point of first resistance as this may result in damage to the membranous labyrinth including the basilar membrane; 4) Continuous intracochlear electrical stimulation for periods of up to 2000 hours, using a carefully controlled charge balanced stimulation regime, does not result in adverse physiological or histopathological effects on the spiral ganglion cell population, or the cochlea in general; 5) The effect of infection can result in severe and widespread loss of spiral ganglion cells and would therefore compromise the safety and efficacy of a cochlear implant. The effectiveness of round window seals to prevent infection requires further investigation; 6) New bone growth, at least with the stimulation regime and charge densities used in the present study, cannot be attributed to electrical stimulation. Its formation, however, appears to be associated with a fibrous tissue reaction adjacent to the endosteal lining; 7) EABR growth responses correlated with cochlear histopathology, and indicate the suitability of the technique in the assessment of implant candidates and as a research tool in assessing implant patients; 8) SEM examination of in
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vitro and in vivo stimulated electrodes indicates that the protein-rich biological environment inhibits platinum corrosion.

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Author/s:
Shepherd, R. K.; Clark, Graeme M.; Pyman, B. C.; Webb, R. L.; Murray, M. T.; Houghton, M. E.

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