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Effects of Semicircular Canal Electrode Implantation on Hearing in Chinchillas

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Abstract

Conclusion—Implantation of vestibular prosthesis electrodes in chinchilla semicircular canal ampullae can be accomplished without significant loss of cochlear function; however, the risk of hearing loss with the current surgical technique is high.

Objectives—To determine if it is possible to implant vestibular prosthesis electrodes into the labyrinth without damaging hearing, and to quantify the extent of hearing loss due to implantation.

Method—The left semicircular canals of 6 chinchillas were implanted with 3 bipolar pairs of electrodes using a transmastoid approach. Right ears, which served as controls, were subjected to the same mastoid approach without fenestration and implantation. Auditory brainstem response hearing thresholds to free field clicks and tone pips at 2, 4, 6, and 8 kHz were measured bilaterally 3–9 weeks after implantation. Hearing thresholds were compared between sides and against data from 6 normal chinchillas.

Results—4 implanted ears suffered severe hearing loss, with thresholds ranging from 5 to 11 SD above the mean threshold of sham surgery control ears across all tested stimuli. 2 implanted ears had preserved hearing, with thresholds remaining within 1 SD of the mean threshold of sham surgery control ears across nearly all stimulus frequencies.

Keywords

Vestibular prosthesis; labyrinth; sensorineural hearing loss; auditory brainstem response; chinchilla; cochlea; implant

Introduction

The vestibulo-ocular reflex (VOR) stabilizes the eyes during head movements, maintaining optimal visual acuity. While other systems such as proprioception, smooth pursuit, and optokinetic nystagmus can compensate in part for vestibular deficiency, these systems only operate up to velocities of approximately 50 degrees/sec and frequencies of approximately 1 Hz, failing to cover the range of rapid head movements encountered in everyday activity [1].

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We are not aware of any previous submissions or publications that might be regarded as the same or very similar to the work presented here.

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Severe damage to sensory hair cells in the vestibular end organs thus results in disabling symptoms such as oscillopsia and disequilibrium, which can interfere with locomotion, voluntary head rotation, and other activities typical of daily life.

Like cochlear implants, which bypass normal cochlear transduction to treat sensorineural hearing loss, a multi-channel vestibular prosthesis has the potential to restore vestibular function in the setting of hair cell damage [2]. Rotation sensors within the prosthesis measure head movements in three orthogonal planes, and these signals are used to modulate the stimulation of vestibular afferent nerve endings via electrodes implanted within each semicircular canal (SCC). Given the close anatomic relationship between the vestibular labyrinth and cochlea, it is possible that a prosthesis meant to restore function in one system may inadvertently affect the other. A subset of cochlear implant patients experience vestibular disturbances ranging from mild decreases in VOR gain to severe dizziness, loss of balance, and vertigo [e.g., 3–7]. In the present study, we assessed the impact of SCC electrode implantation on hearing in chinchillas (*C. laniger*) as measured by auditory brainstem responses (ABR). Our primary goal was to determine whether electrodes could be implanted in SCC ampullae (near the distal ends of the respective branches of the vestibular nerve) without causing significant hearing loss. Other specific aims were to (1) establish the normal range of hearing thresholds in chinchillas, as measured by our detection system; (2) quantify change in hearing threshold due to operative procedures on the mastoid bullae (sham surgery); and (3) quantify change in hearing threshold caused solely by the placement of electrodes into the SCCs.

Methods

Adult female wild-type chinchillas (450–600g, Ryerson Chinchilla Ranch, Plymouth, OH) were used for all experiments, which were performed in accordance with a protocol approved by the Johns Hopkins Animal Care and Use Committee.

Auditory Brainstem Response

Animals were anesthetized with an initial intramuscular injection of ketamine (5.83mg/kg) and xylazine (0.83mg/kg). Repeated doses equal to the original were given as needed to maintain a suitable level of anesthesia, up to a total of 2–3 times the original dose administered over a period of 1–1.5 hours of testing. Hearing thresholds were determined by ABR [8]. Apparatus and set-up were similar to that described by May et al [9]. Animals were placed inside an acoustic isolation chamber where they were exposed to clicks and tone pips at 2, 4, 6, and 8 kHz emitted from a free-field speaker. The maximum sound intensity generated by this speaker was 100 dBSPL at 2 kHz, 90 dBSPL at 4 kHz, 83 dBSPL at 6 kHz, and 75 dBSPL at 8 kHz. To selectively probe monaural function using the free field system, the contralateral ear canal was occluded using a foam plug. In a separate experiment to test the effectiveness of the earplug, we used 3 chinchillas that each had only one hearing ear after receiving an infusion of gentamicin through the tympanic membrane of the other ear. With the normal ear patent, ABR responses were reliably elicited at thresholds no greater than 20–40 dBSPL. Use of the earplug increased thresholds by 35–55dBSPL for all sound stimuli.

Evoked potentials were recorded using subcutaneous difference electrodes placed just anterior and posterior to the base of the pinna of the tested ear. The common electrode was placed midline on the forehead approximately 1cm above eye level. The electrode signal was filtered with cutoff frequencies of 100 and 3000 Hz, amplified with a gain of 300,000x, and digitized at a sampling rate of 195 kHz. The average ABR waveform was based on 500 presentations of the stimulus given at a rate of 30 per second. The response magnitude was defined as the maximum peak-to-peak voltage of the ABR waveform during a 5 ms interval beginning 2.5 ms after the onset of each stimulus. Background activity was measured for a 5 ms interval

beginning 25 ms after each stimulus onset, well after the cessation of ABR activity. At each frequency, the level of the stimulus was presented in 10 dB descending increments until the ABR waveform was no longer visible, then in alternating 5 dB ascending increments until a clear waveform reappeared. The response magnitude was plotted as a function of stimulus level, and intermediate values were interpolated. The hearing threshold was defined as the stimulus level at which the ABR response magnitude was 2 SD greater than the average background activity of all recordings in the same data set.

Surgical Implantation of Electrodes

Eight chinchillas were implanted on the left side with SCC ampulla electrodes while the right side served as a sham surgery control. Animals were anesthetized with an initial intramuscular injection of ketamine (11.66mg/kg) and xylazine (1.66mg/kg). Repeated doses that were half the original were given as needed to maintain a suitable level of anesthesia, up to a total of 3–4 times the original dose administered over a period of 3–4.5 intraoperative hours. The skin over the mastoid bullae was infiltrated with local anesthetic (2mg/kg lidocaine with 2µg/kg epinephrine) to supplement the general anesthetic.

The electrode implantation technique used for this study is identical to that described previously [2]. An otologic drill was used to open each mastoid bulla. No further drilling was done on the right (control) side. On the left side, a small window was opened near the junction of the thin segment with the ampulla using a 1 mm diamond bur. Electrodes were made from twisted pairs of 75–125 µm diameter Teflon[®]-coated Pt/Ir wire (AS169-40, Cooner Wire, Chatsworth, CA) stripped approximately 250 µm and ganged to an 8-pin DIP socket connector. Each pair of electrodes was inserted into one ampulla lumen and advanced medially toward the ampullary nerve. A reference electrode was embedded in the neck musculature.

A small amount of dental cement (ESPE ProTempII, 3M Corp, Minneapolis, MN) was used on the implanted (left) side to stabilize the electrodes where they entered the SCC, thus sealing the openings and preventing the leakage of perilymph. Both bullae were then filled with Gelfoam (Upjohn, Kalamazoo, MI) prior to closing the skull defect on both sides with additional dental cement. The purpose of the Gelfoam was to protect against conductive hearing loss that could otherwise occur with dental cement touching the ossicles. The DIP socket was secured in the dental cement overlying both bullae. In addition, a phenolic head post was embedded in the dental cement to allow head fixation for future eye movement recordings. As described above, the only difference in treatment between left and right ears was that, on the right, the SCCs were not opened and no electrodes were inserted. This allows the right ear to serve as a sham surgery control. Animals were allowed to fully recover prior to testing 3–9 weeks post-implantation. Specifically, animals e and f were tested at 3 weeks post-implantation; animals a, b, and d were tested at 4 weeks; and animal c was tested at 9 weeks.

To confirm placement of electrodes in the ampullae prior to ABR testing, eye movements of each implanted animal were observed during stimulation via each pair of electrodes. Alert animals were restrained via the head post in a video-oculographic system described in detail elsewhere [2]. Stimuli were 200–400 uA/phase, 200–400 uS/phase charge-balanced, biphasic pulses, modulated over pulse rates of 20–300 pulses/S by a 0.5 Hz or 2 Hz carrier and delivered either via a bipolar pair within an ampulla or via one ampullary electrode with respect to a distant reference in the neck. In each case, excitation via ampullary electrodes elicited eye rotations in phase with the modulating carrier, confirming functional electrical stimulation of one or more branches of the vestibular nerve.

Statistical Analysis

A directional Wilcoxon Signed-Rank test was used to compare hearing thresholds between implanted left ears and sham surgery right ears. A directional Mann-Whitney test was used to compare hearing thresholds between sham surgery right ears and normal ears. A significance level of 0.05 was used for all comparisons. Upon examination of the middle ear through the tympanic membrane, 2 of an original cohort of 8 implanted animals were excluded from the analysis because displacement of the Gelfoam resulted in dental cement filling the middle ear cavity.

Results

Normative Data

To generate a set of normative chinchilla hearing thresholds for our ABR testing apparatus, we tested the 12 ears of 6 normal animals ($n = 12$). The average hearing threshold was 31.6 ± 1.8 dB SPL (mean $\pm$ SD) for clicks, 35.7 ± 5.4 dB SPL for 2 kHz tones, 16.5 ± 4.4 dB SPL for 4 kHz, 7.5 ± 4.2 dB SPL for 6 kHz, and 21.0 ± 6.4 dB SPL for 8 kHz (Figure 1A).

Effect of Sham Surgery

Eight chinchillas underwent surgery with the left and right sides treated identically with the exception that on the right, the SCCs were left intact and no electrodes were inserted. The right side thus served as a within-individual sham surgery control, and differences in hearing threshold between the implanted and control ears could be attributed to electrode implantation.

Two of 8 chinchillas originally implanted were excluded from the analysis due to settling of dental cement into the middle ear cavity, which we detected via post-operative otomicroscopy during sedation for ABR testing. These ears showed ABR thresholds in the range of 20–60 dB SPL above normative values. This hearing loss must be due at least in part to the disruption of ossicle mobility, because dental cement was seen to be impinging on the ossicles. Since conductive hearing loss was known to confound data from these ears, they were excluded from the analysis.

Since preoperative data were not available on the implanted animals, ABR thresholds recorded from the sham surgery right ears ($n = 6$) were compared with the normative values obtained from the ears of untreated chinchillas ($n = 12$). Figure 1B shows thresholds in 6 individual right ears after sham surgery. Average hearing thresholds after sham surgery were 35.9 ± 5.1 dB SPL (mean $\pm$ SD) for clicks, 44.2 ± 2.9 dB SPL for 2 kHz tones, 22.0 ± 9.0 dB SPL for 4 kHz, 16.2 ± 8.5 dB SPL for 6 kHz, and 20.8 ± 8.8 dB SPL for 8 kHz. The average threshold difference (sham surgery minus normative) ranged from -0.2 to 8.7 dB SPL across all tested stimuli. Significant differences were seen at 2 kHz and 6 kHz, for which sham surgery caused small threshold increases of 8.5 dB SPL ($p = 0.005$) and 8.7 dB SPL ($p = 0.017$), respectively.

Effect of Electrode Implantation

Figure 1C shows ABR thresholds in 6 individual left ears after SCC implant. Figure 2 shows within-individual comparisons of thresholds in implanted and sham surgery ears at each stimulus—clicks in Figure 2A, 2 kHz in Figure 2B, 4 kHz in Figure 2C, 6 kHz in Figure 2D, and 8 kHz in Figure 2E. The average hearing threshold difference (left minus right) of the 6 operated animals was 31.28 ± 18.43 dB SPL for clicks, 20.32 ± 16.54 dB SPL for 2 kHz tones, 34.77 ± 19.71 dB SPL for 4 kHz, $\geq 33.63 \pm 24.93$ dB SPL for 6 kHz, and $\geq 37.05 \pm 21.65$ dB SPL for 8 kHz ($p \leq 0.05$ for all). The threshold differences at 6 kHz and 8 kHz are given as conservative estimates of hearing loss because at these frequencies, an ABR waveform could not be detected in the implanted ears of some animals even at the highest sound intensities generated by our speaker system.

It was evident from the large standard deviations that the outcome distribution was not homogeneous. Four of the 6 implanted animals (c, d, e, and f) showed hearing thresholds on the implanted left side that were 5 to 11 standard deviations (SD) above the mean threshold of all sham surgery right ears across all tested stimuli. The average hearing threshold difference (left minus right $\pm$ SD) in these 4 animals was 43.60 ± 7.22 dBSPL for clicks, 30.93 ± 5.36 dBSPL for 2 kHz tones, 48.50 ± 3.86 dBSPL for 4 kHz, $\geq 50.40 \pm 9.43$ dBSPL for 6 kHz, and $\geq 51.18 \pm 9.36$ dBSPL for 8 kHz. These data indicate that, in 4 out of 6 animals, electrode implantation into the SCCs resulted in a severe hearing loss beyond damage caused by the bulla approach.

On the other hand, the other 2 implanted animals (a and b) showed much smaller threshold differences. For animal a, the threshold difference (left minus right) was 8.7 dBSPL for clicks, 8.5 dBSPL for 2 kHz, 9.4 dBSPL for 4 kHz, -0.6 dBSPL for 6 kHz, and 14.6 dB SPL for 8 kHz. For animal b, the threshold difference (left minus right) was 4.6 dBSPL for clicks, -10.3 dBSPL for 2 kHz, 5.2 dBSPL for 4 kHz, 0.8 dBSPL for 6 kHz, and 3.0 dBSPL for 8 kHz. For most tested stimuli, the implanted left ear thresholds of these 2 animals were no greater than 1 SD above the mean threshold of all sham surgery right ears. The only exceptions were seen in animal a, for which the implanted ear threshold was within 2 SD of the sham surgery mean for clicks and within 3 SD for 2 kHz tones. These data indicate that in 2 out of 6 animals, electrode implantation into the SCCs did not cause hearing loss beyond that caused by the bulla approach.

Discussion

Although SCC electrode implantation caused severe hearing loss in 4 out of 6 animals, the remaining 2 animals retained hearing to the same degree in the implanted ear as in the sham surgery control ear as measured at 4 weeks post-implantation. These results confirm that it is possible to implant vestibular prosthesis electrodes within the labyrinth without compromising hearing as measured a month later.

The only significant threshold changes associated with sham surgery were the small increases of 8.5 dBSPL above normative values seen at 2 kHz and 8.7 dBSPL above normative values seen at 6 kHz. This increase might reflect a conductive rather than a sensorineural hearing loss; a bone conduction ABR (not available on our system) would be necessary to confirm this. Identification of a conductive component to the hearing loss we observed using free-field ABR would further support the conclusion that SCC electrode implantation can be achieved without loss of cochlear function.

Hearing outcome did not correlate with the order in which the chinchillas were implanted (i.e., with experience of the surgeon who performed all implantations), amount of intraoperative anesthesia, or time elapsed between implantation and ABR testing. Future studies will further explore variations in method to identify specific factors that do contribute to hearing loss. Electrode design and surgical technique will be refined to maximize hearing preservation.

It is likely that the hearing loss we observed is due to mechanical disruption of the membranous labyrinth during insertion of electrodes into the ampullae. Alternatively, the loss might be related to other factors, such as the materials used. However, neither the electrode materials (Pt/Ir wire, Teflon, silicone) nor the dental restoration material we used are known to be neurotoxic. Since all electrode insertions involved the same materials, we would expect a neurotoxin to affect all 6 of the implanted ears, but we observed that 2 of the implanted ears had preserved hearing. We might also expect to see a positive correlation between degree of hearing loss and length of exposure time to the cement. The time elapsed between implantation and ABR testing ranged from 3 to 9 weeks, and we did not see more severe hearing loss with

longer exposure time to cement. The 2 hearing-preserved animals were both tested 4 weeks after implant. Of the 4 animals that lost hearing (all to a similar degree), 2 were tested at 3 weeks, 1 at 4 weeks, and 1 at 9 weeks after implant.

It is possible that damaging effects of electrode implantation could evolve slowly, resulting in the onset of hearing loss months or years after implantation. Similarly, it is possible, though it seems unlikely, that animals with severe hearing loss at 4 wks postoperatively might exhibit recovery of cochlear function later. Future studies could address this issue by following cochlear function out to longer post-operative durations. The present study tested hearing changes due to the surgical trauma of implantation. Therefore, although pulsatile electrical stimuli were delivered postoperatively via each electrode to confirm proper placement of electrodes (as indicated in each animal by reflexive eye movements in phase with pulse rate modulation), we did not deliver prosthetic electrical stimuli *during* ABR measurements. Another way that a vestibular prosthesis could affect hearing is through spurious excitation of the auditory nerve by prosthetic electrical stimuli. We will address this question in future studies by measuring ABR thresholds in the setting of concurrent prosthetic electrical stimulation via the implanted electrodes.

Risk of hearing loss will be an important determinant of the clinical utility of vestibular prostheses intended for treatment of patients with profound loss of vestibular sensation but intact hearing. Whereas cochlear implants can be inserted into the scala tympani and thus kept within the perilymphatic compartment of the inner ear, we expected that ampullary electrode implantation would be impossible without violation of the membranous labyrinth and consequent disruption of the endolymph-perilymph electrochemical gradient upon which normal cochlear function depends. Our results show that even in the chinchilla, which has inner ear dimensions much smaller than do humans, functional vestibular prosthesis electrodes can be implanted without significant cochlear injury.

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Figure 1.

Audiograms showing ABR thresholds at 2, 4, 6, and 8 kHz.

A) Mean $\pm$ SD of normal ears. B) Individual sham surgery ears. C) Individual implanted ears.

Figure 2.

Within-individual comparison of ABR thresholds in sham surgery and implanted ears. Gray error bars show mean $\pm$ SD of all 6 animals together. Black error bars show mean $\pm$ SD of the 4 animals that lost hearing in the implanted ear. Stimuli were A) clicks and B) 2kHz, C) 4kHz, D) 6kHz, E) 8kHz tone pips. * This data point is a conservative estimate of hearing loss because an ABR could not be elicited even at the highest sound intensity that could be generated by the speaker at this frequency. The actual hearing threshold is greater than or equal to this value.