A Technique for Implantation of a 3-Dimensional Penetrating Electrode Array in the Modiolar Nerve of Cats and Humans

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Background: We believe that direct intraneural stimulation of the modiolar nerve using an array of electrodes will have lower thresholds, offer greater frequency selectivity and more stimulation sites, and have a greater frequency representation than conventional cochlear implants.

Objectives: To describe a potential auditory prosthesis based on electrical stimulation of the modiolar cochlear nerve and to report the development of a surgical approach in human and animal models.

Design: Cadaveric human and animal studies conducted in temporal bones indicated that an array of penetrating microelectrodes could be implanted in the modiolar nerve. Cat studies using anesthesia were performed to develop the surgical procedure in an animal model. Nerve viability was assessed by measurement of electrically evoked auditory brainstem responses at different stages of the surgery.

Subjects: Two fresh cadaveric human temporal bones, 3 cat cadavers, 1 pig cadaver, and 6 anesthetized cats were used in the experiments.

Results: We were able to implant arrays containing 20 microelectrodes in the human modiolar nerve after exposure by a modified extended facial recess approach. In animals, the modiolar nerve was accessed by the transbulla and the middle fossa approach. The cat was chosen as the appropriate animal model, and the transbulla approach was selected. The round window was exposed by ventral access to the bulla and after cochleostomy; drilling the modiolar bone exposed the modiolar nerve. The mean±SD diameter of the exposed nerve in cats was 1.64±0.07 mm (n=9), and the mean±SD exposed length was 2.50±0.11 mm (n=9); this is adequate to accommodate 20 microelectrodes. The electrically evoked auditory brainstem responses indicated nerve survival during and after the surgery.

Conclusions: The surgical technique allows implantation of up to 20 microelectrodes in the cat and human modiolar nerve. The nerve survives the surgical procedure. This work enables studies in the electrophysiological properties and consequences of long-term implantation.


CONVENTIONAL cochlear implant (CI) prostheses are routinely used to restore a sense of hearing for the profoundly deaf.1 The spiral ganglion cells are the target of stimulation by the CI electrodes, and it is postulated that electrodes close to the modiolus may allow more focused and discrete electrical stimulation, reducing the stimulation threshold and channel interaction.2,3 We suggest that direct intraneural stimulation of the modiolar nerve using an array of penetrating microelectrodes will be better than such attempts at “modiolus hugging” and, hence, we propose that direct cochlear nerve stimulation using such an array can be better than conventional intrascalar cochlear stimulation.

A significant feature of intraneural stimulation with an array of penetrating electrodes is that the active tips of the electrodes are directly apposed to the fibers of the nerve.4 This apposition, and the small diameters of the tips of the penetrating electrodes, result in highly selective stimulation of nerve fibers. Such stimulation can have the following advantages over conventional intrascalar cochlear stimulation:

1. Lower threshold stimulation current: Because the electrodes are intraneural, they are much closer to the fibers than in a conventional CI, in which the modiolar bone is intervening. This will result in thresholds that will be lower than in current CIs.
2. Greater selectivity: Because the array is intraneural, the stimulation is ex-
To realize the potential advantages of the UEA as an intraneural auditory prosthesis, we first had to create reasonable surgical access to the auditory nerve. If such surgical access were considerably more complex than the surgery required to implant a conventional cochlear electrode array, then the potential benefits of a cochlear nerve auditory neuroprosthesis might not justify the costs and risks of a more complex surgical procedure. After the development of surgical access in humans, we had to develop an appropriate animal model for subsequent electrophysiological experiments. The nerve exposed by the surgical procedure in the animal model should have the demonstrated capability to survive the procedure. Intraoperative auditory-evoked and electrically evoked potential assessment of nerve functioning performed periodically provided proof that the nerve was not damaged during the surgical procedure. Given the difficulty of implanting the fragile UEA in a cavity with complex contours, implantation of dummy UEAs was performed to demonstrate the feasibility of implanting the UEA in the modiolar nerve.

### SUBJECTS AND METHODS

#### HUMAN TEMPORAL BONE STUDIES

Human anatomical studies were performed at the Temporal Bone Laboratory, Division of Otolaryngology–Head and Neck Surgery, School of Medicine, The University of Utah. Two human temporal bone surgical procedures were performed using an operating microscope and a high-speed drill. The extended facial recess approach was modified to expose the modiolus.

Dimensions of the exposed nerve were measured with a tungsten microelectrode (World Precision Instruments, Inc, Sarasota, Fla) with a shaft diameter of 0.25 mm and a tip diameter of 1 to 2 µm, positioned with a calibrated micromanipulator.

#### ANIMAL MODEL SELECTION

Animal model selection was performed by trying transbulla and middle fossa approaches to the modiolar nerve in 1 cadaver pig (Sus scrofa) and 3 cadaver cats (Felis catus). In each case, the ease of surgery and the origin and insertion of cervical musculature were identified. Exploratory drilling for the cochleostomy was performed in all animal cadaver specimens, and dimensions of the exposed nerve were measured as in the human cadaver experiments. The anatomical features of the area were reviewed by comparing the cervical musculature and the temporal bone with data in standard textbooks.9,10 This helped us become familiar with the anatomical features while helping us select the best animal model.

#### ANESTHETIZED ANIMAL STUDIES

This part of the study was conducted in 6 cats. Animals were treated in accordance with guidelines of the Institutional Animal Care and Use Committee. The University of Utah. Anesthesia was induced using a 1:1 combination of tiletamine hydrochloride and zolazepam hydrochloride. 9 to 12 mg/kg intramuscularly. The animal was intubated, and general anesthesia was maintained by 0.5% to 1.5% halothane inhalation. Maintenance of the depth of anesthesia and vital signs were periodically assessed. Lactated Ringer solution was administered intravenously, 8 to 12 mL/kg per hour, through an intravenous cannula in the arm to compensate for blood loss. A
warmed water blanket was used to prevent hypothermia. The surgical site was prepared by shaving the ventral and lateral part of the neck.

Surgical exploration was performed using the transbulla approach in the anesthetized cats. An initial auditory-evoked brainstem response (ABR) was performed to rule out deafness in the cats (the method of performing ABR is described later). The cat was placed in a specially designed head holder in a left lateral position, with the head facing anteriorly and extended; this facilitated surgical access to the tympanic bulla.

Dimensions of the exposed nerve were measured as described in the “Human Temporal Bone Studies” subsection of this section. We also attempted to measure the spontaneous electrical activity in the modiolar nerve using a tungsten microelectrode (0.5-μm impedance at 1 kHz) in 21 different sites and at different depths of the modiolar nerve in one preparation. We were able to obtain spontaneous action potentials in the nerve at all sites and depths. The neural activity was recorded differentially between the tungsten microelectrode and a silver/silver chloride electrode placed in the middle ear as a reference. The differential signal was amplified 5000 times using a commercially available system (Neural Signal Acquisition System; Bionic Technologies, LLC, Salt Lake City). Each channel was high- and low-pass filtered with cutoff frequencies at 250 Hz and 7.5 kHz, respectively. The filtering reduces noise and minimizes distortion of the action potentials spikes.

The filtered signal was digitized at 30000 samples per second using a commercial data acquisition system (Bionic Technologies, LLC), and the data were stored for off-line unsupervised statistical spike classification using mixture-modeling techniques.13 The sorted spikes were plotted, and results were compared with published spike characteristics.

Serial ABRs and electrically evoked auditory brainstem responses (EABRs) were obtained in 3 cats to demonstrate nerve survival throughout the surgery. Serial measurements of ABRs were performed before surgery, after exposure of the bulla, and after bullostomy. Electrically evoked auditory brainstem responses were obtained by placing a ball electrode (Standard Prass Electrode, Medtronic Xomed Surgical Products, Inc, Jacksonville, Fla) on the round window, in the scala, and on the exposed modiolar nerve. Electrically evoked auditory brainstem responses were also measured by stimulating a single tungsten microelectrode (0.5-μM impedance at 1 kHz) inserted in the modiolar nerve. For all EABRs, the nerve was electrically stimulated with a charge-balanced biphasic waveform of amplitudes ranging from 2 to 350 μA, with 75 microseconds per phase. The pulse was generated using a stimulator (model S888K; Grass Instrument Division, Astro-Med, Inc, West Warwick, R.I), and the stimulus was delivered by using a pair of photoelectric stimulus isolation units (model PSIU6; Grass Instrument Division, Astro-Med, Inc); the nerve was stimulated cathodically, with the return placed in the clavotrapezius muscle. The ABR and the EABR were measured using a commercial ABR system (Navigator SE; BioLogic Systems Corp, Mundelein, Ill). The ABR/EABR measuring electrodes were placed intradurally, as described by Achor and Starr15, the brainstem response was measured differentially across the vertex and the base of the auricula, with a distant ground in the neck. The signal was amplified 100000 times and averaged across 1024 stimuli. The resultant waveforms were compared with published literature, and the waveform peaks were identified by 2 independent observers (A.N.B. and T.H.). The presence of a consistent positive deflection in wave I and III was defined as threshold; this was done to avoid the variability reported in the latency of negative deflection of wave II.16

A dummy UEA was implanted in the exposed modiolar nerve to assess the possibility of implantation. In each surgical exposure, a UEA of a 4 × 5 (20-electrode) configuration was carefully positioned on the modiolar nerve using a micromanipulator, and implanted using a process of rapid pneumatic insertion. The method for pneumatic insertion has been described in detail elsewhere1 and is briefly described herein. This is a pneumatically actuated system that was originally developed for the optimal insertion of a 10 × 10 configuration of the UEA in the cerebral cortex. The insertion of arrays is accomplished via moment transfer from a pneumatically driven piston to the inserter head, which is positioned stereotaxically against the UEA. The UEA has been previously positioned in the implantation site. The travel of the inserter head, hence, the insertion depth, is precisely controlled by mechanical stops. It works by delivering an impulse generated by a pneumatically driven piston traveling a distance predetermined by a “spacer” stop. The insertion is accomplished in less than 1 millisecond to ensure complete implantation. Histological and electrophysiological studies performed in the cat’s nervous system demonstrate that this procedure produces only minimal insult to the tissues. We modified the inserter head by machining the tip down to a diameter of 1.2 mm to facilitate insertion of the inserter into the cochleostomy site. We also reduced the insertion pressure to 20 psi, keeping in mind that the cochlear nerve lacks a tough epineurium like the cat’s sciatric nerve.

HISTOLOGICAL CHARACTERISTICS

A determination of the histological characteristics of the implanted cochlear nerve was performed in 2 animals to reveal the position of the electrodes. At the end of the study, the animals were deeply anesthetized and perfused with the array in place, with formaldehyde acting as a fixative. The array was left in place while the head was immersed in formaldehyde. This allowed preservation of the electrode implantation site in the nerve. After a week in formaldehyde, we removed the array from the nerve and dissected the entire length of the nerve from the temporal bone. This tissue was embedded in plastic to facilitate sectioning. Osmium tetroxide staining was used to demonstrate the lipid-rich myelin sheath of the nerve fibers.

HUMAN TEMPORAL BONE STUDIES

Surgical procedures were performed in 2 human temporal bones to establish access to the human modiolar nerve and to measure the dimensions of the exposed nerve. A postauricular incision was made and flaps were raised, the ear was reflected anteriorly, and a self-retaining retractor was used to expose the mastoid; a standard mastoidectomy was performed using a high-speed drill; and the promontory and round window were exposed by the extended facial recess approach. Next, a cochleostomy was performed by removing the bone of the round window, exposing the basal turn of the cochlea. The modiolar bone was thinned with a diamond burr, and the thinned bone was picked with an otologic pick to expose the nerve. Figure 2 shows a labeled photograph of the surgical access to the modiolar nerve in the left temporal bone. The exposure was not significantly more difficult than the procedure for implanting the CI, as both involve the extended facial recess approach; while the CI surgery exposes the scala, our technique is modified to expose the modiolar nerve.
Exposure by such a modified extended facial recess approach yielded a diameter of 2 mm and a length of 3 mm in 2 studies. This was adequate to implant the 4 × 5 arrays used in this study; however, given the dimensions of the exposed nerve, it would have been possible to implant 6 × 8 arrays (48 electrodes).

ANIMAL MODEL SELECTION

The pig was rejected as an animal model because the temporal bone drilling for a transbulla approach was difficult (the bulla is located more medially than in cats). The depth of the bulla on exposure of the modiolar nerve created problems of visualizing the insertion of the array.

A middle fossa approach was rejected in cats and pigs, as this approach to the modiolar nerve was impractical. In the case of pigs, this surgery was difficult because of fleshy dorsal cervical muscles and a thick sloping crest at the back of the skull, formed by the supraoccipital and parietal bones. There are several significant advantages to the use of cats for these experiments.

The anatomical features of the cat temporal bone are well described, and the topology of the cat cochlear nerve is well-known; this affords a unique opportunity to selectively stimulate fibers for specific frequencies. This is the most significant advantage of the model.

The present generation of human cochlear prostheses was partly developed using cat models. Hence, there is much literature relating to the development and evaluation of an auditory prosthesis in cat models. We may be able to comparatively evaluate the utility of the UEA as an auditory prosthesis by using the cat model.

The size of the cat cochlear nerve is comparable to that of the human cochlear nerve; this is an important factor in choosing the cat model, as smaller nerves will complicate implantation of the UEA because of size and access constraints. Logistical and surgical constraints rule out bovine and simian models.

The cat is a common model used in auditory neurophysiology. There is a potential that our data and methods can be used to further elucidate the role of cochlear efferents in auditory neurophysiology.

An incision was made just medial to and parallel with the digastric muscle in the ventral aspect of the neck. The incision was approximately 7 cm long and located directly over the hollow bulla, the tympanic part of the temporal bone. The skin, subcutaneous tissue, platysma, and mylohyoid muscle were incised; the bulla was exposed by blunt dissection between the digastric, styloglossus, and hyoglossus muscles. Care was taken not to damage the hypoglossal nerve, the anterior lobules of the sublingual salivary gland, and the internal maxillary vessels. The lingual artery, which is lateral to the hypoglossal nerve, was spared. The base of the skull was thus exposed. A 2-cm-diameter access site in the bulla was made using a rotary burr tool mounted on a dental drill. Isotonic sodium chloride solution was used for regular suction-irrigation to prevent dehydration of tissues and heat from the cutting and diamond burr. The mucosa internal to the bulla was freed with alligator forceps, which allowed visualization of the round window in the posterolateral wall of the bulla. This provided access to the cavity of the middle ear without damage to the tympanic membrane. The location of the round window was verified by identification of the promontory and the attachment of the stapes to the oval window. The round window was drilled with a diamond burr under a surgical microscope to reach the basal turn of the cochlea. The access site was expanded by further drilling to expose the modiolar bone. The modiolar bone was thinned out, and the bone fragments were picked with a Rosen needle to expose the modiolar portion of the VIII nerve. Figure 3 shows a magnified photograph of a typical exposure of the cat modiolar nerve using the procedure described. The modiolar nerve is seen emerging out of the basal turn of the cochlea; we expect this portion of the nerve to have purely auditory fibers.

Given these results, the cat was chosen as a good animal model and the transbulla approach was chosen over the middle fossa approach.
NERVE SURVIVAL

Serial ABRs and EABRs at different stages of the surgery demonstrate nerve survival during the surgery. Figure 4 shows sample ABRs/EABRs from a cat to suprathreshold stimuli at different stages of the surgical exposure. The presurgery ABR was obtained to rule out any hearing loss in the cat. Although the presence of EABRs after the opening of the modiolar would have been sufficient proof regarding nerve survival, we recorded EABRs to stimulation at surgical stages before that to pinpoint the stage of failure and to validate the stimulation and recording system before modiolar stimulation was attempted. The waveforms corresponded to the latencies suggested by Achor and Starr and to the waveforms published by Black et al and Simmons et al. The presence of independently identifiable and consistent peaks in the EABR at each stage of the surgery suggests that the nerve was intact at each stage. The Table shows that the thresholds for stimulation were within limits of published results for the electrodes used. The variation in thresholds compared with published data can be attributed to the different biphasic pulse durations used in the experiments and to intraspecies differences.

In our experiments, the thresholds decrease as we get closer to the modiolar nerve, with the lowest threshold being for intraneural stimulation using the single tungsten microelectrode. This indicates that the thresholds for intraneural stimulation using the UEA are likely to be close to 8 µA, with a 75-microsecond biphasic stimulation pulse. In all 3 experiments, the EABR waveforms were never lost. We were able to obtain stable EABR waveforms from the time of implantation to the time the animal was euthanatized. This period varied from 4 to 8 hours in the 3 experiments.

We were also able to record spontaneous action potentials in one preparation when we attempted to record the modiolar nerve activity. Figure 5 shows the spontaneous action potentials recorded from the nerve. The characteristics of the action potentials were compared with the typical action potentials in published data and we conclude that the spike characteristics are similar to them. Although this is an anecdotal observation, it also indicates nerve survival after surgery.

DUMMY UEA IN CAT NERVE

The measurement of nerve dimensions was crucial, because we wanted to show that the size of the cat’s modiolar nerve is comparable to that of the human’s modiolar nerve. The dimensions of the exposed nerve would also dictate the dimensions of the UEA that could be implanted and, hence, the number of electrodes in the implanted array. The mean ± SD diameter of the exposed nerve was 1.64 ± 0.07 mm (n = 9), and the mean ± SD length was 2.50 ± 0.11 mm (n = 9), as measured with a tungsten microelectrode mounted over a micromanipulator. We implanted nonfunctional but otherwise geometrically accurate UEAs in all exposed modiolar nerves to examine the feasibility of such implantation. This exposure was adequate to accommodate a 4 × 5 UEA (20 electrodes) of 400-µm spacing used in the study, without any insertion difficulty. There was an adequate area in which to work, and we could gain perpendicular access to the nerve. The inserter spacing at 1 mm allowed us to insert the array to a depth of 1 mm from the nerve surface. However, given the exposed nerve dimensions, it should be possible to implant 6 × 10 UEAs (60 electrodes) with 200-µm electrode spacings.

Comparison of Stimulation Site and EABR Thresholds

<table>
<thead>
<tr>
<th>Location of the Electrode</th>
<th>In Present Experiments</th>
<th>In Published Studies</th>
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</thead>
<tbody>
<tr>
<td>Round window (using a ball electrode)</td>
<td>400 µA, 75 µs, and biphasic</td>
<td>300 µA, 500 µs, and monophasic</td>
</tr>
<tr>
<td>Scala (using a ball electrode)</td>
<td>300 µA, 75 µs, and biphasic</td>
<td>100 µA</td>
</tr>
<tr>
<td>Surface of the modiolar nerve (using a ball electrode)</td>
<td>150 µA, 75 µs, and biphasic</td>
<td>200 µA, 500 µs, and monophasic</td>
</tr>
<tr>
<td>In the modiolar nerve (using a tungsten microelectrode)</td>
<td>8 µA, 75 µs, and biphasic</td>
<td>100 µA, 100 µs, and biphasic (using Teflon-coated wires)</td>
</tr>
</tbody>
</table>

* The decreasing thresholds as we get closer to the modiolar nerve indicate that the threshold for intraneural stimulation using the Utah electrode array is likely to be close to 88 µA, with a 75-microsecond biphasic stimulation pulse. EABR indicates electrically evoked auditory brainstem response; ellipses, data not available.
HISTOLOGICAL CHARACTERISTICS

When the animals were humanely killed, a visual inspection was performed on the site of implantation and of the explanted UEA. In all cases, there was no visual hemorrhage in the implanted site as evidenced by an unaided eye examination of the implanted site and by a microscopic examination (with ×40 magnification). None of the explanted UEAs had any broken electrodes, and the microscopic examination (with ×40 magnification) of the implanted site did not reveal any formation of connective tissue. This was expected, as the array was implanted for the short-term. Electrodes were located inside the tissue. This was expected, as the array was implanted for the short-term.

Figure 6 shows a cross section of the nerve taken at the implantation site. It demonstrates minimal damage to the nerve, as evidenced by the absence of hemorrhage in the implanted site and by preservation of normal tissue architecture compared with the proximal control (not shown). The histological features distal to the implantation site seem normal (not shown), indicating no nerve damage to the axons going from the implanted site to the brainstem. However, we believe that the issue of nerve survival can be better investigated using the histological features of an animal with a long-term implant, and are working toward this goal.

COMMENT

The feasibility of implanting UEAs in humans and in animal models was demonstrated in this work. Human temporal bone studies indicated a surgical access site in which a 20-electrode UEA with 400-µm spacing was implanted. But the dimensions would theoretically permit up to 48 electrodes to be implanted. If we use a UEA with 200-µm spacing, we may be able to implant up to 192 electrodes in the human modiolar nerve.

Two surgical techniques were investigated in the candidate animal cadavers of cat and pig: the suboccipital and transbulla approaches. The cat was chosen as the animal model, and the transbulla approach was selected. The exposed modiolar nerve was in the basal turn of the cochlea and, hence, intraneural stimulation at this site is expected to produce purely auditory sensations. Serial EABRs obtained during surgical exploration of animals with short-term implants determined that the nerve survives the procedure. Also, a 20-electrode UEA with 400-µm spacing can be implanted in live animals. But the dimensions of the exposed nerve could permit implantation of up to 60 electrodes with 200-µm spacings in the cat’s modiolar nerve.

Electrophysiological work should be performed in cats and humans on nerve VIII using the access site delineated in this article. Such electrophysiological work will demonstrate the functioning of the implanted UEA. Because EABRs are an easy and effective assay of whole nerve VIII function, electrophysiological experiments should involve stimulation of nerve VIII through a UEA implanted in the modiolar portion of the nerve and recording of EABRs. Single-unit electrically evoked responses could also be recorded from the primary auditory cortex, A1. This will allow exploration of the selectivity and sensitivity of such modiolar nerve stimulation. Future work also has to address the long-term biocompatibility issues of the implant (ie, tissue reaction, threshold changes, and the mechanical stability of the implant). Human psychophysical experiments will allow us to optimize the stimulation variables and refine the system to transform it into an auditory prosthesis. The experimental setup can also be used to study cochlear efferents because the implanted UEA can also record neural activity in the modiolar nerve.

It is anticipated that the present work will lead to the development of an intraneural auditory prosthesis that is superior to current CIs, by having lower stimulation thresholds and, thus, lower power requirements and less cross talk. Also, if the electrodes are more selective than current intracochlear electrodes, then improved frequency selectivity could be anticipated.
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