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Design and Fabrication of Multichannel Cochlear Implants for Animal Research

Stephen J. Rebscher, M.A.¹, Alexander M. Hetherington, B.S.¹, Russell L. Snyder, Ph.D.¹, Patricia A. Leake, Ph.D.¹, and Ben H. Bonham, Ph.D.¹

¹Department of Otolaryngology – Head and Neck Surgery Epstein Laboratory, University of California San Francisco

Introduction

Cochlear implants are now well established as a successful treatment for severe to profound hearing loss in individuals of all ages. During the past 25 years approximately 90,000 of these devices have been implanted and a steady increase in subject performance has been reported over this period. Despite this increase in efficacy across the patient population there is still a significant group of individuals that receive minimal benefit from the implant, and a small subset of these patients choose to have the device explanted because it does not meet their expectations. Several research strategies are being utilized to address the needs of these underperforming subjects as well as to further increase the performance of users who receive greater benefit. These strategies include psychophysical testing in human subjects, computer modeling studies and direct measurement of neural responses to intracochlear electrical stimulation in animals.

Auditory neural activation patterns in response to electrical stimuli have been reported in cats, guinea pigs and primates at the levels of the auditory nerve, the inferior colliculus and the auditory cortex (van den Honert and Stypulkowski, 1987; Snyder et al., 1990; Shepherd et al., 1993; Xu et al., 1993; Raggio and Schreiner, 1994; Hartmann and Klinke, 1995; Pfungst et al., 1995; Schreiner and Raggio, 1996; Kral et al., 1998; Shepherd et al., 1999; Leake et al., 2000; Rebscher et al., 2001; Bierer and Middlebrooks, 2002; Middlebrooks and Bierer, 2002; Moore et al., 2002; Snyder et al., 2004). These studies provide a basic understanding of how the auditory system responds to electrical stimuli and a framework for the development of intracochlear electrode arrays and signal processing strategies for use in human cochlear implant systems. Early research examined fundamental parameters such as neural thresholds to electrical stimuli, characterized responses to stimuli from electrode arrays placed at different locations and in different configurations within the cochlea and studied the effects of chronic stimulation on the organization of the central auditory system. More recent studies have begun to examine responses to more complex multichannel stimulation, modulated electrical signals and interactions between stimuli presented on multiple channels in masking and simultaneous interaction paradigms (Leake et al., 2000; Snyder et al., 2000). We anticipate that these physiological experiments will continue to provide important guidance for the future development of cochlear implants. In addition, these experiments will yield information

Address for Correspondence: Stephen J. Rebscher, Department of Otolaryngology, Box 0526, University of California, San Francisco, San Francisco, California 94143-0526, Telephone 415 476 9060, Facsimile 415 502 2923, srebscher@ohns.ucsf.edu.

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necessary for the successful implementation of new applications for cochlear implants, which include bilateral cochlear stimulation, combined acoustic-electrical stimulation in ears with residual hearing and devices that incorporate drug delivery to directly support increased survival or regeneration of auditory neurons.

These previous physiology studies used intracochlear electrode arrays that modeled human cochlear implants in use during the 1970s and 1980s (Walsh et al., 1981; Shepherd et al., 1983; Leake et al., 1985; Snyder et al., 1990; Xu et al., 1993; Pfungst et al., 1995; Rebscher et al., 2001). More recently, two perimodiolar electrode arrays, the HiFocus™ and Contour™ models (Advanced Bionics, Inc., www.advancedbionics.com, and Cochlear Corporation, www.cochlear.com, respectively), were introduced and are now in widespread use throughout the world (Cords et al., 2000; Tykocinski et al., 2000; Tykocinski et al., 2001; Zwolan et al., 2001; Balkany et al., 2002). Both of these arrays differ significantly from their predecessors in the size and location of stimulating contacts and in overall position within the scala tympani and are thus very different than the scale animal arrays that were developed to model earlier devices. At the time of this report there are no commercially available animal electrode arrays that model current human devices or act as platforms for the evaluation of new strategies. Our goal is to present a simple, cost-effective method for the design and fabrication of species-specific intracochlear electrode arrays for use in chronic and acute animal experiments. Ideally, these methods must allow the flexibility to model any device currently in clinical use and the capacity to create novel configurations.

Approach

All contemporary commercial cochlear implant electrodes are fabricated using platinum-iridium alloy stimulating contacts and lead wires. These components are molded in an elastomer carrier that holds the contacts in their intended location after implantation in the scala tympani and contributes to the mechanical properties that facilitate surgical insertion. At UCSF we originally developed animal electrode arrays to evaluate the safety and efficacy of intracochlear stimulation and a limited number of investigational arrays for use in human subjects participating in early psychophysical studies. These prototype multichannel arrays were fabricated using either flush-cut wires (25 μm diameter) as stimulating sites or small flamed-ball contacts (100 μm diameter) resulting in small exposed surface areas and high interface impedances (50–300 kohms at 1 kHz). The small surface areas of these electrodes raised concerns that non-reversible chemical reactions might occur at the current levels required to produce adequately loud percepts for subjects or adequate dynamic ranges for animal experiments. Therefore, the contacts for experimental electrode arrays were enlarged to 200–300 μm as illustrated in Figure 1.

Profiles of the molded elastomer carriers for the human and animal electrode arrays were also modified based on laboratory and clinical experience. The earliest UCSF human electrode arrays were injection molded using cavities derived from cadaver scala tympani to create inserts that exactly fit the scala tympani. Unfortunately, significant variation occurs in both size and shape of the scala tympani (Ketten et al., 1998; Skinner et al., 2002) and this variability may result in unpredictable insertion depth and potential damage to delicate structures within the cochlea (Aschendorff et al., 2003; Eshraghi et al., 2003; Wardrop et al., 2005). To accommodate this variability a tapering cylindrical form was chosen to fit a wider range of individuals. Dimensionally accurate casts were made from cochleae of each species and molded silicone carriers were designed to fit within the volume of the smallest casts measured (Loeb et al., 1983). These methods were used to design the UCSF/Advanced Bionics Spiral Clarion™ device and animal electrode arrays that modeled this device were used in both acute and chronic studies in cats until the introduction of the arrays described in this report.

Recent Contour™ and HiFocus™ electrode arrays, which have gained widespread clinical acceptance, share many design features. Both arrays are tightly curved to achieve a perimodiolar position when fully inserted and have large contact sites. The arrays described in this report incorporate design options to permit modeling of these and many other features.

Integrated drug delivery

One presumed important factor underlying relative success with a cochlear implant is survival of auditory neurons. Previous studies have shown that chronic delivery of neurotrophic factors such as brain derived neurotrophic factor (BDNF), neurotrophin-3 or GDNF can prevent the degeneration of spiral ganglion neurons (Staecker et al., 1996; Miller et al., 1997; Shinohara et al., 2002; Gillespie et al., 2003) and that chronic electrical stimulation promotes survival of these cells in the deafened cochlea (Lousteau, 1987; Leake et al., 1991; Leake et al., 1999; Leake and Rebscher, 2004). Furthermore, Shepherd et al. (2005) suggested that application of electrical stimulation and neurotrophic factors concurrently may have an additive effect. With these studies in mind, we included components to enable chronic intracochlear delivery of therapeutic agents in our designs.

Methods and Results

The methods used to fabricate experimental intracochlear electrode arrays for cats and guinea pigs are presented in this section. These methods can be adapted to suit other species or different anatomical locations with relatively minor alterations. The fabrication process is divided into sections describing the design and machining of the injection mold, formation of Pt:Ir stimulating contacts, component assembly, drug delivery options, connectors and device testing. Because the design and fabrication processes are inherently sequential the results of each fabrication step are presented immediately after the description for each fabrication step in the process. This section concludes with a brief description of the application of these electrode arrays in neurophysiology experiments.

This research, and all procedures involving live animals, were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of California, San Francisco and conform to NIH guidelines for animal research.

Mold design and fabrication

The radius of curvature and cross sectional dimensions of the scala tympani are required to accurately design the shape of the silicone electrode carriers. To make these measurements we produced metal replicate casts of the scala tympani using preserved temporal bones harvested from cats and guinea pigs as described previously for cadaveric human temporal bones (Loeb et al., 1983; Rebscher et al., 1996). These casts were digitally imaged and measured using Canvas graphics software (ACD Systems, Inc., www.acdamerica.com). Average height and width measurements were used to create cross sectional profiles for the silicone carrier and the radius of curvature was measured at 90° intervals along the cochlear spiral to determine the overall shape of the molded carrier.

To model the overall shape of current human devices a round profile or rectangular shape with rounded corners was chosen for the cross section of each device and the size of each profile was adjusted to fit the scala tympani at the 90° intervals measured. The mean cross-sectional dimensions were reduced by 20% to accommodate individual variability. The profiles were drawn in a 2-D layout of the silicone carrier at UCSF and transmitted to Wright Engineered Plastics (WEP, www.wepmolding.com). Figure 2 illustrates assembly of the cross sections perpendicular to the line defining the inner margin of the scala tympani, which was generated by fitting a continuous line to the radius at each 90° interval measured in the metal casts.

Defining the medial wall measurement as the inner edge of the molded silicone carrier ensured that the completed carrier will have an elastic memory that will position it near the modiolus. Draft CAD drawings were completed at WEP, rendered in 3-D (see Figure 3), reviewed at UCSF via portable Solidworks™ drawing files and modified based on our feedback. High speed machining capacity to fabricate these miniature molds using tooling as small as 100 μm – 200 μm (0.004”– 0.008”) diameter is now widely available from independent vendors. The first electrode mold in this series was fabricated in aluminum to simplify machining. However, subsequent molds were made from hardened stainless steel to minimize wear. The highest precision part of the mold, the cochlear spiral, was machined in a small, removable insert to minimize the cost of iterative design changes.

Each mold was inspected and digitally imaged to confirm dimensional accuracy. In general, the surface finish and feature details of these molds were superior to those of previous molds produced by electrical discharge machining (EDM) or lower speed CNC milling. As a result, these new molds required only minimal polishing with diamond abrasive paste prior to initial testing. Figure 4 illustrates the lower mold cavity for the guinea pig electrode array.

Initial injection molding tests were conducted without stimulating contacts or lead wires. For these tests the mold surfaces were cleaned with ethanol and a very thin layer of medical silicone fluid (Dow Corning 200 Fluid, www.dowcorning.com) was applied as a mold release. Platinum cure silicone elastomer (NuSil MED 4011, www.nusil.com) was mixed according to the manufacturer’s specifications, outgassed in a vacuum centrifuge for 5 minutes and injected into the mold cavity at a pressure of 50 psi. MED 4011 elastomer was chosen because this formulation offers low viscosity, excellent tissue compatibility, high tensile strength and good adhesion at significantly lower cost than the same formulation certified for unrestricted human implant use (NuSil MED 4211).

Top and side views of the guinea pig silicone carrier are shown in Figure 3. To accurately locate each stimulating contact during the assembly process, dimples or shallow holes, located at 250 μm intervals for the guinea pig mold, were machined at each pre-determined contact location (Fig. 4B).

Stimulating contact fabrication

Stimulating contacts were fabricated using Pt:Ir (90:10) alloy due to the ductility, high charge transfer capacity and corrosion resistance of this material. The contacts were formed directly on Teflon insulated wire leads by melting an appropriate length of wire to form a sphere of desired size (100–150 μm for the guinea pig electrode and 200–300 μm for the feline electrode). This simple method reduces the possibility of lead breakage or corrosion that might occur with welds or mechanical connections between fine leads and more robust cables or dissimilar metals.

Teflon insulated 0.001” diameter Pt: 10% Ir wire was used to fabricate electrode arrays for acute experiments (Medwire, www.sigmundcohn.com). For all arrays intended for chronic implantation in cats, Teflon insulated multistranded cable (Pt: 10% Ir, 5×0.0015”, www.calfinewire.com) was used to increase reliability in the presence of long-term mechanical strain. To reduce the overall size and stiffness of this larger wire in the confined intracochlear portion of the electrode array, the five stranded cable was reduced to a single strand by stripping the Teflon insulation from the distal 35 mm of each lead, removing four of the strands, and re-insulating this segment with Parylene C (www.morganadvancedceramics.com, Parylene Coating Division). Spherical contacts were melted on the end of each lead using a miniature oxy-acetylene torch (www.littletorch.com). We found that the large volume of the ball contacts often made it difficult to route lead wires within the mold cavities when the number of contacts in an electrode exceeded eight. To reduce this interference, and to more closely model current

human electrodes, we used a small mechanical press (PanaPress, www.panavise.com) to form the contacts into either hemispheres or flat disks.

Component assembly

To begin the assembly process, the upper and lower mold cavities were coated with a thin layer of medical grade silicone oil (Dow Corning 200 Fluid) and the lower mold plate was placed on a hotplate at 240° F. Beginning with the most basal stimulating site, the wire lead for each contact was held in a three axis micromanipulator and the contact was lowered directly over the positioning dimple in the mold surface (see Figure 4B). Vertically advancing the micromanipulator applied gentle pressure to hold the contact in a centered position within the dimple. Next, a thin layer of silicone elastomer (MED 4011) was applied over the contact using a pneumatically driven syringe with a blunt 30 gauge needle (www.glenmarc.com). At 240° F the silicone elastomer cured in 10–20 seconds and securely held the contact in place. The first lead wire was routed through the mold and tacked in place along its length by applying small droplets of silicone at regular intervals. Subsequent contacts were positioned and secured in sequence toward the tip of the electrode array. When it was possible, the lead wires were positioned in a vertical stack or rib and held in place with silicone. This feature increased stiffness in the vertical plane of the cochlear spiral reducing the probability of damage to delicate structures above the scala tympani. To minimize lead breakage a zigzag pattern was formed by wrapping the leads around a series of staggered stainless steel pins in the straight cable section of the mold. This modification greatly reduced the frequency of breakage during fabrication and allowed the electrode arrays to be used in multiple experiments. After all of the contacts and lead wires were held in position with silicone, the mold was closed, removed from the hotplate to cool and freshly mixed, degassed silicone elastomer (Med 4011) was injected into the mold at 50 psi. After filling, the entire mold was placed in an oven at 220° F for 12 hours to thoroughly cure the elastomer. Care was used during the assembly process to ensure that sulfur containing materials, in particular latex rubber, did not contact the mold or elastomer as such contaminants can inhibit the curing of the MED 4011 elastomer.

As described above, one goal of this study was to facilitate the production of experimental electrode arrays with customizable features to meet the requirements of individual experiments. Figure 5 illustrates guinea pig and feline arrays with various contact configurations designed to evaluate different stimulation strategies. The guinea pig electrode array shown in Figure 5A includes a series of eight stimulating contacts on the upper surface of the carrier and two contacts positioned on the undersurface of the array. In addition to the longitudinal series of monopolar, bipolar or tripolar stimulus combinations available on the upper array surface these two contacts on the lower surface make it possible to evaluate novel configurations including radial bipolar, offset radial bipolar and offset radial tripolar. Electrode arrays with more closely spaced contacts (250 μ m c-c), as shown in Figure 5B, can be used to explore the practical limitations of increasing contact density and numbers of channels. The feline array shown in Figure 5C was fabricated with larger diameter, flattened contacts oriented toward the modiolus to model current human prostheses.

Connecting cable and external connector

Cabling varied according to the intended use of each device. For acute use the full length of the mold was filled with silicone to form a continuously molded silicone sheathed cable. After removing the array and cable assembly from the mold the end of the assembly was glued to a small printed circuit board with a connector attached and the individual wire leads were soldered to the connector. After confirming continuity the backplane of the connector was encapsulated in epoxy.

Electrode arrays intended for chronic stimulation were terminated in a different configuration. In these devices, the individual leads were wound around a mandrel (0.5 mm diameter) to produce a tightly coiled helix. A preformed silicone tube (Silastic™, www.dowcorning.com) was slipped over the helical leads and a miniature connector (Microtech G Series, Microtech, Inc. Boothwyn, PA) was attached. The ends of the silicone tube were slipped over the molded electrode array and connector and glued in place using MED 1137 silicone adhesive (NuSil). To reduce kinking the silicone tube was filled with MED 4011 elastomer.

To prevent movement of chronically implanted devices patches of Dacron fabric were attached to the array at the point where it will traverse the round window and at several locations along the molded cable. No stabilization was needed during acute physiology experiments where the subject animal was anesthetized and remained in a fixed position throughout the experiment.

Drug delivery component assembly

A small hub was included in the design of the chronic cat electrode array to support a cannula leading from the array to a remotely located osmotic pump (Figure 6). The outer diameter of the molded drug delivery channel was specified to match the 21 gauge output of the Alzet™ (www.durect.com) osmotic pump so that a single piece of vinyl tubing (0.027"/0.68 mm I.D., www.scicomimc.com) could be used to directly connect these two components. This hub also acted as a simple adaptor between the vinyl tubing and the much smaller polyimide tubing required in the scala tympani (see Figure 6B, 0.0064" OD polyimide tubing, www.coleparmer.com).

The small bore polyimide tube (7.0 mm in length) was placed in the upper half of the mold prior to injection molding. To prevent back filling during the injection molding process a temporary plug of MED 1137 silicone was formed at each end of the tube and cured. Next, the tubing was set in the heated mold, tacked in place with silicone (MED 4011) and the mold was cooled to room temperature. To create an open well for the terminus of this drug delivery catheter a small drop of high viscosity polyvinyl alcohol (PVA) was formed over the tip of the polyimide tube and in contact with the surface of the mold. Later, soaking the molded carrier in warm water removed the PVA and exposed a small open cavity around the tip of the catheter. The sealed ends of the catheter were clipped off to expose the open tube and a piece of vinyl tubing (12 cm in length) was slipped onto the hub and attached with MED 1137 adhesive. The end of this vinyl tubing was left open to permit pre-filling with sterile saline or active drug solution prior to attachment of the osmotic pump.

Testing of components and assemblies

Electrode array—Following complete assembly each array was rinsed in ethanol, dried and inspected. From prior experience we have found that particularly careful inspection is necessary at the junction between any two components. These include the connection between the molded intracochlear electrode array and the silicone tubing covering the percutaneous cable, the interface to the connector shell and the attachment of Dacron fabric cuffs. Defects were repaired by applying a small amount of MED 1137 elastomer thinned with an equal quantity of heptane.

Each contact site was carefully examined to ensure that elastomer did not obscure the metal surface. Small areas of excess elastomer were removed with fine forceps. In addition, any silicone flash resulting from imperfect alignment of the mold surfaces was removed. After this physical inspection, the electrode array was placed in a saline bath, a DC voltage of +15 V (vs. Pt ground) was applied to each electrode contact for 15 seconds to remove surface oxidation, and the impedance of each stimulating site was then verified using a commercial impedance meter (BAK Imp-1, www.bakelectronicsinc.com). The acceptance criteria for 250 µm diameter

contacts in physiological saline was < 10 kOhms. All electrode contacts met this criteria (range = 3 – 9 kOhms at 1 kHz). To identify short circuits between stimulating sites each array was removed from the saline bath, dried, and the impedances between all site combinations were verified to be > 1 MOhm.

Drug delivery components—To assure reliable long-term delivery of neurotrophic compounds via the integrated drug delivery system we carefully examined the connections between these device components following fabrication and during surgical implantation. We found that the vinyl tubing had separated from the silicone hub in two of the initial devices, one during inspection following fabrication and one during the implantation surgery. Following these failures we added a preparation step of gently abrading both the inner and outer surface of the vinyl tubing for a length of 4 mm using 400 grit silicon carbide abrasive cloth prior to application of the silicone adhesive. No subsequent failures have occurred at this junction.

We also calibrated the output rate of the Alzet™ osmotic pumps used in these experiments. Of the three manufacturing lots tested to date two lots were within specification while the flow rate of the third lot was approximately 50% greater than specified with a consequent decrease in total pumping duration. The calibration test for this lot was repeated with the same result and the lot was replaced by the manufacturer. The flow rate for the replacement pumps was within specification.

Implantation and electrophysiology—To date, we have completed approximately 45 acute physiology experiments and 10 chronic stimulation experiments using the latest electrode arrays described in this report, and more than 100 acute and chronic experiments with earlier versions. To illustrate the efficacy of these arrays, and the unique neural response patterns seen with different stimulus configurations, we have included representative examples from one of these experiments in which we recorded neural activity across the tonotopically organized central nucleus of the inferior colliculus (IC) using a silicon multichannel recording probe.

The experimental protocols used for cats and guinea pigs have been described in detail (Snyder et al., 1990; Snyder et al., 1995; Snyder et al., 2000; Snyder et al., 2004; Snyder et al., 2007). In brief, the animals were sedated and normal hearing was confirmed using auditory brainstem response recording (ABR). The right inferior colliculus was exposed and a 16 or 32 channel recording probe (www.neuronexustech.com) was inserted into the IC using a hydraulic microdrive (www.kopfstruments.com). The neural responses to a matrix of single tone stimuli (2 to 40 kHz at 0–80 dB SPL) delivered to the left ear were recorded to verify that the recording probe was inserted to a depth that included the full representation of this frequency range within the IC (Figure 7A) and the probe was fixed in place. This acoustic calibration enabled us to relate the location of neural responses in the IC to the frequency of acoustic stimuli and, in turn, the basilar membrane location of these stimuli using the place frequency relationship developed by Greenwood (1990). Animals were then deafened unilaterally using intrascalar injection of neomycin or systemically using kanamycin followed by ethacrynic acid (Xu et al., 1990). Deafness was confirmed by monitoring the auditory-evoked brainstem response (ABR) up to a level of 105 dB SPL. After this, the left auditory bulla was surgically exposed and the bulla and round window were opened. After manually straightening the curved tip, the intracochlear array was introduced into the scala tympani and the lead cable was secured to the skull or surrounding musculature using cyanoacrylic tissue cement. Because of the orientation and small diameter of the round window in the guinea pig we found that it was necessary to laterally enlarge the window in these animals using a diamond burr to permit full visualization of the modiolus and first cochlear turn.

Insertion of the respective electrode arrays was successful in guinea pigs and cats. In each case the array was inserted to full depth without discernable resistance noted by the surgeon. After

the arrays were positioned in the basal cochlea we found that the pre-molded spiral shape of the silicone carrier was restored and the electrode arrays followed the curvature of the basal turn with minimal resistance. To facilitate straightening the tightly curved guinea pig arrays we subsequently stiffened the electrode tip by increasing the diameter of the apical lead wires from 0.001" (25 μ m) to 0.0015" or 0.002" (37.5 or 50 μ m). The enlarged cross section of the silicone carrier immediately inside the round window held the array in position and prevented accidental withdrawal. In chronic preparations Dacron tabs on the array were glued directly to bone of the round window ventrally and adjacent to the margin of the bulla using Vetbond™ tissue cement (www.3m.com) and the electrode cable was externalized through a small incision. The vinyl tube connecting the osmotic pump to the electrode array was routed separately from the electrode cable to minimize the chance of infection tracking from the percutaneous exit site to the large foreign body of the osmotic pump.

Figure 7 illustrates three of the stimulating site configurations used in physiology experiments with these electrode arrays and typical responses recorded across the tonotopic frequency gradient of the inferior colliculus (IC) in a guinea pig. These responses were recorded using a single multisite recording probe that was fixed in position with dental acrylic cement prior to deafening the animal. As described previously, the relationship of frequency, and thus inferred basilar membrane location, to recording site depth in the IC was documented using acoustic tones as shown in Figure 7A (same subject). Each panel in Figures 7B–D represents the response patterns generated by different contact configurations and location along the length of the electrode array. The row of panels in Figure 7B illustrates the response patterns observed with activation of five tripolar sets of stimulating contacts. In this series, the location of these tripoles moved from the apical contacts (left panel in the row, sites <1,2,3>) to the basal contacts (right panel, sites <5,6,7>). The center and lower rows (Fig. 7C and 7D) illustrate responses to bipolar and monopolar stimulus configurations. In each of these series the most sensitive location moves in a clear progression from superficial (near 500 μ m IC depth or 9.5 kHz) in the IC to deep (near 1,100 μ m IC depth or 20.7 kHz) as the locus of electrical stimulation moves from the apical tip of the electrode to the base. It is also clear that although the location of maximum sensitivity was similar for these three basic stimulus configurations, the spread of neural activity across the tonotopic gradient was very different, i.e. the specificity of the response was greatest for the tripolar configuration and poorest with monopolar stimuli.

Discussion

As mentioned previously, cochlear implants have been used by more than 90,000 subjects with increasing success over the past 25 years. Despite a high rate of acceptance for cochlear implant users as a whole, a relatively small group of recipients receive very limited benefit from their devices. These patients often describe perceptual distortions that may be the result of channel interaction, an inability to discriminate electrode channels or a very limited useful dynamic range for some or all channels. Previous animal experiments using model cochlear implant devices have shown that the design of the implanted electrode array and its location in the scala tympani directly affect these limitations (Shepherd et al., 1993; Xu et al., 1993; Rebscher et al., 2001). Specifically, the location of the stimulation sites on the insulating carrier, the configuration of these sites (radial, longitudinal or diagonal geometries) and the mode of stimulation used (monopolar or bipolar) measurably affected threshold, dynamic range and specificity of responses to electrical stimuli. Physiological experiments using the electrode arrays described in this report allow the direct comparison of alternative design features and novel stimulation strategies. In addition, these experiments add to our fundamental understanding of how electrical stimuli are processed in the central nervous system and how this processing might best be manipulated to increase overall performance for cochlear implant users.

From a practical standpoint two technical developments have facilitated both the fabrication of these experimental electrode arrays and the investigational methods to iteratively optimize their design. First, sophisticated CAD/CAM design and machining systems required to produce miniature molds are now readily available through contract vendors. Many of these facilities allow design, specification and quotation via internet communication using pdf, jpeg or commercial 3-D drafting formats making these services accessible worldwide on an efficient, relatively low cost basis. The use of higher cutting tool speeds, up to 100,000 rpm, combined with smaller tooling results in smaller minimum feature size and smoother surface finish. The second area of innovation that has improved the efficiency and power of these animal experiments is the ongoing development of multichannel recording probes and the hardware and software to support them. The use of these probes, in parallel with a software driven electrode switching system developed at UCSF, has reduced the experimental time needed to record IC responses to a series of monopolar, bipolar and tripolar electrode combinations from an average of 14 hours to less than one hour.

We have successfully used the electrode arrays described in this report in a wide range of electrophysiology experiments in both guinea pigs and cats. These experiments have included systematic evaluation of the effects of stimulating contact configurations (Rebscher et al., 2001; Snyder et al., 2004), the long-term effects of intracochlear stimulation on the survival of peripheral neurons (Leake et al., 1999) and central nervous system reorganization (Snyder et al., 1990; Leake et al., 2000; Moore et al., 2002; Snyder et al., 2004), the temporal response characteristics of IC and cortical neurons to acute and chronic electrical stimulation (Snyder et al., 1991; Snyder et al., 1995; Schreiner and Raggio, 1996; Vollmer et al., 1999; Snyder et al., 2000), the effects of chronically administered neurotrophins on the peripheral and central nervous system and studies documenting how input signals presented at different intracochlear locations inhibit, mask or excite neuronal responses. The scientific study of the interaction between multiple electrical stimuli, or between electrical and acoustic stimuli, and how these stimuli are processed in the central nervous system is in its infancy. Through the effective use of multichannel stimulating electrodes and multisite recording techniques we believe that this understanding will soon progress from descriptive to analytical and will offer valuable insights for the development of cochlear implants with greater benefit.

Future Directions

Clinical application of cochlear implants is in a state of dramatic change. As technical innovations lead to further improvement in CI performance it is clear that an increasing number of hearing aid users will meet the changing criteria for implantation and that in many cases the performance of these new CI users will exceed their previous performance with a hearing aid (Frayssé et al., 1998). In addition, many of these individuals suffer from progressive hearing loss that is most severe in the basal cochlea. The specific needs of this group has led to the development of cochlear implant devices designed to stimulate the high frequency region of the cochlea while maintaining mid and low frequency acoustic function (Kiefer et al., 2004; James et al., 2005; Lenarz et al., 2006) and limited clinical trials of these devices have been reported (Turner et al., 2004; Gantz et al., 2005; Kiefer et al., 2005; Gantz et al., 2006; James et al., 2006). Animal studies will be invaluable in understanding how electrical and acoustic signals interact in the cochlea and central nervous system and how to minimize perceptual distortions resulting from these interactions through changes in signal processing and/or electrode array design (von Ilberg et al., 1999; Nourski et al., 2005; Vollmer, 2006, personal communication). Based on computer modeling, this group of patients may perform best using an intracochlear electrode array specifically designed to selectively activate peripheral dendrites within the osseous spiral lamina (OSL) rather than spiral ganglion cells in the modiolus (Frijns et al., 1995; Frijns et al., 1996).

Other novel applications of cochlear implants currently being studied include the use of bilateral implants or bimodal stimulation to improve localization ability (van Hoesel and Tyler, 2003; Seeber et al., 2004; Verschuur et al., 2005; Litovsky et al., 2006), speech perception in the presence of noise (Au et al., 2003; van Hoesel and Tyler, 2003; Vermeir et al., 2003; Ching et al., 2004; Ramsden et al., 2005) and the creation of “virtual channels” by proportionally dividing stimulus current between two or more electrode sites to generate a potentially large number of perceptually distinct pitches using a minimum number of electrode sites (McDermott and McKay, 1994; Donaldson et al., 2005; Kwon and van den Honert, 2006). In each of these areas animal experiments could play an important role in understanding the complex interactions between multiple inputs and how specific electrode design features might be optimized for each purpose.

In addition to stimulation of the auditory system there are several potentially effective targets for electrical stimulation either to treat loss of sensory capacity, to mitigate the symptoms of neurological disease or to someday enhance normal function. These include, but are not limited to, the use of electrical stimulation to treat chronic pain, incontinence, blindness, Parkinson’s disease, epilepsy and vestibular dysfunction. All of these applications have been evaluated in preliminary clinical trials and many of the technical obstacles facing widespread use of these devices are similar to those that challenge the development of higher performance cochlear implants. Minimizing channel interaction, avoiding stimulation of adjacent neural populations, optimizing signal processing and increasing the functional dynamic range for stimulation are considered important goals for future development of all of these devices. The studies from our laboratory, and others as reviewed in this report, demonstrate that the design and position of the stimulating electrode array strongly influences each of these factors. We believe that the availability of effective, customized electrode arrays to evaluate strategies to optimize these devices will greatly facilitate future development of these systems.

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Figure 1.

The experimental electrode arrays described in this study are intended to model human cochlear implants. Over the past three decades these human electrode arrays have evolved in several ways. Most notably, early human arrays developed at UCSF were space filling with very small stimulating contact sites (A). Second generation UCSF arrays, licensed to Advanced Bionics, Inc. (B) were smaller in profile with larger stimulating contacts configured in offset radial pairs. Recent clinical electrode arrays manufactured by Advanced Bionics, Inc. and Cochlear Corp. are relatively small in cross-section and have large contacts oriented toward the modiolus. A straight version of the HiFocus™ electrode from Advanced Bionics, Inc. is shown in C.

Figure 2.

Average measurements of the scala tympani were used to draw two dimensional cross-sections along the cochlear spiral for each electrode array. These profiles were assembled along a spline (shown here as a single line) representing the inner margin of the ST to draft a three dimensional shape for the electrode carrier. The cross-sections for the guinea pig electrode array are shown in this figure.

Figure 3. Rendered forms for the guinea pig silicone carrier (top and side views) are shown on the left. After review, these 3-D files were used to generate the machining paths to create the mold cavities. A trial silicone injection molding of each cavity was made to confirm the surface features and overall dimensions of the carrier (right images).

Figure 4.

Shallow holes or dimples were machined into the surface of the mold cavity to designate the location for each possible stimulating contact. During the molding process these dimples also help to hold the contact securely as the elastomer is injected. The left image illustrates the machined mold cavity prior to drilling the dimples. A magnified view of the dimples within the mold cavity is shown on the right. In the guinea pig mold, 125 μm diameter dimples were machined at 250 μm intervals to permit many possible configurations of stimulating contacts with spacing as close as 250 μm .

Figure 5.

Completed electrode arrays for the guinea pig (A and B) and cat (C) are shown above. Strategies were developed to fabricate arrays with unique stimulus configurations required for specific experiments. The guinea pig electrode array in the top panel (A) was fabricated with an apical set of five stimulating contacts at 750 μm intervals and a basal set of three contacts at 750 μm intervals. Two additional contacts were located on the undersurface of the array 180° opposed from contacts #6 and #8 (numbered from the electrode tip). The center image (B) illustrates the basal region of another guinea pig electrode. In this array all contacts were located on the upper surface of the array at intervals of 250 μm . An eight-contact feline electrode is shown in the lower image (C).

Figure 6.

A miniature cannula was added to the underside of the electrode array to permit concurrent electrical stimulation and long-term intracochlear administration of therapeutic agents such as brain derived neurotrophic growth factor (BDNF) *via* an implanted osmotic pump. The upper image (A) illustrates the mold features that form a hub to incorporate these two functions. The molded channel holding the drug delivery tubing is straight to avoid kinking. In the second image (B) arrows indicate the fine polyimide cannula that opens into a length of vinyl tubing connecting the osmotic pump, passes through the molded round window segment of the electrode array (RW) and terminates in the basal section of the array (left arrow). Wire leads for electrical stimulation pass through the molded silicone cable. Inset images illustrate

diffusion of a dye solution pumped through the terminus of the cannula. The stimulating contacts and lead wires were not included in this model device to better illustrate the drug delivery features. Figures 6C and 6D illustrate the molded chamber surrounding the terminus of the cannula. The dashed line (“D”) in the left image represents the location of the cross section shown in the right image (D). The hollow chamber was designed to protect the tip of the cannula and permit the larger volume of the electrode array to collapse, enabling it to pass through the smaller round window without surgically enlarging the opening.

Figure 7.

Recording of neural responses in the inferior colliculus (ICC) of the guinea pig was used to document the regions of activation generated by intracochlear electrical stimulation. Prior to deafening the animal a series of pure tones was presented to the left ear and neural responses were recorded in the contralateral ICC using a multichannel recording probe. This procedure calibrated the depth of the recording probe, allowing the location of activity in the ICC to be directly related to the location of the site of stimulation in the cochlear spiral. The panels shown in A illustrate the location and strength of the neural response for pure tones of increasing frequency (5.7 kHz on the left to 26.9 kHz on the right). Increasing intensity is plotted along the abscissa for each panel and the response magnitude is represented by pixel color. The

maximum response for low frequency tones is consistently located near the surface of the ICC. This focus shifts deeper as the acoustic signal increases in frequency. In all cases, the region of activation spreads across the ICC as loudness increases.

Panels B, C and D illustrate how the configuration of stimulating sites, in this case tripolar (B), bipolar (C) and monopolar (D) strongly affects the spread of excitation for stimulation with each channel of the electrode array. For each configuration, stimuli were presented with the cathodic phase (−) first on the contact indicated, i.e. the center contact in a tripolar configuration, the apical contact in a bipolar configuration and the intracochlear contact in a monopolar configuration. Under all conditions, stimulation of an apical location in the cochlea (a low frequency tone, electrode configuration 1,2,3 tripolar, 1,2 bipolar, or monopolar, resulted in neural activity focused near the surface of the ICC. Conversely, stimulation of a more basal electrode site or high frequency tone resulted in maximum activity deeper in the nucleus. Clearly, the neural responses to monopolar stimulation are more broadly distributed in the ICC than those for bipolar or tripolar stimuli.