2nd Quarterly Progress Report

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The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

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Abstract

This Quarterly Progress Report presents our progress in the second three months of this contract. We have made progress in four areas: 1) We have completed the design and fabrication of our first multi-channel intracochlear electrode for the guinea pig. 2) We have conducted three physiological experiments in guinea pigs using this electrode. 3) We have continued our experiments using acoustic two-tone stimulation in normal guinea pigs. 4) We have begun developing software for experiments presenting acoustically processed and electrically processed speech stimuli. In this QPR, we will describe our results in the first two of these areas.

This contract's RFP specifies that as contractors we must stimulate the cochlea using "stimulating electrodes, that mimic those used or being considered for use in human auditory prostheses." In this quarter, we have completed the construction of a guinea pig electrode mold and fabricated our first guinea pig intracochlear electrode. This electrode had 9 contacts distributed along its length. In order to maximize the range of frequency representations, which could be stimulated by this electrode while maintaining their frequency selectivity, these 9 contacts were distributed in two sets of closely spaced contacts, an apical set of 6 contacts and a basal set of three contacts. All these contacts were positioned so that they would face toward the habenula. Thus, this electrode will allow us to stimulate the guinea pig cochlea in longitudinal bipolar (BP) mode with different intracochlear locations (basal vs. apical) and with different spacing between contacts from 500 μm to 3 mm, in monopolar (MP) mode and in longitudinal tripolar (TP) mode.

In addition to fabricating our first guinea pigs intracochlear electrode, we have inserted this electrode into the guinea pig cochlea and used it to stimulate the auditory nerve in three electrophysiological experiments. In these experiments, we recorded the responses evoked by activation of this electrode in inferior colliculus (IC) neurons. We measured spread of excitation across the IC evoked by acoustic tones in the normal hearing guinea pig, we then deafened the animal, inserted the intracochlear electrode and measured the spread of excitation evoked by electrical stimulation using several different electrode configurations. For example, using each adjacent pair of electrode contacts (adjacent bipolar stimulation), we compared the location of the response focus (RF) and the spread of excitation with increasing stimulus intensity (6 dB width) of the spatial tuning curves (STCs). We compared these results with those using non-adjacent bipolar contacts and those using monopolar activation modes. The results of these experiments were encouraging. They indicate that we can excite different highly restricted frequency regions of the cochlear with different electrode pairs. They also indicated the these excitation patterns are more restricted than those we have observed in previous experiments stimulating cats with our UCSF cat electrode or stimulating guinea pigs using a modified banded array or using visually placed bipolar electrodes. They also indicate that we can systematically vary the spread of excitation at a fixed level above threshold by varying the spatial separation between bipolar pairs or by activating the contacts in monopolar mode.

Finally, very little physiological information is available regarding channel (two-tone) interactions in normal hearing subjects or channel interactions in deaf implanted subjects. Therefore, we have continued our experiments examining the responses of IC neurons to simultaneously and non-simultaneously presented two-tone combinations in

normal hearing guinea pigs. We have also begun experiments look at electrical channel interactions in implanted guinea pigs. The preliminary results of these experiments suggest that the responses interactions evoked by two non-simultaneously presented tones or pulses produce response patterns that are dramatically different in IC neurons from those observed in the auditory nerve. The results of our two-tone experiments will be the focus of our next QPR.

Development of a Guinea Pig Intracochlear Stimulating Electrode

As described in the first quarterly progress report, we have designed an intracochlear stimulating electrode to fit the specific dimensions and shape of the guinea pig cochlea (see Appendix I). The goal of this project is to provide a flexible research tool to allow electrical stimulation of selected regions of the auditory nerve array with a variety of electrode contact configurations and strategies. In addition, we desire to minimize electrode insertion trauma, and at the same time locate these stimulating contacts as close to the modiolus as possible, we started the design process by measuring several casts from guinea pig cochleae as shown in Figure 1.

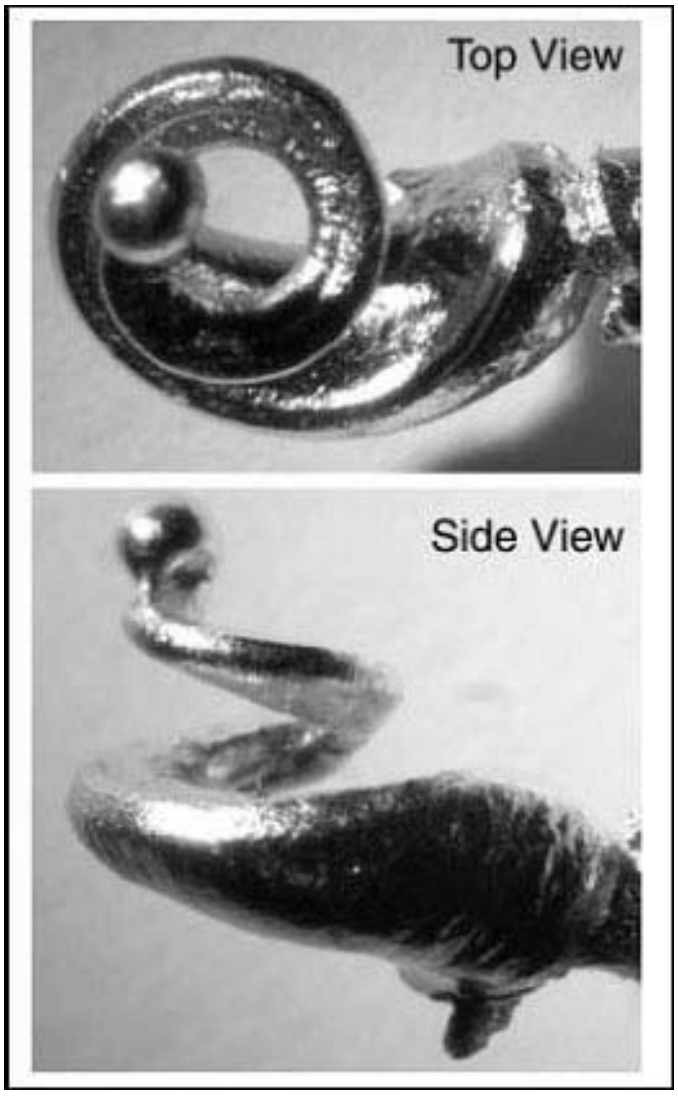

Figure 1. Low melting point alloy metal casts were made directly from guinea pig cochleae. The casts were measured using digitized images analyzed with Canvas™ software to create a dimensional database for electrode mold design. The mold cavities were drawn using computer assisted design (CAD) software and machined directly from this design using computer controlled milling.

Dimensions from the guinea pig casts were used to draw the outlines of a silicone carrier and these drawings were used to machine a two-part cavity mold from aluminum. The mold was fabricated by a subcontractor using computer controlled milling and standard machine tooling. Upon receipt, the mold was inspected for dimensional accuracy and polished using diamond polishing compound. A series of shallow dimples were located and milled into the cavity surface of the lower half-mold. These dimples allow us to position the stimulating contacts prior to encasing the electrode array in silicone rubber (see Figure 2). The mold was washed in a degreasing solution, rinsed in ethanol and water and ultrasonicated to remove all traces of machining lubricants and particles of metal resulting from the milling process. After thorough drying, the mold cavity was coated with a layer of medical grade silicone oil and wiped clean to leave a very thin coating of silicone to act as a release agent.

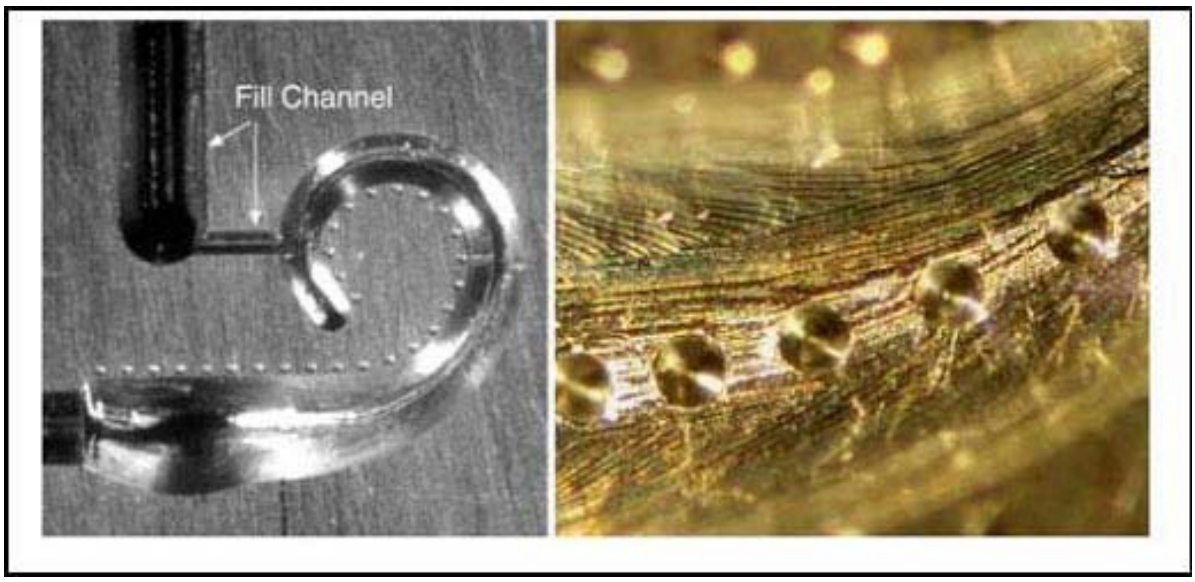

Figure 2. Mold cavities were machined in aluminum using computer controlled milling (left image). After receipt of the machined mold plates each plate was measured to verify dimensional accuracy and a series of dimples (150µ diameter, 150µ depth) were machined into the lower mold half to locate stimulating contacts during fabrication (right image). This series of dimples was located along the center line of the lower mold half to produce electrode sites facing upward toward the habenula perforata when inserted in the guinea pig scala tympani. Twenty-seven dimples were placed at 250µ intervals along the length of the mold cavity. We plan to place additional dimples along the modiolar surface of the mold and along the centerline of the upper mold half. The striations visible on the mold surface in the higher magnification view on the right are the machining marks left from the CNC milling operation using a ball end mill.

To form stimulating contacts the tip of each electrode lead was melted to form a sphere using an oxygen/acetylene micro-torch. For this first series of experiments, the balls were 175 µm in diameter. 90% Pt: 10%Ir wire (.001" diameter) was used for all lead wires.

As shown in Figure 3 nine contacts were mounted in the first electrode produced. Six contacts separated by 500 µm were positioned at the apical tip of the electrode and three contacts also separated by 500 µm were positioned nearer the base. These two sets of contacts were separated by 2250 µm. This configuration was chosen to permit several combinations of different longitudinal spacing near the tip of the carrier and monopolar, bipolar and tripolar strategies at both locations. Figure 4 illustrates the six contacts located near the electrode tip at higher magnification. We plan to build subsequent electrodes with greater numbers of contacts separated by 250 µm and with additional location options. Additional placement dimples will be milled in the mold facing the modiolus and 180° from the current set of contacts.

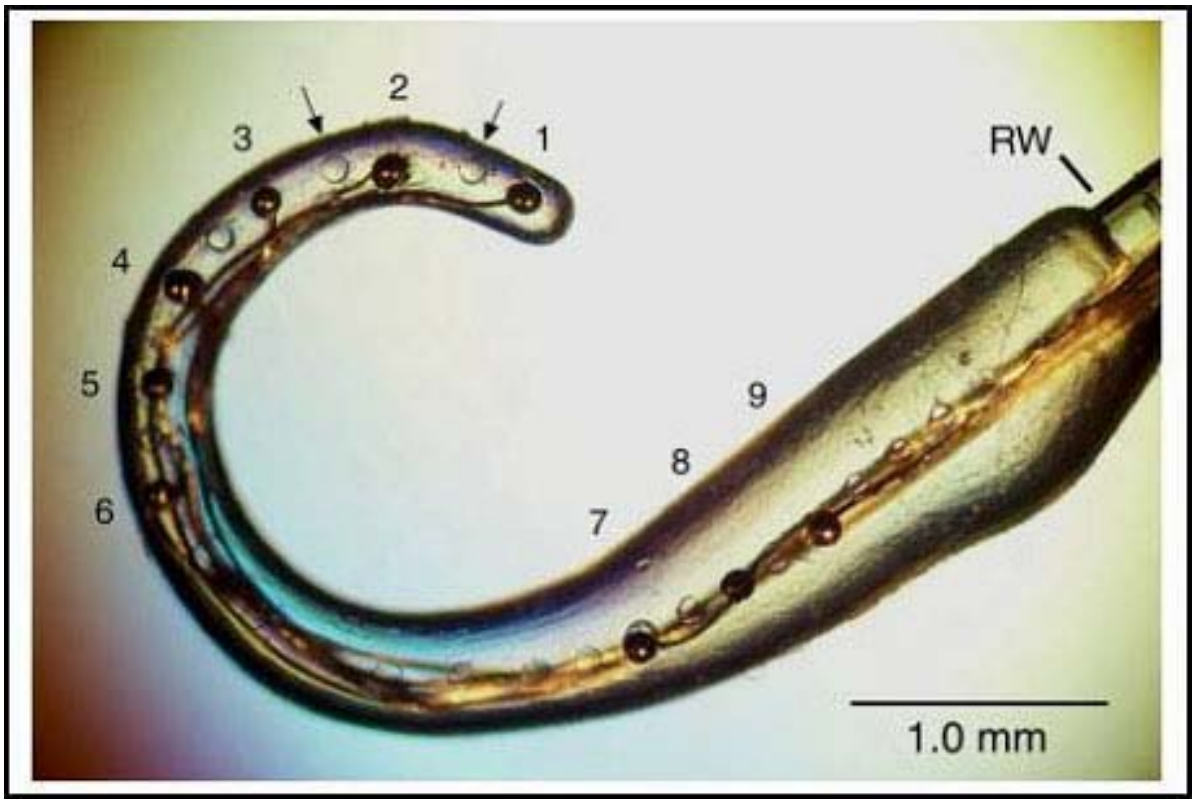

Figure 3. The first electrode produced with the guinea pig mold was fabricated with nine contacts 175µ diameter. Six of the contacts are located near the electrode tip with 500µ spacing between centers. A series of three contacts was located nearer the base also with 500µ spacing. A space of 2.25 mm separates the apical and basal contact sets in this electrode. Arrows indicate unused contact placement dimples at intermediate locations. Thus, the minimum contact spacing designed for the mold is 250µ. During the next quarter, we will complete electrodes with greater numbers of contacts and machine placement dimples at other radial positions on the array.

We calculated charge densities for the stimulating contacts to evaluate the electro-chemical safety limits of the array in this configuration. Assuming a surface roughness factor of 1.5, these contacts have an exposed area of approximately 3.62×10^{-4} cm^2. Assuming a threshold

of 100μ amps and a phase-duration of 200 μsec (see the section on electro-physiological results) this contact would have a charge density of approximately 55 μC/cm2 at threshold. If we take 300-400 μC/cm2 as a safe operating limit for 90%Pt:10%Ir we expect that these electrode contacts will have a safe dynamic range of approximately 6-8 times threshold or 12-18 dB.

Figure 4. The tip section of the electrode is shown at higher magnification in this image. The electrode tip is 350μ in diameter.

B. Physiological experiments using the new guinea pig intracochlear electrode.

Introduction:

In previous experiments (Arenberg et al, 2001, Snyder et al, 2003), we evaluated factors that influence intracochlear spread of activation within the guinea pig cochlea. We used two types of intracochlear electrodes: 1) an electrode similar to one clinical device consisting of linear series of ring contacts positioned along a silicon elastomer carrier and 2) a pair of visually placed (VP) ball electrodes that could be positioned relative to particular intracochlear structures, e.g., the spiral ganglion. The results indicated that monopolar (MP) stimulation with either electrode type produced very broad excitation across the ICC. Bipolar (BP) stimulation with banded electrodes produced activation that was somewhat less broad than MP stimulation, and tripolar (TP) stimulation produced activation that was more restricted than MP or BP stimulation. Bipolar stimulation with radially oriented pairs of VP ball electrodes produced the most restricted activation, although we did not test tripolar stimulation with VP ball electrodes. The activity patterns evoked by radial VP balls were comparable to those produced by pure tones in normal-hearing animals. Variations in distance between radially oriented VP balls had little effect on activation spread, although increases in inter-electrode spacing tended to reduce thresholds. Bipolar stimulation with

longitudinally oriented VP electrodes produced broad activation that tended to broaden as the separation between electrodes increased.

In the current quarter, we have initiated a similar series of experiments using an electrode that is similar to a different clinical device. Our goal is to compare the activity patterns evoked by these different intracochlear electrodes types in order to determine the one that activates the auditory nerve with the lowest threshold and greatest selectivity. In the current experiments, we will systematically examine the effects of electrode configuration (BP, MP or TP stimulation), electrode separation in BP and TP mode, and electrode orientation (radial vs. longitudinal in BP and TP mode).

Methods:

Anesthesia and surgery:

Data were collected from 3 healthy adult pigmented guinea pigs (500–900 g) with normal hearing. Animals were initially sedated with a subcutaneous injection of ketamine hydrochloride (25 mg/kg) and xylazine (10 mg/kg). Additional intramuscular injections of a 4:1 mixture of ketamine/xylazine were given as needed to maintain an areflexive state. Heart rate, respiratory rate, and body temperature were monitored continuously. Core body temperature was maintained at 38°C with a thermostatically controlled heating pad. A tracheal cannula was inserted to insure an unobstructed airway. A dorsal midline incision was made in the scalp to expose the dorsal surface of the skull. The head was fixed in place by an insulated metal rod that was attached to the skull anterior to the bregma using small self-tapping screws and dental acrylic. The temporalis muscle was reflected, and a 5 mm opening was made in the right parietal bone just dorsal to the parietal/temporal suture and just rostral to the tentorium. The dura was incised and reflected to expose the lateral and posterior occipital cortex. This cortex was aspirated to allow direct visualization of the dorsal and lateral surface of the IC.

Once the IC was visualized, a silicon-substrate, thin-film, 16-channel-recording probe (Center for Neural Communication Technology, Ann Arbor, MI; Drake et al. 1988; Najafi et al. 1985), was inserted into the center of the IC using a micromanipulator. The probe was mounted on a custom-built head-stage that was held by the micromanipulator. The probe was inserted into the IC on a dorsolateral to ventromedial trajectory at a 45º angle off the parasagital plane in the coronal plane. Using this trajectory, the probe traversed the central nucleus at a right angle to its iso-frequency laminae (Snyder et al., 1990.1991, 2000). Each recording probe had 16 recording sites along a single shank. The separation between sites was 100-µm (center to center). The shank was 15 µm thick and 100 µm wide at the most proximal site and tapering to 15 µm at the most distal site. The impedances at each site were 10-30 kΩ. In the guinea pig, the 1.5 mm distance from the most distal to the most proximal recording site allowed simultaneous recording of responses from neurons sensitive to frequencies spanning approximately 4.5 octaves (2-24 kHz, see Fig. 5). The probes were advanced until the most distal site recorded activity from neurons with a characteristic frequency (CF) of approximately 24 kHz. Once this location had been reached, the cortical deficit was filled with warm 2% agar dissolved in Ringer's solution. When the agar had solidified, the agar and the surrounding parietal and temporal bones were covered with a thick layer of dental acrylic sealing the bony deficit and fixing the probe in place. After the probe had been fixed in place, acoustic responses from all probe sites were recorded using

contralateral tones (see below) at 12-16 levels separated by 5 dB (usually 0 to 60-75 dB SPL). Tone frequencies were separated by 1/8 of an octave and ranged from 2 to 42 kHz.

Once these preliminary acoustic recordings had been made, the probe was detached from its pre-amplifier and the animal was re-positioned to allow access to the left (contralateral) cochlea. After re-positioning, a second series of acoustic responses was recorded. In every case, the position of the recording probe remained unchanged relative to the tonotopic map, demonstrating the stability of the preparation. The tonotopic mapping with sounds permitted a CF to be assigned to each probe recording site, effectively calibrating the sites and allowing both a relative intracochlear location and CF to be assigned to each site. After this second series of acoustic recordings, the left cochlear bulla was opened so that the round window could be visualized. The animals were deafened by injecting a 10% solution of neomycin sulfate into the cochlea through a small slit in the round window membrane.

After the animals had been deafened, a cochleostomy was made in the lateral wall of the cochlea at the junction of the 'hook' and first cochlear turn. A guinea pig electrode (see Figure 3 above) was inserted into scala tympani. After insertion, electrical stimuli were presented in various configurations and ICC responses were recorded. Electrode configurations included monopolar stimulation (an intracochlear 'active' electrode activated against an extracochlear 'return' electrode, a silver wire in the skin of the neck), bipolar stimulation (an intracochlear active electrode activated against an adjacent intracochlear return electrode), and tripolar stimulation (an intracochlear active electrode activated against two adjacent electrodes serving as the return). All procedures were conducted in accordance with the policies of the University of California's University Committee on Use and Care of Animals.

Stimulus generation and calibration:

Acoustic signals: Experiments were conducted in a sound-attenuating chamber and were controlled by an Intel-based personal computer. Acoustic stimuli were synthesized digitally using equipment from Tucker-Davis Technologies (TDT) (Gainesville, Florida). The sample rate for audio output was 100 kHz with 16-bit resolution. The levels of these signals are controlled by digital attenuators (TDT model PA-5), amplified by Samson model 220 audio amplifiers, and presented monaurally to the ear contralateral to the studied inferior colliculus. A headphone (RadioShack Supertweeter, model 40-1310) enclosed in a small case was connected to a rigid delivery tube that was inserted into the external auditory meatus near the tympanic membrane and sealed in place. After calibration, the speaker transfer function was flat within +/- 2 dB SPL from 2000 - 41500 Hz. All tone stimuli were 50 ms long, and had 2 ms raised-cosine onset/offset ramps. The sound system was calibrated using a ½" microphone (B&K model 4182) and custom software. The resulting calibration table was used for online correction of the headphone response. Stimulus frequencies ranged from 1–24 kHz in 1/8-octave steps. Levels ranged from 0 to as high as 80 dB sound pressure level (SPL) in 5-dB steps.

Electrical signals: Electrical stimuli were generated by the same TDT System III RP2 signal generators. The electrical signals were delivered by custom-made optically isolated current sources. Electrical stimuli consisted of two charge-balanced biphasic pulses 200 μsec/phase. The pulses were separated by 50 ms. Polarity was initially cathodal at the active electrode. Stimuli were presented at a rate of 3 per sec.

Multi-channel recording and spike sorting:

Multi-channel probes permitted simultaneous recording of spike activity from 16 sites arrayed linearly across the ICC. Signals from these sites were amplified with custom 16-channel pre- and post-amplifiers, digitized at a 20 kHz rate, and stored on the computer hard disk. Unit activity was isolated on-line from the digitized responses using simple supra-threshold peak picking software; off-line spikes were discriminated using custom spike-sorting software. Spike times were stored at a resolution of 20 μs for further analysis. Well-isolated single units were recorded as well as multiunit clusters consisting of a small number of unresolved units.

Data analysis:

Spike counts were normalized at each recording site according to the maximum response to acoustic stimulation or electrical activation. By normalizing in this manner, our results emphasize stimulus-driven changes in activity rather than differences in absolute spike counts across channels. The results include data from individual recording sites as well as the distribution of activity across multiple recording sites. For individual recording sites, the lowest level that elicits a stimulus-locked response is defined as threshold. CF is defined as the frequency that gave a detectible response at the lowest stimulus level. BF is defined as the frequency at suprathreshold levels that evoked the largest response. The temporal distribution of activity evoked by a tone at a given frequency and intensity across all recording sites was estimated from a spatiotemporal image (STI) of that stimulus. The STI of any particular stimulus was derived from simultaneous recordings at 16 sites, so the activity across all sites reflected the response to that stimulus. The spatial distribution of spike activity across all recording sites as a function of stimulus level was represented by spatial tuning curves (STCs). The response focus (RF) was defined as the ICC recording site that produced driven activity at the lowest threshold.

Results:

Acoustic Stimulation:

Prior to inserting the stimulating electrode, the recording probe was calibrated by presenting acoustic tones to the contralateral ear. A series of tones across a range of frequency/ intensity combinations were presented and the responses to each tone at each probe site was recorded. After all tones were presented, frequency response areas (FRAs)

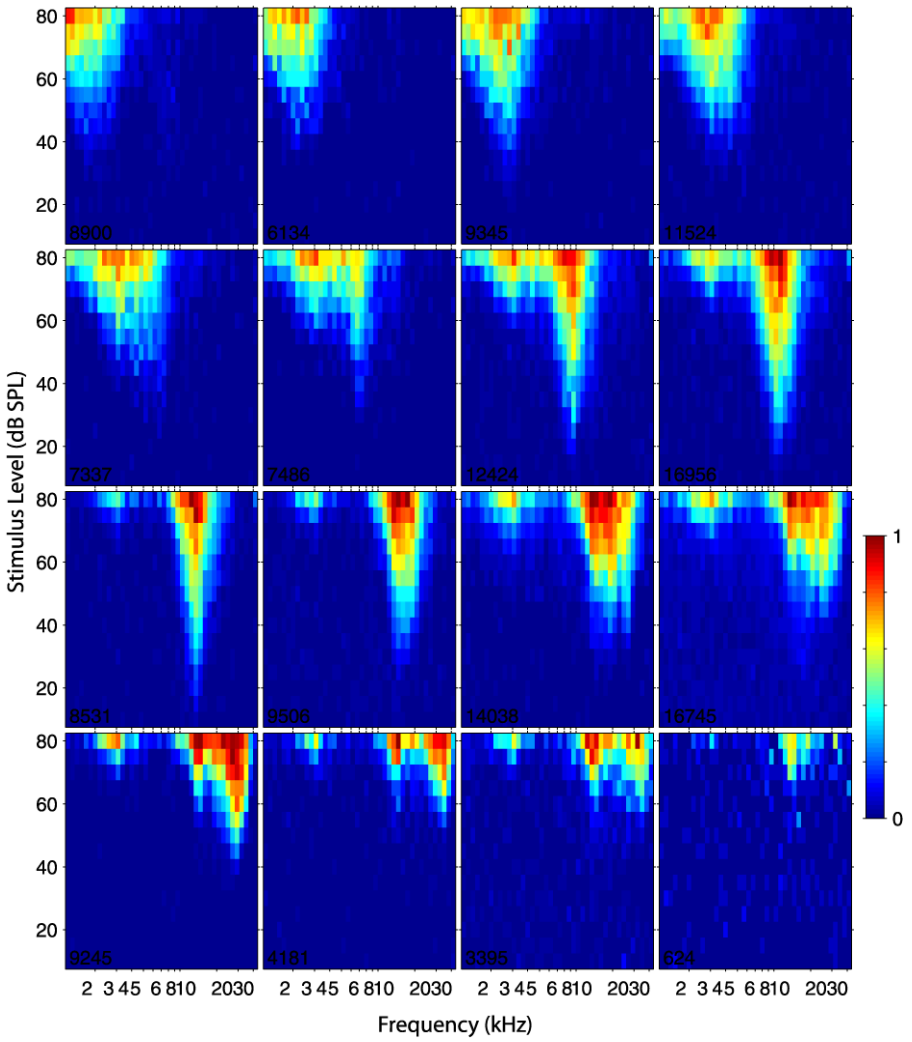

Figure 5. Frequency response areas (FRAs) evoked by acoustic tones and recorded prior to deafening of the animal and insertion of the intracochlear electrode. Each panel represents responses recorded at one probe site. Responses from the most superficial recording site are illustrated in the upper left panel. Responses from successive sites are illustrated from left to right and top to bottom. Within each panel, each facet represents the response to a single frequency/level combination. Response rates are scaled between the minimum spike rate (usually zero spikes) and the maximum rate recorded at that site. These scaled rates are color coded according to the scale on the right.

for each site were constructed (Figure 5). From these FRAs, the CF of each site was estimated. These CF estimates were used to 'calibrate' the recording electrode so that not only a depth but also a characteristic frequency can be assigned to each recording site.

Intracochlear Bipolar Electrical Stimulation:

Once the recording electrode had been inserted, calibrated and fixed in place, the animals were deafened and the stimulating electrode (see Figure 3) was inserted into the scala tympani. After the stimulating electrode was inserted, pairs of contacts could be activated, the IC responses recorded and spatial tuning curves STCs constructed. From these STCs, measures of the electrode threshold, response focus (RF) and spread of excitation (6 dB widths) can be estimated. Figure 6 illustrates the spatial tuning curves (STCs) evoked by activating adjacent pairs of intracochlear contacts. As expected, activation of the most apical pair of contacts (1,2) excited IC neurons, which were tuned to the lowest frequencies and which were located most superficially in

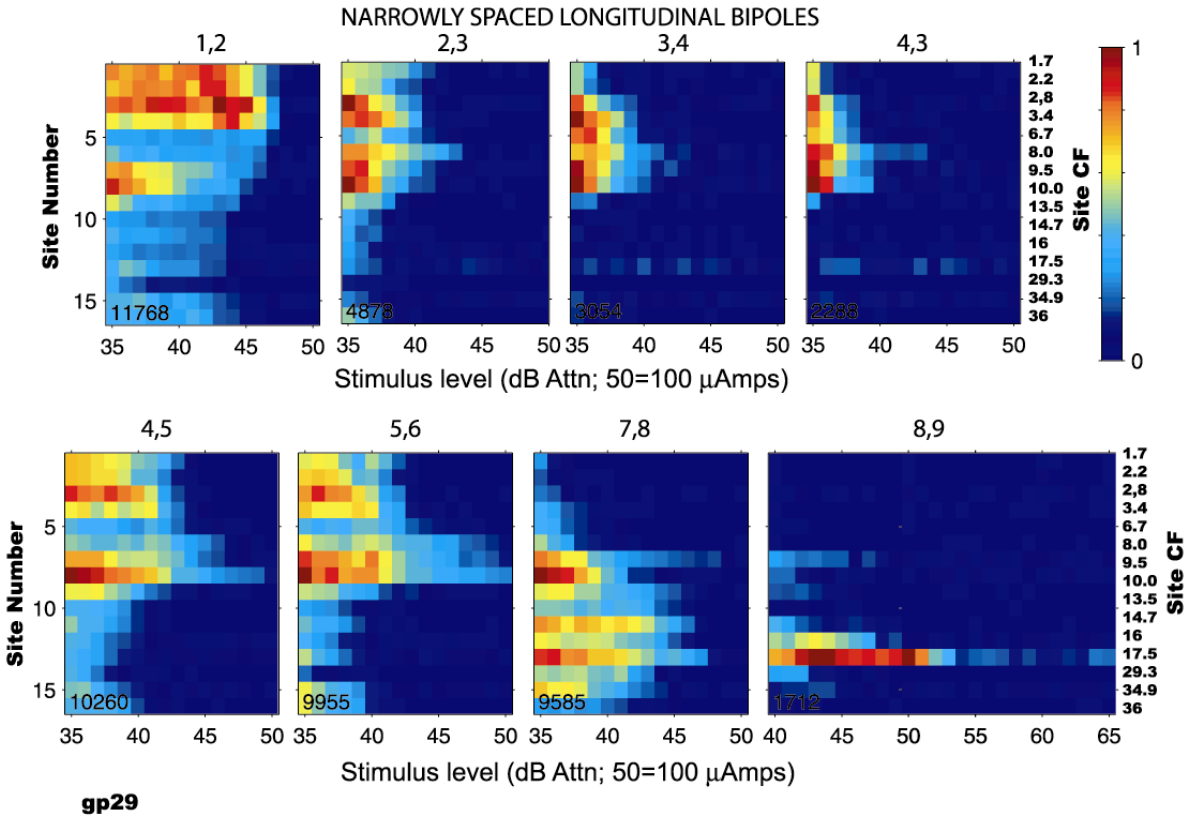

Figure 6. Spatial tuning curves (STCs) evoked by bipolar intracochlear electrical stimulation. Each panel is an STC evoked by activation of an adjacent electrode pair (separated by 500 µm, see Figure 3). The STC evoked by the most apical pair (1.2) is illustrated at the upper left. STCs from successively more basal pairs are illustrated from left to right and top to bottom. The STC recorded from the most basal electrode pair is illustrated at the lower right. Recording probe site numbers (relative IC depth x 100 µm) are indicated at the left of each panel row. The recording site CFs derived from Figure 5 are indicated to the right of each row of panels. Abscissa is stimulus current. Within each panel, a facet represents the scaled number of spikes evoked at a recording site by activation of that electrode at the specified current level.

the IC, whereas activation of the most basal contracts (8,9) excited neurons, which were tuned to the highest frequencies and were located deepest within the IC. Moreover, there is a relatively smooth shift in the RF of the STCs evoked by these most apical electrode contacts to the most basal contacts. However, there is an abrupt shift in RF between the STCs evoked by pairs 5,6 and that evoked by pairs 7,8. This abrupt shift is due to the more than 2 mm gap between contact 6 and contact 7(see Figure 3). Although this topographic correspondence between stimulation electrode location within the cochlear and recording site CF (or depth) within the IC is expected both from the tonotopic organization of the IC and from our previous studies, the spread of excitation within these STCs is relatively narrow, especially considering that the stimuli were 200 μsec/phase pulses (see Rebscher et al, 2001).

Monopolar vs. Bipolar Stimulation:

Figure 7 compares the STCs evoked by closely spaced (500 mm separation) bipolar contacts in our guinea pig electrode and those evoked by one of the same contacts activated as monopoles,

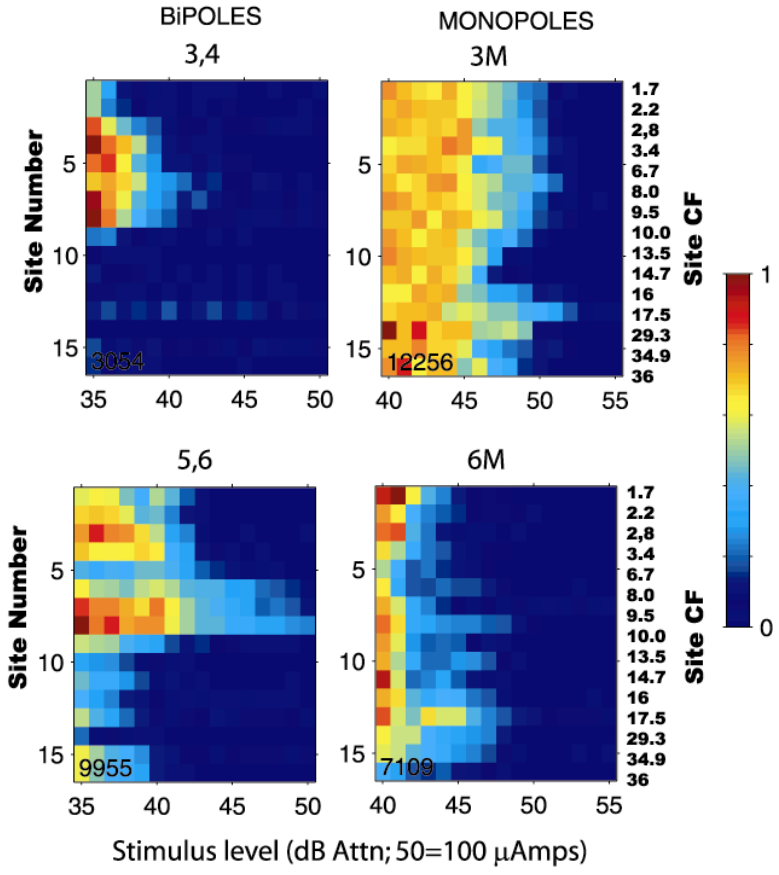

Figure 7. Bipolar STCs evoked by closely spaced (500 mm) bipolar contacts on the left. Monopolar STCs evoked by one of the bipolar contacts activated as a monopole (i.e., activation of an intracochlear contact with extracochlear electrodes serving as a return). Probe site number or relative depth in the IC (x 100 mm) is indicated on the left ordinate. Site CF in kHz is indicated on the right. Response amplitude scale is on the far right.

i.e., with the intracochlear contact acting as the active electrode and an extracochlear contact acting as the return electrode. Although often higher in minimum threshold, the bipolar STCs are usually more restricted in their spatial tuning than the monopolar STCs (Rebscher et al, 2001). This generalization appears to hold true in these preliminary guinea pig experiments. Bipolar STCs evoked by pairs 3,4 and 5,6 are quite sharply tuned having 6 dB widths of 500 & 300 μm respectively, where as the STCs evoked by contacts 3 and 6 as monopoles have 6 dB width wider than our ability to measure, i.e., beyond the extent of our recording probes.

Widely Spaced vs. Closely Spaced Bipolar Stimulation:

Our current guinea pig electrode allows us to place intracochlear contacts at any of 27 locations distributed from the basal hook to the middle of the 2nd turn. These locations are separated by integer multiples of 250 μm for to up to 7 mm. Thus,

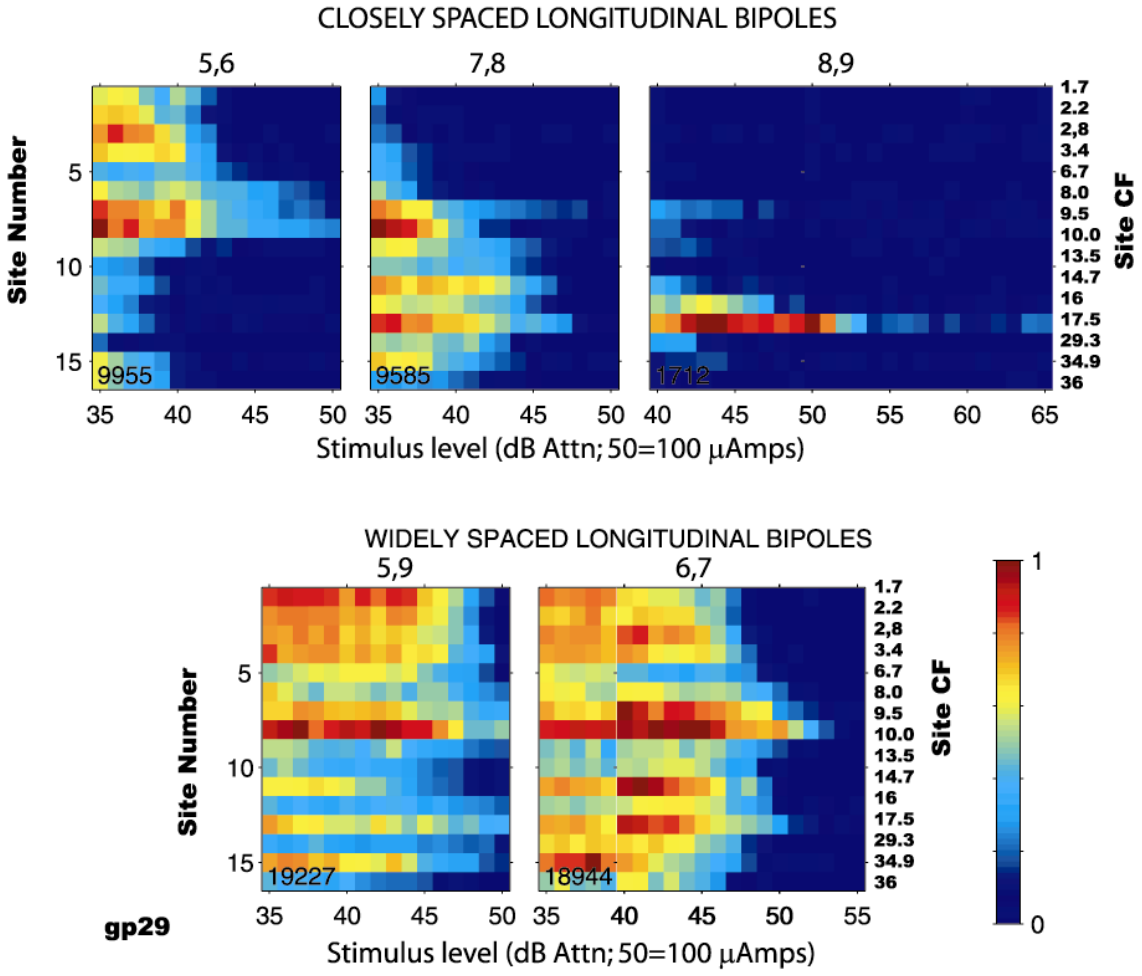

Figure 8. Upper row of STCs were evoked by activation of two closely spaced (500 μm separation) longitudinal contacts. These contact either were in the apical set of contacts (5,6) or in the basal set of contacts (7,8 & 8,9), see Figure 3. Lower row of

STCs were evoked by activation of contacts that spanned the gap between the apical and basal contacts. They, therefore, were widely separated longitudinal contacts.

pairs of contacts can be separated by as little as 250 μm and by as much as 7 mm. Figure 8 compares bipolar STCs evoked by activation of apical and basal pairs of contacts separated by 500 mm (5,6; 7,8, and 8,9), 2.25 mm (pair 6,7) or 3.75 mm (pair 5,9). Comparison of the spread of excitation in these STCs clearly illustrates that widely separated contacts activate broad areas of the IC and by inference broad sectors of the auditory nerve array. From these data, it is logical to assume that more closely separated intracochlear contacts will activate regions of the IC more selectively. In the coming quarter we plan to construct an electrode in which some sites are separated by as little as 250 μm. We expect that the sites with these reduced separations will allow activation of the IC that is even more selective than that see with the current electrodes.

Discussion

These results of these experiments suggest that our guinea pig electrode will allow us to selectively activate the auditory nerve array with short phase duration pulses. In previous cat experiments, we have observed that pulse evoked STCs were much broader than those evoked by 100 Hz sine waves. In most of these previous experiments, the pulse evoked STCs were so broad that stimulation of even two independent channels at 6 dB above threshold would not have been possible. In these preliminary guinea pig experiments, a minimum of three independent channels was possible. It is hoped that by decreasing the separation between electrode contacts, by stimulating in tripolar mode or by stimulating with radial bipolar contracts the selectivity of intracochlear activation can be further increased.

Meanwhile, the thresholds are relatively high. Thresholds evoked by different closely spaced bipolar contacts varied from as high as 200 μAmps to less than 30 μAmps. The reasons for this variance are not clear at the moment. Therefore, we are considering a number of strategies to decrease electrical artifacts including using larger ball contacts, using concave contacts or roughened/sintered contacts and also iridium plating combined with activation to decrease the impedance and stimulus artifacts.

Work Planned for the Next Quarter

1) We will begin experiments looking at channel interaction using electrical stimulation. We will attempt to correlate the spread of excitation as defined by spatial tuning curves in the IC with the spread of excitation as defined by reduction of EABR amplitude using inter-pulse intervals between 4 and 50 msec.

2) We will begin experiments employing electrodes with closer contact spacing between contacts. Our current electrode uses a minimum spacing of 500 μm between contacts. In the next quarter we will fabricate an electrode in which at least some contacts have a minimum spacing of 250 μm.

3) Work will continue on the acoustic model of channel interaction. We will quantify the spread of stimulus inhibition using a non-overlapping two-tone (forward masking) paradigm. We will define the time course of the inhibition by varying the gap between the end of the first tone and the beginning of the second tone. We will define the development of the interaction by varying the duration of the first tone. Finally, we will estimate the relative magnitude of the interaction by varying the intensity of the second tone.

4) Experiments will be continued to look at the effects of electrode configuration on single channel and multi-channel stimulation. We will examine the spread of excitation using tripolar as well as bipolar and monopolar configurations.

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Appendix I. Figure illustrating details of guinea pig scala tympani measurements for electrode mold #1`: