Seventh Quarterly Progress Report

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Feasibility of an Intra-Neural Auditory Prosthesis Stimulating Electrode Array

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1. Introduction

The objective of this research is to evaluate the feasibility of intra-neural stimulation as a means of auditory prosthesis. We are stimulating the auditory nerve with penetrating multi-channel electrode arrays and monitoring the tonotopic spread of activation in the central nucleus of the inferior colliculus (ICC) of cats.

2. Summary of activities for the quarter

In the present quarter, we conferred with engineers about possible designs for chronic intra-neural stimulating arrays, we conferred with otologic surgeons on practical approaches to the auditory nerve in human patients, we extended our quantitative analysis of data obtained from intra-neural stimulation using a lateral approach to the auditory nerve, and we conducted acute physiological experiments in four cats using intra-cranial (two cats) and lateral (two cats) approaches to the auditory nerve. A manuscript was accepted for publication in the *Journal of the Association for Research in Otolaryngology* (Middlebrooks and Snyder, "Auditory Prosthesis with a Penetrating Nerve Array"). A pdf version of the manuscript should be available on the ARO website by January, 2007.

The principal accomplishments of this quarter were the following:

- *Conference with otologic surgeons.* We met with the otologic surgeons at the University of Michigan and presented our results from intra-neural stimulation in an animal model. We solicited their comments regarding the feasibility of translating that procedure to human patients. In particular, we were interested in whether, based on their practical experience, they favored a lateral approach or an intracranial approach to the nerve. In favor of the intracranial approach is the possibility that surviving acoustical hearing might be preserved with that approach, although subsequent to that conference we also have been successful in preserving hearing using a lateral approach (see below). Weighing against the intracranial approach is the risk of meningitis associated with any intracranial procedure; we are told that, as a rule of thumb, the rate of incidence of meningitis is ~10% of craniotomies. Of even greater concern is the difficulty of stabilizing the stimulating electrode array relative to the intracranial segment of the auditory nerve. In particular, there would be a risk of damage to the nerve from motion of the pulsating nerve relative to a fixed penetrating nerve array. In favor of the lateral approach is the relative familiarity of the surgery. According to these surgeons, the lateral approach should be comparatively straightforward, rather similar to the facial recess approach that is used for implantation of conventional intra-cochlear electrode arrays. Moreover, although damage to surviving cochlear hair cells is a concern associated with the lateral approach, the risk presumably would be no greater than the risk due to insertion of a conventional cochlear implant into the scala tympani. We have made arrangements to work with one of the surgeons to explore and document lateral approaches to the human auditory nerve human temporal bone dissections.
- *Extended quantitative analysis.* We quantified the spread of activation along the tonotopic axis of the ICC in response to acoustic stimulation with tones and electrical stimulation with intra-neural, monopolar scala-tympani, and bipolar scala-tympani electrodes. Analysis of variance shows a significant effect of stimulus mode on spread of activation, with spread increasing from acoustic to intra-neural to bipolar to monopolar. Allowing for the differences in dynamic range among the various stimulation modes, the spread of activation in response to intra-neural stimulation at 3 dB above threshold corresponds closely to that for tonal

stimulation at 10 dB above threshold. We also examined a measure of interference between pairs of electrodes stimulated simultaneously. At each ICC recording site, we computed the difference in threshold between two electrodes stimulated alone and the amount by which simultaneous stimulation reduced the lower of the two single-electrode thresholds. The results demonstrate two factors by which interference between electrodes is less for intra-scalar than for scala tympani stimulation. First, intra-neural stimulation provides greater possibility for non-overlapping activated areas along the ICC tonotopic axis. This is a result of reduced spread of activation and of access to a broader range of the frequency representation. Second, for a given amount of overlap (represented by the single-electrode threshold difference), the threshold reduction is less for intra-neural stimulation. We attribute that to more complicated current paths within the fasciculated structure of the auditory nerve compared the free current paths within the electrolyte-filled scala tympani. These two new analyses appear in the manuscript that is in press.

- *Continuing evaluation of the intracranial approach to the nerve.* We have continued our study of intra-neural stimulation using an intra-cranial approach to the auditory nerve. Consistent with our previous observations, the spread of activation tends to be somewhat greater with the intra-cranial approach than we typically observe with the lateral approach. We speculate that that is due to differences in the organization of nerve fascicles in more central compared to more peripheral segments of the nerve. The map between depth in the nerve and tonotopic position in the ICC also is less consistent in stimulation of the intra-cranial segment. In some instances we see a monotonic progression of frequency representation with depth, whereas in other instances we see a non-monotonic progression that is like the progression that we see consistently using the lateral approach. In recent studies using the intra-cranial approach to the auditory nerve we have preserved the animal's acoustic hearing and have been able to record sound-evoked unit activity through the multi-site stimulating array. Acoustic responses show the familiar V-shaped tuning curves expected from auditory nerve fibers. When we record from a particular site and stimulate at that same site, the acoustical frequency tuning curve consistently lies within the tonotopic range activated in the ICC by intra-neural electrical stimulation. In many cases, however, the spread of activation in the ICC is substantially larger than the corresponding width of the acoustic frequency response area. We interpret this wider ICC activation spread as due to the spread of electrical current to auditory nerve fibers in adjacent fascicles that are tuned to different frequencies.
- *Electrical stimulation of the cochlear nucleus.* In one cat in which we exposed the auditory nerve using an intra-cranial approach, we also tested electrical stimulation (and recording of acoustically-elicited responses) in the cochlear nucleus using our penetrating multi-electrode array. On the bases of gross anatomical landmarks, we believe that the electrode placements were in the dorsal cochlear nucleus (DCN) and posterior ventral cochlear nucleus (PVCN). In response to acoustical tones, we recorded more robust unit activity from neurons in those structures than we typically encounter in recordings from the nerve. Frequency tuning was sharp. When we stimulated with the intra-nuclear electrode array, the spread of activation within the ICC in most instances was relatively broad, roughly two octaves or more along the ICC tonotopic axis, like the broad spread that we typically obtain with stimulation of the intracranial segment of the auditory nerve. The responses to cochlear nucleus electrical stimulation differed from auditory nerve stimulation in regard to transmission of temporal information (see below).

- *Lateral approach to the auditory nerve with preservation of hearing.* In one animal, we attempted to preserve the animal's normal acoustical hearing while implanting a penetrating intra-neural stimulating array using a lateral approach through the osseous spiral lamina. We monitored the status of hearing throughout the procedure by recording thresholds in the ICC for tones presented at one-octave intervals from 0.5 to 32 kHz. We observed negligible change in thresholds as the tympanic bulla was opened to expose the cochlea and as the round window membrane was opened. Only after the round-window margin was enlarged and a stimulating probe implanted did we observe a ~25-dB elevation in threshold at 16 kHz and a ~10-dB elevation at 32 kHz; thresholds were stable at all lower frequencies. Recordings through the stimulating array in response to tonal stimulation generally produced multi-unit activity, with only occasional well-isolated single units. The frequency responses areas showed the typical V shape characteristic of auditory nerve fibers. Responses of the ICC to electrical stimulation of the nerve were as described in previous quarterly progress reports.
- *Transmission of temporal fine structure from the electrically stimulated auditory nerve to the ICC.* In three animals, we evaluated the transmission of temporal fine structure from intra-scalar and intra-neural stimulating electrodes to the ICC by monitoring ICC phase locking to unmodulated electrical pulse trains. We measured the ICC responses to 20 repetitions of a 300-ms electrical pulse train at each of a range of pulse rates and computed the vector strength of the response and the Rayleigh criterion for significant phase locking at the criterion of $p<.001$. The phase locking cutoff rate was the highest pulse rate at which significant phase locking was observed. We observed a rather striking difference in temporal responses between intra-neural sites that activated the low frequency representation in the ICC (i.e., characteristic frequencies <~2 kHz) and those that activated the high frequency representation. In response to intra-neural stimulation of fibers presumed to innervate the upper-middle or apical turns of the cochlea, low-frequency ICC neurons phase locked to pulse rates >400 pulses per second (pps), whereas the cutoffs were around 250 pps for higher-frequency ICC neurons. Our preliminary interpretation of that observation is that the low-frequency pathway from the nerve to the ICC is specialized for preservation of temporal fine structure in sounds. In contrast, the high-frequency pathway is specialized to process frequencies that are above the high-frequency cutoff for auditory nerve phase locking; that is, normally, the high pathway never receives input from the auditory nerve that is phase locked to stimulus fine structure. Electrical stimulation with conventional scala tympani electrodes produced ICC phase locking only up to ~250 pps, lower than the maximum rate that was obtained with intra-neural stimulation. It is not yet clear whether that difference reflects a fundamental property of transmission of temporal information through scala tympani electrode. A simpler explanation is that the scala tympani electrodes in our preparation did not provide low-threshold direct access auditory pathways originating in the low-frequency region of the cochlea. We regard these observations of transmission of temporal fine structure as preliminary and will pursue them in future experiments.
- *Transmission of temporal fine structure from the electrically stimulated cochlear nucleus to the ICC.* In one animal, we quantified ICC phase locking to electrical stimulation of the DCN and PVCN. Somewhat surprisingly, the highest rate of phase locking observed in that condition was ~150 pps, lower than that observed with intra-neural or scala tympani stimulation of auditory nerve fibers. Tentatively, we interpret that observation to indicate that optimal transmission of temporal fine structure to the ICC requires the pathway through the

anterior ventral cochlear nucleus, which was bypassed by direct stimulation of DCN or PVCN; that hypothesis accords with the results described in the preceding paragraphs. Again, this is a preliminary observation that warrants further investigation.

- *Transmission of envelope information from the electrically stimulated auditory nerve to the ICC.* In two animals, we measured phase locking of ICC neurons to amplitude modulated electrical pulse trains delivered through penetrating intra-neural electrodes using the lateral approach. Carrier pulse rates were 508, 2035, or 4069 pps. Modulation frequencies ranged from 21 to 127 Hz; the maximum modulation frequency was set to ¼ of the 508-pps carrier frequency. We explored modulation depths ranging from -40 dB (re 100% modulation) to -5 dB; that is, 1% to 56% modulation. We used a signal detection procedure to determine the minimum modulation depth that could be distinguished from no modulation on the basis of phase locking of ICC neurons on single trials. The results were parallel in some respects to the results of tests of transmission of temporal fine structure. That is, modulation sensitivity tended to be greater for low-frequency regions of the ICC than for high-frequency regions, and sensitivity was greater for intra-neural stimulation than for scala tympani stimulation (again confounded by lack of access to low-frequency fibers with scala tympani stimulation). In the scala tympani stimulation condition, sensitivity to modulation of the 4069-pps carrier was substantially less than that for the 508-pps pulse train. That result is consistent with our previous observations in the guinea-pig, using scala tympani stimulation and auditory cortex recording (Middlebrooks, *Abstract Conference on Implantable Auditory Prostheses, 2005).* The difference in sensitivity between 508- and 4069-pps was not observed with intra-neural stimulation. We speculate that the difference between stimulation sites reflects the difference in time constants for temporal integration (reported in our Fourth Quarterly Progress Report). The time constant for 2-pulse temporal integration averages 103 µs for intra-neural stimulation, compared to 260 µs for scala tympani stimulation. The 260-µs value is comparable to the period of the 4069-pps carrier, indicating that substantial temporal integration takes place among carrier pulses in the scala tympani stimulation condition, whereas less temporal integration takes place in the intra-neural condition. We will pursue that observation, which has implications for speech processing using pulsatile stimulation strategies.

3. Plans for next quarter:

- Conduct dissections of human temporal bones to develop approaches for optimum placement of a human intra-neural stimulating array.
- Conduct physiological experiments in 4 cats, using a lateral approach to the nerve, with the following goals:
  - Confirm preservation of hearing during placement of an intra-neural stimulating array.
  - Continue studies of transmission of fine-structure and envelope information, comparing high- vs low-CF pathways with intra-neural stimulation and comparing intra-neural vs intra-scalar stimulation at corresponding CF regions.
  - Test modulation sensitivity for intra-neural and intra-scalar stimulation at low and high carrier pulse rates. Test the hypothesis that modulation sensitivity decreases at carrier rates at which substantial temporal integration takes place.

- Examine the histology of the auditory nerve after a 24-hr implantation of an intra-scalar stimulating array (using a lateral approach). Stimulating arrays will be fixed in place at the end of physiological experiments, the animal will be maintained under anesthesia for 24 hrs, and then will be perfused. The intrameatal sesgment of the auditory nerve will be removed, post-fixed in osmium tetroxide, embedded in plastic, and sectioned for microscopic examination. The goal is to begin to document the extent of gross damage due to electrode insertion and pulsation of the nerve. Longer-term studies of the effects of chronic implantation will be conducted at a later time, when chronic stimulating arrays become available.