Effects of Remaining Hair Cells on Cochlear Implant Function

2nd Quarterly Progress Report

Neural Prosthesis Program
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C.A. Miller, P.J. Abbas, N. Hu, B.K. Robinson

Department of Otolaryngology-Head and Neck Surgery
&
Department of Speech Pathology and Audiology

University of Iowa

Iowa City, Iowa, USA

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Neural Prosthesis Program

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I. Introduction

Cochlear-implant candidates with residual hearing can maintain significant hair-cell integrity after cochlear implantation (von Ilberg et al., 1999), raising the possibility that functional hair cells can influence the response of auditory nerve fibers to electric stimulation. Our previous contract research (N01-DC-9-2106) began investigations using animal models to explore how functional hair cells can interact with the electrical stimulation produced by a cochlear prosthesis. That contract focused exclusively on measures based on the electrically evoked compound action potential (ECAP), a potential that can be routinely recorded from research animal preparations as well as cochlear implant users equipped with neural response telemetry systems. Work in that contract demonstrated significant effects of viable hair cells on the response of auditory nerve fibers to electrical stimulation. We also demonstrated that the ECAP in response to single pulses or pulses trains could be modified both during and after the presentation of an acoustic noise stimulus.

Research conducted under this contract expands upon those findings to include more detailed ECAP measures and single-fiber measures (which are the focus topic of this report). The general goal of this research is to develop a better understanding of the effects of viable hair cells on the response to electrical stimulation of the cochlea in order to eventually develop more effective paradigms for stimulation with cochlear implant in individuals with residual hearing.

II. Summary of activities of the 2nd quarter

During the second quarter of this contract (October 1 through December 31), we accomplished the following:

1. We attended the Neural Prosthesis Workshop (Oct. 16-18) and presented the status of work performed over the previous reporting year.

2. We performed several acute experiments with guinea pig preparations to examine the combined effects of acoustic and electric stimuli presented simultaneously to the same ear. A primary goal of this research is to investigate the time course of adaptation and recovery of the evoked response. In these preparations, the ECAP is used as the physiological measure.

3. Three acute cat studies of single-fiber responses with acoustic and electric stimulation have been completed and we have analyzed the data from two of those experiments. These results form the focus topic of this report.

III. Focus topic: Acoustic / electric stimulus interactions at the single-fiber level: initial findings

A. Introduction

Our earlier studies of auditory-nerve responses to combined acoustic/electric stimulation were conducted using the ECAP, a gross measure of auditory-nerve activity. We have recently conducted measures using responses from single fibers from acute cat preparations. Single-fiber measures provide detailed descriptions of spike timing, fiber dynamic range, and other response properties that cannot be unambiguously assessed by gross-potential measures. In our very first studies (Abbas et al., 2002), we compared response patterns from hearing and deafened cats. Here we report on the affect of acoustic stimulation (in the form of

wideband noise) on the responses of fibers stimulated with either single electric pulses or brief pulse-train stimuli. With acoustically sensitive preparations, fibers can respond through several mechanisms:

1) spontaneous activity (neurotransmitter release)
2) acoustic stimulation (normal transduction)
3) direct electrical stimulation (via membrane depolarization by the electric field),
4) electrophonic activation through electrical stimulation (Moxon's β response),
5) hair-cell depolarization through electrical stimulation (van den Honert's & Stypulkowski'sδ response)

While we can select for fibers without spontaneous activity, our experimental control over these excitation mechanisms can be, under some conditions, limited. Direct electrical stimulation of fibers by single-pulse stimuli can be deduced by spike latency and to an extent by stimulus level (e.g., van den Honert & Stypulkowski, 1984; 1987). Our ability to parse these mechanisms, however, becomes problematic when investigating responses to pulse trains. Nonetheless, we can explore the differences in response characteristics of the electrically stimulated fiber observed with and without the simultaneous presentation of acoustic stimuli.

B. Methods

For this initial investigation at the fiber level, we chose a wide-band noise to maximize the likelihood of an interaction effect on typical fiber excited by a monopolar electric field. To maintain acoustic sensitivity, we used a minimally invasive monopolar electrode that was inserted approximately 1 mm into the scala tympani via a cochleostomy medial to the round window. The return electrode was a needle electrode placed in neck muscle. With the cochleostomy electrode, we could maintain hearing sensitivity (as assessed by click-evoked ABR) to within 10 dB of pre-surgical levels. Wideband gaussian noise (30 Hz -10 kHz spectrum flat within 10 dB) was presented to the ear canal through a Beyer DT48 earphone and speculum. Electric stimuli were in the form of 40 us/phase biphasic pulses (cathodic-leading phase) presented either singly (with an inter-stimulus interval of 30 ms) or in short pulse trains. Stimuli were delivered by a constant-current source that was capacitively coupled to the stimulating electrode. Standard single-fiber recording techniques were used and a template-subtraction method was used to reduce electrical stimulus artifact (Miller et al., 1999).

C. Results

The data presented in this report are from two of three cat experiments performed to date. The results from the third cat will be presented later, as data analysis is currently in progress.

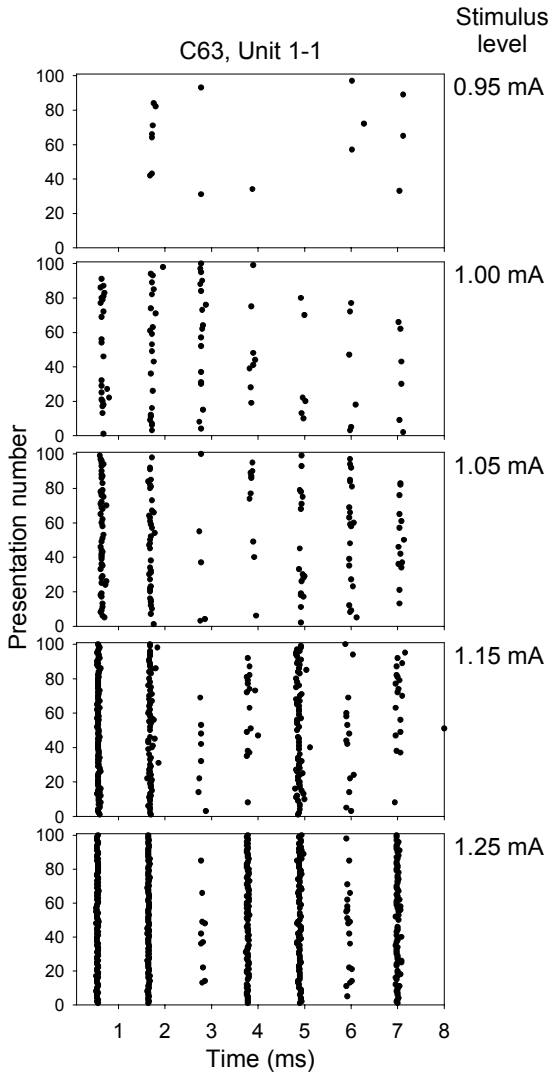

Figure 1 Dot-raster plots of single-fiber responses from a deafened cat stimulated with a 926 pps electric pulse train.

Previous work in our laboratory has demonstrated single-fiber response patterns to pulse-train stimuli. Figure 1 (above) shows dot-raster plots of fiber responses obtained from a chemically deafened cat in response to the first 7 pulses of a pulse train presented with an interpulse interval of 1 ms (a pulse rate of 926 pps). Plots are shown for several stimulus levels spanning a 2.4 dB range, which covers the dynamic range of a typical feline fiber stimulated with single pulses. These plots illustrate the strong synchrony obtained with electrical stimulation and the effects of refractoriness. The latter phenomenon is observed as a failure to respond to the second pulse at low stimulus levels (I = 1.00 mA and I = 1.05 mA) and the *third* pulse at the highest two levels. These level-dependent patterns of responses demonstrate the need to reconsider single-fiber models of refractoriness.

We previously presented similar dot-raster plots from a cat with intact hearing and under several conditions of electric and acoustic-noise stimuli. Using the same electric pulse train, these plots demonstrated apparent noise-induced desynchronization of the patterns that characterize the Figure 1 data (Abbas et al., 2002). Additional analyses of that data are shown in Figure 2, which characterize firing efficiency (FE) and spike jitter (i.e., standard deviation of spike times) for each pulse of the train. Although

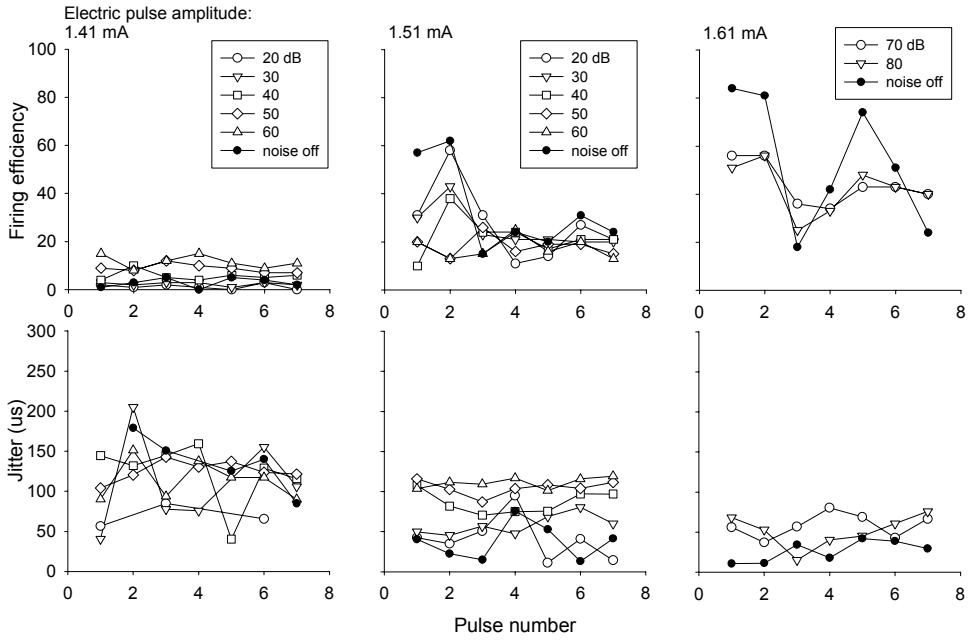

Figure 2. Additional analysis of single-fiber responses from a cat (subject C64) with intact acoustic sensitivity and stimulated simultaneously with an electric pulse train and wideband acoustic noise. The top row of panels plot firing efficiency and the bottom row plots jitter, or the standard deviation of the latency of all the action potentials.

there is some electric-level dependence, the presence of the acoustic noise generally reduces the per-pulse firing efficiency and distributes responses more evenly across the pulse train. Although this analysis does not account for the effects of random, acoustic-driven activity or electrophonic effects, it does result in a reduction in the strong electrically driven effects caused by the combination of strong synchrony and refractoriness.

We have made more detailed analysis of acoustic / electric interactions in a second cat stimulated with single electric pulses. Figure 3 summarizes the spontaneous rates and maximum rates obtained using the maximum level (100 dB OAL) of the wideband acoustic noise. In this way, electrophonic responses could be eliminated by latency. In

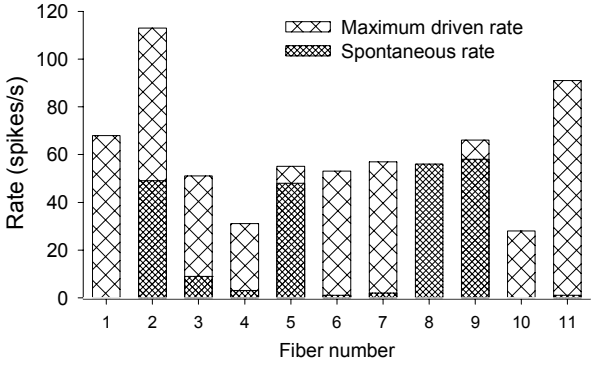

Figure 3. Spontaneous and maximum acoustically driven rates of 11 fibers of cat C93 for the study of acoustic/electric interactions.

analyzing rate-vs-level plots of these fibers' responses to electric stimuli, we accounted for spontaneous firing rates and driven acoustic rates by subtracting those rates from the input-output functions (cf. Sachs & Abbas, 1974).

One of the 11 fibers was held for over 30 minutes, providing us with the opportunity to investigate electric / acoustic interactions over a range of electric levels and acoustic levels. Some of these results are shown in Figure 4. For these data sets, the electric stimulus level was fixed at a level that yielded a firing rate near 50% for the quiet (no noise) condition. The levels of acoustic noise are plotted for a series of measures acquired over time (note that the no-noise condition is plotted as 0 dB only for the convenience of plotting the data). The second plot from the top depicts the acoustically driven spike rates and the remaining three plots show response measures for the electric stimuli. These latter plots have been adjusted for the acoustically driven rates.

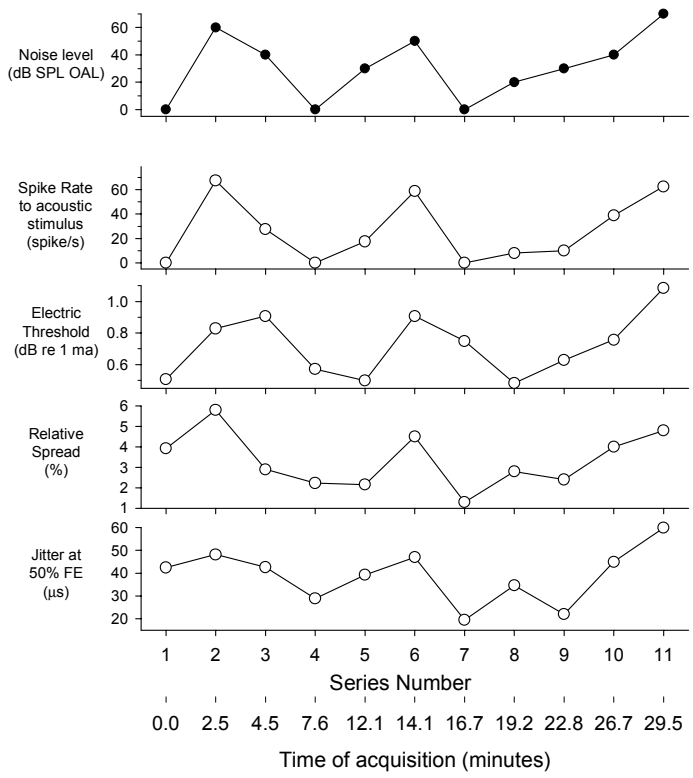

Figure 4. Effects of the presentation of continuous acoustic wideband noise on single-fiber responses to single electric pulses. Electric stimuli were 40 us/phase biphasic pulses delivered by a monopolar electrode. Data are plotted in the order of collection to illustrate cumulative changes in neural responsiveness.

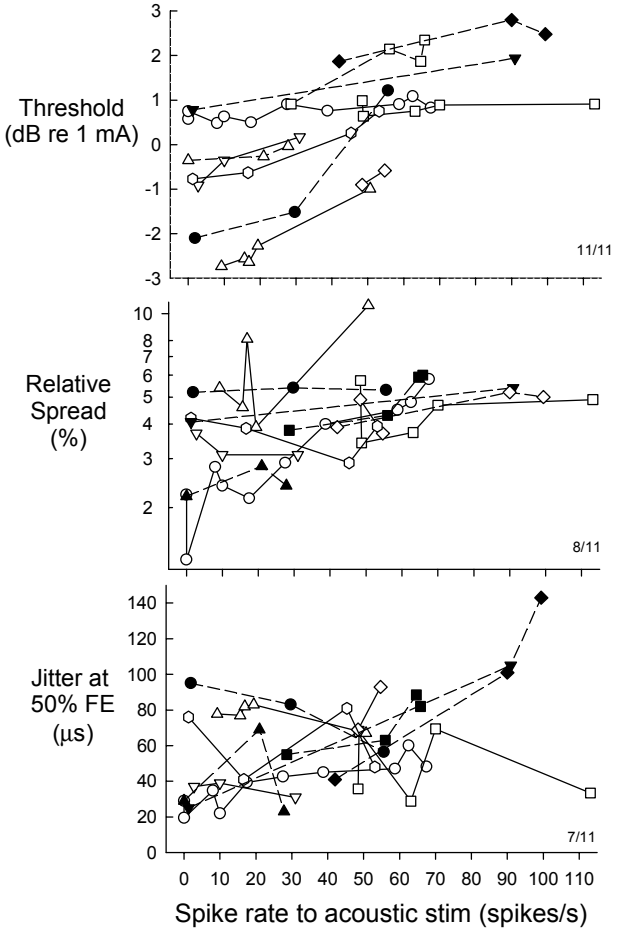

Figure 5. Group analysis of the effects of acoustically driven spike activity on measures of electrically evoked single-fiber responses. Data are shown for 11 units from one cat. The ratio in the bottom right of each panel indicates the number of fibers showing positive slopes of linear -regression fits.

Several trends are evident. First, corrected electric thresholds increase in the presence of acoustic noise, due, presumably to refractory effects. Relative spread (Verveen's measure of the fiber's dynamic range) is also correlated with acoustic noise level. This could be viewed as an enhancement that results from an increased level of refractoriness caused by the competing stimulus. Jitter also demonstrates a correlation with noise level. The increases in jitter and relative spread provides further evidence that noise can produce salutary changes in single-fiber responses by

enhancing dynamic range and temporal uncertainty. Finally, the sequential analysis of data shows cumulative effects of the acoustic stimulation on fiber threshold (arrows in Figure 4). We have previously reported similar cumulative effects of acoustic stimulation on the electrically evoked compound action potential in an earlier report (Abbas et al., 2001). Future single-fiber studies of acoustic-electric interactions will take into account these cumulative effects on a sequence of measures.

We collected measures such as those of Figure 4 (though less complete) from a total of 11 fibers. To determine the effect of the acoustic stimulus across this group of fibers, we plotted electric threshold, relative spread, and jitter measures as a function of the acoustically driven spike rate (Figure 5). The strongest effect of the noise stimulus was found on electric threshold measures (Top panel), while the data suggest a trend toward greater relative spread with increased acoustically driven activity. Additional data on these trends will be reported in a future report.

D. Discussion

The results presented in this report are consistent with the trends that we have reported in ECAP-based comparisons of the auditory nerve's responses from acoustically sensitive and chemically deafened animal subjects. We have previously reported that the slope of the ECAP input-output (i.e. amplitude vs. current level) function is decreased in the hearing animal relative to the deafened animal. Furthermore, these decreases in slope correlate with the intensity of wide-band acoustic stimuli presented continuously during the presentation of the electric stimulus (Abbas et al., 1999). We have not observed an additive effect of acoustic and electric stimuli such as that observed by Moxon (1971) with sinusoidal stimuli. Our experiments have shown that the dominant effect of wideband noise and sinusoidal stimuli on the electric response is consistent with a diminution of the electric response.

Our responses to electric pulse-train stimulation in the presence of acoustic noise are also consistent with our earlier ECAP studies (Abbas et al., 1999; Abbas et al., 2002), which suggested that active hair-cell responses reduce the degree of entrainment of fiber responses to produce a pattern of ECAP responses with less pulse-by-pulse amplitude alternation. All available data suggest that these single-fiber effects and ECAP manifestations are caused by conditions of greater refractoriness across the actively responding fibers. We note that refractoriness evoked by electrical stimulation of the deafened cochlea also appears to result in increased fiber dynamic range. However, refractoriness *per se* does not seem to be sufficient to cause increases in spike jitter, as we demonstrated in our earlier study of refractory effects caused by a single, previous electric masking pulse (Miller et al., 2001). Results from our computer-modeling studies (Rubinstein et al., 1999) also indicate that some increases in stochastic response properties result from a cumulative, sustained, excitation of fibers, suggesting that both refractory and longer-term (adaptation-like) phenomena underlie the observed effects.

IV. Technical note on kanamycin / ethacrynic acid deafening

A common animal model of the electrically stimulated nerve of a deaf individual employs the application of aminoglycoside drugs that result in widespread hair-cell death. This model is appropriate for research of electrical excitation of the cochlea that is generally bereft of any significant involvement of viable hair cells. We, along with other groups, have used several different chemical deafening techniques, including topical (intracochlear) application of neomycin (Leake-Jones, 1982), a two-week course of daily kanamycin injections (Kiang, et al., 1970) and the combined administration of single doses of kanamycin and ethacrynic acid (Xu et al., 1993).

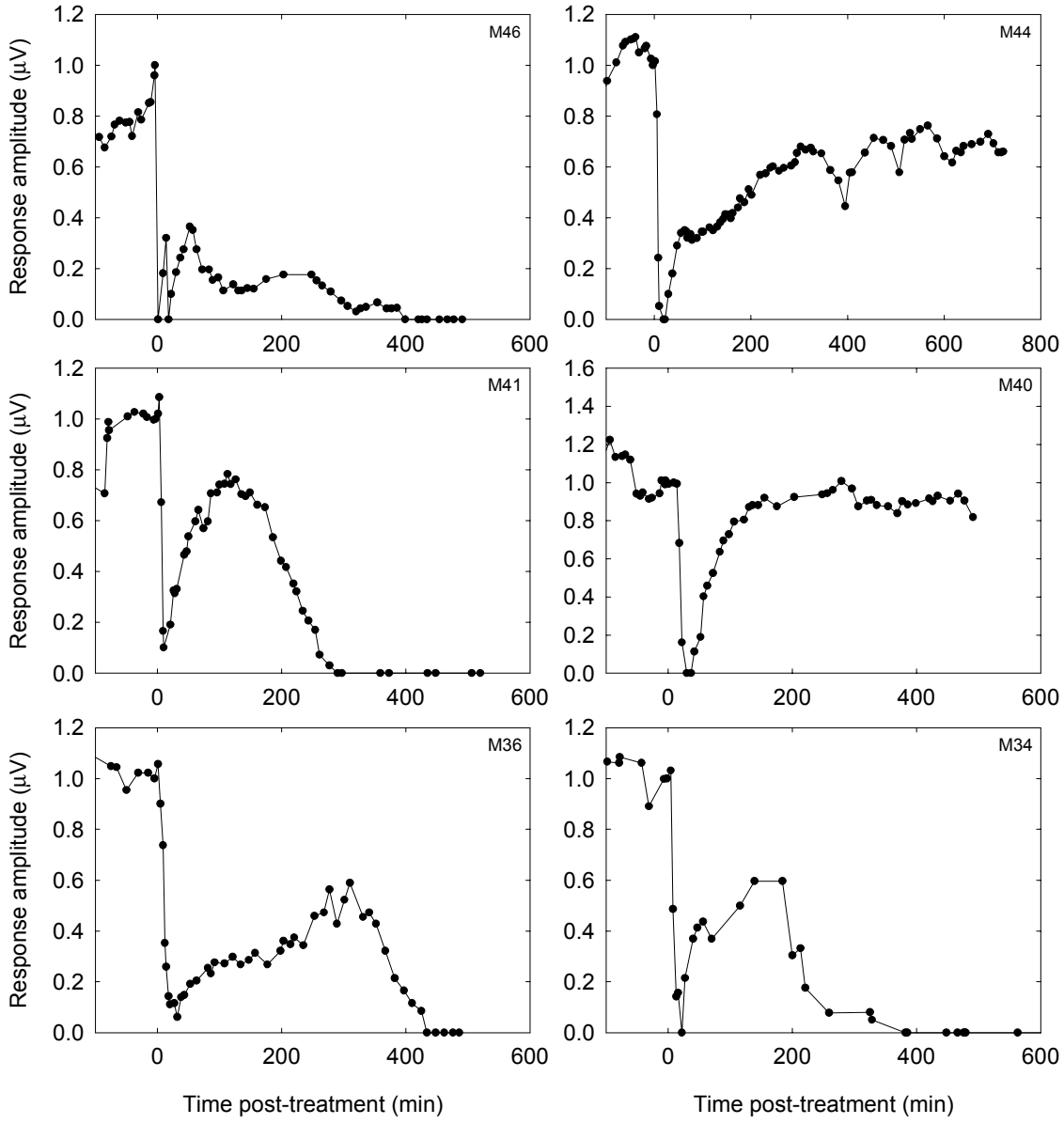

Figure 6. Auditory evoked compound action potential amplitude plotted as a function of time relative to the administration of ethacrynic acid. Responses are shown for 6 different guinea pig subjects. In each case, the response amplitude is normalized to the response amplitude obtained prior to the administration of ethacrynic acid, which occurred at time=0 in each case.

Our experience with the Xu et al. (1993) method indicates that it can be an effective means of inducing profound hearing loss (i.e., shifts of 80 dB or greater), but it should be used with caution when applied to acute experimental sessions. Specifically, monitoring of the hearing loss must be done not only at the time of ethacrynic acid administration, but also for several (4-6) hours following the initial loss of hearing, as hearing sensitivity can recover over that time period. Examples of repeated electrophysiological measures from 6 guinea pigs are shown in Figure 6. Each plot shows the click-evoked auditory brainstem response to a 84 dB SPL click stimulus as a function of time relative to the administration of ethacrynic acid. In each case, the response amplitudes are normalized to the amplitude obtained immediately preceding ethacrynic acid administration. In all six cases there is a precipitous drop in response at this high level (accompanied by a loss in hearing sensitivity) within minutes of administration of ethacrynic acid. We attribute this loss to a transient disruption of the endocochlear potential (Russell et al., 1979). This loss is typically followed by some recovery in response amplitude over the period of 1-2 hours. That recovery, in most cases, is temporary in that responses subsequently decrease over time. In 4 of the 6 cases shown, there is complete loss of the evoked response after 4-5 hours.

These observations of permanent loss are consistent with previous observations and presumably the result of a permanent effect induced by the prior administration of kanamycin (Russell et al., 1979). However, in some cases (subjects M40 and M44) we have also observed hearing recovery in some animals. Litvak (2002) has also reported recovery of hearing sensitivity in his cat preparations. Due to the fact that several hours may likely be needed to assure against this rebound, we recommend that the application of the combination of kanamycin and ethacrynic acid for acute experimentation be done during a separate session 1-2 weeks prior to the acute experimental session.

V. Plans for the next quarter

In the next quarter, we plan to do the following:

1. Attend and present material related to this contract at the 2003 Midwinter Meeting of the Association for Research in Otolaryngology.

2. Conduct additional experiments using guinea pig preparations on the effects of simultaneous acoustic noise and electric pulse train stimulation, with focus on adaptation effects.

3. Conduct additional feline single-fiber experiments to study interactions of acoustic and electric stimuli. Future experiments will incorporate studies of adaptation-like effects induced by acoustic stimulation.

VI. References

Abbas, P.J., Miller, C.A., Rubinstein, J.T., Robinson, B.K. 1999. Effects of remaining hair cells on cochlear implant function. First quarterly progress report. N01-DC-9-2106. University of Iowa, Iowa City.

Abbas PJ, Miller CA, Rubinstein JT, Robinson BK. 2001. Effects of remaining hair cells on cochlear implant function. Seventh quarterly progress report. N01-DC-9-2106. University of Iowa, Iowa City.

Abbas, P.J., Miller, C.A., Rubinstein, J.T., Robinson, B.K., Hu, N., Mino, H., Abkes, B.A., Nichols, J. 2002. Effects of remaining hair cells on cochlear implant function. Final Report. N01-DC-9-2106. University of Iowa, Iowa City.

Kiang, N.Y., Moxon, E.C., Levine, R.A. 1970. Auditory-nerve activity in cats with normal and abnormal cochleas. In: Sensorineural hearing loss. Ciba Found Symp, 241-73.

Leake-Jones, P.A., Vivion, M.C., O'Reilly, B.F., Merzenich, M.M. 1982. Deaf animal models for studies of a multichannel cochlear prosthesis. Hear Res 8, 225-46.

Litvak, L.M. 2002. Towards a better sound processor for cochlear implants: Auditory-nerve responses to high-rate electric pulse trains. Doctoral, Massachusetts Institute of Technology, Cambridge.

Miller C.A., Abbas, P.J., Rubinstein, J.T., Robinson, B.K., Matsuoka, A.J. and Woodworth, G.(1998). Electrically evoked compound action potentials of guinea pig and cat: responses to monopolar, monophasic stimulation. Hear. Res. 119:142-154.

Miller, C.A., Abbas, P.J., Robinson, B.K., Rubinstein, J.T., Matsuoka, A.J. 1999. Electrically evoked single-fiber action potentials from cat: responses to monopolar, monophasic stimulation. Hear Res 130, 197-218.

Miller, C.A., Abbas, P.J., Robinson, B.K. 2001. Response properties of the refractory auditory nerve fiber. J Assoc Res Otolaryngol 2, 216-32.

Moxon, E.C. 1971. Neural and mechanical responses to electric stimulation of the cat's inner ear. Massachusetts Institute of Technology Dept of Electrical Engineering Thesis 1971 Ph D.

Rubinstein, J.T., Wilson, B.S., Finley, C.C., Abbas, P.J. 1999. Pseudospontaneous activity: stochastic independence of auditory nerve fibers with electrical stimulation. Hear Res 127, 108-18.

Russell, N.J., Fox, K.E., Brummett, R.E. 1979. Ototoxic effects of the interaction between kanamycin and ethacrynic acid. Cochlear ultrastructure correlated with cochlear potentials and kanamycin levels. Acta Otolaryngol 88, 369-81.

Sachs, M.B., Abbas, P.J. 1974. Rate versus level functions for auditory-nerve fibers in cats: tone-burst stimuli. J Acoust Soc Am 56, 1835-47.

van den Honert, C., Stypulkowski, P.H. 1984. Physiological properties of the electrically stimulated auditory nerve. II. Single fiber recordings. Hear Res 14, 225-43.

van den Honert, C., Stypulkowski, P.H. 1987. Temporal response patterns of single auditory nerve fibers elicited by periodic electrical stimuli. Hear Res 29, 207-22.

von Ilberg, C., Kiefer, J., Tillein, J., Pfenningdorff, T., Hartmann, R., Sturzebecher, E., Klinke, R. 1999. Electric-acoustic stimulation of the auditory system. New technology for severe hearing loss. ORL J Otorhinolaryngol Relat Spec 61, 334-40.

Xu, S.A., Shepherd, R.K., Chen, Y., Clark, G.M. 1993. Profound hearing loss in the cat following the single co-administration of kanamycin and ethacrynic acid. Hear Res 70, 205-15.