Effects of Remaining Hair Cells on Cochlear Implant Function

7th Quarterly Progress Report

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K.V. Nourski, P.J. Abbas, C.A. Miller, B.K. Robinson, F.C. Jeng, H. Noh

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

University of Iowa
Iowa City, Iowa, USA

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1. Summary of Activities in This Quarter

During the seventh quarter of this contract (January 1 - March 31, 2004), we accomplished the following:

1. We attended the Association for Research in Otolaryngology Midwinter Meeting and presented results related to NPP contract work (Miller et al., 2004; Robinson et al., 2004).

2. We submitted for peer-review a manuscript describing the differences between evoked compound action potentials (ECAP) recorded from intracochlear and nerve-trunk recording sites. This work sought to detail substantive differences between animal-research ECAP results (i.e., nerve-trunk recordings) and ECAPs obtained from clinical cochlear-implant systems (i.e., the use of intracochlear recordings). The main finding indicated that intracochlear recording electrodes were capable of recording antidromic compound action potentials under specific conditions that depended upon stimulus polarity and stimulus electrode configuration.

3. We began preparation of a manuscript on the effects of acoustic noise on pulse-train evoked ECAPs.

4. The manuscript on the ototoxic interaction of kanamycin and ethacrynic acid in acute experimental preparations was published in Hearing Research (Nourski et al., 2004).

5. We replaced the operating table in the sound booth to reduce low-frequency vibrations that resulted from installation of a more massive (double walled) sound booth. This table provided more stable support than our old hydraulic-piston table and markedly improved data collection yield.

6. We began preliminary work with acute cat preparations to expose and record from the central nucleus of the inferior colliculus. Work to date has mainly involved developing the surgical approach, constructing additional fixtures, and expanding our single-unit data-collection code to provide simultaneous recording from 8 of 16 channels of a 16-site Michigan single-shank thin-film array. To date, we have demonstrated success in recording multi-unit activity in response to tone-burst stimuli in 2 cats.

7. We performed 7 additional acute guinea pig experiments that addressed acoustic-electric interactions using ECAP measures. The experimental paradigm was expanded compared to that presented previously (QPR #3 – Nourski et al., 2003a; QPR #5 – Nourski et al., 2003b). Specifically, data were collected using single electric pulses presented at different times relative to the acoustic stimulus to further examine acoustic-electric interactions using electric probes that will introduce little, if any, adaptation to the electric stimuli.

8. We performed 2 acute cat experiments that addressed acoustic-electric interactions using ECAP measures to provide a comparison with our single-fiber data from cat preparations as well as ECAP data from guinea pig experiments.
2. Introduction

2.1. Summary of previous findings

In previously reported work, we examined acoustic-electric interactions at the auditory-nerve level using both gross-potential responses from guinea pigs (QPR #5) and feline single-fiber measures (QPR #6 – Abbas et al., 2003b). Simultaneous presentation of broadband acoustic noise typically decreased the amplitude of electrically-evoked compound action potential (ECAP) while single-fiber results demonstrated that this effect was associated with increased thresholds, reduced firing synchrony as well as decreased amplitude of individual spikes. Thus, spike desynchronization, refractory effects, and adaptation-like effects were all viewed as underlying contributions to the ECAP effects.

In our standard paradigm, the auditory nerve was stimulated with electric pulse trains to provide probes of the time-course of acoustic-electric interactions. The simultaneous masking effect of acoustic noise on ECAP was demonstrated to decrease throughout the duration of the acoustic stimulus. Following the onset of the acoustic noise, ECAP amplitudes underwent partial recovery to a steady state, which followed the form of a two time-constant decaying exponential function. Additionally, we observed a unique pattern of post-stimulatory effect of the acoustic noise. Following cessation of the acoustic stimulus, ECAP amplitudes recovered in a complex, non-monotonic fashion. This residual effect of noise on ECAP often spanned an interval of 100-200 ms and exhibited variability across subjects and experimental conditions.

2.2. New stimulus paradigms

In most of the previous experiments, electric pulses were presented with a 4 ms interpulse interval (IPI). Such a rate of stimulation produced adaptation of the ECAP response to electric pulses, as evidenced by measuring ECAP amplitudes of the “electric only” condition (i.e., without simultaneous acoustic stimulation). We attempted to account for that effect in two ways, by: 1) presenting the acoustic stimulus at 50-100 ms following the train onset, to avoid the large transient effects to the electric train, and 2) by collecting ECAPs to an “electric only” condition to provide a comparison condition.

Nonetheless, pulse-train effects were superimposed on the interaction data and adaptation to the electric pulse trains may influence the acoustic-electric interactions. In particular, it might contribute to the complex time course of simultaneous and post-stimulatory effects of acoustic noise on ECAP. To address this, we evaluated acoustic-electric interactions in a condition free from adaptation to the electric stimulus by presenting single electric pulses at a low rate (5-10 pps) and at different times relative to the onset of a 400 ms acoustic noise burst.

A second new approach was introduced to more carefully examine interaction effects at and near the time of the onset of the acoustic noise stimulus. Given the impulsive nature of some speech tokens, such onset effects may be particularly relevant to interactions that may occur in implanted human ears. Furthermore, a more precise description of the onset effect is needed for accurate estimates of the fast decaying component of our two time-constant model of adaptation effects (see QPR #5). To provide this description, we chose to use a relatively brief (10 ms) noise burst – adequate to examine onset effects, yet sufficiently short to avoid large and unnecessary degrees of adaptation that would reduce data collection efficiency. As in the previous paradigm, a single electric pulse was systematically presented at different times relative to the noise burst to provide a detailed assessment of the temporal course of interactions.
2.3. Interspecies issues

Previous ECAP measures were conducted in guinea pig preparations, while single-unit experiments were performed in cats. We have demonstrated significant differences in the ECAP responses from these two species (Miller et al., 1998; Matsuoka et al., 2000), some of which could complicate comparisons between gross-potential and single-unit data the acoustic-electric interactions. Accordingly, we have begun to examine possible interspecies differences in our interaction measures. To date, we have performed two ECAP experiments with acute cat preparations.

2.4. Focus of this report

In this report, we examine simultaneous and post-stimulatory effects of acoustic noise on the auditory nerve ECAP responses using experimental paradigms used in previous studies as well as new paradigms described above. We also present ECAP data from acute cat preparations for comparison with our earlier results from guinea pig experiments and single-fiber measures.

3. Materials and Methods

Acute experimental sessions were performed in adult guinea pigs and cats. Animal preparation and surgical methods have been described in previous reports and involved exposure of the auditory nerve and cochlea. A small cochleostomy positioned within 2 mm of the round window margin provided for insertion of a bare Pt/Ir wire (in guinea pigs) or ball electrode (in cats) for intracochlear monopolar stimulation. This insertion usually resulted in an upward shift in acoustic sensitivity of 20 dB or less (as assessed by click-evoked CAP), although additional shifts were sometimes observed over the course of the day-long experimental session.

Stimuli were generated by a 16-bit digital-to-analog converter (100,000 samples/s) controlled by custom software. Short-duration (40 µs/phase) biphasic electric pulses were presented in 600-800 ms pulse trains separated by silent inter-train intervals set at 2 times longer than the train duration. In contrast to earlier experiments, our use of a single stimulus polarity (cathodic-first biphasic pulses) improved the rate of data collection. Interpulse interval (IPI), defined as time between the onsets of adjacent pulses, was systematically varied from 1 to 6 ms. For data collection at IPI=3 ms and higher, we again used a staggered stimulus onset approach, shown schematically in Figure 1A. As described in the third QPR, this entailed collection of responses using three different noise-onset times relative to the onset of the pulse train to triple the temporal resolution of our measures of ECAP changes over time. Presentation of these three stimulus conditions was followed by the presentation of a control, electric only, condition (i.e., an electric pulse train without simultaneous acoustic noise; trace 4 in Figure 1A). Thus, a total of four stimuli were repeatedly presented and the response to each was averaged separately.

To address acoustic-electric interaction in a condition free from adaptation to the electric stimulus, electric pulses were presented with a 200 ms IPI (Figure 1B). A series of electric + acoustic stimuli was presented with a delay of the electric stimulus onset, Δt, increasing from 0 to 150 ms in roughly logarithmic steps (Δt=0, 1, 2, 3, 4, 5, 7, 10, 15, 20, 35, 50, 70, 100, 150 ms). Each electric + acoustic stimulus was followed by an electric-only control; responses to each stimulus were averaged independently.
Acoustic clicks were generated by driving the earphone with 100 µs/phase biphasic electric pulses at a repetition rate of 33 clicks per second. Bursts of broadband acoustic noise were produced by a Grason-Stadler noise generator. The output was fed to an attenuator, an impedance-matching transformer and a Beyer DT-48 earphone coupled to a speculum. Sound pressure in the ear canal was monitored during each experiment using a probe-microphone system described in QPR #4 and overall sound levels were computed by accounting for the system frequency response. Levels were controlled by the attenuator. Acoustic noise, gated using a 1 ms rise-fall time, was presented with a total duration 400 ms in most experiments. As described earlier, we also examined acoustic-onset effects by using a relatively short-duration (10 ms) noise burst and presenting single electric pulses at various times with respect to the noise onset. Specifically, these delays ranged from 1 to 9 ms, using a delay increment of 0.2 ms in order to describe onset effects with relatively high resolution.

As in previous experiments, auditory nerve responses were recorded using a ball electrode positioned on the auditory nerve trunk. The evoked potentials were amplified (gain=10x) and low-pass filtered at 20 kHz (6 pole Butterworth low-pass filter) prior to digital sampling at a rate of 50 kHz for subsequent analysis. Acoustic sensitivity was assessed by measuring the acoustically evoked compound action potential (ACAP) in response to a click stimulus and determining a threshold response level. ECAP response growth functions were obtained by presenting alternating-polarity single biphasic electric pulses (40 µs per phase) at different levels. ACAP thresholds and single-pulse ECAP growth functions were obtained repeatedly throughout the course of each experiment to monitor the stability of the animal preparation.

ACAP responses to acoustic clicks were analyzed for threshold using visual criterion. ECAP responses were analyzed by measuring their amplitudes using custom-designed software. The ECAP amplitudes of the electric + acoustic condition were subtracted from those of the electric-only condition to evaluate the absolute change in response amplitude and thus demonstrate the net effect of the acoustic stimulus. ECAP amplitudes in response to electric pulses as well as decrease in ECAP amplitude in the electric + acoustic condition were plotted as functions of time after the acoustic stimulus onset.

Figure 1. Schematic of stimulus presentation paradigms. A: Pulse-train electric stimuli. B: Single electric pulses (vertical bars). Rectangles indicate bursts of noise; dashed lines indicate onset and offset of the noise stimulus. IPI, interpulse interval; Δt, pulse onset delay time. In A, Δt=IPI/3; in B, Δt was varied from 0 to 150 ms. See text for additional details.
4. Results

4.1. Simultaneous and post-stimulatory effects of acoustic noise on the auditory nerve responses to single electric pulses

Figure 2 provides a comparison between results obtained with the new single-pulse (low rate) stimulus paradigm (top panel) and our previous, standard, pulse train paradigm (remaining, lower, panels). As in our previous reports, we provide both the raw data (panels in left column) and the subtraction of the \textit{electric + acoustic} condition (right column) to provide a more direct picture of the effect of the added acoustic stimulus. In each panel, the electric + acoustic data are accompanied by the \textit{electric-only} condition to provide comparison with that control condition.

Comparison of the trends produced by these two types of electric probes reveals some interesting differences. When pulses are presented at a 200 ms IPI, no adaptation to the electric stimulus is expected. Thus, the magnitude of the onset effect of acoustic noise is similar to that of the pulse train presented at the lowest rate (6 ms IPI). This is consistent with our previous findings that, as the IPI of the pulse train is increased to 6 ms, the magnitude of the onset effect approaches a saturation level (QPR #5). With the low-rate, single-pulse paradigm, there is no detectable trend of adaptation due to repeated presentation of the electric stimulus.

Furthermore, the shape of the post-onset partial recovery of the ECAP amplitude is different between the single-pulse condition and pulse-train stimulation. When single pulses are presented, the ECAP appears to undergo very modest recovery, and, consequently, a greater steady-state effect is observed. Another important difference can be seen in the magnitude of the post-acoustic effects on the ECAP. The post-stimulatory effect of acoustic noise is more prominent in the case of responses to single pulses than in the faster-rate pulse-train data sets.

4.2. Acoustic-electric interactions in the cat as assessed with the ECAP: preliminary findings

Figure 3 presents the ECAP amplitudes obtained from a cat in response to 900 ms pulse trains presented at several IPIs both with and without simultaneous presentation of acoustic noise. Onset and steady-state effects of acoustic noise on ECAP obtained from this cat exhibit a dependence on IPI similar to that in the guinea pig. However, several features are different from our previous observations in guinea pigs. First, the simultaneous effect of acoustic noise has a steeper recovery curve, indicative of shorter time constants associated with adaptation of the auditory nerve response to the acoustic stimulus. In addition, there is a particularly interesting post-stimulatory effect of acoustic noise. Following offset of the acoustic stimulus, the ECAP amplitude undergoes a decrease that exceeds the magnitude of the steady state effect and reaches its maximum approximately 40 ms following offset of the noise. Moreover, such prominent post-stimulatory effects can be observed in the absence of noticeable simultaneous effects of noise (IPI=1.5 ms and IPI=1 ms in Figure 3). A residual effect of this magnitude has not been observed in any of our analogous guinea pig measures and highlights a possible species-specific response.
Figure 2. Effects of acoustic noise on the auditory nerve response to single (low-rate) electric pulses and pulse trains presented at different interpulse intervals (IPI). A: ECAP amplitudes in response to individual pulses are plotted as a function of time after acoustic stimulus onset. Electric pulses were presented at 0.81 mA (60% saturation of single-pulse ECAP growth function), with or without simultaneous acoustic noise (open and filled symbols, respectively). Acoustic noise was presented at 95 dB SPL. B: data shown in (A) presented as difference-functions (electric + acoustic condition subtracted from the electric only condition). Horizontal bars indicate presentation time of the acoustic noise stimulus.
Figure 3. Effects of acoustic noise on the auditory nerve response to electric pulse trains presented at different interpulse intervals (IPI) (circles) and single pulses (squares in the upper right graph) in the cat. A: ECAP amplitudes in response to individual pulses are plotted as a function of time after acoustic stimulus onset. Electric pulses were presented at 1.12 mA (60% saturation of single-pulse ECAP growth function), with or without simultaneous acoustic noise (open and filled symbols, respectively). Acoustic noise was presented at 95 dB SPL. B: data shown in (A) presented as difference-functions (electric + acoustic condition subtracted from the electric only condition). Horizontal bars indicate the presentation time of the acoustic noise stimulus.
We also collected acoustic-electric interaction data using the single-pulse, low-rate (200 ms IPI) electric probe. The time course of those ECAP measures is shown in the upper right panel of Figure 3 (see dashed plot with square symbols). Two response patterns evoked by this stimulus paradigm are worth noting. First, the magnitude of the onset effect of acoustic noise on single-pulse ECAP is very similar to that of the pulse train presented at 6 ms IPI, whereas the steady-state effect is greater in the single-pulse condition (Figure 3B). This is consistent with our previous observations described in QPR #5 and also in Figure 2B of this report. Secondly, the very prominent post-stimulatory effects observed particularly with the 1 ms and 1.5 ms IPI pulse trains were not observed using the single-pulse, low-rate stimuli.

Figure 4 provides descriptions of the effects of electric pulse rate on both the onset and steady-state effects (circles and squares, respectively) of the acoustic noise. Panels A and B illustrate data sets from both a guinea pig (subject J04) and a cat (subject D28) respectively. Both simultaneous effects of the acoustic noise (i.e., the onset and steady-state measures) exhibit a similar dependence on inter-pulse interval in both the guinea pig and cat subject. Both the onset and the steady-state measure are sensitive to IPI manipulation, with the latter undergoing a greater change from the 6 ms to the 200 ms IPI condition.

**Figure 4.** Summary of data from two subjects (A: J04, guinea pig; B: D28, cat) demonstrating onset and steady-state effects of acoustic noise on auditory nerve response to trains of electric pulses at various interpulse intervals (IPI). Maximum decrease in ECAP amplitude relative to the electric only condition following noise onset (circles) and average decrease within 50 ms prior to noise offset (squares) are plotted as functions of IPI. Electric stimuli were presented at levels corresponding to 60% saturation of a single-pulse ECAP growth function (0.81 mA in J04 and 1.12 mA in D28). Acoustic noise was presented at 95 dB SPL.
4.3. Time course of the onset of the masking effect

The onset of the masking effect, although not instantaneous, is relatively abrupt as evidenced in Figures 2 and 3. Using single-pulse stimulation as described above, we can investigate this effect in greater temporal detail. We have examined these acoustic onset effects in several subjects and an example is shown in Figure 5. Plots of ECAP amplitude in response to pulses presented before and after noise onset demonstrate that the effect of noise stimulation is clearly not instantaneous. The maximum decrement in ECAP amplitude occurs between 3-4 ms following onset of the acoustic noise (Figure 5B). The latency as well as the time course is dependent on acoustic stimulus level, with the maximum decrement occurring earlier at higher acoustic stimulus levels. These findings are consistent with our earlier and less fine-grained analyses (QPR #5).

Adequate descriptions of this onset effect are necessary for accurate characterization of the two time-constant decaying functions that describe the adaptation-like phenomenon over the course of several hundred milliseconds. Specifically, estimates of the short (fast) time constant can be exquisitely sensitive to the accuracy of our description of the peak region of the onset effect. The use of short analysis intervals (shown in Figure 5) allow us to determine the precise peak of the interaction function, the timing of which is subject to delays related to acoustic propagation and synaptic delays, as well as acoustic levels effects. Thus, the use of our general single-pulse paradigm, coupled with the use of the short-duration noise burst for this onset characterization, will together provide an effective means of describing the interaction time course.

Figure 5. Onset of the masking effect of acoustic noise on ECAP. A: ECAP amplitudes in response to individual pulses are plotted as a function of time after acoustic stimulus onset. Electric pulses were presented at 0.86 mA (80%) with or without simultaneous acoustic noise (open and filled symbols, respectively). Bursts of acoustic noise were presented for 10 ms. B: data shown in (A) presented as difference-functions (electric + acoustic condition subtracted from the electric only condition).
4.4. An initial comparison between ECAP and single-fiber data

One goal of this contract is to provide a better understanding of the relationship between ECAP and single-fiber acoustic-electric interaction measures in order to determine the degree to which ECAP measures reflect underlying single-fiber physiology. This work is on-going and will be a focus topic of a later report. However, as we now have collected both ECAP and single-fiber data from cats, some preliminary comparisons can be made.

Figure 6 (next page) plots data sets from two subjects, one showing a typical time course of ECAP amplitude in response to a pulse train before and after acoustic noise stimulation and the second showing single-fiber histograms in response to the same combined acoustic-electric stimulation.

We note several similarities between the two measures. First, while we observe a clear decrease in ECAP amplitude during noise stimulation, we observe an analogous decrease in synchronization to the pulse train as evidenced in the PST histogram for single fibers. Secondly, there is a “residual” effect after offset of the acoustic noise, resulting in decreased ECAP amplitudes to pulses presented after noise offset. The PST histogram of the fiber also demonstrates a decreased synchronous response to the pulse train after noise offset. This occurs despite a clear decrease in background activity and is likely related to the adaptation and recovery of spontaneous activity that is evident in the acoustic alone condition of panel B. Finally, presentation of the electric pulse train alone shows adaptation across the duration of the train. While the single-fiber histogram does not show such an effect as clearly, analyses in QPR #6 have demonstrated consistent adaptation effects under similar stimulus conditions.

While there are similarities, we note also differences, particularly in the complexity in the responses to ECAP after acoustic noise offset as compared to that observed with single fibers. Further studies will investigate these differences in more detail.

5. Plans for the Next Quarter

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

1. Continue measures of acoustic-electric stimulation at the level of the auditory nerve using acute guinea pig preparations, with a focus on examining the contribution of adaptation to the electric stimulus on the nature of interaction effects.

2. Conduct additional experiments using acute cat preparations to access acoustic-electric interactions using ECAP measures with a focus on post-stimulatory effects as well as perform intra-subject comparisons of ECAP and single-unit data.

3. Continue developing the model inferior colliculus recordings, which will allow us to assess interactions to binaural stimulation as well as to make comparisons between interactions at the peripheral and central levels of the auditory system. This will involve some adjustment of surgical procedures that involve exposure of the inferior colliculus.
Figure 6. Comparison between ECAP and single-fiber data on the acoustic-electric interactions in the cat auditory nerve. Data were collected from two subjects (D29 and D15). A. ECAP amplitudes in response to individual pulses are plotted as a function of time after acoustic stimulus onset (upper panel). Electric pulses were presented with an IPI of 4 ms at 0.98 mA (50% saturation of single-pulse ECAP growth function), with or without simultaneous acoustic noise (open and filled symbols, respectively). Differences in the amplitudes of the two conditions are plotted in the lower graph. Acoustic noise was presented at 95 dB SPL. B. PST histograms of the single unit response to an electric pulse train (duration 400 ms, IPI=4 ms, current level 1.05 mA; upper graph), a burst of acoustic noise (duration 200 ms, intensity 96 dB SPL; middle graph), and the two stimuli presented simultaneously. Bin width 0.1 ms. Horizontal bars indicate presentation time of the noise stimulus.
6. References


