Effects of Remaining Hair Cells on Cochlear Implant Function

5th Quarterly Progress Report

Neural Prosthesis Program
Contract N01-DC-2-1005
(Quarter spanning July-Sept, 2003)

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1. Summary of Activities in This Quarter

During the fifth quarter of this contract (July 1 through September 30, 2003), we accomplished the following:

1. Attended the Conference on Implantable Auditory Prostheses and presented our research results related to this contract (Miller *et al.*, 2003b; Nourski *et al.*, 2003a).

2. Revised a peer-reviewed manuscript on the ototoxic interaction of kanamycin and ethacrynic acid in acute experimental preparations (see QPR #2 - Miller *et al.*, 2003a).

3. Conducted two acute experiments with guinea pig preparations to examine the effects of acoustic noise on ECAP response to electric pulse trains presented at high pulse rates (*i.e.*, >250 pps).

4. Conducted one acute experiment with cat preparation involving single-fiber responses to combined acoustic and electric stimulation. Also performed analysis of the single fiber data from that and previous cat experiments.

5. Performed additional analysis of the results presented in the QPR #3 (Nourski *et al.*, 2003b) to obtain quantitative descriptions of the onset, steady-state, and offset effects of an acoustic noise stimulus on the ECAP response to ongoing electric pulse trains.

6. Installed a double-walled IAC sound booth in our laboratory to replace the single-walled booth. This involved structural changes to the lab space (wall removal, floor replacement, asbestos abatement) that suspended our experiment schedule for six weeks. This down time was scheduled to coincide with extended absences of personnel over the last six weeks of this reporting period.

7. Manuscript submitted to Hearing Research (Hu *et al.*, 2003) that details the experiments and findings described in QPR #1 was accepted for publication.

2. Focus Topic: Quantitative Analysis of Acoustic-Electric Interactions during Stimulation with Electric Pulse Trains

2.1. Introduction

In previous work, we addressed the effects of acoustic stimulation on the auditory nerve response to electric stimulation. Interaction effects were first assessed using measures based on ECAP responses (Miller *et al.*, 2000). When presented simultaneously, wideband acoustic noise was found to decrease the amplitude of ECAP response to single electric pulses. Our general hypothesis for this trend assumed that acoustically driven neural activity desynchronized the response of nerve fibers, thereby reducing their contribution to the gross potential. Subsequent single-fiber experiments in this contract period confirmed this by demonstrating increased single-fiber thresholds and reduced synchrony (Miller *et al.,* 2003a; Abbas *et al.,* 2003). We also observed another contributing mechanism - reductions in spike amplitude – that were presumably due to the increased influence of refractoriness from the noise-induced increment in overall spike rates.

Our recent work has employed trains of constant-amplitude electric pulses and gated acoustic noise to assess the time course of acoustically induced adaptation and subsequent recovery (Abbas *et al.,* 2003; Nourski *et al.,* 2003b). It was demonstrated that acoustic noise produced a decrease in the ECAP responses to the pulse train, with a precipitous decrease in the ECAP at the noise onset followed by a partial recovery of ECAP amplitude. There were also residual effects of the noise on the ECAP after noise offset. After offset, ECAP amplitudes eventually recovered to the levels corresponding to the control condition that featured presentation of the electric pulse train alone ("electric-only"). However, this recovery was not instantaneous, as it might have been expected considering the activity-based hypothesis mentioned above. In some cases, there was a continued depression of ECAP amplitude after noise offset. In fewer cases, we observed a more complex recovery function, which included a period of enhanced response amplitude. In most of our observations the offset effects had a complex time course that featured a fast recovery component and a slower residual effect.

We have hypothesized that the observed effects were driven by neural activity (specifically, discharge rate) rather than stimulus level, *per se*. Also, as acoustic stimulation affected the response to electric-current induced depolarization of auditory nerve fibers, we attributed this effect to a mechanism at the level of the neural membrane. This view is also consistent with the post noise-offset effects noted above. The observation of adaptation effects produced by acoustic stimulus demonstrated a previously unreported type of acoustic/electric interaction. Such interaction could be relevant to the design of cochlear implants (and associated hearing aids) in cases where individual fibers are responsive to both modes of stimulation.

In this report, we present a summary of the onset and steady-state effects of acoustic noise across the group of subjects studied to date. In addition, we provide quantitative descriptions of their time courses in these subjects. The variable parameters used in the present study were the levels of acoustic and electric stimulation, duration of acoustic and rate of electric stimulation.

2.2. Materials and Methods

Adult guinea pigs with normal hearing were used in acute experimental sessions. General surgical methods have been described elsewhere (Miller *et al.,* 1998). Briefly, the guinea pig was anesthetized with ketamine and the auditory nerve trunk was surgically accessed. The left bulla was opened and a cochleostomy placed in the basal turn of the cochlea to allow insertion of a bare Pt/Ir wire electrode. This

insertion usually resulted in acoustic sensitivity shift of less than 20 dB, as assessed by click-evoked compound action potential recordings. Biphasic (40 μs/phase) electric pulses with alternating stimulus polarity were presented in 600 ms pulse trains separated by 900 ms silent inter-train intervals. Interpulse interval (IPI), defined as time between the onsets of adjacent pulses, was set at 4 ms in most experiments. To assess the effects of IPI on the ECAP response to pulse trains, the IPI was varied from 1 to 6 ms. To evaluate the effects of noise duration on the ECAP response to pulse trains following the offset of noise, pulse train duration was varied from 600 ms to 2000 ms, with inter-train interval set at 1.5 times longer than the train duration.

Acoustic noise stimuli were produced by a Grason-Stadler noise generator whose 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 previously described probe-microphone system (Abbas *et al.*, 2003) and overall sound levels were computed by accounting for the system frequency response. Levels were controlled by the attenuator. The onset and offset of the acoustic stimulus could be varied relative to the onset and offset of the electric pulse train. The acoustic noise, gated using 1 ms rise-fall time, was presented between 50-350 or 100-400 ms (total duration 300 ms) in most experiments. To assess the effects of noise duration on the ECAP response to pulse trains following the offset of noise, the duration of the noise stimulus was varied from 50 to 1600 ms.

Auditory nerve evoked responses were recorded using a ball electrode positioned on the surgically accessed auditory nerve trunk. The evoked potentials were amplified (gain=10x) and filtered at 20 kHz (6 pole Butterworth low-pass filter) prior to digital sampling at a rate of 50 kHz and storage for subsequent analysis. Acoustic sensitivity was assessed by measuring acoustically evoked compound action potential (ACAP) in response to single acoustic clicks and determining a threshold response level. Clicks were generated by driving the earphone with a 100 μs/phase biphasic electrical pulses at a repetition rate of 33 clicks per second. ECAP response growth functions were obtained by presenting single biphasic electric pulses (40 μs per phase) at various 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.

For pulse-train data collection at rates below 333 pps, we took advantage of staggered noise onset paradigm, described in the third QPR (Nourski *et al.,* 2003b). This approach entailed the collection of responses using three different noise-onset times. In this way we could examine the response to the pulse train sampled at three times the pulse rate, increasing the temporal resolution of our adaptation measures. The three electric+noise stimuli were interleaved with an "electric only" condition (i.e., electric pulse train without simultaneous acoustic noise) to continuously provide that control condition. The same sequence was then repeated with the opposite polarity pulse train. Thus, a total of eight stimuli were repeatedly presented and the response to each was averaged separately and stored to disk.

2.3. Results

The primary goal of this report was to quantify the effects of the acoustic noise on the pulse-train ECAP response across fundamental stimulus parameters (i.e., electric and acoustic levels, electric pulse rates). As noted earlier, the time course of these effects can be described as onset effect, followed by post-onset ECAP amplitude recovery to a steady-state level and, in some cases, offset effects following cessation of the noise stimulus. These effects can be seen in the example shown in Figure 1. The magnitude of the noise onset effect was computed as the mean difference between “electric+noise” and “electric only” responses over a time window of 4-7 ms following noise onset. This window was chosen to encompass the peak onset effect. The steady-state effects of noise were addressed in a similar fashion by calculating an average decrease in the ECAP amplitude within a 50 ms time window beginning 50 ms prior to the

time of the noise offset. Figure 2 summarizes these onset (panel A) and steady-state (panel B) effects for six subjects over a range of acoustic levels and electric levels. Note that electric stimulus level is expressed as "normalized ECAP amplitude" to facilitate across-subject comparisons. On this scale, a value of one corresponds to the saturated (maximum) ECAP amplitude. In some instances, acoustic effects could be elicited with a moderate (i.e., 65 dB SPL) level of wideband noise. In most cases, the maximum onset and steady-state effects of noise are achieved at high acoustic noise and electric stimulus levels.

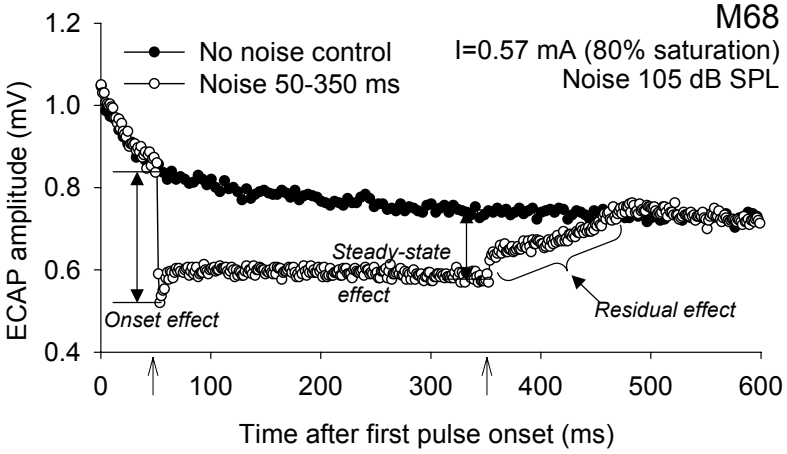

Figure 1. The time-course of the effects of wideband acoustic noise on the ECAP responses to a train of pulses. ECAP response amplitudes to individual pulses are plotted as a function of time after first pulse onset. Electric pulses were presented at a level of 0.57 mA (80% saturation of the single-pulse ECAP growth function), with or without simultaneous acoustic noise (open and filled circles, respectively). Acoustic noise was presented at a level of 105 dB SPL during the period from 50 to 350 ms after first pulse onset. Arrows indicate noise onset and offset time. Interpulse interval (IPI)=4 ms.

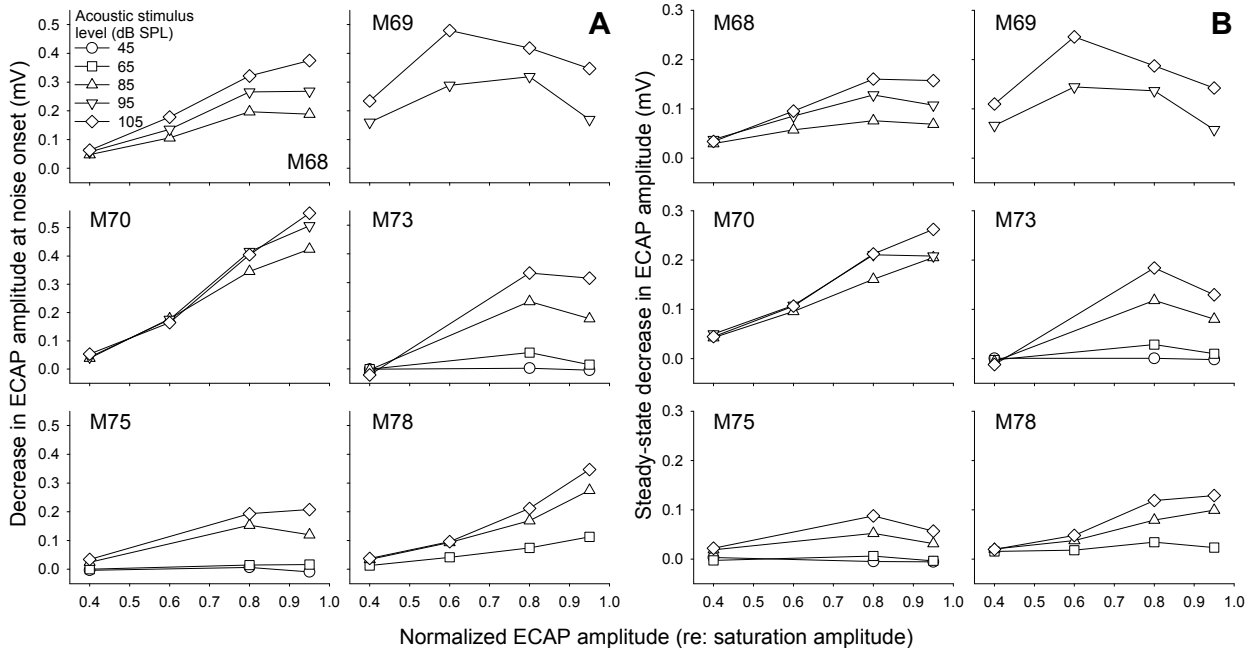

Figure 2. Summary of data from six subjects demonstrating onset (**A**) and steady-state (**B**) effects of acoustic noise presented at various levels, on auditory nerve response to electric pulse trains. Average decreases in ECAP amplitude relative to the "electric-only" condition within 4-7 ms following noise onset (**A**) and within 50 ms prior to noise offset (**B**) are plotted as functions of normalized ECAP amplitude (relative to response saturation). IPI=4 ms.

Figure 3 demonstrates the ECAP amplitudes in response to 600 ms electric pulse trains presented at various IPIs both with and without the simultaneous presentation of acoustic noise. At higher pulse rates (1 and 1.5 ms IPI), there are substantial decreases in the response amplitude during the first several milliseconds following onset of the electric train. At these rates, the addition of acoustic noise causes only slight (but detectable) decrements in the electric responses. When the pulses are presented at lower rates (3 ms and 6 ms IPI), the initial decrease in the response amplitude to the electric train is substantially less. Under these conditions, acoustic noise produces large decreases in the electric response.

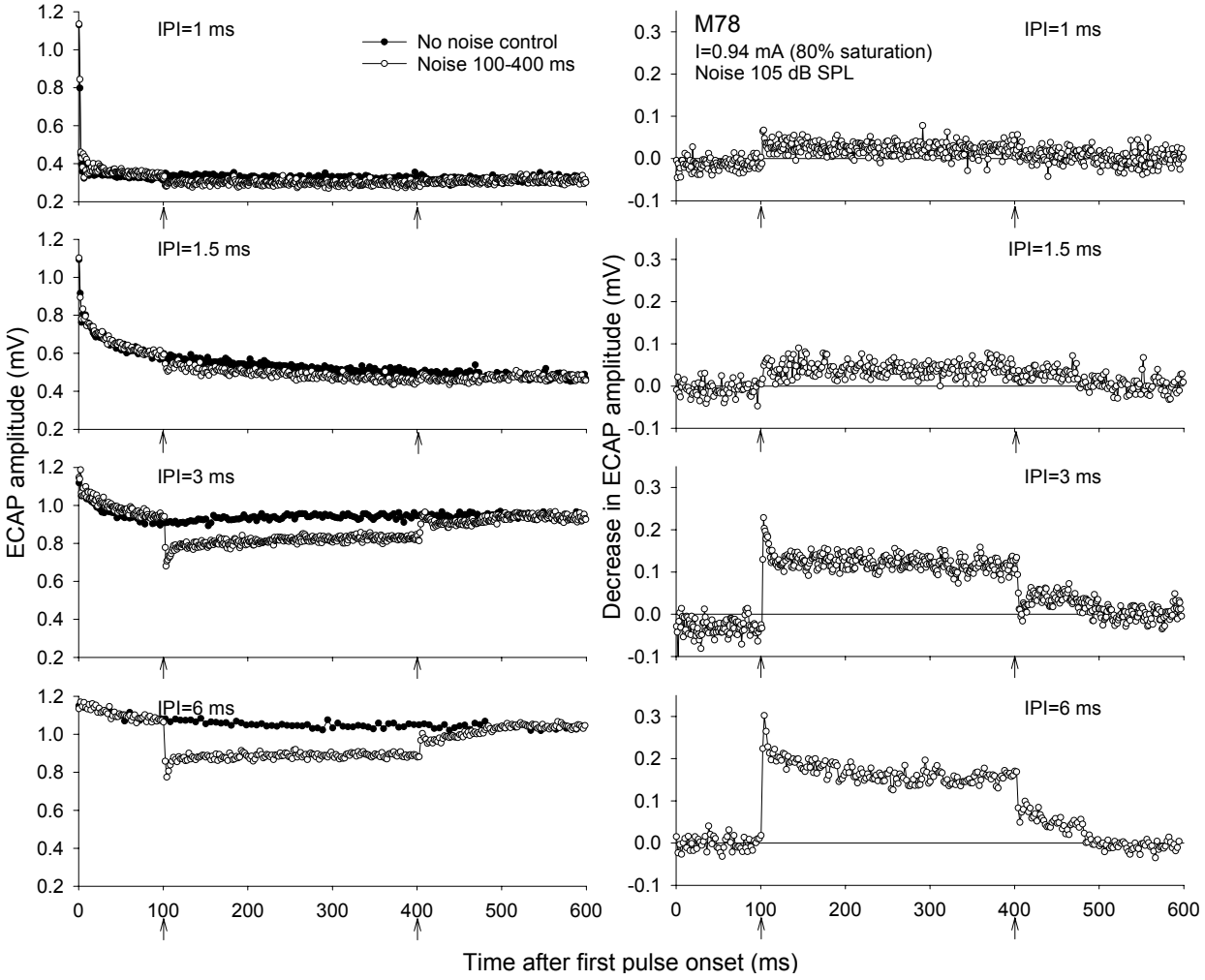

Figure 3. Effects of interpulse interval (IPI) on auditory nerve response to electric pulse trains. Left graphs: ECAP amplitudes to individual pulses are plotted as a function of time after first pulse onset. Right graphs: data shown in graphs of the left column presented as difference-functions ("electric+noise" condition subtracted from the "electric only" condition). Electric pulses were presented at a level of 0.94 mA (80% saturation of the single-pulse ECAP growth function), with or without simultaneous acoustic noise (open and filled circles, respectively). Acoustic noise was presented at a level of 105 dB SPL from 100 through 400 ms after first pulse onset. Arrows indicate noise onset and offset time.

Figure 4 summarizes the onset (panel A) and steady-state (panel B) effects of noise at various pulse rates in two subjects as well as provides a comparison between the "electric+noise" and the “electric only” condition in terms of the steady-state ECAP amplitudes (panel C). These data indicate that the effect of noise on ECAP amplitude is more prominent at lower pulse rates (Figure 4A, 4B). In addition, Figure 4C shows that as the rate of electric stimulation decreases, the adapted ECAP response amplitude increases in both "electric+noise" and “electric only” conditions in a similar pattern. This behavior suggests that the magnitude of the effect of acoustic noise is determined by the degree of ECAP response adaptation to the electric stimulation.

Next, we addressed the time course of the partial recovery of ECAP amplitude that followed the onset of the noise stimulus. As noted earlier, this recovery demonstrated an approximately exponential pattern (see Figure 1). Therefore, we attempted to describe it by fitting an exponentially decaying equation to the post-noise onset ECAP amplitude decrease data using the least squares method. A single exponential function with a constant term (a three-parameter equation) did not produce a good fit to the initial phase of post-onset ECAP amplitude recovery (data not shown).

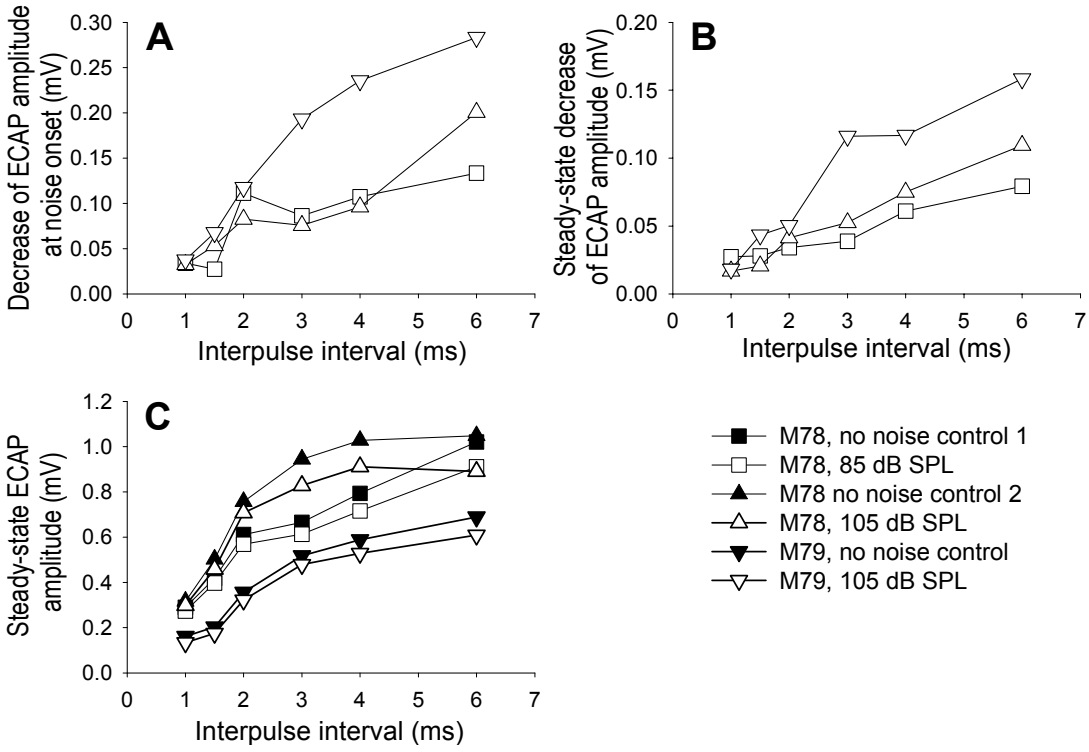

Figure 4. Summary of data from two subjects demonstrating onset (**A**) and steady-state (**B, C**) effects of acoustic noise on auditory nerve response to trains of electric pulses at various interpulse intervals (IPI). Average decrease in ECAP amplitude relative to the no-noise condition within 4-7 ms following noise onset (**A**) and within 50 ms prior to noise offset (**B**) are plotted as functions of IPI. **C**: Average ECAP amplitudes within 50 ms prior to noise offset (open symbols) and the average ECAP amplitudes within the corresponding time interval of the no-noise control conditions (filled symbols) are plotted as functions of IPI. Electric stimuli were presented at levels corresponding to 80% saturation of a single pulse growth function (0.94 mA in M78 and 0.63 mA in M79).

We therefore used the following two exponential term model:

$$A(t) = A_1 e^{-t/\tau_1} + A_2 e^{-t/\tau_2} + A_{ss},$$

where A(t) - decrease in ECAP amplitude, t - time after noise onset, A_1, A_2 - magnitudes, τ_1, τ_2 - time constants, A_{ss} - steady-state decrease in ECAP amplitude. This model was fit using the Marquardt-Levenberg least squared error algorithm.

An example of the results of the fitted recovery curve is shown in Figure 5. Analysis of residuals (inset, Figure 5) demonstrates that a double exponential function provides a reasonably good fit both to the initial phase of post-onset ECAP recovery and to the later phase, as the response approaches the steady-state. Within-subject comparisons of ECAP recovery time constants did not demonstrate any systematic dependence on either electric or acoustic stimulus level (data not shown). Analysis of individual data from six subjects yielded mean recovery time constants τ_1=7.48 ms (S.D.=4.41 ms, n=27) and τ_2=78.8 ms (S.D.=24.1 ms, n=27). These results suggest that at least two distinct mechanisms are responsible for the decrease in ECAP amplitude observed following the onset of the noise stimulus.

To characterize the offset effect of acoustic noise on ECAP response, we conducted an experiment in which the duration of the acoustic stimulus was varied from 50 ms to 1600 ms. This wide range of acoustic stimulus durations was chosen to explore the effect of duration on this effect. Following the noise offset, a residual decrease in the ECAP amplitude was observed, consistent with our previous observations. An example of such residual effect of noise is demonstrated in Figure 6. It can be noted that, for longer noise bursts, the pattern of post-offset ECAP amplitude recovery exhibits a more complex shape. We addressed the time course of the post-offset ECAP recovery by fitting two- or three-component exponential equations to the post-offset ECAP decrease data. In most cases, a two-component exponential decay function provided a reasonably good fit to the data.

However, in several cases, specifically following longer noise bursts, the shape of the recovery function was could be better described by a three-component exponent with two decaying and one rising component. These cases are marked with asterisks on Figure 6. This suggests that there may be a cumulative effect of noise that is dependent upon the duration of the acoustic stimulus.

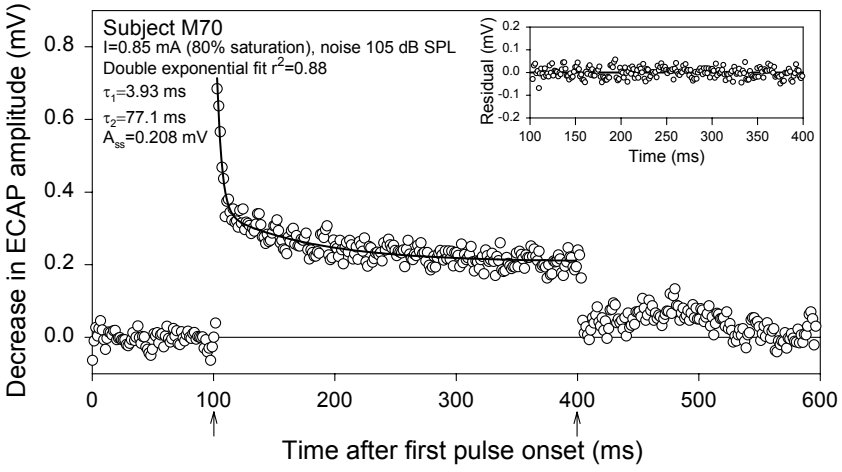

Figure 5. Double exponential curve fitting of post-onset ECAP amplitude recovery. Decrease in the ECAP amplitude ("electric+noise" condition subtracted from the "electric only" condition) is plotted as a function of time after pulse train onset. Arrows indicate noise onset and offset time. **Inset:** Residuals of the least-squares method double exponential curve fitting are plotted as a function of time.

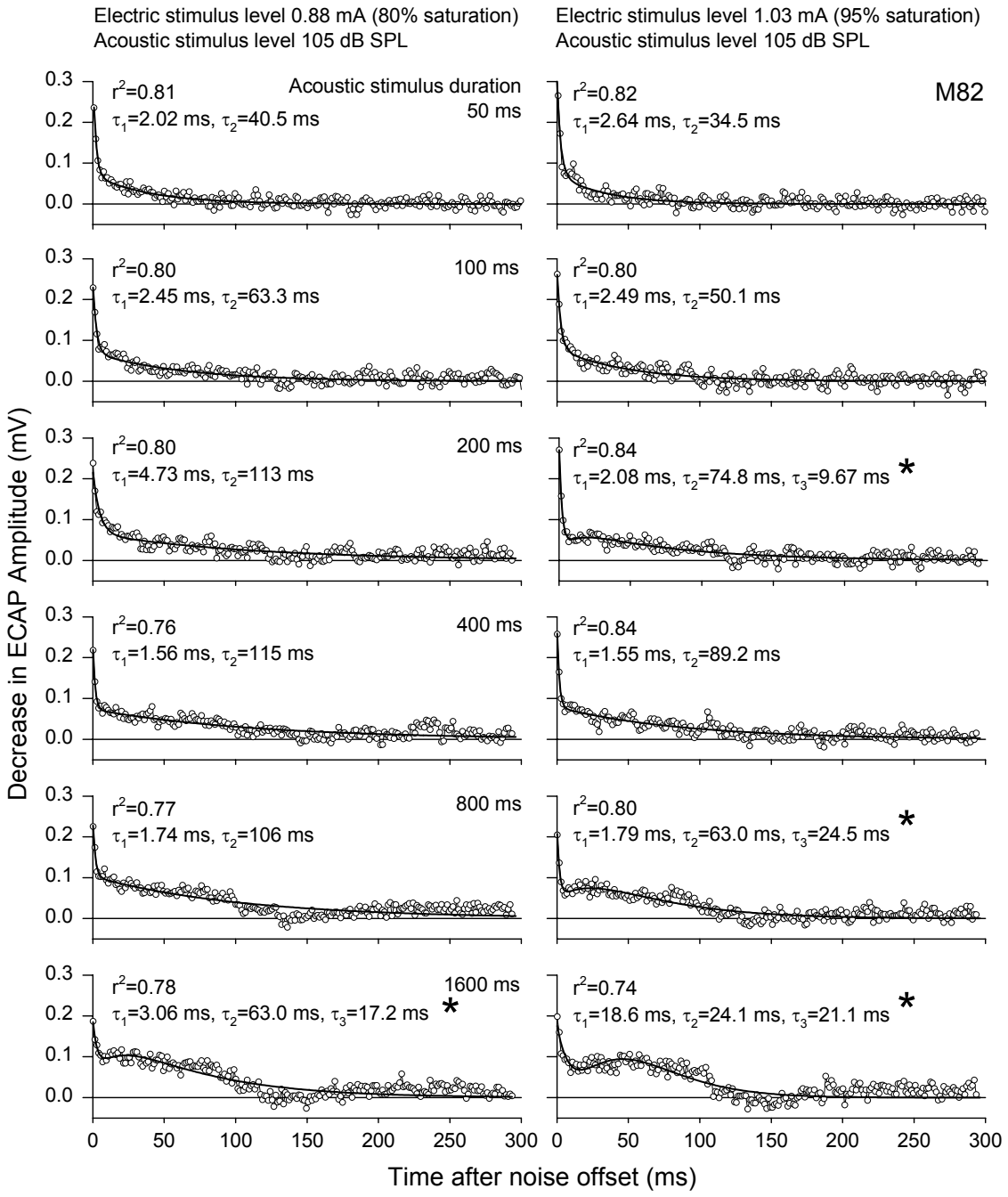

Figure 6. Residual effects of noise following noise offset at various duration of the noise stimulus. Decrease in the ECAP amplitude (response of the "electric+noise" condition subtracted from the "electric only" response) is plotted as a function of time after noise offset. Electric pulses were presented at a level of 0.88 mA (80% saturation of the single-pulse ECAP growth function) (left graphs) or 1.03 mA (95% saturation) (right graphs). Acoustic noise was presented at a level of 105 dB SPL for 50-1600 ms starting at 100 ms after first pulse onset.

2.4. Discussion

The results presented in this report extend and complement our earlier findings on the effects of acoustic noise on pulse-train ECAP responses, described in the 3rd QPR. A systematic comparison across the pulse train data obtained with various IPIs demonstrated that the effect of acoustic noise on ECAP response amplitudes is dependent on the rate of electric stimulation. At high rates (IPI<4 ms) the ECAP responses to individual pulses underwent a relatively large decrease during the initial part of the train. This phenomenon is consistent with the findings of Haenggeli *et al*. (1998) as well as earlier work from our lab (Matsuoka *et al.*, 2000); it represents short-term adaptation of the auditory nerve response to electric stimulation. The short-term adaptation to the electric stimulus (mainly due to refractory effects) seems to dominate the ECAP response dynamics at high pulse rates, so that acoustic noise has little additional effect.

In our previous reports, we hypothesized that the observed effects of noise on ECAP may arise at least in part due to acoustically-driven neural activity that desynchronizes the population response of the auditory nerve. Regression analysis of the time course of post-onset decay in the effect of acoustic noise demonstrated that it may be described as a process that has a distinct fast (rapid) and slower (short-term) component. Changes in the ECAP amplitudes and discharge rate during the presentation of the noise burst (onset effect and recovery to a steady state – see Figure 1) have morphology similar to the shape of a single-fiber poststimulus time (PST) histogram in response to an acoustic stimulus (Kiang *et al.*, 1965).

The studies described in this report also examined stimulus level effects. Generally, these level effects were graded as one might predict from a model that considers total spike activity as the dominant predictor of acoustic/electric interactions. It is worth noting that, in some cases, moderate levels of wideband acoustic noise could produce an effect on the ECAP response.

Decrease in single-fiber firing rate in response to an acoustic stimulus over time can be described in terms of adaptation – a decrease in sensitivity to a constant stimulus. Westerman and Smith (1984) demonstrated that rapid and short-term adaptation in the auditory nerve responses can be mathematically described by a double exponential function, with the two time constants corresponding to rapid and short-term component, and the asymptote corresponding to the steady-state. They used this approach to describe the time course of the auditory nerve firing rate in response to acoustic tone bursts. The time constant of the rapid component was in the range of 1-10 ms, whereas the short-term time constant ranged from 20 to 89 ms. The time constants of the post-onset decay in the effect of acoustic noise determined in the present work are comparable with the time constants of rapid and short-term adaptation reported by Westerman and Smith (1984). This indicates that the partial recovery of the pulse-train ECAP that follows the onset of the noise burst to some extent may reflect the adaptation of the auditory nerve response to the acoustic stimulus.

Our working hypothesis has been that there are at least two possible mechanisms by which acoustic stimulation can affect the response to electrical stimulation. One may be, as noted above, the result of ongoing activity to the acoustic stimulus that desynchronizes and modifies (through refractoriness) the response to the electric pulses. A second mechanism may be due to the adaptation of the neuron due to acoustic stimulation. The large effect at noise onset observed in these data suggests that the first mechanism may be important in simultaneous noise-electric pulse interactions. After noise offset, the background activity would be expected to decrease (decreased spontaneous activity after stimulus offset) and therefore the effect of the noise may be expected to recover immediately or even produce an enhanced amplitude response. The considerable residual effect after noise offset observed in these data as well as in single-fiber responses suggests that the second mechanism also contributes significantly to these response patterns. The data and exponential fits in Figure 6 suggest that the contribution of each of these mechanisms may be dependent on the duration of the noise stimulus.

Experiments planned during the next quarter will focus on stimulus duration and further investigate these effects in the ECAP as well as in single-fiber recordings where background activity can be directly evaluated.

As noted earlier, the acoustic-electric interactions that we have observed may occur in cochlear implant candidates having surviving complements of auditory nerve fibers that possess sensitivity to both acoustic and electric stimuli. This case may not be likely in candidates with minimal residual hearing or in patients with a short electrode array where there is spatial segregation of fibers responsive to acoustic and electric stimuli. However, histological studies of chronically implanted subjects have established that hair cell survival can occur in implanted cochleae at sites apical to the implanted electrode array. It is possible that acoustic-electric interactions could occur in such cases or in cases where the electric stimulus field is purposefully generated to provide a broad pattern of neural excitation. In those cases, an understanding of possible acoustic-electric interactions such as those demonstrated in this report may provide insight into the optimal processing of both the electric and acoustic stimuli delivered to such individuals.

3. Plans for the Next Quarter

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

1. Attend the Society for Neuroscience Annual Meeting and present findings related to the research conducted under this contract.

2. Conduct additional experiments using acute guinea pig preparations to study interaction of acoustic and electric stimuli with a focus on long-term effects.

3. Conduct additional experiments using acute cat preparations to investigate single-fiber responses to simultaneous acoustic and electric stimuli.

4. Prepare and submit a manuscript for publication of the work described in this and previous reports.

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