Effects of Remaining Hair Cells on Cochlear Implant Function

3rd Quarterly Progress Report

Neural Prosthesis Program
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1. 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 pulse 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. 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.

2. Summary of Activities in This Quarter

During the third quarter of this contract (January 1 through March 31, 2003), we accomplished the following:

1. Attended the ARO Midwinter meeting and presented our research results related to this contract (Abkes *et al.*, 2003; Hu *et al.*, 2003a).

2. Submitted a manuscript to Hearing Research for publication (Hu *et al.*, 2003b) detailing the experiments and findings of the first QPR (Hu *et al.*, 2002).

3. Developed new multichannel data acquisition software (using Labview code) to collect auditory nerve compound action potential recordings and single-fiber recordings.

4. Performed several acute experiments with guinea pig preparations to examine the combined effects of pulsatile electric stimuli and wideband acoustic noise presented simultaneously to the same ear. The main goal of the study was to investigate the time course of acoustic noise effects on the auditory nerve response to electric pulse trains. The results from this study form the focus topic of the present report.

3. Focus Topic: Effects of Acoustic Noise on the ECAP Responses to Pulse Trains

3.1. Introduction

In our previous work, we described the effects of acoustic stimuli on the auditory nerve ECAP responses to single electric pulses (Miller *et al*., 2000; Abbas *et al*., 2001) as well as conducted initial studies on electric/acoustic interactions at the single-fiber level (Miller *et al.*, 2003). Our findings indicated the ability of acoustic stimuli to alter ECAP responses to simultaneously presented electrical stimuli. In general, acoustic noise was found to decrease the amplitude of ECAP response.

Single-pulse ECAP studies are helpful in providing an initial insight into the interactions in question, however, they provide little information about the temporal characteristics of the observed effects of acoustic noise. Previous work in deafened animals, using electric pulse trains, has demonstrated significant changes in the responsiveness of the auditory nerve over time. These changes can occur over several hundred (Matsuoka et al, 2000) as well as long-term changes that occur over several seconds (Abkes *et al*., 2003). Previous results reported under this contract have demonstrated that adaptation to electrical pulse trains can be affected by the presence of viable hair cells (Hu *et al*., 2002). The studies described in this QPR examine the interactions of refractory effects, adaptation and driven activity in response to the acoustic stimulus on the time course of the response to electric pulse trains.

3.2. Materials and Methods

Acute experimental sessions were performed on adult healthy guinea pigs. Animal preparation methodology has been described elsewhere (Miller *et al.,* 1998). Broadband acoustic noise was generated by a noise generator and its level was controlled by an attenuator. Acoustic stimuli were presented directly to the ear canal by a Beyer DT-48 microphone, coupled to a speculum. Electric stimuli were presented through a monopolar wire electrode, positioned within scala tympani of the basal turn of the cochlea via a cochleostomy. Auditory nerve evoked responses were recorded using a ball electrode positioned on the auditory nerve trunk. The recorded evoked potentials were amplified by a custom-designed amplifier and recorded 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. The clicks were generated by driving the earphone with a 100-μs electrical pulse. ECAP 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 ensure the stability of the animal preparation.

The basic stimulus paradigm is illustrated in Figure 1. Trains of biphasic electric pulses (40 μs per phase) were used as electric stimuli. The acoustic noise was gated on and off (1 ms rise-fall time) under computer control. The onset and offset of the noise could be varied relative to the onset and offset of the electric pulse train. Total duration of the noise varied from 50 to 300 ms in different experiments. For data collection, identical pulse trains presentations with and without the acoustic noise were alternated and separate averages were calculated for the two conditions were saved. With this method we could directly compare the responses to electric pulses, with and without acoustic noise.

In several early experiments, train duration was set at 200 ms; and acoustic noise was presented between 20 and 70 ms. Interpulse intervals (IPI), which were defined as time between the onsets of adjacent pulses, were set at 1 or 2 ms in these experiments. For later experiments, we used 600 ms pulse trains with IPI=4 ms; acoustic noise was presented between 50-350 or 100-400 ms.

3.3. Results

In early experiments, the electric pulses were presented at the higher rates (1-2 ms IPI) pulse rates. Figure 2 demonstrates the ECAP amplitudes in response to 200 ms electric pulses presented at 1- or 2-ms IPI with and without simultaneous acoustic noise. At 1-ms IPI (Fig. 2, upper graph) there was a substantial decrease in the response amplitude during the first 10 ms following the train onset, reaching a plateau amplitude of about one-third of the response to the first pulse of the train. At this rate, the acoustic noise had little demonstrable effect. When the pulses were presented at 2-ms IPI, the initial decrease in the response amplitude without the noise was substantially less. In that case, the same level of acoustic noise produced a substantial decrease in response to the electric pulse train (Fig. 2, lower graph, open circles). The initial decrease in response at the onset of noise was followed by a gradual recovery to an approximately steady-state response amplitude. This recovery was not complete, i.e., the responses did not reach the no-noise levels while the noise was on. Following noise offset the response levels returned to response amplitudes identical to the no-noise condition. The effect of the acoustic noise was observed primarily at high electric stimulus levels (80-100% relative to ECAP growth function saturation).

Based on responses such as those shown in Figure 2, we elected to use a lower rate of electric pulse presentation in order to more clearly observe the effect of added acoustic noise. Presenting electric stimuli at a lower rate also would cause a decrease in the resolution of the time-course of the effect, particularly, at the onset and offset of the noise. To preserve temporal resolution of the recordings, we incorporated a modification to the data collection paradigm. This modification entailed the collection of responses using three different noise-onset times, as illustrated in Figure 3. In this way we could effectively examine the response to the pulse train sampled at 3 times the pulse rate. The three pulse+noise stimuli were interleaved a pulse only condition for comparison. The same sequence was then

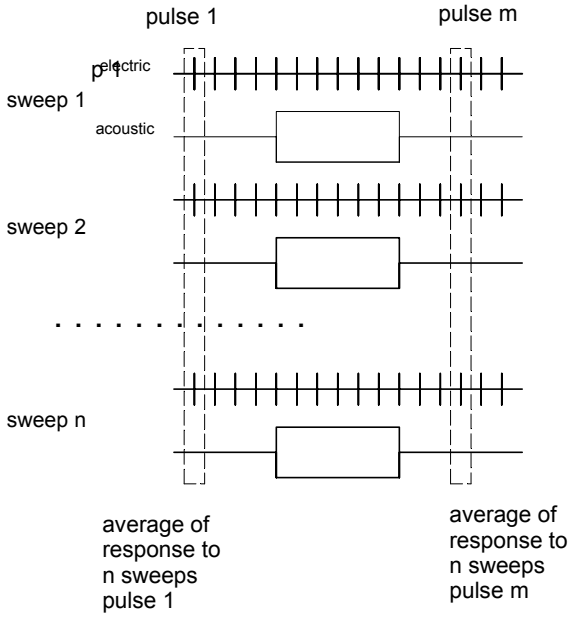

Figure 1. Schematic of stimulus presentation and response averaging paradigm used to assess time course of adaptation, recovery and acoustic/electric interaction.

repeated with the opposite polarity pulse train. Thus, eight stimuli (no noise plus three offset noise conditions for each stimulus polarity) were repeatedly presented and the response to each of the stimulus conditions was averaged separately.

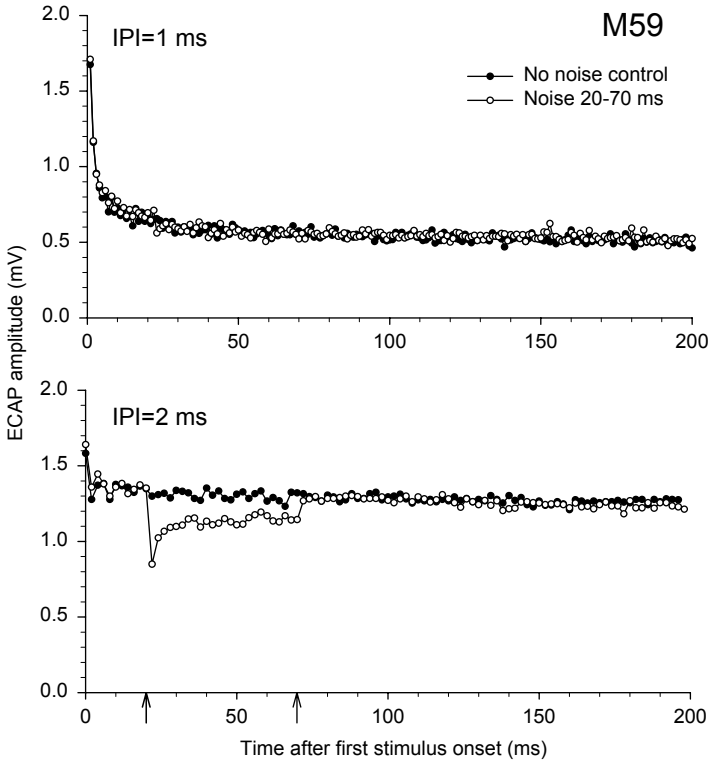

Figure 2. Effects of interpulse interval (IPI) on auditory nerve response to electric pulse trains. ECAP response amplitudes to individual pulses are plotted as a function of time after first pulse onset. Electric pulses were presented with IPI of 1 ms (upper graph) and 2 ms (lower graph), with or without simultaneous acoustic noise (open and filled circles, respectively). Electric stimulus level was 1.0 mA (100% saturation of the single-pulse ECAP growth function). Acoustic noise was presented at 105 dB SPL from 20 through 70 ms after first pulse onset. Arrows indicate noise onset and offset time.

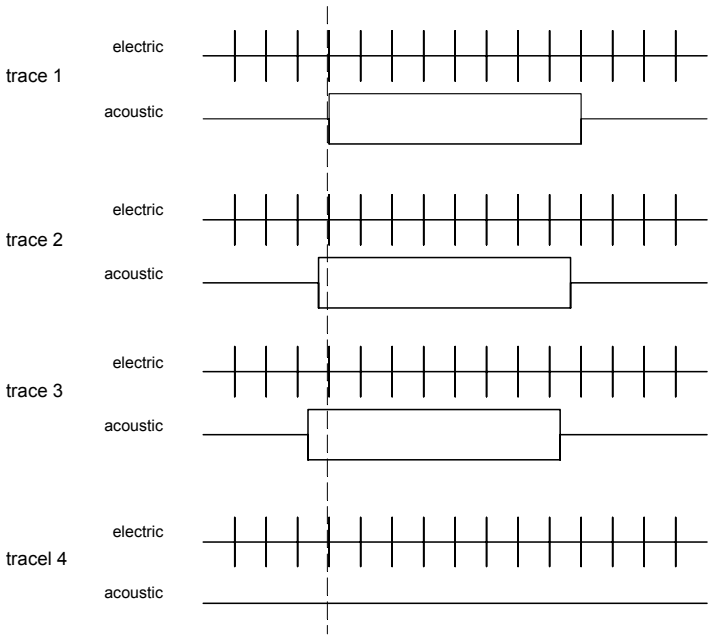

Figure 3. Schematic of the staggered noise onset paradigm. See text for details.

Figure 4 illustrates an example of responses collected using this staggered onset paradigm. Response amplitudes in response to one stimulus polarity (cathodic-first biphasic pulses) are shown. In initial experiments we used a 4-ms interpulse interval. Thus if the onset of the noise was set to 100 ms after pulse train onset, then for the second and third train the noise onset was set to 98.67 and 97.34 ms after the onset of the pulse train (1.33 and 2.66 ms earlier). Response amplitudes as a function of time to the three noise conditions (A, B, C) and the no-noise condition (D) are shown.

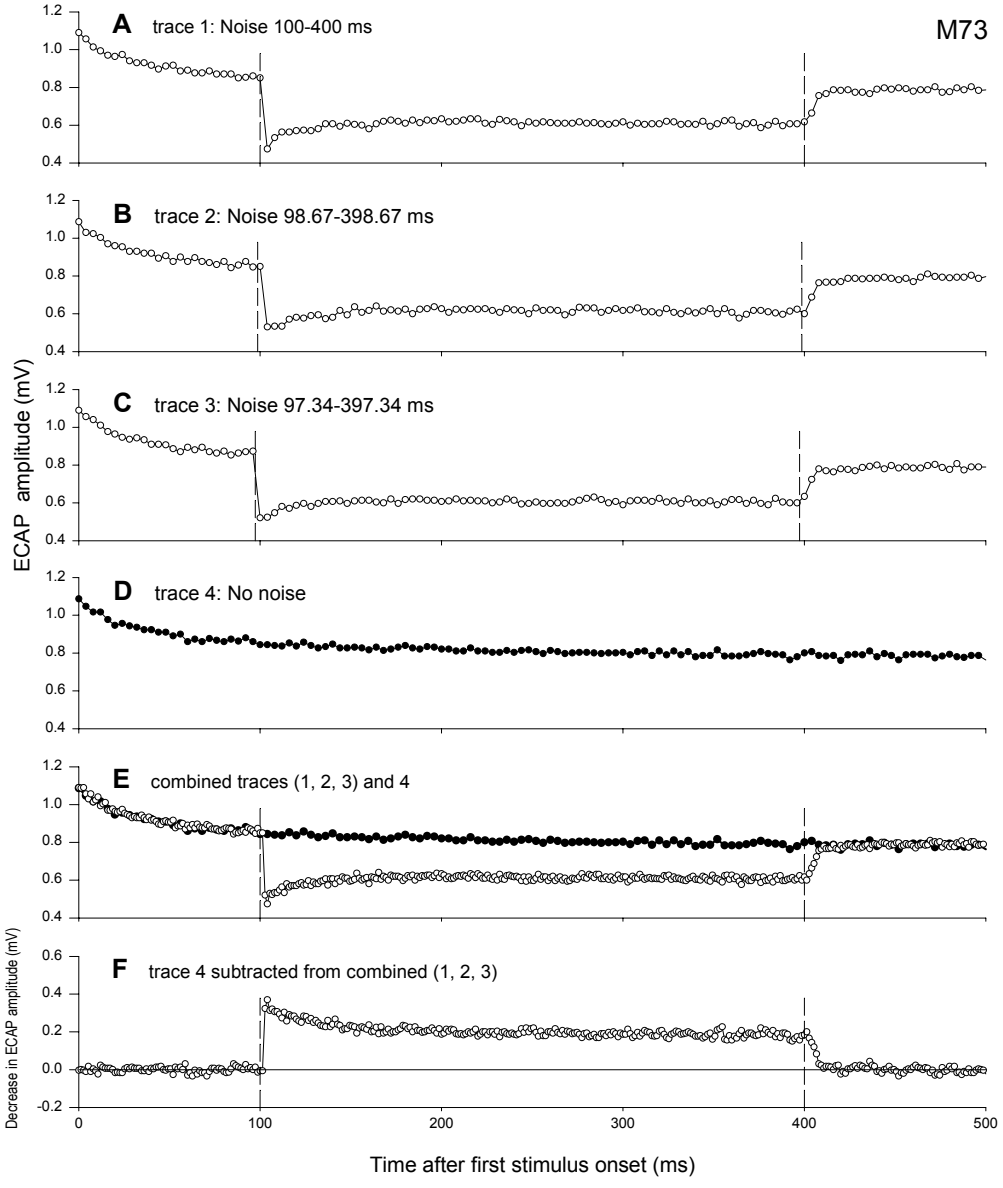

Figure 4. Staggered noise onset recording paradigm. ECAP amplitudes in response to each pulse in the train are plotted as a function of time after first stimulus onset. **A-D**: Electric pulses were presented with IPI of 4 ms with (A-C; traces 1,2, and 3) or without simultaneous acoustic noise (D; trace 4). **E**: Traces 1,2, and 3 (noise-on conditions; open circles) combined and plotted together with trace 4 (no-noise condition; filled circles). **F**: Trace 4 subtracted from traces 1, 2, and 3. Electric stimulus level was set at 0.78 mA (80% saturation of the single-pulse ECAP growth function). Acoustic noise level was 105 dB SPL. Responses to the first 500 ms of each train are shown. Dashed lines indicate noise onset and offset.

Stimulus current level was the same for all four conditions. The time course of the effect of noise, i.e., the initial decrease in response amplitude at noise onset and the subsequent recovery, is similar for the three noise conditions.

After the ECAP amplitudes were picked for each trace, the times corresponding to part B and C were corrected to relative to the noise onset time. The data from the three noise conditions (A,B,C) were then combined and replotted with the no-noise condition in part E. Thus, a three-fold increase in the temporal resolution of the recording technique was achieved for the "noise" condition (1.33 ms, compared to the actual IPI of 4 ms). Finally the response amplitudes in the no-noise condition were then subtracted from the "noise-on" condition to provide a measure of the decrease in response amplitude. This final graph demonstrates the net effect of noise independent of auditory nerve adaptation to electric stimuli. The data presented throughout the rest of the report were collected and analyzed in this manner.

The time course of the effect of the noise shown in Figure 4E demonstrate the effects similar to those described in Figure 2. The initial decrease in amplitude of response at noise onset is followed by a gradual recovery that reaches a steady-state amplitude. These data also show a significant effect on the response to the pulse train after the offset of the noise. This observation has implications relative to the mechanism of "masking" of the electric response by the acoustic noise.

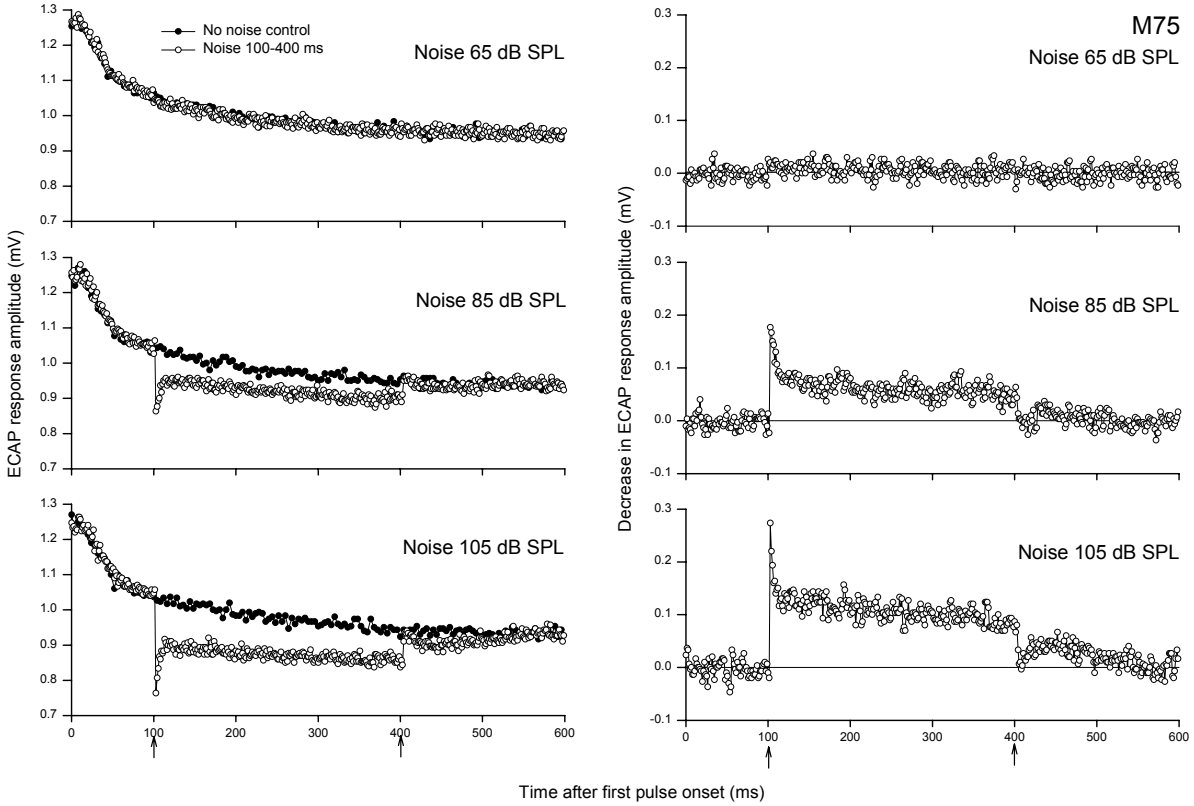

Figure 5. Effect of acoustic noise level on auditory nerve response to electric pulse trains. Left graphs: ECAP response amplitudes to individual pulses are plotted as a function of time after first pulse onset. Electric pulses were presented with IPI of 4 ms, with or without simultaneous acoustic noise (open and filled circles, respectively). Electric stimulus level was set at 0.74 mA (80% saturation of the single-pulse ECAP growth function). Acoustic noise was presented from 100 through 400 ms after first pulse onset. Right graphs: data shown in graphs of the left column presented as difference-functions (no noise condition subtracted from the "noise on" condition). Arrows indicate noise onset and offset time.

One hypothesis may be that the addition of acoustic noise primarily causes an increase in background neural activity and consequently decreases the responsiveness and synchrony to the electric pulse. After noise offset that activity is decreased. This residual effect of the noise after noise offset suggests a mechanism of masking different than simply increased activity in response to the noise, perhaps involving adaptation mechanisms.

Figure 5 demonstrates the effect of acoustic noise level on ECAP response to the pulse train. It is evident that for a particular electric stimulus level, the maximum decrease of ECAP amplitude is achieved at high noise levels. These data also demonstrate the variations in the effect after noise offset that we have observed in our data; in this case the effect at noise offset is relatively small but there is a slight recovery and residual effect for approximately 100 ms at the highest nose level.

Figure 6 illustrates another example where there is what might be termed an overshoot effect. In this case, ECAP responses underwent complete recovery almost immediately following noise offset, with amplitude exceeding that of the no noise condition. In other cases, residual effects of noise following noise offset were observed, i.e., the response amplitude was decreased relative to the noise-noise condition after noise offset. Another example is shown in Figure 7. Here, as in Figure 5, the effect of noise persisted for some time after noise offset. In this example there appears to be two components of recovery from noise masking: a fast recovery component that immediately followed noise offset, and a slow component that spanned over the course of 100-150 ms following noise cessation. Fast recovery was more prominent at high electric stimulus levels, whereas the slower component dominated at lower levels of electric stimulus. These data also show a delayed enhancement of ECAP response (compared to the no noise condition, occurring around 450-500 ms epoch (i.e., 100-150 ms after the noise offset) and reaching its maximum at around 475 ms.

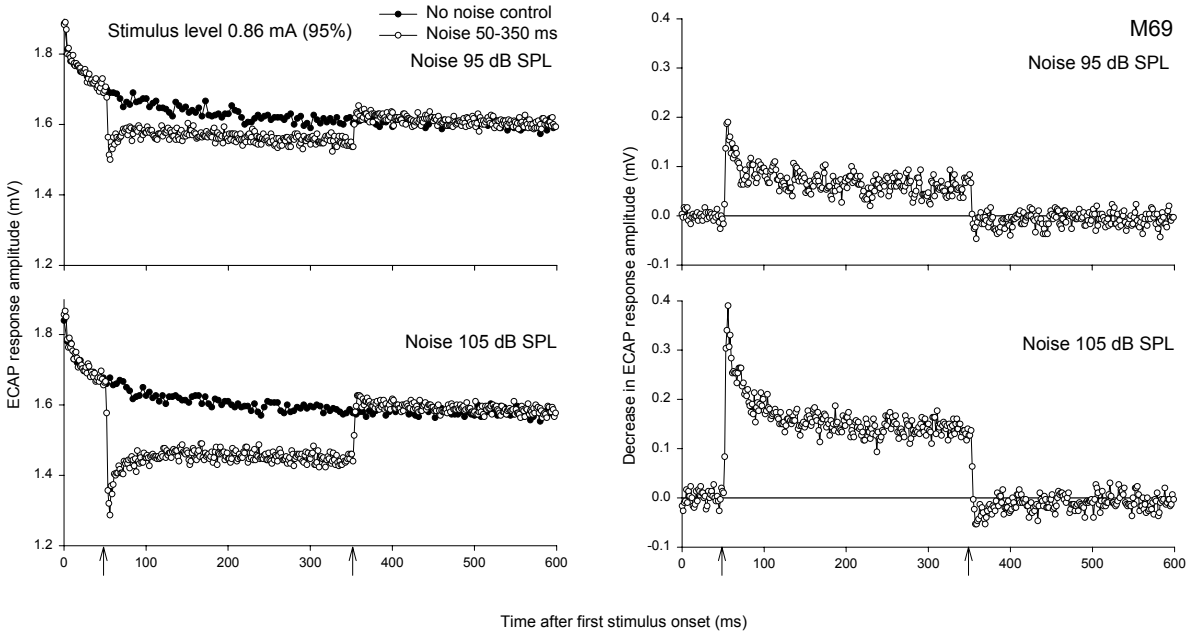

Figure 6. Enhancement of ECAP response following noise offset. Left graphs: ECAP response amplitudes to individual pulses are plotted as a function of time after first pulse onset. Electric pulses were presented with IPI of 4 ms, with or without simultaneous acoustic noise (open and filled circles, respectively). Electric stimulus level was set at 0.86 mA (95% saturation of the single-pulse ECAP growth function). Acoustic noise was presented from 50 through 350 ms after first pulse onset. Right graphs: data shown in graphs of the left column presented as difference-functions (no noise condition subtracted from the "noise on" condition). Arrows indicate noise onset and offset time.

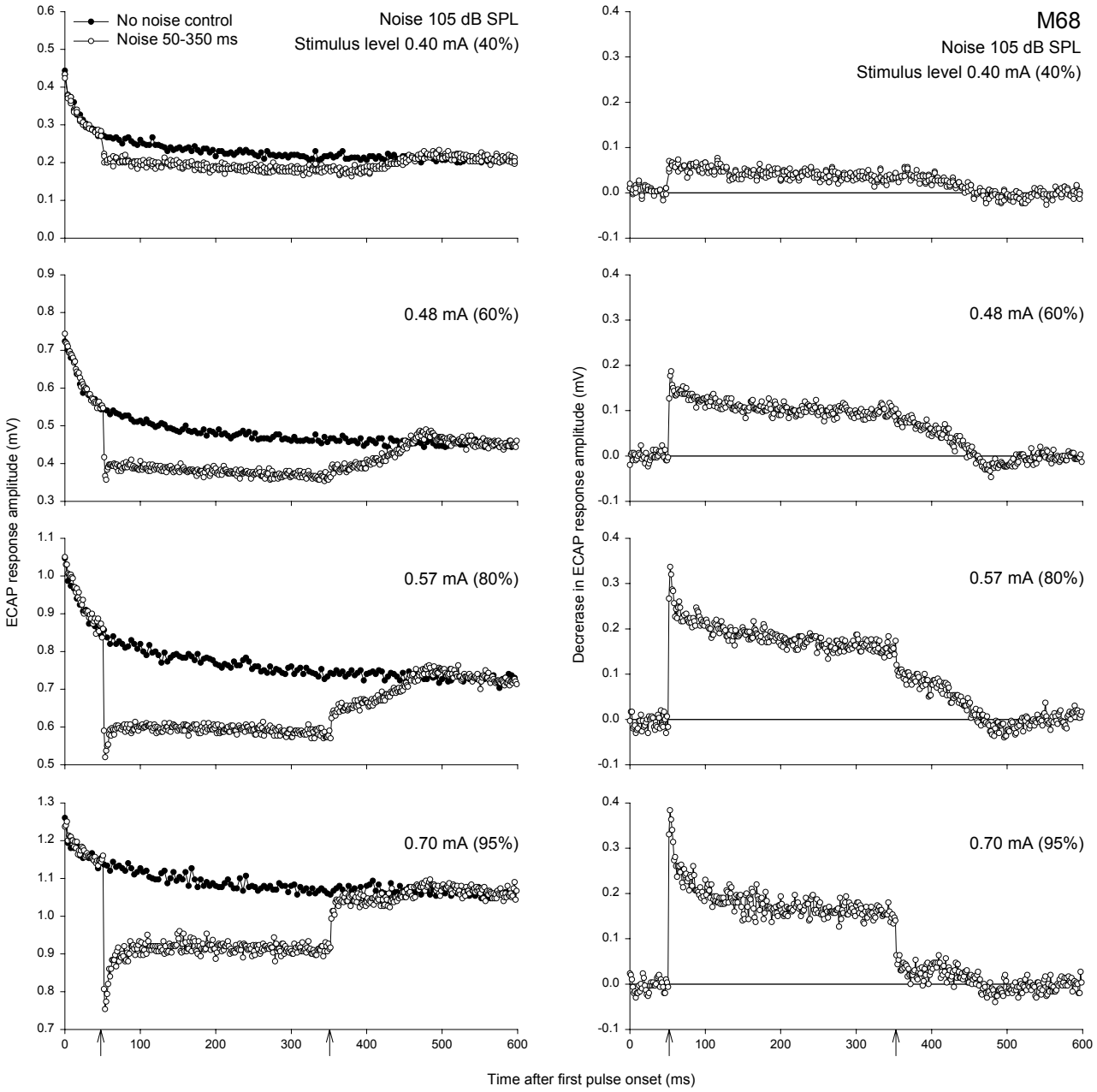

Figure 7. Residual effects of noise following noise offset. Left graphs: ECAP response amplitudes to individual pulses are plotted as a function of time after first pulse onset. Electric pulses were presented with IPI of 4 ms, with or without simultaneous acoustic noise (open and filled circles, respectively). Acoustic noise was presented at 105 dB SPL from 50 through 350 ms after first pulse onset Right graphs: data shown in graphs of the left column presented as difference-functions (no noise condition subtracted from the "noise on" condition). Arrows indicate noise onset and offset time.

3.4. Discussion

The results presented in this report are consistent with our previous data on the effects of acoustic noise on single-pulse ECAP responses (Miller *et al.,* 2000; Abbas *et al.,* 2001). It is evident that the electric and acoustic stimuli, when presented simultaneously, can produce a combined effect in auditory neurons, with acoustic noise having the principal effect of decreasing the amplitude of ECAP response.

Comparisons across the pulse train data obtained with 1 ms, 2 ms, and 4 ms IPI revealed a difference in the effect of acoustic noise on ECAP response amplitudes. When the electric pulses were presented at the higher rate (1 ms IPI), no effect of added noise was observed. At that rate the ECAP responses underwent a relative large adaptation when presented without acoustic noise. At least part of this effect is likely related to the refractory properties of the auditory nerve fiber membrane. The majority of fibers within the auditory nerve have recovery time constants between 0.7 and 1.3 ms (Miller *et al*., 2001). So, when the interval between electric stimuli is as low as 1 ms, it becomes comparable with the refractoriness of neuronal membrane. Thus, the refractory effects may dominate the response dynamics at high pulse rates, and the addition of acoustic noise may have little effect.

As noted earlier, a straightforward hypothesis relative to the effect of noise on the electric response may be that neural activity in response to the noise may reduce or desynchronize the responses to the electric pulse train. The time course near noise onset is largely consistent with this hypothesis in that there is initially a large effect of the noise followed by an approximately exponential recovery. The expected activity in response to the noise would show a similar time course. The overshoot or increased response observed after noise offset in some cases is also consistent with this hypothesis. Decreased spontaneous activity after noise offset is expected and could the source of that overshoot. Nevertheless, as noted earlier, the residual masking effect observed in many cases is not consistent with that simple hypothesis.

Complex recovery functions such as those in Figure 7 suggest that there may be multiple mechanisms involved in the masking effects observed here. Clearly, more data are needed to resolve this issue. Detailed descriptions of auditory nerve fiber response properties such as spike rate, jitter, fiber dynamic range, and synchronization index would be helpful in providing a better understanding of the observed effects of acoustic noise. As these properties cannot be directly assessed by gross-potential (ECAP) measures, additional single-fiber studies of acoustic/electric interactions should be conducted.

4. Plans for the Next Quarter

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

1. Perform additional analysis of the results presented in this report. This will include quantitative description of the time-course of the observed effects of noise on ECAP.

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 on ototoxic interaction of kanamycin and ethacrynic acid.

5. References

1. **Abbas, P.J., Miller, C.A., Rubinstein, J.T., Robinson, B.K. (2001).** Effects of remaining hair cells on cochlear implant function, *Seventh Quarterly Progress Report, Neural Prosthesis Program contract N01-DC-9-2106 NIH.*

2. **Abkes, B.A., Miller, C.A., Hu, N., Abbas, P.J. (2003).** Adaptation in the auditory nerve in response to a continuous electric pulse train. *Abstracts of the Twenty-Sixth Annual MidWinter Research Meeting of the Association for Research in Otolaryngology. February 22-27, 2003, Daytona Beach, Florida, USA.* Abstract #775. p. 197.

3. **Hu, N., Abbas, P.J., Miller, C.A., Robinson, B.K., Nourski, K.V., Jeng, F.C., Abkes, B.A., Nichols, J.M. (2002).** Effects of remaining hair cells on cochlear implant function, *First Quarterly Progress Report, Neural Prosthesis Program contract N01-DC-2-1005 NIH.*

4. **Hu, N., Abbas, P.J., Miller, C.A., Robinson, B.K. (2003a).** Auditory nerve responses to electric pulse trains following treatment with furosemide. *Abstracts of the Twenty-Sixth Annual MidWinter Research Meeting of the Association for Research in Otolaryngology. February 22-27, 2003, Daytona Beach, Florida, USA.* Abstract #774, p. 197.

5. **Hu, N., Abbas, P.J., Miller, C.A., Robinson, B.K., Nourski, K.V., Jeng, F.C., Abkes, B.A., Nichols, J.M. (2003b).** Auditory response to intracochlear electric stimuli following furosemide treatment. (submittted to *Hear. Res*).

6. **Matsuoka, A.J., Abbas, P.J., Rubinstein, J.T., Miller, C.A. (2000).** The neuronal response to electrical constant-amplitude pulse train stimulation: Evoked compound action potential recordings. *Hear. Res.*, 149:115-128.

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

8. **Miller, C.A., Abbas, P.J., Rubinstein, J.T., Runge-Samuelson, C., Robinson, B.K. (2000).** Effects of remaining hair cells on cochlear implant function, *Fifth Quarterly Progress Report, Neural Prosthesis Program contract N01-DC-9-2106 NIH.*

9. **Miller, C.A., Abbas, P.J., Robinson, B.K. (2001).** Response properties of the refractory auditory nerve fiber. *J. Assoc. Res. Otolaryngol.* 2:216-232.

10. **Miller, C.A., Abbas, P.J., Hu, N., Robinson, B.K. (2003).** Effects of remaining hair cells on cochlear implant function, *Second Quarterly Progress Report, Neural Prosthesis Program contract N01-DC-2-1005 NIH.*

11. **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.