

Fifth Quarterly Progress Report
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**Effects of Remaining Hair Cells on
Cochlear Implant Function**

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1 Introduction

In this contract, we are conducting physiological experiments and computational model simulations to assess the effects that functional hair cells have on the auditory nerve's response to electrical stimulation. This work is relevant to the widening pool of cochlear implant candidates as audiological criteria (e.g., pure-tone thresholds) are becoming more relaxed and patients with more residual hearing are being implanted. Intact hair cells may interact with the electrically transduced signal in several ways. Acoustically evoked neural activity may interact or compete with electrically evoked activity. Also, the very presence of hair cells - without any exogenous acoustic stimuli-may also modify the electrically evoked neural response. It is possible that electrical stimuli may depolarize hair cells and initiate the release of neurotransmitter and nerve-fiber activation. It is also possible that quiescent release of neurotransmitter may modulate the response characteristics of nerve fibers, thereby changing their responsiveness to electrical stimuli. The experiments of this contract are designed to acquire evoked potential data from sets of experimental animals that have functional and nonfunctional hair cells. Comparisons will then be performed to assess the effect of functional hair cells on the neural coding of electrical stimuli delivered by intracochlear electrodes.

2 Summary of activities in this quarter

In our fifth quarter (1 August through 31 October, 2000), the following activities related to this contract were completed:

1. A working version of our new data collection software (using Labview code) is now being used to acquire compound action-potential data. It offers new capabilities that our old system did not have, including: 1) automatic sequencing of the collection of a series of stimulus conditions, 2) automatic peak-picking algorithm, 3) automatic evaluation of signal to noise level (used with the 2nd feature to improve speed of data collection), 4) automatic randomization of stimulus conditions, and 5) simultaneous output of independent waveforms on multiple channels. The software also allows the collection of up to 8 channels of data (using time-division multiplexing) for use with our planned multichannel neural recordings.

2. We have improved our surgical procedures for making direct (intracranial) recordings of the electrically evoked compound action potential (ECAP) in guinea pigs with intact hearing. Earlier preparations sometimes suffered from significant losses in hearing sensitivity (i.e. greater than 20 dB threshold shifts). We believe these shifts were due to compromised cochlear blood supply caused by retraction of the brain. While we continue to place our recording electrodes intracranially, we use a more conservative approach and avoid medializing the brain. This has improved maintenance of hearing in most preparations, with threshold shifts as low as 10 dB.

3 Introduction

In the third Quarterly Progress Report, we presented comparisons of ECAP responses obtained both before and after chemical deafening in the same preparations. Repeatable differences were seen in ECAP threshold, rate of growth, and response patterns to pulse train stimuli. These differences reinforced the hypothesis that intact hair cells modify the neural responses to electrical stimulation in ways consistent with the notion of enhancements due to stochastic (hair-cell mediated) activity. In this report, we first present additional data on comparisons between hearing and deafened preparations. We then present results concerning a second focus of this contract: the effects of simultaneous presentation of acoustic and electric stimuli on the evoked neural response.

Methodology was outlined in the third QPR of this contract. Briefly, acute guinea pig preparations were used in which the auditory nerve was surgically exposed to allow for the insertion of a recording electrode. A cochleostomy was carefully made on the bony capsule of the cochlea immediately ventral to the round window, facilitating insertion of a Pt/Ir stimulation electrode (approximately 1 mm in length) into the basal turn of the cochlea without greatly disturbing acoustic sensitivity. The pinna of the same ear was excised and sound was delivered to the ear canal with a Beyer DT-48 earphone coupled to a speculum. The animal was maintained on a oxygen ventilator and continuous intravenous drip (Ringer's solution) through catheterization of the external jugular vein. This route was also used for the administration of the ethacrynic acid, the diuretic used as part of a systemic chemical deafening protocol, again described in the third QPR. In all cases, the electric stimuli were delivered to the monopolar

intracochlear electrode; a needle electrode located in the forepaw served as the return stimulus electrode.

4 Electrically evoked responses before and after deafening

In the third QPR, we presented data suggesting changes in ECAP threshold and rate-of-growth. Since then, we have collected ECAP amplitude-level data from nine additional guinea pigs. These data have been added to the group-data plots shown in Figure 1. In this figure, ECAP data obtained both before and after systemic deafening are plotted. Each datum of the graph of panel A represents the stimulus level needed to evoke an ECAP amplitude of 10 percent of maximum (i.e. 10 percent of saturation amplitude), while the data of panel B describe the stimulus levels required to evoke amplitudes half that of the saturation (maximum) level. Note that in panel A, the stimulus levels required to evoke the criterion response were generally higher when the animals were deafened. Paired-comparison t-tests were performed on both data sets (panels A and B) to determine the effects of deafening on each measure. In the case of the 10 percent criterion levels, a statistically significant difference ($p = 0.012$) was found between ears in the hearing and deafened states. However, at the higher (50 percent) criterion, no significant difference was found. Thus, our data suggest that intact hair cells impart an effect at low stimulus levels whereby ECAP thresholds are decreased. The findings at the higher (50 percent) response criterion indicate that this hair-cell-mediated effect is restricted to relatively low stimulus levels.

5 The effect of the simultaneous presentation of acoustic and electric stimuli

The above trends are consistent with our hypothesis that functional hair cells improve neural thresholds to electric stimuli, presumably through spontaneous synaptic activity. Such a finding motivates the study of externally-generated acoustic stimuli to determine how the addition of acoustic energy changes the evoked response. We have proposed to use various wideband and sinusoidal acoustic stimuli to assess the ability of exogenous stimuli to interact and alter ECAP responses. Some of this work was motivated by

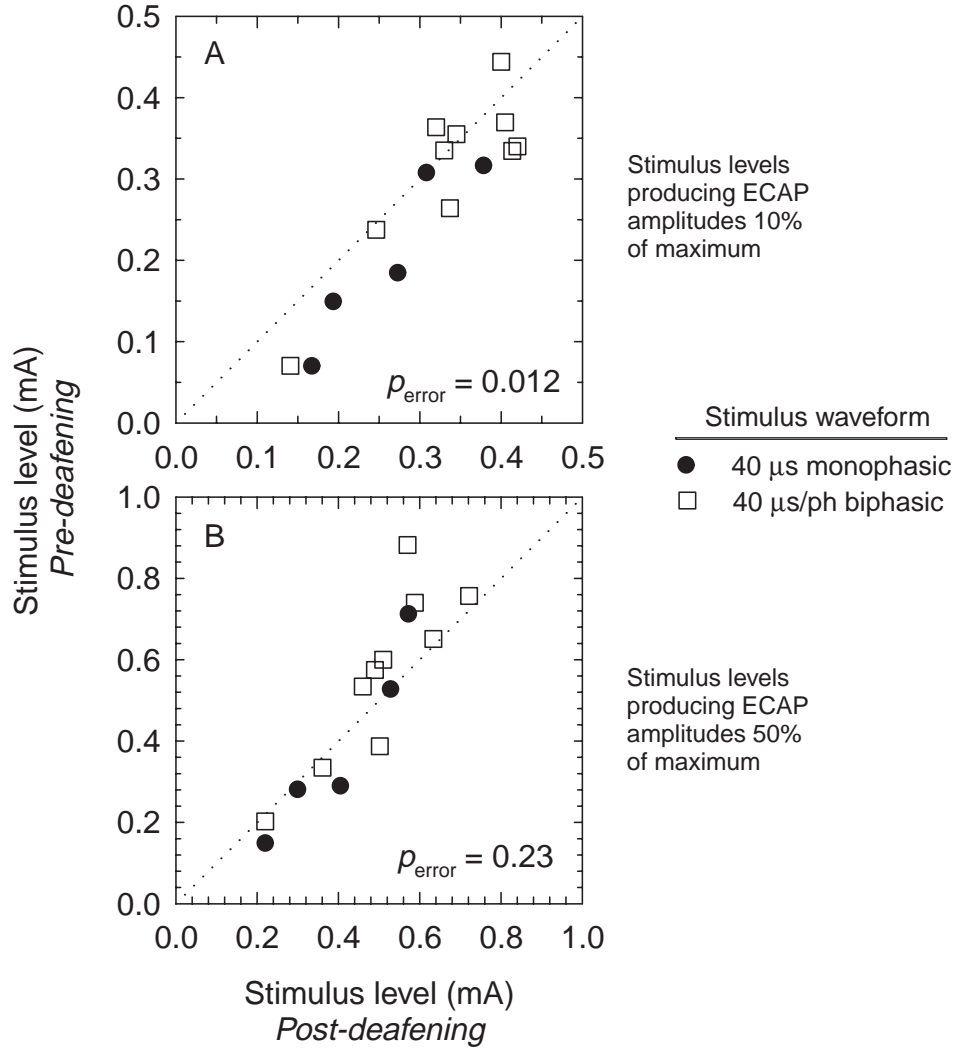


Figure 1: Scatter plots of stimulus current levels required to evoke a criterion ECAP response amplitude in guinea pigs before and after systemic chemical deafening. Each datum represents the before- and after-deafening current level obtained from one of a total of 15 animals. Data were obtained using either monophasic (filled symbols) or biphasic (open symbols) current pulses. In the top graph (A) is plotted the current levels required to evoke an ECAP response 10 percent of the maximum (i.e., saturation) amplitude. In the lower graph (B) is plotted data characterizing the levels required to evoke amplitudes one-half that of saturation. The dotted diagonal lines indicate equal current levels for both pre- and post conditions. The error probability shown in each panel indicates the result of a paired-comparison t-test performed across the pre- and post-deafening conditions

that of Moxon (1971), who demonstrated that interaction of acoustic and electric stimuli could be observed at the level of the single-fiber.

5.1 Wideband acoustic noise stimuli

Our first and most basic experiments investigated the effect of wideband acoustic noise on ECAP responses. A wideband (20 kHz) gaussian noise generator was used to drive an earphone coupled by a speculum to the guinea pig ear canal. This noise was presented continuously throughout the course of data acquisition and the highest overall noise level was approximately 100 dB SPL. Figure 2 illustrates the effect of wideband acoustic noise on ECAP growth for two guinea pig preparations. From these data, we note that wideband noise can reduce ECAP response level over a range of levels of at least 30-40 dB, with the largest effects occurring at relatively low current stimulus levels. In Figure 3, these data have been normalized to the unmasked conditions of each animal in order to illustrate the relative effect of the masking noise at each current level.

The data of both animals show similar trends. In both animals, the magnitude of the response decrement is generally between 10 and 20 percent. Over a wide range of electric stimulus levels, acoustic masking reduces the amplitude of the evoked response, with the largest proportional response occurring at low-to-middle current levels. The relative response decrements become smaller as stimulus level is reduced to low levels. At the lowest stimulus levels, there appears to be an increase, in some cases, in the amplitude of the noise-masked responses. However, these low-level responses also demonstrate increased variability across the different levels of the acoustic stimulus, suggesting that the apparent enhancements in the ECAP may be artifactual. The relatively poor signal-to-noise conditions inherent to responses obtained at the lowest stimulus levels may produce sufficient variability in the measured responses such that some of the relative response measures produce ratios greater than one. This low-level region is clearly an area of interest and will be investigated by more specific measures in future experiments.

5.2 Sinusoidal acoustic stimuli

We have also begun investigating the interaction of electric stimuli with an acoustic stimulus presented as a continuous sinusoid. With tonal acoustic

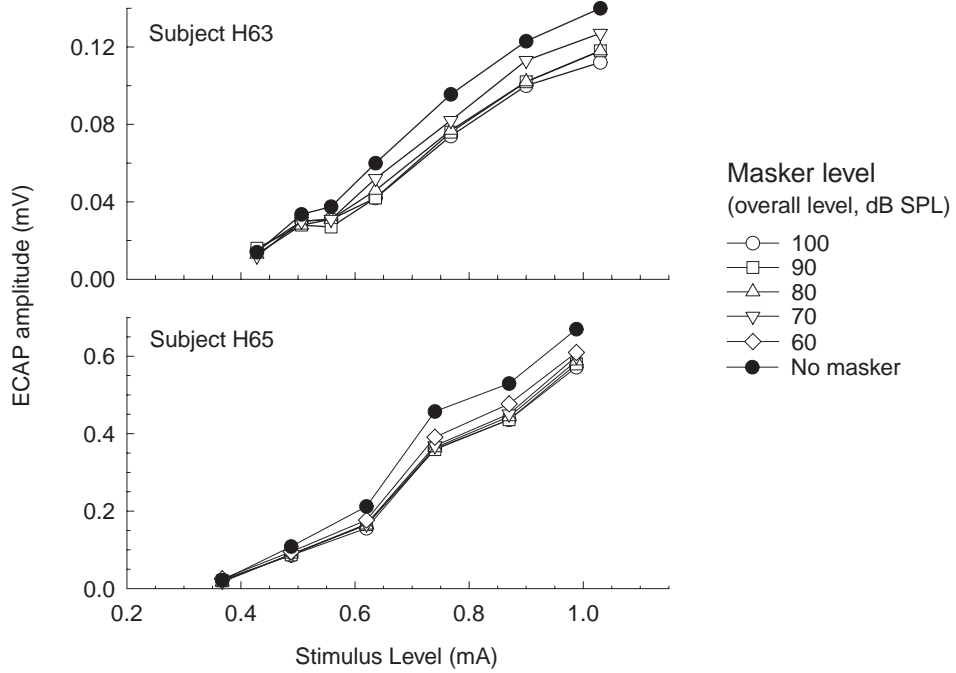


Figure 2: ECAP amplitude-level functions obtained from two guinea pigs preparations demonstrating the interaction of electric and acoustic stimulation. The electrically evoked responses were obtained using 40 microsecond/phase biphasic current pulses. Wideband acoustic noise stimuli were delivered to the same ear through an earphone and speculum sealed to the external auditory meatus. The overall sound pressure of the noise is indicated by the symbol type and legend.

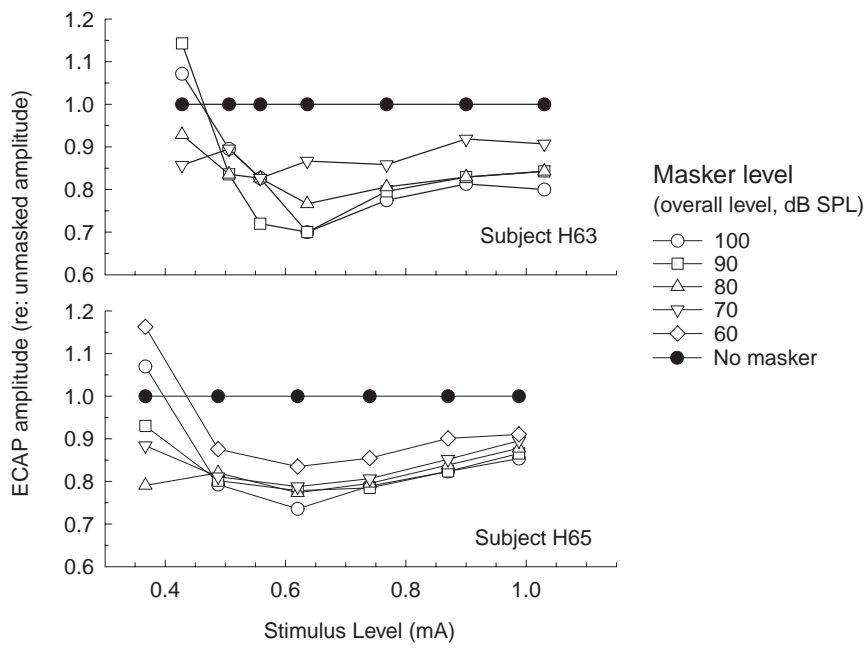


Figure 3: Data of Figure 2, normalized to the no-noise condition to illustrate the effects of the acoustic noise stimulus on ECAP amplitude

stimuli, we can examine the influence of the phase of the acoustic stimulus relative to the time at which the electrical stimulus is presented. The stimulus paradigm is summarized in Figure 4. A high level 100 Hz tone is presented continuously to the ear through a speculum attached to the external canal. ECAP responses are then evoked by a single biphasic stimulus pulse delivered at a specific phase relative to the sinusoid. Separate time-averaged ECAP responses are obtained at six different relative phases, as indicated in the figure. The level of the tone and the electric pulse are also systematically varied.

To date, we have obtained measures of tone and electric pulse interactions from five guinea pig preparations. In three cases, we noted an interaction between the two stimuli. Results from two of those subjects are shown in Figures 5, where ECAP amplitudes are plotted as a function of the relative phase of the electric pulse and the pulse level. Also shown are data obtained at different levels of the 100 Hz tone stimulus. Note that "relative phase" does not indicate the phase relationship between the tone and pulse as delivered to the basilar membrane as we have not accounted for sound propagation delays. Tone and electric pulse interactions are observed at only the highest level of the tone stimulus (i.e., between 85 and 95 dB SPL). Furthermore, the phase effects are greatest at the higher levels of the electric stimulus. To date, we have not observed any interactions between the phase (at which maximum effect is observed) and stimulus levels.

The observed phase effects are explored further in the normalized plots of Figure 6. In this figure, ECAP amplitudes have been normalized by dividing their values by those obtained without the presentation of the tone. While the data from the two subjects indicate some different trends, they also demonstrate the common feature of a maximal decrement in ECAP amplitude at a relative phase of approximately 180 degrees. Note that the magnitude of the greatest decrement in response amplitudes is about 20 to 30 percent, comparable to the magnitudes observed with the wideband acoustic stimuli. The data from subject H75 suggest that the addition of the tone stimulus results in a phase-dependent attenuation of ECAP amplitude. The data of subject H67, however, suggests that phase dependent attenuation and enhancement occur. At this point of our investigation, we would caution against the interpretation of the presence of an enhancement mechanism. The normalized ECAP values of Figure 6 that are greater than unity are not observed consistently across the two subjects. Furthermore, the apparent

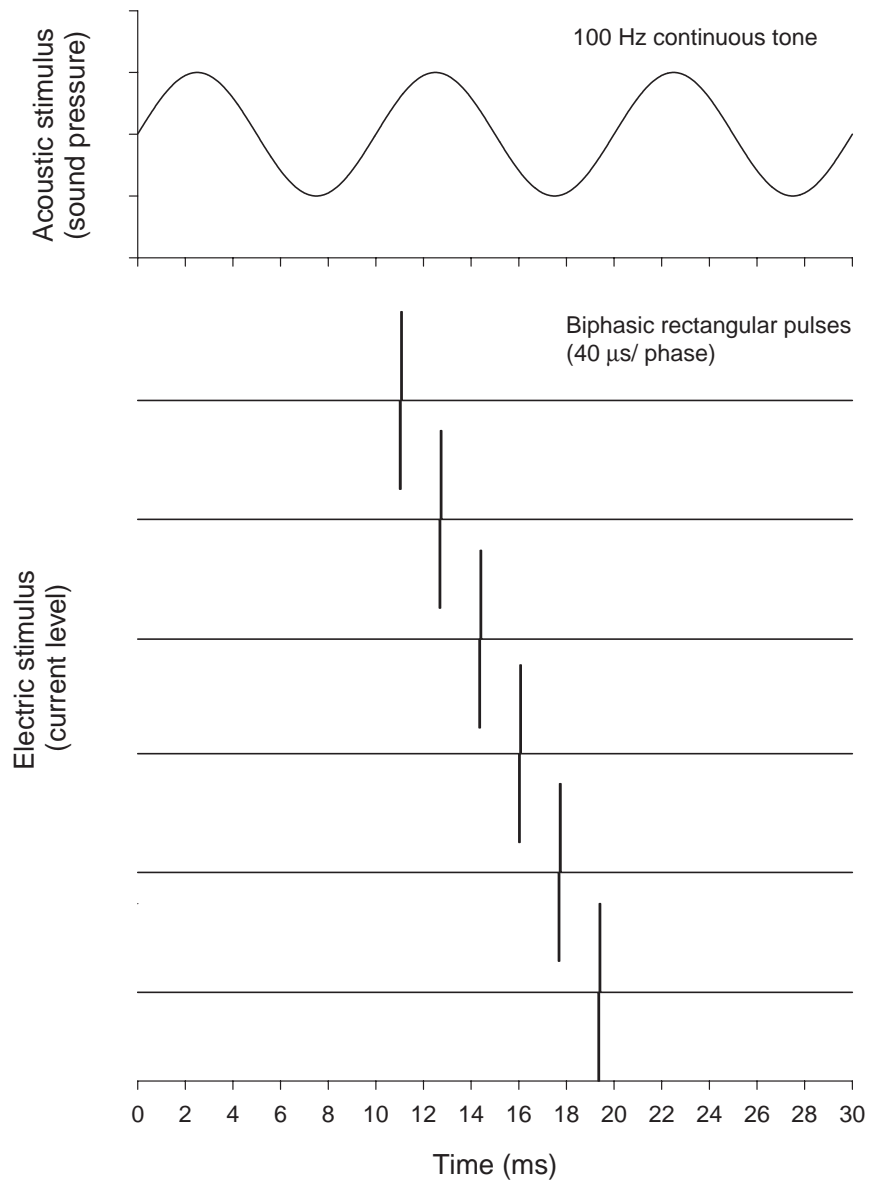


Figure 4: Schematized representation of the stimuli used to investigate interactions between an acoustic 100 Hz sinusoid and a single biphasic current pulse. The 100 Hz tone was presented continuously and one of six different electric stimuli was presented to obtain the electrically evoked response. Shown are the six different electric stimuli used to evoke the ECAP responses to evaluate relative phase effects. The six stimuli varied only by their phase relative to the sinusoid (in 60 degree increments).

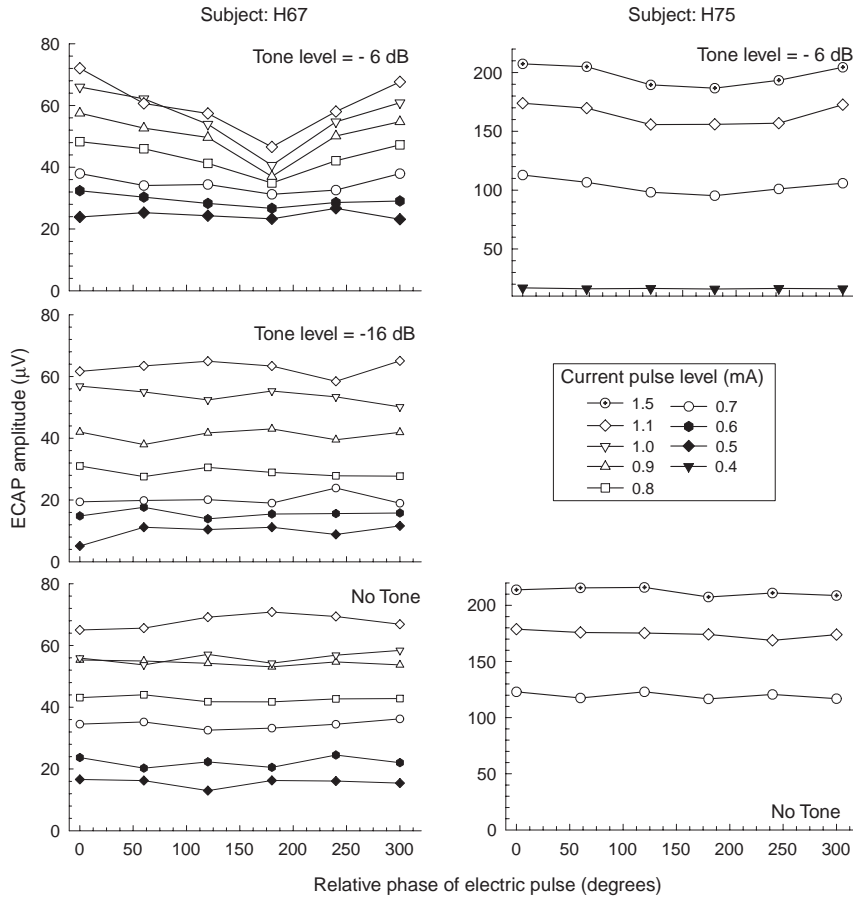


Figure 5: Results of the acoustic tone and electric pulse interaction studies conducted in two guinea pig preparations. ECAP amplitudes are plotted as a function of the relative phase of the electric stimulus pulse, with the pulse level shown as a parameter. The pulse stimulus levels were chosen to span the dynamic range of the ECAP amplitude-level function. The tone levels labeled as "- 6 dB" corresponded to a stimulus level of 85 to 95 dB SPL. Tone-and-pulse interactions are observed only at that highest level of acoustic stimulus. The data obtained under the "No Tone" condition (bottom graphs) were used to normalize the data depicted in Figure 6.

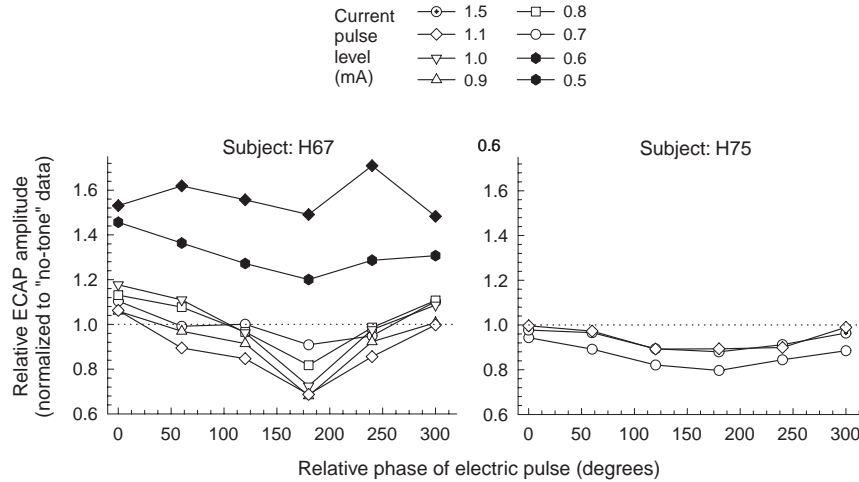


Figure 6: Data of the top two graphs of Figure 5, normalized to the "No Tone" data to illustrate the relative effect of the 100 Hz acoustic tone on the ECAP response. The dotted horizontal line indicates the values that would be obtained if no acoustic - electric interactions were observed.

amplitude enhancements observed in the data of H67 at low current stimulus levels (filled symbols) may simply be an artifact of relatively noisy measures typically obtained at low stimulus levels. Finally, time-dependent shifts in the amplitude level sometimes occur in our animal preparations over the course of data collection and may contribute to the apparent "enhancement". Future experiments will explore these issues by obtaining repeated measures over time and accounting for any drifts in evoked measures over time.

6 Discussion

The data presented in this report again reinforce earlier findings that the presence of viable hair cells can influence the response patterns of the auditory nerve as determined by gross-potential measures. The trends observed in the scatter plots of Figure 1 support our hypothesis that hair cells may provide an enhanced threshold response. Note that threshold improvements were only noted when a relatively low threshold response criterion (i.e., an ECAP amplitude 10 percent of maximum) was used; an enhanced response was not observed using the higher response criterion. These findings are consistent with predictions obtained with a version of our computational

stochastic neuronal model that incorporates a synaptic noise source (these model studies are ongoing and will be the subject of a future report). Other work with computational models (Rubinstein et al., 2000) suggest that the presence of viable hair cells results in a more stochastic pattern of neural responses to electrical stimuli that not only enhances threshold responses, but improves the representation of temporal details of the electric stimulus.

Our finding of altered ECAP response properties in subjects with intact hair cells led us to explore the next logical step, that is, the effect of externally applied acoustic stimuli on the electrically evoked response. New findings obtained in this quarter include our preliminary measures using both wideband noise and tonal acoustic stimuli. The addition of wideband noise resulted in a reduction in ECAP amplitudes from all animal preparations studied to date. The pattern of this interaction is interesting in that it occurs over a wide range of acoustic (noise) levels as well as wide range of electric stimulus levels (as demonstrated in Figure 3). Although we have failed to observe any enhancements in the evoked responses with exogenous noise, it may be the case that our measures, based upon ECAP amplitude, may not be the most sensitive indicators of any relatively subtle enhancements that could occur. Additional studies conducted at the level of the single fiber would provide additional insight into this issue. We should also note that we have obtained some measures of the effects of wideband acoustic noise using the electrically evoked auditory brainstem response (EABR). Trends using this metric show similar results as those shown here in Figures 2 and 3; however, the effects are more pronounced (i.e., larger relative decrements in amplitude are observed with the EABR measure than with the ECAP measure). We attribute this larger effect in the EABR measures to the fact that we measure the most sensitive component of the guinea pigs EABR - wave 3 - which is a more centrally generated potential subject to additional stages of synaptic masking.

Our findings obtained with the use of tonal acoustic stimuli support our original hypothesis that interactions will be phase-sensitive. As noted earlier, additional measures are needed to ascertain whether or not our 100 Hz tonal stimuli result in both enhanced and attenuated responses or simply just attenuated responses. Some of our acute preparations are subject to time-related effects that can alter the amplitude of the evoked response. In future experiments, we will obtain repeated measures (in an A-B-A format) in order to both characterize and correct any drift in our amplitude measures

that may occur over time.

The use of tonal acoustic stimuli provide additional insight into the mechanism of the acoustic and electric interactions and comparisons of data obtained with tonal stimuli and wideband acoustic may be instructive. Since we used a continuous 100 Hz tonal stimulus, we assume that the observed interactions are due to the phase sensitivity of hair cells to a mechanical disturbance propagated as a traveling wave. Due to the phase response characteristics of the basilar membrane as a function of longitudinal position (Rhode, 1971), only the set of fibers innervating the base of the cochlea can respond in a synchronous and in-phase fashion. Since the magnitude of the acoustic - electric interaction observed with the 100 Hz tone is comparable to that observed with the wideband noise stimulus, we assume that a comparable subset of fibers are involved with both types of acoustic stimuli. In the case of interaction with the 100 Hz tone, we speculate that the locus of interaction occurs within the basal portion of the cochlea. Unlike the results obtained with wideband noise, we noted interaction with the 100 Hz tone only at the highest level of the acoustic stimulus. This result may be consistent with the fact that the basal fibers of the intact cochlea respond best to high-frequency stimuli and will only respond to low frequencies (i.e., 100 Hz) if relatively high sound pressure levels are employed. Given that assumption, it is not surprising that phase-specific responses were only obtained with the use of acoustic stimuli presented at the highest level.

7 Plans for the next quarter

In the sixth quarter, we plan the following activities:

- We will conduct additional experiments examining the effects of exogenous acoustic noise on the electrically evoked compound action potential.
- We will continue to collect data examining the phase relationship between sinusoidal acoustic stimuli and pulsatile electric stimuli.
- We will expand our investigation of exogenous acoustic noise on the ECAP by using bandlimited noise stimuli. Through the use of low-pass-filtered noise (and systematically varying the cut-off frequency) we will attempt to collect data that may be effective in identifying the

loci of the acoustic-electric interactions along the longitudinal dimension of the cochlea.

- We will proceed with computational simulations of noise and sinusoidally modulated synaptic activity to complement the investigations described in this QPR.

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