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

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Contents

1 Introduction

Patients who have significant residual hearing are presently receiving cochlear implants and that it is likely that patients with more hearing will be become implant candidates in the future. Electrical stimulation in ears with functional hair cells brings up the possibility of interactions between hair-cell mediated and direct stimulation of auditory nerve fibers as well as the possibility of acoustic and electrical interactions. To address these issues, we have proposed a sequence of experiments designed to first characterize the response patterns and interactions and then to explore techniques to best exploit them. These experiments employ both physiological measures and computational modeling of the effects of hair cells on the response to electrical stimulation. The initial experiments use measures of the electrically evoked compound action potential (EAP) as well as measures of single fiber activity. In the course of this contract, a direct comparison will be made of the response properties with and without functioning hair cells as well as comparisons of the responses to electrical stimulation with and without acoustic stimulation.

2 Summary of activities in this quarter

In our third quarter (1 January - 31 March, 2000), the following activities related to this contract were completed:

1. We attended and presented at the Midwinter Meeting of the Association for Research in Otolaryngology in St. Petersburg Beach Florida.
2. Presentations of work under this contract were included in invited talks at House Ear Institute and at University of Kentucky.
3. Experimental EAP data were collected on five guinea pigs including those data that make up the main section of this report.
4. We have been developing a new laboratory control system using Labview software from National Instruments.

5. As part of the relocation of the Otolaryngology department that occurred this quarter, we have moved our staff offices to a new location within the hospital complex. This move has relieved the overcrowded conditions within our lab space and facilitated the arrival of additional research staff to support efforts related to our Neural Prosthesis Program contracts.

3 Comparison of EAP before and after deafening

3.1 Introduction

The data presented in this quarterly progress report represent measurements in a series of seven guinea pigs. In these experiments we measured the EAP, comparing the responses of ears with functional hair cells (based on acoustic sensitivity) to the responses from aminoglycoside-deafened ears without functional hair cells. We have designed the experiments so that the same electrode configurations (both stimulation and recording) are used to conduct the measurements in hearing and deaf ears. The comparison provides a means of assessing the effects of functional hair cells on the response of the auditory nerve to electrical stimulation.

3.2 Experimental methods

3.2.1 Surgical procedures

Details of general experimental techniques have been outlined in prior QPRs and publications (Miller et al., 1998, 1999a).

The animal's head is immobilized by a custom-designed fixture. The pinna is excised to provide consistent coupling of the earphone onto the external auditory meatus. To access the middle ear and auditory nerve, an incision (from midline, through bregma, and then laterally toward the jugular process) is made to expose the left posterior aspect of the skull. A small defect is made in the bulla to expose the base of the cochlea.

A defect is then be made in the skull to expose the auditory nerve using a posterior fossa approach. After surgical exposure, the head position is locked to allow placement of the earphone and stimulus and recording electrodes. A Beyer DT-48 earphone coupled through a speculum is placed into the ear canal. A Pt/Ir ball electrode with a rigid, insulated shank is used for EAP recording. It is placed in contact with the auditory nerve with a micromanipulator and connected to the positive input of a differential amplifier.

After initial acoustic measures, a small fistula is drilled in the bone adjacent to the round window to place an electrode into the scala tympani of the basal turn of the cochlea. A stimulating ball electrode is advanced through that opening such that the ball is inside the scala but not directly touching the spiral lamina or membranous structures. This approach is used to minimize trauma and to assure a stable stimulating conditions throughout the experiment.

3.2.2 Deafening procedure

After the stimulating and recording electrodes have been placed, the acoustic response to 100-us click stimuli is measured and a threshold determined. We then proceed with the measurements of responses to electrical stimulation of the cochlea. After the set of measurements is completed, typically taking approximately three hours, the ear is deafened using a combination of kanamycin and ethacrynic acid to permanently inhibit hair cell function (West et al., 1973; Brummett et al., 1979; Xu et al., 1993). An intramuscular injection of kanamycin is administered, followed by intravenous injection of ethacrynic acid. The animal's hearing sensitivity is then assessed to assure that there is no acoustic response. Finally, responses to electrical stimulation using the same stimuli as before deafening are measured. This procedure allows for comparisons of response properties with and without functional hair cells using several stimulus paradigms.

We have measured responses to monophasic and biphasic pulses as a function of level, responses to constant amplitude pulses and responses to amplitude modulated pulse trains under both the hearing and deafened conditions. The growth functions and responses to constant amplitude pulse

trains are reported here.

3.3 Results

3.3.1 Single-pulse growth functions

We presented data from a single subject in QPR1 (Abbas et al., 1999) demonstrating changes in both the growth of response and responses to pulse trains with the loss of hair-cell function. This QPR presents data collected from more subjects using the same methods and provides a more detailed analysis of the results.

Figure 1 illustrates the growth functions for the subject initially described in QPR1. Response amplitudes are illustrated for measures taken before and after the deafening procedure. In each case, the responses show a monotonic growth, in some cases reach a saturation amplitude at high stimulus levels. Several trends are evident in the data for both anodic and cathodic stimuli. Growth functions obtained before deafening tend to have relatively lower thresholds and shallower slopes.

The graphs in Figure 2 illustrate growth functions for 6 subjects for whom we have data both before and after deafening. In these cases we have plotted only the responses to cathodic stimulation since that condition is generally less contaminated by stimulus artifact. While the differences with deafening are not always as clearcut as those seen with subject H34, there is a trend for responses before deafening to have lower threshold and steeper growth. To demonstrate these effects more clearly, we defined the criterion EAP amplitude for threshold as either 10% of the saturation amplitude or 50% of the saturation amplitude. Slope was calculated across adjacent points in the growth function and the peak slope (in mV/mA) is calculated for each stimulus condition. In Figure 3, we show scatter plots for each of these measures, plotting the measure before deafening (hearing) on the ordinate and after deafening (deaf) on the abscissa for each subject. The trend for higher thresholds in deaf ears is evident for low criteria (10% of saturation) but not at the higher criterion level (50% of saturation). This difference is consistent with the trend in Figure 3C showing steeper slope in deaf ears.

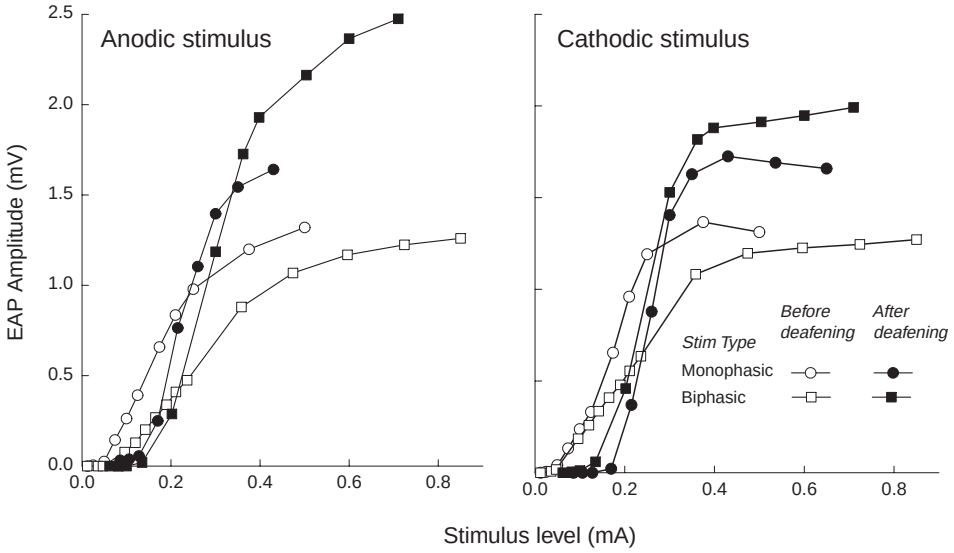

Figure 1: Comparisons of EAP growth functions before and after deafening. Response amplitude is measured from N1 to P2 peaks. Responses to monophasic and biphasic pulses are shown for anodic (first) and cathodic (first) stimulation.

3.3.2 Response to pulse trains

Stimulation through an actual cochlear implant typically involves a complex pattern of stimulation, with multiple pulse trains presented to multiple electrodes. The sequence of responses to each pulse in a train becomes an important consideration in that the resulting sequence of response amplitudes is often the basis of stimulus encoding.

In previous work with pulse train stimuli we have observed that the response patterns can be highly dependent on stimulus level and response amplitude. Since we were concerned with the possibility of changes in the preparation over time (see Miller et al., 2000b), we chose to limit our comparisons of response to pulse trains to five animals which had similar response amplitudes before and after aminoglycoside treatment. In that way we could be sure that any differences observed were not due to changes in overall sensitivity or responsiveness.

Figure 4 plots representative EAP response measured in response to a series of pulses presented in a train at a rate of 1000/pps. The responses plotted for the deaf animals are typical of data that we have previously obtained from acutely deafened animals (Matsuoka et al., 1998). Responses are characterized by an alternating pattern that tends to be evident within the first 20-30 ms following stimulus onset; in some cases this alternating pattern persists throughout the entire pulse train. The degree of alternation is highly dependent on the level of stimulation, as is evident in Figure 4. In addition, there tends to be a significant overall decrease in the response amplitude over the time course of the pulse train; the response to the initial pulse is largest, the average amplitude decreases over the time and eventually asymptotes. Without implying a specific mechanism for this decrease we will refer to this behavior as adaptation, signifying a decrease in the response over the time course of the pulse train.

Both the degree of alternation and the time course of adaptation is dependent on the hearing status of the ear as is evident comparing Figures 4A and 4B. There is a tendency for larger alternation patterns after deafening as well as a faster time course of adaptation. It is apparent from the exemplar data in Figure 4 that the EAP response pattern to pulse trains can be characterized by multiple indices: (1) the magnitude of response alter-

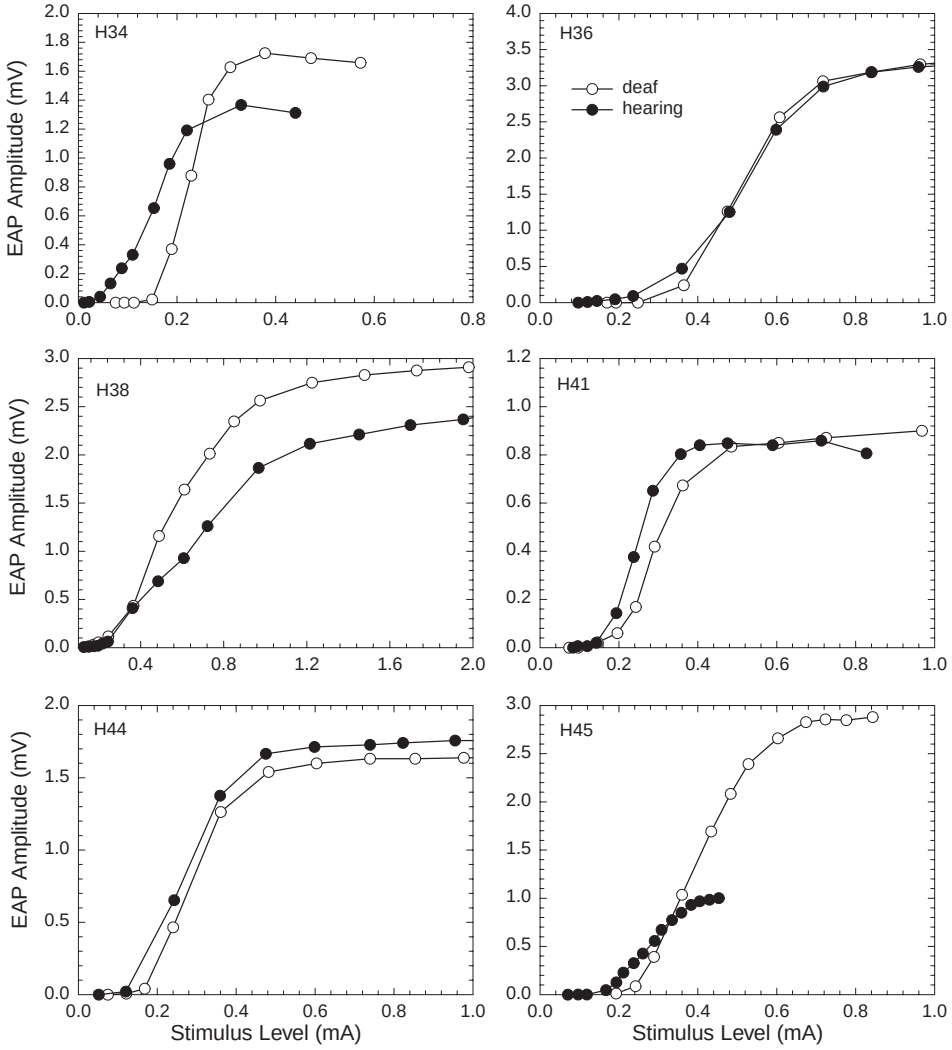

Figure 2: EAP amplitude growth functions in response to monophasic, cathodic pulses 40 μs in duration. Each graph shows data from a different animal, comparing the response growth before (hearing) and after (deafened) treatment.

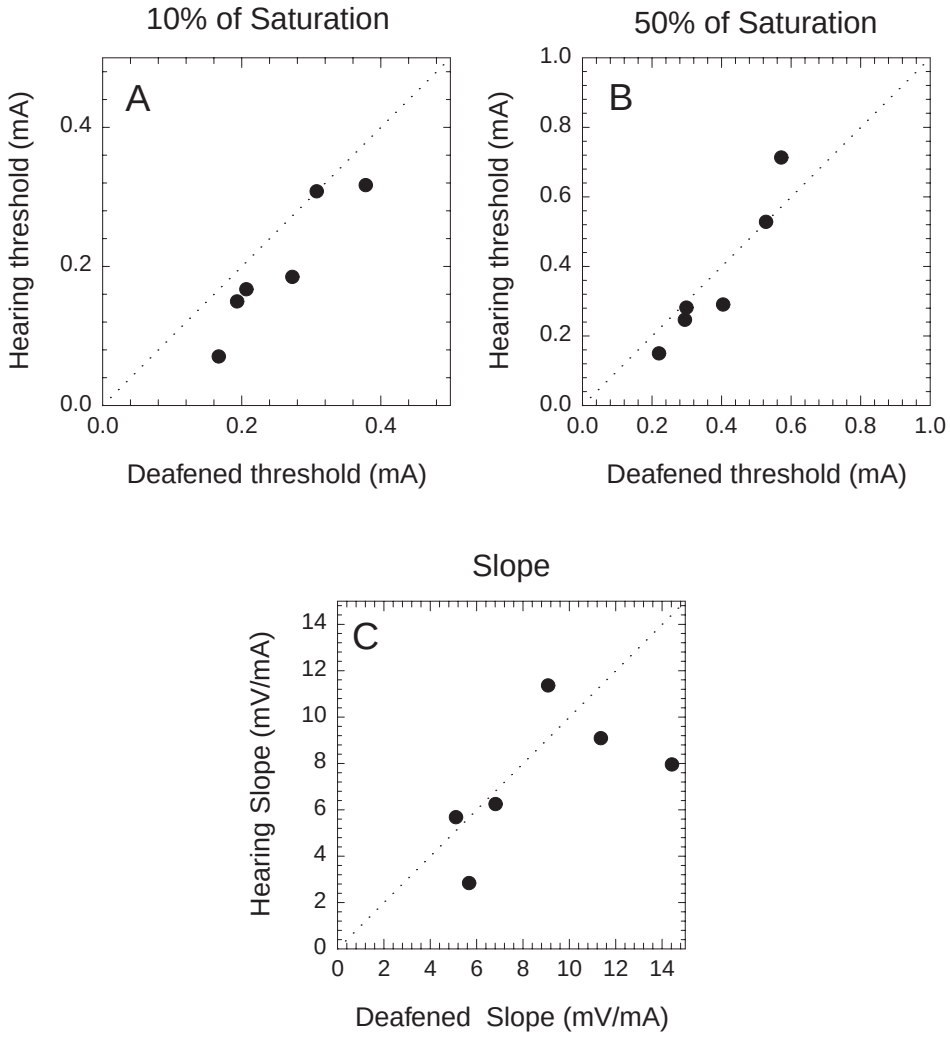

Figure 3: Scatter plots plotting data from six guinea pig ears before (hearing) and after (deafened) treatment. (A) plots threshold measured for a criterion amplitude of 10% of saturation amplitude. (B) plots threshold measured for a criterion amplitude of 50% of saturation amplitude. (C) plots maximum slope of EAP growth function.

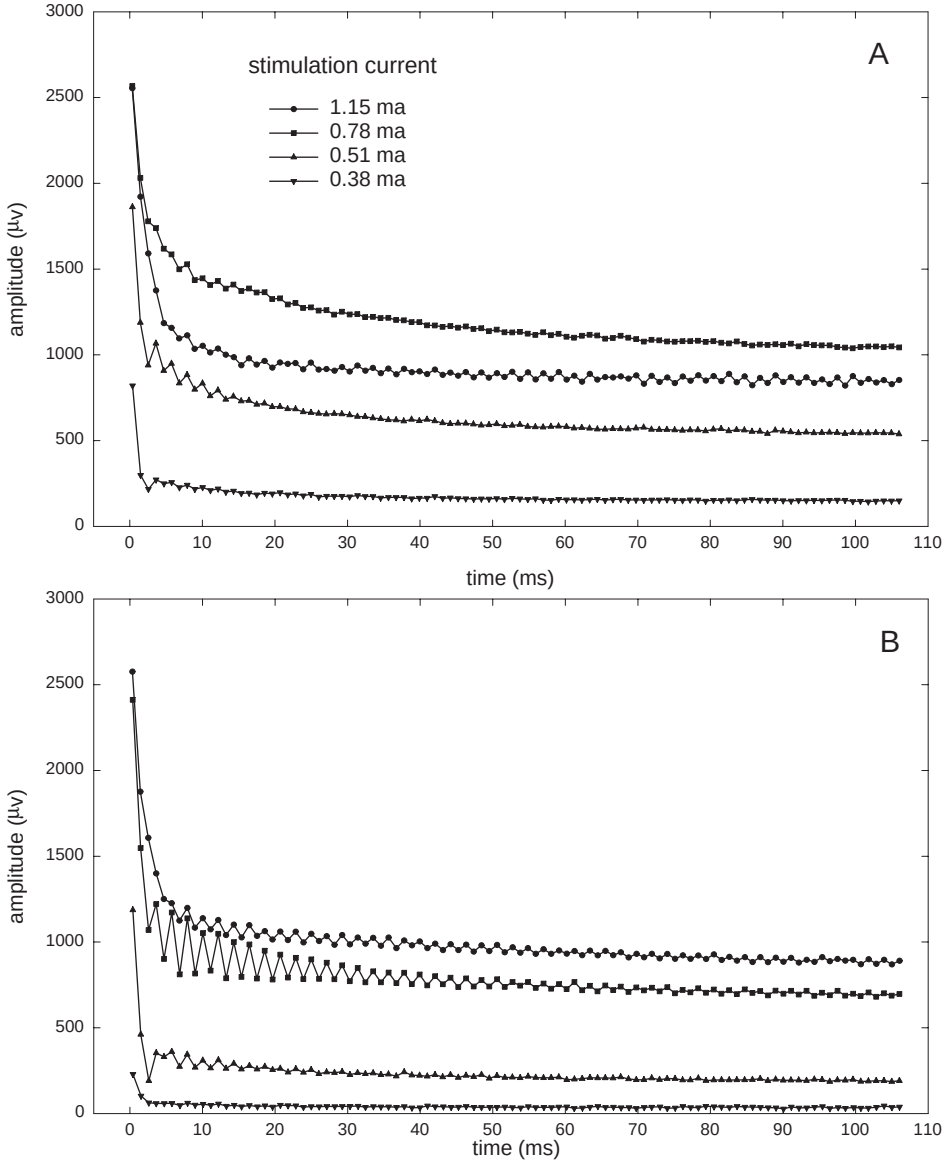

Figure 4: Response amplitudes to each successive pulse in a pulse train presented at a rate of 1000 pulses/s. Stimulus level is the parameter as indicated in the legend. Data are shown from the same animal both before (A) and after deafening (B). Response amplitude over time shows both an overall decrease as well as an alternation at some stimulus levels.

nation, (2) the degree of adaptation over the initial portion of the train and (3) the degree of final or asymptotic adaptation. To quantify these inidices we have first, applied a smoothing filter (3-point boxcar) to the response amplitude over time in order to eliminate the alternation. The smoothed functions, shown in Figure 5, illustrate the adaptation over the pulse train. By subtracting the smoothed functions from the original data in Figure 4, we can view the effects of alternation independent of the average decrease over time, i.e., adaptation. This result is shown in Figure 6. Finally, by normalizing the response amplitudes in each plot to the response to the first pulse in the train, we can eliminate effects of overall response amplitude.

From the plots in Figures 5 and 6 we have extracted appropriate indices to compare the characteristics before and after deafening. Processed data from five subjects for whom we have both hearing and deaf pulse train data are plotted in Figures 7-10. In each of the four figures, the response parameter is plotted as a function of stimulus level for both before (hearing) and after aminoglycoside treatment (deaf). Early adaptation (Figure 7) is defined as the averaged EAP amplitude over the 9-11 ms epoch relative to the response to the initial pulse. This value is used to compare the time course of the average amplitude decrease across conditions. Late adaptation (Figure 8) is defined as the EAP amplitude averaged over the 70-80 ms epoch relative to the response to the initial pulse. This value approximates the asymptotic values of response relative to the unadapted response amplitude. Indices of both the early and late adaptation are plotted for five subjects as a function of stimulus level in Figures 7 and 8. Early response alternation is defined as the average absolute difference between adjacent responses over the interval 10-20 ms after stimulus onset. Late response alternation is defined as average absolute difference between adjacent responses over the interval 70-80 ms after stimulus onset. In both cases alternation amplitude is normalized to the initial response amplitude and plotted in Figures 9 and 10.

As noted above, there are significant variations among subjects and across conditions for these parameters. The plots in Figures 7-10 also show significant variations in the response indices across stimulation level. Nevertheless, there are clear trends the data. We wished to summarize these trends with scatter plots similar to those used in Figure 3. To do this we chose a single value for each subject for each of the four indices. We chose the response using a stimulus level that elicited a response amplitude near

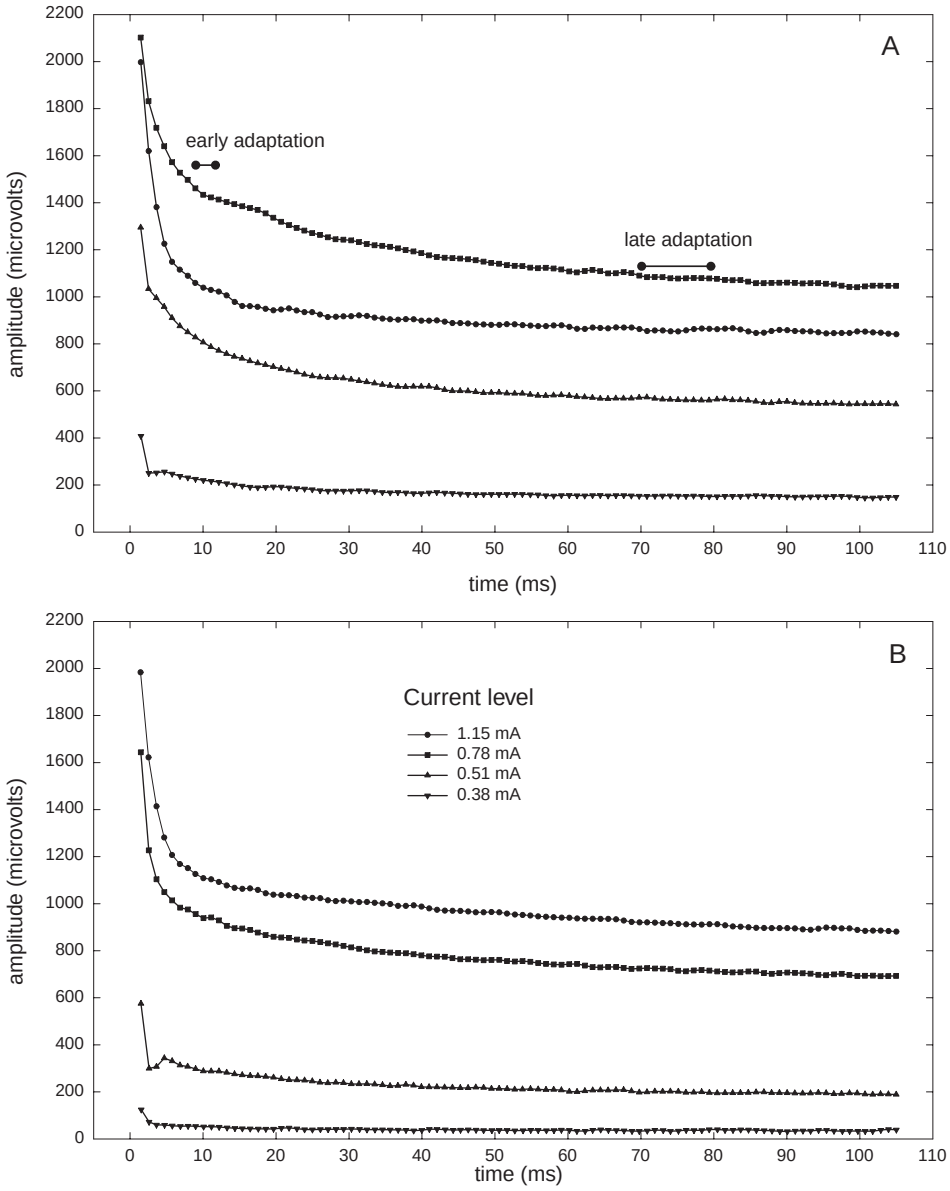

Figure 5: Response amplitudes to each successive pulse in a pulse train (as shown in Figure 4) have been passed through a smoothing filter (3-point weighted boxcar) in order to eliminate alternating response pattern. Data are shown from the same animal in Figure 4 before (A) and after deafening (B). Bars in part A indicate the time intervals over which early and late adaptation are evaluated in the normalized functions (see text).

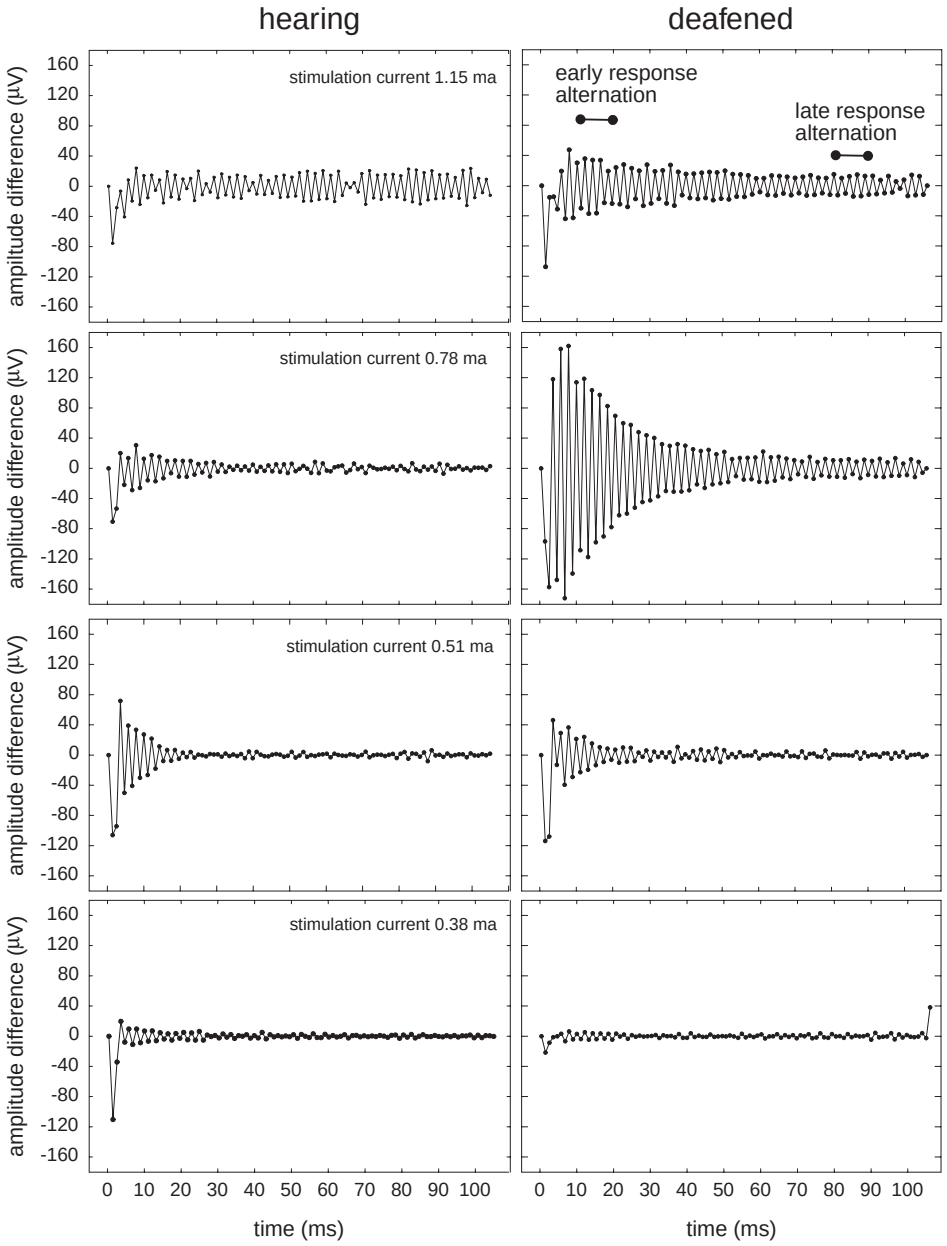

Figure 6: Each graph shows data derived from that in Figures 5 and 6. At each level the smoothed response amplitude (Fig. 5) is subtracted from the original response amplitude (Fig. 4) resulting in a series of plots showing the degree of alternation. Data are shown from the same animal both before (A) and after deafening (B). Bars in part A indicate the intervals over which early alternation and late alternation are evaluated (see text).

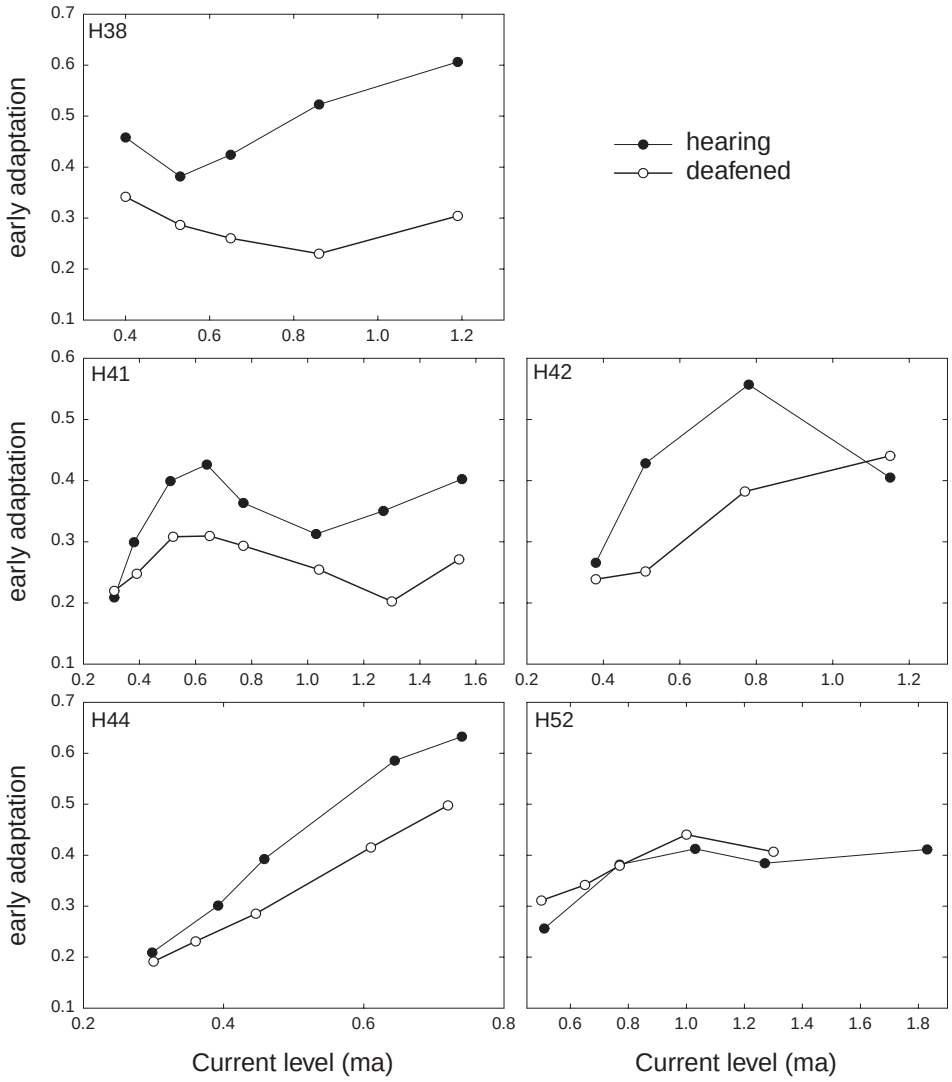

Figure 7: Each graph plots data early adaptation as a function of current level both before (hearing) and after (deafened) treatment. Data from five guinea pigs are shown as indicated on each graph.

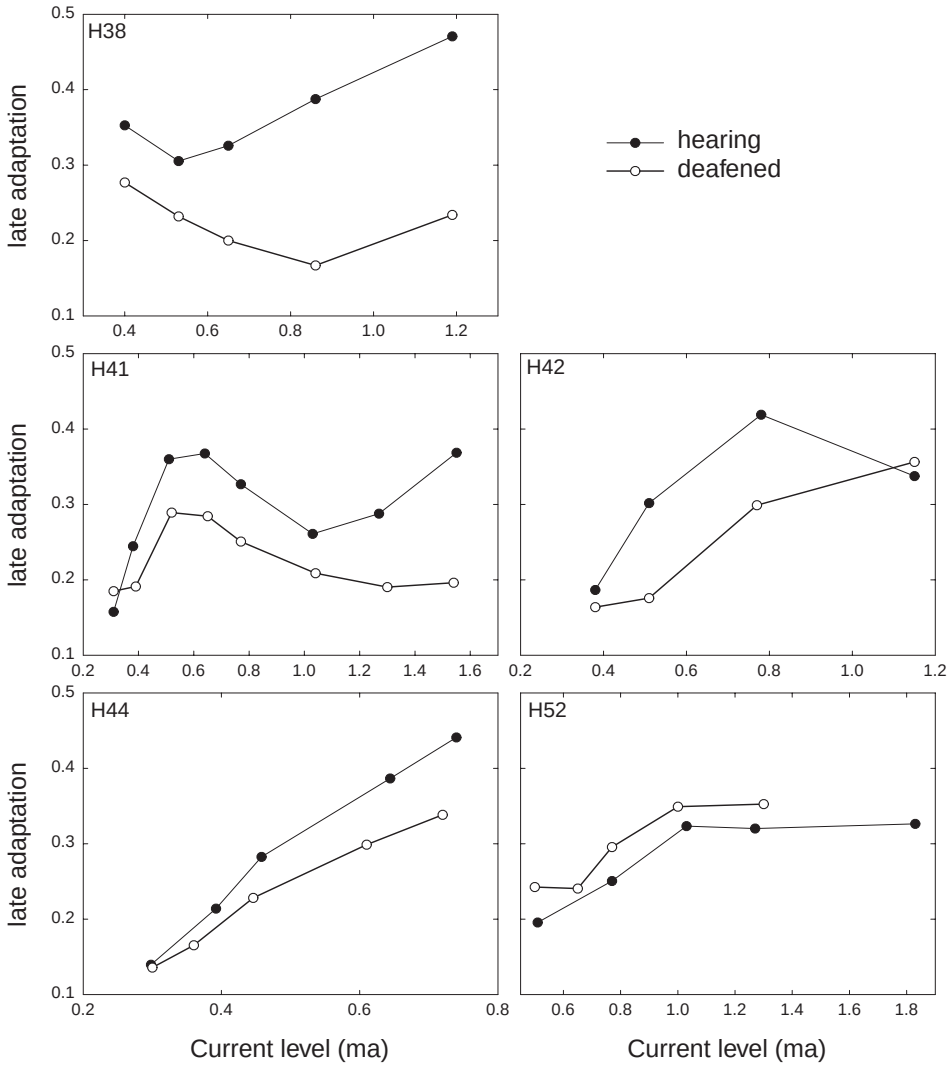

Figure 8: Each graph plots data late adaptation as a function of current level both before (hearing) and after (deafened) treatment. Data from five guinea pigs are shown as indicated on each graph.

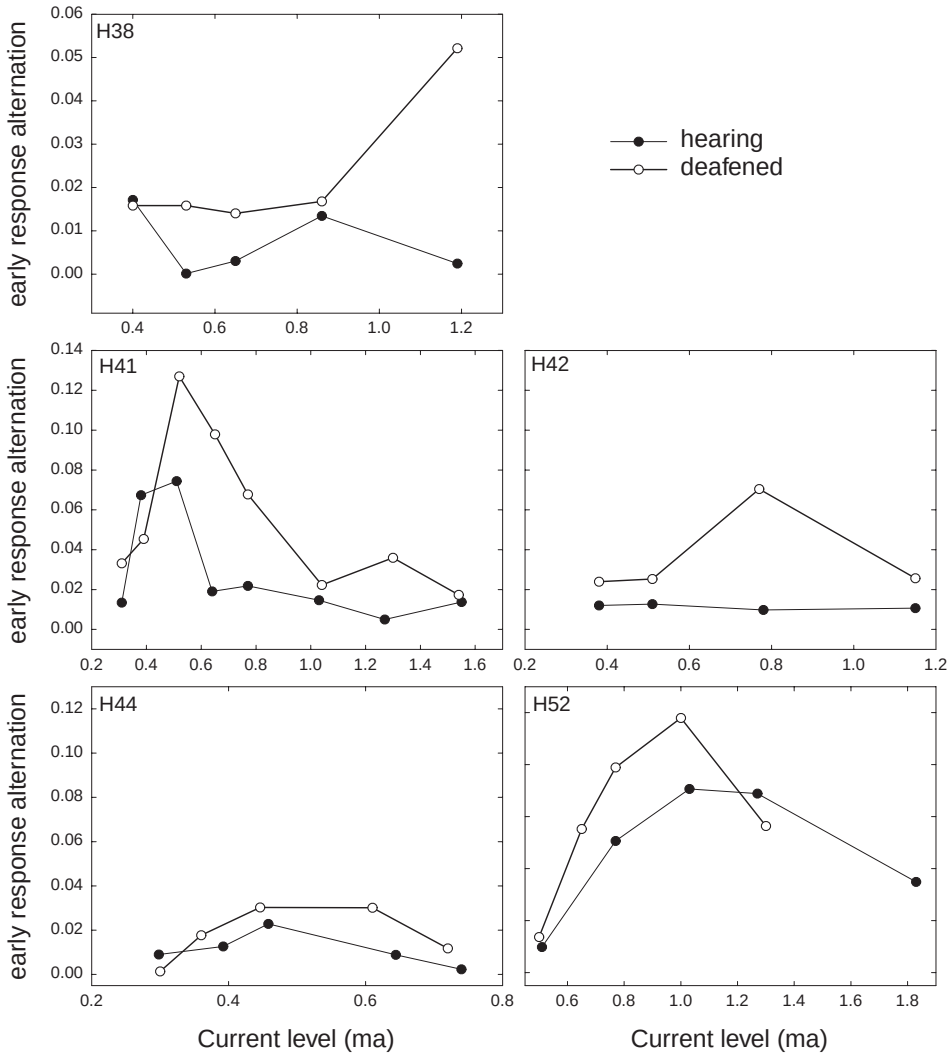

Figure 9: Each graph plots data early response alternation normalized to the initial response amplitude as a function of current level both before (hearing) and after (deafened) treatment. Data from five guinea pigs are shown as indicated on each graph.

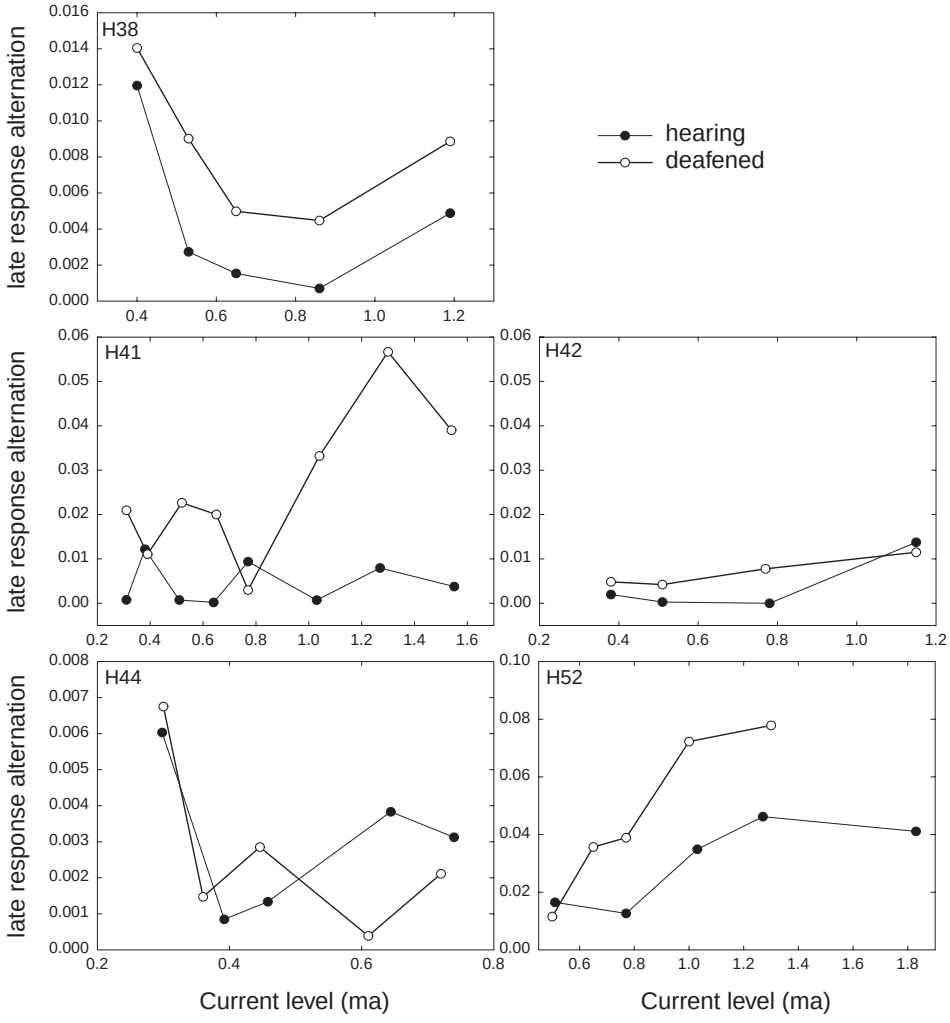

Figure 10: Each graph plots data late response alternation normalized to the initial response amplitude as a function of current level both before (hearing) and after (deafened) treatment. Data from five guinea pigs are shown as indicated on each graph.

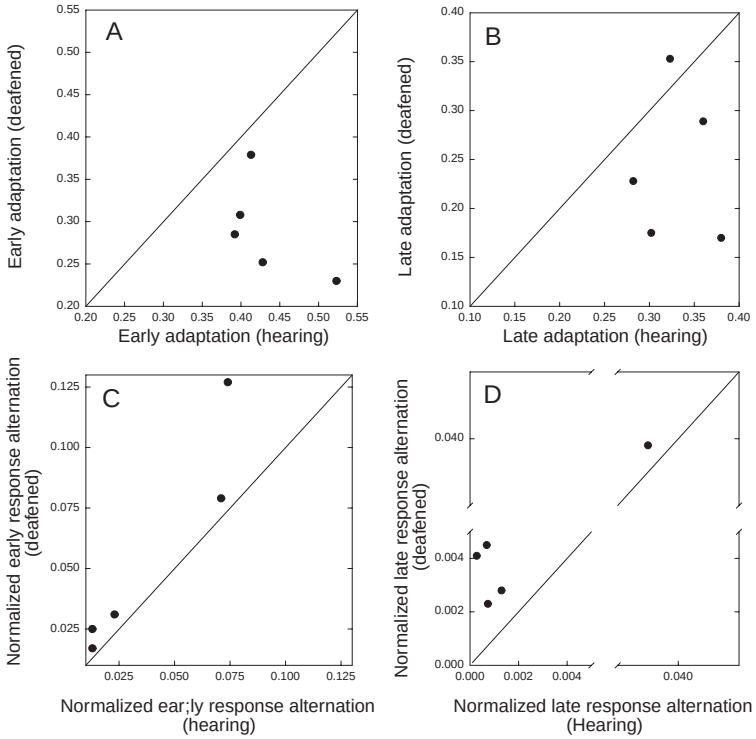

Figure 11: Scatter plots plotting data from the five guinea pig ears shown in figs. 7-10 before (hearing) and after (deafened) treatment. (A) plots early adaptation. (B) plots late adaptation. (C) plots early normalized response alternation. (D) plots late normalized response alternation.

50% of the dynamic range. Using this method, comparisons between hearing and deafened ears are not only at the same stimulus level but also are always at a moderate level for that ear. The results are plotted in Figure 11. Comparing hearing to deafened ears, normalized initial alternation tends to be smaller, normalized asymptotic amplitude tends to smaller, initial adaptation is larger (slower adaptation), and asymptotic adaptation is larger (less of a decrease over time).

4 Discussion

In this QPR we have presented both single-pulse and pulse-train response trends in subjects both before and after experimental deafening.

Data from single pulse growth functions have demonstrated a trend toward lower thresholds and shallower input-output slopes with functional hair cells. These trends are similar to that observed in single neuron modeling work reported in QPR2 (Rubinstein et al., 2000a). These trends are consistent with a hypothesis that the presence hair cells results in a more stochastic response pattern (decreasing threshold). Since the pattern is less deterministic, the population response at high levels is less synchronous and therefore lower in amplitude. In addition, if there is stochastic background activity at higher stimulus levels, each pulse will recruit fewer neurons and each neuron will tend to have a smaller action potential due to refractory effects (Miller et al., 2000a). The result would be a smaller EAP amplitude at higher levels with functional hair cells.

While we expect that changes in single fiber properties will affect the EAP response, we need to exercise some caution in simply drawing parallels. Changes in threshold of the most sensitive neurons may be expected to change the threshold of the EAP. Nevertheless, our previous work with deafened ears has demonstrated that the growth of the EAP is likely to be much more influenced by threshold distribution of neurons in response to the electrical stimulus rather than the input-output functions of the individual neurons (Miller et al. 1999b). Changes in single-fiber RS had relatively little effect on EAP growth characteristics. We suggest then, based on the results with EAP growth, that while the presence of hair cells may affect threshold and growth of individual neurons, they may also affect the recruitment pattern across the population. Such changes in the recruitment pattern could be the result of a number of factors, including changes in stimulability of hair cells, dendrites, and/or axons, in addition to possible changes in the current pathways from the stimulating electrodes.

In our previous work measuring the responses to pulse trains in deafened ears, we have systematically examined the effects of stimulus characteristics and interpulse interval on the patterns of responses evoked by pulse trains (Matsuoka et al., 1998). The response amplitudes demonstrated refractory

properties in that the response to the second pulse was smaller than that to the first pulse. In addition, the response to successive pulses showed an alternating pattern which is highly dependent upon IPI, with the greatest degree occurring at short (1 ms) IPIs. We interpret this alternating pattern to be attributable to refractory recovery and stochastic effects of the stimulated neurons. The present data in deafened ears have demonstrated similar alternation and adaptive patterns, although in this report we have limited our attention to pulse trains with IPI of 1 ms since we have typically observed the greatest alternation patterns in that range of IPI.

Figures 7-11 illustrate the trends in both alternation pattern and adaptive properties observed with and without hair cell function. It is interesting to speculate on the possible causes for these observed differences. Wilson et al. (1994), based on modeling work, have suggested that the alternation pattern may be dependent on the degree of noise inherent in the neural membrane. We hypothesize that hair cells may contribute to the response properties in a number of ways. The synaptic activity producing spontaneous activity can certainly affect the stochastic properties of the stimulated neurons. The presence of an electrophonic response or other responses to electrical stimulation mediated through the hair cells could be expected to have significantly different stochastic response patterns. Based on comparisons to responses with acoustic stimuli (Smith et al., 1977; Smith and Brachman, 1982), we may expect that the adaptive properties of the response to electrical pulse trains may be affected by the presence of hair cells. Our observations are consistent with such hypothesized results of functional hair cells, i.e., a more stochastic pattern and greater cumulative adaptation effects.

These results from permanently deafened animals, while still preliminary, suggest that hair cells may significantly affect both the growth and temporal properties of the response to electrical stimulation. We plan to further investigate these issues in a number of ways. First, having identified specific stimulus conditions that demonstrate differences, we will perform experiments using furosemide deafening (Sewell, 1984) under similar stimulus conditions. These will allow us to confirm these trends using a different mechanism of disabling hair cell activity. In addition, the reversible nature of furosemide treatment will allow us to confirm recovery from treatment, which is not possible with the experimental procedure described here. In addition, we will continue our efforts described in QPR2 (Rubinstein et al.,

2000), to model synaptic activity and the effects on electrical stimulation, particularly for the types of stimulus paradigms described here.

5 Plans for the next quarter

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

- Perform additional EAP experiments to trends reported here, examining the same trends using furosemide deafening.
- Begin experiments investigating the interactions of acoustic and electric stimulation.
- Develop model simulations related to the trends observed in this report.
- Begin testing and using Labview-based data acquisition system and refine its operation

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