Tenth Quarterly Progress Report
N01-DC-9-2106

Effects of Remaining Hair Cells on Cochlear Implant Function

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1 Introduction

In this contract, we are conducting physiological and computational model experiments to assess the effects that functional hair cells have on the auditory nerve's response to electrical stimulation. This work is relevant to a widening pool of cochlear implant candidates as audiological criteria (e.g., pure-tone thresholds) are becoming more relaxed and patients with residual hearing are being implanted. Intact hair cells may interact with or modify electrical stimuli in several ways. Acoustically evoked neural activity may interact or compete with electrically evoked activity. It is also possible that the very presence of viable hair cells - without any exogenous acoustic stimuli - can modify electrically evoked neural responses. For example, electrical stimuli may depolarize hair cell membranes and initiate the release of neurotransmitter, resulting in nerve-fiber activation. It is also possible that the spontaneous 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 non-functional hair cells. Comparisons will then be performed to assess the effect of functional hair cells on the transduction of electrical stimuli delivered by intracochlear electrodes.

2 Summary of activities in this quarter

In our tenth quarter (1 October through 31 December, 2001), the following activities related to this contract were completed:

1. We attended the 2001 NPP Workshop in Bethesda in October 2001 and reported on results from this contract research.

2. We have begun ototoxic antibiotic treatments of cats to effect partial hearing losses in these animals. These subjects will then be used as a more realistic model of the pathology encountered in candidate implant patients. Four animals have been treated and recordings have been made on two of those to date.

3. We have continued experimental recordings examining the effects of furosemide injections on the response of auditory nerve fibers to elec-

trical stimulation. Preliminary results from that work are summarized in this QPR

4. The upgrades in our software used for computer simulations that is reported on in the Quarterly Progress Report for Contract N01-DC-9-2107 is also relevant to the modeling work being done under this contract. With the upgrades we have benchmarked the system at over 6 GFlops for single precision calculations. Using the new VAST fortran and c-compilers, and MacMPI we expect to be able to both automatically vectorize and parallelize our simulation codes permitting computational speed to scale with the number of Macs in our cluster.

3 Auditory Response to Electric Pulse Trains Before and After Furosemide Treatment

3.1 Introduction

Previous work under this contract evaluated responses before and after deafening using a combination of kanamycin and ethacrynic acid to permanently inhibit hair cell function (QPRs 1 and 3). Results presented previously demonstrated changes in response growth to single pulses as a function of stimulus level as well as changes in the response properties to electric pulse trains with loss of hair cells. The results were basically consistent with a hypothesis that the presence of hair cells is a source of background noise that results in more stochastic response properties. The responses to pulse trains demonstrated a decrease in the alternation response pattern with hair cells as well as a less adaptation over time.

This report describes initial measures using furosemide, an ototoxic diuretic, injected intravenously. This agent has been shown to have a rapid and reversible effect on the inner ear, which causes temporal hearing loss (Pike et al., 1980, Sewell, 1984a,b). These experiments afford the opportunity to disable hair cells but to also evaluate the reversible nature of the observed effects.

3.2 Methods

Guinea pigs were used as experimental subjects in these experiments. A monopolar stimulating electrode was inserted into the scala tympani in the basal turn of cochlea through cochleostomy, a recording electrode was placed near the auditory nerve. Furosemide (50 to 100 kg/mg) was delivered through the external jugular vein. One round or several rounds of injection were given until the click-evoked CAP was no longer evident. ECAP was sampled before injection of furosemide, and at different intervals after injection to assess changes in the response to pulse trains. CAP was also monitored periodically after injection to monitor recovery of hearing status.

Stimuli were biphasic pulse trains, 40 microseconds/phase, IPI=0.92 ms resulting in a presentation rate of 1000 pulses/s. The duration of the train was 100 ms (100 pulses/train). Stimulus level was determined by the growth function of ECAP to the single pulse. Three stimulus levels were chosen in order to elicit a response of 90-100%, 60-80% and 40-60% of maximum ECAP amplitude. The same three levels were repeated before and after furosemide injection.

Three parameters were used to characterize the response to the pulse train: amplitude to the first pulse, normalized alternation amplitude, and normalized adaptation amplitude. The amplitude in response to each pulse in the train was measured from peak N1 to P2. To compare responses over different stimulus levels and conditions, the response amplitude to each successive pulse in a train was normalized to the response to the first pulse. Normalized response alternation was calculated as the average amplitude difference to adjacent pulses, from the 10th to 19th pulses (or over the interval 10 to 19 ms after onset of pulse train). The average difference was then normalized to the amplitude in response to the first pulse in the train. Adaptation amplitude was calculated as the average amplitude of the response to the 80th to 99th pulses in the train (or over 80-99 ms after onset of pulse train) relative to the amplitude in response to the first pulse.

3.3 Results

Data from 5 animals deafened with furosemide (M07, M09, H91, H92 and H94) are presented. An example of the response to pulse trains is shown in Figure 1. The data are plotted before furosemide treatment (hearing), after

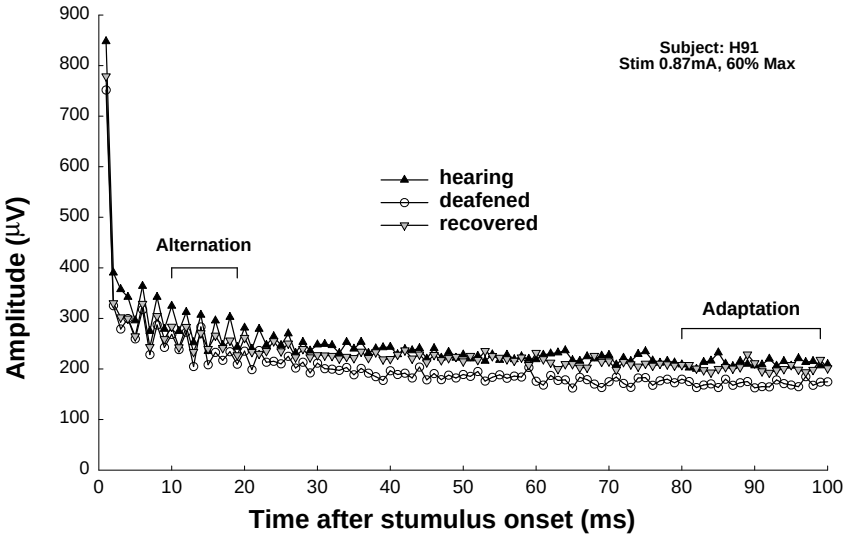

Figure 1: Response amplitude of ECAP to each successive pulse in a train is plotted as a function of time after stimulus onset. Parameter in each case is the hearing status: before treatment with furosemide (hearing), after treatment with furosemide (deafened) and after CAP recovery (recovered). Alternation is calculated on the basis of pulses 10-19, normalized to the amplitude in response to the 1st pulse. Adaptation is calculated on the basis of pulses 80-99 normalized to the response to the 1st pulse. Animal code and stimulus level are indicated on the figure.

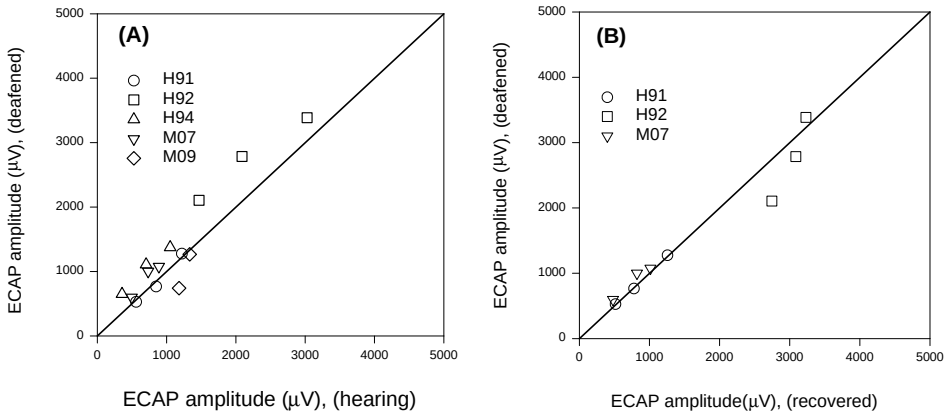

Figure 2: Scatter plots show response amplitude to the first pulse in the deafened vs hearing condition (A) and in the deafened vs recovered condition (B). Data from each animal are displayed with different symbols.

treatment (deafened) and after recovery of CAP amplitudes (recovered). In this case there was relatively little difference in the alternation pattern before and after furosemide treatment. There was, however, a change in the asymptotic amplitude, assessed as the degree of adaptation, normalized to the response amplitude to the first pulse. In general the changes observed with furosemide treatment were small compared to those observed with permanent deafening procedure used in previous experiments (Abbas et al., 2001).

Several general trends were assessed among these three conditions in the data from the five animals. Results from each parameter (response amplitude, alternation and adaptation) are plotted in Figures 2-4. The amplitude of ECAP to the 1st pulse in a train tends to increase slightly after treatment (deafened vs hearing, Figure 2A). There is no apparent difference after recovery however (deafened vs recovered, Fig 2B). In most cases ECAP to a pulse train demonstrates an alternation pattern. The amplitude of alternation was in some cases larger after treatment, but no clear trends are evident in the group data. The decrease in amplitude over the 100 ms pulse trains was assessed as normalized adaptation amplitude. The adaptation amplitude for hearing was consistently greater than that for deafened condition (Figure 4A). Again, no trend was apparent comparing deafened and recovered conditions (Figure 4B).

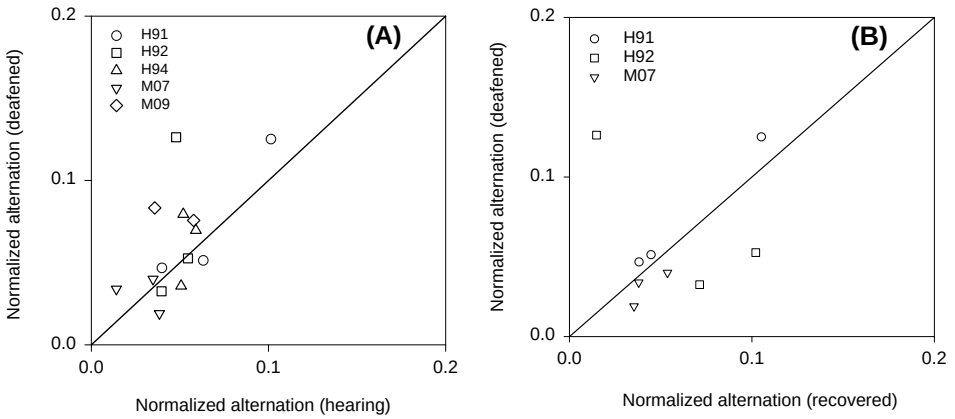

Figure 3: Scatter plots show normalized response alternation in the deafened vs hearing condition (A) and in the deafened vs recovered condition (B). Data from each animal are displayed with different symbols.

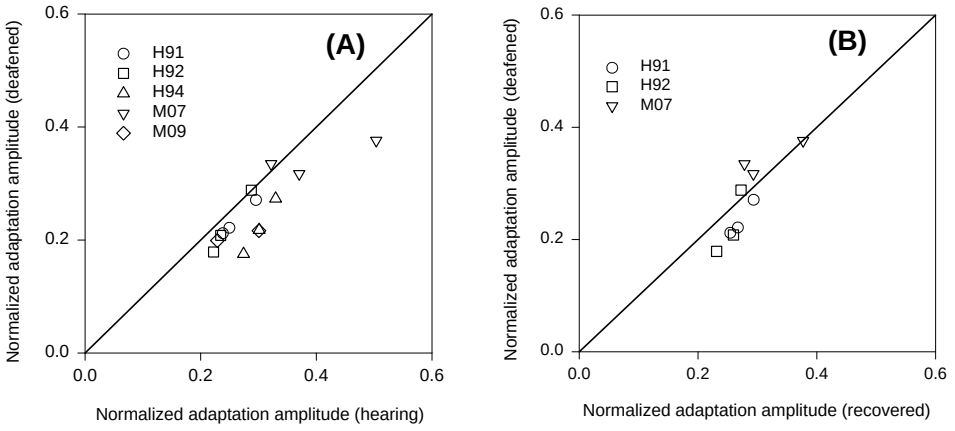

Figure 4: Scatter plots show response normalized adaptation amplitude in the deafened vs hearing condition (A) and in the deafened vs recovered condition (B). Data from each animal are displayed with different symbols.

3.4 Summary

In these experiments, animals were temporarily deafened with furosemide. The pattern of ECAP to a pulse train revealed some changes relative to those before treatment. Although the effects are small, the trends are consistent with previous results from our laboratory of permanently deafened animal treated with kanamycin and ethacrynic acid (Abbas et al, 2000).

We hypothesized that the effects that we observed with kanamycin and ethacrynic acid deafening to be the results of decreased synaptic activity affecting the stochastic nature of the neural response to electrical stimulation. The changes observed with temporary deafening were small compared to those in the permanently deafened animals. Nerve fibers in animals deafened with furosemide do not demonstrate spontaneous activity (Sewell, 1984b). Nevertheless, the hair cells in those animals are obviously still viable and the effects of hair cells on the nerve fiber membrane may be less severe. For instance, subthreshold synaptic activity may result in a greater level of noise than that with no hair cell present.

In addition, we observed no consistent changes after recovery in these experiments. Since only three of the five animals demonstrated complete ACAP amplitude recovery, small changes in response patterns may not be evident. Further experiments planned where we will attempt to adjust the dose of furosemide to allow for more consistent recovery of the CAP in order to further investigate the changes in the electrically stimulated response after recovery of hair cell function.

4 Plans for the next quarter

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

- We will continue experiments with chronically deafened animals. Assessment of hair cell and neural degeneration will be conducted on animals in which recordings have been made. A preliminary report on that data is planned for the next QPR.

- We will also continue recordings with furosemide discussed in this QPR to further assess recovery patterns.

References

[1] Abbas PJ, Miller CA, Rubinstein JT, Abkes BA, Runge Samuelson C, Robinstein BK (2000). Effects of remaining hair cells on cochlear implant function. Third Quarterly Progress Report, NIH contract, N01-DC-9-2106.

[2] Pike DA, Bosher SK. (1980). The time course of the strial changes produced by intravenous furosemide. Hear Res, 3, 79-89.

[3] Sewell WF (1984a). The effects of furosemide on the endocochlear potential and auditory-nerve fiber tuning curves in cats. Hear Res, 14, 305-14.

[4] Sewell WF (1984b). The relation between the endocochlear potential and spontaneous activity in auditory nerve fibers of the cat. J Phyisol, 347, 685-696.