Response Properties of the Refractory Auditory Nerve Fiber

CHARLES A. MILLER,^{1,2} PAUL J. ABBAS,^{1,2} AND BARBARA K. ROBINSON¹

¹*Department of Otolaryngology–Head and Neck Surgery, University of Iowa, Iowa City, IA 52242, USA*

²*Department of Speech Pathology and Audiology, University of Iowa, Iowa City, IA 52242, USA*

Received: 12 October 2000; Accepted: 6 March 2001; Online publication: 14 May 2001

ABSTRACT

The refractory characteristics of auditory nerve fibers limit their ability to accurately encode temporal information. Therefore, they are relevant to the design of cochlear prostheses. It is also possible that the refractory property could be exploited by prosthetic devices to improve information transfer, as refractoriness may enhance the nerve's stochastic properties. Furthermore, refractory data are needed for the development of accurate computational models of auditory nerve fibers. We applied a two-pulse forward-masking paradigm to a feline model of the human auditory nerve to assess refractory properties of single fibers. Each fiber was driven to refractoriness by a single (masker) current pulse delivered intracochlearly. Properties of firing efficiency, latency, jitter, spike amplitude, and relative spread (a measure of dynamic range and stochasticity) were examined by exciting fibers with a second (probe) pulse and systematically varying the masker–probe interval (MPI). Responses to monophasic cathodic current pulses were analyzed. We estimated the mean absolute refractory period to be about 330 μ s and the mean recovery time constant to be about 410 μ s. A significant proportion of fibers (13 of 34) responded to the probe pulse with MPIs as short as 500 μ s. Spike amplitude decreased with decreasing MPI, a finding relevant to the development of computational nerve-fiber models, interpretation of gross evoked potentials, and models of more central neural processing. A small mean decrement in spike jitter was noted at small MPI values. Some trends (such as spike latency-vs-MPI) varied across fibers, suggesting that

sites of excitation varied across fibers. Relative spread was found to increase with decreasing MPI values, providing direct evidence that stochastic properties of fibers are altered under conditions of refractoriness.

Keywords: refractory period, action potential, electric stimulation, cochlear nerve, cochlear implant, evoked potentials, cat

INTRODUCTION

From the perspective of information transfer, the refractory property of nerve fibers is a source of distortion, reducing the signal bandwidth that can be encoded by spike timing and introducing a regularity in firing patterns not present in the stimulus. Physiologists have studied auditory nerve fiber refractory characteristics in order to more accurately interpret spike firing patterns and understand acoustic-to-neural signal transduction (e.g., Gray 1967). Refractory effects are also relevant to studies of the electrically stimulated auditory nerve. Many cochlear implant devices excite the auditory nerve by presenting amplitude-modulated pulse trains to intracochlear electrodes. Wilson et al. (1994) showed that speech perception can be improved when modulated pulse trains are presented at relatively high rates—rates sufficient to place nerve fibers in a refractory state. A better understanding of fiber response properties under refractory conditions could assist in the development of more effective prosthetic stimulation protocols. Knowledge of refractory properties is also needed to accurately model auditory nerve fiber physiology with computational techniques (Rubinstein 1995; Bruce et al. 1999; Mino et al. 2000). Such efforts require information not only on fiber threshold functions but also on how temporal response properties (i.e., latency and jitter) and spike

Correspondence to: Charles A. Miller, Ph.D. · Department of Otolaryngology–Head and Neck Surgery · University of Iowa Hospitals and Clinics—21201 PFP · 200 Hawkins Drive · Iowa City, IA 52242. Telephone: (319) 394-6758; email: charles-miller@uiowa.edu

amplitude are altered by refractoriness. Bruce et al. (1999) have shown that the parametric values chosen to characterize refractoriness affect the ability of computational models to explain experimental data.

Previous relevant research

Most studies of the electrically stimulated auditory nerve have examined refractory threshold properties using a two-pulse masker–probe paradigm. Hartmann et al. (1984) reported data from a cat fiber, finding reduced excitability for masker–probe interval (MPI) values less than 5 ms. Dynes (1996) reported threshold-vs-MPI data for 8 fibers, confirming these findings. He also commented that the absolute refractory period was, minimally, about 500 μ s, and typically between 600 and 700 μ s. Bruce et al. (1999) estimated an absolute refractory period of 700 μ s and a recovery time constant of 1.3 ms. Cartee et al. (2000) obtained threshold-vs-MPI data for 25 single fibers and estimated a time constant of 0.7 ms. That value was derived by a fitted curve that did not include an absolute refractory period, which may have biased the estimate upward. Analyses of the cat's electrically evoked compound action potential (ECAP) have also been used to infer single-fiber refractory properties. They suggest that the relative refractory period is about 5 ms long and the absolute refractory period—at least for some fibers—is between 300 (Stypulkowski and van den Honert 1984; Miller et al. 2000) and 500 μ s (Brown and Abbas 1990). In his study of antidromic compound action potentials, Brown (1994) reported data consistent with those ECAP studies. In summary, although previous single-fiber studies have estimated recovery time constants to be between 0.7 and 1.3 ms, there is reason to suspect that at least some fibers may recover faster.

Goals and approach

A fuller characterization of refractory properties is needed to validate computational models that incorporate both stochastic and temporal properties of auditory nerve fibers. Input–output functions (i.e., plots of firing efficiency [FE] vs. level) have not been assessed at various MPI values. Furthermore, little is known about fiber temporal response properties and spike amplitude under refractory conditions. Dynes (1996) reported that across-fiber threshold variability was largest for the shortest MPI (2 ms) he investigated. This suggests that FE-vs-level functions and stochastic properties of fibers may vary with MPI. Other findings indicate that fibers presumably stimulated to a state of refractoriness have altered stochastic properties that may result in more faithful encoding of temporal details (Wilson et al. 1994, 1997; Hartman and Klinke

1995; Rubinstein et al. 1997, 1999; Litvak et al. 1999). To address these issues, we collected threshold data, input–output functions, and temporal and amplitude measures from cat auditory nerve fibers. We stimulated the nerve with monophasic current pulses delivered by a monopolar intracochlear electrode, as we believe such stimulus delivery reduces the complexities of data interpretation inherent in studies using biphasic waveforms or bipolar stimulus electrodes.

METHODS

Experimental subject preparations

Cats free of middle-ear infection were anesthetized and used as acute preparations. Surgical and experimental protocols were approved by the University of Iowa Animal Care Unit and complied with NIH animal-use standards; details are described in Miller et al. (2001). Single-fiber data were obtained from 37 units of 7 cats. Prior to insertion of an intracochlear, monopolar, stimulating electrode, each subject was chemically deafened to avoid the confounding effects of hair-cell-mediated responses. This was done using one of two different techniques. In the first four preparations, the round window was partially excised with a 30-gauge needle to allow local infusion of ototoxin and insertion of a Pt/Ir ball electrode (0.5–0.7-mm diameter) which was positioned with a manipulator (Miller et al. 1998). In these preparations, deafening was accomplished by intracochlear infusion of a 10% (w/v) solution of neomycin sulfate through the round window defect, as described in Miller et al. (1998). Histological and physiological assessments have shown this procedure to be effective in eliminating hair-cell function (Leake–Jones et al. 1982). In the remaining subjects (C55, C56, and C57), systemic chemical deafening was used, obviating the need to open the round window. In those cases, a cochleostomy was performed and a ball electrode (0.4–0.5-mm diameter) was inserted into the scala tympani (to an approximate depth of 1.2 mm) for intracochlear stimulation. Kanamycin and ethacrynic acid were administered systemically following the protocol of Xu et al. (1993). Loss of acoustic sensitivity was confirmed in those animals by observing the elimination of a click-evoked compound action potential or auditory brainstem response. With our equipment, we were able to record evoked responses over a minimum stimulus intensity range of 65 dB for normal-hearing cats. Thus, losses of at least that magnitude were induced in the preparations. None of the fibers from which we obtained data demonstrated spontaneous firing.

Stimulus presentation

Stimuli were generated by custom software and a 12-bit digital-to-analog converter (50,000 samples/s). The converter, in turn, was connected to a capacitively coupled, optically isolated current source (10%–90% rise–fall time: 10 μ s), followed by a monopolar stimulating electrode positioned in the basal turn of the scala tympani. A needle electrode in the forepaw served as the return electrode. Prior to recording single-fiber action potentials, ECAPs were recorded (Miller et al. 1998) to obtain an amplitude–level function and assess the overall sensitivity of the preparation. To record single-fiber action potentials, a search stimulus was presented at a level sufficient to evoke an ECAP at least 75% of its maximum amplitude.

A forward-masking paradigm, consisting of a probe pulse preceded by a masking pulse, was used to put each measured fiber in a refractory state. Both the masker and probe pulses were monophasic, rectangular current pulses of the same polarity separated by a masker–probe interval. Once a fiber was encountered, we first determined its unmasked firing properties through a series of repeated stimuli presented at several levels encompassing the fiber's dynamic range (as determined by firing rate). For each stimulus level, 100 probe-alone stimuli were presented (with a 30-ms interstimulus interval) to obtain firing probability and spike-timing statistics. After characterizing the unmasked state, a masker–probe combination was presented, with the masker level chosen so that the fiber responded to each masker pulse. Masked response properties were then assessed at several probe levels (incremented in linear current steps) for several MPI values ranging from 0.5 to 4 ms. Data for the MPI condition of 1.0 ms was collected first, followed by data sets for 3–5 additional MPI values selected in random order. Throughout data collection, the nerve was stimulated with both cathodic masker–probe pairs and anodic masker–probe pairs presented sequentially in an interleaved fashion. The duration of time between presentations of each masker–probe pair was 30 ms.

Recording techniques

Our preliminary recording of gross neural potentials employed an electrode (0.4–0.6-mm-diameter Pt/Ir ball) positioned directly on the nerve trunk and used techniques described in Miller et al. (1998). Standard micropipette techniques were used to record single-fiber action potentials (Miller et al. 1999a). Potentials were amplified (20 or 40 dB gain) and low-pass-filtered (10-kHz cutoff, 40 dB/decade) by an Axoprobe headstage and amplifier (Axon Instruments, Union City, CA). Additional bandpass filtering (100-Hz Butterworth high-pass, 40 dB/decade; 10-kHz low-pass, 40

dB/decade) was used prior to the digital acquisition of 400 samples with 16-bit resolution. A sampling rate of 100,000 sample/s was used for most MPI conditions; a slower (50,000) rate was used when assessing MPI values greater than 2 ms. This was done to ensure that at least a 2-ms recording epoch (after probe onset) was recorded. All response waveforms were stored digitally for analysis after the conclusion of the experiment.

Data analysis

As stimulus artifacts were typically much larger in amplitude than the neural spikes, a template-subtraction technique (Miller et al. 1999a) was used to eliminate this contaminant almost completely and facilitate spike detection. An example of this technique is shown in Figure 1 for a fiber stimulated with masker and probe pulses separated by a short (0.6 ms) interval. "Raw" response waveforms are shown superimposed for 100 repeated presentations (panel A). As was typical in this study, the fiber produced an action potential in response to each masker pulse (peaks labeled "b"). The fiber responded to only 66 of the probe pulses (traces labeled "c"). The remaining 34 probe presentations ("d") failed to elicit a spike. These 34 waveforms were averaged together to form a single template waveform (panel B) which was subtracted from the raw waveforms to obtain the resultant waveforms (panel C). In the example of Figure 1, the raw waveforms and template contain a relatively large-amplitude ECAP response ("e," panel B). The template-subtraction technique eliminates this contaminant as well as the stimulus artifacts. By applying the technique after data collection was completed, we were able to visually confirm the quality of the resultant waveforms in every case and carefully select an optimal spike-amplitude criterion that reliably detected spike activity. Spike detection was usually limited by insufficient spike amplitude, not by stimulus artifacts.

Custom analysis software was used to obtain several measures. Action potential *amplitude* was measured from the spike peak to the subsequent minimum (i.e., the after-hyperpolarization). Latency was measured from the onset of the probe pulse to the spike peak. For each stimulus condition, *mean latency* was computed from all the spike latencies obtained across the 100 stimulus presentations. *Jitter* was defined as the standard deviation of spike latencies. *Firing efficiency* (FE) was computed as the percentage of stimuli that evoked an action potential. *Threshold* (θ) was defined as the stimulus level yielding an FE of 50% and was typically computed using linear interpolation. *Relative spread* (RS) is a measure based on a fiber's FE-vs-level function that characterizes the fiber's dynamic range and hence its probabilistic nature (Verveen 1961). We

FIG. 1. Demonstration of the template-subtraction scheme for isolating action potential waveforms. **A.** Potentials recorded in response to 100 presentations of cathodic masker and probe pulses using a masker–probe interval of 0.6 ms. Stimulus artifacts are denoted by the arrows labeled “a”. Arrow “b” points to action potentials in response to the masker and “c” points to action potentials in response to the probe. The traces in which the probe failed to elicit a spike (“d”) were averaged together to obtain the template waveform (**B**). This template was then subtracted from each waveform of **A** to obtain the resultant waveforms of **C**. In the example shown here, relatively high-level stimuli were used which elicited a large-amplitude compound action potential (“e” in **B**). Different voltage calibration bars are shown for **A** and **B** and for **C**.

computed RS by first fitting the FE-vs-level function to an integrated Gaussian curve by means of the probit transformation. RS was then defined by Eq. (1):

$$RS = \sigma / \theta \quad (1)$$

where σ is the standard deviation of the Gaussian curve and θ is the fiber’s threshold current level. In this study, we multiplied the ratio of Eq. (1) by 100 to express RS as a percent value. Roughly speaking, RS is inversely proportional to the slope of the FE-vs-level function. A completely deterministic FE-vs-level function (i.e., a step function) would have an RS of 0. We have found that the mean cat fiber has an RS of 6%–7% when stimulated with 40- μ s monophasic pulses, which

corresponds to a dynamic range of about 1.5 dB (Miller et al. 1999a).

Effects of refractoriness were evaluated by plotting threshold, mean latency, jitter, amplitude, and RS as functions of MPI. The first four of these five measures were computed for the 50% FE condition. For each fiber, the plot of threshold vs. MPI was fit to the decaying exponential function of Eq. (2):

$$\theta = \theta_{SP} / (1 - e^{-(MPI - ARP)/\tau}) \quad (2)$$

where θ is the fiber threshold, MPI is the masker–probe interval, θ_{SP} is the single-pulse (unmasked) threshold, ARP is the absolute refractory period, and τ is the recovery time constant. The fit was performed using the Marquardt–Levenberg algorithm as implemented by Sigmaplot software (version 4; SPSS, Inc., Chicago, IL). All three parameters on the right side of Eq. (2) (θ_{SP} , ARP, and τ) were allowed to vary during curve fitting but were constrained to positive values. A threshold recovery curve was computed for each fiber to provide a pool of estimates for τ and ARP.

RESULTS

Refractory recovery data were obtained from 37 fibers of 7 cats. Of those, 34 responded to cathodic pulses and 5 responded to anodic pulses at the stimulus levels examined. In 33 of the 37 fibers (89%), cathodic thresholds were lower than anodic thresholds, consistent with a strong bias of lower cathodic thresholds in cats (Miller et al. 1999a). For this reason—and the fact that our anodic data set was very small—we focused exclusively on the data obtained with cathodic stimuli.

Example data

Another example of response waveforms is shown in Figure 2. The top panel shows the “raw” waveforms resulting from 100 repeated presentations of cathodic masker and probe pulses. This data set is particularly illustrative of refractory phenomena, since in 1 of the 100 traces (labeled “spike failure” in panel A), the fiber failed to respond to the masker. In that instance, the probe elicited an “unmasked” spike characterized by shorter latency and greater amplitude than the “masked” spikes. Also, the “masked” spikes were somewhat wider than the “unmasked” spike. These effects are seen more readily in panel B of Figure 2, where our template-subtraction method was applied to remove most of the waveform contamination caused by the stimulus artifact. In these processed waveforms, the action potentials to the masker pulse have also been subtracted out.

In Figure 3, the types of data sets obtained for each fiber are shown for two example fibers. In the left

FIG. 2. Illustration of the effect of forward masking on action potential morphology. **A.** One hundred superimposed responses to presentations of a masker and probe stimulus. Action potentials can be seen in response to both stimuli. Two different responses to the probe are evident. In 99 of 100 cases, the probe response was preceded by an action potential to the masker pulse. In the one exception (labeled "spike failure"), the masker failed to elicit an action potential. In that case, the response to the probe has shorter latency and larger amplitude. The amplitude differences between the "unmasked" and "masked" spikes are more clearly seen in **B**, where distortions resulting from stimulus artifacts and residual ECAP have been reduced by the template subtraction scheme. Different vertical scales are used in the two panels.

column, FE, mean latency, and jitter are plotted versus stimulus level with MPI as the parameter. Each of these three functions demonstrates trends that have been previously reported (Miller et al. 1999a). The FE-vs-level functions are well described by integrated Gaussian functions, while the latency and jitter functions typically decrease with increasing stimulus level. From each of these plots, we derived measures of threshold, mean latency, and jitter for the 50% FE

condition. These three measures, along with RS and mean spike amplitude (at 50% FE) are plotted versus MPI in the graphs of the right column.

The effects of MPI on the measures from these two fibers warrants attention, as they were evident in other fibers. The threshold-vs-MPI functions of the two fibers of Figure 3 (right column) fit our model function [Eq. (2)] quite well, as did most fibers (see "Group trends" section below). In both fibers, relative spread was greatest at the smallest MPI values and jitter decreased with decreasing MPI. The latency-vs-level functions of fiber C56-4-4 (left column, second panel) reveal a pattern seen in 16 of 34 (47%) fibers: increasing latencies with decreasing MPI values. Those functions also indicate reduced ranges of latencies with decreasing MPI. The trend toward longer latencies with smaller MPI values, however, was not consistently observed, as is evident in the data of fiber C46-3-4. In this case, response latencies were smaller for the shorter masker-probe intervals. This trend was observed in 7 (21%) of the 34 fibers. Constant or indeterminate latency-vs-MPI trends were seen in the remaining 11 fibers. Finally, the amplitude-vs-MPI data for the two fibers have relatively complex, nonmonotonic functions. This is due, in part, to amplitude variations that were likely caused by uncontrolled movement of the fiber relative to the electrode. Additional variation was caused by time-related effects, which we address in the following section. Therefore, caution is needed in interpreting amplitude data of individual fibers.

Assessment of time-related effects

The amplitude-vs-MPI data of fiber C46-3-4 (Fig. 3) demonstrate a trend often observed across fibers in that spike amplitude tends to be smallest at the shortest MPIs. However, both fibers of Figure 3 produced relatively large amplitudes at MPIs of 1 and 30 ms. These larger values reflect a measurement bias resulting from the nonrandom order in which MPI was varied during data collection. For each fiber, we first collected data for the unmasked condition, then for the MPI = 1.0 ms condition, and then for other MPI values in randomized order. While collecting data from a fiber, we often observed reductions in spike amplitude over time. As we recorded the unmasked and MPI = 1.0 ms conditions first, amplitude measures (and perhaps other measures) collected at those MPIs may have been biased by order effects. This problem is suggested in the amplitude data for fiber C56-4-4 as well, where

FIG. 3. Examples of data obtained for all fibers of this study. Input-output plots of the left column show how firing efficiency, mean spike latency, and jitter varied with stimulus level and parametric variation of masker-probe interval. The symbol legend lists the vari-

ous MPI conditions in the order in which data were collected. Plots of the right column indicate how spike threshold, mean latency (at 50% FE), jitter (at 50% FE), relative spread, and spike amplitude (at 50% FE) varied with MPI.

repeated measures were obtained for the unmasked (MPI = 30 ms) condition (Fig. 3, right column).

To address this temporal order complication, we obtained repeated measures (typically for the unmasked stimulus condition) in 16 fibers. The five measures of threshold, mean latency (at 50% FE), jitter (at 50% FE), relative spread, and amplitude (at 50% FE) collected over repeated trials are plotted in the left column of Figure 4. In these plots, the abscissa ("sequence number") represents the relative order in which the measures were taken. For these fibers, we typically collected a sequence of 8 sets of data, with a set defined as all data for a particular MPI. Inspection of the five plots of the left column reveals that, with the exception of amplitude, all measures failed to demonstrate consistent order effects. To explore this further, we normalized the data for each fiber by dividing each measure by that obtained in the first repeated measure (Fig. 4, right column). A first-order regression line was then fit to each set of group data. Again, the amplitude measures reveal a large decrement over time. In contrast, the normalized changes in threshold were very small. To quantify the changes over time, we measured the vertical change of each regression line that occurred between the first and the eighth data sequence numbers. These changes are listed as percentages in each graph of the right column. As expected, the amplitude measures underwent the largest changes.

The disparate trends in the threshold and amplitude plots suggest that the order effects were primarily due to changes in either spike amplitude or recording conditions rather than changes in fiber sensitivity. Furthermore, although the latency, jitter, and RS measures revealed overall changes of 5%–10%, the across-fiber variability in these measures was comparable to or greater than the magnitude of the order effects. These stability measures suggest that amplitude data collected across time are subject to significant bias, as certain experimental conditions (i.e., the unmasked and MPI = 1.0 ms conditions) were not collected in random order. Our subsequent data analyses were conducted with this in mind.

Group trends

Estimate of threshold recovery characteristics. A primary goal of our study was to quantify the relationship between threshold and MPI. We did so by fitting each fiber's threshold-vs-MPI data to the recovery function [Eq. (2)]. Group trends were then characterized by computing the mean values of the parameters obtained from each fit. In doing so, we first excluded some fiber data. Across the 34 fibers, the mean variance explained by the fitted functions (i.e., r^2) was 0.892; 19 fibers had r^2 values of 0.95 or greater. We

FIG. 4. The effects of time on single-fiber measures (threshold, mean latency, jitter, RS, and amplitude) as assessed with repeated measures obtained from 16 fibers. In the left column, the five measures are plotted as a function of the "sequence number", or order in which the data were collected. For a typical fiber, data at each MPI value were collected in a sequence of 8 series. Repeated measures were usually obtained under the no-masking condition. Order effects are more clearly seen in the plots of the right column, where, for each fiber and set of repeated measures, the data were normalized (by division) to the value obtained at the first of the repeated measurements. Linear regressions (thick lines) indicate general trends across all fibers. The percentages shown in each plot indicate the change in the regression line from sequence 1 to sequence 8.

TABLE 1

Statistics summarizing results of fitting decaying exponential curves to the threshold-vs-MPI data of a group of 20 fibers^a

	Threshold (mA)	ARP (μ s)	τ (μ s)	r^2	Data points per fiber
Mean	0.768	332	411	0.972	6.1
Standard deviation	0.296	97.9	226	0.0236	1.07
Maximum value	1.30	461	894	0.999	8
Minimum value	0.283	139	131	0.923	4

^aARP is the absolute refractory period, τ is the recovery time constant, and r^2 is the amount of variance explained by the fit. On average, about 6 threshold-vs-MPI data were used in each curve fit.

FIG. 5. Histograms of the absolute refractory periods (ARP) and recovery time constants (τ) estimated for 20 fibers by fitting curves (see Methods) to threshold-vs-MPI data. Mean values are also indicated.

identified the relatively poor-fitting data sets (i.e., those with $r^2 < 0.9$) and excluded data from 10 fibers that together had a mean r^2 value of 0.613. Of the remaining 24 fiber data sets, 4 produced fits to curves having ARP values of 0, meaning that the fitting algorithm constrained the ARP value. These 4 fibers were eliminated from the group to avoid biasing the mean ARP estimate to a smaller value. The statistics describing the curve-fitting results on the remaining 20 fibers are presented in Table 1. Included are mean, standard deviation, minimum, and maximum values for the threshold, ARP, and τ estimates, as well as the r^2 values and number of points used to fit each curve.

FIG. 6. Plot summarizing the range of firing efficiencies recorded from all 34 fibers of this study. FE values obtained across all fibers and stimulus levels are plotted as a function of every MPI value that yielded data for at least 5 fibers. Open circles show mean values. Above the graph are listed the number of fibers contributing to the data at each MPI.

The ARP and τ data are shown as histograms in Figure 5. From the pool of 20 fibers, the mean ARP was 332 μ s and the mean time constant was 411 μ s.

Another way of characterizing recovery is through an examination of the FE values that were attained by fibers at each MPI. We assume that, as MPI is reduced and approaches a fiber's absolute refractory period, firing efficiency will decrease and approach zero. A simple way of examining this issue is to plot the FE values produced by all fibers at each MPI, as is done for all 34 fibers in Figure 6. Since we characterized each fiber's dynamic range, FE data were collected at several stimulus levels at each MPI. Therefore, each fiber contributed multiple data points at each MPI. Listed along the top of the figure are the numbers of fibers contributing data at each MPI. Not all fibers contributed to each MPI value because of variable time in "holding" a fiber and, in the case of short MPIs (500 and 600 μ s), occasionally unfavorable spike-amplitude-to-noise ratios. Data are shown for all MPIs that yielded data from at least 5 fibers. Also plotted is the mean FE vs. MPI (open circles), a trend that suggests that FE may be limited to slightly lower values at the smallest MPI values. Nonetheless, these data indicate that fibers are capable of responding over wide FE ranges, even at the smallest MPI evaluated.

Other trends across fibers. In addition to estimating threshold-recovery parameters, we examined how the

other measures varied with masker-probe interval. We pooled data from all 34 fibers and plotted threshold, mean latency, jitter, amplitude, and RS versus MPI, with the first 4 of these 5 measures again characterized for the 50% FE condition. To better discern across-fiber trends, each fiber's measures were normalized to the value obtained in the unmasked state. The mean latency and jitter data were normalized by subtracting the unmasked values from each fiber's data. The threshold, amplitude, and RS measures were normalized by dividing each fiber's data by the unmasked values. Scatter plots of these normalized data are shown in Figure 7, with open circles denoting mean values. Since each fiber did not contribute data at each MPI, these plots should not be used to infer specific functional relationships with the MPI variable. An estimation of an "average" threshold recovery function obtained by fitting a function would be biased. However, these data are valuable in discerning the degree of dependence of each measure on MPI.

The scatter plots of Figure 7 have been fit to functions using the Marquardt-Levenberg algorithm. To describe trends as a function of MPI, we first attempted to fit each data set using hyperbolic, exponential, logarithmic, and rational series, i.e., "plausible" functions that followed a monotonic course and had a horizontal asymptote at large MPI values. If those functions failed to reveal a significant correlation, we expanded the set of functions to include n th-order polynomials. The specific form of each function is shown in each panel of Figure 7, along with the variance (r^2) explained by each fit. In all but one scatter plot (latency vs. MPI), statistically significant functional relationships were found, as determined by the test for correlation between two variables (Bevington 1969). The results of these tests are shown in Table 2. They indicate that, with the exception of spike latency, all single-fiber measures (threshold, jitter, RS, and amplitude) were dependent upon MPI.

As noted earlier, the order of data collection influenced spike-amplitude measures. We were thus concerned that the trends of Figure 7 may be biased, as the data were normalized to the values obtained in the unmasked condition, which was the first condition evaluated for each fiber. Therefore, we reanalyzed the

FIG. 7. Five measures (threshold, mean latency, jitter, RS, and amplitude) obtained from all 34 fibers are plotted as a function of MPI. For each of the measures, the data for each fiber was normalized to the value obtained under the no-masking condition. Each scatter plot was fit to a function (the form of which is listed in each panel) in order to assess whether each dependent variable was significantly correlated with MPI. These fits are also plotted, and the amount of variance accounted for by each fit (r^2) is listed in each panel. Open circles indicate mean values at specific MPIs.

TABLE 2

Summary of tests for no correlation between each of five listed measures and masker-probe interval^a

	Threshold	Latency	Jitter	RS	Amplitude
<i>r</i> (correlation coefficient)	0.645	0.033	0.358	0.311	0.422
<i>n</i> (observations)	208	208	208	205	206
Probability of no correlation	<0.001	0.636	<0.001	<0.001	<0.001

^aTests were performed on the data shown in Fig. 7. In all cases except the latency-vs-MPI data, highly significant correlations are indicated.

data by eliminating the unmasked data and normalizing all data to that obtained for MPI = 4000 μ s. Because the order of this MPI condition was selected randomly, it would not be subject to order bias. We also eliminated all amplitude data obtained at MPI = 1000 μ s, as that data could also produce an order effect. The results of these reduced data sets and curve fits are shown in Figure 8. Comparisons of the data and fitted curves of Figures 7 and 8 reveal relatively minor changes in the trends. The most notable difference between the two analyses are evident in the RS and amplitude data, which demonstrated the largest time-order effects (Fig. 4). When normalized to the MPI = 4000- μ s data, the RS measures show a somewhat larger increase with decreasing MPI, while spike amplitudes demonstrate somewhat smaller decrements that are limited to a smaller range of MPI values. Given the large dependence of spike amplitude on order of data collection, the amplitude trends shown in Figure 8 are likely more representative than those of Figure 7. With regard to the significance of each regression of Figure 8, the elimination of the unmasked data did not appreciably change the level of statistical significance of any of the fitted curves. Table 3 presents results of the statistical tests performed on the data in Figure 8.

The group analysis of latency effects does not adequately describe single-fiber trends. From the scatter plots of Figures 7 and 8, mean spike latency is apparently independent of MPI; however, data from individual fibers indicate a more complex picture. Nearly half (47%) of our 34 fibers demonstrated a tendency toward increasing spike latency as MPI decreased as was clearly demonstrated by the waveforms of Figure 2. In contrast, 7 (21%) of 34 fibers—including fiber C46-3-4 of Figure 3—demonstrated reduced latency at small MPI values.

Another temporal effect of refractoriness is evident in the latency-vs-level plots of Figure 3. It is apparent that the *range* of mean spike latencies that occurs across levels decreases as MPI decreases. This trend is seen in both fibers of Figure 3, even though they exhibit opposing trends in mean latency (measured at 50% FE) as a function of MPI. To further explore this compression of latency changes, we determined mean

spike latencies for each fiber and MPI at firing efficiencies of 20% and 80% (this typically required interpolation of the latency-vs-FE functions). By doing so, we could express how latency varied over the dynamic range of a fiber as a function of MPI. These data are shown for all fibers in Figure 9, along with a straight-line fit to the data. Both the individual-fiber data and the regression line demonstrate a decreasing range of mean latencies as MPI is decreased. A test of the significance of the correlation (Bevington 1969) indicates that the latency range is correlated with MPI at a probability of error less than 0.001 ($r = 0.233$, $n = 209$).

Effect of stimulus level on recovery rate. Finally, we conducted a limited study of the effect of probe level on recovery rate by obtaining FE-vs-MPI functions at several probe levels, with masker level held constant across conditions. Data collected from one fiber are shown in Figure 10A. Two trends are worth noting. First, the rate of recovery is clearly dependent on probe level, with faster recovery evident at higher probe levels. Note that, in this example, increases in probe level decreased both the relative refractory period and the absolute refractory period. Second, the plots demonstrate that the shapes of threshold recovery functions depend upon the criterion used to define threshold. Throughout this study, threshold was defined as the stimulus level producing 50% FE. This choice is somewhat arbitrary and other criterion firing efficiencies could be chosen, which would affect the threshold recovery curves. This is illustrated in Figure 10B, where the data of panel A were interpolated and replotted as threshold-recovery curves. Note that as the criterion is shifted to lower FE values, the recovery period is reduced. These curves also suggest that both the absolute and the relative refractory periods are influenced by the choice of threshold criterion.

DISCUSSION

The refractory recovery data presented here modify and extend our understanding of feline auditory nerve fiber physiology. On average, fibers appear to have shorter absolute refractory periods and recovery time

constants than previously reported. We also found that, at short MPI values, action potentials have reduced amplitudes and fibers have larger dynamic ranges (as assessed by relative spread). These and other findings are discussed below.

Threshold recovery

Compared with those of previous studies, our results indicate that cat auditory nerve fibers have a relatively short absolute refractory period (on average, $330 \mu\text{s}$) and that a significant number of fibers can respond at a masker-probe interval of $500 \mu\text{s}$. More than one-third of our sampled fibers responded at that interval and with only a modest mean decrease in firing efficiency (Fig. 6). The data also suggest that fibers recover at a faster rate than previously reported. The average time constant of our fibers was $410 \mu\text{s}$, roughly 2–3 times faster than reported by Bruce et al. (1999) or Cartee et al. (2000). Some of these discrepancies may be attributable to different model equations and assumptions used across the studies. Cartee et al. (2000) used the same recovery equation that we did [Eq. (2)], although they assumed an ARP of zero. That assumption could bias the time-constant estimate to a larger value. Bruce et al. (1999) used a different equation that constrained the maximum relative refractory threshold to 1.97 times that of the single-pulse threshold. Our data (Figs. 7 and 8) suggest that that upper limit is somewhat conservative. Our estimates may also differ from previous reports since they were based on measures obtained at a smaller minimum MPI than those of (Dynes (1996)) or (Cartee et al. (2000)). We found that the accuracy of ARP estimates obtained with curve-fitting algorithms depends strongly upon the minimum MPI value for which data are available.

Electrically evoked gross-potential data from cats support our finding of relatively short, absolute refractory periods, at least in a subset of fibers. Brown and Abbas (1990) examined the recovery of the ECAP from forward masking and reported that a $500\text{-}\mu\text{s}$ MPI typically produced maximum refractoriness. Some of their data (their Fig. 2) suggest that a smaller MPI may, in some cases, be more appropriately chosen as the ARP value. Stypulkowski and van den Honert (1984) were able to record diminished-amplitude ECAPs at a masker-probe interval of $500 \mu\text{s}$. They estimated single-fiber ARP to be $300 \mu\text{s}$, as the gross potential was

FIG. 8. Plots similar to those of Fig. 7, with data in this case normalized to the values obtained at an MPI = $4000 \mu\text{s}$. In the case of the spike-amplitude data (bottom plot), the data at MPI = $1000 \mu\text{s}$ has been removed; thus, the curve fitted to that data is not biased by the order effect problem discussed in the text.

TABLE 3

Summary of tests for no correlation between each of five measures and MPI^a

	Threshold	Latency	Jitter	RS	Amplitude
<i>r</i> (correlation coefficient)	0.671	0.0101	0.339	0.554	0.420
<i>n</i> (observations)	208	208	208	205	127
Probability of no correlation	<0.001	0.885	<0.001	<0.001	<0.001

^aTests were conducted over the data sets of Fig. 8, in which data collected for the unmasked condition were excluded. Also, amplitude data at the MPI = 1-ms condition were excluded, as noted in the text. As in the cases shown in Table 2, significant correlations were found in all but the scatter plot of latency-vs-MPI.

FIG. 9. The effect of masker-probe interval on the difference in mean spike latencies measured at two FE values (20 and 80%). Data are shown for all 34 fibers, with different symbols denoting different fibers. The thick line indicates the first-order linear regression computed across all data.

abolished in their preparations at that interval. Miller et al. (2000) found a similar result. With single-fiber studies, the issue of adequate sampling across the nerve population is a significant concern. Assessments based upon the ECAP may be advantageous for estimating response properties, since the gross potential presumably represents most, if not all, active fibers. However, the characterization of single-fiber refractoriness from ECAP measures is not straightforward. Estimates are complicated by the reductions in spike amplitude at small MPI values (Figs. 2 and 8). Also, the ECAP will underestimate the desynchronized spike activity that characterizes fibers responding at low firing efficiencies.

Auditory nerve fiber recovery has also been assessed using acoustically sensitive cats. One approach assumes that the absolute and the relative recovery periods can be derived from the timing of spontaneous spike activity (Gray 1967). This approach relies on analysis of spike interval histograms and hazard functions (i.e.,

FIG. 10. Illustration of the effect of probe level on FE recovery curves. **A.** FE-vs-MPI data are plotted for several probe levels. **B.** Interpolated values obtained from the plot of **A** are replotted as threshold recovery curves using three different criterion FE values to define "threshold."

the probability density function of spike rate as a function of the time after a prior spike). Use of this technique has shown that threshold recovery occurs not only over a relatively short period (about 2 ms), but also over a long period on the order of 20–40 ms (Gray 1967; Lutkenhoner et al. 1980; Gaumond et al. 1982; Karamanos and Miller 1988; Li and Young 1993). The slow component was not always evident, however, and was typically of small magnitude. We studied only a

limited range of MPIs and were unable to see evidence of a slow recovery component. However, our data (Fig. 8, top panel) suggest that the magnitude of threshold improvements at MPIs > 3 ms is small. Other studies using electrical stimulation also indicate that, if any slow recovery is present, it is of negligible magnitude (Stypulkowski and van den Honert 1984; Brown and Abbas 1990; Cartee et al. 2000). It may be that the slow component observed in the acoustic preparations arises from a depletion process occurring at or near the synapse (Li and Young 1993).

Karamanos and Miller (1988) reported that average firing rate influenced the shape of the hazard function and, hence, the rate of recovery. Li and Young (1993) examined this issue and found that the relative refractory period was proportional to the mean spike interval. A small recovery time constant (0.2 ms) was needed to account for interval data characterized by low spike rates. The correlation of recovery rate and spike rate seems counterintuitive unless stimulus level effects are considered. Since the spike rates reported by Li and Young (1993) were correlated with the level of their acoustic stimulus, they conjectured that stimulus level influenced fiber recovery rate. They also estimated ARP from the "dead time" of hazard functions and obtained mean values ranging from 560 to 860 μ s. Unlike the case of their relative refractory period measures, however, they found no dependence of ARP on mean spike interval.

Our estimate of the recovery time constant agrees reasonably well with the smaller time constant that Li and Young (1993) observed at high discharge rates. Our ARP estimate, however, is about one-half that of their estimate. The finding of Li and Young (1993) that the recovery time constant was dependent on spike rate led them to speculate that their refractory function $r(t)$ was dependent on the rate of neurotransmitter vesicle release at the hair-cell synapse. It may also depend on stimulus level, as our level-dependent recovery rates (Fig. 10) suggest.

It is not surprising that our findings vary from those obtained using undeafened animal preparations, where different excitation mechanisms are involved. In the case of acoustic stimulation, the transduction process occurring at the postsynaptic region must be considered. While it could be argued that electrical stimulation provides a "purer" means of assessing refractory properties *per se*, it should be noted that stimulus-related effects also evidently influence refractory measures obtained with electrical stimulation. Also, as it is likely that electrical stimulation depolarizes fibers at the axon (at least in some cases), characterization of refractory properties with that stimulus will be descriptive of axonal properties but will be less sensitive to the physiology of the postsynaptic terminal region.

Temporal properties

Our group analyses of temporal properties (Figs. 7 and 8) suggest that MPI has little or no influence on mean spike latency. However, these scatter plots characterize only the mean response properties. The plots reveal a significant amount of variability in mean latency at each MPI value. This variability may be a result of multiple sources. First, analyses of individual-fiber data revealed that almost half (47%) of the 34 fibers demonstrated a trend of increasing spike latency as MPI was decreased. Such a trend is plausible from the biophysical perspective of an axon recovering from refractoriness. Presumably fewer ionic channels are available during the relative refractory period, reducing the speed at which a second action potential could be initiated and propagated. The remaining fibers demonstrated either flat or increasing latency-vs-MPI functions. We speculate that these trends may be due to a stimulus-level effect in which the action potential initiation site shifts to a more central locus with increasing current level. This central shift is apparently capable of overcoming any spike-delaying effects that occur during refractoriness. It is, therefore, likely that some of the variability seen in the group analyses is due to heterogeneous modes of fiber excitation across the sampled fibers. This is not surprising given the variations in fiber orientation, electrode-fiber distance, and membrane properties. Our estimates of mean latency (at 50% FE) are also subject to statistical variation as each is based on only 50 measures of spike latency. Previous work in our lab (Miller et al. 1999a) indicates that, in response to a single pulse, the mean jitter at 50% FE is about 100 μ s.

Related to this issue is our observation (Figs. 3 and 9) that the range of mean latencies recorded over the dynamic range of the fiber decreases as MPI decreases. Thus, while in the average across all fibers, mean latency was not dependent on MPI, the range of latencies produced over a uniform range of FE was dependent on MPI. The reduced range of latencies is a more uniform and robust phenomenon than are the trends in mean latency measured at 50% FE. We speculate that the range reduction may be a result of systematic change in the site of action potential initiation with MPI. Because of interaction with stimulus level, excitation at short MPIs may occur at a more remote site relative to the stimulus electrode. If we assume that the gradient of stimulus field diminishes with distance, one would predict smaller central shifts in the excitation site with increasing level.

As in the case of spike latency, we might suspect that jitter would increase as MPI was decreased because of a "noisier" fiber during the period of refractory recovery. However, our data (Figs. 7 and 8) do not support that notion: A trend toward less jitter with

smaller MPI is evident. We speculate that effects related to stimulus level may again contribute to the observed jitter reductions. In some fibers, we noted reduced mean spike latencies at small MPI values that were, presumably, due to stimulus level effects. Migration of the spike initiation site toward more central locations could result in jitter reductions in two ways. First, the initiation site could move to a more central site having biophysical properties favorable to lower jitter (i.e., larger axonal diameter, greater myelination). Such peripheral-to-central gradients in anatomical properties are known to exist in the cat auditory nerve (Arnesen and Osen 1978; Liberman and Oliver 1984). Second, by shifting to a more central excitation site, the propagating action potential may pass through fewer nodes of Ranvier and accrue less jitter resulting from action potential propagation. Of course, these mechanisms are speculative and their relative contributions (if any) to the effects reported here cannot be adequately addressed by our techniques. Realistic modeling of auditory nerve fiber response properties and their spatial distributions within the cochlea and temporal bone could help resolve these issues.

Amplitude effects

In the scatter plots of Figures 7 and 8, we observed reductions in spike amplitude at $\text{MPI} < 1$ ms. Because of the aforementioned complications of time-related effects on spike amplitude (Fig. 4), the trends presented in the plot of Figure 8 are probably more reliable than those of Figure 7. The Figure 8 data indicate that spike amplitude at a $500\text{-}\mu\text{s}$ MPI is typically reduced by about 40% of that recorded at an $\text{MPI} = 4$ ms. Consideration should be given to this effect if accurate interpretations of gross evoked potentials are desired. Reduced-amplitude responses are likely the result of a combination of some fibers becoming unresponsive and others having reduced spike amplitudes. Therefore, smaller gross potentials at small MPIs will not simply reflect some fibers becoming absolutely refractory. Smaller spikes may also have implications for central processing, since they could result in weaker excitation of the cochlear nucleus and ascending sites. Finally, it is possible that smaller spike amplitudes could result in a higher probability of conduction failure. If, at short MPIs, significant conduction failures result from reduced spike amplitudes, then our single-fiber measures may overestimate the firing efficiencies at the *output* of the fibers. If that is the case, our estimates of the ARP and the recovery time constant would be functionally too small. We do not know the degree to which such spike failure or amplitude recovery occurs in the nerve and such issues

are difficult to address with our experimental preparation. Highly accurate biophysical computational models may help resolve this issue.

Stochastic response behavior

The measure of relative spread reflects the probabilistic nature of action potential generation (Verveen 1961) which has been described in studies of the electrically stimulated cat auditory nerve (van den Honert and Stypulkowski 1984; Javel et al. 1987; Dynes 1996; Miller et al. 1999a; Javel and Shepherd 2000). The properties of RS and jitter have recently garnered increased attention because of interest in exploiting the "stochastic resonance" effect in which representations of stimuli are enhanced by the inherent noisiness of action potential generation. Several studies have proposed various means of exploiting the stochastic properties of fibers to enhance speech perception with cochlear implants. Proposed techniques include adding noisy electrical "conditioning" signals through cochlear implant electrodes and stimulating fibers at high pulse rates so as to induce a greater degree of stochastic behavior. Both schemes have shown some promise. Using measures of frog ECAPs, Morse and Evans (1996) demonstrated that additive electrical noise enhanced the spectral representation of the formant frequency of vowel-like stimuli. Matsuoka et al. (2000) recorded guinea pig auditory nerve ECAPs in response to electrical pulse trains and analyzed the degree of ECAP amplitude alternation to sequences of stimulus pulses. They noted reduced amplitude alternation when pulse trains were presented with an electrical noise and assumed that reduced alternation was due to increased neural stochasticity.

The second approach to decreasing the deterministic response of nerve fibers is based on using high rates of pulsatile stimulation to place nerve fibers in a mode of responding with greater stochasticity. Repetitive stimuli presented at sufficiently high rates could presumably cause fibers to operate in a state of relative refractoriness, which could result in greater jitter and/or threshold uncertainty. Wilson et al. (1997) recorded ECAPs from an implant patient and noted that the neural representation of stimulus pulse trains (as assessed by ECAP amplitudes) was enhanced at higher pulse rates. Perceptual performance was also enhanced in their patient through the use of high-rate pulse trains. Using pulse-train stimulation, Matsuoka et al. (2000) noted a change in the slope of ECAP amplitude-level functions at specific interpulse intervals. They speculated that those changes were a result of underlying increases in single-fiber RS caused by the repetitive stimuli.

Enhanced stochastic response properties have been inferred mainly through analyses of gross potential

amplitudes; however, the extent to which stochastic behavior is altered on a fiber-by-fiber basis has yet to be determined. Using a computational model of the biophysics of an auditory nerve fiber, Rubinstein et al. (1999) demonstrated that modeled fibers conditioned with high-rate (5000 pps) pulse trains exhibited enhanced stochastic response properties. Also, Rubinstein et al. (1997) presented model results indicating that fibers have greater relative spread when in a relative refractory state. Actual single-fiber data are limited, in part, by the technical difficulties of recording spikes at high rates of electrical stimulation. Using pulse-train stimuli, Javel (1990) showed that the mean firing probability (computed over the duration of the pulse train) of a fiber decreased as the pulse rate was increased from 100 to 800 pps. This result is consistent with the notion that fibers become partially refractory with repeated stimulation, although reduced mean probability could have been due to other processes (e.g., long-term adaptation). In a limited investigation, Hartmann and Klinke (1995) reported reduced synchrony in a fiber stimulated with high-rate pulse trains. Litvak et al. (1999) analyzed the spike interval histograms of cat auditory nerve fibers to determine if electrical pulse trains could induce spontaneous-like firing patterns. Stimulating fibers at pulse rates ranging from 1200 to 24000 pps, they recorded spontaneous-like interval histograms at relatively low pulse rates (1200 pps).

Dynes (1996) reported that across-fiber threshold variability increased as MPI decreased. We also observed greater variability at the smallest MPI values (Figs. 7 and 8). These observations are consistent with the notion that the degree of stochasticity in single-fiber responses increases during the relative refractory period. Our relative spread data provide direct evidence that mammalian auditory nerve fibers in a relative refractory state have increased stochastic response properties. At the shortest MPI tested (500 μ s), mean fiber RS increased almost twofold over the mean RS value obtained at a 4000- μ s MPI. Relatively larger RS values were also observed at MPI values of 600 and 750 μ s. We note that this degree of RS increase is much smaller than that predicted by Matsuoka et al. (2001) with a computational model. It is yet to be determined how a twofold increase in RS would change the aggregate neural representation of electrical signals. Presumably, increased RS would result in better representations because of higher levels of stochastic activity.

Possible limitations of this study

Our ability to characterize ARP and τ was constrained to some degree by technical and methodological limitations. At very short MPIs (500–600 μ s), the recorded

artifact produced by the masker and probe stimuli made it impossible, in a few cases, to detect the reduced-amplitude spikes. Although we reported threshold data for 13 of 34 fibers at an MPI = 500 μ s, we could discern the presence of spikes (but not reliably analyze them) in at least three other fibers. Our examination of mean FE at each MPI (Fig. 6) suggests that the 13 fibers responding at 500- μ s MPI could, on average, respond with a wide range of firing efficiencies. Also, it is important to note that our threshold criterion of 50% FE could be considered rather stringent. A thorough examination of the effect of threshold criterion on recovery parameters would be a useful future study. It is not clear what firing efficiency is most salient to the perception of electrical stimuli by a human cochlear implant patient. A parametric evaluation of recovery functions may assist efforts in relating data from animal experiments to human perceptual data.

We stimulated fibers with a monopolar intracochlear electrode. Stimulus electrode configuration (e.g., monopolar, bipolar, etc.) and electrode position influence how fiber membranes are depolarized. Bipolar stimulation may produce patterns of membrane depolarization that vary significantly from one fiber to another as a function of the orientation of the fiber and the bipolar electrodes. For this reason, we chose monopolar stimulation to reduce the degree of spatial variations in the electric fields produced by the stimulating electrode. We also employed monophasic stimuli to avoid complications that may occur from the interaction of two stimulus phases. We believe that the use of this relatively simple stimulus delivery improves our ability to interpret findings and make them applicable to a relatively large number of cases. However, alternate modes of exciting fibers may produce excitation patterns that differ from those produced in this study.

Our results provide a description of *mean* refractory properties of the fibers encountered in our preparations. Our group analyses (Figs. 7 and 8) indicate significant across-fiber variation in recovery properties. While some variations are likely due to limitations of our data sampling, some may be inherent to the animal model. Anatomical surveys of cat fibers reveal that fiber diameters are distributed across a roughly twofold range (Arnesen and Osen 1978; Liberman and Oliver 1984). A range of diameters could presumably result in a range of fiber recovery rates, as restorative local circuit currents are dependent on axonal resistance and, hence, fiber diameter (Kandel et al. 2000). It is also likely that some response properties—in particular, threshold—will vary significantly as a function of the location of the fiber relative to the stimulating electrode. A relatively small number of fibers with close passage to the electrode may have markedly lower

thresholds. It is not clear to what extent refractory properties will vary with electrode–fiber distance. Our data set is too small to characterize the across-fiber variations in recovery properties that likely exist in the nerve. A survey of a very large number of fibers may be needed to resolve questions of across-fiber variations. In previous work (Miller et al. 1999b), we studied fiber response properties across a population of about 150 fibers and detected generally modest changes in jitter, latency, and RS properties as a function of fiber threshold. One way of assessing the effects of relative fiber and electrode position is to estimate the characteristic frequency of the fiber under study (van den Honert et al. 1997) or use fiber-tracing techniques. Such approaches require significantly more time and still would require large fiber samples to adequately characterize response variations as a function of place.

SUMMARY

We collected data from single auditory nerve fibers of cats that characterize their response properties when stimulated with forward-masked cathodic current pulses. These data provide a fuller understanding of how auditory nerve fibers respond when placed in a refractory state. In contrast to previously published studies, we found that fibers, on average, have relatively short absolute refractory periods ($<500 \mu\text{s}$) as well as relatively short ($<500 \mu\text{s}$) recovery time constants. We also noted that fibers produce reduced-amplitude action potentials in the relative refractory period. They also demonstrate increased dynamic range and stochastic properties during this period. All of these findings are relevant to ongoing efforts to develop accurate computational models of the mammalian auditory nerve fiber. These modeling endeavors could significantly advance our understanding of information transfer in the electrically stimulated auditory nerve as well as accelerate the design of better auditory prostheses.

ACKNOWLEDGMENTS

We gratefully acknowledge the support of the NIH Neural Prosthesis Program, which funded this study under Contract N01-DC-9-2107.

REFERENCES

- ARNESSEN AR, OSEN KK. The cochlear nerve in the cat: topography, cochleotopy, and fiber spectrum. *J. Comp. Neurol.* 178:661–678, 1978.
- BEVINGTON PR. Data reduction and error analysis for the physical sciences. McGraw–Hill New York, 1969.
- BROWN CJ, ABBAS PJ. Electrically evoked whole-nerve action potentials: parametric data from the cat. *J. Acoust. Soc. Am.* 88:2205–2210, 1990.
- BROWN MC. The antidromic compound action potential of the auditory nerve. *J. Neurophysiol.* 71:1826–1834, 1994.
- BRUCE IC, IRLICHT LS, WHITE MW, O'LEARY SJ, DYNES S, JAVEL E, CLARK GM. A stochastic model of the electrically stimulated auditory nerve: pulse-train response. *IEEE Trans. Biomed. Eng.* 46:630–637, 1999.
- CARTEE LA, VAN DEN HONERT CC, FINLEY CC, MILLER RL. Evaluation of a model of the cochlear neural membrane. I. Physiological measurement of membrane characteristics in response to intrameatal electrical stimulation. *Hear. Res.* 146:143–152, 2000.
- DYNES SBC. (1996) Discharge characteristics of auditory nerve fibers for pulsatile electrical stimuli. Ph.D. dissertation, Massachusetts Institute of Technology, Cambridge, MA.
- GAUMOND RP, MOLNAR CE, KIM DO. Stimulus and recovery dependence of cat cochlear nerve fiber spike discharge probability. *J. Neurophysiol.* 48:856–873, 1982.
- GRAY PR. Conditional probability analyses of the spike activity of single neurons. *Biophys. J.* 7:759–777, 1967.
- HARTMANN R, TOPP G, KLINKE R. Discharge patterns of cat primary auditory fibers with electrical stimulation of the cochlea. *Hear. Res.* 13:47–62, 1984.
- HARTMANN R, KLINKE R. Spatial and temporal resolution in multi-channel cochlear implants. *Ann. Otol. Rhinol. Laryngol. Suppl.* 166:113–115, 1995.
- JAVEL E, TONG YC, SHEPHERD RK, CLARK GM. Responses of cat auditory nerve fibers to biphasic electrical current pulses. *Ann. Otol. Rhinol. Laryngol. Suppl.* 128 96:26–30, 1987.
- JAVEL E. Acoustic and electrical encoding of temporal information. In: Miller JM, Spelman FA, (eds) *Cochlear Implants*. Springer-Verlag New York, 1990.
- JAVEL E, SHEPHERD RK. Electrical stimulation of the auditory nerve. III. Response initiation sites and temporal fine structure. *Hear. Res.* 140:45–76, 2000.
- KANDEL ER, SCHWARTZ JH, JESSELL XX. *Principles of Neural Science*, 3rd ed. Elsevier Science, New York, 2000.
- KARAMANOS N, MILLER MI. A new method for estimating stimulus and refractory related functions from auditory nerve discharges. In: Duifhuis H, Horst JW, Wit HP, (eds) *Basic Issues in Hearing. Proceedings of 8th International Symposium on Hearing*. Academic, New York, 1988.
- LEAKE-JONES PA, VIVION MC, O'REILLY BF, MERZENICH MM. Deaf animal models for studies of a multichannel cochlear prosthesis. *Hear. Res.* 8:225–246, 1982.
- LI J, YOUNG ED. Discharge-rate dependence of refractory behavior of cat auditory nerve fibers. *Hear. Res.* 69:151–162, 1993.
- LIBERMAN MC, OLIVER ME. Morphometry of intracellularly labeled neurons of the auditory nerve: correlations with functional properties. *J. Comp. Neurol.* 223:263–176, 1984.
- LITVAK L, DELGUTTE B, EDDINGTON DK, CARIANI PA. (1999) Auditory nerve fiber responses to electric stimulation: modulated and unmodulated pulse trains [abstract]. Conference on Implantable Auditory Prostheses, Asilomar, CA, August 29–September 3, 1999.
- LUTKENHONER B, HOKE M, BAPPERT E. Influence of refractory properties on the response of single auditory nerve fibers to sinusoidal stimuli. *Hear. Res.* 2:565–572, 1980.
- MATSUOKA AJ, RUBINSTEIN JT, ABBAS PJ, MILLER CA. The neuronal response to electrical constant-amplitude pulse train stimulation: evoked compound action potential recordings. *Hear. Res.* 149:115–128, 2000.
- MATSUOKA AJ, RUBINSTEIN JT, ABBAS PJ, MILLER CA. The effects of interpulse interval on stochastic properties of electrical stimulation: models and measurements. *IEEE Trans. Biomed. Eng.* 48:416–424, 2001.

- MILLER CA, ABBAS PJ, RUBENSTEIN JT, ROBINSON BK, MATSUOKA AJ, WOODWORTH G. Electrically evoked compound action potentials of guinea pig and cat: responses to monopolar, monophasic stimulation. *Hear. Res.* 119:142–154, 1998.
- MILLER CA, ABBAS PJ, ROBINSON BK, RUBINSTEIN JT, MATSUOKA AJ. Electrically evoked single-fiber action potentials from cat: responses to monopolar, monophasic stimulation. *Hear. Res.* 130:197–218, 1999a.
- MILLER CA, ABBAS PJ, RUBINSTEIN JT. An empirically based model of the electrically evoked compound action potential. *Hear. Res.* 135:1–18, 1999b.
- MILLER CA, ABBAS PJ, BROWN CJ. An improved method of reducing stimulus artifact in the electrically evoked whole nerve potential. *Ear Hear.* 21:280–290, 2000.
- MILLER CA, ROBINSON BK, RUBINSTEIN JT, ABBAS PJ, RUNGE SAMUELSON C. Auditory nerve responses to monophasic and biphasic electric stimuli. *Hear. Res.* 151:79–94, 2001.
- MINO H, RUBINSTEIN JT, MILLER CA, ABBAS PJ. Effects of remaining hair cells on cochlear implant function. Fourth Quarterly Progress Report Contract N01 DC-9-2106, NIH, Washington, DC, 2000.
- MORSE RP, EVANS EF. Enhancement of vowel coding for cochlear implants by addition of noise. *Nat. Med.* 2:928–932, 1996.
- RUBINSTEIN JT. Threshold fluctuations in an N sodium channel model of the node of Ranvier. *Biophys. J.* 68:779–785, 1995.
- RUBINSTEIN JT, MATSUOKA AJ, MILLER CA, ABBAS PJ. Computational model of the auditory nerve: interesting aspects of the recovery process. *Assoc. Res. Otolaryngol. Abstr.* 226, 1997.
- RUBINSTEIN JT, WILSON BS, FINLEY CC, ABBAS PJ. Pseudospontaneous activity: stochastic independence of auditory nerve fibers with electrical stimulation. *Hear. Res.* 127:108–118, 1999.
- STYPULKOWSKI PH, VAN DEN HONERT C. Physiological properties of the electrically stimulated auditory nerve. I. Compound action potential recordings. *Hear. Res.* 14:205–223, 1984.
- VAN DEN HONERT C, STYPULKOWSKI PH. Physiological properties of the electrically stimulated auditory nerve. II. Single fiber recordings. *Hear. Res.* 14:225–243, 1984.
- VAN DEN HONERT C, FINLEY CC, XUE S. Microstimulation of auditory nerve for estimating cochlear place of single fibers in a deaf ear. *Hear. Res.* 113:140–154, 1997.
- VERVEEN AA. *Fluctuation in Excitability*. Drukkerij, Holland N.V., Amsterdam, 1961.
- WILSON BS, FINLEY CC, ZERBI M, LAWSON DT. Speech processors for auditory prostheses. Seventh Quarterly Progress Report, NIH Contract N01-DC-2-2401, NIH, Washington, DC, 2000.
- WILSON BS, FINLEY CC, LAWSON DT, VAN DEN HONERT C. Speech processors for auditory prostheses. Seventh Quarterly Progress Report, NIH Contract N01-DC-5-2103, NIH, Washington, DC, 1997.
- XU SA, SHEPHERD RK, CHEN Y, CLARK GM. Profound hearing loss in the cat following the single co-administration of kanamycin and ethacrynic acid. *Hear. Res.* 70:205–215, 1993.