Changes Across Time in Spike Rate and Spike Amplitude of Auditory Nerve Fibers Stimulated by Electric Pulse Trains

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ABSTRACT

We undertook a systematic evaluation of spike rates and spike amplitudes of auditory nerve fiber (ANF) responses to trains of electric current pulses. Measures were obtained from acutely deafened cats to examine time-related changes free from the effects of hair-cell and synaptic adaptation. Such data relate to adaptation that likely occurs in ANFs of cochlear-implant users. A major goal was to determine and compare rate adaptation observed at different pulse rates (primarily 250, 1000, and 5000 pulse/s) and describe them using decaying exponential models similar to those used in acoustic studies. Rate-vs.-time functions were best described by two-exponent models and produced time constants similar to (although slightly greater than) the “rapid” and “short-term” components described in acoustic studies. There was little dependence of these time constants on onset spike rate, but pulse-rate effects were noted. Spike amplitude changes followed a time course different from that of rate adaptation consistent with a process related to ANF interspike intervals. The fact that two time constants governed rate adaptation in electrically stimulated and deafened fibers suggests that future computational models of adaptation should not only include hair cell and synapse components, but also components determined by fiber membrane characteristics.

Keywords: auditory nerve, electric stimulation, adaptation, cat, cochlear implant, single fiber

INTRODUCTION

Acoustic and electric excitation of auditory nerve fibers (ANFs) produce markedly different response characteristics (Kiang et al. 1965; Hartmann et al. 1984; van den Honert and Stypulkowski 1984; Javel et al. 1987; Javel and Shepherd 2000; Parkins and Colombo 1987; Litvak et al. 2001). However, our understanding of how ANFs respond to repetitive electric stimuli is limited. This presents roadblocks to: (1) the creation of accurate computational models of ANF responses to repetitive electric stimuli (e.g., Wilson et al. 1995; Bruce et al. 1999; Rubinstein et al. 1999; Briare and Frijns 2005; Cartee 2006), (2) the ability to exploit the electrically evoked compound action potential (ECAP) as a convenient means of understanding underlying ANF responses, and, perhaps, (3) the improvement of stimulus coding regimes used in auditory prostheses.

Earlier studies of ANF responses to repetitive electric stimuli were based on small sample sizes (Javel et al. 1987; van den Honert and Stypulkowski 1987a; Parkins 1989; Javel 1990; Dynes and Delgutte 1992; Killian 1994) and, perhaps not surprisingly, variously characterized the nature of “electric” adaptation. Consistent with earlier work, Javel and Shepherd (2000) reported threshold or rate adaptation in a limited number of fibers, but did not quantify the effects. Dynes and Delgutte (1992) suggested that

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adaptation to electric sinusoids follows a single negative exponential course across several hundred milliseconds. Parkins (1989) was more equivocal about the existence of electric adaptation.

Exploring the possible benefits of high-rate (e.g., 5000 pulse/s) electrical stimulation, Litvak et al. (2001) first reported systematic data on adapted ANF responses of deafened ears. They noted adaptation over the course of 100–200 ms after pulse train onset, reporting that rate decrements increased as pulse rate increased from 1200 to 4800 and from 1200 to 24,000 pulse/s. Greater adaptation was observed as stimulus rate was increased from 1200 to 4800 pulse/s. Because of technical limitations, Litvak et al. (2001) were unable to investigate the existence of a “rapid” adaptation component.

Our study focuses on quantifying ANF adaptation to pulse trains at rates used by cochlear prostheses (i.e., from 250 to 5000 pulse/s). Several goals were pursued in this study. First, by means of effective reduction of stimulus artifacts, we were able to investigate the existence of both rapid and short-term components of electric adaptation. Adaptation to acoustic stimuli is known to follow rapid, short-term, and long-term time constants (Smith 1977; Westerman and Smith 1984; Javel 1996); however, studies have not quantified adaptation rates to repetitive electric stimuli. By quantifying adaptation attributable only to membrane depolarization, our data may be useful for modeling efforts that have, to date, included only hair-cell and synaptic components. This clarifying approach—studying adaptation in electrically stimulated, deafened animals—was suggested by Chimento and Schreiner (1991) who concluded that not all acoustic adaptation effects could be attributed to the hair cell and synapse. A second goal was to examine the effect of onset spike rate on adaptation. Third, because earlier work demonstrated that spike amplitude is affected by repeated stimulation (Miller et al. 2001), we examined spike rate and spike amplitude trends across pulse train presentations. Finally, previous work has noted considerable across-fiber variability in rate adaptation (Dynes and Delgutte 1992; Litvak et al. 2001). We therefore also examined the possibility that this variability is correlated with other physiologic properties.

METHODS

Surgical preparation. This study used eight adult cats with no visible middle ear pathology. Each was first sedated with ketamine (22 mg/kg, i.m.) and xylazine (1.1 mg/kg, i.m.), then maintained at surgical levels of anesthesia with Nembutal (8–13 mg/kg, i.v.) given at intervals indicated by pinch reflex and altered vital signs. Atropine sulfate (0.04 mg/kg per 8 h, s.c.) was

given to reduce mucosal secretions and dexamethasone (1.0 mg/kg per 12 h, i.v.) was given to reduce brain edema. The trachea was intubated and connected to a Harvard Apparatus Model 665 ventilator set for 12- to 15-ml tidal volume and, approximately, a 50 cycles/min rate. Room air was used unless, late in the experiment, declining blood oxygen levels warranted an oxygen supply. Vital signs (heart rate, non-invasive blood oxygen, and core temperature) were monitored throughout the experiment using a Pace Tech (4000B) monitor. Expired CO₂ was measured using a BCI Industries capnometer.

The auditory nerve was exposed using a standard posterior fossa approach. Brain tissue dorsal to the nerve was retracted medially by cotton balls and a head-mounted device. The bulla was exposed and a cochleostomy made approximately 0.5 mm central and posterior to the round window for later insertion of a stimulating electrode array. Seven of eight cats were deafened by intracochlear infusion of 50 μ l of neomycin sulfate (10% w/v), by repeatedly removing and replacing perilymph with 5- μ l boluses of the aminoglycoside. This resulted in, minimally, an 80-dB shift in the click-evoked ABR threshold. Chemical deafening was not performed in one cat (which provided data from three fibers) because auditory brain stem responses to click stimuli indicated a 70-dB loss in sensitivity during the experiment before ANF recordings. There was also a lack of acoustic-evoked and electrophonic responses, as well as spontaneous activity, from the ANFs. Surgical and experimental protocols were approved by the University of Iowa Animal Care and Use Committee and complied with NIH standards.

Stimuli. An eight-band Nucleus stimulating electrode array (Cochlear Corp.) was inserted apically through the cochleostomy to insertion depths of 5–6 mm. Only the most apical band was used so that electric stimuli were presented in a monopolar mode, with a return needle electrode positioned in muscle. Stimuli were controlled and generated by custom programs written using Labview, which drove an Instrutech Corporation ITC-18 data acquisition board with 16-bit resolution and 100,000 sample/s output rate. This, in turn, drove an optically isolated, capacitively coupled current source. Search stimuli consisted of single 40 μ s/phase biphasic pulses (cathodic leading phase) presented at 30 pulse/s. This stimulus was employed to evoke electrically evoked compound action potentials (ECAPs) that were used to assess nerve sensitivity and determine the search stimulus level (defined as the level that evoked ECAP amplitudes approximately 90% of maximum).

Unless otherwise noted, experimental stimuli consisted of pulse trains of 300 ms duration. Pulse rates

of 250, 1000, and 5000 pulse/s were chosen to span rates used by most cochlear prostheses. A limited amount of data was collected using 10,000 pulse/s trains of shorter (20 μ s/phase) pulses. Pulse trains were presented repeatedly to obtain ANF firing statistics. At minimum, 30 presentations were used; at maximum, 100 trains were used. The intertrain interval was 900 ms. Whenever possible, ANFs were presented with trains of all rates and at several levels. Levels were chosen to cover a wide range of response probabilities, considering both the onset response and the asymptotic (adapted) response. Whenever possible, levels spanned the range that produced a low (20–40%) firing probability to the first pulse and a maximal (saturated) response rate over the final 100-ms epoch of the stimulus train.

Recording conditions. ECAPs were recorded before ANF data collection and at later intervals to assess nerve sensitivity. They were recorded using a Pt/Ir two-ball electrode (0.3–0.4 mm diameters), with one ball placed on the nerve-trunk surface and the other 2 mm dorsal to it. Micropipettes pulled from 1.0 mm I.D./0.58 mm O.D. glass (A-M Systems) and filled with 3 M KCl were used to record ANF spikes. Potentials were amplified ($\times 10$) and filtered (first-order 10 kHz low pass) by an Axon Instruments Axoprobe amplifier. Additional filtering was provided by a 100-Hz two-pole Butterworth high-pass filter and by a 30-kHz six-pole Butterworth low-pass filter. Power-line induced artifacts were reduced using a Humbug noise-template subtraction circuit (Quest Scientific Instruments, Inc.).

Data analysis. Analyses were conducted after each experiment using custom Matlab programs (Natick, MA, USA; version 6.1). Two means of stimulus artifact reduction were employed. For pulse rates of 250 and 1000 pulse/s, an extension of the template subtraction method (Miller et al. 1999) was used. This used a spike amplitude threshold to select individual response waveforms (traces) deemed free of action potentials. All such “no spike” traces were then averaged to form an “artifact template” that was then subtracted from all traces. This procedure was partially automated by initially computing the amplitude threshold on the basis of the waveform noise floor. The software required manual observation of the “templated” results to confirm good results. Importantly, a separate template waveform was computed for the response epoch after each pulse. This scheme thus accounted for changes in ECAP or stimulus artifact contaminants over the course of the pulse train. After some pulses, it was not possible to derive a template (because of, say, 100% firing probability to that pulse). In those cases, a template

created for an “adjacent” or “nearby” stimulus pulse was used. For the highest two pulse rates (5000 and 10,000 pulse/s), the moving boxcar filter approach of Litvak et al. (2003) was used. In most cases, artifacts were successfully eliminated or largely reduced. In the few cases in which artifact rejection was inadequate, the data were discarded.

To quantify rate and spike amplitude changes across the pulse trains and perform curve-fitting, eight non-overlapping analysis windows were defined for which spike rates and amplitudes were computed. These “wide bin” windows were: 0–4, 4–12, 12–24, 24–36, 36–48, 48–100, 100–200, and 200–300 ms after pulse-train onset. These wide bins are typically specified by their midpoints. An additional 0- to 12-ms window was used in some analyses to compute an “onset” spike rate less prone to across pulse-rate variations. Finally, smaller (1 ms) bins were used for a limited number of poststimulus-time histograms (PSTHs) presented in this report. For each fiber, PSTHs were obtained at a minimum of two pulse rates (typically 250 and 5000 pulse/s) and three stimulus levels per pulse rate. The collection of a PSTH typically required about 1 min.

Time constants were computed by linearization of the wide-bin PSTHs using the log function and applying linear regression. This approach assumed that asymptotic rates were achieved by 300 ms and therefore was insensitive to long-term adaptation effects. However, it provided a model with few (i.e., two) free variables, a desirable property considering the small number of analysis windows. Both single-exponent and double-exponent models were fit to the wide-bin data. For the latter model, a two-stage linearization process was used in which the larger time constant was first estimated using PSTH data from the last four bins. The fitted curve was then subtracted from the raw data, allowing for estimation of the smaller time constant through a second linearization. This procedure is valid only if the underlying time constants are sufficiently different in magnitude (say, by a factor of four) such that their effects can be temporally separated, as noted above. A pilot study was conducted on PSTH data of a subset of ANFs to arrive at rough estimates of the two time constants and to aid our selection of appropriate bounds of the eight wide-bin windows. It determined that the two-time-constant model yielded time constants that typically differed by factors between 7 and 9.

To facilitate group ANF analyses, stimulus levels were expressed as decibels relative to each subject’s ECAP threshold, the latter defined by the level evoking an ECAP amplitude 10% of the maximum evoked amplitude. Slopes of the rate-level functions were computed by fitting a line to the linear portion of these functions, with at least three points required

for each estimate. ANF thresholds were defined by the level that elicited a 100 spike/s rate over the aforementioned “onset” (0–12 ms) response epoch. This moderately high rate was chosen as it was at or near the minimum rate obtained across the different pulse rates for most fibers. Dynamic range (DR) was computed for a smaller number of ANFs and was defined as the dB range over which rate changed from 50 to 250 spike/s, with the upper rate determined by the maximum rate elicited by 250 pulse/s trains. In most cases, interpolation was required and, in a few cases, extrapolation was used, based on linear regression. As observed previously (Miller et al. 1999), slow, upward shifts in threshold can occur while collecting data from ANFs. Such shifts occurred in less than 10% of fibers and necessitated limiting comparisons across levels or rates over time periods in which the ANF exhibited stable responses.

RESULTS

Data from 89 fibers of eight cats are reported here. No fibers exhibited spontaneous activity or electrophonic responses. Examples of spike waveforms obtained before and after performing artifact rejection are shown in Figure 1. In each case, the superimposed traces represent the responses to 30 repeated presentations of the pulse-train stimulus. Across-pulse integration is evident in the spikes evoked by the 1000 pulse/s train, i.e., there is a greater probability of response to the second or third pulse relative to that of the first pulse. Responses to the 5000 pulse/s trains are clustered at intervals of about 4 ms, suggesting a strong influence of refractoriness, at least shortly after pulse-train onset.

PSTHs from two ANFs are shown in Figure 2, with one ANF contributing data at 250, 1000, and 5000 pulse/s and another contributing the 10,000 pulse/s data. In each case, responses are shown for three stimulus levels. Histograms based on 1-ms bins and the “wide bin” windows are shown using vertical bars and open circles, respectively. Casual inspection of the narrow-bin PSTHs may suggest that they overemphasize the degree of adaptation. For example, the narrow-bin PSTH of the lower left panel suggests that adaptation occurred; however, the flat wide-bin histogram indicates that this decrement is caused by desynchronization that may be difficult to see in the 1-ms bin PSTHs of this figure.

Looking across stimulus rates, it appears that rate adaptation increases with pulse rate. Level, however, interacts with this effect, warranting more careful analysis. In several cases, the wide-bin PSTHs (circles) describe two adaptation rates. Particularly for the

FIG. 1. Examples of waveforms recorded in response to pulse trains presented at three rates. In each of the three cases shown, “raw” waveforms (with large electrical stimulus artifacts) are plotted above the processed waveforms. See text for explanations of stimulus artifact reduction schemes. Each of the three sets of “raw” traces and each of the three sets of processed waveforms are plotted to the same scales (indicated by the two calibration bars in the upper plots). Stimulus parameters (pulse rate, stimulus level) are shown at the upper right of each graph.

FIG. 2. Examples of spike-rate adaptation observed in the PSTHs from the responses of two auditory nerve fibers (ANFs) at the four stimulus rates used in this study. Histograms for stimulus rates of 250, 1000, and 5000 pulse/s were provided by one fiber, whereas a second fiber provided the 10,000 pulse/s rate data. Each column contains poststimulus-time histograms (PSTHs) obtained at three stimulus levels. Histograms based on 1-ms bins are plotted with vertical bars, whereas those based on progressively wider bins (defined in the text) are plotted using open circles.

pulse rates greater than 250 pulse/s, adaptation is, in many cases, characterized by both “rapid” and “short-term” components, using the terms defined in the acoustic-adaptation literature (Smith and Brachman 1982; Westerman and Smith 1984). Finally, it is worth noting in these exemplar histograms that onset spike rates can be very high and increase as pulse rate goes from 250 to 5000 pulse/s.

Rate-level functions. Rate-level functions are shown in Figure 3 for 15 fibers of six cats. The ANFs of this figure were chosen to provide across-rate comparisons, as in most cases, three stimulus rates were examined. Levels are expressed relative to each cat’s ECAP threshold. Each abscissa spans 9 dB to ease across-fiber comparisons. Functions for 250 and 5000 pulse/s rates are plotted for each fiber, whereas data for 1000 and 10,000 pulse/s rates are shown for only 10 and 3 ANFs, respectively. Note that the data obtained using the 10,000 pulse/s stimuli were collected using a shorter pulse duration (20 μ s/phase

vs. 40 μ s/phase), but in all cases, stimulus levels are normalized to those used to evoke ECAPs using 40 μ s/phase pulses. Across fibers, there is a general trend for lower thresholds as pulse rate was increased, although the degree of this trend varied considerably across fibers. It is notable that thresholds for the 20 μ s/phase, 10,000 pulse/s, stimuli were the lowest in the three fibers tested, in spite of strength-duration effects (see Discussion). As plotted, the functions follow generally linear growth rates. Some fibers (D66-3-11, D66-3-5, and D67-1-2) exhibit more gradual growth for the highest pulse rate. The slopes also demonstrate considerable across-fiber variability. In most of the plots of this figure, it is evident that the levels used in this study were not sufficiently high to reveal rate saturation.

Rate-level functions for 5000 pulse/s stimuli and for three different response epochs are shown in Figure 4a. Specifically, functions are shown for response rates computed over the first millisecond of response, the first 12 ms after train onset, and the

FIG. 3. Rate-level functions for 15 ANFs obtained at multiple stimulus pulse rates, demonstrating greater sensitivity (left-shifted plots) for functions obtained with high-rate stimulation. Abscissa and ordinate scaling is identical for all graphs. Dotted lines indicate cases in which linear regression was used to estimate threshold values. Data for 10,000 pulse/s stimuli (diamond symbols) were available in only three of the fibers.

final 100 ms of the response to the 300-ms pulse train. In comparison to the functions of Figure 3, these plots generally span greater ranges of stimulus level and response rates. In most cases, the initial (0–1 ms) response grows most rapidly and saturates, typically at a 1000 spike/s rate (i.e., 100% firing efficiency). In one case (top left panel), the fiber responded at a maximal rate of 2000 spike/s, indicating fast recovery from refractoriness within the 1-ms analysis window. The increase in the initial rate seen for fiber D66-3-11 at a level above apparent saturation is consistent with this explanation. Spike

FIG. 4. Examples of the effect of adaptation on rate-level functions assessed across different temporal analysis windows. (a) Functions obtained from six fibers of this study using three windows to characterize onset response (0- to 1-ms window), the “rapid” response (0- to 12-ms window) and the steady state, or adapted (200–300 ms) response. Stimulus rate was 5000 pulse/s. (b) Normalized ANF rate-level functions obtained in response to pure-tone stimuli. The functions of the left graph are reproduced from those reported by Westerman and Smith (1984, Fig. 6), whereas the functions in the right graph have been normalized to the maximum value of each function in the left graph. Their data are based on mean values of 19 ANFs. Their “onset” responses are the maxima that occurred within a 1-ms window near stimulus onset. “Rapid”, “short term”, and “steady state” functions were derived from their two-exponential model fits.

rates increased more slowly for the two other response epochs, reflecting refractory and adaptation effects. As discussed later, the trends apparent in this figure are different than those observed with acoustic stimulation. The format of our rate-level functions facilitates comparison of our electric adaptation data with similar analyses of acoustically driven fibers provided by Westerman and Smith (1984). Figure 4b (bottom-left panel) presents their group (mean) data and their same data normalized to the maximum values (bottom right panel), which facilitates comparisons of the shapes of these functions. Whereas the acoustic functions (for the four indicated response epochs) have similar shapes, the longer-term functions (“short term” and “steady state” curves) have regions of somewhat greater compression. The electric functions (Fig. 4a) reveal a different pattern. Across the three time epochs, the rapid (onset) electric function shows precipitous growth and saturation, whereas relatively stable growth is observed over much greater ranges of level for the later response windows.

Table 1 summarizes threshold and DR data for all available ANFs at 250, 1000, and 5000 pulse/s rates. The table shows threshold data for the onset (0–12 ms) analysis window and DR data for both the onset and late (200–300 ms) windows. A one-way repeated analysis of variance (ANOVA) and a post hoc Bonferroni test were run to compare ANF thresholds (for the onset window) across the three pulse rates. Data were available from 15 fibers. The effect of pulse rate on threshold was significant ($F_{(2,13)} = 17.1$, $p = 0.01$). Specifically, threshold for the 5000 pulse/s rate was significantly lower than that for 250 pulse/s (at $p_{\text{error}} = 0.01$) and 1000 pulse/s (at $p_{\text{error}} = 0.01$). There was no statistically significant difference in the thresholds between pulse rates of 250 and 1000 pulse/s.

As fewer data were available for within-fiber (i.e., repeated ANOVA) analyses of pulse-rate effects on DR, a one-way ANOVA was conducted so that data from all available fibers could be included. The test assessed DR effects across the three pulse rates and 15 fibers. For onset DR measures, the pulse rate

effect on DR was significant ($F_{(2, 46)} = 4.26$, $p_{\text{error}} = 0.02$). A post hoc Bonferroni test showed that DR for the 5000 pulse/s rate was significantly greater than that for 250 pulse/s (at $p_{\text{error}} = 0.07$) and for 1000 pulse/s ($p_{\text{error}} = 0.04$). For the late (200–300 ms) responses, pulse-rate effects were also significant ($F_{(2, 28)} = 3.78$, $p_{\text{error}} = 0.035$). A post hoc test showed that DR for 5000 pulse/s was significantly greater than that for 1000 pulse/s ($p_{\text{error}} = 0.05$). In summary, 5000 pulse/s trains elicited greater DRs than were obtained at lower pulse rates. To compare our results with those from eight fibers reported by Litvak et al. (2001), DRs were computed from their rate-level functions using our criteria, noting that their data were based on a 4800 pulse/s stimulus and an analysis window 140–150 ms after train onset. Their dynamic ranges were compared against our data obtained with 5000 pulse/s stimuli, using the 200- to 300-ms analysis window. On average, our DRs were 1.2 dB greater than those of Litvak et al. (2001). Using an unpaired t test, the 5000 pulse/s DRs our study were found to be significantly greater than theirs ($t_{(18)} = 4.32$, $p_{\text{error}} = 0.01$).

Spike rate adaptation. Three metrics were used to describe spike rate adaptation: rate decrement, normalized rate decrement, and time constants of decaying exponential functions fit to PSTHs. Rate decrements were computed by subtracting the rate in the final window (200–300 ms) from that of the onset (0–12 ms) window and normalized decrements were computed by dividing by the onset rates. The absolute and normalized decrements are plotted in the left and right columns of Figure 5, respectively, for all ANFs and pulse rates. The gray areas in each graph define regions bounded by lines with slopes of 1.0 and 0.9. The normalized decrement of 0.9 was used as a boundary to somewhat arbitrarily define “strong” and “weak” adapting ANFs. For an ANF to qualify for one of these categories, all normalized decrements measured from that fiber had to either be greater or less (respectively) than 0.9. Dark lines plotted in the graphs of the left column indicate

TABLE 1

Summary of mean single-fiber threshold and dynamic range (DR) data for all available auditory nerve fibers (ANFs) at 250, 1000, and 5000 pulse/s rates									
Stimulus rate (pulse/s)	Threshold for 0- to 12-ms epoch (dB re: ECAP threshold)			DR for 0- to 12-ms epoch (dB)			DR for 200- to 300-ms epoch (dB)		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
250	2.11	2.68	39	1.10	0.48	20	1.77	0.56	12
1000	1.24	3.15	18	0.95	0.39	10	1.61	0.49	8
5000	0.26	3.00	42	1.56	0.81	19	2.28	0.64	11

Threshold and DR data are expressed as decibels relative to each cat’s ECAP threshold. Standard deviation (SD) and number of contributing fibers (n) are also listed.

linear regression fits, whereas lines defined by open circles refer to data from Litvak et al. (2001).

Several trends are evident in Figure 5. At the lowest (250 pulse/s) rate, spike rate decrements were generally proportional to the onset spike rate, with some deviation from that trend at the lowest and highest spike rates. That is, the normalized rate decrement is largely independent of the onset spike rate. Also, for onset spike rates spanning 25 to 225 spike/s, the mean normalized decrement was relatively constant at 0.47 (panel B). However, at low (<25 spike/s) and high (>225) onset spike rates, the normalized decrements span lower values. Panel C of Figure 5 isolates individual data sets collected from 12 fibers of panel B that spanned the greatest range of onset spike rates. These plots confirm that individual ANF functions follow the “inverted U” shape suggested by the scatter plot of panel B.

Finally, at 250 pulse/s, only 1 (1.2 %) of 80 fibers was a “strong adapter” (with all normalized decrements above the 0.9 criterion), whereas 55 (69%) of 80 were “weak adapters”, having all data below that criterion. In contrast, at the 5000 pulse/s stimulus rate, 27 (33%) of 82 fibers were “strong adapters”, whereas only 9 (11%) of 82 were “weak adapters”. For the higher pulse rates, spike rate decrements became proportionally smaller with increases in the onset spike rate, consistent with the observation that greater stimulus levels can partially overcome adaptation. This is also suggested by the wide range of decrements observed for the 250 pulse/s rate for response rates near 250 spike/s. Finally, the ability of fibers to overcome adaptation depends both on pulse and spike rate. With low (250 pulse/s)-rate pulses, some fibers can be driven to fully overcome adaptation, as can be seen by the wide range of normalized decrements in the top panel for the 250 pulse/s rate. This is not the case at higher stimulation rates. Indeed, for the 1000 and 5000 pulse/s rates, the lowest achievable normalized decrements were near 0.4.

One question arising from the above data is whether or not the degree of adaptation observed for one pulse rate is correlated with that observed in response to another pulse rate. The two graphs of Figure 6 compare absolute rate decrements observed for 250 pulse/s stimuli (upper panel) and 1000 pulse/s stimuli (lower panel) against the decrements observed for 5000 pulse/s stimuli. To control for onset rate, these comparison plots were made by selecting x - y data pairs such that their onset response rates did not differ by more than 10%. From these plots, it is clear that the degree of adaptation observed at one pulse rate is correlated with that obtained at other pulse rates. For both the linear regressions shown in Figure 6, nondirectional tests of the significance of the correlations (e.g., Bevington 1969) had very low error probabilities ($p < 0.001$). Not

FIG. 5. Group ANF data showing the effect of pulse rate and response rate on rate adaptation. Rate decrements (left column) and normalized rate decrements (right column) for each ANF are plotted as a function of onset spike rate for four pulse rates. Normalized data were computed as described in the text. Gray regions indicate normalized decrements greater than or equal to 0.9, the criterion used to define an ANF as a “strong adapter” (as defined in the text). The line segments defined by gray circles indicate linear regression trends from Litvak et al. (2001) for stimulus rates of 1000 and 4800 pulse/s. Panel C plots a subset of the data in panel B, with data from 12 fibers selected on the basis that they spanned the greatest ranges of onset spike rate. Those functions confirm the inverted U-shaped function suggested by the general trend seen in panel B.

FIG. 6. Demonstration of correlations in spike-rate decrements (adaptation) observed across different pulse rates. Spike rate decrements caused by 250 pulse/s trains (upper graph) and 1000 pulse/s trains (lower graph) are plotted versus the decrements caused by 5000 pulse/s stimuli. To control for spike onset rate effects, each datum represents x - y pairs obtained from an ANF such that the difference of onset spike rates for the x and y values did not exceed 10%. Regressions indicate that the degree of adaptation observed at one pulse rate is correlated to that observed at other pulse rates. The upper graph contains data from 53 fibers and the lower graph contains data from 35 fibers.

surprisingly, this correlation is somewhat weaker for the comparison against the lowest (250 pulse/s) stimulus rate. Figure 6 again demonstrates that spike decrements are quite similar for 1000 and 5000 pulse/s stimuli (lower plot), whereas low-rate (250 pulse/s) stimuli result in less adaptation.

To describe the time course of rate adaptation, wide-bin PSTHs (see Fig. 2, circle plots) for each fiber, pulse rate, and level were fit to both single-exponent and double-exponent decaying functions.

Figure 7 shows the results of those fits for 250, 1000, and 5000 pulse/s stimulus rates by plotting the time constants versus the onset spike rate. Whereas each PSTH was fit to both models, in the case of Figure 7, each PSTH is described either by the single- or double-exponent model, the choice based somewhat arbitrarily on which model yielded a greater correlation coefficient. Data are plotted only for those fits that resulted in r values greater than or equal to 0.7 (across all PSTHs, 79% fit this criterion). Across the six graphs, each fiber contributed, on average, 3 points to each scatter plot. In the plots of the lower row, both the rapid and short-term time constants are plotted for each PSTH. With the notable exception of the single-exponent model for 5000 pulse/s stimuli, the time constants show no dependence on the initial spike rate. The functional dependence seen in the upper right plot may simply reflect limitations of the single-exponent model, which may not adequately model PSTH trends across spike rates. This is corroborated by the fact that the two-exponent model data fail to demonstrate a spike rate dependency. Data from the remaining five plots suggest constancy of both the rapid and short-term time constants. Table 2 presents medians, means, and standard deviations of each time-constant estimate for both the single- and two-exponential models at each of pulse rate.

As larger correlation coefficients may simply result from the use of a more complex model (i.e., the double-exponent model), a comparison of the two models was run by fitting both to all data using the nonlinear mixed model analysis (NLMIXED) provided by the SAS/STAT (version 9.1) statistical analysis software. Separate analyses were run for each of the three stimulus rates. To capture any effect of onset spike rate, separate analyses were run across different ranges of onset spike rates, with the ranges selected to span the total range observed for each stimulus rate while dividing each data set into 4-5 subgroups. Akaike's Information Criterion (AIC) was computed for each onset-rate subgroup, pulse rate, and model to determine which model better fits the data (unlike the correlation coefficient, the AIC accounts for model complexity by effectively penalizing the addition of free model parameters). Ratios of the AIC computed for the double- and single-exponent model fits are plotted in Figure 8 for different pulse rates and ranges of onset spike rates. Values less than 1 indicated that the double-exponent model is "more optimal" than the single-exponent model. With the exception of one ratio (obtained at low spike rates for 250 pulse/s stimuli), all AIC ratios were less than 1, indicating that the data generally fit the double-exponent model better than they do the single-exponent model.

FIG. 7. Across-fiber summary of rate-adaptation time constants obtained using a single-exponent (upper row) and a two-exponent (lower row) model of adaptation for pulse rates of 250, 1000, and 5000 pulse/s. Numbers of data points and contributing fibers are shown in each panel. Results indicate that the rapid and short-term adaptation time constants are generally independent of onset response rate, used here as a correlate to stimulus level. The curved trend seen in the upper-right plot is believed to be an artifact of the limitations of the single-exponent model.

The rapid and short-term time-constant data (obtained from the double-exponent model), combined across spike rates, are plotted versus stimulus rate in Figure 9, along with median values. Linear regressions are also plotted and indicate that the time constants decreased as the pulse rate was increased. The test of significance of the correlation coefficient (for rapid time constant: $r=0.03$, $t_{(502)}=0.65$, $p_{\text{error}}=0.26$; for short-term time constant: $r=0.26$, $t_{(502)}=5.91$, $p_{\text{error}}=0.01$) indicates statistically significant dependencies of the short-term time constants on pulse rate.

“Strong” and “weak” adapters. As noted above, the categories of “strong” and “weak” adapting fibers

were defined using the normalized decrement of 0.9 as the boundary value. These categories provided a means of exploring possible correlations between degree-of-adaptation and other physiologic properties. In the following analysis, “strong” and “weak” adapting ANFs were defined on the basis of data obtained at 5000 pulse/s. ANF thresholds and ANF rate-level slopes are plotted in Figure 10 for the two categories of strong and weak adapters for stimulus rates of 250 and 5000 pulse/s. Dependence on these categories is seen for both ANF threshold (upper plot) and rate-level slopes (lower plot).

A two-way ANOVA was performed to assess the effect of pulse rate and fiber category (i.e., “strong”, “weak” adapters) on threshold. The effect of fiber

TABLE 2

Summary of the spike rate adaptation time constants computed for the data collected at 250, 1000, and 5000 pulse/s stimulus rates

Stimulus rate (pulse/s)	τ values (ms) Single-exponent model			τ values (ms) Two-exponent model					
	Median	Mean	SD	Rapid			Short-term		
				Median	Mean	SD	Median	Mean	SD
250	64.4	74.6	44.8	10.7	11.8	6.80	90.58	98.0	42.3
1000	47.5	49.9	39.9	8.01	8.1	4.09	79.3	88.6	39.4
5000	35.9	40.0	32.2	7.69	8.2	4.12	69.7	73.4	33.6

As there was little dependence on onset spike rate (cf Fig. 7) the estimates were collapsed across spike rate. Medians, means, and standard deviations for the single time-constant values and the two time-constant values are listed. Data were selected such that only model fits that produced correlation coefficients of 0.7 were accepted.

FIG. 8. Results of comparisons of “goodness of fit” of the single-exponent and double-exponent models used to fit PSTH data. Ratios of the Akaike’s information criterion (AIC) computed for the double-exponent model (“Model 2”) and the single-exponent model (“Model 1”) are plotted as a function of different ranges of onset spike rates, with pulse rate as a parameter. Values less than 1 indicate that the double-exponent model was, on average, a better fit than the single-exponent model. The horizontal brackets about each plotted datum indicate the range of onset spike rates used for each AIC computation.

category ($F_{(1, 30)} = 20.1$, $p_{\text{error}} = 0.01$) was significant, whereas the effect of pulse rate and its interaction with fiber category were not. Data were collapsed across pulse rates to perform a follow-up assessment of fiber category effects. Results showed that the

FIG. 9. Rate adaptation time-constants estimated with the two-exponent model. Regression lines are shown by the thick line segments. The correlation coefficient for short-term time constant is statistically significant but that for rapid time constant is not (see text). Median values for each pulse rate are plotted using open symbols.

mean threshold for strong adapters was greater than that of the weak adapters ($p_{\text{error}} = 0.01$). After removing one outlier (Fig. 10, slope = 520 spike/s per dB), a second ANOVA assessed pulse-rate and fiber-category effects on the rate-level slope. A significant effect of fiber category ($F_{(1, 42)} = 11.80$, $p_{\text{error}} = 0.001$) was found. Analysis of data collapsed across pulse rates indicated that the strong adapters had greater slopes than did the weak adapters ($p_{\text{error}} = 0.001$).

Spike amplitude changes. We observed that spike amplitude also changed across the duration of the pulse train. Figure 11 provides example response waveforms obtained from one ANF in response to three stimulus levels that illustrate spike amplitude reductions to ongoing 5000 pulse/s stimuli. Because of the large differences in onset latencies across the three sets of responses, it is clear that these reductions are not caused by uncanceled ECAP or a stimulus-onset artifact. Figure 11a shows 30 superimposed responses (traces) to as many repeated pulse trains. The second spike in each trace (occurring between 2 and 3 ms) has diminished amplitudes. Figure 11b isolates two segments of one trace that illustrates the influence of interspike interval (ISI) on the amplitude of the second spike of any spike pair, with the largest spike reduction occurring for the shortest ISI.

Spike amplitude reductions are quantified across fibers in Figure 12, which plots spike amplitude (normalized to mean amplitudes within the first 4 ms) across six analysis windows that span the 300-ms pulse-train response. Mean spike amplitude and standard error are plotted for each analysis window for 250 pulse/s trains (upper panel) and 5000 pulse/s trains (lower panel), with data grouped into three categories defined by the onset spike rate. Amplitude decrements are generally seen for both pulse rates. The degree of amplitude reduction is dependent on onset spike rate, analysis window, and pulse rate. For the low-rate trains, the smallest decrements were observed for low (<100 spike/s) response rates, probably because of longer ISIs. Means decrements are typically 10% or less and across individual fiber data (not shown, most decrements are less than 20%). These amplitude decrements are lower than the maximum (40%) decreases observed under refractory conditions as assessed by a two-pulse masker-probe paradigm (Miller et al. 2001), possibly because of long-term adaptation that could affect all spike amplitudes. Interestingly, amplitudes do not appear to recover across the 250 pulse/s train, but do show recovery for the higher-rate pulses. Thus, spike amplitude changes have a temporal pattern quite different from that of spike rate adaptation. Because rate adaptation across the pulse trains was generally

FIG. 10. Comparisons of ANF thresholds (upper panel) and rate-level slopes (lower panels) for stimulus rates of 250 and 5000 pulse/s. For both rates, the fiber categories of “strong” and “weak” adapters were defined on the basis of data obtained at 5000 pulse/s. Statistically significant differences were found between the strong and weak adapters for both measures and pulse rates (see text). The number of contributing ANFs is indicated immediately below each plotted data set.

greater for the 5000 pulse/s rate than for the 250 pulse/s rate, a parsimonious explanation for the amplitude change is that its degree is related to the rate of spike activity.

The relatively large analysis windows used in Figure 12 preclude the examination of refractory effects. To explore such effects, we computed the ratio of the amplitudes of the second and first spikes elicited by each pulse train. To characterize group trends for each stimulus rate, fibers were selected on the basis that each provided amplitude ratios for first-to-second-spike intervals as great as 20 ms. Amplitude ratios are plotted as a function of ISI in Figure 13 in

response to 250, 1000, and 5000 pulse/s (panels A–C, respectively). As these ratios are based only on the first two spikes of each pulse-train response, the data are free of long-term (i.e. adaptation) effects. Little or no ISI effects were observed for the 250 pulse/s data (top panel), consistent with the fact that the ISIs (multiples of 4 ms) are beyond the temporal window for significant refractory effects (cf. Miller et al. 2001). Significant amplitude reductions were observed for 1000 and 5000 pulse/s trains (middle two panels), with reductions as great as 50%. Median normalized spike amplitudes were computed for each of the three pulse rates. For data obtained at the 250 pulse/s rate, spike intervals were observed to cluster around integer values of the stimulus pulse period. Median amplitude ratios were therefore computed for each cluster. A similar approach was used to compute medians for the 1000 pulse/s data; however, larger analysis windows were used for ISIs

FIG. 11. Examples of ANF spike amplitude changes in response to 5000 pulse/s stimuli. The three panels show response waveforms from one ANF stimulated at three levels (italicized numbers). The vertical scale of the three panels is identical. The upper two panels (a) show 30 superimposed traces in response to the high-rate pulses. Reductions in the amplitude of the second spike of each response are evident. The lowest panel (b) shows two response epochs of a single trace (i.e., response to a single pulse train). The number above each spike indicates the spike amplitude relative to the first spike. Note how the amplitude of the second spike of any spike pair is influenced by the ISI.

greater than 8 ms because of the smaller number of spikes. For the 5000 pulse/s data (which are more smoothly distributed across ISI, windows were chosen so that each sampled a comparable number of amplitudes (approximately 250 points).

Median amplitude ratios for the three pulse train rates are plotted together in panel D of Figure 13. Spike amplitude trends for the three rates are similar, indicating that amplitude reductions caused by refractory effects were independent of pulse rate

FIG. 12. Effect of (1) pulse rate, (2) time after train onset, and (3) response rate on spike amplitude. Plotted are the mean normalized amplitudes (computed across fibers) versus time for responses obtained with 250 pulse/s trains (upper panel) and 5000 pulse/s trains (lower panel). For each ANF, amplitudes were normalized to those measured in the first temporal analysis window (i.e., the 0- to 4-ms response epoch). For each graph, data are parsed into three onset spike rate ranges (indicated by different symbols).

FIG. 13. Influence of ISI on the amplitudes of the first and second spikes in response to pulse-train stimuli. Amplitude changes are expressed as the ratio of the second spike amplitude and the first spike amplitude of the recorded response to each train presentation. These ratios are plotted as functions of the time interval between the two spikes. Data were included from all ANFs that contributed data at ISI's equal to or greater than 20 ms. The number of contributing ANFs is indicated by "n" in each panel. Separate plots are provided for three stimulus pulse rates (panels a, b, and c), with the greatest decrements observed at small ISIs. Median values, plotted for each pulse rate using open symbols, were computed as described in the text. These median values are replotted in panel d for the three pulse rates, showing the similarity of the functions across stimulus rates.

and highly dependent on the instantaneous spike rate. This trend is consistent with the data of Figure 12, in which the degree of amplitude reduction was observed, indirectly, to correlate with spike rate.

DISCUSSION

Summary of findings. This study systematically described ANF adaptation to electric pulse trains. Spike rate adaptation was observed for 250, 1000, and 5000 pulse/s stimuli, with the degree increasing with pulse rate. Adaptation was described as a function of onset spike rate, which correlates with stimulus intensity. Adaptation was largely independent of onset rate for 250 pulse/s stimuli. However, at higher pulse rates, adaptation could be partially overcome by increasing the onset spike rate through level increases. For most

stimulus conditions, however, the mean minimum normalized decrement was about 0.4, indicating a lower limit on adaptation effects.

PSTHs were fit by single- and double-exponent decaying functions. The single-exponent model generally produced τ estimates similar to the longer, “short term” time constants of the two-exponent models. At low spike rates for 5000 pulse/s, this model produced τ values that decreased as onset spike rate decreased. This was likely caused by inadequacy of the single-exponent model, as it must “switch” from a small τ at low spike rates to a larger one at higher rates. Statistical testing indicated that the two-time-constant model fits the data better than the single-time-constant model.

ANFs can produce high onset spike rates in response to electric stimuli (Kiang et al. 1965). Of course, the choice of bin width will affect onset spike rate estimates. Together with strong phase locking typically produced by electric stimuli, a small (1 ms) analysis window can introduce variability in rate estimates, as zero, one, or (in some cases) two spikes will fall within that narrow window. We note, however, that in 2 of 6 fibers of Figure 4, initial (1-ms window) rates were greater than 1000 spike/s, as two spikes were often registered within a single bin. Relatively high onset rates with electric stimuli are consistent with the observation that, when compared with acoustic stimuli, electric stimuli can transiently drive fibers to respond with short ISIs, i.e., more effectively drive fibers out of states of partial refractoriness (van den Honert and Stypulkowski 1987b; Miller et al. 2001). Comparisons of onset rates obtained across studies that used different bin widths are problematic. In estimating onset rates to acoustic stimuli, Westerman and Smith (1984) also used 1-ms bin widths and typically reported rates less than 1000 spike/s. We conclude that, with present cochlear-implant stimulation technologies, electrical stimulation not only drives relatively large fiber populations, but also can drive individual ANFs to higher rates.

For comparison against other “electric” studies, we examined how pulse rate affected ANF threshold and DR. Thresholds for 250 and 1000 pulse/s rates were similar, but were 2 dB lower for 5000 pulse/s, consistent with data of Javel and Shepherd (2000). Thresholds for 10,000 pulse/s trains were lower than those of all lower rates in the three fibers examined (bottom row, Fig. 3). This is in spite of the fact that shorter pulse durations (20 μ s/phase vs. our typical 40 μ s/phase) were used exclusively for this rate. For pulse durations in the 20–40 μ s/phase range, one would predict that thresholds for a single 20 μ s/phase pulse would be nearly 6 dB greater than that for a 40 μ s/phase pulse (Javel et al. 1987; Parkins and Colombo 1987). We therefore conclude that across-

pulse integration plays a large role in determining threshold at high pulse rates. DR was similar for our two lower pulse rates, but increased by about 2 dB for 5000 pulse/s. Litvak et al. (2001) explored high-rate (4800 pulse/s) trains similar to the 5000 pulse/s stimuli of our study. Their DRs were slightly (1.2 dB) lower than ours. The “steady state” analysis window of Litvak et al. (2001) was earlier (140–150 ms) than our 200- to 300-ms window. Our spike rate time constants suggest that this difference in analysis windows (and thus, adaptation) may account for the DR difference. There are two possible mechanisms through which DR may be increased at high rates. The first involves placing ANFs in partial refractory states that alter Na channel activity (Rubinstein et al. 1999) and increase DR. Another factor is the ability of ANFs to integrate energy across pulses presented at relatively high rates (Dynes, 1996; Cartee et al., 2000, and this study).

ANF adaptation effects will, of course, propagate to the central nervous system. Using guinea pig whole-brain preparations, Babalian et al. (2003) measured firing probabilities to electric trains in ANFs and cochlear nucleus (CN) cells. Using wide (10 ms) analysis bins and rates from 100 to 1000 pulse/s, they observed reductions in ANF firing probability for rates greater than 300 pulse/s, with proportionally more adaptation as rate increased from 500 to 1000 pulse/s. “Primary-like” bushy cells produced similar adaptation patterns, although greater reductions in probability were reported and adaptation was observed at a lower (300 pulse/s) stimulus rate. One possible source of greater rate adaptation in CN cells is the reduction in ANF spike amplitude, such as that reported here. Such reductions would presumably reduce postsynaptic potentials.

Comparison with acoustic data. Acoustic-electric comparisons of ANF adaptation are facilitated by the data of Westerman and Smith (1984), which measured gerbil ANF responses to 300-ms tone bursts at each fiber’s characteristic frequency and described two-exponent adaptation functions. Their time constants are similar to ours, obtained from deafened and electrically excited fibers, although our “electric” time constants are somewhat greater. Averaging data across response rates and stimulus rates, our rapid time constant was 8 ms, whereas the mean (across level) rapid-time constant from Westerman and Smith (1984) was 3 ms. Our median short-term time constant was 80 ms, whereas their mean acoustic value was 55 ms. Our rapid-time constant was not influenced by level (spike rate) effects, consistent with previous results, suggesting that it is determined by refractory effects (Gaumond et al. 1983; Eggermont 1985; Chimento and Schreiner 1991). Spike rate

growth to electric pulses was examined (Fig. 4) in a manner similar to that of Westerman and Smith (1984; their Fig. 6). Their rate-level functions were similar to one another in shape (Fig. 4b). With our electric stimulation, however, onset responses underwent rapid growth to saturation, whereas the adapted responses showed continued, slow growth. Electric spike rate growth does not demonstrate the proportionality observed with acoustic stimulation.

Our comparisons are complicated by the fact that different stimulus waveforms (sinusoids vs. pulses), excitation sites (cochlea vs. ANF membrane), and species were used. Electric stimuli would be expected to produce greater synchrony and could possibly deposit residual membrane charge never present with acoustic stimulation. However, our findings suggest that it is spike activity, not stimulus rate *per se*, which determines the extent of adaptation. Spike rate decrements observed for 1000 pulse/s and 5000 pulse/s trains were highly correlated and similar in value (Fig. 6). Furthermore, across rates of 250, 1000, and 5000 pulses/s there were some changes in regression slopes for the decrement-vs-onset-rate plots (Fig. 5). However, the changes were small, suggesting that adaptation is related to spike activity, not stimulus rate. We tentatively conclude that residual charge effects that might result from direct (electrical) depolarization have little impact on our results.

Our findings suggest the possible need to reevaluate mathematical models of ANF adaptation (e.g., Meddis 1986; Zhang and Carney 2005). Rapid and short-term adaptation components are traditionally attributed to the hair cell and synapse, although, in their acoustic study, Chimento and Schreiner (1991) suggested that ANF membrane properties may be influential. It is not possible to determine the extent to which the “acoustic” adaptation mechanisms (hair cell and synapse) and the “membrane” mechanism each contribute to the degree of adaptation observed with acoustic excitation. However, our study demonstrates that “membrane” adaptation can occur at moderate spike rates that are relevant to acoustic excitation of fibers.

A remaining question concerns the exact site of membrane excitation that was assessed in our study. Computer modeling (Frijns et al. 2001) and physiologic data (Miller et al. 2003) suggest that both the peripheral processes and the central axons may be excited by intracochlear electrical stimulation. It is reasonable to assume that these two excitable regions have different response properties, with the possibility of the peripheral processes having more capacitance and a possible site of spike propagation failure (van den Honert and Stypulkowski 1984). Because of the monopolar mode of excitation and the wide

range of stimulus levels used in our study, we believe that, of the fibers studied here, most were excited at the central axons (Miller et al. 1999; Miller et al. 2003). If that is indeed the case, the data presented here may not be representative of the membrane-related adaptation that occurs at the peripheral processes. This point is relevant, as action potentials initiated by acoustic stimuli must pass through the peripheral and central aspects of spiral ganglion cells. Even if the site of electric excitation was quite variable across the fibers of this study, a robust finding was that electric adaptation occurs in most cases and over a wide range of ANF response rates.

It may be difficult to design a physiologic study to directly compare acoustic and electric adaptation using a within-subject design. A possible solution would be to develop a computational model that incorporates both acoustic (cochlear) sources of adaptation and those from our study that implicate the ANF membrane. Our group has recently embarked on such an approach. A preliminary, phenomenological model has been developed (Nourski et al. 2006) that integrates synaptic and ANF membrane adaptation components and can demonstrate physiologic phenomenon such as input–output functions, level dependence of spike latency and jitter, and adaptation to electric and acoustic stimuli.

Threshold, dynamic range, and adaptation. Using single electric pulses, our group has shown that ANF “relative spread” (RS, Verveen 1961) is correlated with threshold, with low-threshold ANFs having greater RS (Miller et al. 1999). As RS is proportional to DR and inversely proportional to the rate-level slope, our earlier finding is consistent with the data of Figure 10, which established that “strong adapters” had higher thresholds and greater DR than did the “weak adapters”. We previously speculated that the high-threshold/high-slope and the low-threshold/low-slope ANF characteristics may correlate with the neural anatomy at the site of excitation. Specifically, smaller-diameter fibers would be expected to have higher thresholds (Bement and Ranck 1969a, b; McNeal 1976) and fiber diameter has been suggested as a major determinant of threshold (van den Honert and Stypulkowski 1987a). In that case, our data indirectly suggest that the rate of electric adaptation is inversely related to fiber diameter at the excitation site. There is evidence that ANFs with low spontaneous rate (SR) undergo larger upper threshold shifts in response to forward masking and recover from prior stimulation more slowly than do high SR fibers (Relkin and Doucet 1991). However, low SR fibers exhibit smaller degrees of rapid adaptation (Relkin and Doucet 1991; Cooper et al. 1993). Thus, some

data suggest that low SR fibers are more susceptible to adaptation, at least after the onset response period. As SR correlates with the diameter of ANFs (Liberman and Oliver 1984), one might speculate that the greater axonal resistance or slower axonal transport of smaller fibers may play a role in the greater longer-term adaptation observed in low SR fibers. Our data cannot adequately address this question; again, computational models of ANFs that incorporate adaptation components may be of some value.

It should be noted that the distance between the stimulating electrode and target fiber influences threshold, even for monopolar stimulation (Liang et al. 1999; Rebscher et al. 2001) and could alter the site (or sites) of excitation on each fiber (Mino et al. 2004). As ANFs have longitudinal changes and discontinuities in membrane properties (Colombo and Parkins 1987; Finley et al. 1990), three factors may contribute to variations in threshold, DR, and degree of adaptation: (1) fiber diameter, (2) electrode-fiber distance, and (3) longitudinal site of excitation. It is most likely beyond the capacity of animal models to simultaneously address these factors; thus, a computational model of a spatial population of ANFs that incorporates adaptation effects would be a welcome addition to the current set of research tools.

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