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Electrical stimulation of the auditory nerve: II. Effect of stimulus waveshape on single fibre response properties

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Abstract

To investigate the generation of action potentials by electrical stimulation we studied the response of auditory nerve fibres (ANFs) to a variety of stimulus waveforms. Current pulses were presented to longitudinal bipolar scala tympani electrodes implanted in normal and deafened cochleae. Capacitively coupled monophasic current pulses evoked single ANF responses that were more sensitive to one phase (the 'excitatory' phase) than the other. Anodic pulses produced a significantly shorter mean latency compared with cathodic pulses, indicating that their site for spike initiation is located more centrally along the ANF. The fine temporal structure of ANF responses to biphasic pulses appeared similar to that evoked by monophasic pulses. An excitatory monophasic pulse evoked a significantly lower threshold than a biphasic current pulse having the same polarity and duration leading phase, i.e. the addition of a second phase leads to an increase in threshold. Increasing the temporal separation of the two phases of a biphasic pulse resulted in a moderate reduction in threshold which approached that of an excitatory monophasic pulse for interphase gaps $> 100 \mu\text{s}$. Greater threshold reductions were observed with narrower current pulses. There was a systematic reduction in threshold with increasing pulse width for biphasic current pulses, reflecting the general charge-dependent properties of ANFs for narrow pulse widths. Chopped biphasic current pulses, which uniformly delivered multiple packets of charge ($2 \times 30 \mu\text{s}$, $3 \times 20 \mu\text{s}$ or $6 \times 10 \mu\text{s}$) with the same polarity over a $120 \mu\text{s}$ period, followed by a similar series in the reverse polarity, demonstrated the ability of the neural membrane to integrate sub-threshold packets of charge to achieve depolarisation. Moreover, thresholds for these current pulses were ~ 1.5 dB lower than $60 \mu\text{s}/\text{phase}$ biphasic current pulses with no interphase gap. Finally, stimulation using charge-balanced triphasic and asymmetric current pulses produced systematic changes in threshold and latency consistent with the charge-dependent properties of ANFs. These findings provide insight into the mechanisms underlying the generation of action potentials using electrical stimuli. Moreover, a number of these novel stimuli may have potential clinical application. © 1999 Elsevier Science B.V. All rights reserved.

Key words: Auditory nerve fiber; Cochlear implant; Cochlear histopathology; Electrical stimulation; Deafness; Neural prosthesis

1. Introduction

The previous papers in this series have described electrically elicited auditory nerve fibre (ANF) and auditory brainstem responses in normal, short-term deafened and long-term deafened cats (Shepherd and Javel, 1997), and have detailed ANF responses from these animals in terms of categorising the site of action po-

tential generation with manipulations in stimulus intensity, waveform polarity and stimulus rate (Javel and Shepherd, 1999). In the present paper we describe the response of ANFs recorded from these animals to stimulation using a variety of stimulus waveforms including monophasic, biphasic, triphasic, chopped, and asymmetric current pulses, as well as temporal manipulations in both pulse width and interphase gap.

Although there have been a number of studies describing ANF responses to a variety of stimulus waveforms, the range studied has been relatively limited. Studies using monophasic or charge-balanced biphasic current pulses have shown that the ANF response is

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dominated by a highly synchronised short-latency (~ 0.5 ms) response (Moxon, 1967, 1971; Kiang and Moxon, 1972; Hartmann et al., 1984; van den Honert and Stypulkowski, 1984, 1987a,b; Javel et al., 1987; Parkins and Colombo, 1987; Parkins, 1989; Hartmann and Klinke, 1990; Javel, 1990; Dynes, 1996; Shepherd and Javel, 1997). Studies using sinusoidal, triangular or square wave stimuli have indicated that threshold is frequency-dependent with the lowest thresholds occurring at ~ 100 Hz and increasing with stimulus frequency, and that action potentials can be elicited by either the anodic or cathodic phase of the stimulus waveform (Hartmann et al., 1984; van den Honert and Stypulkowski, 1987a; Parkins, 1989).

An increased understanding of the response of ANFs to manipulations in stimulus waveshape has potentially important clinical implications. While biphasic current pulses are almost universally used clinically, from an electrochemical point of view other short duration charge-balanced current pulses would also appear to be suitable (Brummer and Turner, 1977; Robblee and Rose, 1990). However, little is known of the effects of these stimuli on ANF response characteristics. Potential clinical applications include: (i) the use of an interphase gap to increase sensitivity of biphasic current pulses (motor nerve: van den Honert and Mortimer, 1979; auditory nerve: P.M. Seligman, personal communication); (ii) employing chopped biphasic current pulses to effectively deliver charge to two or three cochlear sites at one time without the potential adverse effects of simultaneous current interaction associated with the vector summation of current density (McDermott, 1989); (iii) using triphasic current pulses to minimise interactions as a result of non-simultaneous stimulation by restoring the neural membrane potential to the resting state rather than leaving residual charge on the membrane (Eddington et al., 1995), and (iv) the use of asymmetric charge-balanced biphasic pulses to provide improved spatial selectivity (Frijns et al., 1996).

2. Methods and materials

2.1. Experimental preparation

Six healthy adult cats with hearing status ranging from normal to a long-term profound hearing loss were used in the present study. A detailed description of each animal's hearing loss and cochlear pathology has been presented previously (Shepherd and Javel, 1997). Each animal was anaesthetised with sodium pentobarbital (40 mg/kg, i.p.) with supplemental doses given throughout the experiment to maintain surgical levels of anaesthesia. The animal was tracheostomised and placed in a rigid head holder. Core temperature was

maintained at 38°C by a rectal probe and thermostatically controlled DC heating blanket. The skin and musculature overlying the posterior of the skull were removed, and one bulla was exposed and opened. The round window membrane was carefully incised, and an electrode array based on the Nucleus (Cochlear Limited) design, inserted approximately 5.5 mm into the scala tympani. Each array consisted of four platinum bands on a Silastic carrier. Each electrode was 0.3 mm wide and 0.4–0.5 mm in diameter with an inter-electrode spacing of 0.45 mm.

The dura overlying the ipsilateral cerebellum was exposed, and part of the cerebellum aspirated to reveal the cochlear nucleus. The auditory nerve was exposed by placing cotton between the brainstem and the lateral wall of the posterior fossa at points anterior and posterior to the nerve. A Davies chamber was positioned on the skull overlying the nerve and cemented in place. The chamber was filled with warm mineral oil and a cover plate, which held the recording electrode, was attached to form an hydraulic seal.

2.2. Electrical stimuli

Electrical stimulation waveforms were generated digitally and fed to an optically isolated voltage to current converter (Bak BSI-1) whose output was capacitively coupled to bipolar scala tympani electrodes (inter-electrode separation was fixed at 1.2 mm). The stimulating electrodes were not shorted between current pulses. Stimuli were presented at stimulus rates of 100 or 200 pulses per second (pps). The stimulus waveforms used included (i) monophasic current pulses; (ii) charge-balanced biphasic current pulses; (iii) biphasic current pulses with variable pulse width; (iv) biphasic current pulses with variable interphase gap; (v) chopped biphasic current pulses; (vi) triphasic current pulses; and (vii) asymmetric current pulses (Fig. 1). Stimulus polarities described here refer to the waveform at the more apical electrode of the bipolar pair, and all electrical intensities in this paper are expressed in dB re 1 μ A (peak).

2.3. Single fibre recordings

Responses of single ANFs were recorded extracellularly with 3 M KCl filled glass micropipettes (20–30 M Ω at 1 kHz). Electrodes were placed on the eighth nerve under visual control and advanced with a remote-controlled stepping motor (Haer). Single-fibre responses were amplified (WPI and Tektronix preamplifiers), capacitance-compensated and displayed on a Tektronix oscilloscope. The oscilloscope triggering was adjusted to discriminate the leading edge of the spike, and the resultant trigger pulses were fed to the programmable clock of a PDP-11/34 computer to register the times of

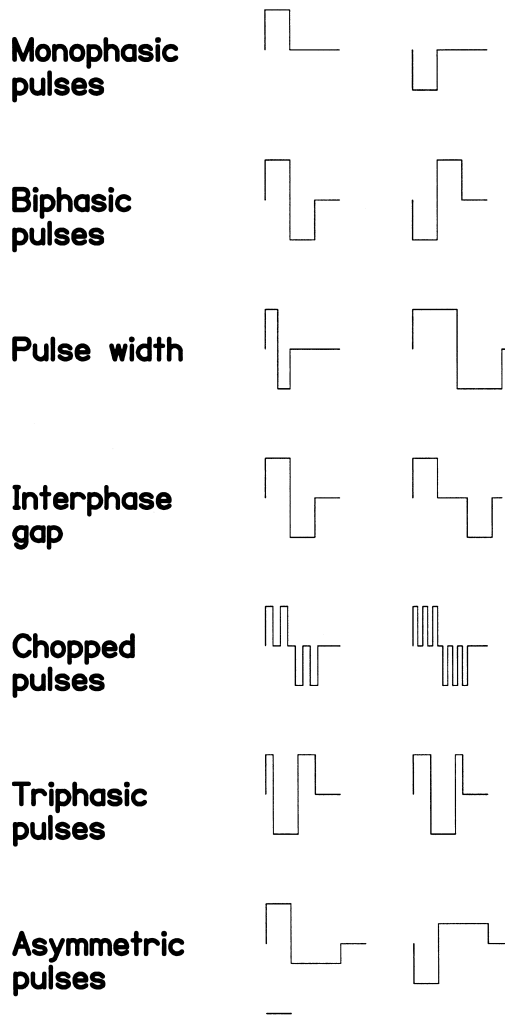


Fig. 1. Diagram illustrating the range of stimulus waveforms used in the present study. Note that all stimuli in the first column deliver an initially anodic current pulse to the most apical electrode.

occurrence of discharges. The PDP-11/34 was also used for generating and controlling all stimuli.

An electrical search stimulus was used to isolate single ANFs. Once a fibre was isolated, rate-intensity functions to bipolar electrical stimulation, using one or more of the stimulus waveforms, were recorded for intensities that ranged from below threshold to saturation. Current pulse trains were presented at 100 or 200 pps, typically 100 ms in duration, and repeated every 200 ms for a total of 50 trials at each current level.

Stimulus artefact was minimised from the recording using a TMS32010 DSP microprocessor on which a sample-and-hold or blanking technique was implemented in software so that the amplifier output was sampled just before the stimulus onset and held at that level for the duration of the stimulus (Black et al., 1983; Shepherd and Javel, 1997).

Post-stimulus time (PSTH), period (PH) and interspike interval (ISIH) histograms were compiled during data acquisition. Mean response latency and its standard deviation were computed from windowed PH peaks using Gaussian procedures. Slope, dynamic range, and threshold and saturation rates were determined from rate-intensity (input-output) functions by least-squares fits of a saturating function (Sachs and Abbas, 1974). Spike probability (Pr) was calculated at each intensity, and threshold ($Pr=0.1$), saturation ($Pr=0.9$), and dynamic range ($Pr_{0.9}-Pr_{0.1}$) determined.

The majority of stimulus waveforms studied were associated with temporal manipulations in their waveform, and the responses were therefore independent of the location of the ANF relative to the stimulating electrode pair. However, interpreting the effects of phase reversal is relatively complex when using longitudinal bipolar electrodes. In these experiments, the excitatory phase was determined by establishing which electrode/phase combination evoked the lowest response threshold for a monophasic current pulse. Latency of the response was used to confirm the excitatory electrode/phase combination as anodic charge depolarises the neural membrane at a site further from the electrode compared with a cathodic pulse (Ranck, 1975; Mortimer, 1981; Parkins, 1989), resulting in a shorter latency.

Only short latency (<1 ms) responses resulting from direct depolarisation of the neural membrane by the electrical stimulus were examined in the present study.

2.4. Statistical analysis

The extent of change in threshold and dynamic range with stimulus waveform was evaluated statistically. If data showed normal distribution (Kolmogorov-Smirnov test), a paired t -test was used to compare the two stimulus waveforms. A Wilcoxon signed rank test was used if the paired data were not normally distributed.

Care and use of animals reported in this study were approved by the Institutional Animal Care and Use Committee of Creighton University, Omaha, NE, USA.

3. Results

The present results are based on recordings from a total of 181 ANFs, although results from any one stimulus waveform are derived from a subset of this population.

3.1. Monophasic current pulses

Fig. 2 illustrates a series of period histograms evoked by 100 μ s anodic and cathodic pulses for two represen-

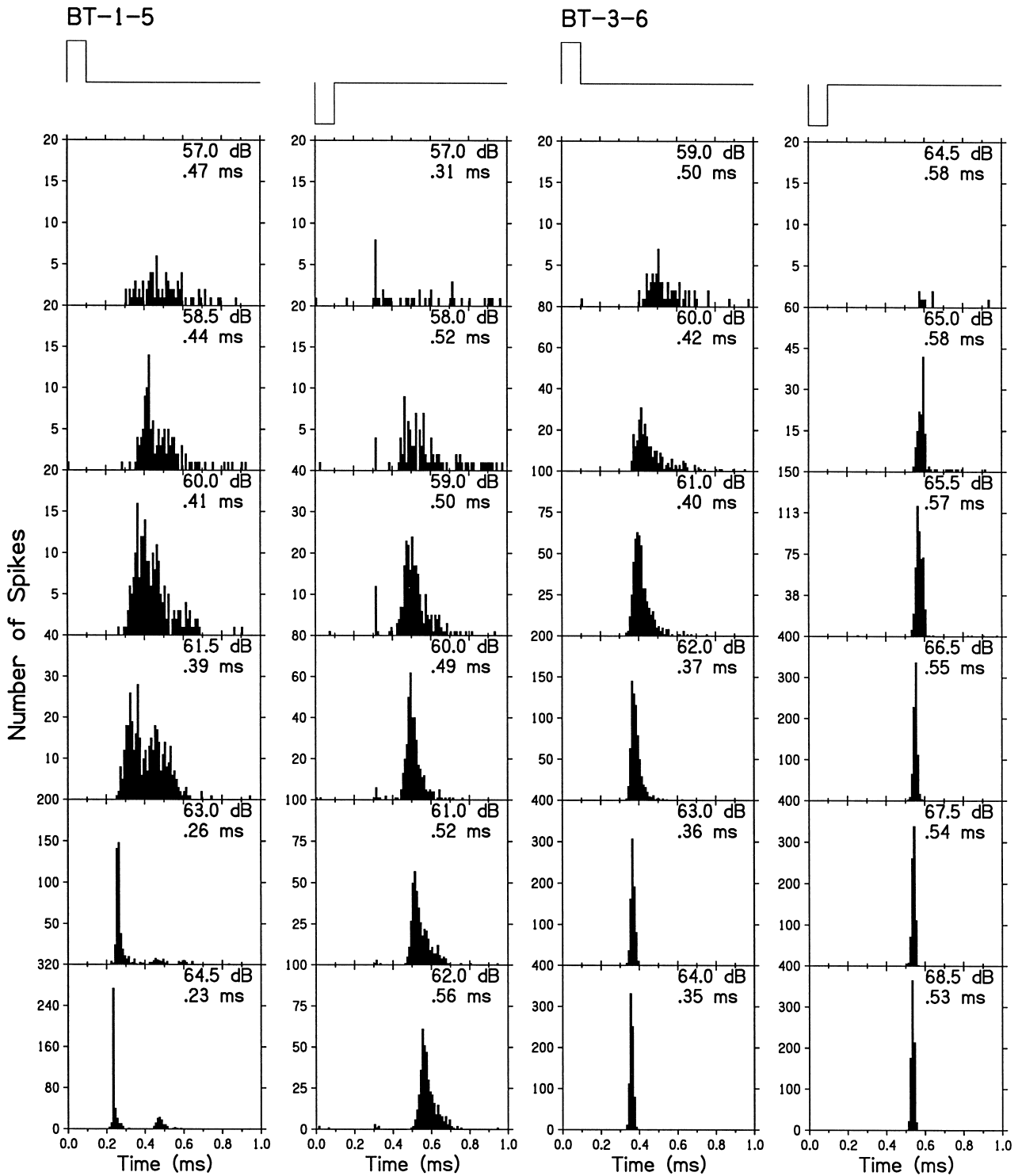


Fig. 2. Representative period histograms illustrating the fine temporal response properties of single auditory nerve fibres to 100 μs anodic and cathodic monophasic current pulses. Note that in both neurones illustrated here, the latency of the response to the anodic pulse was shorter than the response evoked by the cathodic pulse. The second, longer latency peak present in the higher intensity PHs for the anodic pulse in neurone BT-1-5 was presumably evoked by the more basal (cathodic) electrode. Stimulus intensity, in dB re 1 μA, increases down each column, and the mean peak latency of the response in ms is also illustrated.

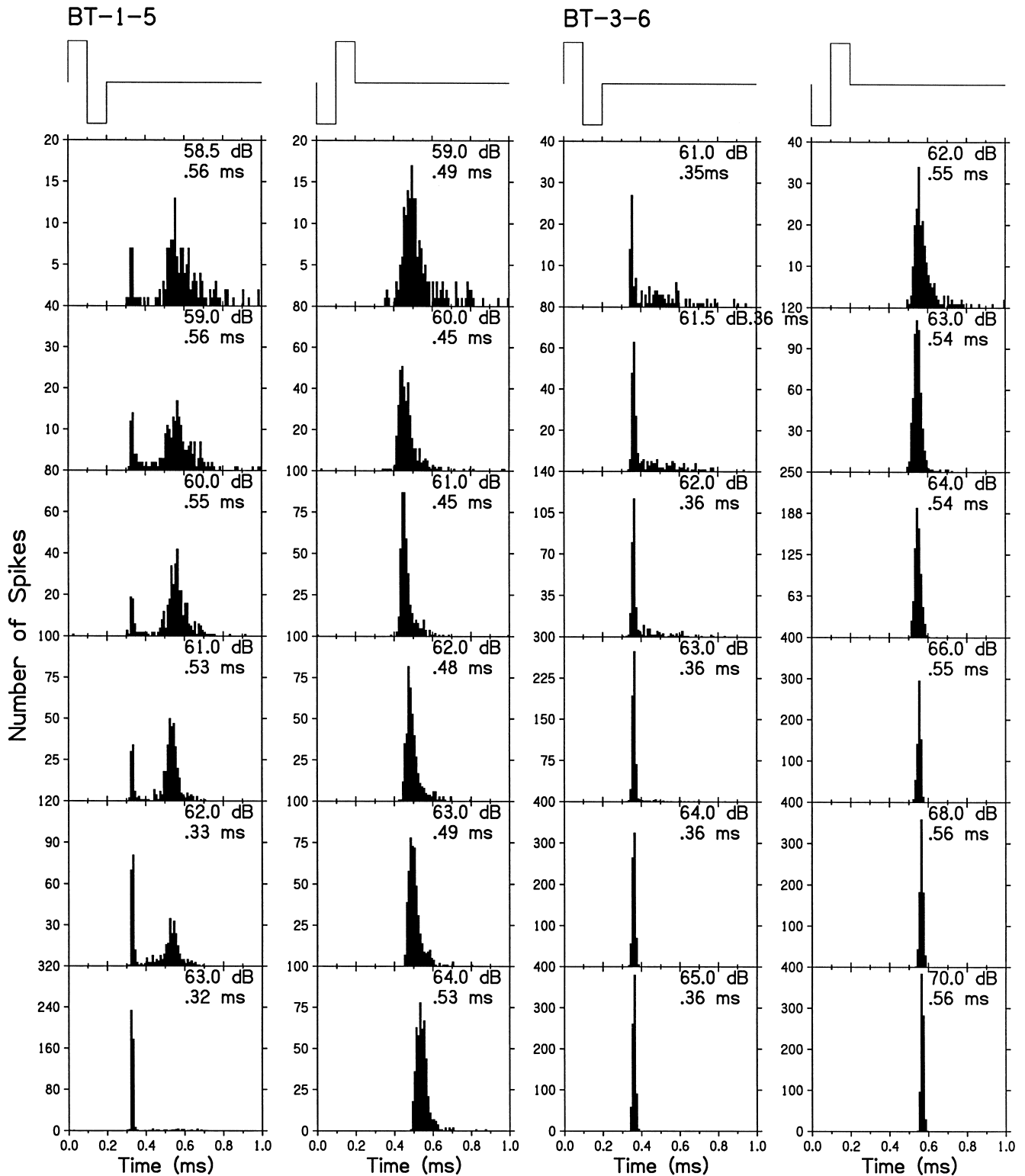


Fig. 3. Representative period histograms from the same two neurones illustrated in Fig. 2, showing their fine temporal response properties to anodic and cathodic leading biphasic current pulses. Based on the latency differences observed for anodic and cathodic monophasic pulses (Fig. 2), it would appear that in general, the leading phase of the biphasic current pulse is responsible for evoking the neural response in these examples. It should be noted, however, that the responses evoked by the anodic leading phase of BT-1-5 illustrates an example of ‘peak splitting’, where the lagging phase appeared to evoke the near threshold activity while the leading phase dominated the response as the neurone approached saturation.

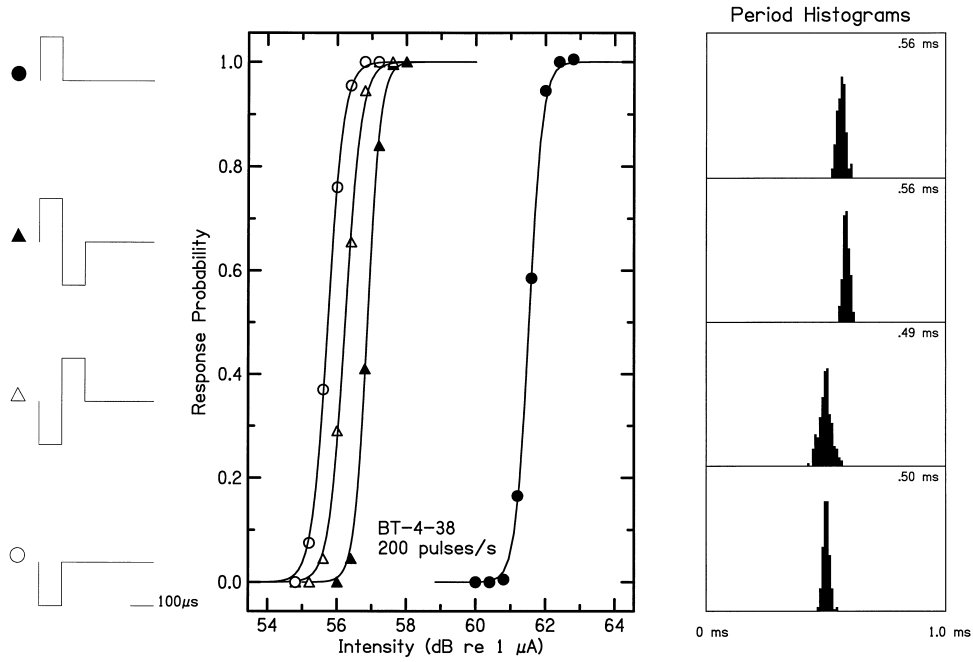


Fig. 4. Input-output functions recorded from one neurone in response to 100 μ s monophasic and biphasic current pulses of both polarity. In this example the cathodic monophasic pulse delivered to the most apical electrode (\circ) exhibited the lowest threshold and was therefore regarded as the excitatory phase. Excitatory monophasic current pulses almost always exhibited lower thresholds than biphasic current pulses with the same polarity leading phase. Furthermore, the non-excitatory monophasic current pulse (the anodic pulse in this example; \bullet) generally exhibited the highest threshold of the four stimulus waveforms as illustrated here. The solid lines represent a least-squares fit of an integrated Gaussian curve to the data.

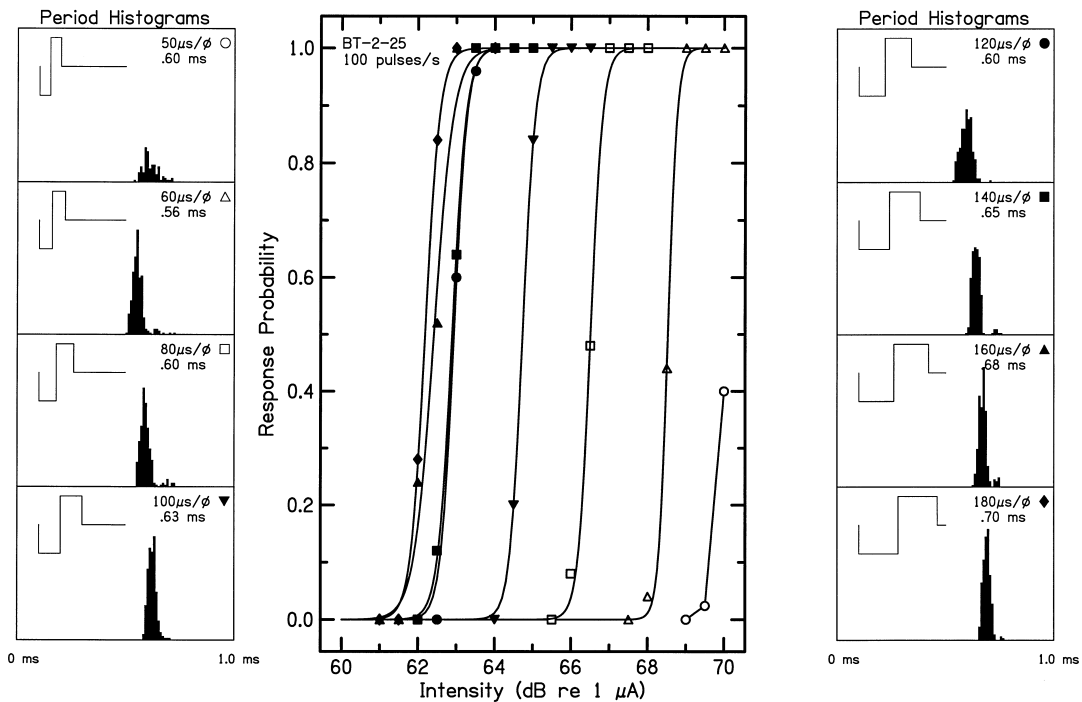


Fig. 5. Input-output functions recorded from one neurone illustrating the influence of pulse width on neural threshold. Period histograms taken at or just below saturation intensity (except for 50 μ s/phase which is taken at the maximum stimulus intensity of 70 dB re 1 μ A) illustrate the fine temporal response of the neurone to this increase in pulse width.

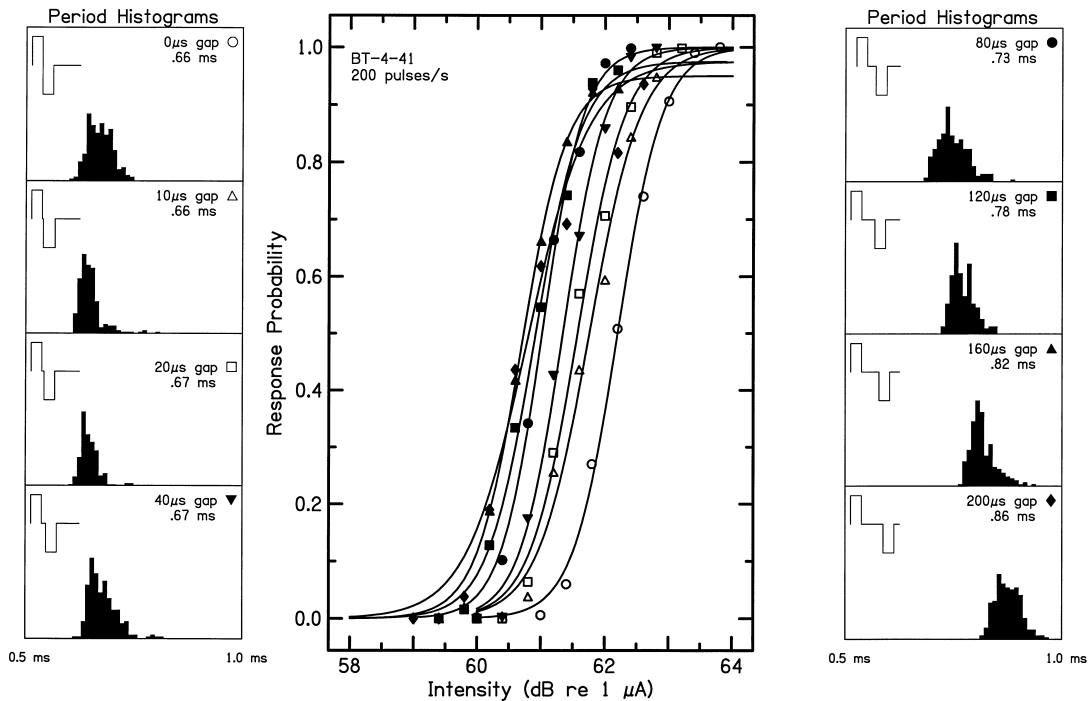


Fig. 6. Input-output functions recorded from a single neurone illustrating the influence of interphase gap on neural threshold. The stimuli consisted of 100 $\mu\text{s}/\text{phase}$ biphasic current pulses. Period histograms, windowed from 0.5 to 1.0 ms, show a general increase in response latency as the cathodic pulse is delayed for periods of up to 200 μs following completion of the leading anodic phase. Note that due to the windowed PH, the stimulus waveforms illustrated in this figure are not drawn to scale.

tative ANFs. Note that an anodic current pulse refers to the stimulus waveform delivered to the most apical electrode of the bipolar pair. Simultaneously, the more basal electrode would deliver a 100 μs cathodic pulse. The converse is true for a cathodic pulse, and hence response threshold to these monophasic stimuli will depend on the spatial relationship of the ANF relative to the electrode array (Ranck, 1975). Responses recorded from the normal hearing animal (BT-1) showed evidence of spontaneous activity at near-threshold current levels. In contrast, responses recorded from BT-3, a profoundly deafened animal, showed little evidence of spontaneous activity. For BT-1-5, the cathodic pulse delivered to the apical electrode evoked a slightly lower threshold and longer latency than the anodic pulse delivered to the same electrode. The cathodic pulse was therefore regarded as the excitatory stimulus. In contrast, neurone BT-3-6 was more sensitive to the anodic pulse delivered to the apical electrode. The short latency associated with this response indicated that this stimulus/electrode combination – rather than the cathodic pulse simultaneously delivered to the basal electrode – was the excitatory stimulus.

Because the ANFs studied were sampled randomly in spatial terms, there was no evidence that one polarity excitatory phase consistently evoked lower thresholds

than the other (Table 1). Moreover, examination of suprathreshold neural response properties showed no evidence of a significant difference in dynamic range between stimulation using anodic versus cathodic current pulses (Table 1). However, significant differences were observed when comparing the mean response latency at saturation ($P_r > 0.9$) for anodic versus cathodic excitatory pulses (anodic: latency = 0.449 ms, S.E.M. = 0.027 $n = 14$; cathodic: latency = 0.539 ms, S.E.M. = 0.022, $n = 14$; $P = 0.019$, paired t -test). The shorter latency response associated with the anodic pulse is evident in both examples illustrated in Fig. 2, irrespective of whether the anodic pulse had a higher or lower threshold than the cathodic pulse.

3.2. Biphasic current pulses: comparison with monophasic pulses and effect of phase reversal

Fig. 3 illustrates a series of period histograms evoked by (i) anodic and (ii) cathodic leading biphasic current pulses for the two auditory nerve fibres whose responses to monophasic pulses were shown in Fig. 2. In general, the fine temporal structure of the auditory nerve response to biphasic current pulses appears similar to that evoked by monophasic pulses. In the examples illustrated in Fig. 3, the leading phase of the biphasic

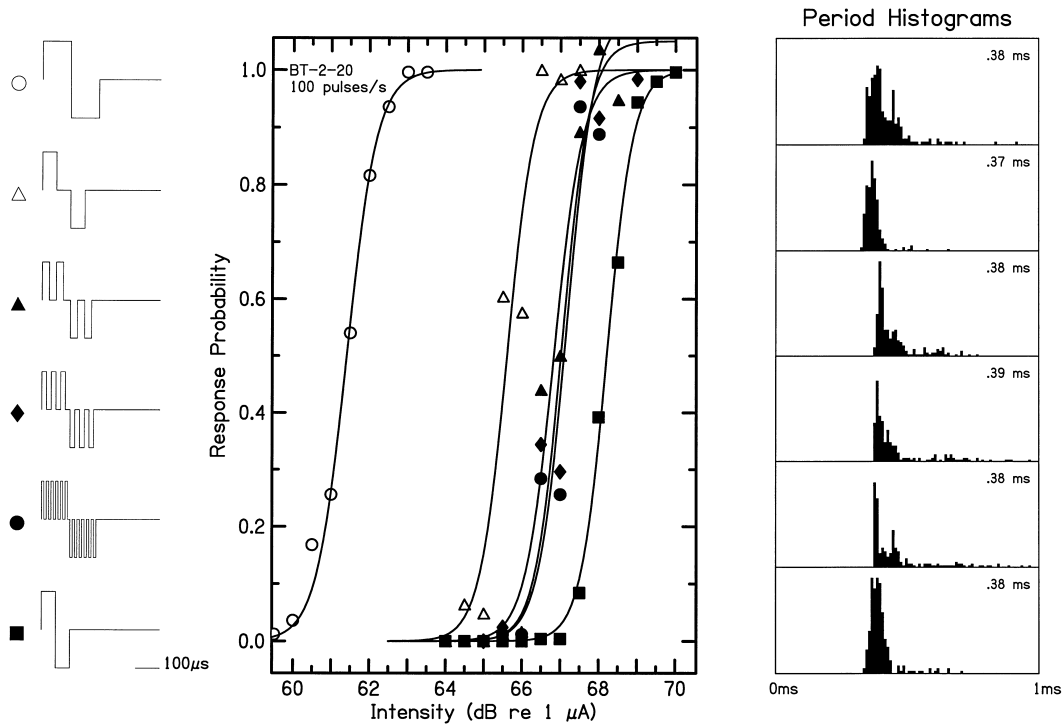


Fig. 7. Input-output functions recorded from a single neurone in response to stimulation using three sets of chopped biphasic current pulses ($2 \times 30 \mu\text{s}$ \blacktriangle ; $3 \times 20 \mu\text{s}$ \blacklozenge , and $6 \times 10 \mu\text{s}$ \bullet). Each of these stimulus waveforms injected the same charge/phase as a $60 \mu\text{s}$ /phase biphasic current pulse with (\triangle), or without (\blacksquare) a $60 \mu\text{s}$ interphase gap, although the charge was delivered over a $120 \mu\text{s}$ period. For comparison, an input-output function in response to a $120 \mu\text{s}$ /phase biphasic pulse is also illustrated (\circ).

stimulus appeared to be the excitatory phase, with the anodic leading phase evoking a short latency response similar to that evoked by the anodic monophasic pulse, and the cathodic leading biphasic pulse evoking a response reminiscent of the cathodic monophasic pulse (e.g. compare BT-3-6 in Figs. 2 and 3). Occasionally, biphasic current pulses evoked two clear peaks through their dynamic range. This can reflect activity evoked by both phases of the current pulse (Javel and Shepherd, 1999). An example of this 'peak splitting' behaviour is illustrated in the PHs evoked from the anodic leading phase of neurone BT-1-5 (Fig. 3). At near threshold current levels the response is dominated by a relatively long latency (~ 0.55 ms), and was similar in features to the cathodic pulse illustrated for the same neurone in Fig. 2. Note that this monophasic cathodic stimulus had a threshold slightly lower than the monophasic anodic stimulus for this neurone (Fig. 2). As the stimulus intensity increased, a shorter latency response (that was present at near-threshold current levels) began to dominate the PH at a latency consistent with the response being evoked from the leading anodic phase of the current pulse. At saturation, the short latency response completely dominated the PH, implying that at this intensity all neural activity was evoked by the leading anodic phase. For this neurone to be influenced by

both phases it was presumably located between the two Pt stimulating electrodes.

Although individual neurones showed clear threshold differences for anodic versus cathodic leading phase excitatory pulses, there was no evidence that one waveform was either more efficient or had significantly different dynamic range than the other (Table 1).

For 17 of 19 neurones studied using both monophasic and biphasic stimuli, the excitatory monophasic current pulse exhibited a lower threshold than the biphasic stimulus having the same polarity and duration leading phase. Analysis of the 14 neurones stimulated using $100 \mu\text{s}$ monophasic pulses revealed a mean reduction in threshold of 1.2 dB compared with threshold evoked using a $100 \mu\text{s}$ /phase biphasic current pulse with the same polarity leading phase. This reduction in threshold, evident for excitatory stimuli of both polarities, was highly statistically significant ($P < 0.001$; Wilcoxon signed rank test; Table 2). Clearly, the addition of a second, non-excitatory phase resulted in an increase in threshold compared with the excitatory monophasic pulse. Furthermore, the majority of neurones (14 of 17) also showed a higher threshold in response to the non-excitatory monophasic current pulse than to a biphasic pulse having the same polarity and duration leading phase. Analysis of 13 neurones stimulated using

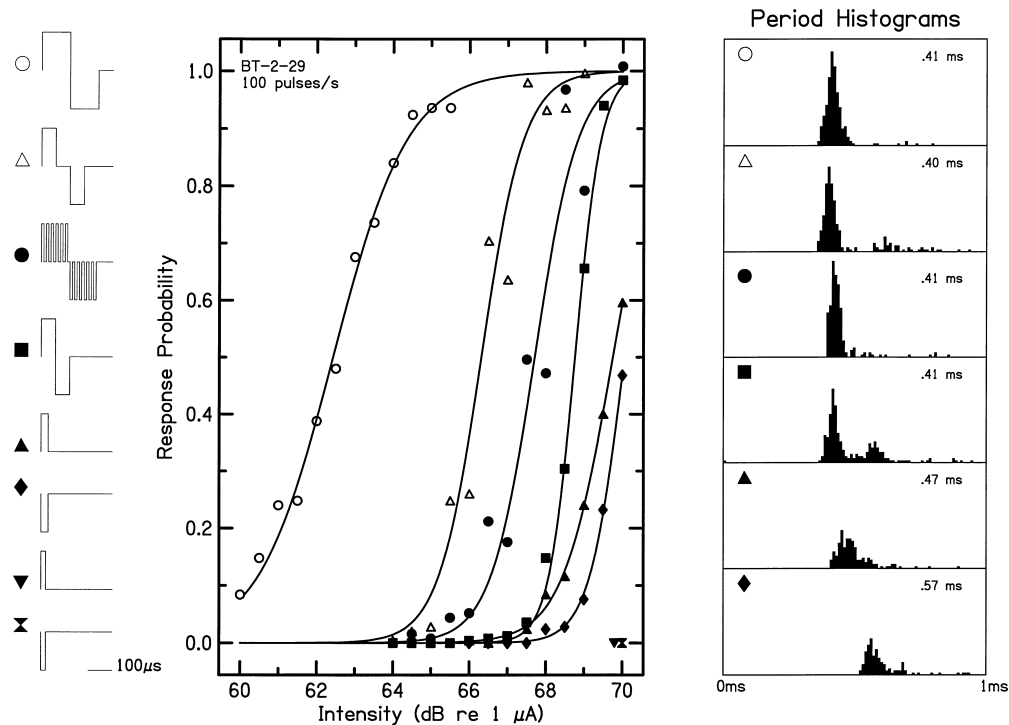


Fig. 8. Input-output functions recorded from a single neurone in response to stimulation using a chopped biphasic current pulse ($6 \times 10 \mu\text{s}$ ●). This stimulus waveform injected the same charge/phase as a $60 \mu\text{s}$ /phase biphasic current pulse with (Δ) or without (\blacksquare) a $60 \mu\text{s}$ interphase gap, delivered over a $120 \mu\text{s}$ period. For comparison, input-output functions are also illustrated for a $120 \mu\text{s}$ /phase biphasic current pulse (\circ), and $30 \mu\text{s}$ monophasic current pulses (\blacktriangle , \blacklozenge). Stimulation using $20 \mu\text{s}$ anodic or cathodic monophasic current pulses failed to evoke neural activity at the maximum stimulus intensity tested ($70 \text{ dB re } 1 \mu\text{A}$; \blacktriangledown , hourglass). Note that all PHs except those for the $30 \mu\text{s}$ monophasic pulses illustrate activity at saturation. The PHs for the $30 \mu\text{s}$ monophasic pulses illustrate activity at $70 \text{ dB re } 1 \mu\text{A}$.

$100 \mu\text{s}$ monophasic pulses revealed a mean increase in threshold of 1 dB over a $100 \mu\text{s}$ /phase biphasic pulse with the same polarity leading phase. However, this increase in threshold was not statistically significant ($P=0.095$, Wilcoxon signed rank test; Table 2).

Variation in threshold with monophasic and biphasic stimuli is illustrated in Fig. 4. This figure shows four sets of input-output functions (response probability versus stimulus intensity) recorded from one neurone evoked by the monophasic and biphasic current pulses illustrated. In this example, the cathodic monophasic stimulus delivered to the apical electrode evoked the lowest threshold (i.e. the excitatory stimulus). The cathodic and anodic leading phase biphasic current pulses exhibited thresholds ~ 0.5 and 1.2 dB higher, respectively, than the cathodic monophasic stimulus. The anodic monophasic stimulus in this example had a threshold $\sim 6 \text{ dB}$ higher.

Stimulation using biphasic current pulses with the hyperpolarising (i.e. non-excitatory) phase as the leading phase resulted in a slight increase in threshold compared with stimulation using the depolarising (excitatory) phase as the leading phase (excitatory leading phase: 58.7 dB , S.E.M. = 0.88 , $n = 13$; non-excitatory

leading phase: 59.1 dB , S.E.M. = 1.07 , $n = 13$; Fig. 4), however this difference was not statistically significant ($P=0.303$; Wilcoxon signed rank test).

Finally, although the mean dynamic range evoked by monophasic current pulses was slightly wider than that seen with biphasic pulses with the same polarity excitatory phase (monophasic: 2.35 dB , S.E.M. = 0.20 , $n = 28$; biphasic: 2.12 dB , S.E.M. = 0.20 , $n = 28$), the difference was not statistically significant ($P=0.086$, paired t -test).

3.3. Pulse width

The effect of varying pulse width on neural response properties is illustrated in Fig. 5. In this example, a series of input-output functions recorded in response to biphasic current pulses varying from 50 to $180 \mu\text{s}$ /phase are shown for a single auditory nerve fibre. These input-output functions demonstrate a systematic reduction in threshold with increasing pulse width—threshold reductions in the order of 8 dB were evident as pulse width increased from 50 to $180 \mu\text{s}$ /phase. Also illustrated in Fig. 5 is a PH for each stimulus waveform taken at saturation current level (except for the $50 \mu\text{s}$ /phase stimulus which was not capable of saturating the

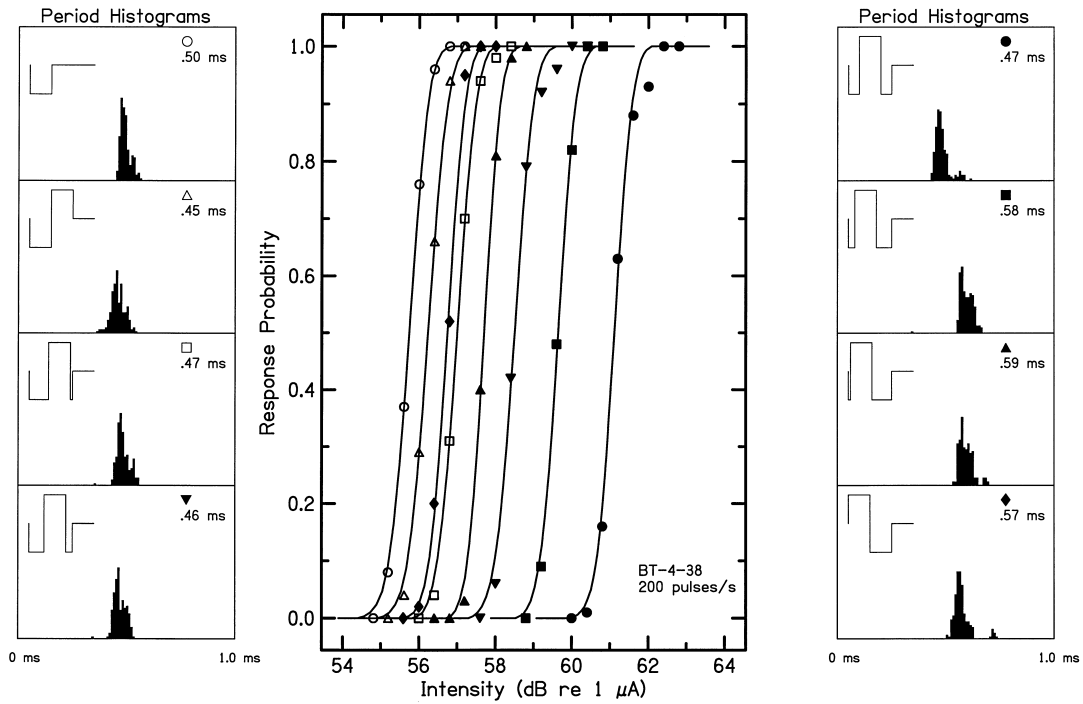


Fig. 9. Input-output functions recorded from a single neurone in response to stimulation using a series of monophasic and triphasic current pulses. The cathodic phase was excitatory as indicated by the low threshold of the 100 μ s monophasic pulse (\circ). In this series, the anodic phase of all triphasic stimuli was held constant (100 μ s) while the leading cathodic phase varied in duration (100 μ s Δ ; 90 μ s \square ; 70 μ s ∇ ; 50 μ s \bullet ; 30 μ s \blacksquare ; 10 μ s \blacktriangle ; 0 μ s \blacklozenge). The second cathodic phase also varied so that the total cathodic duration was 100 μ s.

neurone at maximum stimulus intensity). Of interest in examining the PHs is the systematic increase in latency as pulse width increases. One explanation is that the second (anodic) phase in this example is excitatory; increasing pulse width is simply increasing the delay

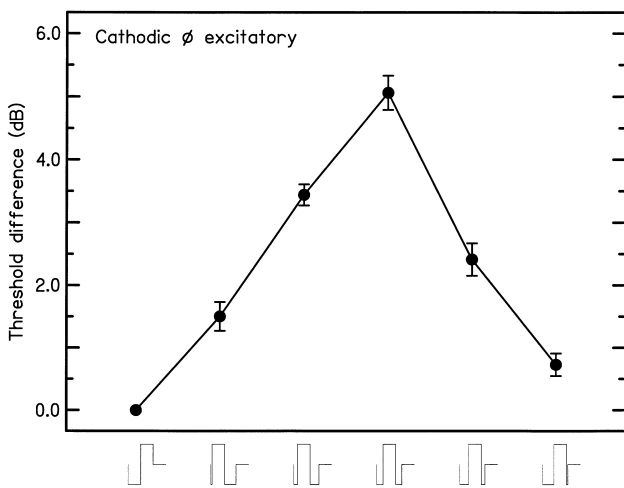


Fig. 10. Mean threshold increase (in dB) of a series of triphasic waveforms relative to 100 μ s/phase biphasic current pulse. The temporal profile of the triphasic current pulses were described in Fig. 9. These results are based on data from seven neurones. Bar = \pm 1 S.E.M.

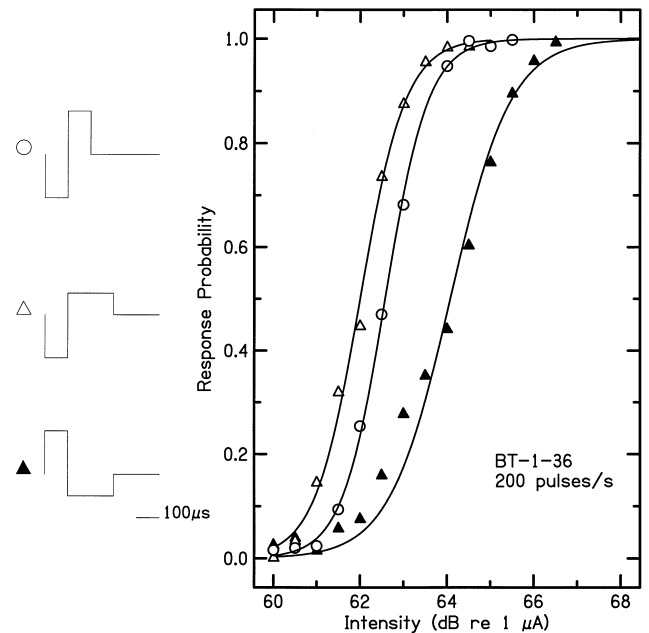


Fig. 11. Input-output functions recorded from a single neurone in response to stimulation using cathodic lead 100 μ s/phase biphasic current pulses and two asymmetrical current pulses. The leading phase of both asymmetrical waveforms was 100 μ s in duration. The second phase was 200 μ s long, however, the current amplitude was half that of the leading phase, thereby ensuring a charge-balanced stimulus.

Table 1
Current pulses: effect of phase reversal^a

	Excitatory phase	Mean (dB re 1 μ A)	S.E.M.	<i>n</i>	<i>P</i> ^b
Monophasic current pulses					
Threshold	Anodic	58.9	0.91	14	0.369 NS
	Cathodic	58.0	0.95	14	
Dynamic range	Anodic	2.49	0.31	14	0.241 NS
	Cathodic	2.21	0.27	14	
Biphasic current pulses					
Leading phase					
Threshold	Anodic	60.8	0.47	47	0.155 NS
	Cathodic	60.6	0.49	47	
Dynamic range	Anodic	2.19	0.18	47	0.681 NS
	Cathodic	2.22	0.20	47	

^aAll data derived from 100 μ s/phase monophasic and biphasic current pulses.

^bPaired *t*-test. NS = not significant.

prior to onset of the excitatory phase. Alternatively, the delay may be associated with an increase in the period required for the neural membrane to integrate charge using longer duration current pulses.

Evaluation of threshold for five neurones showed a mean reduction of 5.3 dB (S.E.M. = 0.34, *n* = 5) as pulse width was increased from 50 to 100 μ s/phase. Not surprisingly, this reduction was highly statistically significant ($P < 0.0001$, paired *t*-test). Dynamic range also increased as a function of pulse width, but only marginally (0.17 dB, S.E.M. = 0.22, *n* = 5). Although based on a limited number of neurones, these results indicate that the efficiency of the current pulse is slightly reduced with increasing pulse width, as a doubling of pulse width would be expected to reduce threshold current by 6 dB. That is, slightly more charge is required to achieve threshold using a 100 μ s/phase current pulse compared to a 50 μ s/phase stimulus.

3.4. Interphase gap

The temporal separation of the two phases of a biphasic current pulse via an interphase gap can significantly increase the efficiency of the stimulus. This variation in efficiency is illustrated for one neurone in Fig. 6. Input-output functions were recorded in response to

a 100 μ s/phase current pulse with an interphase gap varying from 0 to 200 μ s. There is a systematic reduction in threshold as the interphase gap is increased from 0 (\circ , Fig. 6) to 200 μ s (\blacklozenge , Fig. 6). Moreover, in this example the cathodic or trailing phase is excitatory, and the accompanying PHs (windowed from 0.5 to 1.0 ms to emphasise the latency shift) show the response latency increasing as the interphase gap widens. This reduction in threshold as a function of increasing interphase gap was routinely observed in normal, short-term and long-term deafened animals, and was independent of whether the excitatory phase was the leading or lagging phase of the current pulse.

Table 3 summarises the changes in threshold and dynamic range for seven neurones studied using 100 μ s/phase biphasic current pulses with interphase gaps of 0, 40 and 80 μ s. While there was an overall reduction in threshold with increasing interphase gap (mean threshold reduction: 40 μ s gap, 0.41 dB; 80 μ s gap, 0.93 dB) which was significant using an interphase gap of 80 μ s, there was no evidence of a significant change in dynamic range. Greater reductions in threshold (> 1 dB) were routinely observed as the interphase gap was extended beyond ~ 100 μ s. It should be noted that an average reduction in threshold of 1.2 dB was observed between biphasic current pulses (with no in-

Table 2
Threshold difference: monophasic versus biphasic^a

		Mean (dB re 1 μ A)	S.E.M.	<i>n</i>	<i>P</i> ^b
Excitatory phase	monophasic	57.7	0.86	14	0.0006
	biphasic	58.9	0.85	14	
Non-excitatory phase	monophasic	60.1	0.87	13 ^c	0.095 NS
	biphasic	59.1	1.07	13	

^aAll data derived from 100 μ s monophasic and 100 μ s/phase biphasic current pulses.

^bWilcoxon signed rank test.

^cOne neurone readily stimulated by the excitatory monophasic pulse could not be driven by a 100 μ s pulse of the opposite polarity.

Table 3
Biphasic current pulses: effect of interphase gap^a

		Mean (dB re 1 μ A)	S.E.M.	<i>n</i>	<i>P</i> ^b
Threshold	Interphase gap (μ s)				
	0	60.46	1.31	7	
	40	60.05	1.32	7	0.124 NS
	80	59.54	1.32	7	0.017
Dynamic range	Interphase gap (μ s)				
	0	3.04	0.74	7	
	40	2.63	0.73	7	0.06 NS
	80	3.01	0.84	7	0.904 NS

^aAll data derived from 100 μ s/phase biphasic current pulses.

^bPaired *t*-test.

terphase gap) and excitatory monophasic current pulses (Table 2). Taken together, these data show that as the phases of a biphasic current pulse are separated by longer interphase gaps, the threshold of the excitatory phase approaches that of a monophasic stimulus.

Reductions in threshold with interphase gap were also dependent on the duration of the biphasic current pulse. For a given interphase gap, greater reductions in threshold were observed for narrower pulse width stimuli. For example, using a 60 μ s/phase current pulse, the introduction of a 60 μ s interphase gap resulted in a mean threshold reduction of 2.45 dB (S.E.M. = 0.097, *n* = 4) which was highly statistically significant (*P* = 0.0001; paired *t*-test).

3.5. Chopped pulses





Typical auditory nerve fibre response to stimulation using chopped current pulses is illustrated in Fig. 7. Here, input-output functions and representative PHs at saturation are illustrated for 120 and 60 μ s/phase current pulses without an interphase gap, 60 μ s/phase current pulses containing a 60 μ s interphase gap, and

three chopped pulses having 2 \times 30 μ s, 3 \times 20 μ s and 6 \times 10 μ s monophasic pulses delivered uniformly over a 120 μ s period in each phase. As in all examples illustrated here, the chopped pulses delivered the same charge/phase as the two 60 μ s/phase current pulses for a common current amplitude. Consistent with the effects of increasing pulse width described above (Section 3.3), there was an \sim 6 dB reduction in threshold when stimulating using a 120 μ s/phase current pulse (\circ , Fig. 7) compared to a 60 μ s/phase current pulse without an interphase gap (\blacksquare , Fig. 7). The 60 μ s/phase current pulse containing a 60 μ s interphase gap showed an \sim 2.5 dB reduction in threshold over the same current pulse with no gap. Finally, not only were all chopped pulses capable of evoking neural activity, their thresholds were \sim 1.5 dB lower than that evoked by the 60 μ s/phase current pulse without an interphase gap. Threshold and input-output functions for these pulses (2 \times 30 μ s, 3 \times 20 μ s, 6 \times 10 μ s) were very similar (2 \times 30 μ s pulses consistently exhibited the lowest threshold and the 6 \times 10 μ s pulses the highest threshold), and nearly as efficient as the 60 μ s/phase signal with a 60 μ s temporal gap.

The efficiency of the chopped current pulse compared to a 60 μ s/phase biphasic current pulse with no interphase gap is illustrated in Fig. 8. For comparison, input-output functions derived from 60 μ s/phase biphasic current pulses with an interphase gap (\triangle), as well as anodic and cathodic monophasic pulses of 30 (\blacktriangle , \blacklozenge) and 20 μ s (\blacktriangledown , hourglass) duration are also illustrated. Significantly, both monophasic pulses of 20 μ s duration were not capable of evoking neural activity at a stimulus intensity of 70 dB (re 1 μ A), implying that the activity evoked by the 6 \times 10 μ s chopped current pulse was a result of the temporal integration of packets of sub-threshold charge stored on the neural membrane.

The mean increase in threshold, relative to a 60 μ s/phase biphasic pulse with a 60 μ s interphase gap, is illustrated in Table 4 for three chopped waveforms and a 60 μ s/phase biphasic current pulse with no interphase gap. They clearly show that the chopped current

Table 4
Efficiency of chopped current pulses^a

Stimulus ^b	Mean threshold increase (dB re 1 μ A)	S.E.M.	<i>n</i>	<i>P</i> ^c
 2x30 μ s	1.32	0.23	7	0.005
 3x20 μ s	1.48	0.19	9	0.008
 6x10 μ s	1.63	0.24	9	0.009
 60 μ s biphasic pulse	2.54	0.38	4	<0.001

^aThresholds compared with 60 μ s biphasic current pulse with a 60 μ s interphase gap.

^bAll current pulses deliver the same charge per phase for a given current level.

^c*t*-test.

pulses evoke a lower threshold than the 60 μs /phase current pulse without an interphase gap, although all waveforms delivered the same charge/phase for a given current level. Finally, there was only a slight increase in threshold from the $2 \times 30 \mu\text{s}$ to the $6 \times 10 \mu\text{s}$ chopped pulse waveform.

3.6. Triphasic current pulses

Typical auditory nerve fibre response to stimulation using charge-balanced triphasic current pulses is illustrated in Fig. 9. Here, input-output functions and representative PHs are shown for a 100 μs cathodic monophasic pulse (the excitatory phase for this neurone), and seven triphasic current waveforms in which the anodic phase was held constant (100 μs) while the leading cathodic phase varied in duration (100 μs \triangle ; 90 μs \square ; 70 μs ∇ ; 50 μs \bullet ; 30 μs \blacksquare ; 10 μs \blacktriangle ; 0 μs \blacklozenge). The second cathodic phase also varied so that the total duration of the cathodic phase was 100 μs , ensuring that the waveform was charge-balanced. Note that two of these waveforms, where the excitatory cathodic phase was equal to 100 or 0 μs , are identical to 100 μs /phase biphasic current pulses. These results show that neural threshold increases systematically as the duration of the excitatory cathodic phase is reduced from 100 to 50 μs , but the slope of the input-output function is unchanged. With further reductions in the duration of the leading cathodic phase, thresholds begin a systematic decrease consistent with the second cathodic phase becoming excitatory. The increase in latency of the PH evoked by the 30 μs leading cathodic phase stimulus (\blacksquare), compared with the 50 μs leading phase stimulus (\bullet), supports this observation. The relationship between threshold and the duration of the leading (excitatory) phase was a common feature of stimulation using triphasic current pulses as illustrated in Fig. 10.

3.7. Asymmetric current pulses

We studied the basic response properties of a small number of ANFs to electrical stimulation using charge-balanced asymmetric current pulses. A typical example is illustrated in Fig. 11, showing input-output functions to a cathodic-leading 100 μs /phase biphasic pulse, and two asymmetric pulses having 100 μs leading phases with 200 μs lagging phases. To achieve charge balance the current amplitude of the leading phase was twice that of the lagging phase. In this example, the cathodic phase was excitatory. The lowest threshold stimulus was evoked by a 100 μs cathodic leading phase with a 200 μs anodic lagging phase. As noted above, the addition of a second, non-excitatory phase results in an increase in threshold compared with an excitatory monophasic pulse (Section 3.2). The present data sug-

gest that the extent of this threshold increase can be controlled by the *rate* at which charge is delivered during the second phase. By delivering the charge slowly, threshold is reduced compared with the standard (symmetrical) biphasic current pulse. Had the rate at which charge was delivered during the second (non-excitatory) phase been greater than the leading phase, an increase in threshold compared with the 100 μs /phase biphasic current pulse would presumably have been observed.

4. Discussion

The experiments reported in this paper indicate that brief monophasic anodic current pulses delivered via longitudinal bipolar electrodes evoke significantly shorter latency ANF responses compared to cathodic pulses of the same duration, implying that the site of spike initiation for the anodic pulse is located at a more central site along the ANF than a spike initiated via a cathodic pulse. This observation is consistent with previous findings using both bipolar and monopolar electrode arrays (van den Honert and Stypulkowski, 1987a). While a cathode will result in depolarisation of neural membrane proximal to the electrode, an anode will hyperpolarise that region of the membrane; depolarisation will only occur at more distal sites (Ranck, 1975; Mortimer, 1981). If ANF conduction velocity is taken to be 11.3 m/s for a myelinated fibre with a diameter of 2.4 μm (Rushton, 1951), a latency shift of 90 μs (the difference between the mean anodic and cathodic monophasic latencies) is equivalent to a distance of approximately 1.0 mm, implying that the site of spike initiation for an anodic pulse is located at a point central to the spiral ganglion cell somata.

Consistent with our previous observations (Shepherd and Javel, 1997; Javel and Shepherd, 1999), action potentials elicited from more central sites along the ANF tend to show smaller temporal dispersion compared with more peripheral initiation sites. This is presumably related to the large surface area of the nodes of Ranvier at these central sites, giving rise to larger numbers of ion channels, and implying low levels of membrane noise and rapid growth of excitation (Verveen, 1962; White et al., 1987; Javel and Shepherd, 1999). However, it should be pointed out that occasionally longer latency responses, apparently elicited from more peripheral sites along the ANF, also showed very small levels of temporal dispersion (eg. BT-3-6, Figs. 2 and 3). These results might be expected due to variation in the diameter of nodes of Ranvier – both on the same fibre and across fibres (Liberman, 1980). If the active site of spike initiation on the peripheral process was as large as that on the central process, temporal dispersion would be expected to be similar. Even though the *aver-*

age diameter of a peripheral process may be less than a central process, temporal dispersion can still be small if the diameter of the active node is large. This argument also suggests that temporal dispersion may vary somewhat with intensity as the active node changes.

Although not studied extensively, a reduction in threshold as a function of pulse width was illustrated in the present study. The inverse relationship between threshold current and stimulus duration (the classical strength-duration curve) has been demonstrated by many electrophysiological and modeling studies (electrophysiological studies: auditory nerve: van den Honert and Stypulkowski, 1984; Parkins and Colombo, 1987; Parkins, 1989; Clopton et al., 1990; other neural tissue: Hill, 1936; BeMent and Ranck, 1969; Gorman and Mortimer, 1983; McNeal et al., 1989; modeling: McNeal, 1976; Reilly et al., 1985). These data consistently demonstrate that short duration (200 μ s) current pulses are more efficient than longer pulses in that they require less charge to evoke an action potential (Solandt, 1936; Loeb et al., 1983; Parkins and Colombo, 1987; Clopton et al., 1990). As the duration of a near-threshold current pulse increases, the sodium conductance falls and potassium conductance begins to rise, i.e. the rate of depolarisation begins to approach the rate at which the neurone undergoes repolarisation, effectively elevating the threshold (Noble, 1966). The present findings are consistent with these earlier results; more charge was required to achieve threshold using 100 compared with 50 μ s/phase current pulses.

The influence of the second phase on auditory nerve excitability is associated with a vulnerable period before the initiation of the action potential, during which time its occurrence can be suppressed. This period is \sim 100 μ s following the depolarising current pulse for myelinated fibres at near-threshold stimulation levels (van den Honert and Mortimer, 1979). At these levels spike initiation is highly vulnerable, and is readily influenced by the instantaneous membrane potential, the membrane's refractory state and the presence of the second hyperpolarising phase of a biphasic (or multiphasic) current pulse. This vulnerable period would appear to be at least in part due to the finite time required for the change in Na^+ permeability to take effect, giving rise to the action potential (Bromm and Frankenhaeuser, 1968). Clearly, increasing the rate of delivering the hyperpolarising charge within this 100 μ s window would reduce the probability of action potential generation and result in elevated thresholds.

Consistent with this argument, we reported a mean threshold reduction of \sim 1.25 dB for 100 μ s/phase biphasic current pulses with interphase gaps of up to 120 μ s compared with identical current pulses with no interphase gap. In addition, the rate of threshold reduction appeared to decrease exponentially as a function of

increasing interphase gap, illustrating the effect of introducing a hyperpolarising charge at a point early within the ANF's vulnerable period. Greater threshold reductions were observed as a function of interphase gap, for current pulses $<$ 100 μ s/phase, suggesting that the vulnerable period is more critical for these very narrow current pulses. The present findings in ANF are in agreement with a previous report describing the effect of interphase gap on the membrane potential of a single node of Ranvier isolated from a myelinated sciatic nerve (van den Honert and Mortimer, 1979).

The reduction in threshold as interphase gap increases from 0 to 120 μ s is similar to the reduction observed for an excitatory monophasic current pulse compared with a biphasic current pulse with no interphase gap. It would appear that as the phases of a biphasic current pulse are separated by a longer period, the threshold of the excitatory phase approaches that of the excitatory monophasic current pulse. Similarly, by delivering the charge associated with the second phase at a slower rate than the leading excitatory phase, thresholds for asymmetric current pulses are reduced relative to symmetric biphasic pulses. That is, as the rate of charge delivery in the second phase is reduced, threshold for an asymmetric current pulse approaches that of an excitatory monophasic pulse.

There are a number of clinical benefits associated with the use of stimulus waveforms that lead to a reduction in threshold. First, with the use of more efficient stimuli, lower charge/phase and hence lower charge densities can be employed. As charge density sets maximum safe stimulus limits (Brummer and Turner, 1977; Robblee and Rose, 1990), the use of more efficient stimuli implies that smaller surface area stimulating electrodes could be used safely. Furthermore, in combination with techniques to improve spatial selectivity, arrays with an increased number of small surface area electrodes may become feasible. Second, more efficient stimuli lead to reduced power consumption, resulting in longer speech processor battery life (cochlear implants are typically powered from an external speech processor via a radio frequency transcutaneous link). This improved efficiency also provides the opportunity to develop smaller, more efficient devices, including speech processors designed to be placed behind the ear (Seligman, 1997).

Modeling studies indicate that the use of asymmetric charge-balanced biphasic current pulses can improve the spatial selectivity of longitudinal bipolar scala tympani electrodes (Frijns et al., 1996). This work suggested that the first phase, of short duration and high amplitude, would excite ANFs while the second phase, having a long duration with low current amplitude, would ensure that the stimulus is charge-balanced with-

out contributing to ANF excitation. Careful attention would need to be given to selection of the current amplitude and duration of the second phase in order to ensure that it did not result in spike initiation. Frijns et al. (1996) estimated a ratio of current amplitude of 5:1 would be required to ensure that the second phase is not excitatory. Improved spatial selectivity, coupled with the reduced thresholds described in the present study, suggests that asymmetric stimulus waveforms may have a number of clinical advantages. Clearly, however, a disadvantage associated with this stimulus waveform would be a lower limit placed on the maximum stimulus rate due to the relatively long duration second phase.

Asymmetric current pulses incorporating a short duration leading phase would have a number of other potential clinical advantages. First, there is evidence that short duration pulses produce more spatially selective stimulation compared with longer duration stimuli (Grill and Mortimer, 1996). This finding also appears to hold for auditory nerve. Recently, using loudness-balanced stimuli, psychophysical data from cochlear implant subjects have shown that longer duration current pulses appear to excite a more spatially extended neural population compared to narrower pulses (McKay and McDermott, 1997). Second, as discussed above, narrower duration pulses appear to be more efficient, thereby providing the additional clinical advantage of lower thresholds.

ANFs were readily stimulated by triphasic current pulses, although the maximum efficiency of this stimulus waveform was somewhat less than the most efficient biphasic current pulse. Coste and Pfingst (1996) drew similar conclusions from psychophysical experiments in which charge-balanced triphasic current pulses were compared with biphasic pulses. In the present study, as the excitatory phase became more symmetrically distributed around the non-excitatory phase, ANF threshold increased. Thresholds reduced when one of the excitatory phases increased in duration at the expense of the other, that is, when the majority of the excitatory charge was delivered in one of the two phases. An increase in latency, equivalent to the duration of the non-excitatory phase, was evident when the ANF switched sensitivity from the first to the third phase of the current pulse.

A number of psychophysical studies have identified two forms of stimulus interaction associated with electrical stimulation of the auditory nerve (e.g. Eddington et al., 1978; Shannon, 1983; White et al., 1984; Favre and Pelizzone, 1993). Simultaneous interaction is a result of the vector summation of current density during simultaneous stimulation from two or more scala tympani electrodes (Merzenich and White, 1977; Black et al., 1981; O'Leary et al., 1985; Hartmann and Klinke,

1990). At present, cochlear implants typically stimulate non-simultaneously in order to eliminate any unpredictable current interactions within the scala tympani, although several studies have suggested techniques in which simultaneous current interaction could be used to produce more focused stimulation of the auditory nerve using multiple electrodes rather than a monopolar or bipolar electrode configuration (Clark et al., 1978; Townshend and White, 1987; Hartmann and Klinke, 1990; Suesserman and Spelman, 1993; Rodenhiser and Spelman, 1995; Jolly et al., 1996; Miyoshi et al., 1996; Kral et al., 1998).

Non-simultaneous interactions on ANFs occur as a result of the non-linear properties of the neural membrane, in particular the sodium transport system (Bromm and Frankenhaeuser, 1968). In this, the excitatory effects of a depolarising phase are not completely eliminated by the following hyperpolarising phase, leading to a change in sensitivity during repetitive stimulation at high rates which can be integrated over time (Shannon, 1983). It has been suggested that the use of triphasic current pulses may be an effective means of restoring the neural membrane to its resting state, thereby reducing the effect of non-simultaneous interaction of ANFs (Eddington et al., 1995). Other multiphasic current pulses, including chopped stimulus waveforms, could also be used in an attempt to restore the neural membrane to its resting state. Further work in this area is clearly warranted.

Stimulation of the auditory nerve using chopped current pulses illustrates the ability of small packets of charge to be stored on the neural membrane over relatively short periods of time ($\sim 120 \mu\text{s}$). Moreover, this charge can be effectively integrated over time to ultimately achieve depolarisation of the neural membrane. This effect was best illustrated in Fig. 8, where anodic and cathodic monophasic pulses of $20 \mu\text{s}$ duration were not capable of evoking an action potential at the highest current amplitude available (70 dB re $1 \mu\text{A}$). In contrast, a chopped waveform consisting of $6 \times 10 \mu\text{s}$ anodic monophasic pulses charge-balanced with $6 \times 10 \mu\text{s}$ cathodic pulses exhibited a threshold of approximately 66.5 dB. Moreover, this stimulus waveform was more efficient than a $60 \mu\text{s}$ /phase biphasic pulse without an interphase gap (both stimulus waveforms deliver the same charge/phase for a common current level). To our knowledge, this is the first demonstration of neural excitation by a series of monophasic current pulses that individually cannot evoke neural activity, but can so collectively.

The present findings support the concept that the neural membrane functions as a leaky integrator (Parkins, 1989; Ross, 1996). Although the $60 \mu\text{s}$ biphasic current pulse with a $60 \mu\text{s}$ interphase gap consistently evoked lower thresholds than the $2 \times 30 \mu\text{s}$, $3 \times 20 \mu\text{s}$

and $6 \times 10 \mu\text{s}$ chopped pulses (Table 4), all four waveforms delivered the same total charge for a given current level. The slight but consistent increase in threshold from $2 \times 30 \mu\text{s}$ to $6 \times 10 \mu\text{s}$ chopped pulses can also be accounted for by the neural membrane acting as a leaky integrator. The elevated thresholds are associated with increased amounts of charge leaking from the neural membrane during the stimulus pulse. While the same amount of charge is delivered per phase, it is done so over a progressively longer duration, resulting in greater amounts of charge leaking from the neural membrane (charge is delivered over $60 \mu\text{s}$ for the $60 \mu\text{s}$ biphasic current pulse; over $90 \mu\text{s}$ for the $2 \times 30 \mu\text{s}$ chopped pulse; $100 \mu\text{s}$ for the $3 \times 20 \mu\text{s}$ pulse; and $110 \mu\text{s}$, $6 \times 10 \mu\text{s}$ pulse). A similar argument can be used to explain threshold differences with triphasic current pulses.

As noted above, the use of chopped current pulses could provide cochlear implant users with a number of 'quasi-simultaneous' channels without the potential adverse effects of simultaneous current interaction, by rapidly delivering small packets of charge non-simultaneously to several scala tympani electrode pairs (McDermott, 1989).

While the present results are based on single ANF data, we have attempted to present statistical evidence, based on a population of fibres, to demonstrate changes in response efficiency with manipulation of the stimulus waveshape. Given that the ANFs presented in this study were selected randomly, we argue that any statistically significant difference across a population of neurones has the potential to also be observed clinically. For example, increasing the interphase gap of biphasic current pulses, shown in the present study to significantly reduce ANF thresholds, is known to result in a lower threshold current level in cochlear implant patients (P.M. Seligman, personal communication).

Finally, although no statistical analysis was performed in this study investigating the effects of varying degrees of deafness on ANF responses, trends in ANF response to a given manipulation in the stimulus waveform were consistent across fibres irrespective of cochlear status.

In conclusion, the present study has described ANF responses to a variety of stimulus waveforms. The variation in their response to different stimuli improves our understanding of the mechanisms associated with direct electrical stimulation of neural tissue. Moreover, the ability to manipulate stimulus waveforms in order to reduce threshold, minimise non-simultaneous current interaction and improve spatial selectivity has implications that may prove clinically useful.

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