ELSEVIER

Hearing Research 112 (1997) 147–157

HEARING RESEARCH

Reduction in excitability of the auditory nerve following electrical stimulation at high stimulus rates. II. Comparison of fixed amplitude with amplitude modulated stimuli

Michael Tykocinski, Robert K. Shepherd *, Graeme M. Clark

Department of Otolaryngology, The University of Melbourne, 32 Gisborne Street, East Melbourne, Vic. 3052, Australia

Received 24 February 1997; revised 26 June 1997; accepted 4 July 1997

Abstract

We have previously shown that acute electrical stimulation of the auditory nerve using charge-balanced biphasic current pulses presented continuously can lead to a prolonged decrement in auditory nerve excitability (Tykocinski et al., Hear. Res. 88 (1995), 124–142). This work also demonstrated a reduction in electrically evoked auditory brainstem response (EABR) amplitude decrement when using an otherwise equivalent pulse train with a 50% duty cycle. In the present study we have extended this work in order to compare the effects of electrical stimulation using both fixed amplitude electrical pulse trains and amplitude modulated (AM) pulse trains that more accurately model the dynamic stimulus paradigms used in cochlear implants. EABRs were recorded from guinea pigs following acute stimulation using AM trains of charge-balanced biphasic current pulses. The extent of stimulus-induced reductions in the EABR were compared with our previous results using either fixed amplitude continuous, or 50% duty cycle pulse trains operating at 0.34 μC/phase (2 mA, 170 μs/phase) at 400 or 1000 pulses/s (Tykocinski et al., Hear. Res. 88 (1995) 124–142). The AM pulse train, operating at the same rates, was based on a 1-s sequence of the most extensively activated electrode of a Nucleus Mini-22 cochlear implant using the SPEAK speech processing strategy exposed to 4-talker babble, and delivered the same total charge as the fixed amplitude 50% duty cycle pulse train. Two hours of continuous stimulation induced a significant, rate-dependent reduction in auditory nerve excitability, and showed only a slight post-stimulus recovery for monitoring periods of up to 6 hours. Following 2 or 4 h of stimulation using an otherwise equivalent pulse train with a 50% duty cycle or the AM pulse train, significantly less reduction in the EABR was observed, and recovery to pre-stimulus levels was generally rapid and complete. These differences in the extent of the recovery between the continuous waveform and both the 50% duty cycle and AM waveforms were statistically significant for both 400 and 1000 pulses/s stimuli. Consistent with our previous results, the stimulus changes observed using AM pulse trains were rate dependent, with higher rate stimuli evoking more extensive stimulus-induced changes. The present findings show that while stimulus-induced reductions in neural excitability are dependent on the extent of stimulus-induced neuronal activity, the use of an AM stimulus paradigm further reduces post-stimulus neural fatigue.

Keywords: Cochlear implant; High-rate electrical stimulation; Auditory nerve; Neural damage; Electrically evoked auditory brainstem response

1. Introduction

Cochlear implants provide profoundly deaf patients with auditory cues important for speech discrimination. A number of psychophysical and clinical studies have suggested that speech processing strategies based on high stimulus rates (> 400 pulses/s [pps]) may lead to an improvement in speech perception due to an improved representation of the rapid variations in the amplitude of speech (Hochmair-Desoyer et al., 1985; Tong et al., 1990; Wilson et al., 1991, 1993; Dillier et al., 1992; McDermott et al., 1992; Busby et al., 1993). However, 'neural fatigue' has been known to occur following brief periods of electrical stimulation at rates sufficiently high to ensure that stimuli occur within

* Corresponding author. Tel.: +61 (3) 9665-9666; Fax: +61 (3) 9663-1958; E-mail: shepherdr@mail.medoto.unimelb.edu.au

PII S0378-5955(97)00117-2

the neurones relative refractory period. The extent of this fatigue has been shown to depend on stimulus intensity, stimulus duration, and the rate of the evoked stimulus-induced neural activity (Forbes and Rice, 1929; Gasser, 1935; Hill et al., 1936; Bowman and McNeal, 1986).

We have extended this work in order to investigate stimulus-induced neural damage mechanisms in the auditory nerve (Shepherd and Clark, 1987; Shepherd et al., 1990; Tykocinski et al., 1995a). In our most recent study, the auditory nerve of the anaesthetised guinea pig was electrically stimulated using a constant amplitude train of current pulses presented continuously over a 2 h period to a fixed pair of bipolar electrodes (Tykocinski et al., 1995a). At high stimulus rates (400 and 1000 pps), operating at intensities that varied from 0.34–1.0 μC/phase – levels that are well above those used clinically – we observed significant and prolonged reductions in auditory nerve excitability as measured by the post-stimulus electrically evoked auditory brainstem response (EABR). The extent of these changes depended on both stimulus rate and intensity, suggesting that these effects were related to the extent of stimulus-induced neuronal activity. Support for this hypothesis came from experiments in which an otherwise equivalent pulse train with a 50% duty cycle was used, thereby reducing the extent of driven neural activity. This stimulus paradigm produced significantly less stimulus-induced change in the EABR. Similar findings have also recently been reported by Killian et al. (1994). These investigators observed stimulus-induced fatigue in the auditory nerve following monopolar round window stimulation using 100 ms bursts of a 16 kHz electrical sine wave. The degree of reduction in neural excitability depended on the amplitude of the stimulus current, and the effects were reduced with the introduction of a duty cycle.

An understanding of the mechanisms responsible for these stimulus-induced changes will have important implications for the safe operating rate of cochlear implants. Furthermore, this information may lead to improvements in the way rapid amplitude changes in speech are presented to the auditory nerve via electrical stimulation, as neural fatigue may result in a reduction in the emphasis of some speech transients. The aim of the present study was, therefore, to compare stimulus-induced reductions in neural excitability for continuous stimulus waveforms using high rates and a fixed stimulus intensity, with stimulus waveforms more representative of those seen in clinical settings, that is: (i) fixed stimulus levels but with a 50% duty cycle; and (ii) an amplitude-modulated (AM) stimulus waveform recorded via a speech processor, reflecting the temporal changes in amplitude typically associated with a cochlear implant. Other stimulus parameters (charge/phase, charge density), which have been shown previously to potentially damage neural tissue (Brown et al., 1977; Pudenz et al., 1977; Yuen et al., 1981; Agnew et al., 1983; McCreery et al., 1988, 1990), were kept at levels known not to induce pathology. A preliminary report of part of this work has been presented earlier (Tykocinski et al., 1995b).

2. Materials and methods

Experimental procedures were identical to those described previously (Tykocinski et al., 1995a). Briefly, eight healthy, pigmented adult guinea pigs with otoscopically normal tympanic membranes were used. Each animal was anaesthetised with ketamine hydrochloride (35 mg/kg) and xylazine 3.5 mg/kg). Anaesthesia was maintained with hourly supplemental doses of a 2:1 ketamine and xylazine mixture. Each animal was bilaterally implanted with a multichannel platinum scala tympani electrode array. Following the surgical procedure each animal was placed in an electrically shielded, sound attenuated room. Respiratory rate (35–60/min) and end tidal CO_2 ($< 5.5\%$) were continuously monitored, while the core temperature was held at 38 ± 0.5°C over the duration of the experiment (approximately 12 h).

Electrical stimulation consisted of charge-balanced biphasic current pulses delivered by an optically isolated current source (Shepherd and Clark, 1987) to bipolar electrodes. Additional charge balancing was achieved by shorting the electrodes between pulses (Patrick et al., 1990). EABRs were recorded differentially using subcutaneous needle electrodes (vertex, positive; neck, negative; abdomen, ground). The responses were amplified by a factor of 10^5 and band-pass filtered (Krohn-Hite 3750R). The output was fed into a 10 bit A/D converter and sampled at 20 kHz for 12.5 ms following stimulus onset. EABRs were recorded just prior to, and periodically following the acute stimulation program. Two responses were recorded at each probe current, which is defined as the current pulse used to evoke an EABR. Current pulses ranged from 2.1 mA to threshold. Thresholds and EABR input-output functions (EABR amplitude versus probe current) of waves I and III were determined. Threshold was taken as the lowest probe current level for both responses at which wave III was at least 0.15 μV, which was always readily visible in the background noise. Mean amplitudes were calculated as the mean of the amplitudes of wave P_1-N_1 (first positive peak and following trough) and the mean of the amplitudes of wave P_3-N_3 (third positive peak and following trough). Post-stimulus EABR amplitudes were normalised to a percentage of the pre-stimulus EABR amplitude.

Two animals were used for each stimulus paradigm, and each EABR amplitude-time function represents the

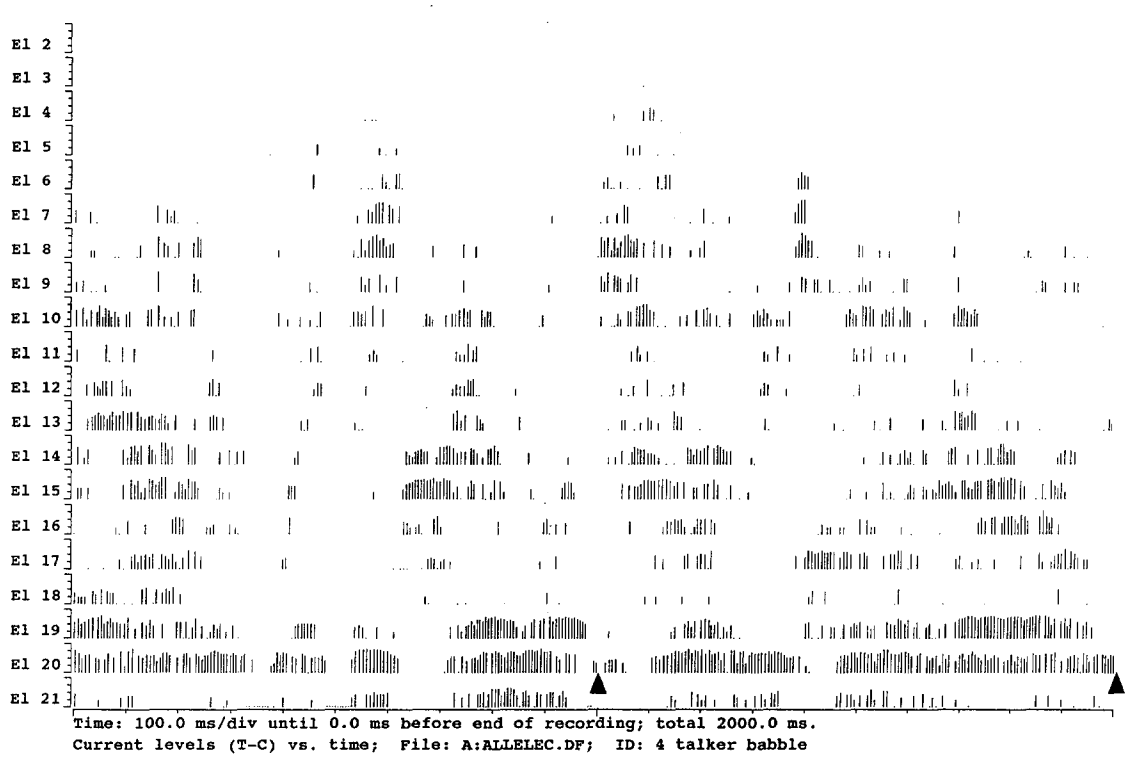


Fig. 1. A representative stimulation profile (2 s) of a Nucleus Mini-22 cochlear implant exposed to 4-talker babble. The extent of each vertical line is proportional to current amplitude. The most commonly activated electrode was #20. The sequence used for the 4-talker babble stimulation is marked by arrows. This sequence was continuously repeated at 400 or 1000 pps during the 2 h or 4 h stimulation programme. Total charge injected during stimulation was the same as for 50% duty cycle stimulation and, therefore, 50% (2 h stimulus period) or 100% (4 h stimulus period) of the total charge injected during the continuous stimulus paradigm.

mean of the normalised EABR amplitude ± S.E.M. The most characteristic stimulus-induced changes are likely to take place within the 'core' neurones close to the stimulating electrode array. We, therefore, recorded the EABR at probe intensities 10 dB below the acute stimulus intensity, although other probe levels were also used. The AM stimulus waveform used in the present study represented a continuously repeated 1-s sequence of the stimulus pattern of the most active electrode of a Nucleus Mini-22 cochlear implant using the SPEAK speech processing strategy when 4-talker babble (Auditec, St. Louis, MO, USA), commonly used as standard source of background noise, was presented to it. The 4-talker babble was presented at a level of 65 dB (SPL). An analysis of electrode current levels during the sequence was performed using in-house software ('OST-4' developed by H.J. McDermott and J.M. Harrison). The resulting stimulus pattern for all electrodes is shown in Fig. 1 at an original pulse rate of approximately 168 pps. The stimulus current amplitudes of the selected 1 s sequence of electrode 20 were adjusted, so that the total charge injection was equal to that of the 50% duty cycle (Fig. 2). The pulse amplitude of the non-zero AM stimuli varied between 0.3 mA and 2.0 mA, while the pulse width was fixed at 170 μs/phase. The minimum stimulus intensity (for non-zero-ampli-

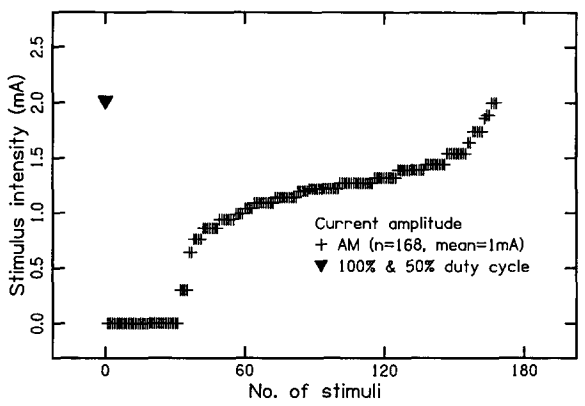


Fig. 2. Distribution of stimulus intensities (+) of the AM sequence (168 pulses, including zero-amplitude pulses) following adjustment of stimulus levels to inject the same charge compared with 50% duty cycle stimulation. The fixed current amplitude for both the continuous and 50% duty cycle stimuli is also illustrated (▼) for comparison. Pulse width (170 μs/phase) was constant for all stimulus paradigms.

Fig. 3. Representative EABR recordings from three different animals stimulated using a pulse rate of 1000 pps and a stimulus intensity of 0.34 μC/phase. The top trace in each panel illustrates the pre-stimulus response (Pre-stim.). The remaining traces illustrate responses recorded immediately (Post-stim.) and 1 and 6 h following stimulation. The stimulation period was 2 h. The waveforms used were: (a) a continuous fixed amplitude waveform; (b) an otherwise equivalent pulse train with a 50% duty cycle (10 ms on/10 ms off); and (c) an AM stimulus waveform. A control (unstimulated) set of EABRs recorded over the same monitoring period is illustrated for comparison (d). Pulses with a probe current of 2.1 mA and a pulse width of 50 μs/phase were used to evoke the EABRs in all examples illustrated here.

→

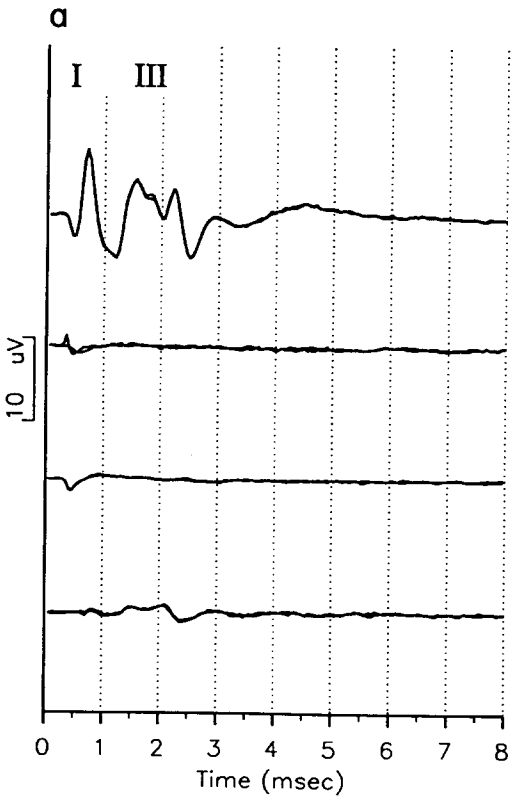
tude pulses) was, therefore, 0.051 μC/phase, while the maximum was 0.34 μC/phase. This AM stimulus waveform, which is more typical of the stimulus patterns used clinically, was then repeated continuously at 400 or 1000 pps. This was achieved by shortening the interpulse period. Although a stimulus intensity of 0.34 μC/phase is realisable using the Nucleus Cochlear implant, it is well above maximum clinical levels. However, in order to compare effects of different stimulus waveforms, this stimulus level was selected, because it produced significant reduction in auditory nerve excitability following continuous stimulation at high rates (>200 pps; Tykocinski et al., 1995a). Stimulus durations of 2 and 4 h were used to control for total charge injection. Each animal was acutely stimulated using one of the four amplitude modulated stimulus paradigms employed in this study (AM, 2 h, 400 or 1000 pps; AM, 4 h, 400 or 1000 pps). The extent of the stimulus-induced change was then compared with earlier results from 12 animals stimulated using (i) a continuous pulse train (2 mA, 170 μs/phase, 0.34 μC/phase, 400 or 1000 pps) for 2 h or (ii) an otherwise equivalent pulse train with a 50% duty cycle (10 ms ON, 10 ms OFF) for 2 or 4 h (Tykocinski et al., 1995a).

Two-way analysis of variance (ANOVA) was performed on post-stimulus EABR amplitudes recorded from the stimulated side comparing the normalised EABR amplitudes across treatments. This was followed by the post-hoc Newman-Keuls test to determine the statistical significance in post-stimulus EABR changes across treatments at a level of $P < 0.05$. Statistical results of the Newman-Keuls test are quoted in the appropriate figure legend. To ensure that the general physiological condition of the animal did not result in changes to auditory nerve excitability, EABRs evoked from the contralateral control cochlea were monitored periodically throughout the experiment. Control EABR amplitudes for both wave I and wave III at probe currents of 2.1, 1.6 and 1.0 mA were measured and found to be normally distributed (Tykocinski et al., 1995a). All control EABRs fell within the 95% confidence interval for such data.

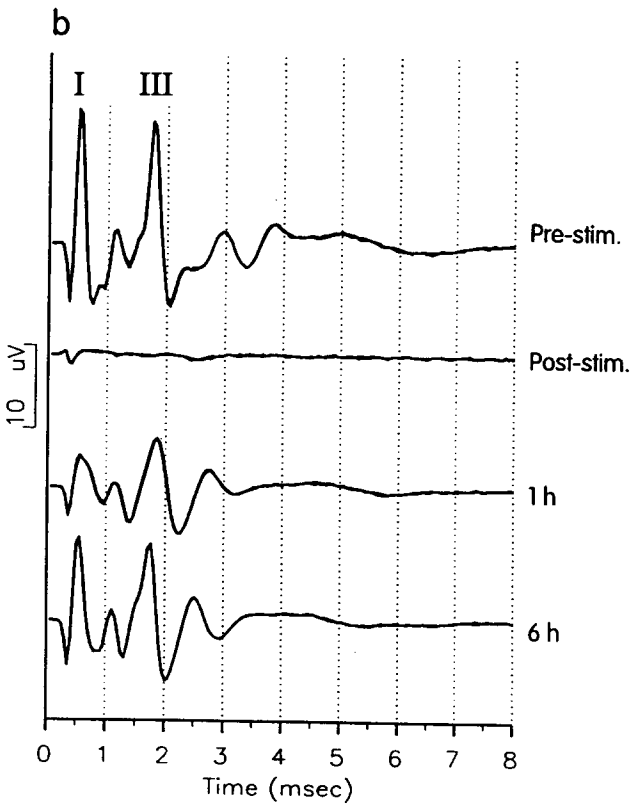
In order to describe the recovery of the EABR amplitude quantitatively, regression analysis was also performed on the raw data using a logarithmic curve fitting function ($y = a \cdot \log[x] + b$). These equations provided slopes [a] which were proportional to the time course of post-stimulus EABR amplitude recovery, as well as the extrapolated minimum post-stimulus EABR amplitude (y-axis intercept [b]) for each stimulus paradigm.

Table 1
Summary of the results of regression analysis, using a logarithmic curve-fitting function ($y = a \cdot \log[x] + b$) indicating the rate of recovery (slope [a]) and the extrapolated stimulus-induced EABR amplitude reduction (y-axis intercept [b]) for all stimulus paradigms. The goodness of fit (R^2) is also illustrated.

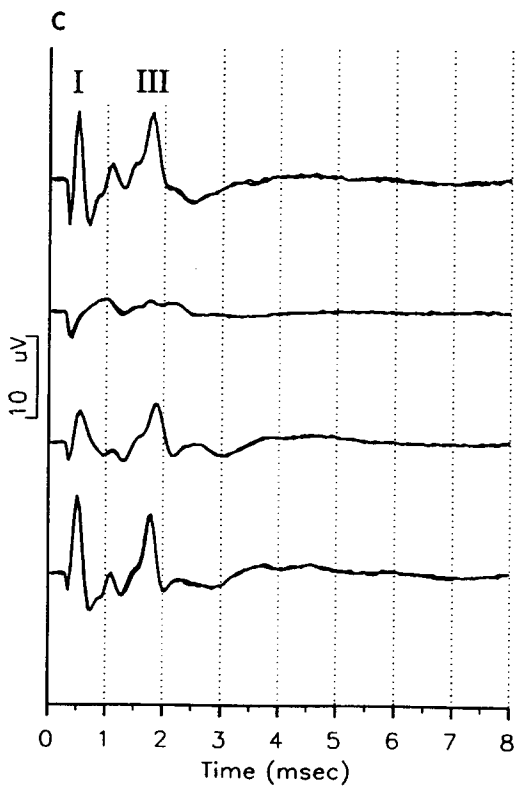
400 pps	Slope	y-intercept	R^2	1000 pps	Slope	y-intercept	R^2
	Wave I				Wave I		
2 h				2 h			
Contin.	12	−7.9	0.79	Contin.	1.8	−2.1	0.40
D-Cyc.	16	66.7	0.80	D-Cyc.	33.6	0.9	0.96
AM-mod.	21.7	57.7	0.81	AM-mod.	43.8	−29.2	0.89
	Wave III				Wave III		
2 h				2 h			
Contin.	20.2	−7.8	0.90	Contin.	9.1	−7.9	0.73
D-Cyc.	15.3	78.5	0.61	D-Cyc.	31.5	5.8	0.82
AM-mod.	10.7	88.1	0.50	AM-mod.	45.1	−1.6	0.97
	Wave I				Wave I		
4 h				4 h			
D-Cyc.	10.8	93.3	0.39	D-Cyc.	15.3	−11.7	0.82
AM-mod.	30.6	50.2	0.98	AM-mod.	31.8	11.7	0.98
	Wave III				Wave III		
4 h				4 h			
D-Cyc.	12.7	90.9	0.85	D-Cyc.	31.2	−4.05	0.97
AM-mod.	17.45	81.3	0.84	AM-mod.	30.9	36.19	0.85



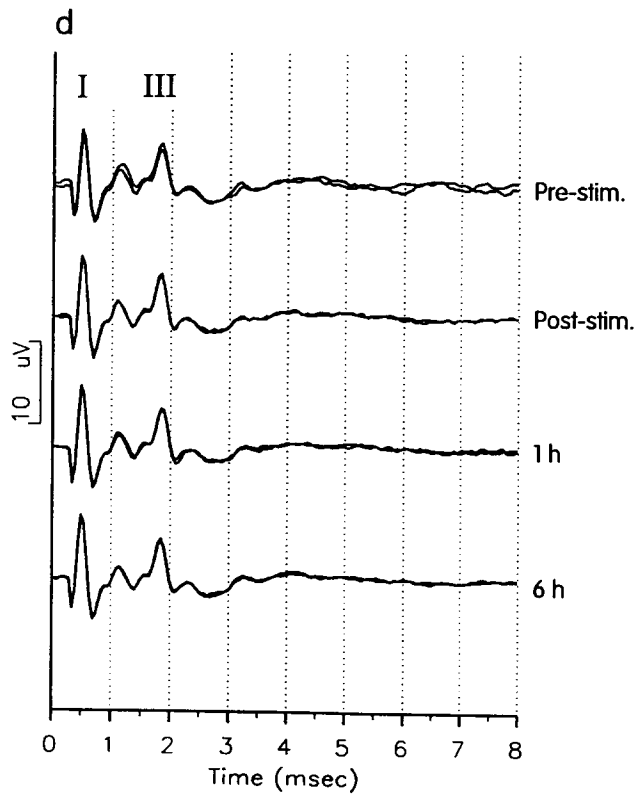
Continuous stimulation



50% Duty cycle stimulation



Amplitude modulated stimulation



Unstimulated Control

As it took approximately 2 min following completion of the stimulus to record the initial EABRs, this time was used for calculation of the first data point following stimulation. A summary of the results is presented in Table 1, the derived logarithmic functions are presented in the appropriate figures. The MS Excel® (v. 5.0) data analysis tool was used for those calculations.

The care and use of the animals reported on in this study were approved by the Animal Experimentation Ethics Committee of the Royal Victorian Eye and Ear Hospital ('Neural Damage Mechanisms in the Auditory Nerve', Register No. 92-016).

3. Results

Acute electrical stimulation of the auditory nerve can result in a significant reduction in EABR amplitude and increase in response threshold compared with control EABRs from an unstimulated cochlea (Fig. 3). Moreover, the extent of these stimulus-induced changes as well as the rate of recovery depended on both stimulus rate and the stimulus waveform used, as is evident from the representative EABR recordings (Fig. 3) and the recovery functions (Figs. 4–7). Table 1 presents a summary of the regression analysis results showing the slope (rate of recovery), y-intercept (extrapolated minimum EABR amplitude) and the goodness of fit (R^2) of the derived logarithmic functions. An optimum fit of the logarithmic curves to the raw data occurred when there was a substantial post-stimulus reduction in EABR amplitude followed by a relatively rapid recovery.

Continuous stimulation at 400 pps and 0.34 μC/phase for 2 h produced a significant decrease in the post-stimulus EABR amplitude of both waves I and III immediately after stimulation, followed by a slow and incomplete recovery during the monitoring period of 6 h (Fig. 4). Both the 50% duty cycle and AM stimulus waveforms showed less initial decrement in the EABR (higher y-intercept) and a more rapid recovery to pre-stimulus levels of both waves I and III (Table 1; Fig. 4). Moreover, both stimulus waveforms produced similar recovery rates (Table 1). Continuous stimulation at 1000 pps and 0.34 μC/phase for 2 h produced an even greater decrease in the post-stimulus EABR amplitude immediately following stimulation (Fig. 5). Recovery was generally minimal, especially for wave I (slope of wave I recovery: 1.8; Table 1). In these cases the logarithmic functions did not fit the raw data very well, as reflected in relatively low R^2. In contrast, while both the 50% duty cycle and AM stimulus waveforms resulted in a significant reduction of the EABR amplitude immediately following stimulation, near complete recovery was observed over the subsequent 4 h (slope of wave I recovery: 33.6 duty cycle; 43.8 AM modulated; Table 1). While the recovery of both stimulus waveforms appeared almost identical during the first 2 h following stimulation, the AM stimulus ultimately resulted in a more complete recovery (Fig. 5).

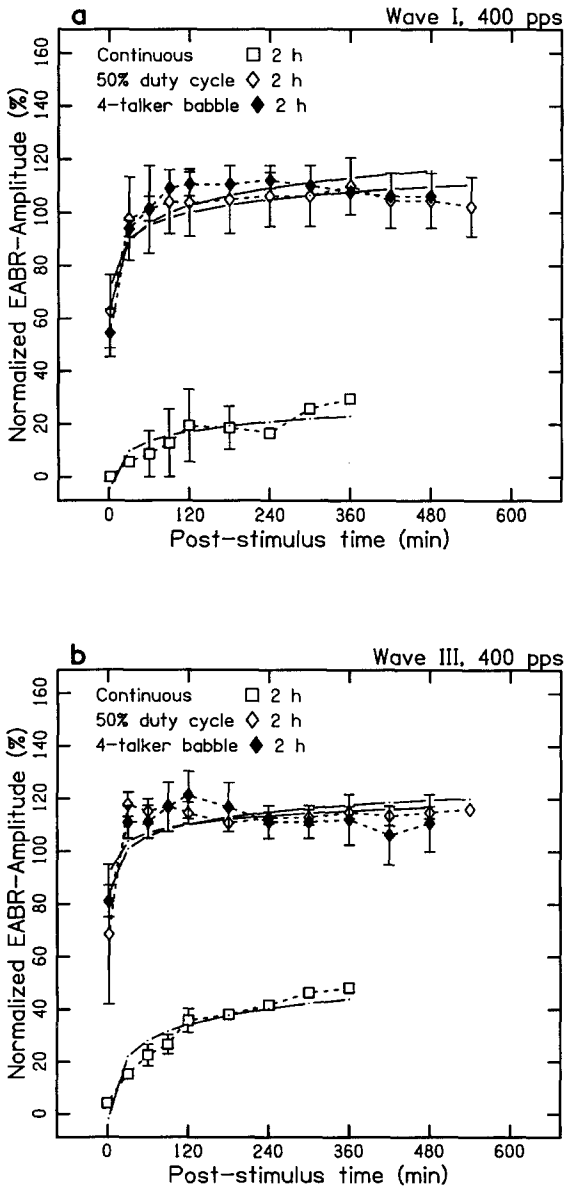


Fig. 4. Normalised EABR amplitudes (mean ± S.E.M.) of waves I (a) and III (b) following stimulation for 2 h at 0.34 μC/phase and 400 pps using a continuous ($n = 2$), a 50% duty cycle ($n = 2$) and an AM ($n = 2$) stimulus paradigm (broken lines). These data were evaluated at a probe intensity 10 dB below the acute stimulus intensity. In addition, the logarithmic curve fitting results are illustrated (full lines). The post-stimulus EABR amplitude recovery was rapid and complete following both 50% duty cycle and AM stimulation compared with recovery following continuous stimulation. This was reflected in the statistical evaluation of both waves I and III, which showed that the EABR amplitude-time functions following both 50% duty cycle and AM stimulation exhibited no statistically significant difference. However, both were significantly greater than the recovery function recorded following continuous stimulation ($P < 0.05$).

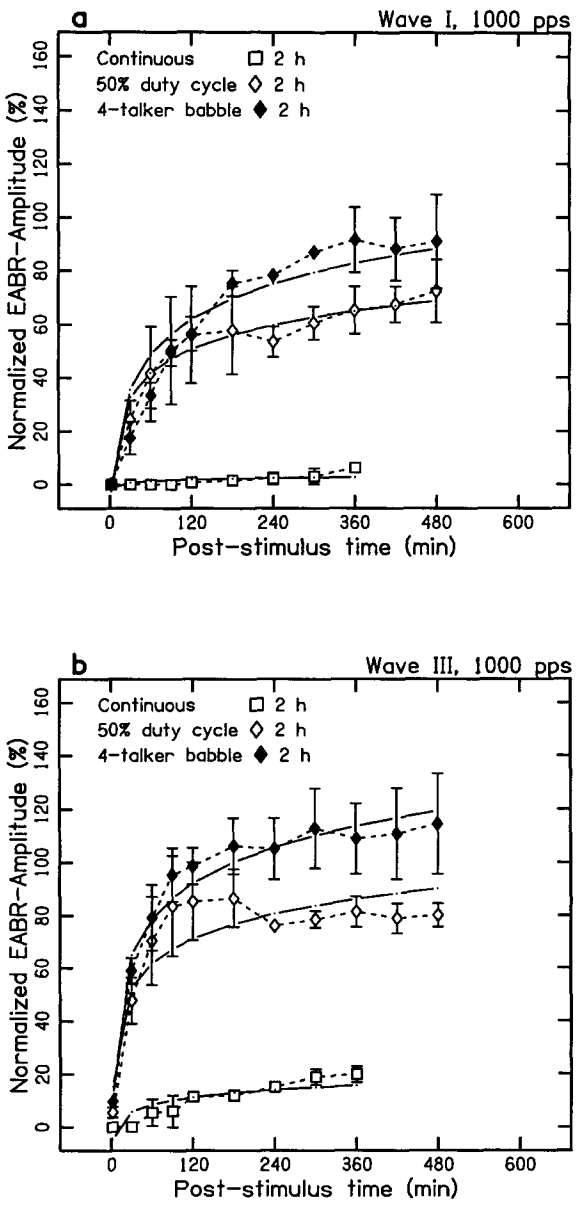


Fig. 5. Normalised EABR amplitudes (mean ± S.E.M.) of waves I (a) and III (b) following stimulation for 2 h at 0.34 μC/phase and 1000 pps using a continuous ($n = 2$), a 50% duty cycle ($n = 2$) and an AM ($n = 2$) stimulus paradigm (broken lines). The data were evaluated at a probe intensity 10 dB below the acute stimulus intensity. In addition, the logarithmic curve fitting results are illustrated (full lines). The post-stimulus EABR amplitude recovery was rapid and complete following AM stimulation. Recovery following 50% duty cycle stimulation did not quite reach pre-stimulus levels during the 8 h monitoring period, but was much more rapid and complete compared with recovery following continuous stimulation. The statistical evaluation of both waves I and III showed that the EABR amplitude-time functions following both 50% duty cycle and AM stimulation were not statistically different from one another,reflecting similarity in the recovery functions during the early post-stimulus phase. However, both were significantly greater than the recovery function following continuous stimulation ($P < 0.05$).

Additional experiments were conducted to ensure that the differences observed in recovery of EABRs following continuous stimulation, when compared with both 50% duty cycle and AM stimulation, were not related to differences in the total charge delivered during the stimulation period. We extended the stimulus period of both the 50% duty cycle and AM stimulus waveforms in order to deliver the same total charge as the 2 h continuous stimulus paradigm. At 400 pps we observed similar initial post-stimulus reductions in the EABR amplitude for both waves I and III as we recorded following 2 h of stimulation using the same waveforms (Figs. 4 and 6; Table 1). This was followed by a rapid recovery to approximately pre-stimulus levels in both the 50% duty cycle and AM waveforms (Fig. 6).

More extensive reductions in the post-stimulus EABR were observed following 4 h of stimulation at 1000 pps (Fig. 7; Table 1). Moreover, significant differences in the post-stimulus recovery of EABRs following 50% duty cycle and AM stimulation were observed, while in general reductions in the slopes of the recovery functions were observed. Stimulation using a 50% duty cycle resulted in an almost complete loss of the EABR immediately following stimulation (negative y-intercepts for both waves I and III; Table 1). Recovery was more complete and the recovery slope steeper compared with continuous stimulation for 2 h (1.8 vs. 15.3 and 9.1 vs. 31.2 for waves I and III respectively; Table 1), although they did not reach pre-stimulus levels for monitoring periods of up to 8 h. In contrast, 4 h of stimulation using the AM stimulus waveform resulted in a less extensive reduction in the EABR (y-intercepts of 11.7 and 36.2 for waves I and III respectively; Table 1). Furthermore, a complete recovery of the EABR waveform was observed during the first hour of the post-stimulus monitoring period. This difference in the extent of recovery following AM and 50% duty cycle stimulation was statistically significant ($P < 0.05$; Newman-Keuls test).

4. Discussion

The results of the present study corroborate and extend our previous findings demonstrating that intracochlear electrical stimulation, delivered to a fixed electrode pair, can result in long-term reductions in auditory nerve excitability (Shepherd and Clark, 1987; Shepherd et al., 1990; Tykocinski et al., 1995a). The extent of this reduction depends on stimulus rate, stimulus intensity and the temporal properties of the stimulus waveform.

Our previous studies have shown that continuous stimulation at a stimulus intensity of 0.34 μC/phase for rates of 400 and 1000 pps can produce severe and prolonged decrements in the post-stimulus EABR amplitude over monitoring periods of up to 6 h (Tykocin-

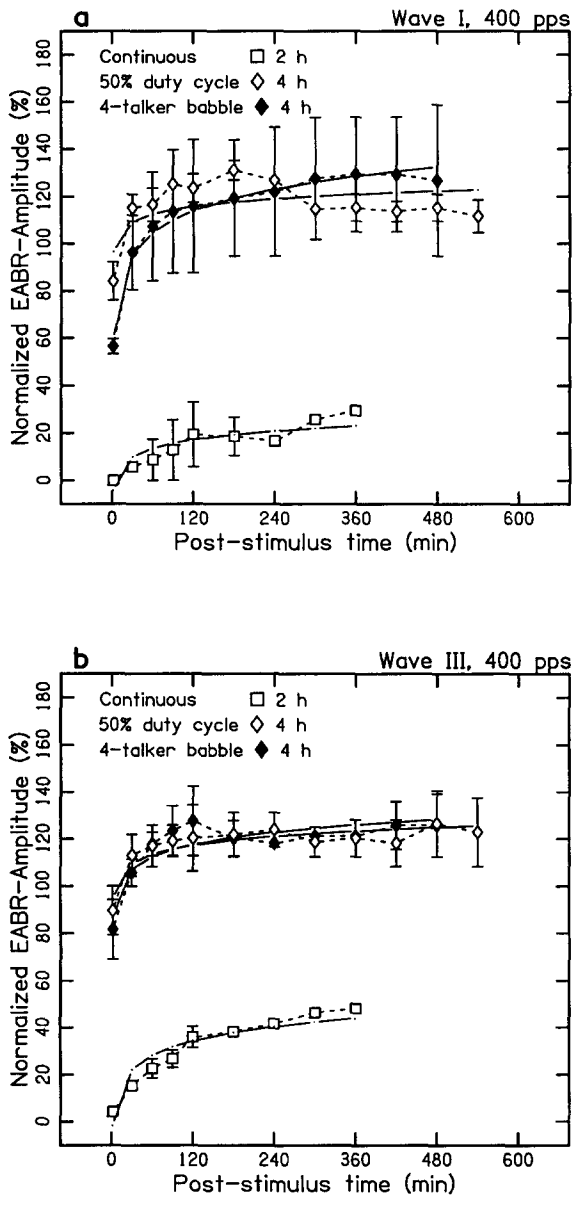


Fig. 6. Normalised EABR amplitudes (mean ± S.E.M.) of waves I (a) and III (b) following stimulation at 0.34 μC/phase and 400 pps using a continuous ($n=2$) stimulus paradigm for 2 h, and a 50% duty cycle ($n=2$) and an AM ($n=2$) stimulus paradigm for 4 h (broken lines). The data were evaluated at a probe intensity 10 dB below the acute stimulus intensity. In addition, the logarithmic curve fitting results are illustrated (full lines). The post-stimulus EABR amplitude recovery was rapid and complete following both 50% duty cycle and AM stimulation compared with recovery following continuous stimulation. This was reflected in the statistical evaluation of both waves I and III, which showed that the EABR amplitude-time functions following both 50% duty cycle and AM stimulation were not statistically different from one another. However, both were significantly greater than the recovery function following continuous stimulation ($P<0.05$). This figure also emphasises that the total charge injected into the cochlea during stimulation, which was equal for all three stimulus paradigms, neither influenced the post-stimulus EABR decrement nor its recovery.

ski et al., 1995a). The introduction of a 50% duty cycle into the 400 pps pulse train induces both a smaller initial post-stimulus decrement in EABR amplitude, together with a complete recovery of the EABR amplitude of both waves I and III. Furthermore, recovery at 400 pps is independent of the total charge injected, that is, no differences are observed when the duration of the 50% duty cycle stimulus is doubled to match the total charge injection associated with the continuous waveform. Following stimulation at 1000 pps using 50% duty cycle stimulation, a more gradual and less complete recovery is observed, illustrating the rate dependent nature of these stimulus-induced reductions. However, at 1000 pps, post-stimulus recovery following AM stimulation was more rapid and complete than that observed using a 50% duty cycle waveform, despite the initial EABR decrement immediately following stimulation being similar for both stimulus waveforms. Significant differences in EABR recovery functions between the 50% duty cycle and AM waveforms became apparent following stimulation for 4 h at 1000 pps (Fig. 7). The EABR amplitude of wave III was only approximately 5% of the pre-stimulus level following 50% duty cycle stimulation and recovered to just over half the pre-stimulus level 3 h after completion of the stimulus. In contrast, the AM waveform induced far less change. The EABR amplitude following AM stimulation was approximately 35% of pre-stimulus level immediately following stimulation, and recovered fully within one hour of the acute stimulation period.

Both the post-stimulus decrement and the subsequent recovery of the EABR following stimulation at high stimulus rates observed in the present study, are in agreement with previous studies (McCreery and Agnew, 1983; Shepherd and Clark, 1987; Shepherd et al., 1990; Tykocinski et al., 1995a). They also agree with the results of both Killian et al. (1994) as well as Haenggeli et al. (1995), who reported a reduction of the amplitude and an increase in latency of the electrically evoked compound action potential (CAP) in rats following high rate (up to 2000 pps) electrical stimulation of the cochlea.

It is important to note that the continuous stimulus paradigm differs significantly from any stimulus paradigms used clinically. The continuous stimulus paradigm delivers current pulses of constant intensity and rate to a fixed electrode pair, while multichannel cochlear implants present stimuli non-simultaneously to an array of electrodes at stimulus intensities that vary with the amplitude of the speech envelope.

The introduction of a duty cycle simulates more closely a clinically relevant stimulus paradigm. Moreover, as prolonged periods of excessive neuronal activity appear to be related to neural damage (Gasser, 1935; Hill et al., 1936; McCreery and Agnew, 1983; Shepherd and Clark, 1987), it is not surprising that

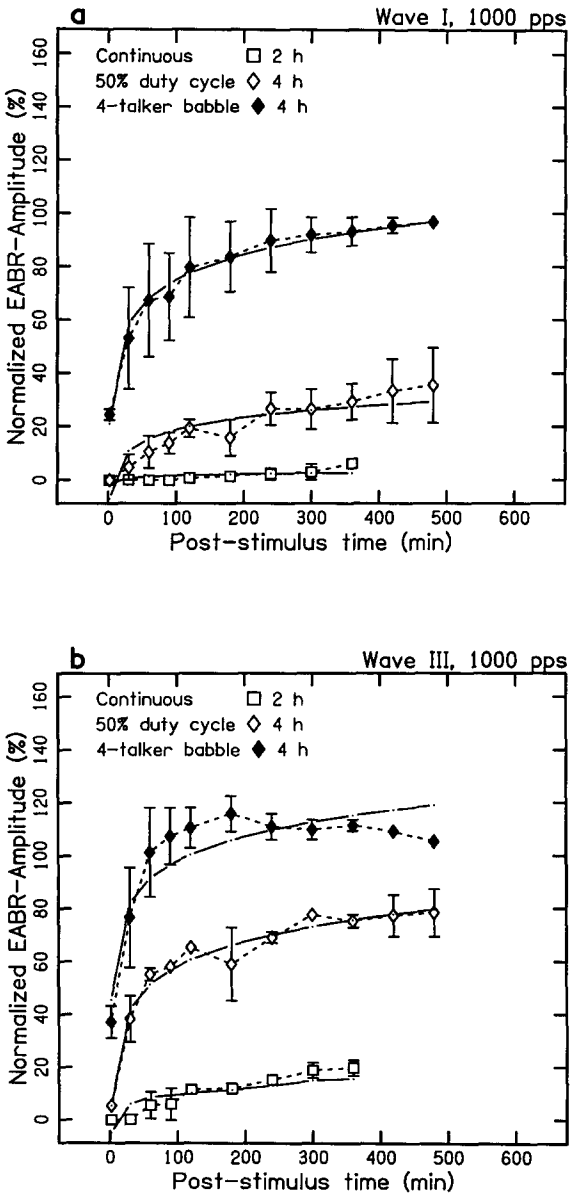


Fig. 7. Normalised EABR amplitudes (mean ± S.E.M.) of waves I (a) and III (b) following stimulation at 0.34 μC/phase and 1000 pps using a continuous ($n=2$) stimulus paradigm for 2 h, and a 50% duty cycle ($n=2$) and an AM ($n=2$) stimulus paradigm for 4 h (broken lines). The data were evaluated at a probe intensity 10 dB below the acute stimulus intensity. In addition, the logarithmic curve fitting results are illustrated (full lines). The logarithmic curves fitted the raw data best when there was a substantial post-stimulus reduction in EABR amplitude followed by a moderately fast recovery to pre-stimulus values (e.g. a: 4-talker babble). The post-stimulus EABR amplitude recovery was rapid and complete following AM stimulation. Following the 50% duty cycle stimulation recovery of wave I was poor, but still more rapid and complete compared with recovery following continuous stimulation. This was reflected in the statistical evaluation of both waves I and III, which showed that the EABR amplitude-time functions following AM stimulation showed significantly greater recovery than EABRs evoked following stimulation using a 50% duty cycle ($P<0.05$). In turn, recovery following stimulation using a duty cycle was significantly greater than that observed following continuous stimulation ($P<0.05$).

the introduction of a duty cycle leads to a reduction in the degree of post-stimulus EABR amplitude change, resulting in a more complete recovery to pre-stimulus levels. However, since duty cycle stimulation still uses fixed-amplitude current pulses, this waveform also differs somewhat from those used clinically.

A stimulus paradigm using AM current pulses simulates most closely the clinical situation. As the stimulus intensity varies temporally, the number of auditory nerve fibres recruited with each current pulse varies considerably compared with fixed amplitude stimuli. The temporally varying excitation pattern of this stimulus waveform effectively reduces the extent of stimulus-induced neuronal fatigue. The EABR amplitude recovery functions following AM stimulation at 400 pps were practically identical to those following 50% duty cycle stimulation at the same stimulus rate. However, following stimulation at 1000 pps, the recovery to AM stimulation was more rapid and complete than the level of recovery observed following the 50% duty cycle stimulation, although both waveforms injected the same total charge over the stimulus period.

It should be noted that in general two types of EABR amplitude recovery functions could be distinguished, depending on the stimulus paradigm used. Both types could be approximated by logarithmic curve fits. The first was characterised by EABR amplitudes, which returned quickly to baseline values, often exceeding them temporarily. This type of recovery function generally did not exhibit large reductions in EABR amplitude immediately following stimulation. A similar logarithmic recovery function has been described for temporary threshold shift (TTS) in both humans (Harris, 1955; Harris and Dallos, 1979; Ward, 1973) and animals (Lonsbury-Martin and Martin, 1981). Moreover, studies in cats showed that single cochlear nerve-fibre activity also displayed rapid and slow phases of recovery from exposure typically causing TTS (Young and Sachs, 1973; Lonsbury-Martin and Meikle, 1978; Yates et al., 1983). However, the time constant in those experiments were much smaller than that observed in the present study. While the initial post-stimulus reduction in excitability of the auditory nerve in the present study indicates the presence of a stimulus-induced disturbance of intracellular homeostasis, the rapid recovery may indicate a dynamic and reasonably fast metabolic process, leading to the restoration of cellular equilibrium.

The second type of recovery function observed in the present study is characterised by a large post-stimulus reduction in EABR amplitude, followed by a slow and incomplete recovery over monitoring periods of up to 8 h. Such long recovery periods may indicate that structural damage at the cellular level might have occurred, from which neurones would take a long period, if ever, to recover. Electrophysiological studies have shown

that current pulses are capable of evoking highly deterministic neural activity within auditory nerve fibres. Given sufficient stimulus intensity, fibres can follow current pulses at rates far above their physiological norm (Moxon, 1971; Hartmann et al., 1984; van den Honert and Stypulkowski, 1984; Javel et al., 1987). It has been suggested, therefore, that electrical stimulation can place considerable metabolic stress on the target neural population, as the neural tissue has a high energy demand, associated mainly with the maintenance of a polarisation voltage across neural membranes. Furthermore, during intense electrical stimulation or otherwise induced prolonged periods of excessive neural activity, changes in intracellular Ca^{2+} concentration have been shown to be associated with neural damage, leading to cell death (Siesjo, 1981; McCreery and Agnew, 1983; Agnew et al., 1993; White and Reynolds, 1996). Previous electrical stimulation studies have suggested that excessive neuronal activity is the principal cause of stimulus-induced changes in neural excitability (McCreery and Agnew, 1983; Shepherd, 1986; Shepherd and Clark, 1987; McCreery et al., 1992; Agnew et al., 1993; Tykocinski et al., 1995a).

However, the present study has shown that the stimulus paradigm which most closely simulates a clinical situation, induces only temporary EABR changes, and is followed by a rapid and complete recovery of auditory nerve excitability. These encouraging findings suggest that even using the relatively low duty cycles associated with clinical speech processing strategies, one might expect little evidence of significant long-term fatigue effects using high stimulus rates, especially as stimulus intensities will be far lower in a clinical setting. Support for this observation comes from a recent chronic stimulation study in which we observed no evidence of reduced EABR amplitudes or spiral ganglion cell loss in animals stimulated for periods of up to 2000 h using stimulus rates of 2000 pps per channel (Xu et al., 1997). These are encouraging findings for the clinical application of improved speech processing strategies based on high stimulus rates.

Acknowledgments

The authors gratefully acknowledge Dr. P. Blamey, J.M. Harrison, K. Hastie, Dr. H. McDermott, R.E. Millard, F. Nielson, Dr. P.M. Seligman, S. Warmsley and Dr. J. Xu. This work was funded in part from the Human Communications Research Centre, the Co-operative Research Centre for Cochlear Implant, Speech and Hearing Research, University of Melbourne, and The Garnett Passe and Rodney Williams Memorial Foundation. Dr. M. Tykocinski was funded by the Deutsche Forschungsgemeinschaft (DFG) Grant Ty 11/2. Finally, three anonymous reviewers provided useful comments on an earlier draft of this manuscript.

References

Agnew, W.F., Yuen, T.G.H., McCreery, D.B., 1983. Morphologic changes following prolonged electrical stimulation of the cats cortex at defined charge densities. Exp. Neurol. 79, 347–411.

Agnew, W.F., McCreery, D.B., Yuen, T.G.H., Bullara, L.A., 1993. MK-801 protects against neuronal injury induced by electrical stimulation. Neuroscience 52, 45–53.

Bowman, B.R., McNeal, D.R., 1986. Response of single alpha motoneurons to high frequency pulse trains. Firing behaviour and conduction block phenomenon. Appl. Neurophysiol. 49, 121–138.

Brown, W.J., Babb, T.L., Soper, H.V., Lieb, J.P., Ottino, C.A., Crandall, P.H., 1977. Tissue reactions to long-term electrical stimulation of the cerebellum in monkeys. J. Neurosurg. 47, 366–379.

Busby, P.A., Tong, Y.C., Clark, G.M., 1993. The perception of temporal modulations by cochlear implant patients. J. Acoust. Soc. Am. 94, 124–131.

Dillier, N., Bogli, H., Spillman, T., 1992. Digital speech processing for cochlear implants. Otorhinolaryngology 54, 299–307.

Forbes, A., Rice, L.H., 1929. Quantitative studies of the nerve impulse IV. Fatigue in the peripheral nerve. Am. J. Physiol. 90, 119–145.

Gasser, H.S., 1935. Changes in nerve potentials produced by rapidly repeated stimuli and their relation to the responsiveness of nerve stimulation. Am. J. Physiol. 96, 35–50.

Haenggeli, A., Zhang, J., Vischer, M., Pellizone, M., Rouller, E.M., 1995. Electrically evoked compound action potential (CAP) of the auditory nerve in the response to pulse trains in an animal model of cochlear implants. Proc. IIIrd International Congress on Cochlear Implant, Paris, p. 202.

Harris, J.D., 1955. On latent damage to the ear. J. Acoust. Soc. Am. 27, 117–179.

Harris, D.M., Dallos, P., 1979. Forward masking of auditory nerve fibre responses. J. Neurophysiol. 4, 1083–1107.

Hartmann, R., Topp, G., Klinke, R., 1984. Discharge pattern of cat primary auditory fibres with electrical stimulation of the cochlea. Hear. Res. 13, 47–62.

Hill, A.V., Katz, B., Solandt, D.Y., 1936. Nerve excitation by alternating current. Proc. R. Soc. Lond. 19, 74–133.

Hochmair-Desoyer, I.J., Hochmair, E.S., Stiglbrunner, H.K., 1985. Psychoacoustic temporal processing and speech understanding in cochlear implant patients. In: Schindler, R.A., Merzenich, M.M. (Eds.), Cochlear Implants. Raven, New York, pp. 291–304.

Javel, E., Tong, Y.C., Shepherd, R.K., Clark, G.M., 1987. Responses of the cat auditory nerve fibres to biphasic electrical current pulses. Ann. Otol. Rhinol. Laryngol. 96, 26–30.

Killian, M.J.P., Klis, S.F.L., Smoorenburg, G.F., 1994. Adaptation in the compound action potential response of the guinea pig VIIIth nerve to electrical stimulation. Hear. Res. 81, 66–82.

Lonsbury-Martin, B.L., Martin, G.K., 1981. Temporary hearing loss from exposure to moderately intense tones in rhesus monkeys. Am. J. Otolaryngol. 2, 321–335.

Lonsbury-Martin, B.L., Meikle, M.B., 1978. Neural correlates of auditory fatigue: Frequency-dependent changes in activity of single cochlear nerve fibres. J. Neurophysiol. 41, 987–1006.

McCreery, D.B., Agnew, W.F., 1983. Changes in extracellular potassium and calcium concentrations and neural activity during prolonged electrical stimulation of the cat cerebral cortex at defined charge densities. Exp. Neurol. 79, 371–396.

McCreery, D.B., Agnew, W.F., Yuen, T.G.H., Bullara, L.A., 1988. Comparison of neural damage induced by electrical stimulation

with faradic and capacitor electrodes. Ann. Biomed. Eng. 16, 463–481.

McCreery, D.B., Agnew, W.F., Yuen, T.G.H., Bullara, L.A., 1990. Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. IEEE Trans. Biomed. Eng. 37 (10), 996–1001.

McCreery, D.B., Yuen, T.G.H., Agnew, W.F., Bullara, L.A., 1992. Stimulation with chronically implanted microelectrodes in the cochlear nucleus of the cat: Histologic and physiologic effects. Hear. Res. 62, 42–56.

McDermott, H.J., McKay, C.M., Vandali, A.E., 1992. A new portable sound processor for the University of Melbourne/Nucleus Limited multielectrode cochlear implant. J. Acoust. Soc. Am. 91, 3367–3391.

Moxon, E.C., 1971. Neural and Mechanical Responses to Electrical Stimulation of the Cat's Inner Ear. PhD Thesis, MIT, Cambridge, MA.

Patrick, J.F., Seligman, P.M., Money, D.K., Kuzma, J.A., 1990. Engineering. In: Clark, G.M., Tong, Y.C., Patrick, J.F. (Eds.), Cochlear Prostheses. Churchill Livingstone, Edinburgh, pp. 99–124.

Pudenz, R.H., Agnew, W.F., Yuen, T.G.H., Bullara, L.A., 1977. Electrical stimulation of the brain. Light and electron microscopy study. In: Hambrecht, T.F., Reswick, J.B. (Eds.), Functional Electrical Stimulation. Applications in Neural Prostheses. Marcel Dekker, New York.

Shepherd, R.K., 1986. The Cochlear Prosthesis: Safety Investigations. PhD Thesis, University of Melbourne, Melbourne.

Shepherd, R.K., Clark, G.M., 1987. Effects of high electrical stimulus intensities on the auditory nerve using brain stem response audiometry. Ann. Otol. Rhinol. Laryngol. 96 (Suppl. 128), 50–52.

Shepherd, R.K., Franz, B.K.H.G., Clark, G.M., 1990. The biocompatibility and safety of cochlear prostheses. In: Clark, G.M., Tong, Y.C., Patrick, J.F. (Eds.), Cochlear Prostheses. Churchill Livingstone, Edinburgh, pp. 69–99.

Siesjo, B.K., 1981. Cell damage in the brain: a speculative synthesis. J. Cereb. Blood Metab. 1, 155–185.

Tong, Y.C., Clark, G.M., McDermott, H.J., Harrison, J.M., Blamey, P.J., Patrick, J.F., 1990. Future directions. In: Clark, G.M., Tong, Y.C., Patrick, J.F. (Eds.), Cochlear Prostheses. Churchill-Livingstone, Edinburgh, pp. 253–257.

Tykocinski, M., Shepherd, R.K., Clark, G.M., 1995a. Reduction in excitability of the auditory nerve following electrical stimulation at high stimulus rates. Hear. Res. 88, 124–142.

Tykocinski, M., Shepherd, R.K., Clark, G.M., 1995b Decrements in auditory nerve function following acute high rate stimulation in guinea pigs. Proc. III. International Congress on Cochlear Implant, Paris, p. 156.

van den Honert, C., Stypulkowski, P.H., 1984. Physiological properties of the electrically stimulated auditory nerve. II. Single fibres recordings. Hear. Res. 21, 109–126.

Ward, W.D., 1973. Susceptibility to TTS and PTS. In: Proceedings of the International Congress on Noise as a Public Health Problem. US Environmental Protection Agency, Washington, DC, pp. 281–293.

White, R.L., Reynolds, I.J., 1996. Mitochondrial depolarization in glutamate-stimulated-neurons – an early signal specific to excitotoxin exposure. J. Neurosci. 16, 5688–5697.

Wilson, B.S., Finley, C.C., Lawson, D.T., Wolford, R.D., Eddington, D.K., Rabinowitz, W.M., 1991. New level of speech recognition with cochlear implants. Nature 352, 236–238.

Xu, J., Shepherd, R.K., Millard, R.E., Clark, G.M., 1997. Chronic electrical stimulation of the auditory nerve at high rates: A physiological and histopathological study. Hear. Res. 105, 1–29.

Yates, G.K., Cody, A.R., Johnstone, B.M., 1983. Recovery of eighth nerve action potential thresholds after exposure to short, intense pure tones: Similarities with temporary threshold shift. Hear. Res. 12, 305–322.

Young, E., Sachs, M.B., 1973. Recovery from sound exposure in auditory nerve fibres. J. Acoust. Soc. Am. 54, 1535–1543.

Yuen, T.G.H., Agnew, W.F., Bullara, L.A., Jaques, S., McCreery, D.B., 1981. Histological evaluation of neural damage from electrical stimulation: considerations for the selection of parameters for clinical application. Neurosurgery 9, 292–299.

Wilson B.S., Lawson, D.T., Zerbi, M and Finley, C.C., 1993. Speech processors for auditory prostheses. Third Quarterly Progress Report, NIH Contract N01-DC-2-2401; Research Triangle Institute, Research Triangle Park, NC 27709.