

# ACUTE EFFECTS OF HIGH-RATE STIMULATION ON AUDITORY NERVE FUNCTION IN GUINEA PIGS

M. TYKOCINSKI, MD; R. K. SHEPHERD, PHD; G. M. CLARK, PHD, FRACS

From the Department of Otolaryngology and the Human Communication Research Centre (all authors), University of Melbourne, and the Cooperative Research Centre for Cochlear Implant, Speech and Hearing Research, Melbourne, Australia (all authors), and the Department of Otolaryngology, Universität Klinikum Rudolf Virchow Hospital, Berlin, Germany (Tykocinski). This work has been supported by the Human Communication Research Centre, and by a grant from the Deutsche Forschungsgemeinschaft (M.T.).

## INTRODUCTION

Cochlear implants have been shown to successfully provide profoundly deaf patients with auditory cues for speech discrimination. Furthermore, a number of safety studies using the Melbourne/Cochlear electrode array indicated that chronic

electrical stimulation using charge-balanced biphasic current pulses and stimulus rates between 100 and 500 pulses per second (pps) do not result in additional spiral ganglion loss or general cochlear pathology.<sup>1-3</sup> However, safe maximum levels for stimulus parameters (stimulus rate, charge per phase,

charge density) have not yet been adequately defined.

New speech-processing strategies developed during the last few years have tended to operate at higher stimulus pulse rates, and psychophysical studies have suggested that speech-processing strategies based on stimulus rates of up to 1,000 pps may lead to an improvement in speech perception, due to an improved representation of the rapid variations in the amplitude of speech.<sup>4-7</sup> However, "neural fatigue" has been known to occur following brief periods of electrical stimulation at rates high enough to ensure that stimuli occur within the neurons' relative refractory period, and has been shown to depend on stimulus intensity and duration, and the rate of the evoked neural activity.<sup>8-10</sup> Prolonged electrical stimulation at these high stimulus rates could, therefore, have an adverse effect on the neurons' metabolism and result in cellular energy depletion. This overstimulation may finally lead to irreversible neuronal damage.

If high stimulus rates are capable of reducing nerve excitability, as has been suggested previously, the reduction is most probably associated with the degree of stimulus-induced neuronal activity. Introducing a duty cycle (ratio of stimulus-on to stimulus-off time) into the pulse train should reduce these stimulus-induced changes, as nerve fibers have time to restore their cellular equilibrium before the next train of stimuli.

This study is part of a series designed to provide data for the envisaged introduction of a speech-processing strategy based on high stimulus rates. We examined the influence of stimulus rate, charge per phase, and duty cycle on the excitability of the auditory nerve of guinea pigs, following acute electrical stimulation using a feline version of the Cochlear Pty Limited scala tympani electrode array. In this initial study, we selected stimulus intensities at both the maximum levels we previously used in chronic experimental studies<sup>1,3</sup> and at intensities significantly above this level. These elevated intensities were used to establish whether or not stimulus-induced changes could be observed in the acute animal model, and to determine the significance of each stimulus parameter on any observed changes in auditory nerve excitability. The electrically evoked auditory brain stem response (EABR) was used to monitor changes in the excitability of the auditory nerve following the acute stimulation.

#### METHOD

Thirty-five adult pigmented guinea pigs with otoscopically normal tympanic membranes were used during the experiments. The animals were anesthetized with ketamine hydrochloride (35 mg/kg) and xylazine hydrochloride (3.5 mg/kg), while supplemental doses were given to maintain a surgical level of anesthesia throughout the experiment. The temperature of the animal was maintained at  $38^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  with a direct current (DC) heating pad. Following tracheotomy, both bullae were opened and the round window membrane was incised. A free-fit electrode array with full-band or half-band platinum electrodes (width, 0.3 mm) on a Silastic silicone rubber (Dow Corning Corp) carrier, was carefully inserted for a maximum distance of 4.3 mm along the scala tympani bilaterally. The round window was sealed with crushed muscle.

The acute electrical stimulation regimen consisted of short-duration biphasic current pulses presented at rates of up to

1,000 pps at stimulus intensities that varied from 0.16 to 1.0 microcoulomb ( $\mu\text{C}$ ) per phase. The output of the stimulator was connected to a pair of bipolar scala tympani electrodes. The electrodes were shorted between current pulses to minimize any residual DC.

All recordings were made in a sound-attenuated, electrically shielded room. The EABRs were evoked by 50-microsecond per phase biphasic current pulses (33 pps) at probe current levels ranging from threshold to 2.1 mA. The EABR responses were recorded differentially (DAM-5A, WPI) with needle electrodes at the vertex (positive), neck (negative), and abdomen (ground). They were amplified by a factor of  $10^5$  and the artifact was suppressed and finally band-pass filtered (0.15 to 3.0 kHz). The amplifier output was fed into a 10 bit analog-to-digital converter and sampled at 20 kHz for 12.5 milliseconds following stimulus onset. Between 250 and 500 responses were averaged for each recording. Two EABR responses were recorded at each probe intensity (threshold, 0.02, 0.04, 0.05, 0.08, and 0.10  $\mu\text{C}$  per phase) prior to and periodically following unilateral stimulation. The contralateral side served as an unstimulated control. Mean amplitudes at each probe current were calculated as the mean of amplitudes of wave P1-N1 (first positive peak and following trough) and wave P3-N3 (third positive peak and following trough). Thresholds, input-output functions (amplitude versus stimulus intensity) of waves I and III of the EABR, and latencies were evaluated.

With increasing stimulus intensity, auditory nerve fibers closer to the stimulating electrodes will be driven in an increasingly deterministic manner, and are likely to exhibit the most characteristic stimulus-induced changes in auditory nerve excitability, compared with neural populations further away. With use of EABRs at probe intensities 10 and 16 to 19 dB below the stimulus intensity, neural populations close to the stimulating electrodes were monitored throughout the study.

To ensure that wave I of the EABR was not associated with stimulus artifact, we included only those experiments in which a latency shift of the first positive peak of the EABR was observed during changes in probe current. Two-way ANOVA and the post hoc Newman-Keuls test were performed on the EABR data in order to test for statistical significance.

#### RESULTS

*Variations in Stimulus Rate and Intensity.* The animals were stimulated unilaterally for 2 hours at stimulus rates of 100, 200, 400, or 1,000 pps and stimulus intensities of 0.16, 0.34, 0.50, or 1.0  $\mu\text{C}$  per phase. While 0.16  $\mu\text{C}$  per phase is within the upper clinical range for bipolar scala tympani stimulation, the higher intensities were well above that range. Charge density was held constant in all experiments ( $75 \mu\text{C}/\text{cm}^2$  geom/phase) by varying the electrode surface area. Two experiments were performed for each stimulus protocol. To evaluate the influence of stimulus rate and intensity independently, only one parameter was changed at a time. Poststimulus EABR input-output functions, thresholds, and the latency of both waves I and III were monitored in every experiment for periods of up to 12 hours following stimulation.

Continuous stimulation at 100 pps did not produce a sig-

nificant reduction in the EABR amplitude of either wave I or III. Stimulation at 200 pps induced a slight to moderate EABR decrement immediately following stimulation, followed by some recovery. The decrement of wave I was found to be more pronounced than that of wave III. However, stimulation at 400 pps produced profound changes in the poststimulus EABR. Immediately following stimulation, wave I was reduced to less than 20% of the prestimulus value at the lowest stimulus intensity (0.16  $\mu\text{C}$  per phase), while at higher intensities, it could not be evoked. Recovery was incomplete during the initial 2-hour recovery period. Stimulation at 1,000 pps for 2 hours resulted in the abolition of wave I during the poststimulus monitoring period of 2 hours for all stimulus intensities used. While wave III could not be evoked immediately following stimulation, significant recovery was observed following stimulation at the lowest stimulus intensity.

The degree of these stimulus-induced changes depended on both stimulus rate and stimulus intensity, although rate appeared to be the more important stimulus parameter. Increasing stimulus rate, while keeping intensity constant, always resulted in a decrement of the EABR amplitude of both waves I and III. However, increasing stimulus intensity while maintaining stimulus rate did not always result in a statistically significant decrement in the EABR.

**Duty Cycle.** Continuous high-rate stimulation is not a particularly adequate model for multichannel speech-processing strategies. To provide a more appropriate model, a 50% duty cycle (10-millisecond on-off periods) was introduced into the pulse train, while stimulating at rates of 400 and 1,000 pps. Stimulus intensity (0.34  $\mu\text{C}$  per phase) and charge density (approximately 75.5  $\mu\text{C}/\text{cm}^2$  geom/phase) were kept constant. The stimulation period was extended to 4 hours in order to inject the same total charge compared with continuous stimulation for 2 hours.

Stimulation at 400 pps with a 50% duty cycle induced a small to moderate decrease in the poststimulus EABR amplitude immediately after stimulation, followed by a rapid recovery of both waves I and III to approximately prestimulus levels. Recovery following continuous stimulation at the same stimulus rate was, in comparison, much slower and was incomplete.

No EABR could be evoked immediately following stimulation at 1,000 pps with a 50% duty cycle for 4 hours. While the recovery was more complete compared with continuous stimulation at 1,000 pps, it did not reach prestimulus levels. These results again highlight the influence of stimulus rate on the excitability of the auditory nerve.

## DISCUSSION

The findings demonstrate that continuous intracochlear electrical stimulation, presented at high rates using stimulus intensities at and above maximum clinical levels for bipolar scala tympani electrodes, may result in long-term reduction of the excitability of the auditory nerve. This seems to be particularly true for neural populations that are located close to the stimulating electrode.

Stimulus rate emerged as the main contributor to stimulus-induced changes in the EABR. Continuous electrical stimulation at higher stimulus rates (400 and 1,000 pps) induced

long-term decrements in the poststimulus EABR at every stimulus intensity investigated. This decrement showed a monotonic increase with increasing stimulus rate. The introduction of a 50% duty cycle decreased, but did not abolish, the EABR decrement immediately following stimulation. A 50% duty cycle stimulation was followed by a more rapid and complete recovery compared with continuous stimulation. However, the time course of the recovery again depended on stimulus rate.

Stimulus intensity, which ranged from an upper clinical level for bipolar scala tympani electrodes to intensities well above those used clinically, also exhibited significant influence on stimulus-induced EABR changes, albeit less than the effect of stimulus rate.

The present data support earlier reports suggesting that neuronal hyperactivity is the principal cause of stimulus-induced changes of neural excitability at high stimulus rates and intensities.<sup>11-13</sup> There are, indeed, indications that overstimulation of neurons can lead to an exhaustion of neural energy resources, needed to maintain the intracellular ion homeostasis following each action potential.<sup>14,15</sup> It is thought that such an energy depletion leads to a derangement of membrane function and, ultimately, cell damage.<sup>16,17</sup>

It is important to note, however, that the stimulus paradigm used in the present study differs somewhat from that used clinically. First, clinical application of high rate speech-processing strategies have typically used monopolar rather than bipolar scala tympani electrode arrays. Monopolar stimulation results in a significant reduction in stimulus levels compared with bipolar stimulation. In addition, the broader current spread for monopolar stimulation may result in a more even distribution of neuronal activity within the cochlea, minimizing the significant increases in threshold that we have observed close to bipolar electrodes. Second, while the lowest stimulus intensity used in the present study matched the upper range for both clinical applications and experimental studies in awake cats, this level may not be tolerated by the awake guinea pig. Reduced thresholds, for example, would be expected in the guinea pig as the electrode array is expected to be located closer to the auditory nerve fibers due to the smaller dimensions of the cochlea. Additional studies are therefore required to extend our understanding of the influence of high stimulus rates on auditory nerve fibers using stimulus paradigms typically encountered clinically, and to investigate the effects of any short-term changes in neural excitability on speech-processing strategies.

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**Author/s:**

Tykocinski, M.; Shepherd, R. K.; Clark, Graeme M.

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