EFFECT OF HIGH ELECTRICAL STIMULUS INTENSITIES ON THE AUDITORY NERVE USING BRAIN STEM RESPONSE AUDIOMETRY

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The response of the auditory nerve to acute intracochlear electrical stimulation using charge-balanced biphasic current pulses was monitored using electrically evoked auditory brain stem responses (EABRs). Stimulation at moderate charge densities (64 \( \mu \text{C cm}^{-2} \text{ geom/phase} \); 0.8 mA, 200 \( \mu \text{s} \) phase) for periods of up to 12 hours produced only minimal short-term changes in the EABR. Stimulation at a high charge density (144 \( \mu \text{C cm}^{-2} \text{ geom/phase} \); 1.8 mA, 200 \( \mu \text{s} \) phase) resulted in permanent reductions in the EABR for high stimulus rates (>200 pulses per second [pps]) or long stimulus durations (12 hours). At lower stimulus rates and durations, recovery to prestimulus levels was slow but complete. The mechanisms underlying these temporary and permanent reductions in the EABR are probably caused by neural adaptation and more long-term metabolic effects. These findings have implications for the design of speech-processing strategies using high stimulus rates.

Although nondamaging stimulus parameters have recently been described for chronic intracochlear electrical stimulation using charge-balanced pulsatile stimuli, maximum safe stimulus levels have yet to be defined. Moreover, the effects of various stimulus parameters on stimulus-induced neural damage is not well understood.

Charge density per phase (\( \mu \text{C cm}^{-2} \text{ geom/phase} \)) appears to correlate closely with the degree of neural damage. Provided that the charge density is maintained below approximately 40 to 50 \( \mu \text{C cm}^{-2} \text{ geom/phase} \), there is little evidence of neural damage. Above this value, there is an increase in neural degeneration with charge density. These findings are consistent for relatively large surface area electrodes such as those used in cochlear implants (ie, 0.5 to 1.0 mm²). However, significantly higher nondamaging charge densities have been reported when stimulating with microelectrodes (areas 10⁻⁴ mm²). This suggests that stimulus parameters other than charge density must also be considered when evaluating biologically safe stimulus regimes.

This preliminary report is part of an ongoing study designed to evaluate the response of the auditory nerve to various stimulus parameters (eg, charge density, pulse rate, charge/phase) by monitoring the electrically evoked auditory brain stem response (EABR), with the objective of defining maximum biologically safe stimulus levels for intracochlear electrical stimulation.

METHODS

Normal-hearing and neomycin-deafened cats were anesthetized with ketamine hydrochloride and xylazine. Anesthesia was maintained throughout the course of the experiment (typically 48 hours) with sodium pentobarbital, and the animal's temperature was maintained at 37°C to 38°C. Atropine sulfate (250 \( \mu \text{g} \)) and antibiotics (0.1% ampicillin sodium and 0.1% cloxacillin sodium) were administered periodically. After a cannula was inserted into the trachea, both bullae were exposed and free-fit, bipolar platinum (Pt) band electrode arrays were inserted approximately 6 mm along the scala tympani. Insertion of the intracochlear electrodes was performed using sterile surgical techniques. Complete surgical and electrode details have been published previously.

Electrical stimulation was provided by an optically isolated, charge-balanced biphasic current source with variable current amplitude, pulse width, and repetition rate. The EABRs were recorded differentially using a stainless steel screw at the vertex and subcutaneous needle electrodes at the neck and thorax (vertex, +ve; neck, -ve; thorax, ground). The differential amplifier (DAM-5A; WPI) was modified to improve common mode rejection at high frequencies and was set to wide band (0.1 Hz to 30 kHz) to ensure rapid recovery following the stimulus artifact. The electrical artifact was subsequently suppressed, and the response band pass filtered (150 Hz to 3 kHz). Overall signal gain was 100 dB. The amplified output was fed to a ten-bit A/D converter and sampled at a rate of 10 kHz for 12.5 ms after the stimulus onset. Stimuli were presented at 33 pps for EABR recordings. Only 100 responses were required for averaging because of the good signal-to-noise ratio obtained with this recording technique and the highly synchronous nature of the EABR.

One cochlea of each animal was stimulated continuously for periods of up to 12 hours at a charge density of 64 or 144 \( \mu \text{C cm}^{-2} \text{ geom/phase} \) and stimulus repetition rates varying from 10 to 400 pps. The EABRs were recorded before, during, and periodically following completion of the stimulus regime, and were also recorded from the contralateral control cochlea. Threshold, latency, and EABR amplitude versus stimulus current (input-output function) were determined for wave IV of the EABR.

RESULTS

Control Cochleas. Implanted, nonstimulated control cochleas had essentially stable input-output and latency function for periods of at least 48 hours following electrode implantation.

Stimulation at 64 \( \mu \text{C cm}^{-2} \text{ geom/phase} \). Continuous stimulation at this level (0.8 mA; 200 \( \mu \text{s} \) phase) for periods of up to 12 hours at 100 pps produced minimal changes in the EABR. Input-output functions remained essentially unchanged during the stimulation period and remained stable at these levels for monitoring periods of up to 12 hours following completion of the stimulus. The stability of input-output functions, following stimulation at 100 pps, are illustrated in part A of the Figure. At higher stimulus rates (300 and 400 pps) there were progressively greater reductions in the initial poststimulus input-output functions; however, recovery was rapid (within 90 seconds) and was followed by a "sensitization" period during which poststimulus EABRs were slightly larger than prestimulus.
Electrically evoked auditory brain stem response input-output functions recorded following continuous stimulation at 100 pps for 12 hours. A) Following continuous stimulation at 64 μC cm⁻² geom/phase. Prestimulus recordings were made at 10 hours (▲) and immediately before (▼) start of stimulation. Seven poststimulus recordings were made periodically over 18-minute period immediately following completion of 12 hours of continuous stimulation. B) Following continuous stimulation at 144 μC cm⁻² geom/phase. Seven poststimulus recordings, made periodically over 18-minute period immediately following completion of stimulus, are significantly smaller than prestimulus recording (▲). This stimulus-induced reduction in input-output function was permanent.

Responses at the same stimulus current. This sensitization period lasted for up to 30 minutes. The input-output functions then returned to prestimulus levels and remained stable at these levels for monitoring periods of up to 12 hours. The EABR latencies remained essentially stable for all pulse rates tested at this charge density.

**Stimulation at 144 μC cm⁻² geom/phase.** Continuous stimulation at this charge density (1.8 mA; 200 μs/phase) generally produced marked changes in the EABR. These changes were dependent on stimulation rate and, to a lesser extent, stimulus duration. Stimulation at 10 pps produced a temporary reduction in the input-output function. Recovery to prestimulus levels was, however, complete. Latencies remained similar to their prestimulus levels. At higher stimulus rates (ie, 100, 200, and 400 pps), progressively greater reductions in EABR input-output functions were observed. These changes were also reflected in significantly increased latency and threshold data. Partial recovery generally followed completion of the stimulus regime. However, the extent of recovery depended on the rate and duration of the stimulus. At high stimulus rates (eg, 400 pps) or long stimulation periods (eg, 12 hours) recovery to prestimulus levels was always incomplete, even for monitoring periods of up to 12 hours following completion of the stimulus. At lower stimulus rates or durations, recovery to prestimulus levels was significantly longer than recovery periods experienced at 64 μC cm⁻² geom/phase. Part B of the Figure shows an example of the significant changes observed in the EABR input-output function following stimulation at this charge density.

**Normal Versus Neomycin-Deafened Cochleas.** Normal and neomycin-deafened animals showed no difference in their response to the acute stimulation regimes used in the present study.

Evoked auditory brain stem response input-output functions derived from normal-hearing animals had lower stimulus thresholds and wider dynamic ranges than input-output functions derived from neomycin-deafened animals. An electrophonic component was present at low stimulus currents in the EABR of normal-hearing animals. Low intensity white noise could readily mask this electrophonic activity. This finding is consistent with previous studies that have investigated EABRs derived from bipolar, intracochlear electrical stimulation.

**DISCUSSION**

The results obtained from the present study, although preliminary, provide good evidence to suggest that charge density alone cannot adequately define biologically safe stimulus levels for intracochlear electrical stimulation. Stimulus repetition rate and, to a lesser extent, stimulus duration appear to be important second order parameters. The effects of other stimulus parameters (eg, charge/phase, pulse width versus current amplitude) on the biocompatibility of the stimulus regime have yet to be determined.

Acute stimulation at a charge density of 144 μC cm⁻² geom/phase produced permanent reductions in the EABR for high stimulus rates (eg, 400 pps, 4 hours) or long durations (eg, 12 hours, 100 pps). We have defined a permanent reduction as an incomplete recovery in the EABR following 12 hours poststimulation. At lower pulse rates and stimulus durations recovery was slow but generally complete. The rate of recovery was inversely related to the stimulus rate. We consider stimulation at this charge density (with Pt electrodes) to be outside the safe biological limits for intracochlear electrical stimulation. Stimulation at 64 μC cm⁻² geom/phase produced only minimal short-term changes in the EABR. Recovery to prestimulus levels was rapid even for high stimulus rates (400 pps) and durations (12 hours). These acute results suggest that this stimulus level (a high charge density for this type of electrode according to both experimental and clinical experience) is within the safe biological limits for intracochlear electrical stimulation using charge-balanced, biphasic, pulsatile stimuli.

The mechanism underlying these temporary and permanent changes in the EABR can be reasonably explained in terms of neural adaptation and more long-term meta-
bolic changes. Stimulation at 64 μC cm⁻² geom/phase produced very small reductions in the EABR. At progressively higher pulse rates, there were slightly greater reductions in the EABR. Reductions such as these recovered rapidly to prestimulus levels, and were probably caused by a combination of adaptation and temporary metabolic changes. The more significant changes observed following stimulation at 144 μC cm⁻² geom/phase were probably caused by long-term metabolic changes. This is supported by the fact that the extent of reduction in the EABR, and its subsequent poststimulus recovery, were dependent on stimulus rate. Recent experimental evidence has shown that electrical stimulation can place considerable metabolic stress on the target neural population, and that this metabolic stress is dependent on stimulus rate.

The present study has shown that the use of highly synchronous stimuli, such as an electric pulse, at unnaturally high stimulus rates results in a considerable reduction in the EABR. This finding has important practical implications for the implementation of speech-processing strategies in cochlear implants. Significantly, a relationship between electrical stimulus rate and reduction in perceptual loudness has been demonstrated psychophysically. Implant patients, stimulated with sinusoidal electrical waveforms, showed a decrease in loudness for prolonged stimulation at frequencies above 200 Hz, with a more pronounced decrease in loudness for stimulation above 300 Hz. No decrease in loudness was observed for stimulation in the 100- to 200-Hz range.

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