ELECTROPHYSIOLOGIC EFFECTS FOLLOWING ACUTE INTRACOCHLEAR DIRECT CURRENT STIMULATION OF THE GUINEA PIG COCHLEA

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Auditory brain stem responses to both acoustic (auditory brain stem response [ABR]) and electrical (electrically evoked auditory brain stem response [EABR]) stimuli, as well as the frequency-specific compound action potential (CAP), were recorded before and periodically following continuous intracochlear DC stimulation (2, 7, and 12 μA) for 2 hours in normal-hearing guinea pigs, by means of a banded intracochlear electrode array. Click-evoked ABR, frequency-specific CAP, and the EABR input-output function remained generally unchanged following stimulation at 2 μA DC. However, following stimulation at 7 and 12 μA, a significant decrement of the amplitude of the click-evoked ABR, frequency-specific CAP, and electrophonic component of the EABR was observed, while there was an increase in the amplitude of the EABR, associated with direct electrical stimulation of the auditory nerve.

INTRODUCTION

Multichannel cochlear implants provide auditory cues by direct electrical stimulation of the auditory nerve. Care must be taken to ensure that these devices stimulate nerve fibers effectively without causing damage to any cochlear tissues.

It has been shown that short duration (100 to 200 microseconds), charge-balanced, biphasic current pulses delivered from platinum (Pt) electrodes minimize the risk of tissue damage,1 as charge is injected in an electrochemically safe manner. The residual direct current (DC) is usually very small and can be further minimized (typically <0.1 μA) by shorting the electrodes between current pulses.2 However, using a continuous stimulus regime with stimulus rates between 100 and 1,000 pulses per second (pps) in an animal model (Tykocinski et al, this suppl, next article), we observed an increase in residual DC with increasing stimulus rate and intensity, despite using charge-balanced, biphasic current pulses and shorting of the electrodes between pulses. During stimulation at the highest stimulus rate (1,000 pps) a moderate DC level of 2.8 μA was recorded at intensities within the range of those used clinically, while the highest DC level (7 μA) was observed at intensities significantly above those used clinically.

Previous studies have shown that acute DC stimulation of the cochlea can induce or suppress tinnitus,3 change the amplitude of the compound action potential (CAP),4,5 and alter auditory nerve activity,5,8 depending on the polarity of the current and its intensity. It has also been shown to induce histologic damage following both intracochlear and extracochlear stimulation.6,9 Moreover, a change in electrically evoked auditory brain stem response (EABR) morphology, widespread spiral ganglion cell loss, and new bone growth extending through all turns of the cochlea has been reported following chronic stimulation, using a non–charge-balanced stimulus without electrode shorting between current pulses, resulting in a residual DC of approximately 2 μA.10

In the present study we describe electrophysiologic changes occurring in the guinea pig cochlea following acute intracochlear stimulation using continuous DC at intensities equal to or higher than those recorded during a previous high-rate study (Tykocinski et al, this suppl, next article).

MATERIALS AND METHODS

Five adult, pigmented guinea pigs weighing between 550 and 900 g with otoscopically normal tympanic membranes
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Fig 1. Electrically evoked auditory brain stem response (EABR) input-output (IO) functions (mean ± SEM) recorded prior to and following continuous stimulation at 2, 7, and 12 µA direct current (DC) for 2 hours. Pre-DC stimulus IO function (open squares) exhibits slow-rising limb at low probe intensities. These responses could be masked by white noise and were considered to be electrophonic in origin. At higher stimulus intensities, direct EABR response was observed, whose amplitude increased much faster with rising probe intensity compared to electrophonic response. Note that stimulation at 2 µA DC did not change IO function significantly; however, following stimulation at 7 and 12 µA DC, increase of EABR amplitude and successive loss of electrophonic limb at low probe intensities can be observed.

Electrically evoked auditory brain stem response (ABR) thresholds below 50 dB peak equivalent sound pressure level re 20 µPa were recorded in the present study. 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. All recordings were made in a sound-attenuated, electrically shielded room. Both ABRs and EABRs were recorded differentially (DAM-5A, WPI) with needle electrodes at the vertex (positive), neck (negative) and abdomen (ground), while the positive electrode for recording CAPs was electrode 1 of the intracochlear array. Responses were amplified by a factor of 10^5, and the artifact was suppressed and finally band-pass filtered (0.15 to 3 kHz). The amplifier output was fed into a 10 bit ADC and sampled at 20 kHz for 12.5 milliseconds following stimulus onset. Each recording was averaged over 125 to 500 responses. Auditory brain stem responses, CAPs, and EABRs were recorded prior to and following DC stimulation, their thresholds established, and the input-output function (amplitude versus stimulus intensity) of wave III of the ABR and EABR evaluated. In addition, ABRs were also recorded before and after implantation. Furthermore, threshold and input-output function of the electrophonic EABR responses were established. (See Results.)

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," Reg. No. 92-016) and complied with the guidelines of the National Health and Medical Research Council of Australia.

RESULTS

Careful insertion of the first three platinum electrodes into the scala tympani was often possible without reducing the click-evoked ABR amplitude or increasing acoustic thresholds significantly. However, high CAP thresholds at high frequencies were sometimes observed, most probably caused by mechanical trauma during insertion.

At low intensities, the pre-DC stimulus EABRs were similar in morphology to wave III of the ABR, were characterized by a long latency (>2.5 milliseconds), and could be masked by white noise. This response was, therefore, considered to be electrophonic in origin. At higher intensities, responses appeared with shorter latencies. These responses could not be masked by noise and were considered to be the direct response of the auditory nerve to the electrical stimulus.11

Following stimulation at 2 µA DC for 2 hours, no significant change in the input-output function of the click-evoked ABR or the EABR (both the direct and the electrophonic responses) was observed. The EABR, ABR, and CAP thresholds remained stable (Figs 1 and 2A, B). However, stimulation at 7 µA DC for 2 hours induced an increase in amplitude of the direct EABR response, while its threshold decreased. The electrophonic response of the EABR was reduced or lost completely, while its threshold increased (Figs 1 and 2C).
Following stimulation at 12 μA DC, an even greater increase in amplitude of the direct EABR response was observed (Fig 1). This was combined with lower thresholds and changes in the morphology of the response. Furthermore, while the electrophonic response was clearly evident before stimulation, it could not be evoked after stimulation (Fig 2E). The DC-induced reductions in the electrophonic response were also reflected in the acoustic responses. Stimulation at 7 μA DC resulted in a decrease in the ABR amplitude and an increase in threshold. This was even more pronounced following stimulation at 12 μA DC (Figs 2C,E). Compound action potential thresholds increased for frequencies above 8 kHz following stimulation at 7 μA DC, for an electrode located 2 mm along the scala tympani (Fig 2D). However, thresholds for all frequencies increased sharply following stimulation at 12 μA DC (Fig 2F). No recovery of CAP thresholds occurred during the poststimulus monitoring period of up to 2 hours (Fig 2D,F).

**DISCUSSION**

The results illustrate the adverse effects of acute intracochlear DC stimulation at relatively small intensities, and also underline the close association of the electrophonic response of the EABR with the hearing status of the cochlea. As noted, a number of previous studies described the effect of acute DC stimulation on the cochlea following intracochlear and extracochlear stimulation. However, while extracochlear stimulation generally requires DC currents of some hundred microamperes, intracochlear stimulation induced changes at much lower intensities. The results of the present study indicate that current levels as low as 7 μA DC can change the electrophysiological properties of the cochlea. This value is substantially lower than previously published values for acute DC stimulation using intracochlear electrodes. However, widespread spiral ganglion cell loss and new bone formation have been reported following chronic intracochlear stimulation using a stimulus with a DC level of 2 μA.

It is unclear whether these DC-induced changes are due to the stimulus per se or are the result of toxic electrochemical products formed at the electrode-tissue interface. However, it is well known that irreversible electrochemical changes associated with DC stimulation can occur at the electrode interface. These changes include electrolysis of water, resulting in pH shift, oxidation of chloride ions and organic compounds, and electrode corrosion. Stimulating our electrode array at 2, 7, and 12 μA in artificial perilymph, gas evolution could be observed at both 7 and 12 μA DC, and coincided with an increase in electrode impedance. Impedance measurements made in vivo resulted in similar changes. While we were unable to ascertain whether or not gas evolution did occur during DC stimulation, it seems most probable...
that the observed decrement in acoustic sensitivity of the cochlea following DC stimulation was caused by the production of toxic electrochemical products, including gas evolution.

Moreover, the data of the present study suggest that the spatial extent of DC-induced decrement of the acoustic sensitivity of the cochlea depends on stimulus intensity. While 7 μA DC stimulation induced an increment in CAP thresholds for approximately 3 mm beyond the electrode tip (2 mm insertion), as the 10-kHz region in the guinea pig cochlea is approximately 5 mm from the round window. 11 12 μA DC stimulation increased thresholds across the whole frequency range. It seems most likely that a spread of toxic products along the scala tympani is responsible for the increase in acoustic thresholds beyond the region of the stimulating electrodes, as it has been shown previously that the electrical field for bipolar intracochlear stimulation is relatively localized to the stimulating electrodes. 15

While this mechanism could account for the reduction of acoustic sensitivity, we also observed an increase in amplitude of the direct EABR response following DC stimulation. This was associated with lower thresholds compared with prestimulus values. Similar changes in the EABR have been observed in previous studies11,16,17 following deafening of the cochlea. The authors concluded that those changes were associated with a change in the impedance pathways within the cochlea following the loss of hair cells, rather than resulting from toxic electrochemical products or direct sensitization of the auditory nerve. This change in current flow, which seems to be the most probable cause of the observed EABR changes in the present study, could have been caused by gas evolution at the electrode surface and its accumulation in the scala tympani, DC-induced hair cell damage, or a combination of both.

The present study both provides some insight into the mechanisms associated with DC-induced damage to the cochlea and also confirms the adverse effects of DC that have been observed in previous studies. It should be noted that the continuous constant amplitude DC used in this study is unlikely to adequately model the temporally varying DC associated with high-rate electrical stimulation (in this context, DC is taken to mean current that does not reverse its polarity). Additional studies are required using stimuli that more accurately reflect these variations in DC level.

REFERENCES


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

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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. 1-3 However, safe maximum levels for stimulus parameters (stimulus rate, charge per phase,
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