CHRONIC MONOPOLAR HIGH RATE STIMULATION OF THE AUDITORY NERVE

Physiological and histopathological effects

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Introduction

There is clinical interest in the development of high rate speech processing strategies, since there are indications that these might enhance speech perception due to an improved representation of the rapid variations in amplitude of speech.\(^1\) Significant improvement in speech perception using high rate stimulation has been demonstrated in cochlear implant recipients.\(^2,3\) However, it is important that the long-term safety of high rate stimulation is clearly established prior to its general clinical application.

This is especially important, since acute animal studies have shown that high rate stimulation can induce a reduction in the excitability of the auditory nerve.\(^4\) This was also associated with an increase in both threshold and latency of the electrically evoked auditory brainstem response (EABR). However, while a chronic stimulation study indicated that monopolar electrical stimulation of the auditory nerve at rates of 1000 pulses per second (pps)/channel (three channels) had no adverse effects on the spiral ganglion cell density (SGCD),\(^5\) there is limited data concerning higher rates.

In the present study, we evaluated the electrophysiological and histopathological effects of chronic monopolar electrical stimulation of the auditory nerve using considerably higher stimulus rates than have been used in previous studies.

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Methods

Six normal hearing cats were implanted bilaterally with three-channel platinum (Pt) scala tympani arrays under sterile conditions and surgical anesthesia. An extracochlear return electrode was placed outside the bulla underneath the temporalis muscle.

Unilateral chronic electrical stimulation commenced two weeks following surgery using portable, programmable stimulators. The stimulus paradigm consisted of charge-balanced, biphasic current pulses with a pulse width of 25 μsec, continuously presented (duty cycle of 100%) at a rate of 4831 pps/channel (total rate: 14493 pps). Each animal received electrical stimulation for approximately 16 hours per day for a total stimulation period between 600 and 2700 hours, during an implantation period of up to 205 days. The electrodes were shorted between current pulses, and the extracochlear electrode capacitatively coupled (0.1 μF) to minimize residual direct current (DC).

Every 300 hours of stimulation, the hearing status of the animals was monitored using click-evoked auditory brainstem responses (ABR) and the frequency-specific compound action potential (CAP). At the same time, monopolar and bipolar EABR were monitored to ensure that the electrical stimulus was above threshold for auditory nerve excitation. Stimulus intensity used for chronic stimulation was maintained ~6 dB above the EABR threshold. Moreover, residual DC, stimulus current, and electrode voltage were monitored twice a day and total electrode impedance \( Z_e \) as well as access resistance \( R_a \) calculated from those data. \( Z_e \) reflects the state of the electrode tissue interface \( R_a \), as well as the electrical status of the electrode (polarisation impedance, \( Z_{pol} \)): \( Z_e = R_a + Z_{pol} \).

At the end of the stimulation period, the animal was killed with an overdose of anesthetic, and systemically perfused with fixative. The cochleas were removed from the temporal bones and histologically processed. This procedure has been described in detail previously. Spiral ganglion cells densities were then assessed in the lower basal turn (LBT), the upper basal turn (UBT), where the stimulating electrodes were positioned, as well as in the middle and apical turn (MAT) of the cochlea.

Results

ABR

Elevated ABR thresholds to click stimuli were found in all cochleas following implant surgery. Subsequent recovery of the ABR thresholds on the electrically stimulated side was less complete compared to the unstimulated side.


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Fig. 1. a. Representative EABR recordings (bipolar configuration, 100 μsec/phase stimulus), using current amplitudes between 1.6 mA and threshold, from a cochlea just prior to commencing electrical stimulation and after 1256 hours of stimulation. b. EABR input/output functions of the same cochlea.

**CAP**

As expected, the CAPs generally showed the most extensive hearing loss in the high frequency region adjacent to the electrode array. However, in general, we also observed further deterioration of the CAP thresholds across all frequencies during the period of electrical stimulation.

**EABR**

Stimulus artefacts often obscured the EABR responses recorded using a monopolar configuration. Therefore, additional EABRs evoked via bipolar electrodes were recorded. These recordings were not severely affected by the stimulus artefact. In these recordings, there was little evidence of a significant change in threshold as a function of electrical stimulation time (Fig. 1a). Suprathreshold amplitude growth of wave IV was analyzed and found to remain generally stable throughout the chronic stimulation period (Fig. 1b).
Both access resistance ($R_a$) and electrode impedance ($Z_e$) varied across animals. At the start of electrical stimulation, $R_a$ ranged between 1.13 and 2.44 kΩ, while $Z_e$ ranged between 2.11 and 3.55 kΩ. However, in one cat we recorded an unusually high initial impedance ($R_a$: 5.4 kΩ, $Z_e$: 7.4 kΩ), which later stabilized at a lower level ($R_a$: 3.5 kΩ; $Z_e$: 5.4 kΩ). Successive histopathological examination showed dense fibrous tissue and inflammation in this cochlea. Another test cochlea showed no increase in $Z_e$ over time, while the remainder generally showed an increase in impedance soon after implantation, which later stabilized at a lower level (Fig. 2). Cochleas exhibiting high impedances were found to have substantial growth of fibrous tissue around the electrode track when examined histologically. In contrast, the cochleas that exhibited low impedances had very little tissue in the basal turn. There was no significant relationship between average electrode impedance and duration of electrical stimulation ($p > 0.05$, Spearman rank order correlation).

Histopathology

No statistically significant difference was found in the SGCD between corresponding regions of the stimulated and the implanted, but unstimulated, control cochleas ($p = 0.394$, Mann-Whitney rank sum test) (Fig. 3). There was a significant correlation between the SGCD of all cochleas and implantation time ($p = 0.0126$, $r = -0.684$) (Fig. 4), but not between the SGCD and stimulation time ($p > 0.05$, $r = -0.0112$, Spearman rank order correlation).

Discussion

It has been previously suggested that very high rates of electrical stimulation (>1000 pps) might lead to acute overstimulation of the auditory nerve and prolonged periods of depolarization. Within the nerve, overstimulation could lead to a loss of cellular homeostasis and ultimately to neural cell damage. In this study, stimulating at a rate of 4831 pps/channel (three channels), there was no evidence of either a significant reduction in the amplitude of wave IV of the EABR or a significant change in bipolar EABR thresholds as a function of electrical stimulation.

Electrode impedance ($Z_e$) in this study showed no obvious correlation to duration of electrical stimulation. However, following histological examination of the stimulated cochleas, a relationship between the extent of tissue growth within the cochlea and electrode impedance was evident. These results are consistent with observations in previous studies from our laboratory. The two animals that exhibited the highest electrode impedance throughout the stimulation period were found to have significant amounts of fibrous tissue in the basal region of the cochlea. However, as one of these animals also showed a
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High rate stimulation of the auditory nerve

Electrical stimulation of the auditory nerve and restimulation could lead to cell damage, which could be seen in the cochlea of animal 119, indicating a substantial growth of fibrous tissue. In contrast, animal 920 showed an increase in the impedance of the cochlea, which was more common in the low-impedance animal (Cat 119), demonstrating the difference in impedance response. More common was the response similar to that seen in Cat 920. In this animal, a thick fibrous tissue sheath had formed around the electrode in the basal turn of the cochlea. There was virtually no fibrous tissue found in the cochlea of the low impedance animal (Cat 119).

Fig. 2. Electrode impedance ($Z_e$) and access resistance ($R_a$) as a function of implantation time of two animals, demonstrating the difference in impedance response.
Fig. 3. Mean SGCD (cells/mm²) of all cochleas in this study at three different locations. LBT: lower basal turn; UBT: upper basal turn adjacent to the stimulating electrodes; MAT: middle and apical turns.

Fig. 4. SGCD in the region of the scala tympani adjacent to the stimulating electrodes (UBT) of all cochleas in this study, shown as a function of implantation time. Z indicates cochleas that exhibited a high $Z_e$ and $R_s$.

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similar response in the contralateral, unstimulated cochlea, this response cannot be attributed to electrical stimulation per se. The fibrous tissue growth is more likely to be related to electrode insertion trauma and/or subsequent inflammation or infection.

We generally observed a more extensive fibrous tissue reaction in the stimulated cochleas, indicating that it might be the test electrode, with its long and percutaneous lead wire, that is facilitating this reaction. The more severe fibrous tissue reaction on the stimulated side might also account for the less complete ABR recovery on this side. Moreover, while there was neither a correlation between the SGCD of corresponding regions of the stimulated and unstimulated cochleas, nor between SGCD and the duration of electrical stimulation, a significant correlation between SGCD and the duration of implantation was seen. These results may indicate that insertion-induced trauma and/or subsequent chronic inflammation has a greater adverse effect on cochlear neuronal elements than electrical stimulation.

However, the stability of both the EABR thresholds and the waveform morphology, together with the SGCDs observed in this study, indicate that electrical stimulation at these high rates did not adversely affect the auditory nerve.

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