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Insertion trauma and recovery of function after cochlear implantation: Evidence from objective functional measures

Bryan E. Pfingst [a, *], Aaron P. Hughes [a], Deborah J. Colesa [a], Melissa M. Watts [a], Stefan B. Strahl [b], Yehoash Raphael [a]

[a] Kresge Hearing Research Institute, Department of Otolaryngology – Head and Neck Surgery, University of Michigan, Ann Arbor, MI, USA
[b] MED-EL GmbH, Innsbruck, Austria

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ABSTRACT

Partial loss and subsequent recovery of cochlear implant function in the first few weeks following cochlear implant surgery has been observed in previous studies using psychophysical detection thresholds. In the current study, we explored this putative manifestation of insertion trauma using objective functional measures: electrically-evoked compound action potential (ECAP) amplitude-growth functions (ECAP amplitude as a function of stimulus level). In guinea pigs implanted in a hearing ear with good post-implant hearing and good spiral ganglion neuron (SGN) survival, consistent patterns of ECAP functions were observed. The slopes of ECAP growth functions were moderately steep on the day of implant insertion, decreased to low levels over the first few days after implantation and then increased slowly over several weeks to reach a relatively stable level. In parallel, ECAP thresholds increased over time after implantation and then recovered, although more quickly, to a relatively stable low level as did thresholds for eliciting a facial twitch. Similar results were obtained in animals deafened but treated with an adenovirus with a neurotrophin gene insert that resulted in good SGN preservation. In contrast, in animals implanted in deaf ears that had relatively poor SGN survival, ECAP slopes reached low levels within a few days after implantation and remained low. These results are consistent with the idea that steep ECAP growth functions require a healthy population of auditory nerve fibers and that cochlear implant insertion trauma can temporarily impair the function of a healthy SGN population.

1. Introduction

While cochlear implants already perform remarkably well at restoring or improving hearing for deaf or hearing-impaired individuals, there is still room for improvement (Wilson and Dorman, 2008). Recently there has been increased attention to preserving the biology of the implanted cochlea, including improved implant designs, “soft surgery” procedures, and tissue engineering (e.g., Cohen, 1997; von Ilberg et al., 1999; Wise et al., 2005; Van De Water et al., 2010; Budenz et al., 2012; Ramekers et al., 2012; Havenith et al., 2013; Usami et al., 2014). In previous studies we have observed significant loss of cochlear implant function following cochlear implant insertion and subsequent recovery of function, suggesting a temporary negative reaction to cochlear implant insertion surgery (Pfingst, 1990; Miller et al., 2000; Su et al., 2008). We use the term “insertion trauma” to refer to the reaction to the entire surgical procedure in which an implant is inserted into the scala tympani of the cochlea. In our animal models, cochlear implant insertion was often done shortly after the ear was deafened by local perfusion of neomycin into the scala tympani so it is possible that the deafening procedure contributed to the temporary loss of neural function in those cases. However, we have seen similar changes over time in implant function when the implant was inserted into a hearing ear, suggesting the surgical insertion procedure alone can produce significant temporary functional impairment (Su et al., 2008). These observations were made in nonhuman primates and guinea pigs using psychophysical detection thresholds as the measure of cochlear implant function. In these studies, psychophysical detection thresholds, when they

Abbreviations: AAV, adeno-associated virus; DPI, days post implantation; ECAP, electrically-evoked compound action potential; IHC, inner hair cell; MSL, maximum stimulus level; μA, microampere; N1, first negative potential; *Ntf3*, gene for neurotrophic factor 3; P2, second positive potential; SGN, spiral ganglion neuron

* Corresponding author.
E-mail address: bpfingst@umich.edu (B.E. Pfingst).

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could be recorded within a day or two after surgery, started out at a low level, increased (showed a loss of sensitivity) over time during the first several days after implantation, and then slowly recovered to near or below the original levels. More commonly, thresholds were high when the first reliable thresholds were obtained and they decreased over a period of several weeks. These initial reactions to implant insertion are of interest for several reasons. First they probably reflect at least a temporary traumatic reaction to the surgical procedure and implant insertion, which could potentially have long-term consequences. Second, the unstable functional response to electrical stimulation during the early days following implant insertion is a concern for experimental studies that take place during this period. Finally the phenomenon of apparent loss and recovery during this relatively restricted time period defines a potentially interesting model for study of features of the implanted cochlea that influence cochlear implant function.

A plausible explanation of the systematic fluctuation in electrical-stimulus detection in the days following implantation is a temporary disruption of neural function, perhaps due to an inflammatory reaction to the implant insertion (Van De Water et al., 2010; Seyyedi and Nadol, 2014). However, one can not completely rule out changes in behavioral performance, due perhaps to the animal not feeling well and not delivering its best performance. Indeed, many animals did not perform the behavioral task at all for several days after the surgery and we were only able to observe a decrease in thresholds over time after the animal began performing the psychophysical task reliably. To address these issues we have used an objective measure of cochlear implant function: electrically evoked compound action potentials (ECAPs). These potentials can be recorded from awake animals daily starting on the day of surgery and thus can provide a more frequent, direct, and objective measure of the response of the auditory nerve to electrical stimulation. Furthermore, using ECAP amplitude-growth functions (ECAP amplitude as a function of electrical-stimulus level) we can monitor both threshold and suprathreshold responses. Here we report on ECAP amplitude-growth functions following implant insertion in three guinea pig treatment groups.

2. Methods

2.1. Overview

Nine adult male specific pathogen free pigmented guinea pigs were used for these experiments. The guinea pigs were bred and maintained by the Unit for Laboratory Animal Medicine at the University of Michigan. The animal-use protocol was reviewed and approved by the University of Michigan Committee on the Use and Care of Animals. The guinea pigs used to follow ECAP amplitude-growth functions over time after implantation were also used for a variety of other experiments; thus there were several different treatment groups and we were able to follow changes over time after implantation in the context of several pre-implant treatments. These groups are described below and summarized in Table 1.

In one group ($n = 3$), guinea pigs received a cochlear implant in a previously-normal ear. Thus the effects of the surgery and implant-insertion could be studied in the absence of any other cochlear trauma. Implanting in a hearing ear typically results in fair to good hearing preservation and presence of surviving hair cells in the region of the cochlear implant (Kang et al., 2010; Pfingst et al., 2011).

The remaining animals were deafened prior to implantation by injection of neomycin into the scala tympani. 10 μl of 5% (w/v) neomycin sulfate solution in sterile water were injected into the scala tympani through the cochleostomy at 5 μl/min. Hair cells are typically destroyed within a few days by this procedure (Kim and Raphael, 2007). Deafening the ear introduced an additional cochlear trauma but allowed us to assess the responses to electrical stimulation in the absence of functioning hair cells.

Three of the deafened animals received inoculation of the ear with an adeno-associated viral vector containing a neurotrophin gene insert (AAV.*Ntf3*). The adeno-associated virus used was AAV2 and the concentration was 1×10^{12} pfu/ml. 5 μl were infused into the scala tympani through the cochleostomy at a rate of 1 μl/min. Treatment of the cochlea with neurotrophin following deafening can have long-lasting protective effects on the auditory nerve (Budenz et al., 2012), but results are variable across animals. The effects of the neurotrophins on the early changes in sensitivity to electrical stimulation following implant insertion have not been reported previously to our knowledge.

Finally, three animals were deafened and then inoculated with an empty adeno-associated virus (AAV.Empty) as a control for the effects of the AAV alone. Neomycin deafening alone (i.e. without neurotrophin support) typically results in ears with no inner hair cells (IHCs) and very low spiral ganglion neuron (SGN) densities (Kang et al., 2010; Pfingst et al., 2011).

2.2. Cochlear implants

The cochlear implant electrode arrays (supplied by Cochlear Ltd., Lane Cove, Australia) consisted of 8 full-band electrodes encircling a straight silicone rubber carrier and spaced at 0.75 mm center to center. Electrodes were labeled A through H with A being the most apical. The implant was gently inserted into the scala tympani through a cochleostomy which was made at approximately 0.7 mm apical to the round window. In the guinea pig, the cochleostomy allows a straighter and deeper insertion than a round-window approach. The diameter of the implant near its apical end was 0.4 mm. Because the scala tympani in the guinea pig narrows dramatically past the first half turn, the implant could be advanced only about 4.5 mm from the cochleostomy without doing physical damage. The primary electrode used for stimulation in the current experiments was the second most apical electrode (Electrode B) which was located an average of 2.83 mm apical to the cochleostomy and typically sat close to the modiolar wall. ECAP potentials were recorded from Electrode A except in one case where the connection to Electrode A was not reliable and Electrode C was used (see Table 1).

2.3. Electrically-evoked compound acton potential (ECAP) amplitude-growth functions

ECAP amplitude-growth functions (ECAP amplitude as a function of stimulus level) were recorded in awake guinea pigs while the animals were standing in a test cage. A MED-EL "Pulsar" CI100 receiver/stimulator, connected to the implant through a percutaneous electrical connector, was used for stimulation and recording. The output of the receiver/stimulator was connected to a Research Interface Box (RIB II; University of Innsbruck). Custom software controlled the stimulus delivery and ECAP recording.

Monopolar electrode configurations were used for stimulation and recording with the stimulating electrode referenced to a skull screw at bregma and the recording electrode referenced to a vertex skull screw. The stimulus was a biphasic pulse, with 45 μs phase duration and 2.1 μs inter-phase interval. Pulses were delivered with alternating leading-phase polarity at 50 pps for 20 iterations. The recording amplifier was blanked for 165 μs following electrical pulse onset to avoid saturation artifact.

The maximum stimulus level (MSL) that could be used for ECAP recording was determined each day prior to the recording session. The MSL was typically set approximately 2 μA below the current

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