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Research paper

Infrared neural stimulation fails to evoke neural activity in the deaf guinea pig cochlea

Alexander C. Thompson [a], James B. Fallon [b, c, d], Andrew K. Wise [b, c, d], Scott A. Wade [a], Robert K. Shepherd [b, c, d], Paul R. Stoddart [a, *]

[a] Faculty of Science, Engineering and Technology, Swinburne University of Technology, Hawthorn, Australia
[b] Bionics Institute, East Melbourne, Australia
[c] Medical Bionics Department, University of Melbourne, East Melbourne, Australia
[d] Department of Otolaryngology, University of Melbourne, East Melbourne, Australia

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ABSTRACT

At present there is some debate as to the processes by which infrared neural stimulation (INS) activates neurons in the cochlea, as the lasers used for INS can potentially generate a range of secondary stimuli e.g. an acoustic stimulus is produced when the light is absorbed by water. To clarify whether INS in the cochlea requires functioning hair cells and to explore the potential relevance to cochlear implants, experiments using INS were performed in the cochleae of both normal hearing and profoundly deaf guinea pigs. A response to laser stimulation was readily evoked in normal hearing cochlea. However, no response was evoked in any profoundly deaf cochleae, for either acute or chronic deafening, contrary to previous work where a response was observed after acute deafening with ototoxic drugs. A neural response to electrical stimulation was readily evoked in all cochleae after deafening. The absence of a response from optical stimuli in profoundly deaf cochleae suggests that the response from INS in the cochlea is hair cell mediated.

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1. Introduction

Despite the great success of the cochlear implant, used by over 300,000 patients worldwide (National Institute on Deafness), many patients are limited in their ability to understand speech in noisy environments or appreciate music (Friesen et al., 2001). This limitation appears to be primarily due to spreading of electrical current in the cochlea (Friesen et al., 2001), which reduces the effective number of independent channels and thus, spectral information that can be delivered. Present research is exploring a range of approaches to improve delivery of spectral information, including techniques to reduce the spread of current from electrodes (George et al., 2014) and the use of optical stimulation techniques (Hernandez et al., 2014; Izzo et al., 2006).

Infrared neural stimulation (INS) is a proposed alternative to electrical stimulation using micro-to milli-second duration pulses of infrared light to activate neurons (Richter et al., 2011; Chernov and Roe, 2014). Compared to traditional electrical stimulation, reports in the sciatic nerve have suggested that INS can be more spatially localised (Wells et al., 2007) and, unlike optogenetic and caged molecule techniques (Kramer et al., 2009), modification of the target tissue is not required (Richter et al., 2011). INS has been demonstrated *in vivo* in a number of targets, including: peripheral nerves (Wells et al., 2005b), visual cortex (Cayce et al., 2014), embryonic heart (Jenkins et al., 2010) and the cochlea (Izzo et al., 2006). The mechanism of INS has been a topic of much discussion in the literature (Brown et al., 2013; Shapiro et al., 2012; Albert et al., 2012). The potential mechanisms that have been identified for INS include a change in the cell membrane capacitance in response to rapid heating (Shapiro et al., 2012) and activation of TRPV heat sensitive ion channels (Albert et al., 2012).

Electrical stimulation in the cochlea targets the primary auditory neurons known as spiral ganglion neurons (SGNs). Applying INS to the cochlea has been an area of particular interest, as the potential for an improvement in the spatial selectivity of INS over electrical stimulation may be advantageous for use in cochlear implants (Thompson et al., 2013b). Previous work has shown that INS activates spatial regions similar to acoustic tones, suggesting

* Corresponding author.
E-mail addresses: thompson.alex.c@gmail.com (A.C. Thompson), pstoddart@swin.edu.au (P.R. Stoddart).

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improved spatial localisation compared to electrical stimulation. Furthermore, excitation is largely restricted to SGNs in the beam path. However, much excitation appears to be on side of the cochlea opposite the optical fibre, where both SGNs and hair cells would be exposed to the light. Rather than those directly in front of the optical fibre (Moreno et al., 2011), where only SGNs were exposed. It should also be noted that radiant exposure thresholds for neural activation reported for INS in the cochlea (3–20 mJ cm^{-2} (Izzo et al., 2006; Richter et al., 2011, 2008; Thompson et al., 2013a)) are much lower than those reported for other neural targets, where thresholds of 320–710 mJ cm^2 are commonly required (Wells et al., 2005a; Teudt et al., 2007), suggesting differences in the mechanisms associated with evoking the neural response.

Many reports of INS in the cochlea use normal hearing animals (Matic et al., 2013; Izzo et al., 2007). Some previous experimental reports discuss the ability of INS to evoke neural activity in animals acutely deafened with ototoxic aminoglycosides (Izzo et al., 2006; Richter et al., 2008), which disable and eliminate the hair cells. This suggests that this INS-evoked neural activity is a direct interaction between the laser and the SGNs. However, the deafening techniques used in these reports have shown varying levels of hearing impairment. Furthermore, INS in chronically deaf animals could only evoke a response when one could also be evoked with an acoustic stimulus (Richter et al., 2008).

This has led to some doubt about the stimulation mechanism in cochlear studies, which questions as to whether INS directly activated the SGNs, or whether SGN activation occurred as a result of hair cell mediated responses (Schultz et al., 2014). This is an important distinction for the application of INS with a cochlear implant where recipients typically have severe to profound deafness with few (if any) functional hair cells remaining. Laser sources used for INS have been shown to generate an acoustic click from rapid expansion of heated water, resulting in an optoacoustic mediated response (Teudt et al., 2011). Optoacoustic generation of sound has been shown to be applicable to many different wavelengths, including those used by INS, and appears to be driven by water or haemoglobin absorption (Schultz et al., 2012; Rettenmaier et al., 2014). Therefore, if the deafening process is not complete and functional hair cells remain, the generation of an acoustic click during INS may lead to a response mediated by activation of residual hair cells by this acoustic artefact. Furthermore, a recent report of INS in the rat cochlear nucleus, an auditory structure remote from hair cells of the cochlea, found no response after deafening that was achieved by cutting the auditory nerve at the internal auditory meatus (Verma et al., 2014).

Given the conflicting results described above, further investigation is required to determine the mechanism of INS in the cochlea and to clarify the potential benefits of the technique. In this paper, results of INS in severe-profoundly deaf guinea pig cochleae are reported. Both acute and chronic deafening techniques have been used, in order to investigate the potential role of the deafening procedure in determining the outcome of INS experiments.

2. Methods

2.1. Animal preparation

All experimental procedures involving animals were performed in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and with the guidelines laid down by the National Institutes of Health in the USA regarding the care and use of animals for experimental procedures. These procedures were approved by the Royal Victorian Eye and Ear Hospital Animal Research and Ethics Committee.

Four ($n = 4$) young adult male or female pigmented guinea pigs were used to collect data for the experimental studies presented in this paper. In two animals both cochleae were tested with INS, while the other two were only tested on one side, giving a total of six cochlea examined ($n_{cochlea} = 6$). Two were used for acutely deafened experiments, while two were chronically deafened four weeks before stimulation experiments. All acutely deafened animals were first tested as control normal hearing animals, with INS experiments performed before the deafening process was carried out. In chronically deafened animals INS experiments were carried out on both cochleae.

Anaesthesia was induced with an intramuscular delivery of ketamine (60 mg kg^{-1}) and xylazine (4 mg kg^{-1}) and was maintained with top-up doses of ketamine (40 mg kg^{-1}) and xylazine (4 mg kg^{-1}), administered at one third to one sixth of the induction volume every 40–50 min, or if a toe pinch withdrawal reflex was present. The animal was kept on a thermostatic heating pad at 38 °C to maintain body temperature in the normal range.

Animals were prepared for surgery by shaving the area near the neck and skull and then injecting a local anaesthetic (lignocaine, 0.1 ml) at the incision site. A post-auricular incision was made and the temporalis muscle retracted, exposing the tympanic bulla. The dorsal region of the bulla was then drilled with a 2 mm cutting burr to expose the cochlea. A cochleostomy was drilled into the otic capsule of the basal turn using a diamond burr to thin the cochlea wall. After clearing the bone debris, the endosteum was perforated to expose the scala tympani and the modiolus (Fig. 1). In some animals a cochleostomy was performed in a more apical turn to assess whether the spiral ganglion neuron population at this location responded differently to those located in the basal turn.

At the conclusion of the experiment, the animals were sacrificed with an overdose of anaesthetic sodium pentobarbital (150 mg kg^{-1}) and intracardially perfused with formalin fixative. Cochleae were collected for histological analysis.

2.2. Deafening

To prevent hair cell mediated electrophonic or optoacoustic (Teudt et al., 2011) activity from being confused with a direct neural interaction with the laser, animals were deafened using procedures

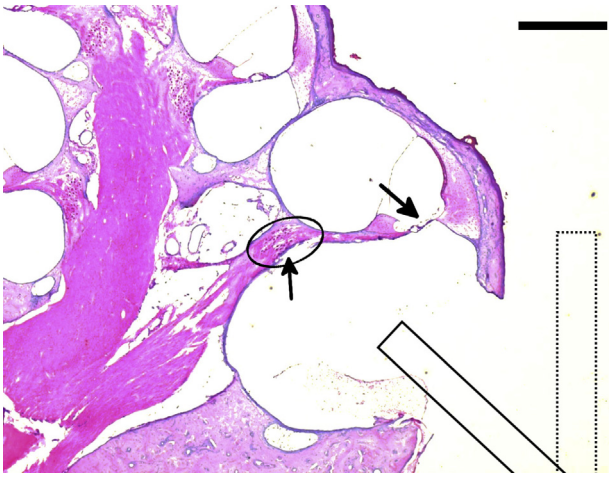

Fig. 1. Histological image of a mid modiolar cochlear section from a normal hearing animal indicating the cochleostomy and the target spiral ganglion neurons (oval). The organ of Corti containing the intact sensory hair cells (arrow) is intact in this example. The osseous spiral lamina was fractured by the optical fibre (arrow at circle). Solid lines represent optical fibre position when targeting the SGNs and dashed lines show optical fibre next to, but not pointing to the cochlea. Scale bar = 500 μm.

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