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Research paper

Thin-film micro-electrode stimulation of the cochlea in rats exposed to aminoglycoside induced hearing loss

B.J. Allitt [a, b, e, *], A.R. Harris [a, b], S.J. Morgan [a], G.M. Clark [a, b, c], A.G. Paolini [a, b, d]

[a] School of Psychological Science, La Trobe University, Bundoora, Victoria, 3086, Australia
[b] ARC Centre of Excellence for Electromaterials Science, Australia
[c] Centre for Neural Engineering, University of Melbourne, Australia
[d] School of Health Sciences, College of Science Engineering & Health, RMIT University, Bundoora, Australia
[e] Department of Physiology, Monash University, Clayton, 3800, Australia

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A B S T R A C T

The multi-channel cochlear implant (CI) provides sound and speech perception to thousands of individuals who would otherwise be deaf. Broad activation of auditory nerve fibres when using a CI results in poor frequency discrimination. The CI also provides users with poor amplitude perception due to elicitation of a narrow dynamic range. Provision of more discrete frequency perception and a greater control over amplitude may allow users to better distinguish speech in noise and to segregate sound sources. In this research, thin-film (TF) high density micro-electrode arrays and conventional platinum ring electrode arrays were used to stimulate the cochlea of rats administered sensorineural hearing loss (SNHL) via ototoxic insult, with neural responses taken at 434 multiunit clusters in the central nucleus of the inferior colliculus (CIC). Threshold, dynamic range and broadness of response were used to compare electrode arrays. A stronger current was required to elicit CIC threshold when using the TF array compared to the platinum ring electrode array. TF stimulation also elicited a narrower dynamic range than the PR counterpart. However, monopolar stimulation using the TF array produced more localised CIC responses than other stimulation strategies. These results suggest that individuals with SNHL could benefit from micro stimulation of the cochlea using a monopolar configuration which may provide discrete frequency perception when using TF electrode arrays.

1. Introduction

Multi-channel cochlear implants (CI) provide sound perception to many individuals who would otherwise be deaf (Clark, 2006), enabling open-set speech perception and the ability to converse via telephone (Brown et al., 1985: Clark et al., 1981; Dawson et al., 1992). CI's electrically stimulate peripheral neurons, providing a number of distinct psychophysical frequency percepts with a corresponding narrow dynamic range (DR) (Clark, 2003). Frequency and amplitude discrimination are restricted by electrical stimulation of broad cochlea frequency regions and a poor translation of amplitude using CIs (Cohen et al., 2001; Drennan and Rubinstein, 2008; Lim et al., 1989; Middlebrooks and Snyder, 2007; Moore, 2007). Micro-electrode stimulation of the cochlea, cochlear nucleus, auditory nerve and the midbrain improve neural localisation via narrow current fields and an increased DR compared to more conventional electrode types (Allitt et al., 2012, 2013; Lim et al., 2013; McCreery, 2008; Middlebrooks and Snyder, 2007). Constraining the current field during stimulation of the cochlea using micro-electrode designs has not yet been assessed in a population with sensorineural hearing loss (SNHL) and may provide an alternative to methods of sound delivery presently available to individuals with hearing loss.

Moderate SNHL limits the ability to discriminate between sound frequencies, inhibits sound localisation and distorts perception of amplitude change, while severe hearing loss eliminates these abilities completely (Lutfi, 2008; Shalit and Avraham, 2008). SNHL can lead to a decrease of spiral ganglion neurons (SGN) (Nadol, 1990) and the remaining cell density dictates the capacity of the

Abbreviations: CI, Cochlear implant; CIC, Central nucleus of the inferior colliculus; DR, Dynamic range; PR, Platinum ring; SGN, Spiral ganglion neuron; SNHL, Sensorineural hearing loss; TF, Thin-film

* Corresponding author. Department of Physiology, Monash University, Clayton, Victoria, 3800, Australia.
E-mail address: ben.allitt@monash.edu (B.J. Allitt).

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auditory periphery to respond to either acoustic or electrical stimulation (Illing, 2001; Russell and Moore, 2002; Shepherd and Hardie, 2001). Cell death, and the subsequent, time dependant, adaptation to stimulation positively correlates with the current required to elicit activity in higher order processing sites when using CIs (Shepherd et al., 2004).

The traditional understanding of CI stimulation indicates that bipolar stimulation localises frequency specific neural activity better than monopolar stimulation (Bierer and Middlebrooks, 2002; Xu and Pfingst, 2008). However, monopolar stimulation of the cochlea has also driven localised auditory neuronal responses (Schoenecker et al., 2012). In contrast to the traditional theory of bipolar stimulation using CIs, research using flat platinum disc electrodes has shown that monopolar stimulation is as effective as both common ground and hexagonal ground configurations in localising cortical activity (Cicione et al., 2012). Perhaps, current flow around flat micro-electrodes through intended peripheral perceptual tissue may be different from that produced when using conventional electrode designs.

Micro-electrode designs have been used to stimulate cortical and sub cortical regions (Middlebrooks and Snyder, 2007; McCreery et al., 2008; McCreery, 2008) including the thalamus and the retina (Cheung and Ferster, 1998; Cicione et al., 2012) with results indicating localisation of neural activity is an outcome of these devices. Our previous results using thin-film (TF) micro-electrode arrays in the cochlea of normal hearing animals demonstrated significant improvements in localising auditory neurophysiological responses and widening of the DR compared to a platinum ring (PR) array (Allitt et al., 2012). It is necessary to ascertain if these improvements are maintained in animals with SNHL so benefits can be transferred to potential future CI users. The aim of this research was to compare electrophysiological responses evoked by an experimental TF electrode array (consisting of 21 individual sites) and a platinum ring electrode array (consisting of eight individual sites). Neurophysiological recordings taken in the central nucleus of the inferior colliculus (CIC) (which receives primarily monaural innervation from the contralateral cochlear nucleus; Winer and Schreiner, 2005) were used to compare threshold, DR and localisation of topographic responses elicited by both electrode types using monopolar and bipolar stimulation combinations.

We anticipated that stimulation using the TF array would elicit more localised responses when using bipolar compared to monopolar stimulation and that both bipolar and monopolar TF array stimulation would produce more localised responses than the PR array. The small platinum disc electrodes on the TF array can provide a greater charge density than larger PR electrodes (Beebe and Rose, 1988; Robblee et al., 1986) requiring weaker current to evoke neural activity. Thus, we anticipated that weaker current would be required to drive CIC responses and an increased DR would be observed using the TF array in comparison to the PR electrode. Contrary to our hypotheses, the results presented below indicate that TF designs can provide more localised topographic responses using monopolar stimulation at the expense of elevated current required to elicit threshold and provide a narrow DR.

2. Methods

2.1. Subjects

Fourteen male hooded Wistar rats were used as subjects. All animals were group housed in temperature controlled rooms with *ad libitum* access to food and water. SNHL was induced (10–14 days old) via intraperitoneal injection of the aminoglycoside gentamycin (250 mg/kg) and via furosemide (125 mg/kg). Animals were randomly assigned to be implanted with either a TF experimental CI electrode ($n = 7$) or a conventional PR electrode array ($n = 7$) via acute surgery. On the day of surgery, animals ranged from 64 to 133 days old weighing between 270 and 454 g. All procedures and protocols were approved by the La Trobe University Animal Ethics Committee (AEC-11-60-P) and adhered to the Australian national health and medical research committee guidelines.

2.2. Surgical procedures

Prior to surgery, animals were anaesthetised using urethane (20%w/v in distilled water, 1.5 g/kg) administered via intraperitoneal injection. A DC-homeothermic blanket, with rectal probe feedback, regulated body temperature (36.5 °C). The head and body of anaesthetised animals were secured with a stereotaxic frame (David Kopf Instruments, Tujunga, CA) which was used as a reference for the insertion of an inferior colliculus (IC) recoding electrode. The head was secured using hollow ear bars through which an electrostatic speaker (ED1, Tucker Davis Technologies (TDT) System III hardware, Alachua, Fl) was attached. Pure tone bursts (1–44 kHz in 1 kHz steps, 10–70 dB SPL in 10 dB steps, 10 repetitions) were produced using a signal generator (RX6 multifunction processor, TDT, sampling at 100 kHz) and delivered via ear bar to ascertain the severity of sensorineural hearing loss. Prior to surgery, the combined speaker and ear bar configurations were calibrated using a Brüel and Kjær (Nærum, Denmark) microphone (4138-A-015) and amplifier (4 Channel Microphone Power Supply Type 2829).

Fur was removed from the dorsal region of each animal's head and a midline cranial incision was made to expose the parietal and interparietal bones. A burr hole was drilled in the anterior of the left interparietal bone and a small stainless steel screw was inserted for use as an earth electrode during neural recording. A craniectomy was performed contralateral to the planned CI electrode insertion to access the right IC. A recording electrode (see below for specifications) was driven 3.5 mm from pia through an incision made in the dura-mater and into the CIC using a micromanipulator (David Kopf Instruments, Tujunga, CA) allowing precision of 0.1 mm. Immediately prior to CIC insertion, electrodes were coated with fluorescent dye (DiI: 1, 1-dioctadecyl1-3,3,3′3,3' – tetramethyindocarbocyaine perchlorate; CAT D3911; Molecular Probes, Eugene, OR; 2.5 mg/ml in absolute ethanol) to facilitate later histological verification of placement.

Muscle was retracted around the caudolateral area of the skull above the left ear bar to expose the squamous bone and the posterior air sinus notch. The left round window was accessed and further exposed using a small burr. When implanting the TF array, as much as 3.5 mm could be inserted into the cochlea through the round window. The PR array was inserted until it could no longer progress (~2 mm). In no case, using the PR array, did more than three rings pass through the round window. The linear length of the rat scala tympani assured neither electrode progressed past the basal turn (Burda et al., 1988). A silver/silver chloride (Ag/AgCl) electrode wrapped in saline soaked cotton wool was placed subcutaneously under the animal's scruff and was used as the ground electrode in monopolar stimulation configurations of both electrode types.

At the conclusion of each experiment animals were deeply anaesthetised via intraperitoneal injection of sodium pentobarbital (Lethobarb, 1.0 ml; Virbac Animal Health, Australia) and perfused transcardially with phosphate buffered saline and paraformaldehyde. Animal skulls were removed and tissue was stored in a 10% paraformaldehyde/PBS solution. Prior to histological sectioning and staining, tissue was transferred (via 10 and 20%