Hearing Research 361 (2018) 45–51

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research Paper

Persistent hair cell malfunction contributes to hidden hearing loss

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ARTICLE INFO

Article history:
Received 11 September 2017
Received in revised form
14 December 2017
Accepted 9 February 2018
Available online 14 February 2018

Keywords:
Hidden hearing loss
Neuropathy
Inner and outer hair cells
Acoustic trauma
Thresholds
Summating potential

ABSTRACT

Noise exposures that result in fully reversible changes in cochlear neural threshold can cause a reduced neural output at supra-threshold sound intensity. This so-called "hidden hearing loss" has been shown to be associated with selective degeneration of high threshold afferent nerve fiber-inner hair cell (IHC) synapses. However, the electrophysiological function of the IHCs themselves in hidden hearing loss has not been directly investigated. We have made round window (RW) measurements of cochlear action potentials (CAP) and summating potentials (SP) after two levels of a 10 kHz acoustic trauma. The more intense acoustic trauma lead to notch-like permanent threshold changes and both CAP and SP showed reductions in supra-threshold amplitudes at frequencies with altered thresholds as well as from fully recovered regions. However, the interpretation of the results in normal threshold regions was complicated by the likelihood of reduced contributions from adjacent regions with elevated thresholds. The milder trauma showed full recovery of all neural thresholds, but there was a persistent depression of the amplitudes of both CAP and SP in response to supra-threshold sounds. The effect on SP amplitude in particular shows that occult damage to hair cell transduction mechanisms can contribute to hidden hearing loss. Such damage could potentially affect the supra-threshold output properties of surviving primary afferent neurons.

1. Introduction

The traditional view of reversible acoustic trauma has been that it affects primarily the functioning of the outer hair cells (OHCs), whose role is to amplify cochlear mechanical responses to sound and so determine the absolute sensitivity of the neural output from the inner hair cells (IHCs) (Ashmore, 2002; Patuzzi and Robertson., 1988; Yates et al., 1992). Full recovery of neural thresholds after acoustic trauma (temporary threshold shift, or TTS), signifies a full recovery of OHC sensitivity and until recently it was presumed that in such cases overall cochlear function also recovered. However, a number of recent studies have elegantly shown that despite the presence of normal neural thresholds after loud sound exposures, cochlear neural responses to supra-threshold acoustic stimuli can remain depressed (Furman et al., 2013; Kujawa and Liberman, 2015; Liberman, 2015; Lin et al., 2011). This reduced neural output, that has been referred to as "hidden hearing loss" is associated with neuropathic changes at the IHC synapse; in particular, with a selective loss of synapses between IHCs and the high threshold, low spontaneous rate population of primary afferent neurons (Furman et al., 2013; Liberman, 2016).

Most previous studies of hidden hearing loss have used the Wave I amplitude of the auditory brainstem response (ABR) to assess cochlear neural output and therefore lack an independent measure of hair cell function. One group has used otoacoustic emissions (DPOAEs) in mice and guinea pigs (Kujawa and Liberman, 2009; Lin et al., 2011), to monitored full recovery of OHC function, but no specific electrophysiological measures of either OHC or IHC output were employed.

Therefore, we have made detailed measurements of both hair cell and neural electrophysiological responses after loud sound exposures of varying severity. We show that changes in the supra-threshold magnitude of the summating potential (SP) also occur after full recovery of neural thresholds, suggesting that hidden hearing loss may reflect not only specific synaptic neuropathy, but also lasting changes in IHC electrophysiological function.

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https://doi.org/10.1016/j.heares.2018.02.001
0378-5955/

2. Methods

Eighteen pigmented guinea pigs of either sex, weighing between 282 and 558 g at the time of acoustic trauma, were used. The experimental protocols conformed to the Code of Practice of the National Health and Medical Research Council of Australia, and were approved by the Animal Ethics Committee of The University of Western Australia. Details of all anaesthetic and surgical procedures have been presented in previous publications from this laboratory (Mulders and Roberston, 2009, 2013; Mulders et al., 2011).

2.1. Acoustic trauma

For initial acoustic trauma, animals were anaesthetized by intraperitoneal injection of Diazepam (5 mg/kg), followed 20 min later by an intramuscular injection of Hypnorm (0.315 mg/ml fentanyl citrate and 10 mg/ml fluanisone; 1 ml/kg). Animals were allowed to breathe unassisted and the left ear was exposed to either 1hr (n = 6) or 0.5hr (n = 6) of a pure tone acoustic trauma (10 kHz, 124 dB SPL) using a calibrated closed sound delivery system as described previously (Mulders et al., 2011). The right ear was blocked with plasticine during the exposure. A silver wire electrode was placed on the round window (RW) with a reference wire adjacent to the tympanic bulla and an indifferent in the neck muscles, and cochlear neural thresholds (CAP thresholds) for tone bursts ranging from 4 to 24 kHz were assessed immediately before and after exposure (Johnstone et al., 1979). Animals were then allowed to recover for 2 weeks. A third group of animals (n = 6) served as sham controls and received identical treatment without loud sound exposure.

2.2. Post-recovery electrophysiology

After the recovery period of 2 weeks, all animals were re-anaesthetized by an intraperitoneal injection of pentobarbitone sodium (30 mg/kg) and a 0.15 ml intramuscular injection of Hypnorm. The maintenance anaesthetic regime consisted of full Hypnorm doses every hour and half doses of pentobarbitone every 2 h. Animals were placed on a heating blanket in a sound proof room and artificially ventilated on carbogen (95% O_2 and 5% CO_2). CAP thresholds were again measured as described above and then detailed input-output (I/O) functions were recorded at 4, 8, 14, and 20 kHz at 5 dB intensity increments. At the end of each experiment, the 4 kHz I/O function was repeated in order to control for any general deterioration of the recording conditions. No changes were seen. To record both CAP and summating potential (SP) waveforms, low and high frequency cut-offs on the recording amplifier (DAM 80, ×1000 gain) were 1Hz and 3 kHz, respectively. Averaged waveforms (32 presentations) were recorded using a 40 kHz sampling rate (AD Instruments Powerlab 4ST and Scope software) and amplitudes were analyzed off-line. For 4 kHz tones, waveforms at higher intensities were significantly contaminated by cochlear microphonic (CM) despite the low pass filtering employed at the recording stage. A four point smoothing was therefore carried out offline in order to yield a clean CAP waveform for peak-peak measurements.

Fig. 1A and B shows typical examples of the RW waveforms recorded in response to a 20 kHz tone burst 25 dB and 45 dB above CAP threshold (1 ms rise-fall time). CAP amplitudes were measured as the N1-P1 peak-to-peak amplitude. As described in detail previously (Brown and Patuzzi, 2010; McMahon et al., 2008; Sellick et al., 2003) the summating potential (SP) can be observed as the d. c. shift in RW potential occurring both at the onset and offset of the tone and there are arguments for and against using either as the SP measure. The onset SP could be under-estimated because of the

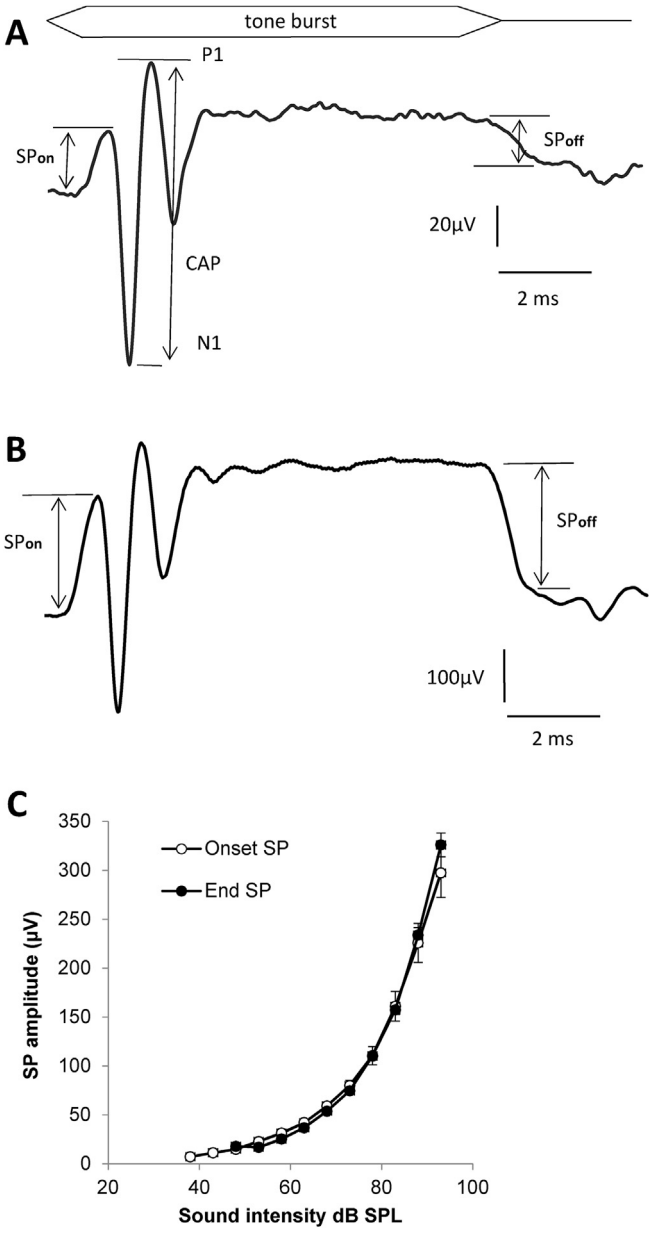

Fig. 1. A,B: Examples of normal RW recording in response to 20 kHz tone bursts 25 dB (A) or 45 dB (B) above CAP threshold (average of 32 stimulus presentations). CAP amplitude defined as N1-P1 peak to peak amplitude. SPon denotes onset summating potential. SPoff denotes offset summating potential. C. Comparison of SP magnitudes estimated from the d. c. change at tone onset and offset in sham animals.

start of the negative-going N1 wave of the CAP, whereas the slower slope of the offset SP is probably the result of contamination by changes in asynchronous neural firing (Sellick et al., 2003). Fig. 1C shows that in the present study, there was no difference in the SP magnitude estimated in these two ways in normal animals. Furthermore, we found that changing the tone burst rise-time from 1 ms to 0.5 ms (which would allow more time for the onset SP to reach its maximum before the CAP response began) caused a negligible change in the measured SP amplitude. For these reasons and because of its steeper rise, the onset SP was used throughout this study for statistical analysis, but in addition the results of offset SP measurements are also shown. SP I/O functions were measured at 14 and 20 kHz only, because unlike the remotely generated CAP, which can be recorded in an unbiased manner using a RW electrode