Effects of Selective Inner Hair Cell Loss on Suprathreshold Auditory Brainstem Response Amplitudes

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INTRODUCTION

Pure tone audiometry is the most common and universally accepted metric for hearing health. However, compelling evidence from animal models demonstrates that significant cochlear damage, such as the loss of inner hair cells (IHC) or deafferentation of IHC afferent nerve fibers, referred to as synaptopathic loss, can go undetected by pure tone threshold measures if outer hair cells (OHC) have minimal damage. Such lesions can occur as a result of aging, noise exposure, or ototoxicity. IHC pathology has been speculated to contribute to functional auditory deficits such as poorer hearing in noise. However, functional, suprathreshold outcomes are often not well correlated with hearing sensitivity, as even hearing-impaired individuals with similar audiograms can vary substantially in speech-in-noise performance, even in the absence of retrocochlear pathology. These findings indicate a need for additional diagnostic tools that are sensitive to various auditory lesions.

Thus far, pre-clinical physiological studies measuring auditory brainstem response (ABR) outcomes after IHC pathology have shown little to no change in thresholds whereas the ABR wave-I amplitudes are typically reduced at suprathreshold levels and has been established as the hallmark of afferent synapse loss. However, the relationship among IHC lesions and other suprathreshold metrics of the ABR are relatively limited.

For the current investigation we sought to evaluate the relationship among suprathreshold ABR wave-I and wave-IV amplitudes in chinchillas before and after administration of carboplatin, an ototoxic drug that reliably and selectively destroys IHCs in this species.

METHODS

SUBJECTS: Young adult (2-3 years-of-age) chinchillas (n=5) were tested at baseline and re-assessed after carboplatin treatment.

DPOAE & ABR THRESHOLD TESTING: Distortion product otoacoustic emissions (DPOAE) and ABR thresholds were used to assess the status of cochlear nonlinearity and as an objective measure of overall hearing sensitivity.

ABR SUPRATHREHSOLD TESTING: ABR testing was performed at 1, 2, 4, 8, 12, and 16 kHz. Tone burst stimuli (5 ms duration, 21.1/sec, 800 presentations) were initially presented at suprathreshold levels (90, 80, and 70 dB SPL) stimuli were then attenuated in 5 dB steps to approximately 10 dB below threshold.

CARBOPLATIN TREATMENT: Following baseline DPOAE, ABR threshold and ABR suprathreshold measures, animals were treated with 75 mg/kg (by body weight) of the anticancer drug carboplatin. This dose has been shown to reliably produce 50-80% IHC loss with little to no OHC loss. Post-carboplatin assessments were then repeated after a 21-day recovery period.

RESULTS

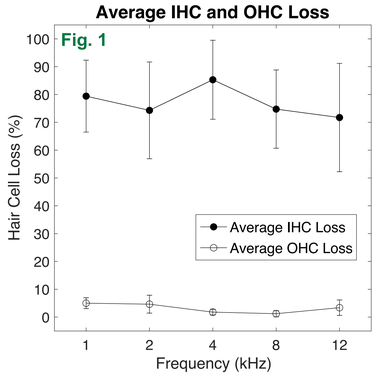


Figure 1: Representative hair cell counts from a previous group (n=5; tissue harvest was performed 2-6 months following carboplatin treatment). Average sensory cell loss (reported as % loss) is shown for IHC and OHC as a function of their location along the basilar membrane from apex to base (% distance from apex) and mapped to represent experimental frequency regions (1/3 octave bands centered at frequencies of interest: 1, 2, 4, 8, 12, and 16 kHz). **Average IHC loss was 56-85% and average OHC loss was 1-17%.** Error bars represent standard deviation.
***For normative reference: the field of view (FOV; diameter = 355 µm) from a region of interest in a normal ear (non-treated control) contains an average of 130 OHCs and 36 IHCs.*

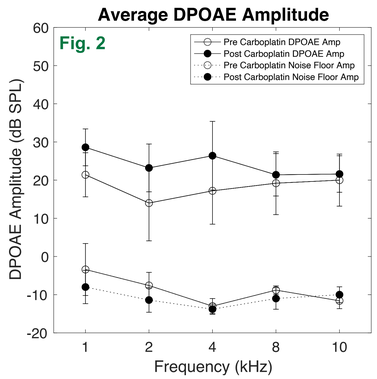


Figure 2: Average (n=5) DPOAE amplitudes obtained at baseline and after carboplatin treatment are shown as a function of test frequency (1, 2, 4, 8, and 10 kHz). **No significant changes were observed following treatment.** Error bars represent standard deviation.

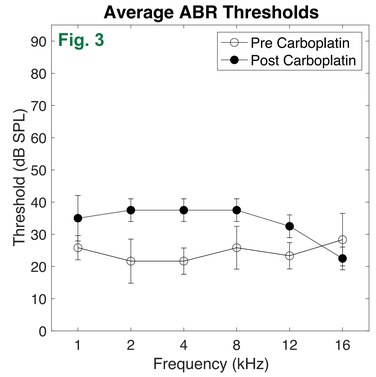
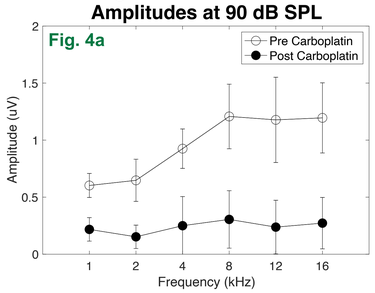
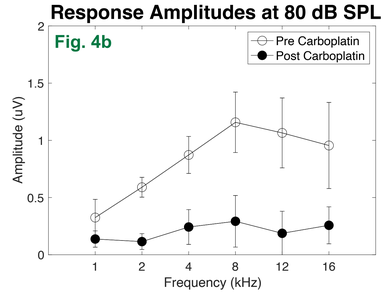


Figure 3: Average (n=4) ABR thresholds obtained at baseline and after carboplatin treatment are shown as a function of test frequency (1, 2, 4, 8, 12, and 16 kHz). **Modest threshold elevations were noted despite substantial IHC loss. Average threshold changes ranged from 10-15 dB SPL across test frequencies.** Error bars represent standard deviation.

RESULTS: SUPRATHRESHOLD ABR TESTING





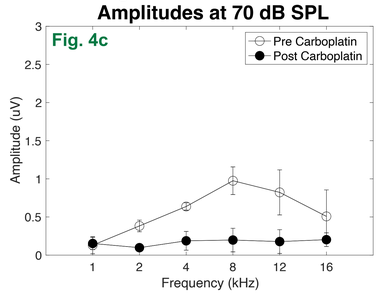
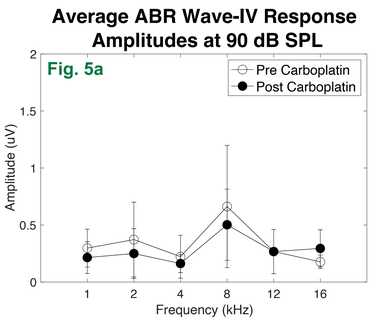
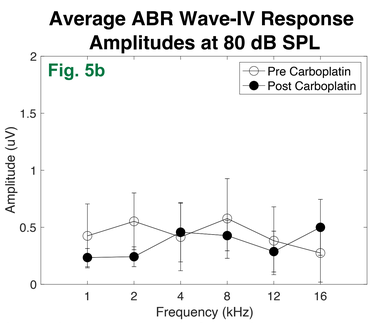


Figure 4: Average (n=4) ABR wave-I amplitudes obtained at baseline and after carboplatin treatment were measured at suprathreshold levels (**4a**) 90 dB SPL (**4b**) 80 dB SPL and (**4c**) 70 dB SPL. Response amplitudes are shown as a function of test frequency (1, 2, 4, 8, 12, and 16 kHz). **Suprathreshold wave-I amplitudes were significantly reduced despite near-normal thresholds and normal cochlear non-linearity.** Error bars represent standard deviation.





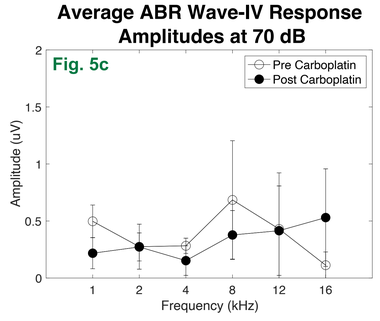


Figure 5: Average (n=4) ABR wave-IV amplitudes obtained at baseline and after carboplatin treatment were measured at suprathreshold levels (**5a**) 90 dB SPL (**5b**) 80 dB SPL and (**5c**) 70 dB SPL. Response amplitudes are shown as a function of test frequency (1, 2, 4, 8, 12, and 16 kHz). **Suprathreshold wave-IV amplitudes remained unchanged.** Error bars represent standard deviation.

SUMMARY & CONCLUSIONS

- Carboplatin treatment had no significant effect on DPOAEs, suggesting survival and function of OHCs.
- Average ABR threshold changes were statistically significant. However, these differences lacked clinical significance as average threshold changes were within 10-15 dB SPL. Clinically, ABR threshold shifts of 10 dB are considered within test-retest reliability.
- Average suprathreshold ABR wave-I amplitudes were reduced significantly at 90 ($p < .001$), 80 ($p < .001$), and 70 dB SPL ($p = .003$) following carboplatin treatment. These changes suggest a reduction in cochlear output despite near-normal thresholds and normal cochlear non-linearity.
- Average suprathreshold ABR wave-IV amplitudes remained unchanged at 90 ($p = .585$), 80 ($p = .237$), and 70 dB SPL ($p = .359$) following carboplatin treatment. The lack of amplitude reductions could indicate central gain compensation for decreased peripheral sensory input following selective IHC loss.
- Findings suggest that wave-I of the ABR could be used to detect IHC loss and nerve fiber deafferentation. Suprathreshold ABR changes may be utilized clinically to better classify patient hearing loss.
- The overall study highlights the importance of suprathreshold testing in assessing cochlear status as they are believed to provide a more sensitive or earlier indication of cochlear damage.
- Future research will continue to explore the effects of IHC loss on assessments with the long-term goal of identifying auditory assessments that provide sensitive differential diagnosis and an early detection of cochlear damage, including subclinical auditory pathologies.

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