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Auditory brainstem responses predict auditory nerve fiber thresholds and frequency selectivity in hearing impaired chinchillas

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Abstract

Non-invasive auditory brainstem responses (ABRs) are commonly used to assess cochlear pathology in both clinical and research environments. In the current study, we evaluated the relationship between ABR characteristics and more direct measures of cochlear function. We recorded ABRs and auditory nerve (AN) single-unit responses in seven chinchillas with noise induced hearing loss. ABRs were recorded for 1–8 kHz tone burst stimuli both before and several weeks after four hours of exposure to a 115 dB SPL, 50 Hz band of noise with a center frequency of 2 kHz. Shifts in ABR characteristics (threshold, wave I amplitude, and wave I latency) following hearing loss were compared to AN-fiber tuning curve properties (threshold and frequency selectivity) in the same animals. As expected, noise exposure generally resulted in an increase in ABR threshold and decrease in wave I amplitude at equal SPL. Wave I amplitude at equal sensation level (SL), however, was similar before and after noise exposure. In addition, noise exposure resulted in decreases in ABR wave I latency at equal SL and, to a lesser extent, at equal SPL. The shifts in ABR characteristics were significantly related to AN-fiber tuning curve properties in the same animal at the same frequency. Larger shifts in ABR thresholds and ABR wave I amplitude at equal SPL were associated with greater AN threshold elevation. Larger reductions in ABR wave I latency at equal SL, on the other hand, were associated with greater loss of AN frequency selectivity. This result is consistent with linear systems theory, which predicts shorter time delays for broader peripheral frequency tuning. Taken together with other studies, our results affirm that ABR thresholds and wave I amplitude provide useful estimates of cochlear sensitivity. Furthermore, comparisons of ABR wave I latency to normative data at the same SL may prove useful for detecting and characterizing loss of cochlear frequency selectivity.

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Keywords

Auditory brainstem response (ABR); auditory nerve; auditory threshold; frequency selectivity; hearing loss

1. Introduction

Sensorineural hearing loss can involve a variety of pathological changes within the cochlea including loss of inner hair cells, outer hair cells, and afferent auditory nerve (AN) fibers. Depending on their relative contributions, these changes degrade cochlear function in fundamentally different ways. Damage to inner hair cells, for example, primarily results in an increase in AN thresholds (Liberman and Dodds, 1984; Wang et al., 1997); higher sound pressure levels are necessary to stimulate neural activity above the spontaneous rate. Damage to outer hair cells, on the other hand, results in both an increase in AN thresholds and decrease in cochlear frequency selectivity (Dallos and Harris, 1978). That is, each AN fiber responds to a broadened range of acoustic frequencies.

Auditory brainstem responses (ABRs) are commonly used to assess hearing loss in both clinical and research settings because they can provide a rapid assessment of physical damage within the cochlea. ABRs are gross potentials recorded noninvasively from the scalp that reflect synchronous neural activity within the AN, brainstem, and midbrain (Fig. 1). The first wave of the ABR is generated by the AN (Buchwald and Huang, 1975). Laboratory animal studies show that increases in ABR threshold following noise induced permanent hearing loss correlate with damage to inner hair cells and loss of AN fibers (Nordmann et al., 2000; Harding et al., 2002). Furthermore, decreases in suprathreshold ABR wave I amplitude have recently been shown to reflect the progressive loss of AN fibers following noise induced temporary threshold shifts (Kujawa and Liberman, 2009).

Relatively few studies, however, have investigated the relationship between ABRs and more direct measures of cochlear function. Ngan and May (2001) studied the relationship between ABR thresholds and AN single-unit thresholds in cats following noise induced hearing loss. ABR thresholds were linearly correlated with the thresholds of AN fibers with characteristic frequencies near the ABR stimulus frequency. In normal hearing animals with AN thresholds near 0 dB SPL, ABR thresholds were approximately 25 dB SPL. In animals with severe hearing impairment, however, AN thresholds and ABR thresholds were similar (e.g., 70–80 dB SPL in both cases). This pattern suggests that ABR threshold shifts following hearing loss may underestimate the threshold shifts of AN fibers with severe impairment.

Several lines of evidence suggest that ABR latency should provide an index of cochlear frequency selectivity. Based on linear systems theory, a decrease in cochlear frequency selectivity is predicted to result in a decrease in cochlear response time (Ruggero, 1994; de Boer, 1996), and consequently, ABR latency. Consistent with this hypothesis, Strelcyk et al. (2009) found a significant positive correlation between frequency selectivity at 2 kHz, measured behaviorally, and wave V latency of derived band ABRs in normal and hearing impaired human subjects (the difference in wave V latency was taken as an index of the difference in cochlear response time). In other studies, however, hearing impairment was found to increase ABR latency (waves I, III, and V in humans [Attias and Pratt, 1984]; waves I and IV in guinea pigs [Cook et al., 1982; Gourevitch et al., 2009]). Note, however, that the loss of frequency selectivity was not quantified. Currently, no study has investigated the relationship between ABR latency and a direct, physiological measure of cochlear frequency selectivity.

In the current study, we evaluated the extent to which ABR thresholds, wave I amplitude, and wave I latency predict changes in cochlear function following noise induced hearing loss. ABRs were recorded in response to tone burst stimuli in chinchillas both before and several weeks after four hours of exposure to a 115 dB SPL narrowband noise stimulus with a center frequency of 2 kHz. Changes in cochlear function were measured from isolated AN fibers in the same animals at approximately the same frequencies used in the ABR experiments. We expected shifts in wave I amplitude at constant SPL and shifts in ABR threshold following hearing loss to reflect changes in AN thresholds. Shifts in wave I latency, on the other hand, were expected to reflect changes in AN frequency selectivity in a manner consistent with linear systems theory. Specifically, we anticipated greater decreases in wave I latency at constant sensation level (SL) with greater increases in AN tuning curve bandwidth.

2. Methods

Auditory data were collected from seven adult male chinchillas weighing between 400 and 650 g. The effects of noise induced hearing loss on envelope coding of AN fibers and the temporal dynamics of AN onset responses in the same animals have been reported previously (Kale and Heinz, 2010; Scheidt et al., 2010). All procedures were approved by the Purdue Animal Care and Use Committee.

2.1. Noise exposure

We induced hearing loss by exposing animals to a 115 dB SPL narrowband noise stimulus with a center frequency of 2 kHz and bandwidth of 50 Hz for 4 hours. Animals were first anesthetized and placed in a stereotaxic device located in an electrically shielded, double walled sound attenuating chamber (Industrial Acoustics Company, Bronx, NY, USA). Anesthesia was induced with xylazine (1–1.5 mg/kg IM) followed by ketamine (50–65 mg/kg IM). Atropine (0.1 mg/kg IM) was also given to control mucous secretions, and eye ointment applied. The noise stimulus was presented through a pair of dynamic loudspeakers (Fostex model FT28D) suspended 25 cm above the animal's head, and calibrated at the ear opening with a type 2 sound level meter (Simpson model 886-2, Elgin, IL, USA). Anesthesia was maintained with supplemental injections of ketamine (20–30 mg/kg IM). Body temperature was maintained at 37 degrees C using a feedback controlled heating pad (Physitemp model TCAT2-LV, Clifton, NJ).

The effects of ketamine and xylazine on the degree and configuration of hearing loss induced by noise are unclear. Previous studies show that ketamine depresses the middle ear reflex in squirrel monkeys (Thomson et al., 1984), which could increase the degree of hearing loss in the low to mid frequency range (e.g., ≤ 4 kHz; Borg et al., 1983). In contrast, isoflurane, halothane, and pentobarbital in mice appear to protect the cochlea to some extent from noise induced damage (Chung et al., 2007). Regardless of the effect of anesthesia on noise injury, it is not expected to affect correlations between ABR and AN data.

2.2. ABR methods

We recorded ABRs to tone burst stimuli both immediately before and several weeks after noise exposure (median: 45 days; range: 24–67 days). Animals were anesthetized with xylazine (1–1.5 mg/kg IM) followed by ketamine (50–65 mg/kg IM) in most cases and placed in a stereotaxic device. In other cases, a mixture of acepromazine (0.5–0.6 mg/kg IM) and ketamine was used (45–60 mg/kg IM) to induce anesthesia. An ear plug was placed in the left ear canal. ABR stimulus frequencies of 1, 2, 4, and 8 kHz were tested in random order. At each frequency, we tested 5–7 stimulus intensity levels in decreasing order from approximately 75 dB SPL to 5 dB below the visual ABR threshold. Stimulus level was

calibrated at the ear opening using a probe tube microphone (Etymotic model ER-7C, Elk Grove Village, IL, USA).

Stimuli were 5 ms duration tone bursts with 0.5 ms linear onset and offset ramps. They were presented 10 per second with alternating polarity through dynamic loudspeakers (Fostex model FT28D) suspended 25 cm above the animal's head. Responses to individual stimuli were conducted from the scalp using needle electrodes inserted subdermally at the dorsal midline between the eyes (non inverting), posterior to the right pinna (inverting), and bridge of the nose (common ground). Individual responses were amplified 20,000 times (World Precision Instruments model ISO-80, Sarasota, FL, USA; Dagan model 2400A, Minneapolis, MN, USA), band pass filtered from 0.3 to 3 kHz (Krohn-Hite model 3550 filter, Brockton, MA, USA), and digitally sampled at a rate of 12.207 kHz (TDT model RP2.1 signal processor, Alachua, FL, USA). Each ABR waveform saved for analysis was the average of 600 individual responses to stimuli of the same frequency and intensity.

We estimated the ABR threshold of each animal at each frequency using a cross correlation method (Henry and Lucas, 2010). In short, two ABRs to high intensity stimuli were time aligned, averaged together, and cropped to form an 8 ms template containing all of the major ABR waves. The template was cross correlated with (1) the ABR at each intensity level and (2) averaged physiological background noise (0.806 seconds concatenated from the seven subjects) to determine a Z score for each ABR waveform. The ABR Z score was calculated as the absolute maximum of the first cross correlation function (template vs. recorded ABR) divided by the standard deviation of the second (template vs. physiological background noise). Next, a weighted regression was performed with stimulus SPL and ABR Z score as independent and dependent variables, respectively, to determine the ABR threshold. The ABR threshold was calculated as the predicted SPL necessary to evoke a Z score of 3. Weighting was assigned based on Z score. Z scores less than 3 were assigned a weight of 0. For higher Z scores, weighting decreased linearly from 1 for a Z score of 3 to 0.1 for the maximum Z score in the dataset. This weighting ensured that ABR thresholds were determined primarily by near threshold responses.

We measured the amplitude and latency of ABR wave I when it was clearly visible in the waveform (Fig. 1). Wave I amplitude was measured as the voltage difference between the first peak of the ABR and the subsequent trough. Latency was measured as the time elapsed between stimulus onset and the peak of wave I.

In each animal at each stimulus frequency, we calculated shifts following noise induced hearing loss in ABR threshold, wave I amplitude, wave I latency, wave I amplitude by intensity slope, and wave I latency by intensity slope. Shifts in slope were calculated by fitting simple linear regression models to amplitude (or latency) by intensity functions taken before and after hearing loss and measuring the difference in slope. Shifts in ABR wave I amplitude and latency were calculated using multiple regression analyses at both equal SPL and equal SL (MIXED procedure; SAS 9.2, Cary, NC, USA). To calculate the amplitude shift at equal SPL (or SL), for example, a multiple regression was performed with amplitude as a dependent variable, SPL (or SL) as a continuous independent variable, and condition (pre or post noise exposure) as a categorical independent variable. The effect of condition, which reflects the average vertical distance between amplitude by SPL (or SL) functions, was taken as the estimate of the amplitude shift. This method provided reasonable estimates of ABR shifts because both amplitude by intensity and latency by intensity functions were approximately linear and parallel before and after noise exposure.

2.3. Single-unit AN responses

We recorded single-unit AN responses shortly after the post exposure ABR session for six of seven animals (median: 3 days; range: 1–20 days). In a single animal, however, 169 days elapsed. The procedure used to access the AN and record single-unit activity has been described previously (Scheidt et al., 2010; Kale and Heinz, 2010). In short, animals were anesthetized with xylazine (1–1.5 mg/kg IM) followed by ketamine (50–65 mg/kg IM) and placed in a stereotaxic device. Subsequently, anesthesia was maintained with sodium pentobarbital (~7.5 mg/kg/h IV). Physiological saline (2–5 ml/h IV) and lactated ringers (20–30 ml/24 h SQ) were also given, and a tracheotomy performed to facilitate breathing. Body temperature was maintained at 37 degrees C using a feedback controlled heating pad (Physitemp model TCAT2-LV). The skin and muscles overlying the skull were transected to expose the ear canals and bullae. The ear canals were dissected and hollow ear bars inserted. The right bulla was vented through 30 cm of polyethylene tubing. A craniotomy was opened in the posterior fossa, and the cerebellum partially aspirated and retracted medially to expose the cochlear nucleus and medial trunk of the AN.

Acoustic stimuli were presented through a dynamic loudspeaker (Beyerdynamic model DT-48, Farmingdale, NY, USA) sealed to the right ear bar, and calibrated using a probe tube microphone (Etymotic model ER-7C) placed within a few mm of the tympanic membrane. Single-unit activity was recorded using a 10–30 M Ω glass microelectrode advanced into the AN by a hydraulic micro drive (Kopf model 640, Tujunga, CA, USA). The electrode signal was amplified (Dagan model 2400A) and band pass filtered from 0.02 to 6 kHz (Krohn-Hite model 3550). Action potentials were identified using a time amplitude window discriminator (Bak Electronics, Mount Airy, MD, USA), and their timing recorded with 10 μ s resolution.

Single fibers were isolated by listening for action potentials while advancing the electrode through the medial trunk of the AN and playing a broadband noise search stimulus. For each fiber encountered, characteristic frequency (CF), threshold at CF, and Q_{10} values (CF/tuning curve bandwidth 10 dB above threshold) were determined using an automated tuning curve algorithm that tracked the minimum sound level required for a 50 ms tone to evoke at least one more action potential than a subsequent 50 ms silent period (Chintanpalli and Heinz, 2007). Figure 2 shows the thresholds and Q_{10} values of 233 AN fibers from 11 noise-exposed animals including the 7 animals in the present study and 253 fibers from 9 unexposed control animals (adapted from Kale and Heinz, 2010; see also Scheidt et al., 2010). For impaired fibers with broad frequency tuning, CF was chosen based on the steep high frequency slope of the tuning curve because this provides a good estimate of pre-exposure CF (Liberman, 1984). Some impaired fibers had W-shaped tuning curves with both a sharp tip and low frequency tail region sensitive to a broad range of frequencies. For these fibers, Q_{10} was calculated based on the bandwidth across the entire W shape (as in Kale and Heinz, 2010; see also Scheidt et al., 2010). We calculated a normalized metric of frequency selectivity for each fiber as the base 10 logarithm of the ratio of the observed Q_{10} to the median Q_{10} of unimpaired fibers at the same CF. This normalization method was selected because $\log_{10}(Q_{10})$ values are normally distributed at any given CF and vary linearly with $\log_{10}(\text{CF})$ in normal hearing chinchillas (Kale and Heinz 2010). Values less than zero indicate tuning broader than the normal hearing median.

2.4. Statistical Analysis

We analyzed (1) the effects of noise exposure on ABR characteristics and (2) associations between ABR shifts and AN-fiber tuning curve properties using repeated measures mixed models (MIXED Procedure; SAS). Statistical inferences drawn from these models make a correction for the non-independence of data collected from the same experimental subject (Littell et al., 2006). To test for noise effects, the independent variable was frequency and

the dependent variable was the ABR shift (ABR threshold, wave I amplitude, wave I latency, wave I amplitude by intensity slope, or wave I latency by intensity slope). We modeled repeated measures within subjects using heterogeneous compound symmetry covariance structure. This structure was selected over homogenous compound symmetry and general (unstructured) covariance based on a lower Bayesian information criterion, suggesting greater parsimony (Littell et al., 2006). To test associations between ABR shifts and AN tuning curve properties (threshold or Q_{10}), the independent variable was the ABR shift and the dependent variable was the AN property. Only fibers with CFs within a quarter octave of the ABR stimulus frequency were included in the analysis. We modeled repeated measures within subjects using a covariance structure specified by random effects of subject and subject by frequency. This structure, which modeled correlated observations (1) within subjects and (2) within subjects at the same frequency, resulted in a lower Bayesian information criterion than alternative structures. Inferences were drawn based on F tests and T tests with degrees of freedom calculated based on the Kenward-Rogers algorithm, as suggested for repeated measures designs with small sample size (Littell et al., 2006).

3. Results

3.1. Effects of noise exposure on ABR characteristics

Figure 3A shows the ABR thresholds of seven chinchillas as a function of frequency before and after noise exposure. As expected, ABR thresholds generally increased following noise exposure. ABR threshold shifts, measured for each animal at each frequency (Fig 3B), were significantly greater than zero at 1 kHz ($t_{6,1}=8.31$, $P<0.001$), 2 kHz ($t_{6,1}=11.54$, $P<0.001$), and 4 kHz ($t_{6,1}=4.34$, $P=0.005$), but not 8 kHz ($t_{4,4}=1.95$, $P=0.12$). Furthermore, threshold shifts were greater at 2 kHz than at 1 kHz ($t_{8,9}=3.91$, $P=0.004$), and similar between other frequency combinations ($P>0.05$). Finally, ABR threshold shifts were more variable across animals at 4 kHz and 8 kHz than at lower stimulus frequencies.

Figure 4 shows ABR wave I amplitude as a function of SPL at each stimulus frequency before and after noise exposure. Noise exposure generally resulted in a decrease in ABR amplitude, but no change in the slope of amplitude by intensity level functions (i.e., changes in slope were not significant at 1 kHz [$t_{6,1}=-0.74$, $P=0.49$], 2 kHz [$t_{6,1}=1.44$, $P=0.20$], 4 kHz [$t_{6,1}=-1.12$, $P=0.30$], or 8 kHz [$t_{5,8}=-0.67$, $P=0.53$]). We measured ABR amplitude shifts following noise exposure for each animal at both equal SPL (Fig. 5) and equal SL (data not shown). ABR amplitude shifts at equal SPL were negative (predicted mean $\pm$ standard error= -0.313 ± 0.130 μ V; $t_{7,3}=-2.41$, $P=0.047$) and broadly similar across stimulus frequencies (frequency effect: $F_{3,9}=0.99$, $P=0.44$). Furthermore, amplitude shifts were more variable at 4 and 8 kHz than at lower frequencies. ABR amplitude shifts at equal SL were not significant (predicted mean $\pm$ standard error= -0.108 ± 0.130 μ V; $t_{7,3}=-1.09$, $P=0.31$).

Figures 6 and 7 show ABR wave I latency as a function of SPL and SL, respectively, at each stimulus frequency before and after noise exposure. In general, noise exposure resulted in a decrease in ABR latency, but no change in the slope of latency by intensity level functions (i.e., changes in slope were not significant at 1 kHz [$t_{4,8}=-1.04$, $P=0.35$], 2 kHz [$t_{6,4}=-2.10$, $P=0.08$], 4 kHz [$t_{5,9}=-0.31$, $P=0.77$], or 8 kHz [$t_{5,5}=-1.08$, $P=0.33$]). We measured ABR latency shifts following noise exposure for each animal at each frequency at both equal SPL (Fig. 8A) and equal SL (Fig. 8B). ABR latency shifts at equal SPL were negative (predicted mean $\pm$ standard error= -0.140 ± 0.043 ms; $t_{7,3}=-3.30$, $P=0.015$) and broadly similar across stimulus frequencies (frequency effect: $F_{3,9,1}=2.40$, $P=0.13$). Latency shifts at equal SL, on the other hand, were greater in magnitude (i.e., more negative) and varied across stimulus frequencies (frequency effect: $F_{3,8,4}=10.2$, $P=0.004$). Specifically, the latency shift at 2 kHz was more negative than shifts observed at 1 kHz ($t_{6,5}=-4.32$, $P=0.004$), 4 kHz ($t_{8,5}=-2.46$, $P=0.037$), and 8 kHz ($t_{5,4}=-4.27$, $P=0.007$).

3.2. Associations between ABR shifts and AN fiber characteristics

Figure 9A shows the threshold elevation of 50 AN fibers as a function of the ABR threshold shift for the same animal in the same frequency band. Points falling above the gray box represent fibers with thresholds exceeding the 95th percentile of a large normal hearing population (from Kale and Heinz, 2010). Larger shifts in ABR threshold following noise exposure were associated with greater AN threshold elevation above the normal reference range ($F_{1,13,1}=7.93$, $P=0.015$). For example, an ABR threshold shift of 10 dB was associated with a 27 dB AN threshold elevation, and an ABR threshold shift of 30 dB was associated with a 40.5 dB AN threshold elevation.

Figure 9B shows AN threshold elevation as a function of the ABR wave I amplitude shift for the same animal in the same frequency band. The reference range of AN thresholds in normal hearing chinchillas is also shown. Greater reductions in ABR amplitude following noise exposure were associated with greater elevation of AN thresholds above the normal reference range ($F_{1,15,7}=5.37$, $P=0.034$).

Figures 10A and 10B show normalized AN frequency selectivity as a function of the ABR wave I latency shift for the same animal in the same frequency band. Points falling below the gray box represent fibers with frequency selectivity values below the 5th percentile of the normal hearing population (i.e., fibers with abnormally broadened tuning; see Fig. 2B). Latency shifts are shown at equal SPL (Fig. 10A) and equal SL (Fig. 10B). Shifts in ABR latency at equal SPL were unassociated with AN frequency selectivity ($F_{1,15,7}=0.88$, $P=0.36$). At equal SL, in contrast, greater reductions in ABR latency were associated with greater reduction of AN frequency selectivity below the median value of normal hearing animals ($F_{1,16,6}=6.29$, $P=0.023$). For example, an ABR latency shift of -0.5 ms was associated with a decrease in AN frequency selectivity of 0.4 normalized units, which corresponds to a 2.5-fold increase in tuning curve bandwidth. The examination of wave I latency shifts at equal SL (as opposed to SPL) was intended to control for the effect of AN threshold elevation on the wave I latency shift and therefore isolate the effect of AN frequency selectivity. Consistent with this reasoning, shifts in wave I latency at equal SL were unassociated with AN thresholds ($F_{1,12,6}=1.37$, $P=0.26$).

4. Discussion

4.1. Effects of noise exposure on ABR characteristics

Noise exposure in chinchillas resulted in shifts in all ABR characteristics. We observed a significant increase in ABR thresholds following noise exposure. Furthermore, ABR wave I latency decreased at equal SL and, to a lesser extent, at equal SPL. Finally, ABR wave I amplitude decreased at equal SPL.

Shifts in ABR threshold and wave I latency following noise exposure were greatest at 2 and 4 kHz. This result is consistent with other studies of noise induced hearing loss, which generally find extensive physical damage at the cochlear region tuned to the noise stimulus (2 kHz in our study) and spreading preferentially towards the base (Cody and Johnstone, 1981). Furthermore, we found extensive variability in ABR shifts across animals (e.g., Fig. 3B). This result mirrors previous findings of individual differences in susceptibility to acoustic trauma (“tough” and “tender” ears; Cody and Robertson, 1983; Maison and Liberman 2000; Nordmann et al., 2000; Harding et al., 2002).

The decrease in ABR latency observed following noise exposure at equal SL is consistent with several studies of humans finding abnormally short wave V derived band ABR latency in hearing impaired listeners (Don et al., 1998; Strelcyk et al., 2009). Differences in wave V latency were interpreted as differences in cochlear response latency in these studies based on

similar wave I-V inter-peak delays in the hearing impaired and control groups (e.g., Strelcyk et al., 2009). Furthermore, our result agrees with reports of drug and noise induced hearing loss in model species documenting shorter response latency of isolated AN fibers and compound action potentials following impairment (Wang and Dallos, 1972; Salvi et al., 1979; Scheidt et al., 2010). These findings are consistent with linear systems theory, which predicts a decrease in cochlear response latency following a reduction in frequency selectivity due to the shorter build up time of broader filters (Goldstein et al., 1971; Ruggero 1994). It is important to note that these studies and the present study quantified shifts in response latency following hearing loss at constant stimulus SL (i.e., stimulus SPL was increased following hearing loss to maintain a fixed dB level above threshold). In other studies comparing response latency at the same stimulus SPL (e.g., Attias and Pratt, 1984; Noursak and Stapells, 2005; Gourevitch et al., 2009), the SL or supra-threshold level of the stimulus was lower following hearing loss due to threshold elevation. Lower stimulus SL is known to prolong response latency, and probably explains why these studies observed increases in response latency.

The decrease in ABR latency at equal SL could also reflect the disruption of tonotopicity within the cochlea commonly associated with hearing loss. Following acoustic trauma, the frequency tuning curves of AN fibers often develop hyper-sensitive tail regions; that is, they become relatively more sensitive to frequencies below CF, and in many cases exhibit a negative shift in the frequency of maximum sensitivity (Liberman, 1984). This change, in turn, could produce a shift towards the base in the cochlear region responding to a pure tone stimulus, and therefore, due to the shorter path of the traveling wave, a decrease in cochlear response time and ABR latency. Presently, the relative contributions of changes in tonotopicity and broadened auditory filter bandwidth to shifts in ABR latency are unclear.

At some stimulus frequencies, we observed slight decreases in ABR latency following hearing loss at constant stimulus SPL, whereas previous studies generally found positive shifts in latency (e.g., Gourevitch et al., 2009). This discrepancy may reflect a difference in the degree of threshold elevation. The positive shifts noted in previous studies are due at least in part to the lower stimulus SL following hearing loss, which prolongs ABR latency as discussed above (and may negate any reduction in latency associated with reduced frequency selectivity). In the present study, mean ABR threshold shifts were smaller (e.g., 10–20 dB vs. 10–50 dB in Gourevitch et al., 2009). Consequently, the difference in stimulus SL between hearing impaired and control groups was smaller in the present study, and thus less prolongation of ABR latency would be expected. Alternatively, the discrepancy could reflect a difference in the survival of basal AN fibers following hearing loss. In the present study, basal fibers with short response latencies experienced relatively minor threshold shifts, and hence, could contribute to the ABR after hearing loss (see Fig. 2A). In Gourevitch et al. (2009) in contrast, the thresholds of surviving basal fibers were more elevated based on ABR thresholds, and hence, basal fibers were probably less able to contribute to the ABR.

We did not detect a change in the slope of wave I latency by intensity functions. In guinea pigs, however, steeper slopes occur following noise induced hearing loss (Gourevitch et al., 2009). In humans, moreover, patients with high frequency hearing loss tend to have steeper slopes than normal listeners while patients with flat loss may have shallower slopes, though variability across listeners is considerable (based on wave V latency; Gorga et al., 1985). Note that in our study, ABRs were recorded over a relatively narrow range of stimulus intensity (~30 dB after impairment). Hence, our ability to detect changes in slopes, if they occurred in our study, was limited.

ABR wave I amplitude at equal SL was unaffected by noise exposure in our study. A study of noise exposure in mice, however, found a permanent reduction due to the loss of fibers from the AN (Kujawa and Liberman, 2009). Following exposure to a 100 dB SPL 8–16 kHz octave band noise, the ABR thresholds of mice recovered while wave I amplitude at equal SL decreased by 20% at 12 kHz and 60% at 32 kHz. In our study, it is possible that shifts in amplitude were not detected because they occurred above the maximum frequency (8 kHz) or SL at which ABRs were recorded. We generally did not record ABRs at SLs above 30 dB, particularly after hearing impairment, whereas shifts in wave I amplitude in mice are most striking at SLs from 30–70 dB (see Fig. 3 of Kujawa and Liberman, 2009).

4.2. Associations between ABR shifts and AN fiber characteristics

The shifts in ABR characteristics following hearing loss described above were significantly correlated with the characteristics of AN fibers in the same animal at approximately the same frequency. Both (1) larger increases in ABR threshold and (2) larger decreases in wave I amplitude were associated with higher AN threshold elevation. Larger decreases in wave I latency at equal SL, furthermore, were associated with greater reductions in AN frequency selectivity.

The positive correlation between ABR thresholds and AN thresholds in chinchillas agrees with a previous study of normal and hearing impaired cats (Ngan and May, 2001). In both studies, ABR thresholds were found to underestimate threshold shifts of AN fibers. In our study, a shift in ABR thresholds of 30 dB following noise exposure was associated with an AN threshold elevation of 40.5 dB above the median of normal hearing animals. Similarly in cats, an ABR threshold shift of 30 dB above normal was associated with an AN threshold elevation of 47 dB above normal (Ngan and May, 2001). As a consequence, ABR threshold shifts may be relatively insensitive to small increases in AN threshold (e.g., less than approximately 5–10 dB). Indeed, a previous study of chinchillas found no shift in the ABR thresholds of noise exposed animals with moderate outer hair cell loss, and presumably elevated AN thresholds (Nordmann et al., 2000). A variety of factors associated with reduced AN frequency selectivity may contribute to the tendency for ABR threshold shifts to underestimate AN threshold shifts. Specifically, reduced frequency selectivity is known to result in greater recruitment of “off frequency” fibers in response to tonal stimuli (Heinz et al., 2005), greater synchrony of neural responses across fibers (Heinz et al., 2010), and greater onset firing rate of individual fibers (Scheidt et al., 2010; Crumling and Saunders, 2007). These changes, in turn, are all expected to increase the ABR signal relative to physiological background noise and therefore decrease the ABR detection threshold. In addition, the tendency for ABR threshold shifts to underestimate AN threshold elevation following hearing loss could reflect compression of the range of thresholds across AN fibers of the same CF (Ngan and May, 2001). Compression of thresholds should result in a greater proportion of fibers that respond to stimulus levels near the lower limit of thresholds in the population, and therefore, a stronger ABR signal to noise ratio and lower threshold. However, studies of noise induced hearing loss in cats and chinchillas have not generally found compression of AN thresholds (Heinz et al., 2005; Kale and Heinz, 2010; see also Fig. 2A).

Though ABR threshold shifts can apparently detect moderate to severe AN threshold elevation following hearing loss, other studies indicate that ABRs are insensitive to the presence of discrete “dead” regions, or focal hair cell lesions, occurring within the cochlea. Consequently, they may miss changes in threshold restricted to a small population of AN fibers. Stimuli falling within a dead region may still evoke robust ABRs (and behavioral responses; see Moore et al., 2000) due to the recruitment of normal, off frequency fibers innervating adjacent cochlear regions. Indeed, in chinchillas exposed to octave band noise,

ABR threshold shifts are not commonly observed in animals with focal outer hair cell lesions (Nordmann et al., 2000; Harding et al., 2002).

We found larger reductions in ABR wave I amplitude at equal SPL in animals with greater AN threshold elevation following hearing loss. To our knowledge, no other study has investigated the relationship between ABR amplitude and AN thresholds. Our finding seems reasonable, however, given that hearing loss results in a lower SL for an equal-SPL ABR stimulus, and therefore a decrease in the recruitment of AN fibers. Recruitment of fewer fibers, in turn, decreases the amplitude of gross potentials such as the ABR. ABR amplitude might be less useful for detecting AN threshold shifts in human listeners, given the lower ABR signal to noise ratio compared to most model species.

Larger negative shifts in ABR latency were observed in animals with lower AN frequency selectivity following hearing loss. This result agrees with the predictions of linear systems theory, which can explain aspects of the relationship between AN fiber tuning curve bandwidth and response latency in normal hearing animals (Goldstein et al., 1971; Ruggero, 1994). For a symmetric band-pass filter with slope S below CF and $-S$ above CF on a logarithmic frequency scale, Goldstein et al. (1971) showed that the group delay of the impulse response, in cycles at CF, is equal to $(4S^2 - 1)(2I(S))/(2\pi)^2$, where $I(S) = (1 + \ln(S)/2)/S$ for values of S greater than 0.5. They demonstrated, furthermore, that group delay varies little between symmetric and asymmetric filters of the same bandwidth (for filters with high frequency slopes up to 4 times the low frequency slope). If values of S are specified that correspond to the mean tuning curve bandwidth of chinchilla AN fibers before and after noise-induced hearing loss, the expected latency shift due to broader filter bandwidth can be calculated. Median Q_{10} following hearing loss in chinchillas decreases from 2.07 to 1.29 at 1 kHz, 2.53 to 1.37 at 2 kHz, 3.91 to 1.72 at 4 kHz, and 4.69 to 2.55 at 8 kHz (see Fig. 2B). The predicted latency shifts due to broader filter bandwidth, in turn, are -0.79 ms at 1 kHz, -0.61 ms at 2 kHz, -0.62 ms at 4 kHz, and -0.32 ms at 8 kHz. These values match the observed latency shifts well except at 1 kHz, where the predicted latency shift is approximately twice the mean observed value (see Fig. 8B). The basis of this discrepancy is unclear.

The observed relationship between ABR latency shifts and AN fiber frequency selectivity is also consistent with several previous studies relating indices of cochlear response time following hearing loss to measures of frequency selectivity. In normal and impaired humans, subjects with broader auditory filter bandwidth at 2 kHz have shorter derived band ABR wave V latency (Strelcyk et al., 2009). Similarly in noise exposed chinchillas, AN fibers with greater normalized tuning curve bandwidth exhibit shorter onset response latency at 30 dB SL (Scheidt et al., 2010). Taken together, these studies suggest that ABR latency might provide a useful, noninvasive index of frequency selectivity. Other factors are known to influence ABR latency, and hence, ABR latency must be measured under carefully controlled conditions. Most importantly, measurements must be made at a constant stimulus SL. When SPL is held constant instead, the SL of the stimulus is lower following hearing loss (or in the hearing impaired group) due to threshold elevation. This prolongs ABR latency, and consequently, may obscure the relationship between latency and frequency selectivity. Furthermore in the case of animal studies, ABRs should be recorded using the same anesthetics and at constant body temperature. Many anesthetics including ketamine and xylazine increase ABR latency (e.g., Church and Gritzke, 1987). Hypothermia is also known to increase ABR latency (Doyle and Fria, 1985). Future studies should investigate the relationship between ABR latency shifts and frequency selectivity in cases of more severe threshold shifts.

The ability to predict the physiological response properties of AN fibers following hearing loss might potentially be improved with the use of other noninvasive measures of cochlear function such as otoacoustic emissions. Previous studies show that distortion product otoacoustic emissions reflect the integrity of outer hair cells following exposure to ototoxic drugs and noise (Trautwein et al., 1996; Hofstetter et al., 1997; Harding et al., 2002), and might therefore correlate with tuning curve bandwidth. Other studies have demonstrated a relationship across CFs between stimulus frequency otoacoustic emission group delay and AN tuning curve bandwidth in normal hearing animals (Shera et al., 2008, 2010). Future studies should quantify the relationships between otoacoustic emissions and AN fiber response characteristics following hearing loss in greater detail.

4.3. Concluding remarks

Previous studies have shown that ABRs are sensitive to patterns of physical damage within the cochlea associated with hearing loss (e.g., Nordmann et al., 2000; Harding et al., 2002). In the present report of chinchillas, we show that ABRs can also predict changes in cochlear function. We found correlations between ABR threshold shifts and AN thresholds, as shown previously in cats (Ngan and May, 2001), and between ABR wave I amplitude shifts and AN thresholds. Furthermore, wave I latency shifts at equal SL were found to predict deficits in AN frequency selectivity. This last result, which agrees with other reports employing different methodologies (Strelcyk et al., 2009; Scheidt et al., 2010), is novel and also noteworthy because it suggests that comparing ABR latency to normative data at the same SL may provide a rapid means of evaluating frequency selectivity in laboratory and clinical environments. Currently available noninvasive methods such as psychophysical tuning curves and auditory filters based on thresholds in notched masking noise are time consuming and require extensive training of subjects.

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Abbreviations

ABR	auditory brainstem response
AN	auditory nerve
CF	characteristic frequency
SL	sensation level

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ABR thresholds increase following noise induced hearing loss in chinchillas

ABR wave I amplitude at equal stimulus SPL decreases, and latency at equal SL decreases

ABR threshold and amplitude shifts correlate with AN-fiber threshold elevation

ABR latency shifts correlate with reductions in AN-fiber frequency selectivity

ABRs can predict changes in cochlear sensitivity and frequency selectivity

Fig. 1. (A) ABRs to a 4 kHz tone burst at various SPLs before noise induced hearing loss and (B) ABRs after hearing loss (middle and lower traces) compared to a pre exposure control (top trace). All ABRs were recorded from the same experimental animal. Comparisons after hearing loss are made at both similar stimulus SPL (~50 dB SPL; middle trace) and similar SL (~30 dB SL; lower trace). The ABR threshold, which we quantified using a cross-correlation algorithm (see text), increased from 18.9 dB SPL before hearing loss to 42.9 dB SPL after hearing loss. “+” symbols indicate ABR wave I. Wave I amplitude was measured relative to the subsequent trough (“-” symbols). Wave I latency was measured relative to stimulus arrival at the ear canal (dotted vertical line).

Fig. 2.

(A) Thresholds and (B) frequency selectivity (Q_{10}) of 253 AN fibers from 9 control animals and 233 fibers from 11 animals with noise-induced hearing loss including the 7 animals in the present study (adapted from Kale and Heinz, 2010; see also Scheidt et al., 2010). Values are plotted as a function of CF. The trend lines in panel A denote the mean thresholds of each population of fibers, calculated using a local regression model with a smoothing parameter of 0.5 (LOES procedure; SAS). The trend line in panel B denotes the median Q_{10} of the unimpaired fiber population (from Kale and Heinz, 2010).

Fig. 3.

(A) ABR thresholds of chinchillas as a function of stimulus frequency before and several weeks after noise exposure. (B) ABR threshold shifts following noise exposure. Thick horizontal bars are least squares means and vertical bars indicate ± 2 standard errors; other symbols in panel B represent individual animals.

Fig. 4. ABR wave I amplitude as a function of stimulus intensity before and after noise exposure. Stimulus frequency is indicated at the top of each panel. Trend lines were calculated using a multiple regression analysis.

Fig. 5. Shifts in ABR wave I amplitude following noise induced hearing loss as a function of stimulus frequency. Thick horizontal bars are least squares means and vertical bars indicate ± 2 standard errors; other symbols represent individual animals.

Fig. 6. ABR wave I latency as a function of stimulus SPL before and after noise exposure. Stimulus frequency is indicated at the top of each panel. Trend lines were calculated using a multiple regression analysis.

Fig. 7.

ABR wave I latency as a function of stimulus SL before and after noise exposure. Stimulus frequency is indicated at the top of each panel. Trend lines were calculated using a multiple regression analysis.

Fig. 8. Shifts in ABR wave I latency following noise exposure as a function of stimulus frequency. Latency shifts are shown at both (A) equal SPL and (B) equal SL. Thick horizontal bars are least squares means and vertical bars indicate ± 2 standard errors; other symbols represent individual animals.

Fig. 9.

AN fiber thresholds following noise induced hearing loss as a function of (A) ABR threshold shifts and (B) ABR wave I amplitude shifts in the same frequency band. Frequency bands are indicated in the legend. AN thresholds are expressed in dB relative to the median threshold of a large population of unimpaired fibers with CFs ranging from 0.84–9.52 kHz (20.1 dB SPL; from Kale and Heinz, 2010; note that the median threshold does not vary appreciably over this CF range; see also Fig. 2A). The lower, middle, and upper dashed horizontal lines indicate the 5th, 50th, and 95th percentiles, respectively, of the unimpaired population. Trend lines indicate predicted mean values of the statistical model.

Fig. 10.

The frequency selectivity of AN fibers following noise induced hearing loss as a function of ABR wave I latency shifts at (A) equal SPL and (B) equal SL in the same frequency band. Frequency bands are indicated in the legend. Frequency selectivity was normalized by taking the base 10 logarithm of the observed Q_{10} value over the median Q_{10} value of unimpaired fibers with the same CF (from Kale and Heinz, 2010; see also Fig. 2B). The lower, middle, and upper dashed horizontal lines indicate the 5th, 50th, and 95th percentiles, respectively, of unimpaired fibers. Trend lines indicate predicted mean values of the statistical model.