

Auditory sensitivity and the outer hair cell system in the CBA mouse model of age-related hearing loss

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Abstract: Age-related hearing loss is a highly prevalent sensory disorder, from both the clinical and animal model perspectives. Understanding of the neurophysiologic, structural, and molecular biologic bases of age-related hearing loss will facilitate development of biomedical therapeutic interventions to prevent, slow, or reverse its progression. Thus, increased understanding of relationships between aging of the cochlear (auditory portion of the inner ear) hair cell system and decline in overall hearing ability is necessary. The goal of the present investigation was to test the hypothesis that there would be correlations between physiologic measures of outer hair cell function (otoacoustic emission levels) and hearing sensitivity (auditory brainstem response thresholds), starting in middle age. For the CBA mouse, a useful animal model of age-related hearing loss, it was found that correlations between these two hearing measures occurred only for high sound frequencies in middle age. However, in old age, a correlation was observed across the entire mouse range of hearing. These findings have implications for improved early detection of progression of age-related hearing loss in middle-aged mammals, including mice and humans, and distinguishing peripheral etiologies from central auditory system decline.

Keywords: presbycusis, hearing loss, hair cells, auditory brainstem response, otoacoustic emissions, mouse hearing

Introduction

Presbycusis, or age-related hearing loss, is highly prevalent clinically and in laboratory animals. In human populations, presbycusis is the leading communication disorder and one of the top three chronic medical conditions in the elderly. Understanding the physiologic, anatomic, and molecular bases of the degeneration of the aging inner ear and brain will pave the way for future biomedical interventions. These will include application of drugs or therapeutic compounds to prevent, slow, or reverse the progression of age-related hearing loss.

These biomedical translational goals underscore the importance of having a full appreciation of the characteristics and time course of deficits in mammalian animal models used in studying the progression of presbycusis. Different species have been utilized to study the biologic bases of age-related hearing loss, for example, gerbils¹⁻² and rats,³⁻¹⁰ and several mouse strains have proven to be quite useful.¹¹⁻²¹ Advantages of using mice include a comprehensive understanding of the mouse genome, the relative ease of creating knockout mice, and the successful production of knockins and transgenics.

In the field of sensory aging, several mouse strains have furthered progress in a noteworthy manner. C57Bl/6 (Black 6) mice, the favorite background strain for knockout

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mice in general, possess a prominent, high-frequency, accelerated age-related hearing loss, wherein middle-aged mice have severe-to-profound hearing impairment.^{22–25} These mice have been a particularly valuable model for examining brain changes and plasticity that result from loss of output channels from an aging auditory inner ear-cochlea.^{26–30}

The CBA strain that, like most humans, loses its hearing on a more gradual time course has also proved to be quite valuable.³¹ For example, middle-aged and older CBA mice display auditory temporal processing alterations that appear to be primarily a result of brainstem neural processing changes, rather than being driven directly by peripheral deafferentation that occurs, in contrast, in Black 6 mice.^{32–36} Studies of the CBA aging auditory system have also revealed significant decline in the physiology of the feedback system from the auditory brainstem to the cochlea, beginning in middle age,^{37–38} similar to what has been discovered in aging human listeners.³⁹ Voltage-gated potassium channels are important for cochlear and brainstem auditory physiologic processing. Decline in the auditory efferent feedback system is related to aging changes in the expression of voltage-gated potassium channels in the brainstem regions containing the cell bodies of the auditory efferent feedback neurons.⁴⁰ Surprisingly, the F1 generation of a Black 6 × CBA cross has been shown to have superior hearing to either parental strain.⁴¹

In most cases of hearing loss, outer hair cells are most sensitive to ototoxic insults and precede the loss of inner hair cells. When outer hair cells are lost, decreases occur in the overall sensitivity of the auditory system. To expand the usefulness of the CBA mouse strain for improving our understanding of the neural changes that take place in the cochlea with age, it is important to delineate the relationship between age changes in the hair cell system and overall changes in auditory physiologic sensitivity. It was hypothesized in the present investigation that, beginning in middle age, there would be correlations between measures of physiologic measures of the health and well being of the cochlear outer hair cell system and physiologic recordings of the overall sensitivity of hearing. To test this hypothesis, we compared auditory brainstem response (ABR) threshold shifts, a measure of overall sensitivity to sound to distortion-product otoacoustic emission (DPOAE) amplitude level shifts, a physiologic measure of outer hair cell function in young, middle-aged, and old CBA mice.

Methods

Subjects

All mice were bred in-house, and housed according to institutional protocols, with original breeding pairs

obtained from Jackson Laboratories. For this very large cross-sectional study, adult CBA mice were divided into three groups according to age, ie, young adult (n = 115, aged 1.5–4 months), middle-aged (n = 126, 11–16 months), and old (n = 86, 22–34 months). Note that 40 of the mice used in the present investigation were also used in a previous high-throughput gene microarray study.^{46–47} All animal procedures were approved by the University of Rochester Committee on Animal Resources and are consistent with NIH guidelines.

Auditory brainstem responses

The ABR and DPOAE testing procedures were similar to those used in our previous reports,^{38,40–43} and are summarized here. Prior to data acquisition, individual mice were microscopically examined for evidence of external ear canal and middle ear obstruction. Mice with clearly visualized, healthy tympanic membranes were included. ABRs were recorded with subcutaneous platinum needle electrodes placed at the vertex (non-inverting input), right mastoid prominence (inverted input), and tail (indifferent site). Calibrated tone pips of 5 msec duration and 0.5 msec rise-fall time (phase alternating 90°) were utilized. Electroencephalographic (EEG) activity was differentially amplified (50× or 100×; Grass [Quincy, MA] model P511 EEG amplifier), then input to an A/D converter (Tucker-Davis Technologies [TDT, Alachua, FL] AD1), and digitized at 50 kHz. Each averaged response was based on 300–500 stimulus repetitions recorded over 10 msec epochs. Contamination by muscle or cardiac activity was prevented by rejecting data epochs in which the single-trace EEG contained peak-to-peak amplitudes exceeding 50 μV. The threshold was defined as the first level that did not evoke a response to a measured frequency, ie, no difference from the baseline. During this procedure an intraperitoneal general anesthetic was used. Normal body temperature was maintained at 38°C with a servo heating pad. The ABR was recorded in a small sound attenuating chamber (IAC).

Distortion-product otoacoustic emissions

Mice were anesthetized with ketamine-xylazine (120 and 10 mg/kg body weight, respectively) by intraperitoneal injection before experimental sessions. All recording sessions were completed in a soundproof acoustic chamber (IAC lined with Sonex) with body temperature maintained with a heating pad. Before recording, the stimulus probe and microphone coupler were placed in the test ear near the tympanic membrane with the aid of an operating stereoscope.

Ipsilateral acoustic stimulation and simultaneous measurement of DPOAEs was accomplished with a TDT BioSig System III. Stimuli were digitally synthesized at 200 kHz using SigGen software with the ratio of f_2/f_1 constant at 1.25, and $L_1 = 65$ dB and $L_2 = 50$ dB SPL, as calibrated in a 0.1 cc coupler simulating the mouse ear canal. Signal duration was 84 msec and repetition rate was 21/sec. After synthesis, f_1 and f_2 were each passed through an RP2.1 D/A converter to PA5 programmable attenuators. Following attenuation, the signals went to ED1 speaker drivers which fed into the EC1 electrostatic loudspeakers coupled to the ear canal via short flexible tubes with rigid plastic tapering tips. For DPOAE measurements, the resulting ear canal sound pressure was recorded with an ER10B+ low noise microphone (gain 20 \times) and probe (Etymotic, Elk Grove Village, IL) housed in the same coupler as the f_1 and f_2 speakers. The output of the ER10B+ amplifier was input to an MA3 microphone amplifier, the output of which went to an RP2.1 A/D converter for sampling at 200 kHz. A fast Fourier transform (FFT) was performed on the resultant waveform. The magnitude of f_1 , f_2 , the $2f_1-f_2$ distortion product, and the noise floor of the frequency bins surrounding the $2f_1-f_2$ component were measured from the FFT. The procedure was repeated for geometric mean frequencies ranging from 5.6 to 44.8 kHz (8 frequencies/octave) to assess adequately the neuroethologically functional range of mouse hearing. Duration of the testing was approximately one hour per animal.

Statistical analysis

The hearing of young adult mice was measured via ABRs and DPOAEs. These measurements served as the reference for comparison with the middle-aged and old subject groups. The statistical analyses were performed with PRISM[®] 4.0 (GraphPad Software, San Diego, CA). Linear regressions were conducted to analyze the correlations between ABR thresholds (3, 6, 12, 24, 32, and 48 kHz) and DPOAE levels in different frequency bands (low 4–15 kHz, middle 15–30 kHz, high 30–48 kHz) for the three different subject groups. Also, two-way analysis of variance (ANOVAs) was performed for subject group mean data at different frequencies, and followed by Bonferroni *post hoc* t-tests, that were corrected for multiple comparisons. Error bars indicate standard error of the mean (SEM) unless otherwise stated.

Results

Auditory brainstem response thresholds

The overall sensitivity of the auditory system lessened with age, as shown in Figure 1. There were statistically significant

differences between the old mice and the other age groups. Also evident was a significant increase in the variability of the thresholds at each frequency with age, as indicated by the larger error bars for the old mice (Figure 1A). The two-way ANOVA main effects for aging and frequency were significant: Age $F(2,5) = 1335$, $P < 0.0001$; frequency $F(2,5) = 588$, $P < 0.0001$. Bonferroni *post hoc* tests showed significant differences between the ABR thresholds for the young adults and the two older age groups, as shown in the Table.

Otoacoustic emission levels

The physiology of the outer hair cell system declined with age, particularly in the old mice, as presented in Figure 2. When the DPOAE amplitude levels for the old group were compared with those for young adults, a significant difference was present using two-way ANOVA for aging \times frequency: Age $F(2,24) = 2837$, $P < 0.0001$; frequency $F(2,24) = 250$, $P < 0.0001$. Bonferroni multiple comparison tests revealed significant differences across all frequencies for the young adult versus the aged group; t values ranged from 5.7 to 20.79, $P < 0.001$. Like the ABRs, noticeable increases in variability take place at each frequency measured for the old mice

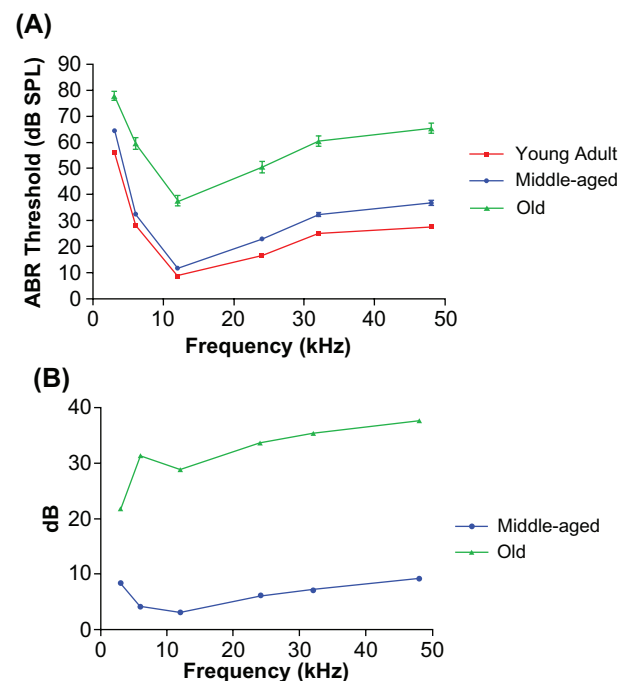


Figure 1 Comparisons of ABR thresholds in three mouse age groups. **A)** Frequency threshold curves for the young adult and middle ages were similar, but a large threshold elevation occurred in old age. The variability of the responses showed a marked increase in the old group, as evidenced by the larger error bars. **B)** ABR threshold shift comparisons between young adult CBA mice and the two older age groups. The middle-aged mice had thresholds within about 10 dB of the young adults. The old group had 22–38 dB ABR threshold elevations compared with young adults. Both of the older subject groups displayed a high frequency hearing loss. **Abbreviation:** ABR auditory, brainstem response.

Table 1 Bonferroni *post hoc* pairwise comparisons of ABR thresholds

	Young adult versus middle age		Young adult versus old age	
	t	P value	t	P value
3 kHz	5.715	$P < 0.001$	13.31	$P < 0.001$
6 kHz	2.831	$P < 0.05$	19.13	$P < 0.001$
12 kHz	2.06	NS	17.6	$P < 0.001$
24 kHz	4.094	$P < 0.001$	20.58	$P < 0.001$
32 kHz	4.865	$P < 0.001$	21.62	$P < 0.001$
48 kHz	6.187	$P < 0.001$	23.0	$P < 0.001$

Abbreviations: ABR, auditory brainstem response; NS, not statistically significant.

relative to the younger age groups (larger error bars for the old mice in Figure 2A). Also, the young adults versus the middle-aged mice showed significant differences above 35 kHz, with t values ranging from 3.268 to 3.514, $P < 0.05$. As with the ABRs (Figure 1B), the greatest change was between the middle-aged and old mice, as shown in Figure 2B.

High-frequency changes begin in middle age

The quantitative relations between the extent of outer hair cell system declines with age, and the progression of the deficits in overall auditory sensitivity comprised the next part of the investigation. Linear regression analyses were performed for

each stimulus frequency region, throughout the full range of mouse hearing. For measurements in the middle-aged mice, it was only in the highest frequency region of hearing that a significant correlation was found between the physiologic measures of the cochlear outer hair cell system and overall sensitivity to sound, as plotted in Figure 3A. Consistent with this, in the older age group, the highest correlation between the two measures was in the highest frequency range, as presented in Figure 3B.

Frequency-specific relations in old age

Although the correlation coefficients were modest, significant correlations were also discovered when comparisons were made for all of the frequency ranges covering the mouse audiogram in the old animals, as presented in Figure 4. Note that the correlation was strongest for the highest frequency range tested (see Figure 3B for comparison with the other frequency bands presented in Figure 4).

Overall relationships in middle-aged and old mice

Linear regressions were conducted to test for significant correlations between ABR thresholds and DPOAE levels across all frequencies of the mouse audiogram, as presented in Figure 5. In middle-aged mice, a significant relationship held, most likely driven by the high frequency data, as presented above (Figure 3A). Not surprisingly, a significant correlation was observed when the data from the old subjects were pooled across all of the frequencies, because the data for each of the individual frequency ranges analyzed were statistically significant, as presented in Figures 3B and 4. Because young adults had uniformly good hearing, there were no significant relationships between the two measures (data not shown).

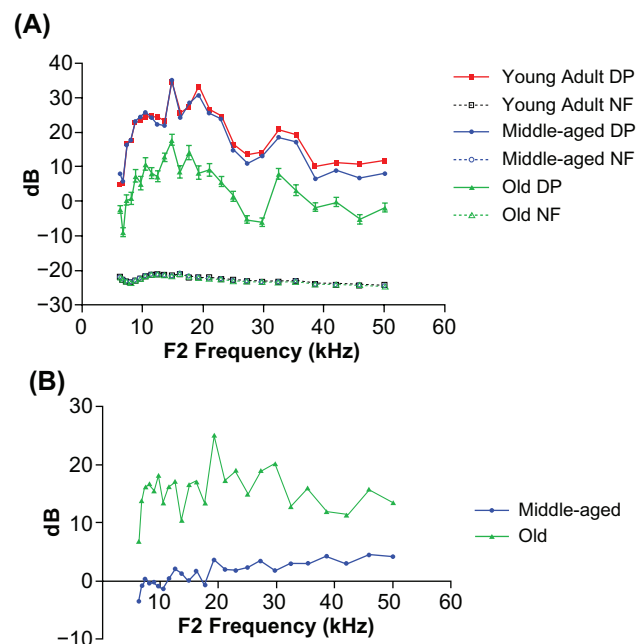


Figure 2 The DPOAE-grams reveal significant differences between the old subjects and the other two age groups. **A)** DPOAE levels were similar between the young adults and middle-aged mice, but large declines occurred in old age. Note the larger error bars in the oldest group. **B)** DPOAE level shifts compared with young adult: the middle-aged subjects showed a 2–5 dB change in the middle and high frequencies of the mouse hearing range, but there were large 10–25 dB shifts for the old group.

Abbreviations: DP, distortion product; DPOAE, distortion-product otoacoustic emission; NF, noise floor.

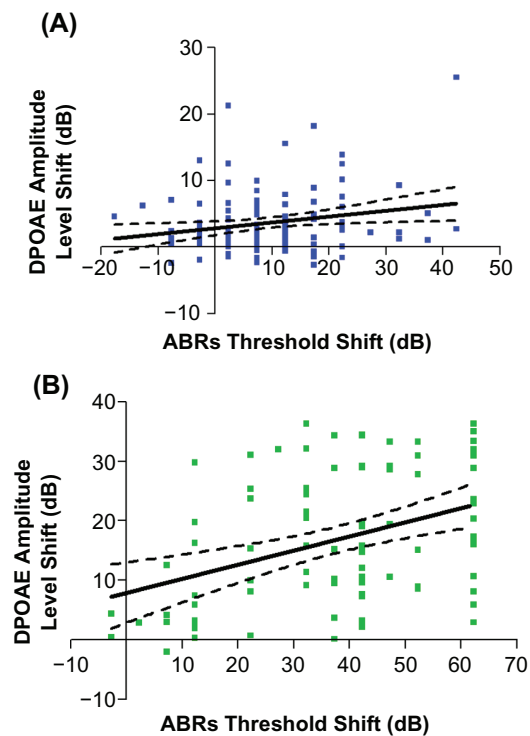


Figure 3 Group correlations between decline in the outer hair cell system and overall auditory sensitivity start to occur in middle age. **A**) Correlations between ABR thresholds and DPOAE level shifts are significant, only at the high frequencies (30–50 kHz) in middle age: $F(1,124) = 5.32, P = 0.0228, r^2 = 0.0411$. **B**) The correlations in the high frequency range become much stronger in old age: $F(1,84) = 15.21, P = 0.0002, r^2 = 0.1533$. Here, and in the remaining figures, dashed lines in the regression plots represent 95% confidence intervals.

Abbreviations: ABR, auditory brainstem response; DPOAE, distortion-product otoacoustic emission.

of the system diminished with age, consistent with previous research involving smaller numbers of subjects.^{20,22–26,37,38,41,43} Consistent with both physiologic and anatomic investigations of the cochlea, the outer hair cell system also declined with age, starting in the middle-age years.^{44,45} One feature of these changes in CBA mice that appears in multiple studies is that age-related deficits are generally larger when comparing middle-aged with old mice than the changes seen when comparing the hearing of young adults with middle-aged subjects.^{46,47} Also, consistent with most previous aging studies, the variability of the physiologic measures reported here show increases with age, as indicated by the larger error bars for the old mice displayed in Figures 1 and 2.

Age changes in sensory systems can be due to environmental factors such as intense stimuli (eg, loud noise), and drugs including antibiotics or chemotherapeutic agents, or may be due to aging changes inherent in the peripheral sensory organs (ear, eye) or parts of the brain used for sensory processing. Currently, the leading theory for “pure” aging in the cochlea implicates different components of the endolymph/ K^+ recycling system. The stria vascularis

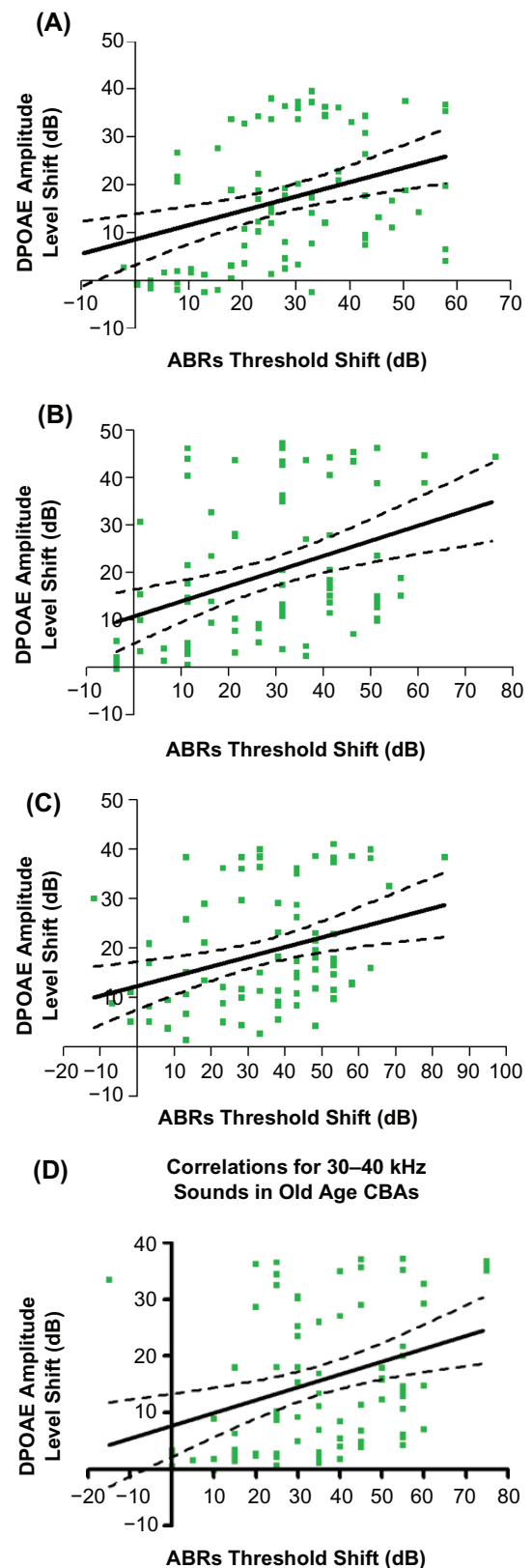


Figure 4 In old age, regression analyses yielded significant relationships between otoacoustic emission levels and ABR thresholds for all of the frequency bands tested. **A**) 1–10 kHz, $F(1,84) = 12.90, P = 0.0006, r^2 = 0.1331$. **B**) 10–20 kHz, $F(1,84) = 14.64, P = 0.0002, r^2 = 0.1484$. **C**) 20–30 kHz, $F(1,84) = 10.08, P = 0.0021, r^2 = 0.1071$. **D**) 30–40 kHz, $F(1,84) = 10.70, P = 0.0016, r^2 = 0.1130$.

Abbreviation: ABR, auditory brainstem response.

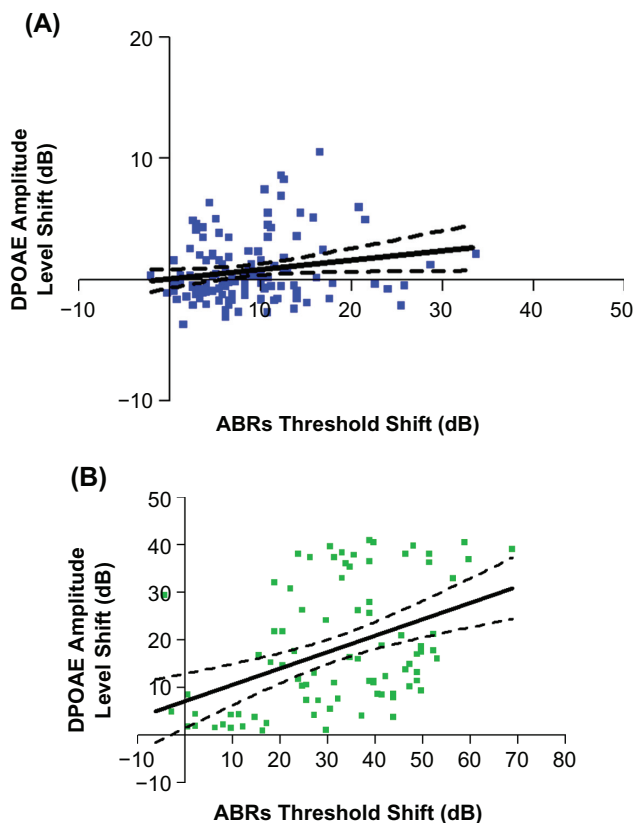


Figure 5 Correlations between ABR thresholds and DPOAE levels across the entire hearing range for mice of different ages. **A)** Correlations for the middle age mice were present, but not as striking as in old age: $F(1,124) = 4.22, P = 0.042, r^2 = 0.033$. **B)** A greater relationship was observed in the old mice: $F(1,84) = 18.43, P < 0.0001, r^2 = 0.18$. Note: Since young adults all had excellent hearing, there were no significant relationships.

Abbreviations: ABR, auditory brain stem response; DPOAE, distortion-product otoacoustic emission.

is the specialized trilaminar organ located on the lateral wall of the scala media, the fluid-filled cavity of the cochlea that bathes the tops of the hair cells with K^+ rich endolymph.^{48,49} Evidence from the gerbil animal model of presbycusis suggests that natural cochlear aging is in large part due to age-linked pathology of the stria vascularis, causing the endolymph-rich “cochlear battery” (endocochlear potential) to discharge with age.^{50–60} Depletion of the K^+ concentration and endocochlear potential in the scala media interferes with the normal exquisite sensitivity of the cochlear hair cell sound transduction mechanisms, resulting in a decline in otoacoustic emission amplitudes and elevation of ABR thresholds. Additional evidence from mouse models indicates that other parts of the cochlear K^+ processing system also become impaired with age, including different aspects of the scala media lateral wall, such as the Type IV fibrocytes.^{61–64} Age deficits in the cochlear endolymph K^+ system tend to cover a wide range of sound frequencies, because the endolymph can diffuse with relatively little fluid resistance

from the cochlear base to the apex. In light of this, correlations across the entire mouse hearing range, reported in the present investigation for old mice, suggest that the physiologic decline of the aged cochlea is likely linked to deficits in the stria vascularis/ K^+ cycling system of the old cochlea, that are not as prevalent in middle-aged mice.

Contributions of the present investigation include new delineations of the quantitative relationships between physiologically measured aging deficits in cochlear outer hair cell responses and the overall sensitivity of the auditory system, occurring in a very useful mouse model for investigations of presbycusis.^{14,16,17} For middle-aged mice, correlations were seen only in the high frequencies. This indicates that for the lower and middle frequency regions of mouse hearing, middle-aged mice that have age-related deficits in the outer hair cell system are not the same mice showing the largest decline in their overall hearing sensitivity. Therefore, the relationship between these two physiologic hearing measures does not reveal itself widely until old age.

Summary and conclusions

This study demonstrates that correlations between ABR thresholds and DPOAE levels become more significant with age, extending throughout the entire frequency range of hearing in old mice. This suggests that decline in the outer hair cell system of the auditory periphery become a greater determinant of overall auditory sensitivity with age. In addition, the physiologic measurement of otoacoustic emissions is now the most widespread clinical screening measure for detecting hearing loss and deafness in newborn infants. One implication of the present investigation is that for clinical detection or diagnosis of age-related hearing loss, the noninvasive DPOAE-level testing paradigm utilizing high frequency sounds as probe stimuli may be a valuable method for early detection of presbycusis in middle-aged listeners. Earlier detection and diagnosis of age-related hearing loss is a necessary prerequisite for maximizing effectiveness of biomedical interventions aimed at preventing this highly prevalent form of sensory impairment.

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Disclosures

The authors report no conflicts of interest in this work.

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