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Genetics of age-related hearing loss in mice. III. Susceptibility of inbred and F1 hybrid strains to noise-induced hearing loss

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Abstract

Some humans and mice are genetically predisposed to age-related hearing loss (AHL), and others are variously susceptible to noise-induced hearing loss (NIHL). The inbred C57BL/6J (B6) mice exhibit AHL at an early age, whereas the inbred CBA/CaJ (CB) mice do not. The B6 mice are much more susceptible to NIHL than are the CB mice (Shone et al., 1991; Li, 1992a). The B6 mice possess an *Ahl* gene which maps to chromosome 10 (Erway et al., 1995). This study was designed, using these two inbred strains plus two F1 hybrid strains of mice, to begin to test the hypothesis that the *Ahl* genotypes may influence the susceptibility to NIHL. These strains of mice (with putative genotypes) are: inbred CB (+/+) and B6 (*Ahl/Ahl*); hybrid CBB6F1 (+/*Ahl*) and B6D2F1 (*Ahl/Ahl*; D2 represents inbred DBA/2J). Twenty-four mice of each of these four strains were exposed to noise (110 dB for 0, 1 or 2 h) and tested for auditory-evoked brainstem response (ABR) thresholds. The CB and CBB6F1 strains of mice did not differ significantly from each other, exhibiting mostly temporary threshold shifts. The B6 and B6D2F1 strains of mice did not differ significantly from each other, but did exhibit permanent threshold shifts. These results support the hypothesis that genetic predisposition to AHL may be revealed at a younger age by NIHL. This suggests that it may be possible to use the NIHL to distinguish segregating genotypes (+/*Ahl* vs. *Ahl/Ahl*) among backcross progeny and thereby to identify and map single genes for AHL.

Keywords: Noise-induced; Age-related; Brainstem; Inbred; Hybrid; Mice

1. Introduction

Workers exposed to the same noise over the same length of career do not suffer the same amount of noise-induced hearing loss (NIHL). This has been known anecdotally for many years. Numerous epidemiological studies have documented the phenomenon of 'tough' and 'tender' ears. For example, Taylor et al. (1965) observed hearing losses in a population of female jute weavers who had been exposed to a constant 99 or 102 dB noise for 1–54 years. Allowing for changes due to aging, there were differences of as much as 70 dB between the least affected and the most affected workers.

Cody and Robertson (1983) exposed outbred guinea pigs to precisely controlled noise levels, but they found large, inter-animal variation in N1 changes and damage measured in cochleograms. Such differences in susceptibility between individual animals or humans could be due to genetic factors.

Auditory sensitivity in mice is most easily determined by auditory-evoked brainstem response (ABR) thresholds. Some strains of mice differ with respect to susceptibility to

Abbreviations: +, wildtype (non-*Ahl*) allele for normal auditory thresholds; ABR, auditory brainstem response — auditory-evoked potential; AHL, age-related hearing loss phenotype; *Ahl*, gene or allele associated with age-related hearing loss; B6, inbred C57BL/6J strain of mice; B6D2F1, hybrid strain of mice from cross of C57BL/6J and DBA/2J; B6′, inbred C57BL/6J and hybrid B6D2F1 strains taken as a group; CB, inbred CBA/CaJ strain of mice; CBB6F1, hybrid strain of mice from cross of C57BL/6J and CBA/CaJ; CB′, inbred CBA/CaJ and hybrid CBB6F1 strains as a group; NIHL, noise-induced hearing loss, phenotype of putative *Ahl/Ahl* genotype; PTS, permanent threshold shift; TS, threshold shift (postexposure ABR threshold minus pre-exposure threshold); TTS, temporary threshold shift

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NIHL as measured by the ABR (Henry, 1982, 1983a, 1992). Shone et al. (1991) exposed the CBA/Ca and C57BL/6 inbred strains of mice to a 101 dB broadband noise for 45 min. The CBA/Ca mice maintain relatively normal ABR thresholds throughout their 2-year life, but the C57BL/6 mice begin to lose auditory sensitivity early in adulthood. Both strains were exposed at 6 months of age when the C57BL/6 mice had moderate ABR threshold shifts. They found an enhanced susceptibility to noise damage in the C57BL/6 mice. Their data do not preclude the possibility that C57BL/6 mice are also susceptible to NIHL at earlier ages.

The C57BL/6 and CBA/Ca mice have been exposed to traumatic noise at various ages (Li, 1992a, b; Li and Borg, 1991, 1993; Li et al., 1993). The mice were exposed for 5 min to a band of 2–7 kHz noise at 120 dB. The 1- and 2-month-old CBA/Ca mice were susceptible to NIHL, but they became much less susceptible by 3 and 5 months of age. The C57BL/6 mice were susceptible to NIHL from 1 to 5 months of age when they exhibited AHL. The 2–7 kHz exposure may have been of too low frequency to produce loss in the 12–16 kHz mid-frequency sensitivity range for mice (Davis et al., 1994). Moreover, there is some evidence that above 119 dB the effect of noise on the cochlea becomes non-linear; metabolic processes no longer dominate, but structural damage to the cochlea becomes dominant (Henderson et al., 1991). Li et al. exposed anesthetized mice which may affect middle ear muscles, efferent fibers to the cochlea and other unknown processes.

Erway et al. (1993) demonstrated predisposition to age-related hearing loss (AHL) among five inbred strains and ten F1 hybrid strains of mice. Based on the patterns of AHL in the mice at 12, 16 and 23 months of age, Erway et al. (1993) postulated that three recessive genes may be responsible for the enhanced susceptibility to AHL. A different gene was postulated for each of the C57BL/6J, BALB/cByJ and WB/ReJ inbred strains of mice. The inbred DBA/2J mice, which exhibit very early onset of auditory deficits, were postulated to contain all three recessive genes. Erway et al. (1995) have obtained evidence that the gene for AHL in the C57BL/6J strain of mice segregates in backcross progeny and maps to chromosome 10. They designated this gene *Ahl* (for age-related hearing loss).

This study for NIHL was conducted when the mice were 3–4 months of age before the onset of major AHL. In addition, the level of noise was set to be less than the level believed to produce structural damage, and the mice were exposed while unanesthetized.

The present study was designed to test the hypothesis that putative genotypes for AHL may make mice more susceptible to NIHL. Despite innumerable other differing genetic loci, all mice in these two pairs of inbred and hybrid strains of mice share in common one of three putative *Ahl* genotypes. This hypothesis would be supported if all three of the following results are realized: (1) the CB (+/+) and CBB6F1 (+/*Ahl*) strains of mice do not differ significantly in their resistance to NIHL; (2) the B6 (*Ahl*/*Ahl*) and B6D2F1 (*Ahl*/*Ahl*) mice do not differ significantly in their susceptibility to NIHL; and (3) the degree of NIHL among individual mice of the two contrasting genotypes (+/+ and +/*Ahl* vs. *Ahl*/*Ahl*) does not overlap. Such results are presented among these two inbred and two F1 hybrid strains of mice.

The critical genetic evidence for a relationship between susceptibility to AHL and to NIHL must come by comparing the segregating +/*Ahl* and *Ahl*/*Ahl* genotypes among backcross progenies. If a genetic relationship can thus be established for susceptibility to AHL and NIHL, then genetic studies of AHL may be done in young mice more quickly than waiting for mice to age for two years or more. Erway and Willott (1996) have presented an overview of potential genetic relationships between noise-induced and age-related hearing loss.

2. Materials and methods

2.1. Subjects

Ninety-six mice were used in this study. Four strains of mice were represented: the model for normal auditory function, inbred strain CBA/CaJ (abbreviated CB); the model for early presbycusis, inbred strain C57BL/6J (abbreviated B6); a hybrid of the CB and B6 strains (CBB6F1) and a hybrid of the B6 and DBA/2J (D2) inbred strains (B6D2F1). Subjects were bred, maintained, and tested at the University of Cincinnati. For noise exposure the mice were transported once in an air-conditioned, noise-limited vehicle to the National Institute for Occupational Safety and Health. Protocols were approved by the Institutional Animal Care and Use Committee of both institutions. Twenty-four mice were included in each of the four strains, each denoted with its putative *Ahl* genotype: inbreds CB (+/+), B6 (*Ahl*/*Ahl*) and hybrids CBB6F1 (+/*Ahl*), B6D2F1 (*Ahl*/*Ahl*). Each group of mice was evenly divided by sex.

Mice of each sex were randomly assigned to one of three groups for noise exposure: (a) unexposed (tested, handled and transported identically but not exposed to noise); (b) exposed to noise (110 dB) for 1 h; and (c) exposed to noise (110 dB) for 2 h. All mice (8 unexposed and 16 exposed) in each strain survived and were tested 5 times from pre-exposure to 1 week after noise exposure. Some mice died of uncertain causes unrelated to noise exposure or to recovery from anesthesia. All deaths occurred sporadically between successive tests (5–9). The total numbers of mice in each strain surviving anesthesia and testing 9 times to 3 months after exposure were: CB (7 unexposed, 12 exposed), B6 (7, 13), CBB6F1 (6, 13) and B6D2F1 (7, 15). Statistical analyses were performed only on survivors tested.

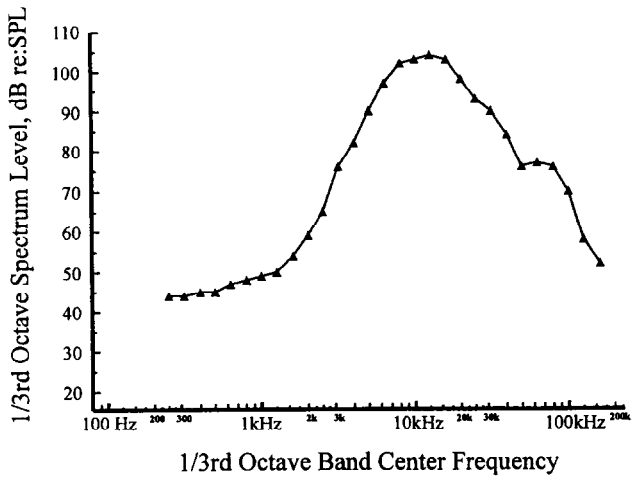

Fig. 1. Third-octave analysis of the exposure stimulus. Noise exposure acoustic stimulus was measured in 1/3 octave bands inside the exposure chamber. Measurements were taken with an ACO model 7016 1/4″ microphone, B&K model 1617 1/3rd octave filter set and a B&K model 2606 measuring amplifier.

2.2. ABR testing

Mice were tested both before and after noise exposure for threshold for the auditory-evoked brainstem response (ABR). Mice were anesthetized with an i.p. injection of Avertin® (tribromoethanol) at 3.5 mg/10 g body weight. Body temperature was maintained with a heating pad. During testing the mouse and heating pad were kept inside a sound-attenuating chamber.

Testing for ABR thresholds was done with an Intelligent Hearing System unit (IHS, North Miami, FL) installed in a Zenith 286 computer. Grass stainless steel electrodes were inserted subcutaneously at the vertex (active), ventrolateral to the left ear (reference) and the dorsum (ground). Signals from the electrodes were amplified 25 000–100 000 times and bandpass filtered (100–3000 Hz) by a Grass 511 pre-amplifier and then presented to the IHS system. Mice were tested with a click stimulus and with 8, 16 and 32 kHz tone pips. The click was 0.1 ms duration; tone pips were 3 ms including 1 ms rise and fall. The stimulus was presented binaurally via AKG-K340 earphones loosely coupled to the pinnae through two plastic funnels. The stimulus output of the IHS system and these earphones was calibrated with a 1/8″ microphone at the tip of the funnel as described by Erway et al. (1993). The ABR was obtained by averaging up to 1024 presentations of the stimulus at 31 presentations per second. Thresholds were determined by reducing the stimulus in 10 dB steps until the ABR disappeared, then by raising and lowering the stimulus intensity in 5 dB steps. Threshold was taken to be the lowest stimulus level at which a normalized ABR wave could still be identified for at least two peak latencies. ABR thresholds were determined pre-exposure and postexposure at 2–7 h, 1, 2 and 3 days and 1 and 2 weeks and 1, 2 and 3 months.

2.3. Noise exposure

The NIOSH noise-exposure facility has been described (Davis and Franks, 1989). In brief, up to four awake mice were placed into each of two compartments of a stainless steel cage. Two cages were placed inside each of two exposure chambers at the NIOSH Noise Research Labora-

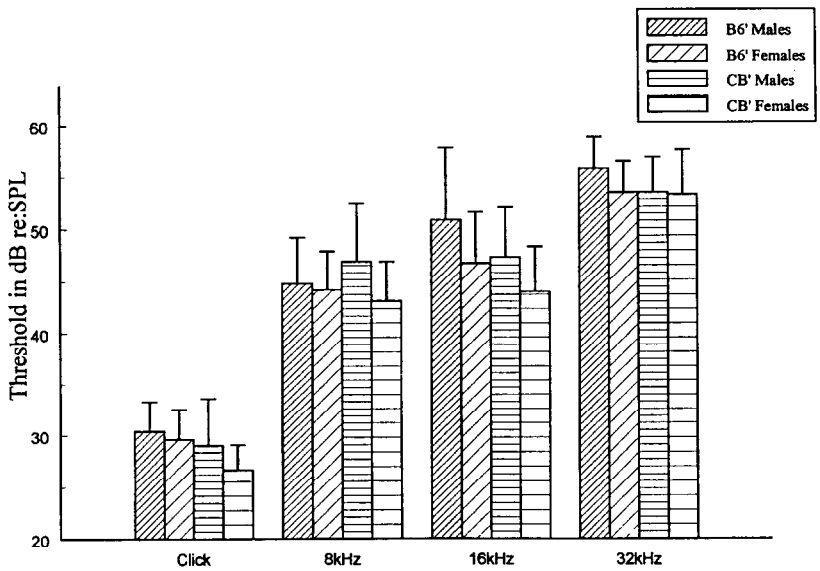

Fig. 2. Pre-exposure ABR thresholds by strain, sex and stimuli. The means + SD are shown separately by sex for thresholds of the combined B6′ and CB′ strains for the click and tone-pip (8, 16 and 32 kHz) stimuli. The CB′ females had consistently lower thresholds than the CB′ males, except at 32 kHz. The B6′ males had slightly higher thresholds than the B6′ females and CB′ males at 16 and 32 kHz. (See text for statistical comparisons.)

tory. A cover consisting of four Realistic 40-1320B super-tweeters was placed on each chamber. The stimulus was generated by a General Radio 1310 Random Noise Generator. The output of the generator was controlled by a Wilsonics BSIT Tone Switch and PATT Attenuators. The output of the attenuators was amplified by a Soundcraftsman 300X4 Power Amplifier and cabled to the Realistic Super-Tweeters. The Super-Tweeters incorporate a 5 kHz high-pass filter. Fig. 1 shows the 1/3rd octave band levels of the noise stimulus. The stimulus level was set to 110 dB. The noise exposure was monitored by an in-chamber Sennhauser MKE 2-3 electret microphone and displayed on a Bruel and Kjaer 2133 Real-Time Frequency Analyzer. Exposures were either for 1 h or 2 h.

2.4. Statistical analyses

Analysis of variance (ANOVA) was used to analyze the data. Between-subject factors included Strain, Sex and Exposure to noise (0, 1, 2 h). Within-subject factors included Test (2–9) and stimulus Frequency (tone pips: 8, 16 and 32 kHz). In the event of any significant main effect or interaction, contrasts were made to compare strains and exposure levels. A main effect, interaction, or contrast was considered significant if $P < 0.01$. The Greenhouse-Geisser estimate of Box's Epsilon was used to adjust the probabilities of the F tests of all within-subject effects. Separate ANOVAs were done for pre- and postexposure data, as well as for threshold shifts for click and tone pips.

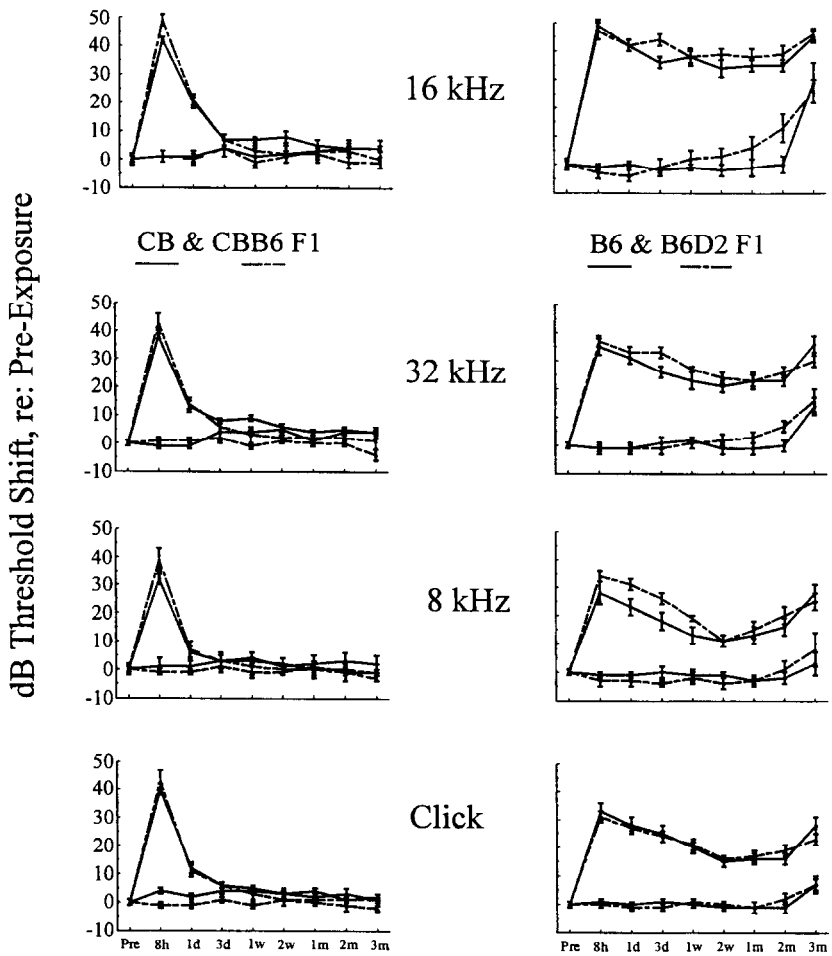

Fig. 3. Time course of threshold shifts (TSs) following noise exposure of four strains of mice. The TSs were computed for each mouse as the difference between the pre-exposure ABR threshold and each postexposure threshold; the TSs are shown as the mean ± SE for each strain of mouse, noise-exposed and unexposed controls. The TSs are shown respectively for the CB and CBB6F1 strains (left panel series) and for the B6 and B6D2F1 mice (right panel series). The top two lines in each graph exhibit the large TS following noise exposure; the bottom two lines were control mice handled and tested identically, except that they were not exposed to noise.

Each series of graphs displays TSs in order by test stimuli from most affected on top to least affected on bottom (16 kHz, 32 kHz, 8 kHz and clicks.) Note that on each graph, the F1 hybrids are represented by broken lines and the inbred strains by solid lines. The CB and CBB6F1 mice all exhibited temporary TSs within 8 h postexposure, recovering rapidly within 1–3 days. The B6 and B6D2F1 mice exhibited comparable TSs within 8 h postexposure, limited recovery by 1 week, and permanent TSs thereafter. The B6 and B6D2F1 mice, both unexposed and noise-exposed, exhibited age-related TSs after 2 months postexposure, when the mice were 5–8 months of age.

3. Results

3.1. Pre-exposure ABR thresholds

Ninety-six mice (24 in each of four strains) were tested for pre-exposure thresholds for clicks and tone pips (8, 16 and 32 kHz). No significant differences were found between the B6 and B6D2F1 (designated B6′) strains or between the CB and CBB6F1 (CB′) strains. The threshold means are shown, separately for males and females, collapsed for the B6′ and CB′ strains (see Fig. 2).

3.1.1. Clicks

Prior to noise exposure the four strains of mice exhibited significantly different ABR thresholds for clicks ($F_{3,\ 72} = 4.62$, $P = 0.005$). This was due to the significant ($P = 0.001$) difference for the contrast between the B6′ and CB′ strains. The main effect of Sex was nearly significant ($F_{1,\ 72} = 5.87$, $P = 0.017$). The mean click thresholds were less for females than for males.

3.1.2. Tone pips

There was a significant ($F_{2,\ 144} = 7.66$, $P = 0.0009$) contrast of the B6′ and CB′ Strains × Frequency interaction, indicating that the B6′ and CB′ strains did not exhibit comparable thresholds across the three stimulus frequencies. The Strain × Sex × Frequency interaction was also significant for tone thresholds ($F_{6,\ 144} = 3.10$, $P = 0.008$). This sex difference for the B6′ mice was greater for 16 and 32 kHz, while the sex difference for the CB′ mice was greater at 8 and 16 kHz. The sex difference for contrasts between the B6′ and CB′ strains was nearly significant ($P = 0.018$).

Regardless of the differences in pre-exposure thresholds by strains, sex and frequency of the stimulus, they present no inherent consequences for analyzing the postexposure threshold shifts (TS).

3.2. Postexposure threshold shifts

TSs were computed and analyzed for each mouse by each stimulus over all eight postexposure tests. There were no significant differences in TSs between mice exposed for 1 h vs. 2 h; thus all TSs were collapsed across these two exposure groups. The mean TSs for all exposed mice and unexposed controls are shown by test stimulus for each of the four strains of mice (Fig. 3). There were no statistically significant differences in TSs between the CB and CBB6F1 strains; the TSs for these two strains were collapsed for statistical comparisons regarding the CB′ strains of mice. Likewise, there were no statistically significant differences in TSs for the B6 and B6D2F1 strains; the TSs for these two strains were collapsed for statistical comparisons regarding the B6′ strains of mice. The statistical contrasts for TSs between the CB′ and B6′ strains of mice were significant ($p < 0.0001$) for all four test stimuli. For click and pip TSs, the Strain × Exposure × Test interaction was significant ($F_{42,\ 385} = 2.56$, $P = 0.0003$, and $F_{42,\ 385} = 3.33$, $P = 0.0001$, respectively), indicating that these four strains of mice differed significantly, between exposed and unexposed controls, in their pattern of TSs over the eight tests. For the CB′ mice, the mean TSs induced by the noise exposure diminished over tests and approached thresholds for the control group by 1 week. By contrast, the mean TSs of the B6′ mice decreased gradually over a 2-week period, but never approached the control group (click,

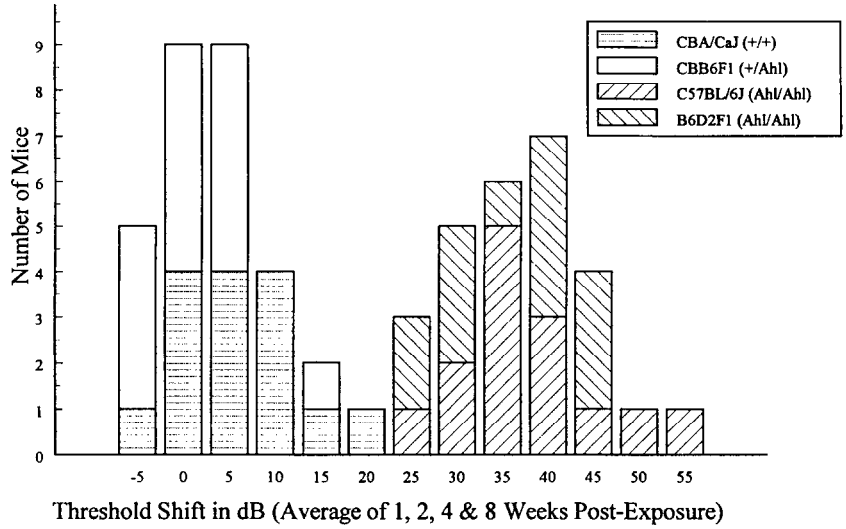

Fig. 4. Bimodal distribution of noise-induced threshold shifts (TSs) among four strains of mice. Following exposure to 110 dB noise for 1 or 2 h, the TSs for each mouse at 16 kHz were averaged for 1, 2, 4 and 8 weeks. All 30 mice of the inbred CBA/CaJ (CB) and hybrid CBB6F1 strains of mice exhibited averaged TSs of −5 to 20 dB. (Most of these mice exhibited ±5 dB, the error of measurement in these studies.) By contrast, all 27 mice of the inbred C57BL/6J (B6) and hybrid B6D2F1 strains of mice exhibited averaged TSs of 25–55 dB. There was no overlap of TSs between these two groups of genotypes (+/+ and +/*Ahl* vs. *Ahl*/*Ahl*).

$P = 0.0001$; tone pips, $P = 0.0001$). There were no statistically significant differences in TSs between sexes for exposure to noise.

In summary, the two CB′ strains of mice exhibited very comparable patterns of temporary threshold shift (TTS) and then recovered rapidly to a level approximating their unexposed controls. The two B6′ strains of mice also exhibited comparable patterns of TSs, exhibiting a modest recovery to about 2 weeks with a permanent threshold shift (PTS), in marked contrast to their unexposed controls. The effect of noise exposure on PTS in the B6′ strains of mice was greatest at 16 kHz (35–40 dB), progressively less for 32 kHz (20–25 dB) and 8 kHz (10 dB), with intermediate effects for clicks (15–20 dB).

3.3. Onset of age-related hearing loss

The unexposed B6D2F1 mice showed a trend for elevated ABR thresholds after 1 month, becoming significant only between 2 and 3 months when the unexposed B6 mice also had significant threshold elevations. Similarly the noise-exposed groups of the B6′ mice exhibited an additional TS between months 2 and 3 postexposure compared to the previously stable PTS. These coincidental ABR elevations appear to be age-related, having occurred when the mice were between 5 and 8 months of age.

3.4. Bimodal distribution of thresholds shifts at 16 kHz

Fig. 4 shows the distributions of the TSs of the four strains of mice at 16 kHz averaged over 1, 2, 4 and 8 weeks postexposure. The CB and CBB6F1 mice exhibited TSs which ranged from −5 to 20 dB. The majority of shifts were within the error of measurement. Only 7 (23%) of the 30 CB′ mice exhibited a low level PTS (10–20 dB). By contrast, all 27 of the B6 and B6D2F1 mice exhibited PTSs between 25 and 55 dB. The two distributions for the CB and CBB6F1 vs. the B6 and B6D2F1 strains of mice do not overlap; combining the TSs for the four genetically distinct strains of mice produces a bimodal distribution.

4. Discussion

The inbred CBA/CaJ (CB) and hybrid CBB6F1 strains of mice exhibited only TTS with rapid recovery after exposure to 110 dB for 1 or 2 h, and they exhibited no evidence of any AHL. By contrast, the inbred C57BL/6J (B6) and hybrid B6D2F1 strains of mice exhibited extensive PTS and subsequent onset of AHL. The B6 mice have normal ABR thresholds from 1 to 2 months of age, but they show gradual, progressive elevation of thresholds for high frequencies. By 5–6 months of age, threshold elevations are substantial above 20 kHz, becoming severe for all frequencies during the second year (see Henry, 1983b; Willott, 1991).

Erway et al. (1993) showed that the CBB6F1 hybrid mice exhibited normal auditory thresholds to 2 years of age, whereas the B6D2F1 hybrid mice exhibited AHL between 16 and 23 months of age. There were no significant differences for NIHL between either pair of the inbred and hybrid strains of mice; we conclude that there is no evidence for F1 hybrid vigor for NIHL or recovery among these strains. This further supports the major effect of the *Ahl* genotype on NIHL.

The major differences observed for PTS in the B6 and B6D2F1 mice and the minimal TS in the CB and CBB6F1 mice support the hypothesis for a major genetic difference among these strains. Moreover, the non-overlapping, bimodal distribution for the averaged TSs supports the hypothesis that the *Ahl* locus makes these strains of mice either highly susceptible (*Ahl/Ahl*) or not as susceptible (+/+ or +/*Ahl*) to noise exposure of 110 dB for 1 or 2 h.

These results demonstrate the advantages of using inbred and F1 hybrid strains of mice which are genetically well-defined, numerous and readily available. The major advantage is that all inbred and F1 hybrid strains of mice are genetically homogeneous, thereby virtually lacking genetic variability. One may assume that most of the residual variability is due to environmental factors and/or interactions of environmental factors with specific, genetically homogeneous backgrounds.

Erway et al. (1995) have mapped the *Ahl* gene for AHL from the C57BL/6J strain of mice to chromosome 10. Based on that information, the CBB6F1 mice were backcrossed to the C57BL/6J mice, yielding progeny of which half were expected to be +/*Ahl* and half *Ahl/Ahl*. Exposure of these mice to noise (110 dB for 8 h) yielded about half with NIHL and half without NIHL (Newlander et al., 1995). Subsequent genetic mapping of these mice demonstrated linkage of the susceptibility to NIHL with two genetic markers on chromosome 10 (Ling et al., 1995). These data effectively demonstrate that the susceptibility to NIHL in these mice is due primarily to the *Ahl* gene.

The minimal variability for NIHL observed within the four genetically homogeneous inbred and hybrid strains of mice used in the current investigation provides a backdrop for an increased variability observed among the genetically heterogeneous backcross progeny. This emphasizes the need for doing such studies first among inbred and F1 hybrid strains of mice before undertaking any new set of backcrosses. The ultimate use of backcrosses is the only way in which non-syndromic genes for auditory deficits can be mapped and identified.

The results reported herein support the hypothesis that a gene affecting AHL also makes individuals of a particular *Ahl* genotype more susceptible to NIHL.

Through the use of these animal models, we are able to examine the long-known phenomenon of 'tough' vs. 'tender' ears in regard to susceptibility of humans to

NIHL. Further work is needed to determine if other genes for AHL also effect NIHL in mice. Genetic studies are needed to determine if presbycusis and NIHL are related in humans, as our data indicate that they are for at least one gene in the mouse.

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References

Cody, A.R. and Robertson, D. (1983) Variability of noise-induced damage in the guinea pig cochlea: electrophysiology and morphological correlates after strictly controlled exposures. Hear. Res. 9, 55–70.

Davis, R.R. and Franks, J.R. (1989) Design and construction of a noise-exposure chamber for small animals. J. Acoust. Soc. Am. 58, 963–966.

Davis, R.R., Shiau, Y.-W. and Erway, L.C. (1994) Temporary threshold shift does not predict permanent threshold shift in a 'low-frequency' exposure of mice. Effects of Noise on Hearing, Vth International Symposium, Gothenburg, Sweden, 12–14 May 1994.

Erway, L.C., Willott, J.F., Archer, J.R. and Harrison, D.E. (1993) Genetics of age-related hearing loss in mice. I. Inbred and F1 hybrid strains. Hear. Res. 65, 125–132.

Erway, L.C., Willott, J.F., Cook, S.A., Johnson, K.R. and Davisson, M.T. (1995) Segregation of genes for age-related hearing loss from C57BL/6J and DBA/2J inbred mice. ARO Midwinter Meeting, Abstr. 548.

Erway, L.C. and Willott, J.F. (1996) Genetic susceptibility to noise-induced hearing loss in mice. In: A. Axelsson et al. (Eds.), Scientific Basis of Noise-Induced Hearing Loss, Ch. 6, pp. 56–64. Thieme, New York.

Henderson, D., Subramaniam, M., Gratton, M.A. and Saunders, S.S. (1991) Impact noise: the importance of level, duration and repetition. J. Acoust. Soc. Am. 89, 1350–1357.

Henry, K.R. (1982) Influence of genotype and age on noise-induced auditory loss. Behav. Gen. 12, 563–573.

Henry, K.R. (1983a) Lifelong susceptibility to acoustic trauma: changing patterns of cochlear damage over the lifespan of the mouse. Audiology 22, 372–383.

Henry, K.R. (1983b) Aging and audition. In: J.F. Willott (Ed.), Auditory Psychobiology of the Mouse. CC Thomas, Springfield, IL, pp. 470–493.

Henry, K.R. (1992) Noise-induced auditory loss: influence of genotype, naloxone, and methyl-prednisolone. Acta Otolaryngol. 112, 599–603.

Li, H.-S. (1992a) Influence of genotype and age on acute acoustic trauma and recovery in CBA/Ca and C57BL/6J mice. Acta Otolaryngol. 112, 956–967.

Li, H.-S. (1992b) Genetic influences on susceptibility of the auditory system to aging and environmental factors. Scand. Audiol. Suppl. 36, 1–39.

Li, H.-S. and Borg, E. (1991) Age-related loss of auditory sensitivity in two mouse genotypes. Acta Otolaryngol. 111, 827–834.

Li, H.-S. and Borg, E. (1993) Auditory degeneration after acoustic trauma in two genotypes of mice. Hear. Res. 68, 19–27.

Li, H.-S., Hultcrantz, M. and Borg, E. (1993) Influence of age on noise-induced permanent TSs in CBA/Ca and C57BL/6J mice. Audiology 32, 195–204.

Ling, X-B., Erway, L.C., Newlander, J.K., Davis, R.R. and Cortopassi, G.A. (1995) Mapping of a mouse gene for noise-induced hearing loss. ARO Midwinter Research Meeting, Abstr. 764.

Newlander, J.K., Erway, L.C., Davis, R.R., Cortopassi, G.A. and Ling, X.-B. (1995) Susceptibility to NIHL and age-related hearing loss in mice. ARO Midwinter Research Meeting, Abst. 356.

Shone, G., Altschuler, R.A., Miller, J.M. and Nuttall, A.L. (1991) The effect of noise exposure on the aging ear. Hear. Res. 56, 173–178.

Taylor, W., Pearson, J. and Mair, A. (1965) Study of noise and hearing in jute weaving. J. Acoust. Soc. Am. 38, 113–120.

Willott, J.F. (1991) Aging and the Auditory System: Anatomy, Physiology, and Psychophysics, Singular Press, San Diego, CA.