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Quantitative measure of genetic differences in susceptibility to noise-induced hearing loss in two strains of mice

Rickie R. Davis [a,b,*], Michael L. Cheever [b], Edward F. Krieg [c], Lawrence C. Erway [b]

[a] *Bioacoustics and Occupational Vibration Section, Physical Agents Effects Branch, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH, USA*

[b] *Department of Biological Sciences, University of Cincinnati, Cincinnati, OH, USA*

[c] *Statistics Activity, Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH, USA*

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Abstract

The CBA/CaJ (CB) and C57BL/6J (B6) inbred strains of mice were exposed for 1 h to noise intensities between 98 and 119 dB SPL. Previous studies indicated that the B6 mice exhibited permanent threshold shifts (PTS) after 1 h exposure to 110 dB, whereas the CB mice did not exhibit any PTS. These differences in susceptibility to noise-induced hearing loss (NIHL) appear to be due to a gene for age-related hearing loss (AHL). The current study was designed to determine dose-response curves for NIHL over the ranges of intensities of noise that would characterize the B6 and CB inbred strains of mice. Because of the considerable differences in sensitivity to NIHL, the noise exposures for the two strains overlapped only at 110 and 113 dB. Nevertheless, the two strains exhibited two different dose-response curves, offset and with different slopes. We postulate that the B6 strain of mice exhibits a more linear increase for PTS from 98–113 dB, consistent with incremental effects on some metabolic physiological mechanism(s); the abrupt transition in NIHL between 113 and 116 dB for the CB mice is consistent with an ototraumatic structural injury.

Key words: Noise-induced; Age-related; Hearing loss; Mice

1. Introduction

A person is more susceptible to noise damage if the same level of noise produces greater damage in that individual than in another. It has long been known that two workers exposed to the same noise do not suffer the same degree of hearing loss. For example, Taylor et al. (1965) demonstrated this phenomenon among jute weavers. Female jute weavers who had been exposed to the same constant noise (99 or 102 dB) for long periods of time (1 to 54 years), when adjusted for age, showed as much as 70 dB difference between the least affected and the most affected workers with noise-induced hearing loss (NIHL).

In experimental animals, Cody and Robertson (1983) showed large differences in N_1 thresholds and cochleograms in outbred guinea pigs when exposed to the same precisely controlled acoustic stimulus. Large variations in auditory brainstem response threshold shift have been documented in chinchillas exposed to both impulse noise and continuous noise (Dunn et al., 1991). Such differences in susceptibility are hypothesized to be due to genetic variability.

Strains of mice differ with respect to susceptibility to NIHL as measured by the auditory brainstem response (Henry, 1982, 1983, 1992). Shone et al. (1991) exposed the inbred mouse strains C57BL/6 and CBA/Ca to 101 dB broadband noise for 45 min. They found that the C57BL/6 mice, which already exhibited presbycusis, were more damaged by the noise than the normally hearing CBA/Ca mice. They had not tested the C57BL/6 mice before the onset of presbycusis.

The C57BL/6 and CBA/Ca mice have been exposed

* Corresponding author. NIOSH, Mailstop C-27, 4676 Columbia Parkway, Cincinnati, OH 45226, USA. Tel.: +1 (513) 533-8142; Fax: +1 (513) 533-8510; E-mail: rrd1@cdc.gov.

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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 hearing of 1- and 2-month-old CBA/Ca mice was more easily damaged by noise, but less easily damaged by noise at 3 and 5 months of age. The C57BL/6 mice were easily damaged by noise from 1 to 5 months of age when they exhibited AHL.

Erway et al. (1993) examined the hearing history of five inbred strains and their ten hybrid strains for age-related hearing loss (AHL). Based on the patterns of ABR threshold shifts in the mice at 12, 16 and 23 months of age, Erway et al. postulated that three recessive genes may be responsible for the enhanced susceptibility to AHL. Johnson et al. (1997) have shown that AHL in the inbred C57BL/6J strain of mice is affected by a recessive gene designated *Ahl* and is mapped to Chromosome 10. Erway et al. (1996) demonstrated that mice which were homozygous for the *Ahl* gene had greater permanent threshold shift to the same noise level than mice heterozygous or homozygous for the wild version of the gene. Newlander et al. (1995) have shown that enhanced susceptibility to NIHL is highly correlated with segregation of the *Ahl* gene among backcross progeny.

The purpose of the present study was to determine how much more sensitive to noise damage the inbred C57BL/6J mice were than the inbred CBA/CaJ mice. Also, by developing a dose-response curve for each strain exposed to noise we hypothesized that it would be possible to determine if the mechanism of action for the ototraumatic effects of the noise is similar or different for the two strains of mice. This can be accomplished by comparing the slopes and inflection points for both noise dose-response curves, a technique routinely used in pharmacodynamic studies (e.g. Goldstein et al., 1974).

2. Materials and methods

2.1. Subjects

Seventy-seven mice were used in this study. Two strains of mice were utilized: the inbred strain CBA/CaJ (abbreviated CB), the model for normal auditory function, and the inbred strain C57BL/6J (abbreviated B6), the model for early presbycusis. The B6 mice were bred at the University of Cincinnati (UC) from Jackson Laboratory stock; the CB mice were either purchased from Jackson Laboratory, Bar Harbor, ME or bred at UC from Jackson stock. Groups of B6 mice consisted of both males and females; CB groups were all males due to unavailability of age matched females. In an earlier study (Erway et al., 1996) there was no significant difference for NIHL between male and female mice of the CB or B6 strains. All mice were maintained and tested at the University of Cincinnati. All exposures were conducted at the National Institute for Occupational Safety and Health (NIOSH) Noise Lab. All procedures were approved by the Institutional Animal Care and Use Committees of both UC and NIOSH.

For noise exposure the mice were transported once in an air-conditioned, noise-limited vehicle to NIOSH. Mice were 3–4 months of age at the time of exposure. All mice were screened for normal ABR thresholds at the time of pre-testing: within ± 5 dB for each test stimulus of 35 dB for clicks; 30 dB for 8 kHz; 35 dB for 16 kHz and 50 dB for 32 kHz. Mice not within ± 5 dB of normal were eliminated from the study. Ten mice died during the course of the study. No data from the dead mice were used.

2.2. ABR testing

Mice were tested both before and after noise exposure to determine the 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 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 needle 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 Hz to 3000 Hz) by a Grass 511 pre-amplifier before presentation 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 prior to use with Brüel and Kjær 1/8 inch microphone at the tip of the funnel as described by Erway et al. (1993). The ABR was obtained by averaging 128 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 waveform disappeared, then by raising and lowering the stimulus intensity in 5 dB steps. The supra-threshold ABR waveform in mice typically exhibits four peaks between 1 and 5 ms after onset of the stimulus. Threshold was taken to be the lowest stimulus level at which a normal ABR wave could still be iden-

tified for at least two peak latencies. A threshold shift was defined as the ABR threshold after noise exposure minus the ABR threshold for that mouse before noise exposure. ABR thresholds were determined before exposure to noise and at 2–7 h, 1 and 3 days, and 1 and 2 weeks after exposure to noise.

2.3. Noise exposure

The NIOSH noise exposure facility has been described (Davis and Franks, 1989). A six compartment hardware cloth cage was constructed allowing one mouse per compartment. Acoustic testing of the compartments showed that noise presentations were within ± 1 dB. Six alert mice were placed into the six compartment cage. A single cage was placed inside an exposure chamber. A cover consisting of four Realistic 40-1320B Super-Tweeters was placed on each chamber. The exposure 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 a Wavetek 7580A attenuator. The output of the attenuator was conditioned by a Mackie 1202 pre-amplifier, amplified by a Soundcraftsman 300X4 Power Amplifier and cabled to the Realistic Super-Tweeters. The Super-Tweeters incorporated a 5 kHz high-pass filter. The spectrum of the noise exposure stimulus was center weighted between 7 kHz and 17 kHz. A graph of the third octave analysis has been published in Erway et al. (1996). The noise exposure was monitored by an in-chamber Sennhauser MKE 2-3 electret microphone and displayed on a Brüel and Kjær 2606 or 2610 Measuring Amplifier operating in the linear mode. The monitoring system was calibrated pre- and post-exposure by use of a Brüel and Kjær 4230 Sound Level Calibrator. Exposures were for 1 h.

Pilot studies indicated that B6 mice appeared to produce maximum threshold shift at 113 dB, and CB mice did not produce any permanent threshold shift until exposed to 110 dB. Based on these pilot data no B6 mice were exposed to noise greater than 113 dB and no CB mice were exposed to a noise lower than 110 dB. This made for an asymmetric exposure sequence but maximized use of mice. Mice were randomly assigned to groups and groups were randomly assigned to exposures. Different groups of mice were exposed to different levels of noise and each group was exposed only once. Groups of B6 mice were exposed to: 0 dB ($n=2$), 98 dB ($n=8$), 101 dB ($n=7$), 104 dB ($n=7$), 107 dB ($n=11$), 110 dB ($n=6$); 113 dB ($n=7$). Groups of CB mice were exposed to: 0 dB ($n=6$), 110 dB ($n=5$), 113 dB ($n=6$), 116 dB ($n=6$); 119 dB ($n=6$).

During the experiment the unexposed control groups of both strains showed no changes in ABR threshold due to handling, transportation or aging.

2.4. Statistical analyses

Analysis of variance (ANOVA) was used to analyze the data. Between-subject factors included strain (B6 vs. CB), sex (male vs. female), noise level (0, 98, 101, 104, 107, 110, 113, 116, 119 dB) and the six compartments within the exposure cage (1–6). Within-subject factors included test sequence (pre-exposure, 2–7 h, 1 and 3 days, and 1 and 2 weeks post-exposure) and test stimulus frequency (click, 8, 16 and 32 kHz). A main effect or interaction 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 for repeated measures. All statistical analyses were conducted in SAS®.

There was no statistically significant difference between males and females of the B6 strain ($F(1,46)=0.00$, $P=0.94$) nor between the six compartments within the exposure cage ($F(14,46)=1.01$, $P=0.45$) on threshold shift. This allowed us to collapse subject data by strain and across sex without concern for confounding variables.

Non-linear regression analysis was used to fit the data with the equation described below. A z-test was used to determine if the parameters of two curves (one for B6 and one for CB at each test frequency) were significantly different. Any z-value greater than 1.96 or less than -1.96 ($P<0.05$) was considered statistically significant.

3. Results

Fig. 1 shows the effect of and the recovery from the noise exposures over time. The overall effects of this particular noise exposure are most clearly shown for the groups of B6 mice at the 16 kHz test frequency. The amount of TTS was incremental with the level of the noise exposure, with each group resolving to lower levels of PTS by 14 days after exposure. The other test frequencies exhibited similar but less well ordered responses. By comparison the groups of CB mice exposed to the two highest noise levels (116 and 119 dB) exhibited about the same maximal TTS over the first two post-exposure tests; for the three pure tone test frequencies both high exposure groups of CB mice resolved to a similar PTS (about 30 dB). For the click stimulus these same high exposure groups of CB mice exhibited higher PTS (about 45 dB). By contrast the groups of CB mice exposed to 110 and 113 dB noise resolved to nearly no PTS by 14 days.

By two weeks these TTS changes resolved to a permanent threshold shift (PTS) for the higher noise exposures in both strains. For the same noise level the PTS was greater in the B6 mice than in the CB mice.

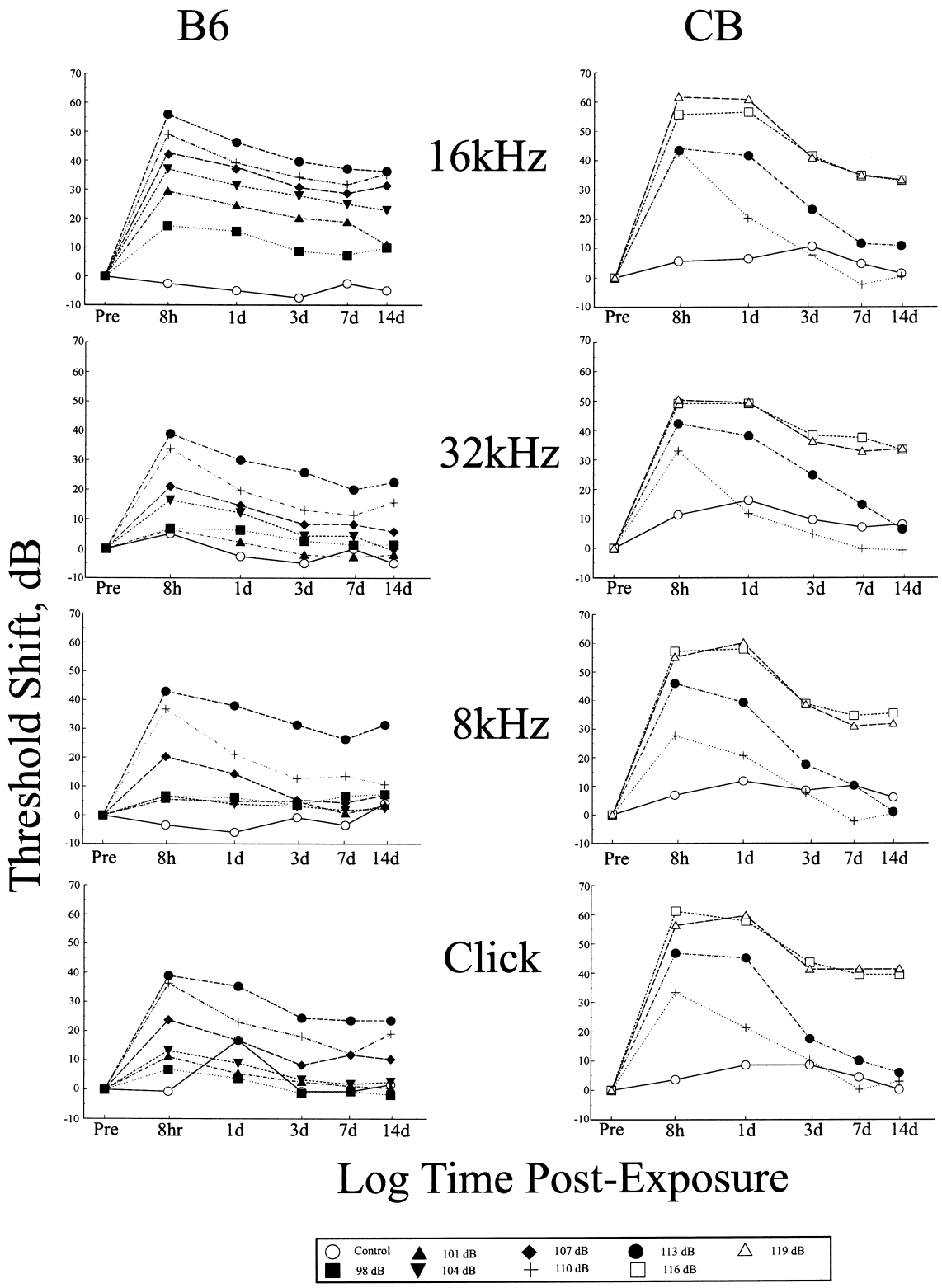

Fig. 1. Time course of threshold shifts due to different levels of noise exposures. B6 (*Ahl/Ahl*) mice are in the left column and CB (+/+) are in the right column. Each row represents different test stimuli: 16 kHz, 32 kHz, 8 kHz and click. Each individual graph presents all noise levels for each strain represented in log time. Only three exposure levels, 0, 110 and 113 dB, are common to both strains. Each curve represents the same group of mice over time. Within the CB and B6 strains, the differences in ABR threshold shift between mouse groups exposed to different levels of noise were statistically significantly different ($F(8,59) = 23.9$, $P = 0.0001$). Post-exposure test sequence within the B6 and CB strains was statistically significant ($F(4,184) = 6.27$, $P = 0.001$) for threshold shift. This is expected given the dynamic shape of the recovery curves.

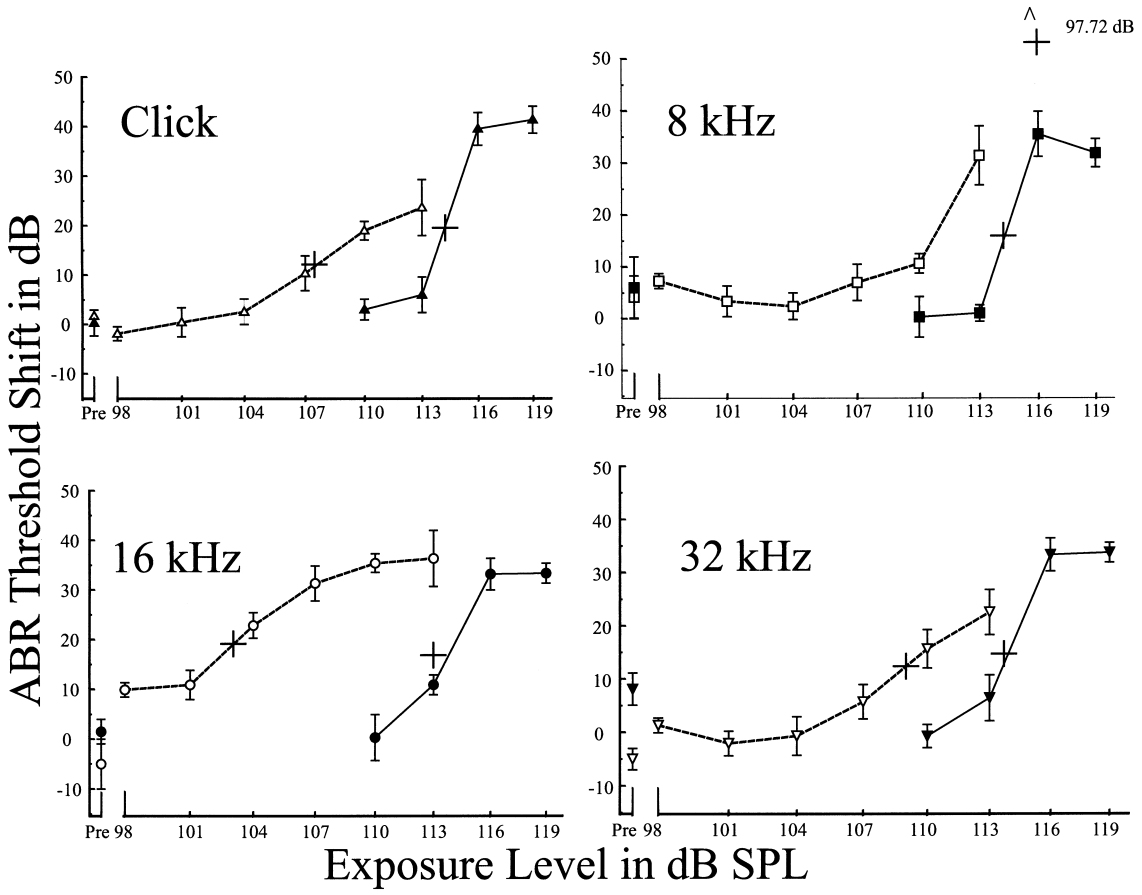

Fig. 2. Dose-response curves for noise effects on ABR threshold. Open symbols are B6 data, filled symbols are CB data. Left-most points on all graphs are unexposed control levels. Each point represents the mean ABR threshold shift of one group of mice exposed to one noise level once, recorded 2 weeks after exposure. Each individual graph represents a different ABR test frequency. The cross represents the inflection point for each curve, the half effect point. Error bars indicate standard error.

The PTS due to the noise exposure was greatest at the 16 kHz test stimulus in both strains, less at 32 kHz and click, and least at 8 kHz. The test stimulus frequency by noise level interaction was statistically significant ($F(32,184) = 3.04$, $P = 0.0001$) indicating that varied noise levels affected different ABR test frequencies. Fig. 2 shows the PTS graphed as a function of log noise exposure for each test frequency. All CB curves are grouped on the right of the graphs and all B6 curves are grouped to the left; also the slope of the CB mice curves are much steeper compared with the B6 mice.

The equation developed by Burns and Robinson (1970) for predicting hearing loss due to noise exposures in human populations was modified to model these data. Their equation was:

$$H = 27.5(1 + \tanh\{L_{A2} + 10\log(T/T_0) + u_p - n\}/15) + u_p \quad (1)$$

where H represents hearing loss in decibels, L_{A2} represents the A-weighted noise intensity and T represents the duration of exposure in years. T_0, u_p and n change for different exposure levels and durations so that the equation can accurately predict the hearing loss suffered. For the present study the above equation was modified to:

$$H = a(1 + \tanh(E - E_0/m)) + H_0 \quad (2)$$

where H represents the PTS when exposed to a certain noise level (E). The parameter H_0 represents the initial hearing level of the mouse; while m is *inversely* related to the slope of the dose-response curve. E_0 is the inflection point or the point at which half the maximum effect occurs. a is the size of the half maximum effect. Values for E ranged from 98 to 119 dB. Eq. 2 was used to fit a curve to the data. The parameter estimates are given in Table 1 and inflection points are included in Fig. 2 as '+' values. The slopes for the CB mice are steeper ($m_{CB} = 0.0$ to 1.18 vs. $m_{B6} = 2.92$ to 6.53) and the inflection points (114 dB vs. 103 dB) are to the right of the B6 mice.

Table 1
Results of the curve fitting procedures (Eq. 2)

Strain	Test stimulus	H_0	E_0	m	a
C57BL/6J (B6) (*Ahl*/*Ahl*)	click	0.0	107.66	3.53	12.27 dB
	8 kHz	4.46	116.53	3.85	97.72 dB
	16 kHz	0.00	102.95	6.53	19.48 dB
	32 kHz	0.00	108.95	2.92	11.87 dB
CBA/CaJ (CB) (+/+)	click	1.62	114.23	1.18	19.87 dB
	8 kHz	2.48	114.43	0.00	15.60 dB
	16 kHz	0.91	113.04	0.10	16.17 dB
	32 kHz	3.65	113.57	0.49	14.93 dB

H_0 represents the initial hearing level of the mouse for that test frequency. m is inversely related to the slope of the dose-response curve (a smaller value results in a steeper slope). E_0 is the inflection point or the point at which half of the maximum effect occurs. a is the size of the half maximum effect.

The z-tests demonstrated that the differences in slopes of the curves as indicated by m between the two strains (B6 vs. CB) were statistically significantly different at 16 kHz ($z = 3.020$, $P = 0.0025$), at 32 kHz ($z = \infty$, $P = 0.0000$) and for the click ($z = 2.664$, $P = 0.00770$). There was no significant difference between the two strains at 8 kHz ($z = 0.6317$, $P = 0.52$). The strain differences between the point at which the half maximum effect occurs (E_0) were statistically significant for 16 kHz ($z = -869228.4$, $P = 0.0000$), for 32 kHz ($z = -3.61$, $P = 0.0003$) and for the click ($z = -15.59$, $P = 0.0000$). The strain difference was not statistically different for the 8 kHz curves ($z = 0.04$, $P = 0.9662$). The difference between the size of the half maximum effect was statistically significant for the click ($z = -4.8291$, $P = 0.0000$) but was not significant for any other frequency (8 kHz: $z = 0.0424$, $P = 0.9662$; 16 kHz: $z = 1.4344$, $P = 0.1515$; 32 kHz: $z = -0.9227$, $P = 0.3562$). Clearly, 8 kHz is a unique situation because the B6 mice didn't demonstrate an upper asymptote and the CB mice didn't demonstrate a lower asymptote. This resulted in an extremely high standard error for the B6 mice which led to a high estimate for the level of the half effect, a, for the fitted curve of 97.72 dB, almost five times higher than the next highest value, 19.87 dB.

4. Discussion

This study shows that, depending upon the test frequency, B6 mice are about 5 to 10 dB more susceptible to noise than CB mice. In addition, the differing slopes and inflection points of the two dose-response curves (Table 1) indicate that the mechanism of action of noise is probably different in the two mouse strains. For B6 mice in the linear region of the curve, noise causes a PTS of about 1 to 3 dB for every dB of noise increase, while for CB mice noise causes a PTS of about 5 to 12 dB for every dB of noise increase. This indicates gradual hearing damage as noise increases for the B6 mice but almost a step function for damage for the CB mice.

If the mechanism of damage were the same in both strains of mice, the two dose-response curves would be parallel, displaced on the x-axis by the difference in susceptibility. Also, if the mechanisms were the same, you would expect to see the same maximum threshold shift. These are the kind of effects seen in pharmacodynamic studies with drug log dose-response curves (Goldstein et al., 1974).

We speculate that the ears of B6 mice are damaged by the effect of noise on a metabolic or physiological process. The linear portion of the dose-response curve being shallow indicates that noise at different levels is having small, incremental effects on the permanent threshold shift. On the other hand, we speculate that the ears of CB mice are being affected by mechanical damage to the cochlea. This is because the difference in noise level between no damage and maximum damage is so small. Henderson and Hamernik (1982) came to a similar conclusion in chinchillas exposed to impact noise. They hypothesized that ears exposed to continuous noise are damaged through metabolic processes, but ears exposed to impact noise are damaged through structural damage to the organ of Corti. This is because continuous noise produced a linear growth in hearing loss while impact noise produced a discontinuity in growth, often called a critical level, over which hearing loss became maximal.

The homozygous *Ahl* gene may produce a general weakening of the hair cells in the organ of Corti. Li (1992b) showed that C57BL/6 mice were also more vulnerable to the ototoxic effect of toluene than CBA mice.

There are a number of implications for humans. First, there may be a gene similar to *Ahl* present in the human population which increases susceptibility to NIHL and causes an early onset of age-related hearing loss.

A second implication may be that ears more susceptible to presbycusis may be more susceptible to noise damage. This may be an important warning sign for

workers: If your parents suffered from early hearing loss, you may need to protect your hearing to a greater extent than other workers.

The results of this experiment indicate that noise-susceptible ears may be damaged through metabolic processes at levels which are not damaging to normally susceptible ears. One can only speculate what these metabolic processes might be. Further research will be necessary to uncover the answers to these questions.

These dose-effect curves provide an important tool in looking at different noise-susceptible mouse strains. By using noise of equivalent spectrum at equivalent decibel levels, dose-response curves for different strains of mice may be compared.

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