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Intensity Difference Limens in Adult CBA/CaJ Mice (*Mus musculus*)

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Abstract

Mice have emerged as important models of auditory perception and acoustic communication. To study and model complex sound perception and communication, basic hearing abilities have to be established, yet intensity difference limens have not been measured in CBA/CAJ mice. Nine mice were trained using operant conditioning procedures with positive reinforcement to discriminate sound intensity across frequencies. Intensity difference limens were measured for 12, 16, 24, and 42 kHz tones at 10 and 30 dB sensation levels. Mice are capable of discriminating intensities across frequencies and sensation levels, but have higher IDL thresholds than other mammals.

Keywords

Intensity discrimination; psychoacoustics; operant conditioning; bioacoustics; animal communication

1. Introduction

CBA/CaJ mice (*Mus musculus*) are frequently used as models for human hearing and communication (reviewed in Willott, 2001). Previous studies have utilized operant conditioning procedures to establish the CBA/CaJ mouse's hearing capabilities. This strain shows peak hearing sensitivity in the 8 to 24 kHz range (Radziwon et al., 2009). CBA/CaJ mice can detect ultrasonic vocalizations (USVs) and pure tones up to 36 months of age (Kobrina and Dent, 2016). Frequency difference limens in these mice are similar to those in other rodents but are higher than thresholds in humans, and they use frequency, not duration, in cue trading experiments (Radziwon and Dent, 2014). CBA/CaJ mice are capable of detecting USVs across the lifespan (Kobrina and Dent, 2016). They use spectrotemporal similarity in discriminating USVs (Neilans et al., 2014), and utilize the USV beginning, not the middle or end, for discrimination (Holfoth et al., 2014).

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Another important step for understanding mouse hearing is to measure intensity discrimination. Intensity difference limens (IDLs) have been reported for a variety of rodents (Figures 1 and 2), but not CBA/CaJ mice. Here, we measured IDLs for 12, 16, 24, and 42 kHz tones at 10 and 30 dB sensation levels (SL) using operant conditioning procedures.

2. Materials and methods

2.1 Subjects

Four mice (2 M and 2 F) participated in the 10 dB SL condition and five mice (3 M and 2 F) participated in the 30 dB SL condition. All mice were housed individually and kept on a reverse day/night cycle (lights off at 6 am and on at 6 pm). They were water restricted and kept at approximately 85% of their free-drinking weights during the experiment. All procedures were approved by the University at Buffalo, SUNY’s Institutional Animal Care and Use Committee, and complied with ARRIVE guidelines and the associated NIH guide for the care and use of laboratory animals.

2.2 Apparatus

The mice were tested in a 23 x 39 x 15.5 cm wire cage in a sound-attenuated chamber. The chamber contained a Tucker Davis Technologies (TDT) ultrasonic speaker (ES1), a Med-Associates response dipper, and Med-Associates nose poke holes surrounded by infrared sensors. The experiments were controlled by Dell Optiplex 580 computers operating TDT modules and custom Matlab software (more details in Kobrina and Dent, 2016).

2.3 Stimuli

The test stimuli were 100 ms 12, 16, 24, and 42 kHz pure tones with 10 ms cosine rise/fall times. IDLs were measured for 10 and 30 dB SL. The SLs were determined by a previously obtained audiogram in this strain using the same apparatus and methods (Radziwon et al., 2009). All sounds were calibrated weekly and never varied by more than 5 dB.

2.4 Procedure

Mice were trained using a go/no-go operant conditioning procedure to discriminate a higher intensity target tone from a reference tone of the same frequency. The mice were tested in two 30-min or one 60-min sessions, 5 to 6 days/week, and ran between 100 and 300 trials/day. The mouse began a trial by nose poking through an observation nose-poke hole during a repeating background reference tone, which initiated a variable waiting interval ranging from 1–4 s. The reference tone was presented at a rate of one tone every 300 ms. After the waiting interval, the target was presented up to four times, alternating with the reference tone. In the “go” condition, the target was presented at a higher intensity than the background. A “hit” was recorded if the mouse correctly responded by nose poking through the report nose-poke hole within the 2-s response window and the mouse received a 0.01 ml of Ensure® reinforcement. A “miss” was recorded if the mouse failed to nose poke to the report nose-poke hole during the response interval.

Thirty percent of trials were “no go” trials, where the repeating background continued through the response interval. These trials were required to measure the false alarm rate and calculate the animal's response bias. 5% of testing sessions with false alarm rates greater than 20% were excluded from final data analysis.

Targets were presented according to the psychophysical Method of Constant Stimuli, where stimuli above and below the presumed threshold were presented to the subjects in a random order in ten trial blocks (7 targets, 3 shams). Every mouse was tested on four stimulus conditions in a randomized order. A different random order was used for each subject. Completion time for each condition varied across subjects (14 – 75 days).

2.5 Data analysis

Mean hit and false alarm rates were used to calculate thresholds using a signal detection theory threshold criterion of d' =1.8. Thresholds were calculated using the last 200 trials out of at least 400 trials. If thresholds varied by more than 3% between the first and last 200 trials, testing continued until thresholds stabilized. A mixed two-factor analysis of variance (ANOVA) was used to compare performance across frequencies and SL. A Holm-Sidak post hoc analysis was used to assess pairwise significance within these results, and coefficient of variations (CV) were used to assess variability within conditions.

3. Results and discussion

The mice were able to discriminate intensity for all tones at 10 and 30 dB SL (Figures 1 and 2). The ANOVA revealed a significant main effect of frequency, $F(3, 28) = 4.07$, $p = 0.016$, $\eta^2 = 0.30$, and SL, $F(1, 28) = 6.49$, $p = 0.017$, $\eta^2 = 0.19$. There was a significant interaction between frequency and SL, $F(3, 28) = 4.90$, $p = 0.007$, $\eta^2= 0.35$. Pairwise comparisons revealed that mice discriminated 16 and 42 kHz pure tones differently across SLs (16 kHz $t = 4.037$, $p = 0.001$; 42 kHz $t = 2.066$, $p= 0.048$). CVs for 10 dB SL were 12 kHz = 13%, 16 kHz = 33%, 24 kHz = 58%, 42 kHz = 87%. CVs for 30 dB SL were 12 kHz = 61%, 16 kHz = 43%, 24 kHz = 16%, 42 kHz = 24%.

Overall, thresholds were somewhat higher than those of other rodents and mammals (Figure 1). CBA/CaJ mice exhibit a decrease in IDLs with an increase in SL for 16 and 42 kHz only (Figure 2). Methodological (shorter intensity tones) or physiological differences could be responsible for the observed higher IDLs in CBA/CaJ mice relative to other mammals. CBA/CaJ mice require higher intervals in spatiotemporal response patterns to discriminate intensity for the same characteristic frequencies than other species (Holmstrom et al., 2010), but auditory nerve firing rates for louder stimuli are necessary to draw further conclusions.

One limitation of this finding is that thresholds from Radziwon et al., 2009 were used for calculating SLs in this study. While both experiments used identical setups and equipment, it is possible that Radziwon et al. (2009) had a more sensitive group of mice than this sample.

In conclusion, the present study expands on the existing behavioral literature in both rodents and mammals. CBA/CaJ mice are capable of discriminating differences in intensity across different SLs, although they were not as sensitive as other mammals tested to date. These results suggest that mice may use intensity differences, in addition to other acoustic cues, to distinguish between their own communication signals, but that large intensity differences would be necessary to do so.

Acknowledgments

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Highlights

- Intensity difference limens (IDLs) were measured for pure tones in CBA/CaJ mice
- IDLs were measured for 10 dB and 30 dB sensation levels
- CBA/CaJ mice exhibit decreases in IDLs with increases in sensation level
- Thresholds were slightly higher than in other mammals

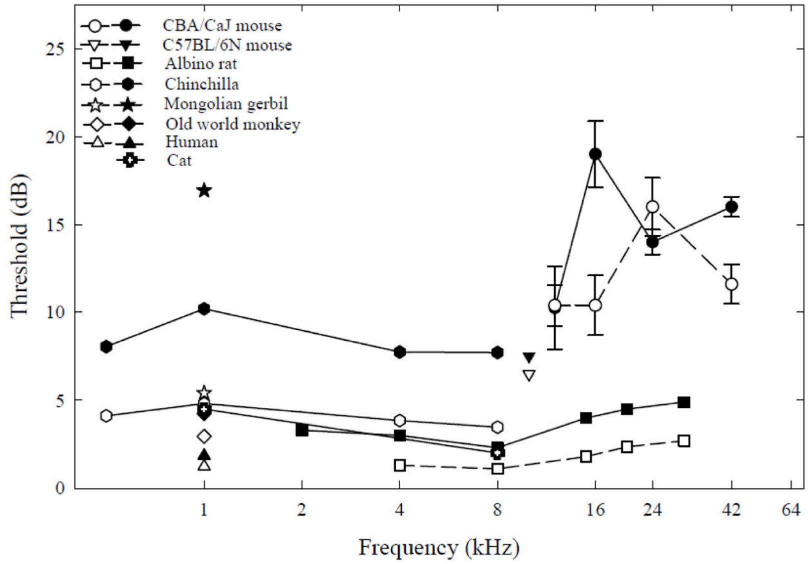

Figure 1.

Raw mean IDLs across frequencies for several mammals measured with operant conditioning procedures and positive reinforcement. CBA/CaJ mouse mean IDLs for 100 ms tones at 10 dB (black circles) and 30 dB SL (white circles) in the current study, with standard error bars. Mean IDLs for C57BL/6N mice for 100 ms tones at 30 dB (black upside-down triangles) and 50 dB SL (white upside-down triangles) (Behrens and Klump, 2015). Albino rat mean IDLs for 1.2 s tones at 20 dB (black squares) and 40 dB SL (white squares) (Hack, 1971). Chinchilla mean IDLs at 10 dB (black hexagons) and 30 dB SL (white hexagons) for 500 ms tone bursts (Saunders et al., 1987). Mongolian gerbil IDLs at 30 dB (black stars) and 50 dB SL (white stars) for 400 ms tones (Sinnott et al., 1992). Old world monkey IDLs at 10 dB (black diamonds) and 30 dB SL (white diamonds) for 400 ms tones (Sinnott et al., 1992). Human IDLs at 10 dB (black triangles) and 30 dB SL (white triangles) for 400 ms tones (Sinnott et al., 1992). Cat IDLs (black plus signs) at 65 dB SL for 250 ms tones (May and McQuone, 1995).

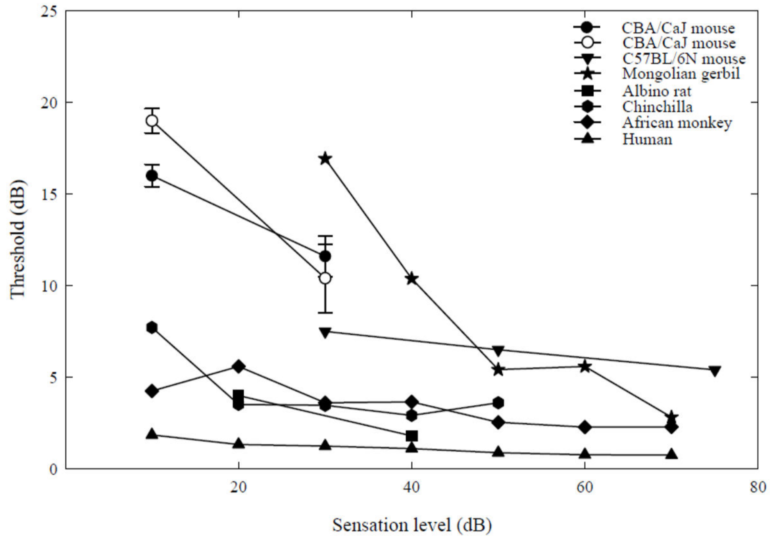

Figure 2.

Raw mean IDLs across SLs for several mammals measured with operant conditioning procedures and positive reinforcement. Mean IDLs with standard error bars for 16 kHz (white circles) and 42 kHz tones (black circles), for the current study. Mean IDLs for the C57BL/6N mouse for 100 ms 10 kHz tones (black upside-down triangles) (Behrens and Klump, 2015). Albino rat mean IDLs (black squares) for 1.2 s 15 kHz tones (Hack, 1971). Chinchilla mean IDLs (black hexagons) for 500 ms 8 kHz tones (Saunders et al., 1987). Mongolian gerbil IDLs (black stars) for 400 ms 1 kHz tones (Sinnott et al., 1992). Old world monkey IDLs (black diamonds) for 400 ms 1 kHz tones (Sinnott et al., 1992). Human IDLs (black triangles) for 400 ms 1 kHz tones (Sinnott et al., 1992). Cat IDLs (black plus signs) for 250 ms tones (May and McQuone, 1995).