



Research Paper

Hyperexcitability of inferior colliculus and acoustic startle reflex with age-related hearing loss



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ABSTRACT

Chronic tinnitus and hyperacusis often develop with age-related hearing loss presumably due to aberrant neural activity in the central auditory system (CAS) induced by cochlear pathologies. However, the full spectrum of physiological changes that occur in the CAS as a result age-related hearing loss are still poorly understood. To address this issue, neurophysiological measures were obtained from the cochlea and the inferior colliculus (IC) of 2, 6 and 12 month old C57BL/6J mice, a mouse model for early age-related hearing loss. Thresholds of the compound action potentials (CAP) in 6 and 12 month old mice were significantly higher than in 2 month old mice. The sound driven and spontaneous firing rates of IC neurons, recorded with 16 channel electrodes, revealed mean IC thresholds of 22.8 ± 6.5 dB ($n = 167$) at 2 months, 37.9 ± 6.2 dB ($n = 132$) at 6 months and 47.1 ± 15.3 dB ($n = 151$) at 12 months of age consistent with the rise in CAP thresholds. The characteristic frequencies (CF) of IC neurons ranged from 3 to 32 kHz in 2 month old mice; the upper CF ranged decreased to 26 kHz and 16 kHz in 6 and 12 month old mice respectively. The percentage of IC neurons with CFs between 8 and 12 kHz increased from 36.5% in 2 month old mice, to 48.8% and 76.2% in 6 and 12 month old mice, respectively, suggesting a downshift of IC CFs due to the high-frequency hearing loss. The average spontaneous firing rate (SFRs) of all recorded neurons in 2 month old mice was 3.2 ± 2.5 Hz ($n = 167$). For 6 and 12 month old mice, the SFRs of low CF neurons (< 8 kHz) was maintained at 3–6 spikes/s; whereas SFRs of IC neurons with CFs > 8 kHz increased to 13.0 ± 15.4 ($n = 68$) Hz at 6 months of age and then declined to 4.8 ± 7.4 ($n = 110$) spikes/s at 12 months of age. In addition, sound-evoked activity at suprathreshold levels at 6 months of age was much higher than at 2 and 12 months of age. To evaluate the behavioral consequences of sound evoked hyperactivity in the IC, the amplitude of the acoustic startle reflex was measured at 4, 8 and 16 kHz using narrow band noise bursts. Acoustic startle reflex amplitudes in 6 and 12 month old mice ($n = 4$) were significantly larger than 2 month old mice ($n = 4$) at 4 and 8 kHz, but not 16 kHz. The enhanced reflex amplitudes suggest that high-intensity, low-frequency sounds are perceived as louder than normal in 6 and 12 month old mice compared to 2 month olds. The increased spontaneous activity, particularly at 6 months, may be related to tinnitus whereas the increase in sound-evoked activity and startle reflex amplitudes may be related to hyperacusis.

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1. Introduction

In the past two decades, many animal studies have investigated the neural mechanisms underlying chronic tinnitus induced by

intense noise exposures or ototoxic drugs (Chen et al., 2015; Eggermont, 2015; Roberts et al., 2010; Sun et al., 2009; Szczepaniak and Moller, 1996). Several studies found significant increases of spontaneous firing rates (SFRs) in the cochlear nucleus and inferior colliculus (IC) (Dong et al., 2010; Kaltenbach, 2000). Increases of SFRs, changes in neural synchrony and aberrant tonotopic map reorganization have also been observed at higher levels of the central auditory system (CAS); these changes have

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been considered as potential neural correlates of tinnitus (Roberts et al., 2010).

The prevalence of tinnitus increases rapidly with age until 60–69 years (Chang and Chou, 2007; Shargorodsky et al., 2010). This increase in the prevalence of tinnitus could be due to aging alone or the progressive increase in age-related hearing loss. The severity of age-related tinnitus ranges widely from being a slight nuisance to severely affecting a person's daily life. Although age-related hearing loss is the most common cause of sensorineural hearing loss, in adults, few studies have explored the neural correlates of tinnitus and hyperacusis related to age-related hearing loss.

The IC is an important binaural relay station which routes information from key auditory nuclei in the brainstem to the auditory thalamus and auditory cortex (AC). Acute acoustic trauma, which decreases the neural output of the cochlea, paradoxically causes a significant increase in the amplitude of IC local field potentials indicative of enhanced central gain, but decreases the SFRs (Niu et al., 2013). Several weeks after acoustic overstimulation, the spontaneous activity of IC neurons increased significantly among neurons tuned to frequencies within the region of hearing loss (Robertson et al., 2013). This spontaneous hyperexcitability in the IC, which could result from reduced central inhibition, has been considered to be a neural correlate of central tinnitus (Dong et al., 2010). Willott et al. had reported functional changes in the CAS induced by age-related hearing loss (Willott et al., 1988a, 1988b). Most IC neurons of 6–12 month old C57 mice were well-driven by suprathreshold stimuli and the spontaneous activity increased with age in the central nucleus but not in other IC subnuclei (Willott et al., 1988b). Ison et al. found that low-frequency acoustic startle responses of C57 mice increased with age, behavior potentially related to hyperacusis (Ison et al., 2007). Studies of noise and drug-induced hearing loss suggest that spontaneous and sound evoked hyperexcitability in the CAS may be linked to tinnitus and hyperacusis; however, this association is not well-established in cases of age-related hearing loss. To test this hypothesis, we measured the spontaneous activity and sound-induced excitatory responses in IC neurons from C57BL/6J mice at 2, 6 and 12 months of age. We predicted that SFRs in the IC of C57BL/6J mice, which develop early onset age-related hearing loss, would increase with advancing age. As hyperacusis is commonly associated with tinnitus, we hypothesized that sound driven activity would also increase with age-related hearing loss and that this would be associated with increases in the amplitude of the startle reflex.

2. Materials and methods

2.1. Animals

Thirty-six C57BL/6J mice (Jackson Lab, Bar Harbor, ME) were used for physiological experiments; 18 mice were used for compound action potential (CAP) recordings and the other 18 were used for IC recordings. For CAP and IC recording, twelve mice at age of 1–2 months were used as the controls (G-2M, $n = 6$), twelve mice between 6 and 7 months and twelve mice between 12 and 14 months were used as the middle-age group (G-6M, $n = 6$) and the old-age group (G-12M, $n = 6$), respectively. Twelve additional mice were used for acoustic startle reflex measurements. All protocols were approved by the Institutional Animal Care and Use Committee (IACUC) of the University at Buffalo and conform to the guidelines issued by the National Institutes of Health.

2.2. CAP recordings

Mice were anesthetized with a mixture of ketamine (100 mg/kg,

i.p.) and xylazine (50 mg/kg, i.p.) and their heads were positioned with a custom head-clamp. The surgical procedure to record the CAP has been described in our recent paper (Wang et al., 2016). The bulla was opened and a silver-ball electrode was placed on the round window under a microscope. The cochlear responses were amplified using a DAM-50 amplifier (WPI, filter setting 300 Hz to 10 kHz). The external auditory meatus was opened at the end of the ear canal and the speaker was placed at the opening of the ear canal. Tone bursts (10 ms duration, rising/fall time 0.5 ms) centered at 4, 6, 8, 12, 16, 20, 24, 35 and 40 kHz were used to elicit the CAP. The threshold of CAP was defined as the minimal intensity of the minimal amplitude of CAP elicited.

2.3. IC surgery and electrophysiology

Mice were anesthetized with a mixture of ketamine (100 mg/kg, i.p.) and xylazine (50 mg/kg, i.p.). The pedal withdrawal reflex of the hind limbs was checked every 45 min to assess the anesthetic depth. Supplemental ketamine (20 mg/kg, i.p.) was given as needed to maintain the proper plane of anesthesia. The skin over the parietal and nasal bone was carefully removed to expose the skull. After removal of the tissue on the surface of the skull, the skull was treated with 3% hydrogen peroxide (H_2O_2) and a head-fixing pole was glued on the parietal bone with dental cement. The fixing pole attached to a magnetic stand was used to firmly hold the mouse's head during the test. A $\sim 3 \times 3$ -mm region of cranial bone overlying the dorso-caudal aspect of the cerebellum was removed to expose left IC (Niu et al., 2013).

A 16-channel microelectrode (NeuroNexus, A1x16-5 mm-100–177, Ann Arbor, MI) was used to record IC responses in anesthetized mice. The electrode was mounted on a hydraulic manipulator (FHC Inc., Bowdoinham, ME) and advanced into the IC at an angle of approximately 75–80° relative to the surface of the IC. The output of the electrode was connected to a 16-channel preamplifier (RA16PA, Tucker-Davis Technology, TDT). The output of the pre-amplifier was delivered to a digital signal processing module (RZ5, TDT) connected to a computer. A stainless-steel electrode inserted into the frontal lobe was used as the ground. Mouse body temperature was maintained at 37 °C using a thermally regulated heating pad system (Harvard Apparatus, Cambridge, MA). The multiunit recording typically finished in 2–3 h. A small dose of supplemental ketamine and xylazine mixture (~ 0.1 ml) was added in every 30 min during the recording.

Recording were obtained from different regions of the central nucleus of the IC; this was accomplished by inserting the electrode into different locations starting from the lateral side and moving medially while avoiding major blood vessels. As the characteristic frequency (CF) of IC neurons increased with depth from the IC surface, the electrode was advanced to ~ 1600 μ m in all the penetrations. Noise bursts (50 ms, 70–90 dB SPL) were presented three times per second as the electrode was advanced into the IC to search for neurons. The multiunit spike discharges were recorded using OpenEx (TDT) and custom software. Data were collected in the form of peristimulus time histograms (PSTH), frequency response area (FRA) maps and spike rate-level functions (Niu et al., 2013; Stolzberg et al., 2011). The CF from each recording site was defined as the frequency with the minimal threshold (MT). The sound-driven spike rate was calculated from a 50 ms window located near onset response of the averaged PSTHs.

Sound stimuli were generated with the TDT System-3 hardware and presented through a multi-field magnetic speaker (MF1, TDT). Tone bursts (50 ms duration, 1 ms rise/fall time, 1–42 kHz, 20 logarithmically spaced steps) were used to elicit responses. The sound intensity was varied from 10 to 90 dB SPL in 10 dB steps. Broadband noise burst rate-level functions (RLFs) were obtained

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