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Research Paper

Early age noise exposure increases loudness perception - A novel animal model of hyperacusis

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ABSTRACT

The neural mechanisms that give rise to hyperacusis, a reduction in loudness tolerance, are largely unknown. Some reports suggest that hyperacusis is linked to childhood hearing loss. However, the evidence for this is largely circumstantial. In order to rigorously test this hypothesis, we studied loudness changes in rats caused by intense noise exposure (12 kHz narrow band noise, 115 dB SPL, 4 h) at postnatal 16 days. Rats without noise exposure were used as controls. The exposed noise group (n = 7) showed a mean 40–50 dB hearing loss compared to the control group (n = 8) at high frequencies (>= 8 kHz) and less hearing loss at lower frequencies. Loudness was evaluated using sound reaction time and loudness response functions in an operant conditioning-based behavioral task using narrow-band noise (40 –110 dB SPL, centered at 2, 4 and 12 kHz). Interestingly, the sound reaction time of the noise group was significantly shorter than the control group at supra-threshold levels. The average reaction time was less than 100 ms in the noise group at 100 dB SPL, which was three times shorter than the control group. Our results indicate that early noise-induced hearing loss leads to a significant increase of loudness, a behavior indicative of hyperacusis. Our results are consistent with clinical reports suggesting that hearing loss at an early age is a significant risk factor for hyperacusis.

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1. Introduction

Hyperacusis is defined as marked intolerance to normal environmental sounds (Vernon, 1987). It is a common symptom in tinnitus (ringing in the ear) (Nelson and Chen, 2004), Williams syndrome (Johnson et al., 2001), autism (Khalfa et al., 2004) and other neurological conditions (Katzenell and Segal, 2001). The cause of hyperacusis is still not clear. Brain imaging studies indicate that hyperexcitability in the brain may be related to hyperacusis symptoms. Like tinnitus, hyperacusis is also related to hearing loss. For example, hyperacusis was reported after acute acoustic trauma in subjects who served in the military or worked in the shipbuilding industry (Axelsson and Hamernik, 1987). A clinical study found that after several weeks post plugging the ear, subjects reported increased hearing sensitivity (Munro and Blount, 2009). This study suggested that sound deprivation may lead to hypersensitivity to sound (Munro and Blount, 2009). In children with Williams syndrome, high-frequency hearing loss resembling the configuration of noise-induced hearing loss is commonly seen (Gothelf et al., 2006; Johnson et al., 2001). Other clinical reports also suggest that children who experience a period of sound deprivation caused by either conductive or sensorineural hearing loss during childhood can be more susceptible to developing tinnitus and hyperacusis (Coelho et al., 2007; Johnson et al., 2001).

Currently there are no objective measurements for hyperacusis. Clinically, hyperacusis is evaluated using questionnaires and the uncomfortable loudness level (UCL) test. Patients who complain of reduced tolerance to environmental sounds typically showed dropped UCL below 90 dB HL (Anari et al., 1999). UCL has been used as an important measurement to quantify hyperacusis (Anari et al., 1999). However, reduced UCL does not always directly relate with the severity of hyperacusis symptom. Therefore, the evaluation of loudness change has been used to develop and measure hyperacusis. Loudness measures have been reported using animals models with different behavioral training paradigms, such as a key releasing to the onset of sound (Miller et al., 1969), pressing and

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holding a lever for a time interval (May et al., 2009), and a two-choice operant conditioning test to sound stimulus at different levels (Zhang et al., 2014). Miller et al. (1969) reported that the sound reaction time of monkeys, which is defined as the time interval between presenting the sound stimuli and the onset of the response, was correlated to the sound intensity; the louder the sound the shorter the reaction time. Accordingly, sounds with the same reaction time were suggested to be equally loud. May et al. (2009) tested the sound reaction time in adult cats before and after noise exposure. They found that the reaction time after noise exposure increased at low intensities, but stayed the same as the preexposure level at middle intensity sounds (~70 dB SPL), indicative of loudness recruitment. As the cats did not respond to sounds above 70 dB SPL, they did not test how the reaction time changed at high intensities by noise exposure. Zhang et al. (2014) tested the loudness change up to 110 dB SPL in rats affected by high doses of salicylate using a two-choice operant conditioning paradigm. They reported reduced sound reaction time and increased loudness response function after high doses of salicylate exposure, suggestive of hyperacusis. Chen et al. (2014) also reported reduced reaction time in rats after exposure to high doses of salicylate using a go/no-go operant conditioning paradigm (Chen et al., 2014). These behavioral methods provided tools to study the causes of hyperacusis.

In our recent study, we found that temporary hearing loss at an early developmental age, not later in adulthood, increased the sound loudness by increasing the loudness response function and the acoustic startle response, an indication of hyperacusis (Sun et al., 2011). In this study we suggested that early age peripheral damage may cause a plasticity change in the brain and serve as a source of hyperacusis. Since noise-induced hearing loss is often found in tinnitus and hyperacusis patients, we undertook this study aiming to explore the effect of early-age noise exposure induced hearing loss in changing the sound loudness sensitivity in later adulthood. We hypothesized that noise exposure soon after the onset of hearing would lead to abnormally rapid loudness growth or hyperacusis in adulthood.

2. Methodology

2.1. Animals and noise exposure

Fifteen newborn male Sprague-Dawley rats (Harlan Laboratories Inc.) were used in the experiment. The animals were randomly divided into control group (n = 8) and noise group (n = 7). The care and use of animals was approved by the Institutional Animal Care and Use Committee at State University of New York at Buffalo.

At postnatal 16–25 days, the noise group was exposed to a narrow band noise centered at 12 kHz (1 kHz band width, 115 dB SPL, 2–4 h). Rats in the control group were left in the exposure cage without being exposed to noise. A sound level meter coupled to a half-inch condenser microphone (Model 824 Audiometer, Larson Davis) was used to calibrate the sound stimuli which were generated by a sound processor (RP 2, TDT, Alachua, FL, USA) and presented by a loud speaker (GMI D-49, GMI Sound Crop., Brooklyn, NY). The loud speaker was placed 10 cm away from the rat's head to expose both ears.

2.2. Hearing evaluation

Auditory brainstem response (ABR) was used for hearing evaluation for both groups of animals. The test was conducted in a sound attenuating room and the thresholds were obtained at 1, 4, 6, 8, 16 and 32 kHz. Rats were anaesthetized with a mixture of Xylazine (6 mg/kg) and Ketamine (50 mg/kg). Needle electrodes (Grass Technologies) were used; non-inverting (+) was inserted at the vertex, the inverting (−) electrode was placed near the pinna of the tested ear and the ground electrode was placed near the pinna of the contralateral ear. TDT system 3 (BioSigRP, Tucker-Davis Technology, Alachua, Florida, USA) was used to generate sound stimuli and data acquisition.

2.3. Audiogenic seizure

Rats were tested individually for audiogenic seizure susceptibility. Sound of 12 kHz narrow band noise (115 dB SPL) was turned on for up to 60 s or until the rats showed signs of seizure behavior. Jumping, wild running and erratic leaping were used as signs for audiogenic seizure. The sound stimulus was terminated immediately after the audiogenic seizure was induced.

2.4. Behavioral training

An operant conditioning based behavioral task was used to evaluate hyperacusis at 2, 4, and 12 kHz, respectively, to test if hyperacusis is related with hearing loss induced by high frequency noise exposure. The behavioral equipment was built using modules from Med-Associates Inc. and was controlled by TDT system (Tucker-Davis Technologies) with custom software (Sun et al., 2011; Zhang et al., 2014). Fig. 1 shows the diagram of the training box which had a head entry (nose-poke) used for initiating the testing trials. Two food dispensers with infrared head-entry detectors were installed on each side of the nose-poke along with a loud speaker on the ceiling of the training box. TDT system (RP6 and RP2) was used to control the food dispensers and sound stimuli.

Our behavioral paradigm was based on the paradigm used in our previous study (Zhang et al., 2014), with modifications on the testing frequencies. Rats were first trained to poke the middle head-entry to initiate a sound stimulus. After the sound was initiated, the rat had to poke the right head-entry or the left head-entry of food dispensers. Food restriction was applied to their home cage to maintain them at 90% of their normal body weight to keep them motivated for the behavioral training. During the training, rats were reinforced by the palatable food pellets (Bio-Serv, NJ, USA) to poke the right food dispenser (H-side) upon perceiving loud sound (90 dB SPL) and the left food dispenser (L-side) for soft sound (50 dB SPL). Choosing the wrong side would trigger a punishment including no release of food pellet and no trial initiation for 10 s. Rats had to keep their nose in the head-entry for at least one second (waiting time) until the sound presented. Withdrawing from the nose-poke earlier (<1 s) would not trigger an acoustic stimulation or the food pellet. This could be used as a procedure to reduce rat's random withdrawals without paying attention to the sound stimuli. The sound stimuli were presented in a random order during the training. These training procedures were repeated using the targeted frequencies (narrow band noise centered at 4, 2, and 12 kHz).

After achieving 95% accuracy, rats were put in a testing mode in which a narrow band noise at 40–110 dB SPL (10 dB step) was randomly presented. The test was conducted to measure the loudness response functions and the sound reaction time. The reaction time was considered the time between the onset-time of the acoustic stimulation to the time that the rats withdrew their nose from the nose-poke. The loudness response function was determined by measuring the percentage responses on the loud-side of the food dispenser when different intensities of the sound were presented (Sun et al., 2011; Zhang et al., 2014). During the test, poking on either side of the food dispenser was rewarded with a food pellet. Rats were required to poke the food dispenser within 10 s after the initiation of sounds. Trials in which the rats did not