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Research Paper

Noise-induced hearing loss induces loudness intolerance in a rat Active Sound Avoidance Paradigm (ASAP)

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ABSTRACT

Hyperacusis is a loudness hypersensitivity disorder in which moderate-intensity sounds are perceived as extremely loud, aversive and/or painful. To assess the aversive nature of sounds, we developed an Active Sound Avoidance Paradigm (ASAP) in which rats altered their place preference in a Light/Dark shuttle box in response to sound. When no sound (NS) was present, rats spent more than 95% of the time in the Dark Box versus the transparent Light Box. However, when a 60 or 90 dB SPL noise (2–20 kHz, 2–8 kHz, or 16–20 kHz bandwidth) was presented in the Dark Box, the rats" preference for the Dark Box significantly decreased. Percent time in the dark decreased as sound intensity in the Dark Box increased from 60 dB to 90 dB SPL. Interestingly, the magnitude of the decrease was not a monotonic function of intensity for the 16–20 kHz noise and not related to the bandwidth of the 2–20 kHz and 2–8 kHz noise bands, suggesting that sound avoidance is not solely dependent on loudness but the aversive quality of the noise as well. Afterwards, we exposed the rats for 28 days to a 16–20 kHz noise at 102 dB SPL; this exposure produced a 30–40 dB permanent threshold shift at 16 and 32 kHz. Following the noise exposure, the rats were then retested on the ASAP paradigm. High-frequency hearing loss did not alter Dark Box preference in the no-sound condition. However, when the 2–20 kHz or 2–8 kHz noise was presented at 60 or 90 dB SPL, the rats avoided the Dark Box significantly more than they did before the exposure, indicating these two noise bands with energy below the region of hearing loss were perceived as more aversive. In contrast, when the 16–20 kHz noise was presented at 60 or 90 dB SPL, the rats remained in the Dark Box presumably because the high-frequency hearing loss made 16–20 kHz noise less audible and less aversive. These results indicate that when rats develop a high-frequency hearing loss, they become less tolerant of low frequency noise, i.e., high intensity sounds are perceived as more aversive and should be avoided.

1. Introduction

Hyperacusis, or loudness intolerance, is an auditory hypersensitivity disorder in which an individual perceives moderate-intensity, everyday sounds as abnormally or uncomfortably loud (Blaesing and Kroener-Herwig, 2012). Approximately 6–9% of adults have loudness intolerance problems, but the percentage is likely higher because many are unaware of their condition. Hyperacusis is often associated with hearing loss and tinnitus. Approximately 40% of tinnitus patients have hyperacusis whereas up to 86% of hyperacusis patients also have tinnitus (Baguley, 2003). This comorbidity suggests that the neural substrate that gives rise to tinnitus and hyperacusis has some common underlying mechanisms.

Hyperacusis, like many other neurological disorders, has considerable phenotypic diversity (Pienkowski et al., 2014; Tyler et al., 2014). The simplest form is pure loudness hyperacusis, a condition in which moderate-intensity sounds are perceived as too loud. A second more complex form, referred to as avoidance hyperacusis, is a condition in which sounds are not only too loud, but also extremely annoying, dangerous or fear-evoking. Those with avoidance hyperacusis attempt to escape from moderately intense sounds by wearing earplugs or avoiding noisy social situations (Ashkenazi et al., 2010; Blaesing and Kroener-Herwig, 2012).

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Finally, some hyperacusis patients not only experience moderate-intensity sounds as too loud, but also painful, a condition referred to as pain hyperacusis (Tyler et al., 2014). For these patients, sound-evoked otalgia evokes painful sensations within and/or around the ear that can begin almost immediately or develop slowly over a few hours (McFerran and Baguley, 2007; Van Campen et al., 1999). Thus, in many cases, it is possible that the affective qualities of sound are just as critical as its acoustic properties for inducing hyperacusis.

While some progress has been made toward identifying the neural mechanisms involved in hyperacusis (Chen et al., 2015, 2016; Diehl and Schaette, 2015), advances have been hampered by the paucity of animal behavioral models that can both identify individual animals experiencing hyperacusis and determine the nature of the disturbance (i.e. if sounds are perceived as too loud, aversive, or painful). Enhanced acoustic startle reflex (ASR) amplitudes have often been used to infer the presence of hyperacusis in animals that have been exposed to noise or ototoxic drugs (Hickox and Liberman, 2014; Salloum et al., 2014; Sun et al., 2009; Turner and Parrish, 2008). Partial support for this metric comes from human studies in which the amplitude of the acoustic startle reflex was inversely correlated with loudness discomfort level (LDL). However, the acoustic startle amplitude was not correlated with another metric of hyperacusis, namely scores on a sound level tolerance questionnaire. These results suggest that LDL and ASR may only reflect loudness, but not other aspects of hyperacusis such as annoyance, fear or avoidance of loud sounds (Knudson and Melcher, 2016).

Reaction time-intensity (RT-I) functions have also been used to assess normal and abnormal loudness growth. Reaction time (RT) decreases with intensity and in humans RT-I measures are closely correlated with numerical estimates of loudness growth and equal loudness contours (Marshall and Brandt, 1980; Pfingst et al., 1975; Stebbins, 1966). In some animal models of noise- or drug-induced hearing loss, RTs initially decrease rapidly with increasing intensity, but the function decelerates eventually catching up to normal RTs observed at high intensities. Thus, RT-I curves recapitulate the basic features of loudness recruitment. Hyperacusis-like RT-I functions have been observed in canaries with a genetic high-frequency hearing loss; RTs in this model were faster than normal-hearing controls at moderate to high intensities (Lauer and Dooling, 2007). Hyperacusis-like RT-I functions have also been observed in rats treated with high-dose salicylate known to cause 20–30 dB hearing loss, tinnitus and neural hyperactivity in the central auditory pathway (Chen et al., 2014a, 2015; Radziwon et al., 2017). However, because collecting RT-I measures typically requires operant training using positive reinforcement, it is difficult to assess if animals with hyperacusis-like RT-I curves also find moderate/high intensity sounds unpleasant or aversive. Because rats and canaries with hyperacusis did not avoid but continued to respond at high stimulus intensities, it is reasonable to assume that RT-I functions are best suited for assessing pure loudness hyperacusis, rather than avoidance hyperacusis.

A recent human study found a strong correlation between self-reported avoidance of loud sounds and distress (Blaesing and Kroener-Herwig, 2012). Based on these human data, we decided to investigate potentially more complex aspects of hyperacusis in which animals avoid intense sounds because of the annoyance or distress it evokes. To accomplish this, we developed an Active Sound Avoidance Paradigm (ASAP) that takes advantage of a rat's innate aversion to bright, open-spaces and preference to stay in a dark, enclosed box (Bourin and Hascoet, 2003; Crawley, 1981). Sound avoidance was quantified by measuring the shift in the rat's preference from the Dark Box to the Light Box as sound level in the Dark Box increased. We then induced a high-frequency hearing loss in the same rats and found that they avoided sounds at a significantly lower intensity than before the noise exposure.

2. Materials and methods

2.1. Subjects

Six male Sprague-Dawley (Charles River Lab, Inc.) rats (~4 months old) were used in the study. The rats were housed in the Laboratory Animal Facility at the University at Buffalo and given free access to food and water. The colony was maintained at 22 °C with a 12 h light/dark cycle. All procedures in this project were approved by the Institutional Animal Care and Use Committee (HER05080Y) at the University at Buffalo and carried out in accordance with NIH guidelines.

2.2. Noise exposure

Details of the noise exposure can be found in our previous study (Chen et al., 2014b). Briefly, the six rats were housed individually in their home cages in the Lab Animal Facility and exposed to a 102 dB SPL (±2.5 dB), 16–20 kHz noise 24 h per day for 4 weeks. The noise exposure was delivered from a speaker mounted above the center of each cage. Sound levels were measured at several locations within each cage at the height of the animals head using a sound level meter (Larson Davis System 824 sound level meter, Larson Davis, half-inch free-field microphone model 2540). The sound level in the 1/3 octave band centered at 16 kHz was 102 dB SPL (±2.5 dB).

2.3. ABR

Our auditory brainstem response (ABR) procedures are described in detail in our earlier publications (Chen et al., 2010, 2014b; Kane et al., 2012). Rats were anesthetized with a ketamine (50 mg/kg)/xylazine (6 mg/kg) cocktail (i.p.) and placed on a regulated heating pad (FHC, model 40-90-2) set to maintain the core body temperature at 37 °C. Subdural electrodes were placed at the vertex (non-inverting), ipsilateral mastoid (inverting) and hind limb (ground). Stimuli were delivered to the ear ipsilateral to the mastoid electrode through the sound delivery tube on the IHS loudspeaker. ABRs were collected using a computerized stimulus presentation and data acquisition system from Intelligent Hearing Systems (IHS, Miami Florida). ABRs were filtered, amplified and digitized (1024 presentations, 40 kHz sampling rate, 30–3000 Hz, 100X) in response to tone bursts presented at 4, 12, 16 and 32 kHz (1 ms rise/fall, cosine gated, 5 ms duration, 21/s). Stimulus presentations began at a high sound level to obtain a clear and consistent ABR waveform and then the intensity was lowered in 10 dB steps until the response completely disappeared. ABR threshold was defined as the lowest intensity at which an ABR waveform could be visually identified.

2.4. ASAP equipment

The ASAP paradigm is based on a rodent's innate aversion to brightly illuminated open areas and preference for a dark enclosed space (Bourin and Hascoet, 2003). The ASAP apparatus is schematized in Fig. 1A with the nominal dimensions of the three main parts. (1) The dark enclosure (Dark Box) consisted of a sound attenuating box (MDF board, 2.54 cm thick) lined with sound absorbing foam panels mounted on the interior walls (Sonex Acoustics, thickness 5 cm). An enclosure with a grid floor (Med Associates, ENV-007) was located near one wall of the Dark Box;

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