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Research paper

Loudness perception affected by early age hearing loss

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ABSTRACT

Tinnitus and hyperacusis, commonly seen in adults, are also reported in children. Although clinical studies found children with tinnitus and hyperacusis often suffered from recurrent otitis media, there is no direct study on how temporary hearing loss in the early age affects the sound loudness perception. In this study, sound loudness changes in rats affected by perforation of the tympanic membranes (TM) have been studied using an operant conditioning based behavioral task. We detected significant increases of sound loudness and susceptibility to audiogenic seizures (AGS) in rats with bilateral TM damage at postnatal 16 days. As increase to sound sensitivity is commonly seen in hyperacusis and tinnitus patients, these results suggest that early age hearing loss is a high risk factor to induce tinnitus and hyperacusis in children. In the TM damaged rats, we also detected a reduced expression of GABA receptor δ and α6 subunits in the inferior colliculus (IC) compared to the controls. Treatment of vigabatrin (60 mg/kg/day, 7 −14 days), an anti-seizure drug that inhibits the catabolism of GABA, not only blocked AGS, but also significantly attenuated the loudness response. Administration of vigabatrin following the early age TM damage could even prevent rats from developing AGS. These results suggest that TM damage at an early age may cause a permanent reduction of GABA tonic inhibition which is critical towards the maintenance of normal loudness processing of the IC. Increasing GABA concentration during the critical period may alleviate the impairment in the brain induced by early age hearing loss.

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1. Introduction

The development of neural circuits in the sensory system is largely triggered by peripheral stimulation during a short period after birth known as the critical period of plasticity (Hensch, 2005b). In the visual system, the typical plasticity remains absent at eye opening, peaks at four weeks, and gradually declines starting from the end of the fifth week (Fagiolini et al., 1994). Closure of one eye, but not both eyes, can cause a permanent loss of visual acuity, known as amblyopia. The central auditory system also undergoes dramatic changes shortly after the onset of hearing (Chang et al., 2005; Kral et al., 2005). Sound stimuli are crucial for the functional development of the central auditory system (Chang and Merzenich, 2003; Kral et al., 2002). Failure to receive proper excitatory input from the cochlea is known to cause various sound processing deficits. For example, hearing loss during development alters the functional properties of the auditory cortex (AC) (Xu et al., 2007) and disrupts the binaural integration of neurons in the inferior colliculus (IC) (Popescu and Polley, 2010). Early age hearing loss in one ear or both ears during postnatal 2–4 weeks, a short time after the ear cannel opens, can increase the susceptibility to audiogenic seizures (AGS) in mice (Henry, 1967) and rats (Sun, 2013; Sun et al., 2011).

Otitis media induced hearing loss is common in children. Hearing loss in children may result in detrimental consequences on their language acquisition, learning capacity, and social interaction (O'Leary and Triolo, 2009). Recent clinical reports suggest that early age hearing loss may be also linked with tinnitus and hyperacusis in

Abbreviations: ABR, auditory brainstem response; AC, auditory cortex; AGS, audiogenic seizure; GABR-α6, $GABA_AR$ alpha 6 subunit; GABR-δ, $GABA_AR$ delta subunit; HPRT-1, hypoxanthine phosphoribosyltransferase 1; IC, inferior colliculus; Ldha, lactate dehydrogenase A; Rpl13a, ribosomal protein L13a; TM, tympanic membrane; s.c., subcutaneously; VGB, vigabatrin

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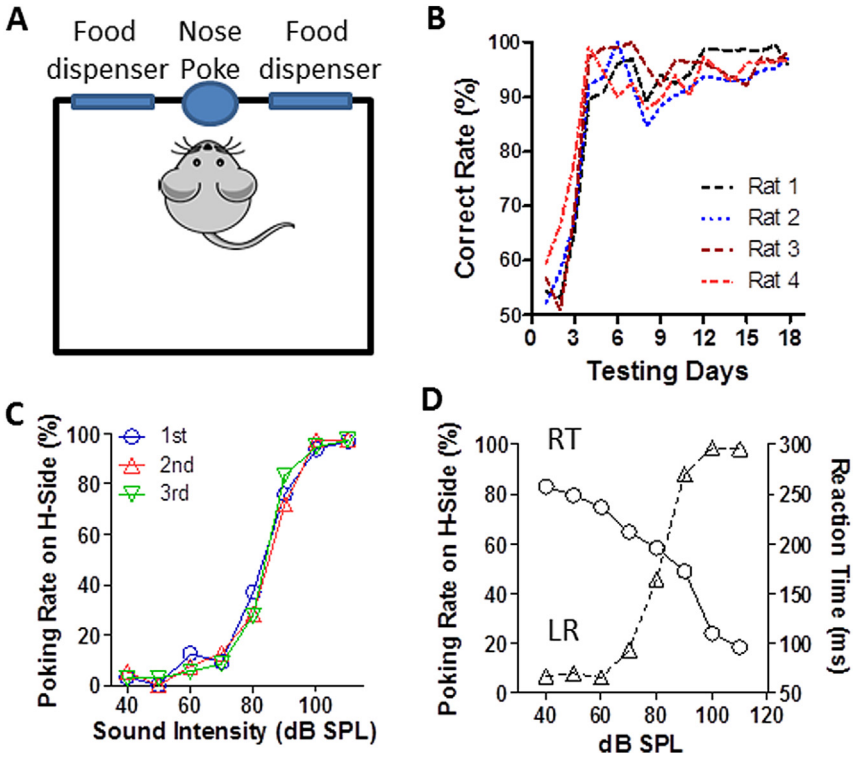

Fig. 1. Sound loudness in tympanic membrane damaged rats and control rats. (A) The diagram for auditory training apparatus. (B) The correct poking rate increased to more than 90% after one week of training. (C) A reliability test of the auditory loudness measurement. The three response curves have been collected from one rat tested once every other day and trained on the off days. The correlation coefficients of the three response curves are higher than 99%, suggesting that this task has very high test-retest reliability. (D) The reaction time level function and loudness response curves showed a nice correlation.

children. Coelho et al. found that 50% of children experiencing tinnitus and hyperacusis also had mild hearing loss (Coelho et al., 2007). Hempel et al. reported that about one third of people who had tympanic membrane (TM) perforations also experienced tinnitus and hyperacusis (Hempel et al., 2012). Most children with Williams Syndrome, a genetic neural developmental disorder that is often diagnosed alongside hyperacusis, have high frequency hearing loss (Gothelf et al., 2006; Klein et al., 1990). However, the mechanisms underlying the effects of early onset hearing loss on sound loudness perception, tinnitus, and hyperacusis remain largely unknown. Given the fact that otitis media is the most prevalent disease in children (Auinger et al., 2003; Lanphear et al., 1997) and the incidence of recurrent otitis media has increased significantly in recent years (Kristjansson et al., 2010; Paradise et al., 1997), revealing how early age hearing loss affects sound loudness changes is critical toward understanding these symptoms.

2. Experimental procedures

2.1. Animal models for early age hearing loss

Sprague–Dawley rat pups have been used in the experiment. The rat pups were randomly assigned to either the TM damaged group or the control group. For the TM damaged group, bilateral TMs were surgically destroyed at postnatal 16 days (P-16), shortly after their ear canals fully opened in the critical period of central auditory system development (de Villers-Sidani et al., 2008). The surgery was performed under a surgical microscope and the rats were under light anesthesia (Isoflurane, 1.5–2%). The TM was visualized under the surgical microscope and entirely ruptured using a sterile 22 gauge needle. The middle ear ossicles were avoided. For each rat, the procedure lasted less than 5 min. Rats in the control group were also anesthetized with isoflurane for 5 min without surgery. All animals were then returned to their cages. The TM damage caused 20–40 dB conductive hearing loss which lasted about 4 weeks until the ear drum automatically healed (Sun et al., 2011).

Fourteen rats (8 rats in the control group and 6 rats in the TM-damaged group) were used for behavioral experimentation. A separated group of rats (14 rats in the control group and 10 rats in the TM damage group) were used for the molecular biology experiment and another subset group of TM damaged rats (29 rats) were used for the early age vigabatrin treatment experiment.

2.2. Auditory training for loudness measurement

An operant conditioning based behavioral task was designed along with appropriate equipment to measure loudness perception changes in adult rats. The operant conditioning training apparatus was built using equipment from Med-Associates Inc. (St. Albans, VT, USA) and was controlled by a TDT system (Tucker–Davis Technologies, Alachua, FL, USA) with custom software (Fig. 1A). The training box had a nose-poke used for initiating the testing trials. Two food dispensers with infrared head-entry detectors were installed on the each side of the nose-poke along with a speaker in the ceiling of the training box (Fostex FT28D, Tokyo, Japan). A TDT system (RP6 and RP2) was used to control the food dispensers and sound stimuli.

First, the rats were trained to use the nose-poke, staying one second in order to release a food pellet and initiate an acoustic stimulation (a broad-band noise, 100 ms duration). Withdrawing from the nose-poke shorter than one second would not trigger an acoustic stimulation and the food pellet would not be released. This was used to prevent the rats from randomly poking the nose-poke without paying attention to the acoustic stimuli. Then the rats were