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Review

Hidden cochlear impairments

Guang-Di Chen

Center for Hearing and Deafness, State University of New York at Buffalo, 137 Cary Hall, 3435 Main Street, Buffalo, NY 14214, USA

A R T I C L E I N F O

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A B S T R A C T

Pure tone audiometry is a routine clinical examination used to identify hearing loss. A normal pure tone audiogram is usually taken as evidence of normal hearing. Auditory deficits detected in subjects with normal audiograms, such as poor sound discrimination and auditory perceptual disorders, are generally attributed to central problems. Does the pure tone audiogram truly reflect cochlear status? Recent evidence suggests that individuals with normal audiogram may still have reduced peripheral auditory responses but normal central responses, indicating that the pure tone audiometry may not detect some types of cochlear injuries. In the cochlea, the outer hair cells (OHCs), inner hair cells (IHCs), and the spiral ganglion neurons that synapse with IHCs are the 3 key cochlear components in transducing acoustical vibrations into the neural signals. This report reviews three types of cochlear damage identified in laboratory animals that may not lead to overt hearing loss. The first type of cochlear impairment, such as missing a certain proportion of IHCs without damage to OHCs, may reduce the cochlear output and elevate response threshold; however, the reduced peripheral auditory sensitivity may be restored along the auditory pathway via central gain enhancement. The second type of cochlear impairment, such as selective damage to the synapses of the high-threshold thin auditory nerve fibers (ANFs), reduces cochlear output at high stimulation levels with no effect on response threshold. In this case the reduced cochlear output may be compensated along the auditory pathway as well. The third type of cochlear impairment, such as missing a certain number of OHCs without damage to others, may not even affect cochlear function at all. These "hidden" cochlear impairments do not result in overt hearing loss, but they may increase the vulnerability of the cochlea to traumatic exposure and lead to disrupted central auditory processing.

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E-mail address: gchen7@buffalo.edu.

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1. Introduction

Both external environmental causes (intense noise and ototoxic agents) and internal biological causes (diseases, gene deficiencies, and ageing) can cause damage to the cochlea (Chen et al., 2007; Bielefeld et al., 2008; Chen and Henderson, 2009; Kong et al., 2009). The pure tone audiometry is a routine method used in clinic to determine the degree, type, and configuration of hearing loss. A normal pure tone audiogram is usually taken as evidence of normal hearing. This measurement is also used in hazard assessment for military and industrial noises or exposure to ototoxic agents (Nelson et al., 2005; Jokitulppo et al., 2008; John et al., 2012). Does the pure tone audiogram truly reflect cochlear status?

In a group of tinnitus patients who had normal pure tone audiogram (auditory perceptual level), a normal wave-V of auditory brainstem response (ABR) (from the midbrain) was observed with a reduced wave-I (from the cochlea) (Schaette and McAlpine, 2011; Xiong et al., 2013). The data indicate that the pure tone audiometry may not detect some cochlear impairments. Cochlear impairment without hearing loss is defined as "hidden hearing loss" (Schaette and McAlpine, 2011), and may be a relatively common auditory disruption (Plack et al., 2014). In a large survey in UK, 26% of adults reported great difficulty hearing speech in noise, while only 16% had pure tone hearing loss (Davis, 1989).

There are likely multiple ways that hidden hearing loss can arise. Some types of cochlear impairment, such as missing a certain number of inner hair cells (IHCs) without damage to others, may reduce the cochlear output and elevate the response threshold, but the auditory sensitivity could be partially or completely restored along the central auditory pathway (Qiu et al., 2000; Lobarinas et al., 2013, 2016; Liu et al., 2018). This is a real hidden hearing loss since a peripheral threshold shift occurs without a central threshold shift (hearing loss). A second type of cochlear impairment, such as damage selectively to the high-threshold thin auditory nerve fibers (ANFs), may result in reduction of cochlear output at high stimulation levels but with no effect on response threshold or sensitivity (Kujawa and Liberman, 2009; Lin et al., 2011; Liu et al., 2012; Furman et al., 2013; Shi et al., 2016a; Chen et al., 2018). This type of cochlear impairment, commonly referred to as "hidden hearing loss", has received extensive attention for its potential role in auditory processing and perceptual disturbances. A third type of cochlear impairment, such as missing a certain number of outer hair cells (OHCs) without damage to others, may not even affect the cochlear input/output function (Chen et al., 2008; Chen and Henderson, 2009). This is a deeply hidden cochlear impairment that cannot be detected even by recording the cochlear response.

These forms of hidden cochlear impairments do not result in overt hearing loss (Lobarinas et al., 2013, 2016), but they may increase the vulnerability of the cochlea to further traumatic stimulation (Chen and Henderson, 2009) and weaken or disturb central auditory processing, leading to poor sound discrimination and perceptual disorders such as tinnitus and hyperacusis (Schaette and McAlpine, 2011; Baiduc et al., 2013; Xiong et al., 2013; Wan and Corfas, 2017; Alkharabsheh et al., 2018). Therefore, it is imperative that we develop better tools for detecting and measuring these hidden cochlear impairments. This report will review all the cochlear damages to the OHCs, IHCs, and the synapses underneath the IHCs that do not affect pure tone hearing thresholds but nonetheless may have significant effects on auditory processing.

2. Damage to the inner hair cells

"Men only use ten percent of their brain." ABC-television, July 1998

Many biological systems have built in redundancy so that the loss of a small amount of cells may not result in a functional deficit. IHCs in the cochlea are auditory receptor cells responsible for signal transduction and sending acoustic information to the brain. There are ~1000 IHCs in each rat cochlea and ~3500 IHCs in each of our human cochleae. However, only a fraction of functional IHCs may be sufficient to maintain auditory sensitivity. In a previous study in chinchillas, carboplatin, an anticancer drug, was found to selectively destroy the IHCs (Qiu et al., 2000). Surprisingly, up to 80% of IHC-loss resulted in only a slight pure tone threshold shift measured behaviorally (Lobarinas et al., 2013). Fig. 1 presents the relation between the IHC-loss and the behavioral hearing loss across frequency showing <5 dB of threshold shift until ~80% of IHC-loss. The data indicate that survival of only 20% of IHCs is sufficient for maintaining auditory sensitivity under quiet conditions. However, the IHC-loss appeared to affect listening in more challenging, noisy environments (Lobarinas et al., 2016). The carboplatin-induced IHC-loss was accompanied by a comparable reduction of the cochlear compound action potential (CAP) amplitude and CAP threshold shift (Qiu et al., 2000). However, in the inferior colliculus (IC), the midbrain, the response amplitude was partially compensated; in the auditory cortex (AC), the sound-evoked responses overshot the pre-drug level (Qiu et al., 2000). The data indicate that a small number of IHCs are sufficient for maintaining the auditory sensitivity at least in the quiet environment, which may be due in part to central compensation of reduced peripheral input. Therefore, an ear with a certain number of IHCs missing but with all other cells being intact may show a normal pure tone audiogram.

3. Damage to the outer hair cells

The movement of the basilar membrane is amplified in an intensity-dependent manner, with greater gain at low stimulation levels that gradually decreases with increasing stimulation level (Heinz and Young, 2004). OHCs are electromotile and play an

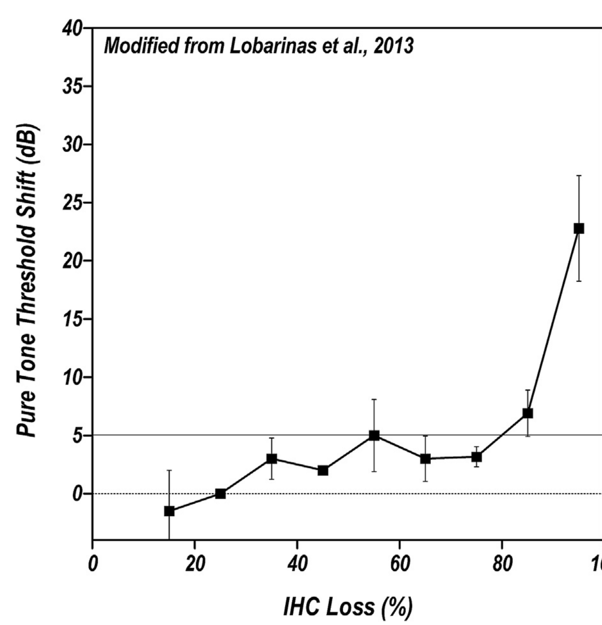

Fig. 1. Behaviorally measured pure tone threshold shifts in the chinchillas as a function of carboplatin-induced IHC-loss, showing less than 5 dB of hearing loss until IHC-loss up to ~80%. The vertical bars are standard errors (SEs). The figure is modified from Lobarinas et al. (2013).