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Review

Hidden cochlear impairments

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ABSTRACT

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.

Contents

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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

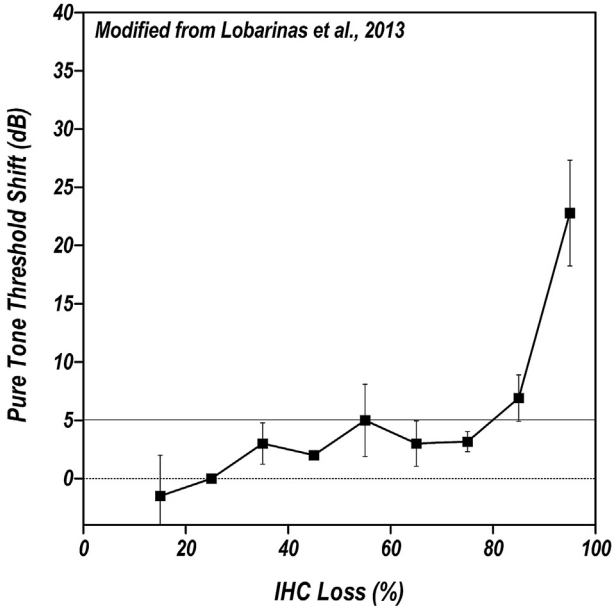

Fig. 1. Behaviorally measured pure tone threshold shifts in the chinchillas as a function of carboplatin-induced IHC-loss, showing less than 5 dB of hearing loss until IHC-loss up to ~80%. The vertical bars are standard errors (SEs). The figure is modified from Lobarinas et al. (2013).

essential role in this cochlear amplification (Nin et al., 2012). When all of the OHCs are lost (death) or become dysfunctional (injury), the cochlea loses its amplification completely and becomes a passive or linear system (increase by 1 dB/dB) (Heinz and Young, 2004). Loss of the cochlear amplification leads to CAP threshold shift up to ~30–40 dB (Chen, 2006; Chen et al., 2008; Murakoshi et al., 2015). Does normal cochlear amplification require a whole set of OHCs?

In the noise-exposed chinchillas, loss of OHCs began with a permanent auditory threshold shift (PTS) below 5 dB with the number of missing OHCs increasing progressively with larger PTS (Hamernik et al., 1989). Fig. 2 presents the relation between the PTS and the noise-induced OHC-loss. The PTS increases linearly with OHC-loss with ~6 dB PTS-increase for each 10% of OHC-loss. Based on this data, it seems that a normal cochlear amplification requires a whole set of OHCs. However, it is unclear whether all the OHCs that survived the noise trauma were normally functioning, as it is known that noise trauma disrupt OHC function without overt hair cell loss in the rat (Chen and Fechter, 2003; Chen, 2006). Therefore, it is still unclear whether the normal cochlear amplification requires all of the OHCs functioning.

Styrene is one of the most ototoxic industrial solvents (Gagnaire and Langlais, 2005; Chen et al., 2007, 2008; Chen and Henderson, 2009) and many workers are occupationally exposed to high levels styrene (Tranfo et al., 2012). Styrene exposure causes damage to the organ of Corti starting from the third row of OHCs (located laterally), then progressively leads to cell death in second row of OHCs, and then the first row of OHCs and, finally, the IHCs (Lataye et al., 2001; Chen et al., 2008). Since the OHCs located medially are not affected by styrene application until the OHCs located laterally are killed, the solvent can be utilized as a tool to investigate the relation between the amount of OHC loss and the loss of cochlear amplification.

It has been shown that the styrene-induced OHC-loss of the third row did not affect the CAP input/output function indicating no change in cochlear amplification; but the loss of both the third and second rows resulted in a complete loss of cochlear amplification (linear CAP input/output function) (Chen et al., 2008). Fig. 3 presents styrene-induced permanent CAP threshold shifts in rats as a function of OHC-loss. The CAP threshold shifts were small, around 5 dB, when OHC loss was restricted to the third row (~1/3 OHC-loss); then the threshold shift increased linearly with OHC-loss (~10 dB per 10% of OHC-loss) up to ~35 dB. Finally, the threshold shift saturated when the OHC-loss exceeded 2/3. Fig. 4 presents examples showing

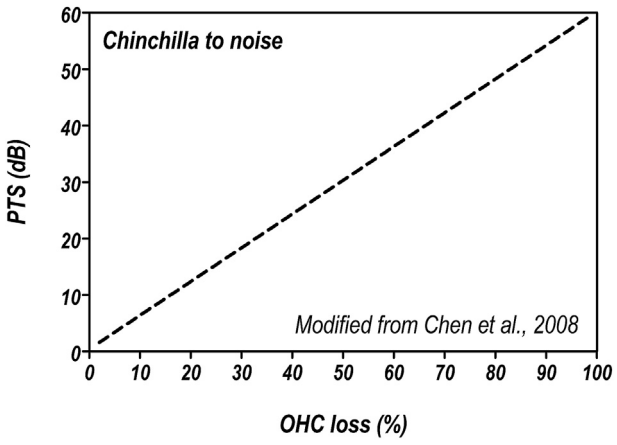

Fig. 2. Noise-induced permanent threshold shift (PTS) in chinchillas increases linearly with the OHC-loss with ~6 dB of PTS per 10% of OHC-loss. The figure is modified from Chen et al. (2008).

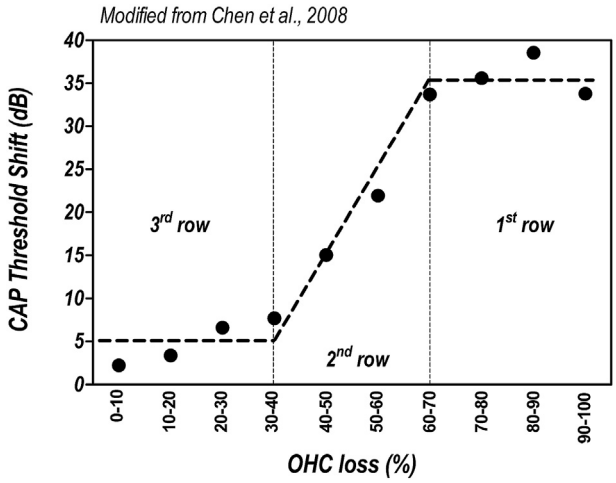

Fig. 3. Styrene-induced permanent CAP threshold shifts in rats as a function of OHC-loss. OHC-loss in the third row only induced a slight threshold shift; then the threshold shift increased linearly with OHC-loss with ~10 dB of threshold elevation for each 10% of OHC-loss; and after the loss of the third and second rows the styrene-induced CAP threshold shift saturated at a level of ~35 dB. The figure is modified from Chen et al. (2008).

styrene-exposed cochleae with a complete loss of OHCs (A) and OHC-loss of the third row only (B). A complete OHC-loss (Fig. 4A), with damage to a few pillar cells but with all the IHCs surviving, resulted in a complete loss of cochlear amplification, indicated by the CAP amplitude decreasing linearly with decreased sound stimulation level, leading to a threshold shift of ~40 dB (the filled squares in Fig. 4C). The slight reduction of CAP at the high stimulation level suggested a minor IHC functional loss. OHC-loss of the third row (Fig. 4B), however, did not significantly affect the CAP input-output function (the filled circles in Fig. 4C) compared to the controls (the open circles in Fig. 4C). The data suggests that only 2/3 of functional OHCs are required for normal cochlear amplification. Although the loss of OHCs in the third row did not affect cochlear amplification, it may affect distortion product otoacoustic emissions (DPOAE); unfortunately, the data is not available.

This opinion (2/3 of the OHCs in the cochlea being sufficient for the cochlear amplification) has been challenged. By measuring the basilar membrane displacement driven by a 16 kHz pure tone at 60 dB SPL in the normal and the injured cochleae, Murakoshi and co-workers claimed that all three rows of OHCs are required for the cochlear amplification (Murakoshi et al., 2015). The sound-driven basilar membrane displacement was 4.42 nm in the normal cochlea, but it dropped to 1.47 and 0.97 nm in the cochlea with dysfunctional OHCs in the first or third single row. As a comparison, the sound-driven basilar membrane displacement in the cochlea with all OHCs injured was 0.47 nm. However, this study did not directly assess if the “unaffected” OHCs were indeed functional. In fact, the force generated by OHC motility at the tone level of 60 dB SPL in the cochlea with single-row damage was ~2–4 nN, which was much lower than 13–15 nN observed in the normal cochlea. This may indicate that the so called “unaffected” OHCs were actually dysfunctional. Therefore, it is possible that patients with OHC-loss up to 1/3, with the remaining cells being functionally intact, may present with a normal pure tone audiogram.

4. Damage to the synapses between the IHCs and the spiral ganglion neuron fibers

The IHCs in the cochlea transduce sound-driven basilar membrane vibration into the membrane potential change, leading to

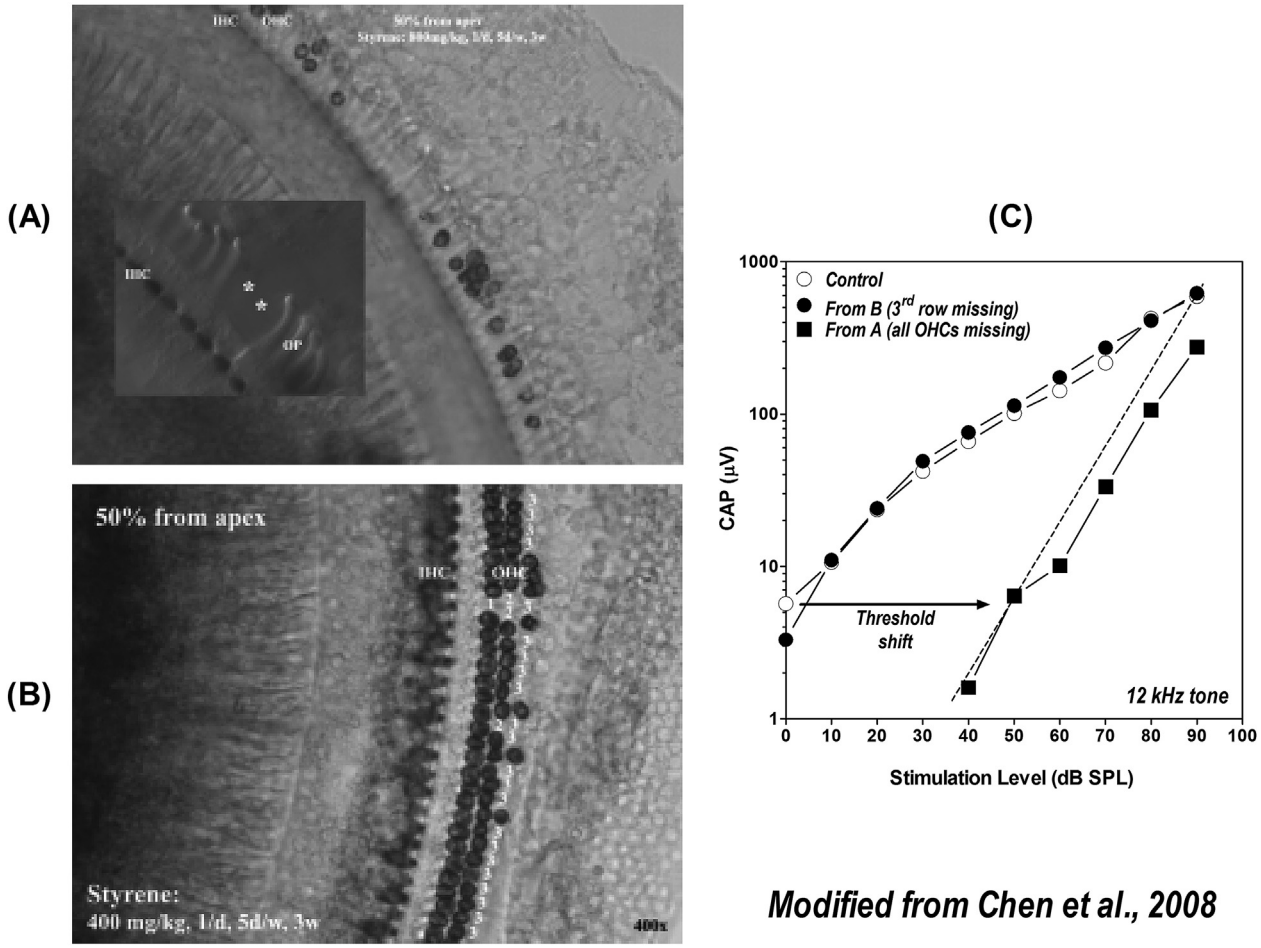

Fig. 4. Styrene-induced cochlear injuries and functional losses. (A) Surface preparation from the mid-turn of the cochlea treated with styrene at a dose of 800 mg/kg; (B) Surface preparation from the mid-turn of the cochlea treated with styrene at a dose of 400 mg/kg; (C) CAP input/output functions at 12 kHz from the 2 rats shown in A and B. The figure is modified from Chen et al. (2008).

neurotransmitter release in the synaptic area underneath each IHC and activation of the auditory nerve fibers (ANFs). ANFs are classified into three groups: (1) those with high spontaneous discharge rate (SR > 18 spikes/s) and low response threshold; (2) those with medium-SR (0.5 < SR = 18) and medium-threshold; (3) those with low-SR (SR = 0.5) with high response threshold (Liberman, 1978). Each fiber is generally unbranched and forms a single synapse with one IHC while each IHC is innervated by 5–30 fibers (Liberman, 1980; Moller, 1983; Shi et al., 2013; Viana et al., 2015; Wan and Corfas, 2015). The high-SR fibers are relatively large in diameter (thick) and form synapses on the IHCs at the pillar side encoding low sound intensities (Liberman, 1980; Young and Barta, 1986; Heinz and Young, 2004; Schaette and McAlpine, 2011; Kujawa and Liberman, 2015; Paul et al., 2017). In contrast, the low-SR fibers are relatively small in diameter (thin) and form synapses on the IHCs at the modiolus (medial) side encoding high sound intensities. The basilar membrane vibration increases linearly with sound intensity at the low stimulation levels but the rate of change in vibration decreases with increasing sound due to the sound-level dependent reduction of the gain of the cochlear amplification (Heinz and Young, 2004). High-SR fibers respond to low intensity sounds and saturate at the sound level at which the basilar membrane becomes compressive (the gain starts to reduce). The higher threshold low-SR fibers began to discharge at this stimulation level and increase discharge rate with the sound level over a broad intensity range (Heinz and Young, 2004). Each synapse underneath the IHC is characterized by a presynaptic ribbon surrounded by microvesicles and a postsynaptic densification of membrane (fiber terminal) (Liberman, 1980; Lin et al., 2011; Song et al., 2016). The synaptic structure allows fast and sustained neurotransmitter release from pre-synaptic vesicles (Safieddine et al., 2012). The sizes of the ribbons on the IHC are relatively smaller at the pillar side than those at the modiolar side (Lin et al., 2011; Furman et al., 2013; Maison et al., 2013; Kujawa and Liberman, 2015; Liberman et al., 2015; Song et al., 2016). The small ribbons on the IHCs at the pillar side are paired with the terminal endings from the thick (high-SR, low-threshold) fibers while the relatively large ribbons at the modiolar side are paired with the terminal endings from the thin (low-SR, high-threshold) fibers (Maison et al., 2013; Kujawa and Liberman, 2015; Song et al., 2016). Loss of the synapses and ANF retraction have been repeatedly observed in the ageing cochleae and following noise trauma (Kujawa and Liberman, 2009, 2015; Lin et al., 2011; Liu et al., 2012; Furman et al., 2013; Maison et al., 2013; Sergeyenko et al., 2013; Shi et al., 2013, 2015a, 2015b, 2016b; Liberman et al., 2015; Shaheen et al., 2015; Viana et al., 2015; Song et al., 2016; Liberman and Kujawa, 2017; Paul et al., 2017; Wan and Corfas, 2017). This synapse-loss, known as synaptopathy, may occur in the ageing or noise-exposed cochleae before hair cell injury.

4.1. The vulnerability of ANF synapses compared to the cochlear hair cells

Progressive hair cell loss is often observed with normal aging. For instance, in the cochlea of a 54-years old man, ~10% of OHC-loss was observed but no significant IHC-loss except at the basal end (Viana et al., 2015). In the cochlea of an 89-years old man, however, ~10–40% of OHC-loss and ~10% of IHC-loss was observed (Viana et al., 2015). Despite of the slight IHC-loss (~10%), the ANFs in the cochlea of the 89-years old man dropped by ~70–80%, from a level of ~13 fibers per IHC observed in the 54-years old man to a level of less than 3 fibers per IHC (Viana et al., 2015). Obviously, the fiber-loss was more than the IHC-loss. This suggests that synaptopathy may precede hair cell deterioration during ageing. The age-related histological and physiological changes in the cochlea have been closely investigated in CBA/CaJ mice (Sergeyenko et al., 2013). These animals do not show significant hair cell loss until they are 80 weeks (20 months) old. Consistent with these anatomical findings, physiological threshold shifts of ABR and DPOAE were not observed until the age of 80 weeks. However, significant loss of spiral ganglion neurons (SGNs) was observed at the age of 64 weeks (16 months). Surprisingly, significant loss of the synapses underneath the IHC were even observed at an age as early as 16 weeks (4 months) (Sergeyenko et al., 2013). The data further confirm that synaptic deterioration precedes IHC-loss during aging (Liberman and Kujawa, 2017).

In noise-exposed animals, synaptopathy has also been observed in some cases without hair cell loss or even without hair cell functional reduction. For example, a noise exposure at 84 dB SPL for 1 week in mice did not induce hair cell loss or a permanent threshold shift of DPOAE and ABR, but it did result in an ~20% loss of the synapses underneath the IHCs (Maison et al., 2013). On these grounds, the classic view that the cochlear hair cells are the primary target of noise-induced cochlear damage (Johnsson, 1974; Bohne and Harding, 2000) is challenged (Kujawa and Liberman, 2015; Liberman and Kujawa, 2017) that "at least in the noise-exposed and aging ear; 1) that cochlear neurons are the primary target, 2) that their peripheral synaptic connections are the most vulnerable elements …" (Liberman and Kujawa, 2017).

4.2. The vulnerability of ANF synapses compared between fiber types

As described above, the thick (low-threshold, high-SR) ANFs terminate on the IHCs at the pillar side encoding low-intensity sounds and the thin (high-threshold, low-SR) ANFs terminate on the IHCs at the modiolar side encoding high-intensity sounds. It appears that the thin fibers are more vulnerable to noise damage than the thick fibers (Liberman et al., 2015). In the normal cochlea, ribbons on the IHC at the modiolar side were found to be more in number than that at the pillar side; however, the ratio of modiolar to pillar ribbons decreased after noise exposure suggesting that there was more damage to synapses at the modiolar side following noise trauma (Liberman et al., 2015). Physiologically, the low-SR thin fibers account for about a quarter (25%) of the total ANFs in guinea pigs, but this ratio was found dropping to ~10% after a noise exposure at 106 dB SPL for 2 h (Furman et al., 2013). This data further indicates that the low-SR thin fibers were most vulnerable to noise-induced degeneration (Furman et al., 2013; Song et al., 2016; Liberman and Kujawa, 2017). Noise exposures in some cases were found to reduce cochlear output selectively at high stimulation levels without response threshold shift or sensitivity remaining unchanged (Kujawa and Liberman, 2009; Lin et al., 2011; Liberman and Kujawa, 2017; Chen et al., 2018). This type of cochlear functional loss is consistent with the observation of selective damage to the high-threshold, low-SR thin fibers.

4.3. The vulnerability of ANF synapses compared between presynaptic ribbons and fiber terminals

The glutamate receptors underneath the IHCs are located on the postsynaptic membrane of the fiber terminals which may be damaged by excessive stimulation of glutamate release inducing high-level of calcium ions entering the cell (excitotoxicity). The number of orphan ribbons (ribbons without terminals) was found to increase after noise exposure and with ageing (Lin et al., 2011; Furman et al., 2013; Viana et al., 2015). The orphan ribbons may represent residual synapses with missing postsynaptic terminals. This data may indicate that the postsynaptic fiber terminals may deteriorate earlier than the presynaptic ribbons.

4.4. Restoration of IHC-spiral ganglion synapses

Noise-induced ribbon loss in adult (4 month old) CBA/CaJ mice appears to be irreversible, as no significant recovery was observed following an octave band noise (8–16 kHz) at 100 dB SPL for 2 h (Kujawa and Liberman, 2009, 2015). Loss of synaptic ribbons underneath the IHCs were measured at different times post-exposure. At the cochlear location of ~45 kHz, for example, the number of ribbons dropped from pre-noise levels of ~15/IHC down to ~6/IHC at post-1day, which remain unchanged at post-3 days and post-8 weeks (Kujawa and Liberman, 2009). However, the noise-induced ribbon loss in guinea pigs showed gradual recovery following the noise exposure (Liu et al., 2012; Shi et al., 2013, 2016b; Song et al., 2016). The adult albino guinea pigs at the age of 2–3 months were exposed to a broadband noise at 105 dB SPL for 2 h. This noise exposure caused ribbon loss of ~65% and terminal loss of ~50% at the 20-kHz region 1-day post-noise; however, this loss was gradually restored with only ~10% of ribbon- and terminal-losses 1 month post-noise (Shi et al., 2013). Thus, there appears to be species specific difference in recovery from noise-induced synaptopathy, the reasons for which remain unclear. However, it is known that CBA/CaJ mice have age-related hearing loss with ribbon-loss and reduction of ABR wave-I starting around 4 months (Sergeyenko et al., 2013). Therefore, there may be an interaction between noise and ageing-related ribbon synapse loss that contributes to the lack recovery following noise trauma in the CBA/CaJ mice.

4.5. Are the synapses underneath the IHCs the primary target of noise trauma?

In the ageing cochlea in both human subjects and laboratory animals, loss of synapses underneath the IHCs and loss of ANFs appeared to be more severe and begin earlier than injury to hair cells (Sergeyenko et al., 2013; Viana et al., 2015). This data supports the idea that the synapses are the primary target of ageing (Kujawa and Liberman, 2015; Liberman and Kujawa, 2017).

Short-term noise exposure (2 h) at a level from 98 to 106 dB SPL does not induce a significant permanent auditory threshold shift in mice and guinea pigs (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013; Liberman et al., 2015). However, this noise exposure does induce a significant and irreversible loss of synapses underneath the IHCs in the cochlear region above the noise band but not within the noise band. Consistent with these anatomical findings, the same noise exposure causes a reduction of cochlear output (ABR wave-I) at the frequencies above the noise band but not in the noise band. Based on the data, it has been proposed that

the cochlear neurons are a primary target of noise trauma (Liberman and Kujawa, 2017). This appears to be true in the frequency-region above the noise band. However, it is interesting to note that the short-term noise exposures does not cause significant cochlear injury within the region of the noise band, while it did induced permanent loss of synapses and reduction of cochlear output as well as OHC functional reduction in the region above the noise band (Liberman et al., 2015).

Long-term exposure to the ambient noise is increasingly being recognized as a serious public health problem (Babisch et al., 2005; Babisch, 2008; Bodin et al., 2009; Bendokiene et al., 2011; van Kempen and Babisch, 2012). Our recent studies reveal that prolonged exposure to noise at ambient or environmental intensity levels (below 85 dB SPL) can significantly reduce peripheral auditory function (Chen et al., 2014, 2018; Sheppard et al., 2017). In the cochlear region above the noise band, long-term low-level noise exposure (18–24 kHz at 85 dB SPL for 6 weeks) selectively reduced the cochlear output (CAP) at the high stimulation levels but did not affect the CAP-threshold, possibly reflecting the loss of the synapses at high-threshold fibers. For example, the 45-kHz-tone-evoked CAP at 80 dB SPL in noise-exposed rats ($n = 6$) was $172.7 \pm 45.8\ \mu V$ (mean ± SD) being significantly smaller ($p < 0.01$) than the CAP amplitude of $269.7 \pm 55.3\ \mu V$ measured in control rats ($n = 11$). However, the CAP at 5 dB SPL in the noise-exposed rats was $2.4 \pm 0.9\ \mu V$, which similar to level of the control CAP of $2.4 \pm 1.3\ \mu V$. The data support the idea that the cochlear neuronal synapses may be the primary target of noise trauma (Liberman and Kujawa, 2017). In the cochlear region of the noise band, the noise exposure (18–24 kHz at 85 dB SPL for 6 weeks) reduced CAP amplitude across stimulation levels, suggesting a combination of cochlear injuries (Shi et al., 2016a). For example, the 20-kHz-tone-evoked CAPs in the noise-group were $114.3 \pm 34.4\mu V$ at 80 dB SPL and $1.6 \pm 0.7\mu V$ at 5 dB SPL, both of which were significantly smaller than the control levels of $187.3 \pm 38.8\ \mu V$ and $5.1 \pm 1.4\ \mu V$, respectively. To determine the most vulnerable cochlear target, the level of the noise (18–24 kHz for 6 weeks) was reduced to a level around 50 dB SPL. Noise exposure at this level resulted in cochlear damage restricted to the band-region, with loss of cochlear amplification or OHC functional loss. For example, the 20-kHz-tone-evoked-CAP at 80 dB SPL did not show significant noise-induced reduction ($201.9 \pm 36.0\ \mu V$ in the noise-group vs $187.3 \pm 38.8\ \mu V$ in the control-group). However, the CAP at 35 dB SPL was $19.4 \pm 5.2\ \mu V$ in the noise-exposed rats ($n = 10$), which was significantly lower than the $31.6 \pm 7.2\ \mu V$ response in the control group ($n = 11$, $p < 0.001$). The data suggest that the low-level noise target the OHCs restricted in the band-related region. Therefore, the primary cochlear target of noise trauma may vary depending on the exposure parameters and cochlear locations affected.

5. Summary

The OHCs, IHCs, and the synapses underneath the IHCs are the 3 key components required for transducing acoustic vibrations into the neural signals. They are vulnerable to intense noise, ototoxic agents, and ageing. Cochlear damage that cannot be detected by routine clinical pure tone audiometry is defined as a hidden hearing loss. In fact, some damage may not even induce a reduction in cochlear function. For example, a certain number of OHCs may be killed following styrene administration without an effect on cochlear output. Some damage, such as loss of the high-threshold thin ANFs during ageing or after a moderate noise exposure, may reduce cochlear output without an effect on the cochlear response threshold. The combined damages to OHCs, IHC, and the neurons may induce cochleae functional loss and threshold shift. However, the reduced peripheral input may be partially or completely restored in the central auditory centers via gain enhancement. Therefore, assessment of central auditory function and/or psychophysical measurements may not necessarily reflect peripheral impairments caused by ageing or noise trauma and peripheral functional loss does not necessarily indicate a loss of auditory sensitivity.

Conflicts of interest

The author declares no conflict of interest.

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