Hidden hearing loss: Primary neural degeneration in the noise-damaged and aging cochlea

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Abstract: In acquired sensorineural hearing loss, the hearing impairment arises mainly from damage to cochlear hair cells or the sensory fibers of the auditory nerve that innervate them. Hair cell loss or damage is well captured by the changes in the threshold audiogram, but the degree of neural damage is not. We have recently shown, in animal models of noise-damage and aging, and in autopsy specimens from aging humans, that the synapses connecting inner hair cells and auditory nerve fibers are the first to degenerate. This primary neural degeneration, or cochlear synaptopathy, leaves many surviving inner hair cells permanently disconnected from their sensory innervation, and many spiral ganglion cells surviving with only their central projections to the brainstem intact. This pathology represents a kind of “hidden hearing loss.” This review summarizes current speculations as to the functional consequences of this primary neural degeneration and the prospects for a therapeutic rescue based on local delivery of neurotrophins to elicit neurite extension and synaptogenesis in the adult ear.

Keywords: Hearing loss, Auditory nerve, Aging, Noise damage

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1. PRIMARY VS. SECONDARY NEURAL DEGENERATION IN THE COCHLEA

Sensorineural hearing loss (SNHL) refers to hearing impairments arising in the cochlea, or inner ear, where sound-evoked mechanical vibrations are normally transduced into graded electrical signals by the sensory cells, or hair cells. Those hair cell potentials, in turn, drive the synaptic contacts with the auditory nerve fibers, which transmit the information about the acoustic environment to the central auditory pathways as action potentials [1]. The most common etiologies of acquired SNHL are aging and overexposure to loud sounds, and the extent to which these two are inextricably related in our increasingly noise-filled environment is a long-standing conundrum in the study of hearing impairment [2].

Hair cells, especially the outer hair cells (OHCs), are particularly vulnerable to noise and aging [3,4]. Once they die, they never regenerate, at least in mammalian ears [5]. Since OHCs are biological motors, whose main function is to amplify the sound-evoked mechanical vibrations of the cochlear sensory epithelium [6], OHC loss leads to elevation of detection thresholds, as measured in a conventional pure-tone audiogram. Selective and complete OHC loss will elevate thresholds by 40–60 dB [7].

Although OHCs are innervated by sensory fibers (Fig. 1), these “type-II” OHC afferents constitute only 5–10\% of the auditory nerve fiber (ANF) population, and their axons are small and unmyelinated [8]. They may function as nociceptors and mediators of auditory pain [9]. The great majority (90–95\%) of ANFs are fast-conducting, myelinated fibers contacting inner hair cells (IHCs; Fig. 1). There are roughly 40,000 “type-I” myelinated fibers in the human auditory nerve [10], each contacting a single IHC somewhere along the frequency-tuned, spiraling, sensory epithelium [11]. Although total IHC loss leads to profound deafness, subtotal IHC loss does not affect audiometric thresholds until it exceeds 80\% [12].

A longstanding dogma in acquired SNHL was that ANF loss occurs if and only if there is degeneration of IHCs [13]. This view that hair cell loss is the primary event and neural loss is secondary arose because IHC loss can be seen within hours or days after acute injury such as acoustic trauma, however, degeneration of ANFs is not obvious until months to years later, at least if neural loss is assessed by counting the cell bodies of these bipolar neurons in the spiral ganglion [14]. Indeed, many spiral ganglion cells survive for years after the loss of all hair cells [15], which, or
course, is why cochlear implants can restore auditory function in the profoundly deaf by direct intracochlear electrical stimulation of the surviving ANFs [16].

2. NOISE-INDUCED AND AGE-RELATED SYNAPTOPATHY

Over the past ten years, my colleagues and I have shown, in animal models of noise damage, that the synaptic connections between IHCs and ANFs are actually more vulnerable than the hair cells themselves [17]. Thus, for example, in mice, rats, guinea pigs, chinchillas, and rhesus monkeys, a single 2–4 hr exposure to narrow-band noise in the middle of hearing range at intensities of 98–108 dB SPL (depending on species) can destroy up to 50% of these synaptic connections, without any loss of hair cells, and with only a temporary threshold elevation that resolves back to baseline within roughly a week post-exposure [17–20]. Although the loss of synapses appears to be immediate [21], the subsequent loss of spiral ganglion cells and their central axons takes months to years in mice [17], and is likely much slower in animals with a much longer lifespan, such as human [15].

This massive noise-induced primary degeneration remained “hidden” for so long, because the synaptic connections are impossible to see in classic light-microscopic pathology material. Counts of spiral ganglion cells were historically used as the main assay of cochlear neural degeneration [22], and the cell-body degeneration does not set in for months to years post exposure. Although the synapses are well seen in the electron microscope [11,23], quantitative analysis required completed 3-D reconstruction of the neuropil in the IHC area, and data acquisition of this type is extremely labor intensive. To reveal cochlear synaptic damage, we developed light-microscopic protocols to immunostain pre- and post-synaptic proteins, allowing us to use the confocal microscope to easily see and count the punctate synaptic contacts studing the basolateral membrane of the IHCs [17] and gather data from hundreds of cells in a relatively short period of time.

We used similar techniques to study the role of synaptopathy and the relative vulnerabilities of hair cells and ANFs in the aging ear. First, we examined a mouse model [24], since the life span of a mouse is (a relatively short) 2.5 years. We found that, as with noise, the synaptic connections between IHCs and ANFs were the most vulnerable elements: by the midpoint of the lifespan, the mean loss of OHCs was <5%, and the mean threshold shift was <10 dB, as measured by otoacoustic emissions which are a sensitive metric of OHC function [25]. In contrast, the mean loss of IHC synapses was ~25%. We went on to examine material from normal-hearing humans, from birth to 89 years of age, and showed that an average 60–70 year-old had lost 50% of the connections between IHCs and ANFs, whereas only 10% of the IHCs had degenerated [26]. In some of our older specimens, 80% of the ANF connections to surviving IHCs had degenerated.

Although each IHC normally makes synaptic contact with multiple ANFs (10–15 in humans, depending on cochlear location [26]), each ANF contacts only a single IHC via a single punctate synaptic contact [23]. Thus, each missing IHC synapse, or peripheral axon (See Fig. 1) indicates an ANF that is disconnected from its sensory receptor and will no longer have any background activity or any response to sound.

3. HIDDEN HEARING LOSS, TINNITUS AND HEARING IN NOISE

To understand the likely functional consequences of this kind of massive loss of cochlear neural connections, it is useful to summarize some fundamental aspects of ANF response. ANFs discharge spontaneously in the absence of sound, and that spontaneous rate (SR) varies across fibers, from near 0 to over 100 spikes/sec. Forty years ago, we suggested that ANFs could usefully be divided into three functional subgroups based on the strict relationship between threshold sensitivity and SR [27]: high-threshold fibers have low SRs (and constitute 60% of the ANFs), low-threshold fibers have high SRs (and constitute 15% of the ANFs), and intermediate-threshold fibers have medium SRs (and comprise the remaining 25%). Interestingly, two recent studies independently showed that cluster analysis of single-cell RNA expression data suggested that, correspondingly, there are three major molecular classes of spiral ganglion cells, corresponding to the three functional classes defined on the basis of SR and threshold [28].

In addition to expanding the dynamic range of the auditory periphery, the existence of ANFs with widely varying threshold sensitivity is important in preserving...
information about signal transients in the presence of continuous background noise [29]. Such continuous backgrounds tend to fatigue the ANF/IHC synapse and reduce its responsiveness to new stimulus transients. Low-SR, high-threshold fibers, simply by virtue of their higher acoustic thresholds, are not as easily masked by moderate-level continuous noise as high-SR, low threshold fibers. Thus, as the level of background noise increases, we must be increasingly reliant on our low-SR fibers to extract signals from the noisy background.

The significance of the SR-based heterogeneity of normal ANFs in the context of SNHL is that, in both noise-induced and age-related cochlear damage, neurophysiological studies of the auditory nerve suggest that the high-threshold, low-SR fibers are the first to degenerate [20,30,31]. Thus, in an animal exposed to synaptopathic noise, which caused primary neural degeneration without hair cell loss or permanent threshold shift, there can be a selective loss of the low-SR and medium-SR populations [20]. This helps explain how there can be 40–50% loss of synaptic connections, without any threshold shift as seen in the pure tone audiogram, if the hair cells recover and the low-threshold, high-SR fibers remain. It also suggests that synaptopathy involving loss of the low- and medium-SR fibers might compromise our ability to understand speech in a noise environment without changing the nature of the hearing loss as measured with the conventional pure-tone audiogram.

Tinnitus, or the perception of phantom sounds, is a common consequence of aging or acoustic overexposure, especially after blast injuries [32]. Since the tinnitus percept is present in the absence of environmental sound, it has been assumed to arise from anomalies in the spontaneous discharge of neurons somewhere in the auditory pathway. An ANF that has lost its hair cell synapse has no spontaneous activity or response to sound. Thus, noise and aging tend to produce regions of the cochlea where ANF spontaneous activity is reduced or eliminated. Paradoxically, that reduction in peripheral activity often leads to hyperactivity in central pathways, as a result of “gain adjustments” that are programmed into the circuitry [32,33], and this type of hyperactivity may be the neurophysiological basis for the tinnitus percept. Correspondingly, profoundly deaf patients often have severe tinnitus, and the implantation and activation of a cochlear implant, which restores some background activity in the otherwise silent ANFs, can greatly reduce the tinnitus percept [34]. The discovery of “hidden hearing loss,” where significant synaptopathy can hide behind a normal audiogram, provides a way to think about why people exposed to a blast can suffer permanently from tinnitus, even if the audiogram returns to normal, suggesting there has been little damage to the hair cells [35,36]. Although synaptopathy-induced silencing of ANFs could be an important elicitor of tinnitus, it is likely not the only one. Because the tinnitus percept likely arises from the complex rebalancing of excitatory and inhibitory inputs to central circuitry, a similar peripheral pathology can have very different perceptual outcomes.

4. PROSPECTS FOR THERAPY

Neurotrophins are a class of gene products that are key to the normal development of the cochlear innervation [37] and to the survival of ANFs in the adult ears [38]. Years ago, it was shown that cochlear perfusion of neurotrophins could enhance the survival of spiral ganglion cells after destruction of the cochlear sensory epithelium by high-dose aminoglycosides [39]. In those animal models of acquired SNHL, the administration of neurotrophins to the adult cochlea also elicited the extension of new peripheral axons from surviving spiral ganglion cells, which migrated to the denuded basilar membrane and spiraled up and down the cochlea, seemingly in search of peripheral targets [40]. These neurotrophin experiments inspired us to ask whether similar treatments after a synaptopathic noise exposure could elicit re-growth of the connections between damaged ANFs and surviving IHCs. Indeed, we and others have now shown that, at least when delivered within 24 hours of the noise damage, application of neurotrophins in a slow-release gel on the cochlea’s round-window membrane can evoke significant recovery of synaptic contacts and corresponding recovery of cochlear sound-evoked response amplitudes [41,42]. This exciting proof-of-principle experiment provides hope that clinical treatments will be available in the future to re-establish the connections between the spiral ganglion and the hair cells, with the prospect of reducing tinnitus percepts and enhancing the understanding of speech in noise environments for a variety of SNHL etiologies.

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