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Experimental Medicines for Hearing Loss: Are Prevention or Restoration Feasible?

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EDITOR'S NOTE: Dr. Le Prell has also given an excellent webinar for the Canadian Academy of Audiology (CAA) earlier this summer. It can be accessed through the CAA site at www.CanadianAudiology.ca.

Exposure to loud sound is hazardous to various cells in the inner ear. Injury to the inner and outer hair cells (IHCs, OHCs) is well documented, with OHC loss typically being more widespread than IHC loss (Wang et al., 2002). The specific injury pattern to these vulnerable sensory cells depends on the level and duration of the sound exposure and the exposure's spectral (frequency) content and impulsivity (for review, see Hu, 2012). It is now known that the synapses between the IHCs and their auditory nerve (AN) targets are also vulnerable to noise-induced degeneration (Kujawa & Liberman, 2009). In addition to the above, fibrocytes located in the lateral wall (Adams, 2009), supporting cells that provide structure to the organ of Corti (Nordmann et al., 2000; Raphael & Altschuler, 1991), and the reticular lamina provide the physical boundary between the endolymph-filled scala media and perilymph-filled scala vestibuli (Bohne and Rabbitt, 1983; Wang et al., 2002) are also subject to noise-induced injury.

Because the OHCs provide about 40 dB of cochlear gain (Davis, 1983), OHC loss is often associated with threshold shift. In contrast, significant loss of either the IHCs (Lobarinas et al., 2013) or the synapses connecting the IHCs to the AN (Kujawa and Liberman, 2009) does not result in significant threshold shift. However, word recognition deficits for words presented in quiet (Grant et al., 2022) or in noise (Guest et al., 2018) can occur without clinically significant hearing loss. Because these word identification deficits are not issues of sound detection but rather difficulty understanding speech when delivered at audible levels, these are termed supra-threshold deficits. Some evidence suggests supra-threshold deficits may be a consequence of OHC

dysfunction (Parker, 2020), and other evidence suggests supra-threshold deficits may be a consequence of disruption of the afferent neural pathway (i.e., the IHCs and/or their connections to the AN) (Grant et al., 2020). Because synaptic pathology can occur with or without OHC loss (Fernandez et al., 2020), and pathology within the organ of Corti structures can only be established with confidence via post-mortem tissue analysis, relationships between pathology and supra-threshold dysfunction are scientifically challenging. Nonetheless, supra-threshold hearing difficulties are an important patient complaint (Carhart and Tillman, 1970; Wilson et al., 2007). Thus, better understanding of the associations between physiological measures of OHC function (distortion product otoacoustic emissions), sound-evoked neural responses (auditory brainstem response, envelope following response), and supra-threshold function (word recognition ability in quiet and in noise) have been and continue to be actively investigated (see for example Bharadwaj et al., 2014; Bramhall et al., 2015; Bramhall, 2021; Bramhall et al., 2017; Bramhall et al., 2018; Carcagno and Plack, 2020; Causon et al., 2020; Guest et al., 2019a; Guest et al., 2019b; Liberman et al., 2016; Mepani et al., 2020; Mepani et al., 2021; Plack et al., 2016; Van Der Biest et al., 2023; Verhulst et al., 2018).

Given the important roles of the OHCs and the afferent neural pathway in sound detection and supra-threshold sound processing, there has been significant attention to how these cells are injured. Death of the IHC and OHC sensory cells can occur via apoptosis or necrosis (for review see Hu, 2012). This distinction may not matter to audiologists in their day-to-day responsibilities. However, this is critically important from a drug development perspective. The specific biochemical events associated with each cell death pathway determine the types of drug families that might be considered for possible therapeutic benefits (Dinh et al., 2015). Mechanisms of noise-induced synaptic pathology are less well understood (Liberman and Liberman, 2015; Liberman and Kujawa, 2017) but treatment of neuropathic injury is nonetheless also of high interest (Hashimoto et al., 2019; Suzuki et al., 2016; Wan et al., 2014). The findings that noise-induced cell death in the inner ear are not strictly a mechanical process but importantly include potentially druggable targets related to active cell stress and specific biochemical reactions have opened the door for assessment of investigational medicines not only for possible prevention of noise-induced hearing loss (NIHL) (Le Prell, 2022) but also for prevention of drug-induced hearing loss (DIHL) (Foster et al., 2022; Le Prell, 2021).

In addition to hearing loss prevention, auditory function restoration is highly interesting. Target populations for possible hearing restoration interventions include not only those born with genetic mutations that negatively affected auditory function but also those who have lost their hearing as a consequence of aging [age-related hearing loss (ARHL)] and those who experienced sudden sensorineural hearing loss (SSNHL) with incomplete hearing recovery (Foster et al., 2022). Interestingly, in many clinical trials investigating hearing restoration in human participants, word understanding in quiet and in noise have been common outcome measures, in addition to the inclusion of audiometric threshold measurement (Le Prell et al., 2022). Published results are limited, but some data are suggesting the potential for improved speech understanding even in the absence of threshold change in clinical trial participants (McLean et al., 2021). In contrast to the high rate at which word tests are included in studies evaluating hearing restoration, there has been minimal inclusion of supra-threshold measures in studies on NIHL and DIHL prevention (Le Prell, 2021).

Audiologists are increasingly likely to receive questions from patients about inner ear medicines for two key reasons. First, many commercial entities are engaged in developing pipeline therapeutics for hearing indications (Isherwood et al., 2022; Schilder et al., 2019). The increased

activity in the commercial space means many press releases publicly share company results and website content summarizing drug development programs, which patients may access if they seek to learn about treatment options. Second, in September 2022, the United States (U.S.) Food and Drug Administration (FDA) approved a proprietary formulation of sodium thiosulfate for the prevention of cisplatin-induced hearing loss in pediatric patients (1 month of age and older) receiving cisplatin for the treatment of localized, non-metastatic solid tumors (Dhillon, 2023). Thus, one medicine has successfully obtained regulatory approval for a hearing loss prevention indication on its product labeling. Despite the narrow labeling and indications, the successful navigation of the regulatory pathway is a major accomplishment and provides a path for other investigational medicines to follow.

Remaining informed on the current status of investigational inner ear medicines is a significant challenge as the landscape is continuously changing. In addition to review papers, which provide a snapshot of what is being developed at a given time, current information on the specific experimental medicines being assessed in clinical trials is available to audiologists and patients through national clinical trial registries. In the U.S., current clinical trial information can be accessed via the National Institutes of Health registry, available at clinicaltrials.gov. In Canada, current clinical trial information can be accessed via Health Canada's Clinical Trials Database, available at https://health-products.canada.ca/ctdb-bdec. Educational opportunities are also sometimes available through professional societies, including invited speakers at annual conferences, recorded webinars, and lay publications (such as this one).

In addition to medicines that are developed through the formal national regulatory pathway, audiologists may be asked about dietary supplements. In the U.S., many vitamins, minerals, and herbs are marketed with names that suggest they will alleviate tinnitus, protect hearing, or even restore hearing. These products are not required to undergo testing that establishes their clinical efficacy and are marketed with an FDA-required disclaimer. It is important to remember that while these dietary supplements are sold "over-the-counter" (i.e., without a prescription), they are not equivalent to over-the-counter medicines such as analgesics, anti-histamines, laxatives, etc., all of which have FDA-approved labeling for specific indications. Significant differences exist between Natural Health Product (NHP) regulations in Canada and dietary supplement regulations in the U.S. (Smith, 2022). Regardless of whether an audiologist is located in the U.S., Canada, or elsewhere, if patients inquire about vitamins, minerals, or herbal products, audiologists should first and foremost consider their scope of practice and whether they have the necessary expertise to guide such products. If an audiologist does provide commentary on vitamins, minerals, or herbal products, they must rely on peer-reviewed information about efficacy (see for example Coelho et al., 2016; Curhan et al., 2015; Shargorodsky et al., 2010) and are knowledgeable about potential adverse side effects. Dietary supplements can be contra-indicated in the presence of some health conditions, and interactions between some dietary supplements and some prescription medications make it essential that risks be understood by those providing guidance (Mello et al., 2020).

Advances in understanding cell death in the inner ear have opened the door for identifying investigational medicines that may prevent hearing loss. At the same time, advances in understanding the molecular development of cells in the inner ear have driven efforts to induce regeneration of cells and synapses to restore auditory function. While much of this work remains experimental, including pre-clinical test models and human clinical trials, one medicine is now approved by the U.S. FDA for a cisplatin-induced hearing loss prevention indication. Based on the large body of clinical research that is ongoing at this time (Foster et al., 2022; Le Prell, 2021), there is reason to be hopeful that additional medicines will successfully navigate the regulatory process

and one day be available for patient populations.

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