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Noise-induced hearing loss and its prevention: current issues in mammalian hearing

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Noise-induced hearing loss (NIHL) has been well investigated across diverse mammalian species and the potential for prevention of NIHL is of broad interest. To most efficiently develop novel therapeutic interventions, a good understanding of the current state of knowledge regarding mechanisms of injury is essential. The overarching goals of this review are to 1) concisely summarize the current state of knowledge, and 2) provide opinions on the most significant future trends and developments.

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Introduction

Noise-induced hearing loss (NIHL) is a major world-wide public health issue. A substantial proportion of disabling hearing has been attributed to occupational noise exposure [1,2]. In addition, there is a significant population of individuals with notched audiometric configurations consistent with noise-induced cochlear injury even in adults who do not have disabling hearing loss. For example, among participants in the 2011–2012 National Health and Nutrition Examination Survey, unilateral or bilateral audiometric notches were detected in 23.5% of those who self-reported good or excellent hearing and 28.3% of those with who self-reported little, moderate, or a lot of trouble hearing [3]. The finding that noise-induced synaptic pathology ('cochlear synaptopathy') does not affect the pure-tone audiogram suggests the possibility that there are many more individuals with noise-induced pathology and dysfunction than are currently diagnosed using threshold-based criteria [4••]. Two of the most exposed, and most at-risk, populations are workers exposed to occupational noise [5••], and service members and veterans [6•,7]. Music industry professionals are also at-risk [8] and there is increasing attention to the potential risks for those exposed to loud recreational sound ('leisure noise') [9••,10,11••].

It is generally agreed that as noise exposure increases (via longer exposure and/or higher sound levels), risk for cochlear injury and hearing loss increases. The most systematic description of relationships between noise exposure and hearing loss is that of the International Standard Organization [12]. Unfortunately, the patterns of occupational NIHL described in several historic reports and other more recently assessed worker populations deviate from that predicted [13,14]. Such discrepancies might be related to differences between the ethnicity and sex of workers contributing data in the 1950′s and 1960s and those working in loud jobs today, as there is significant variation in NIHL as a function of ethnicity and sex [14–17].

National regulations, such as that of the Occupational Safety and Health Administration [18] and national guidance documents, such as that of the National Institute on Occupational Safety and Health [19], are based not only on assumptions about the levels at which occupational exposure becomes hazardous, but also public health decisions about how much hearing loss is 'acceptable' and in what proportion of the population this hearing loss is 'acceptable'. Recent reviews discussing prevention of NIHL in adults and children suggest that an exposure limit of 80 dB-A L_{EX} (with L_{EX} being the 8-hour equivalent continuous average sound pressure level) would protect all but the most vulnerable individuals against NIHL, and that 75 dB-A L_{EX} limits would be necessary if the goal were to protect even the most vulnerable individuals [9••,10] . Given the much higher sound levels in many workplaces and during many recreational activities, NIHL is, unfortunately, likely to remain a major public health issue. Animal models and mechanisms of injury are thus of high scientific interest and pharmaceutical intervention has become a commercial goal. Significant current interest also includes the identification of damage-risk criteria for cochlear synaptopathy, the diagnostic tests and corresponding functional deficits associated with synaptopathy, and the relevance of this pathology to workers exposed to occupational noise. This review

briefly addresses each of these 'hot' topics in which future developments are likely to occur.

Animal models of noise-induced hearing loss

Comprehensive review of noise injury in rodent models was recently provided for the mouse [20], rat [21,22], chinchilla [23,24], and Guinea pig [25]. Although data directly establishing differences in vulnerability across mammalian species are extremely limited, a recent review of hearing loss induced by octave band noise exposures revealed the chinchilla is more vulnerable than both Guinea pig and rat, with the rat being intermediate to the Guinea pig and chinchilla [26]. The chinchilla, and thus presumably other rodents, are much more vulnerable to noise injury than humans [27], and non-human primates (NHPs) [28–30].

Given genetic and structural similarities, it is not surprising that the overall vulnerability of humans to noise injury more closely parallels NHPs [28]; therefore, NHPs provide an important model for investigating supra-threshold noise-induced deficits [29,30]. While the two most common metrics used to study NIHL in mammals are distortion product otoacoustic emissions (DPOAEs), which measure outer hair cell (OHC) function, and the auditory brainstem response (ABR), which is used to measure sound-evoked neural activity, powerful behavioral assessments of both threshold and suprathreshold function can be conducted in primates. Hypotheses of major interest at this time are that selective synapse loss and later neural pathology can result in functional difficulties such as degraded auditory processing in noise, as well as tinnitus and/or hyperacusis, even when OHCs have not been damaged. These hypotheses have been difficult to test in humans since human participants at risk for synapse loss also commonly show high frequency audiometric loss. NHPs permit controlled exposures with audiologic, behavioral and histological assessments that form a bridge to human susceptibility.

Mechanisms of injury

There is a wealth of information on the effects of noise on the inner ear. Much of the early investigation of noise-induced pathology focused on mechanical damage to hair cells, the reticular lamina, and other physical elements composing the organ of Corti [see for example, Ref. [31•]. As the understanding of both apoptotic and necrotic cell death in the cochlea increased, the important role of metabolic stress in apoptosis emerged and there are now multiple comprehensive reviews of mechanical and metabolic injury mechanisms in the cochlea [32–34]. The more complete understanding of metabolic stress as a key factor in noise-induced cell death and NIHL has resulted in the design and conduct of multiple human trials assessing not only prevention of NIHL [for review see Ref. 35] but also prevention of medication-induced ototoxicity given the key role of metabolic stress as a shared mechanism of injury [for review see Ref. 36].

The mechanisms of noise-induced cochlear synaptopathy are increasingly well understood in rodent models [37]. Human temporal bone studies show evidence of age-related synapse loss [38•,39]that parallels age-related synapse loss in rodents [40]. Thus, there is significant interest in whether the noise-induced synaptopathy seen in rodents occurs in humans [41•,42,43]. Given mixed data, several detailed reviews concluded that differences in the patterns of participant exposure may drive the observed differences in results [44,45••]. Humans at the lower end of the exposure continuum may be less vulnerable to noise-induced cochlear synaptopathy than initially speculated when the first human findings emerged [46•,47]. New data continue to emerge regarding human pathology, however. Recent studies add new evidence that aging tends to lead to a reduction of ABR Wave I amplitude, but relationships with noise exposure have continued to remain elusive [48,49]. Because many of the studies assessing the effects of aging did not specifically include participants with significant occupational noise exposure histories, the extent to which synaptopathic injury might occur in such workers remains an open question.

Occupational noise injury

There is significant evidence of OHC injury in workers exposed to occupational noise. OHC damage is commonly inferred based on evidence of permanent threshold shift (PTS), but data revealing reduced or absent DPOAEs also have been used to infer OHC loss or dysfunction in noise-exposed workers [50]. The potential for occupational noise to cause cochlear synaptopathy was suggested by data from rodents subjected to exposures ranging from a longer-duration lower-level noise exposure (7 days, 84 dB SPL) to a shorter-duration higher-level noise exposure (2 hours, 100 dB SPL) [51,52]. The differences between occupational noise exposure (repeated daily exposures over many years with nightly recovery periods) and the single exposure models used to induce cochlear synaptopathy in animal models (noted above) have led to questions about the relevance of animal laboratory tests to understanding occupational worker hearing loss [53•]. For occupational noise exposure, the presence of overt hearing loss confounds the interpretation of decreased wave I amplitude as evidence of cochlear synaptopathy, but the finding of wave I amplitude deficits at high stimulus levels, above the operating range for the cochlear amplifier, is consistent with a mixed pathology including both OHC and synapse loss [44]. More recent discussions suggest careful selection of the stimulus paradigm can reduce confounding of the effects of OHC loss and synapse loss [54]. Other recent data clearly document the possibility of cochlear synaptopathy

occurring with or without accompanying sensory cell loss, as a function of the specific exposure parameters [55].

Suprathreshold deficits

While there is significant speculation regarding the specific functional deficits that are associated with cochlear synaptopathy, there is little direct evidence of functional deficits in work with rodents to date. A single study assessing the perceptual consequences of ABR Wave I amplitude deficits in a rat model reported decreases in the detection of masked signals, with deficits limited to the poorest signal to noise ratios at signal frequencies that evoked decreased ABR amplitudes [56]. Efforts to detect deficits in the detection of masked signals have not revealed deficits in tinnitus patients, a group speculated to be at risk for cochlear synaptopathy [57]; these results are consistent with recent preliminary data from the authors' laboratory in animals that experienced noise exposures that have been previously shown to cause cochlear synaptopathy. Age-related declines in Wave I amplitude in humans were not associated with deficits in hearing in noise; in addition there was no consistent relationship between ABR Wave I amplitude and lifetime noise exposure [48]. In contrast, several reports suggest that veterans and civilian firearm users may be at increased risk of cochlear synaptopathy [58•,59]. Additional research with those exposed to firearm noise and occupational noise is warranted, with careful efforts to control for potential OHC pathology required.

Pharmaceutical intervention

Decades of research using animal models to assess mechanisms of noise injury and therapeutic interventions at the selected targets have advanced into clinical trials for a variety of agents [for recent review see Ref. 35] despite the many challenges associated with development of drugs for auditory indications [see Ref. 60]. Indeed, there are now more than 40 companies with pharmaceutical interventions in various stages ranging from pre-clinical to Phase I or even Phase II clinical trials [61••]. In addition to long standing interest in pharmaceutical prevention of NIHL, there is a burgeoning interest in regeneration and stem cell therapeutics to combat noise-induced hearing deficits. Many of these are being tested in animal models, and hope to follow the success of Vortigene, a genetic therapeutic for visual dysfunction that was first tested in rodents, then tested in a larger animal model before being translated to humans [62–64]. Pharmaceutical therapies that restore cochlear synaptic connections are also a focus of current investigation [65–67]. The clinical (and commercial) development of neurotrophic factors that stimulate repair or regeneration of the neural connections between the auditory nerve and the inner hair cells is poised to quickly accelerate if cochlear synaptopathy and associated functional deficits can be reliably diagnosed and quantified. Note that translation of such therapies to humans requires careful consideration of many factors, including species susceptibility to noise exposures, genetic differences between the animal model and humans, therapeutic window, delivery windows and delivery methods [28,60].

Summary and conclusions

NIHL is likely to remain a major public health issue given the high levels of environmental, recreational, and occupational noise exposure. Animal models evaluating mechanisms of injury have provided significant insight into the vulnerability of both OHCs and cochlear synapses to noise injury. Related research identifying drugs that alleviate metabolic stress has allowed pharmaceutical intervention for NIHL prevention to become a major commercial goal. With greater understanding of cochlear synaptopathy and corresponding functional deficits, it may be possible to envision updates to the occupational noise regulations used to protect workers against noise injury as well as the potential for regeneration or repair of lost synapses. Given the prevalence of NIHL and the potential that age-related and/or noise-induced cochlear synaptopathy could be associated with hearing-in-noise difficulty, tinnitus, or hyperacusis, the pursuit of clinical interventions is likely to remain a major topic of investigation with the potential for major advances in hearing care.

Conflict of interest statement

Nothing declared.

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