

Science Matters: Towards a Differential Diagnosis of Cochlear Synaptopathy as a Contributor to Sensorineural Hearing Loss

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Many people with a history of exposure to loud music or noise report a deterioration of their ability to understand speech in noisy settings, even if their audiograms and otoacoustic emissions (OAEs) remain normal, suggesting good outer hair cell (OHC) function.¹ Some of these people develop tinnitus, hyperacusis, or both. Eventually, they may acquire audiometric losses at an earlier age than those who avoided loud noise.

These observations had been a challenge to explain until a series of studies on rodents,^{2,3} and recently one on primates,⁴ showed that a fraction of inner hair cell (IHC) synapses with auditory nerve fibers (ANFs) could be destroyed by noise doses that left the hair cells intact, resulting in an auditory neuropathy, or “synaptopathy.” A telltale sign of auditory neuropathy (and by extension, of synaptopathy) is that speech perception deficits, particularly in noise, are worse than expected from the audiometric loss.⁵ Synaptopathy is also seen well before OHC loss in normally aging mice,⁶ a finding corroborated by several postmortem studies of human temporal bones.^{7,8}

Furthermore, the synaptopathic effects of noise exposure and aging appear to be additive.⁹

While reduced wave I amplitudes of subcutaneously recorded auditory brainstem responses (ABRs), together with normal OAEs, allow for the routine detection of synaptopathy in animal models, differential diagnosis of synaptopathy as a contributor to human sensorineural hearing loss has proven more difficult, as discussed further below. Despite this, *an obvious message to people who report changes in their ability to hear in noise should be: limit your exposure to loud sounds and/or wear hearing protection.* This applies even if their clinical speech-in-noise scores remain within normal limits, as is common in musicians whose better-trained auditory/cognitive faculties can partly compensate for potentially noise-damaged ears.¹⁰

A number of authors have made the valid points that humans are less susceptible to loud noise than rodents, that exposures which cause synaptopathy in rodents (e.g., 100 dB SPL for 2 h) already exceed OSHA¹¹ limits of 85 dB A for 8 h, or 100 dB A for 1 h, and that the relatively narrowband exposures used in animal work are not representative of real-world noise.¹² However, two studies in CBA/Ca mice showed that exposures to 8–16 kHz noise at 84 dB SPL for 1 week¹³, and 75 dB SPL for 2 months¹⁴, also caused synaptopathy without affecting OHC function. Furthermore, the work of Valero et al.⁴ revealed that susceptibility differences between mice and rhesus monkeys could be as small as 10 dB. It is thus not yet clear if years or decades of occupational noise at the OSHA limit (with potential recreational exposures on top) are indeed safe for the ear, sparing both

cochlear hair cells and synapses.

Another recent mouse study showed that not all noise doses that led to temporary threshold shifts (TTS) – even as high as 30 dB at 24 h post-exposure – caused synaptopathy.¹⁵ While a 2 hour exposure to 8–16 kHz noise at 100 dB SPL reliably induced synaptopathy, the same exposure at 91 dB SPL did not.¹⁵ Interestingly, there was no simple relationship between the amount of TTS and the extent of synapse loss. Indeed, at frequencies just above the 8–16 kHz exposure band (i.e., 16–24 kHz), the 91 dB dose caused *more* TTS than the 100 dB dose, but did not lead to synaptopathy.¹⁵ A similar unclear relationship between the noise dose and the amount of TTS has been observed in many human studies. As a recent example, Grinn et al.¹⁶ reported on a group of young adults who attended a typical loud recreational event (in most cases a concert), with an average dose of 93 dB A for 4 h, and a range of 73–104 dB A for 1.5–16 h. Most showed a 1 day TTS of <10 dB (with full recovery at 7 days), accompanied by correspondingly small but significant temporary decreases in words-in-noise scores. There was no correlation between the noise dose and the amount TTS across study participants. Furthermore, compound action potential (CAP) amplitudes to clicks and 2–4 kHz tone bursts were not affected, arguing against the development of synaptopathy after a single recreational noise dose. What about many of these exposures? Prendergast et al.¹⁷ studied a large sample of young adults with clinically normal audiograms whose estimated lifetime recreational noise energy doses varied by a factor of more than 100. There was no correlation between this lifetime noise dose and click-ABR wave I amplitude at 80 and 100 dB peSPL. However, it may be that people who frequently subject themselves to high levels of recreational noise do so because of their “tougher” ears, which sustain less damage than the potentially more “tender” ears of those who avoid loud music and noise (see Ref. 18 for a general discussion of this issue).

Other recent studies on human subjects showed that electrocochleography (ECoChG) could potentially detect noise-induced synaptopathy. College student musicians with normal audiometric thresholds up to 8 kHz, but mild losses at 10–16 kHz, showed slightly decreased click-evoked CAP amplitudes but significantly increased summing potential (SP) amplitudes.¹⁹ Thus, the SP/CAP ratio was increased in the musicians, a finding also associated with endolymphatic hydrops in Meniere’s disease.²⁰ This study¹⁹ also suggests that elevated thresholds above 8 kHz might point to synaptic losses at lower frequencies, but this remains to be substantiated. Bramhall et al.²¹ found reduced CAP amplitudes in military veterans with high noise exposure histories, and in non-veteran firearm users, compared with veterans with lower noise histories and non-veterans who did not fire guns. Importantly, the reduced CAP amplitudes could not be explained by OHC dysfunction, as assessed with distortion product OAEs (DPOAEs). Finally, other studies have found reduced CAP or ABR wave I amplitudes in human tinnitus subjects with normal audiograms, suggesting that synaptopathy can trigger tinnitus.²²⁻²⁴ Note that ABR wave V was not decreased in these tinnitus subjects, implying a renormalization of the reduced auditory nerve responses within the brainstem.²²⁻²⁵

What other promising approaches might lead to a differential diagnosis of cochlear synaptopathy in noise-exposed and aging ears? The acoustic or middle ear muscle reflex (MEMR) could be a sensitive metric because high-threshold ANFs are likely the main inputs to the MEMR pathway, and high-threshold ANFs appear to be especially vulnerable to loud noise.²⁶ Wojtczak et al.²⁷ found that the MEMR evoked by contralateral broadband noise was significantly weaker in human

tinnitus subjects with normal or near-normal audiograms compared to non-tinnitus controls. In a recent mouse study, Valero et al.²⁸ used narrowband reflex-eliciting stimuli and demonstrated that the MEMR was normal when activated from non-synaptopathic cochlear regions, but greatly weakened in synaptopathic regions. They also showed that this was a more sensitive measure of synaptopathy than reduced ABR wave I.²⁸ Finally, Zhao et al.²⁹ reported some encouraging results with CAPs recorded in the presence of a broadband noise, which was intended to mask the contributions of the better-preserved low-threshold ANFs to the CAP (see also Ref. 30). They found an increase in chirp-evoked CAP-in-noise thresholds in people with histories of noise exposure, despite good OHC function as demonstrated with DPOAEs.²⁹

One of the holy grails of audiology has been to differentiate OHC from IHC or presynaptic losses, and from ANF or postsynaptic losses, which are all presently lumped together as sensorineural hearing loss. There is little doubt that such differential diagnosis would prove useful in improving hearing aid fitting, in better predicting cochlear implantation outcomes, and in individualized auditory training and future regenerative medicine. A landmark example has been the diagnosis of auditory neuropathy on the basis of an absent or abnormal CAP or ABR, even at high stimulus levels, in the presence of a robust cochlear microphonic and/or OAEs.⁵ As outlined above, noise- and/or age-related cochlear synaptopathy has been more challenging to detect, especially in individuals with normal or near-normal audiograms. This is presumably because synaptic losses remain relatively mild in these cases, even if they are functionally significant, affecting speech perception in noise, and potentially leading to tinnitus and/or hyperacusis. The full impact of synaptopathy might only be revealed when it can be differentially diagnosed in individuals with more traditional OHC loss. The question of how this should be done remains an old and unanswered one.^{31,33}

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Editor's Note

For additional information we encourage please see [Colleen Le Prell's article in in Volume 5 Issue 2 of Canadian Audiologist](#).