Canadian Audiologist

The Official Publication of the Canadian Academy of Audiology

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

Published May 6th, 2018

Martin Pienkowski, PhD

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 OSHA[11] 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 week[13], and 75 dB SPL for 2 months[14], 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 summating 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 study[19] 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]

Acknowledgement

I thank prospective AuD student Anastasia Chobany for carefully proofreading this article.

References

1. Pienkowski M. On the etiology of listening difficulties in noise despite clinically normal audiograms. Ear Hear 2017;38:135–48.
2. Kujawa SG, and Liberman MC. Adding insult to injury: cochlear nerve degeneration after “temporary” noise-induced hearing loss. J Neurosci 2009;29:14077–85.
3. Kujawa SG, and Liberman MC. Synaptopathy in the noise-exposed and aging cochlea: primary neural degeneration in acquired sensorineural hearing loss. Hear Res 2015;330:191–99.
4. Valero MD, Burton JA, Hauser SN, Hackett TA, Ramachandran R, and Liberman MC. Noise-induced cochlear synaptopathy in rhesus monkeys (Macaca mulatta). Hear Res 2017;353:213–23.
5. Rance G, and Starr A. Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. Brain 2015;138:3141–58.
6. Sergeyenko Y, Lall K, Liberman MC, and Kujawa SG. Age-related cochlear synaptopathy: an early-onset contributor to auditory functional decline. J Neurosci 2016;33:13686–94.
7. Makary CA, Shin J, Kujawa SG, Liberman MC, and Merchant SN. Age-related primary cochlear neuronal degeneration in human temporal bones. J Assoc Res Otolaryngol 2011;12:711–17.
8. Viana LM, O'Malley JT, Burgess BJ, Jones DD, Oliveira CA, Santos F, Merchant SN, Liberman LD, Liberman MC. Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. Hear Res 2015;327:78–88.
9. Kujawa SG, and Liberman MC. Acceleration of age-related hearing loss by early noise exposure:

Evidence of a misspent youth. J Neurosci 2006;26:2115–23.
10. Moreno S and Bidelman GM. Examining neural plasticity and cognitive benefit through the unique lens of musical training. Hear Res 2014;308:84–97.
11. OSHA. Hearing conservation. Occupational Safety and Health Administration, U.S. Department of Labor, Publication No: OSHA 3074; 2002. Available at: http://www.osha.gov/Publications/osha3074.pdf.
12. Dobie RA, and Humes LE. Commentary on the regulatory implications of noise-induced cochlear neuropathy. Int J Audiol 2017;56:74–78.
13. Maison SF, Usubuchi H, and Liberman MC. Efferent feedback minimizes cochlear neuropathy from moderate noise exposure. J Neurosci 2013;27:5542–52.
14. Pienkowski M. Prolonged exposure of CBA/Ca mice to moderately loud noise can cause cochlear synaptopathy but not tinnitus or hyperacusis as assessed with the acoustic startle reflex. Trends Hear 2018;22:1–18.
15. Fernandez KA, Jeffers PW, Lall K, Liberman MC, and Kujawa SG. Aging after noise exposure: Acceleration of cochlear synaptopathy in “recovered” ears. J Neurosci 2015;35:7509–20.
16. Grinn SK, Wiseman KB, Baker JA, and Le Prell CG. Hidden hearing loss? No effect of common recreational noise exposure on cochlear nerve response amplitude in humans. Front Neurosci 2017;11:465.
17. Prendergast G, Guest H, Munro KJ, Kluk K, Léger A, Hall DA, Heinz MG, and Plack CJ. Effects of noise exposure on young adults with normal audiograms I: Electrophysiology. Hear Res 2017;344:68–81.
18. Henderson D, Subramaniam M, and Boettcher FA. Individual susceptibility to noise-induced hearing loss: an old topic revisited. Ear Hear 1993;14:152–68.
19. Liberman MC, Epstein MJ, Cleveland SS, Wang H, and Maison SF. Toward a differential diagnosis of hidden hearing loss in humans. PLoS One 2016;11:e0162726.
20. Hornibrook J. Tone burst electrocochleography for the diagnosis of clinically certain Meniere's disease. Front Neurosci 2017;11:301.
21. Bramhall NF, Konrad-Martin D, McMillan GP, and Griest SE. Auditory brainstem response altered in humans with noise exposure despite normal outer hair cell function. Ear Hear 2017;38:e1–e12.
22. Schaette R, and McAlpine D. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. J Neurosci 2011;31:13452–457.
23. Paul BT, Bruce IC, and Roberts LE. Evidence that hidden hearing loss underlies amplitude modulation encoding deficits in individuals with and without tinnitus. Hear Res 2017;344:170-182.
24. Bramhall, Konrad-Martin D, and McMillan GP. Tinnitus and auditory perception after a history of noise exposure: Relationship to auditory brainstem response measures. Ear Hear 2018 (in press)
25. Brotherton H, Plack CJ, Maslin M, Schaette R, and Munro KJ. Pump up the volume: could excessive neural gain explain tinnitus and hyperacusis? Audiol Neurootol 2015;20:273–82.
26. Furman AC, Kujawa SG, and Liberman MC. Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates. J Neurophysiol 2013;110:577–86.
27. Wojtczak M, Beim JA, and Oxenham AJ. Weak middle-ear-muscle reflex in humans with noise-induced tinnitus and normal hearing may reflect cochlear synaptopathy. eNeuro 2017;4(6).
28. Valero MD, Hancock KE, Maison SF, and Liberman MC. Effects of cochlear synaptopathy on middle-ear muscle reflexes in unanesthetized mice. Hear Res 2018 (in press).
29. Zhao H-B, Zhu Y, Mei L, Earl B, Roggia SM, Frederick A, and Pinkl J. A simple and novel method to diagnose noise-induced “hidden” hearing loss and cochlear synaptopathy. 2018

Midwinter Meeting of the Association for Otolaryngology, PD120.
30. Bourien J, Tang Y, Batrel C, Huet A, Lenoir M, Ladrech S, Desmadryl G, Nouvian R, Puel JL, and Wang J. Contribution of auditory nerve fibers to compound action potential of the auditory nerve. J Neurophysiol 2014;112:1025–39.
31. Moore BC, Vickers DA, Plack CJ, and Oxenham AJ. Inter-relationship between different psychoacoustic measures assumed to be related to the cochlear active mechanism. J Acoust Soc Am 1999;106:2761–78.
32. Johannesen PT, Pérez-González P, and Lopez-Poveda EA. Across-frequency behavioral estimates of the contribution of inner and outer hair cell dysfunction to individualized audiometric loss. Front Neurosci 2014;8:214.
33. Verhulst S, Jagadeesh A, Mauermann M, and Ernst F. Individual differences in auditory brainstem response wave characteristics: relations to different aspects of peripheral hearing loss. Trends Hear 2016;20:1–20.

Editor's Note

For additional information we encourage please see Colleen Le Prell's article in in Volume 5 Issue 2 of *Canadian Audiologist*.