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Discussion

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Abstract

Objective: A discussion on whether recent research on noise-induced cochlear neuropathy in rodents justifies changes in current regulation of occupational noise exposure. *Design*: Informal literature review and commentary, relying on literature found in the authors' files. No formal literature search was performed. *Study sample*: Published literature on temporary threshold shift (TTS) and cochlear pathology, in humans and experimental animals, as well as the regulations of the US Occupational Safety and Health Administration (OSHA). *Results*: Humans are less susceptible to TTS, and probably to cochlear neuropathy, than rodents. After correcting for inter-species audiometric differences (but not for differences in susceptibility), exposures that caused cochlear neuropathy in rodents already exceed OSHA limits. Those exposures also caused ''pathological TTS'' (requiring more than 24 h to recover), which does not appear to occur with human broadband noise exposure permissible under OSHA. *Conclusion*: It would be premature to conclude that noise exposures permissible under OSHA can cause cochlear neuropathy in humans.

Key Words: Noise-induced, neuropathy, occupational safety and health administration, temporary threshold shift, species, regulation, permissible exposure limit

Excessive noise exposure can damage multiple cell types in the cochlea, including the spiral ganglion cells of the auditory nerve, most of which innervate the inner hair cells (IHCs; Saunders et al, 1985). Nevertheless, almost all studies known to the authors have shown that outer hair cell (OHC) damage or loss occurs before, or concomitant with, damage to other cell types (see, for example, Wang et al, 2002). In addition, OHC loss has been correlated, albeit imperfectly, with pure tone thresholds (reviewed by Clark & Bohne, 1986). Accordingly, most clinical and field studies of noise-induced hearing loss have relied on audiometric pure tone threshold shifts as outcome measures.

Conventional wisdom held that single temporary threshold shifts (TTSs) were harmless, because anatomic studies had usually failed to show any permanent inner-ear damage in animals when thresholds had returned to pre-exposure levels (Saunders et al, 1985). Human TTS_2 (measured 2 min after cessation of noise exposure) was compared to noise-induced permanent threshold shifts (NIPTS) measured in groups of workers who had had many years of daily exposure. These comparisons led to the conclusion that ''a noise capable of causing significant TTS_2 with brief exposures is probably capable of causing significant permanent losses in hearing, given prolonged or recurrent exposures'' (National Institute of Occupational Safety and Health [NIOSH], 1972). ''Significant TTS_2'' was defined by Kryter et al (1966) as 10 dB for frequencies of 1000 Hz and below, 15 dB at 2000 Hz, or 20 dB at 3000 Hz or above. Kryter et al also stated that ''A TTS_2 that approaches or exceeds 40 dB can be taken as a signal that danger to hearing is imminent'' (such ''pathological TTS'' is discussed later). Based on the Kryter et al report, it has been assumed that a single TTS (if less than about 30 dB at 2 min) was safe, but that repeated exposure to the same noise for many years would probably cause NIPTS about as large as the TTS_2. Conversely, an exposure that caused no TTS_2 was considered safe even for daily career-long exposure. This conventional wisdom has now been challenged by a series of experiments from Harvard's Eaton-Peabody Laboratory.

Initially, Kujawa and Liberman (2009) obtained a variety of physiological and anatomical data from mice that had been exposed to an octave band of noise (8–16 kHz) at 100 dB SPL for 2 h. Mean TTS, as measured by the auditory brainstem response (ABR), was 40 dB 1 day following exposure (this was the earliest post-exposure measure interval); TTS was about half that at 3 days post exposure

Abbreviations

ABR	auditory brainstem response
dB	decibel
CAP	compound action potential
dBA	decibel, A-weighted
IHC	inner hair cell
NIPTS	noise-induced permanent threshold shift
OHC	outer hair cell
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
SPL	sound pressure level
TTS	temporary threshold shift
TTS2	TTS two minutes after exposure
TWA	time-weighted average

and recovered to baseline values (i.e. there was no NIPTS) by 2 weeks post exposure. Despite return to normal physiological threshold sensitivity, neural anatomy (synaptic ribbons and spiral ganglion cells) and physiology (ABR wave I amplitude) were abnormal. Thus, although NIPTS was absent in these mice, neural pathology was present: the IHCs from the base of the cochlea (best frequencies above 16 kHz) had been partially, but apparently permanently, disconnected from the auditory nerve. A later study (Furman et al, 2013) showed that the affected nerve fibres were the low spontaneous rate (high threshold) fibres. In humans, one would expect these fibres to be important for the processing of suprathreshold sounds, possibly including understanding speech in noise. Similar neuropathy (referred to as synaptopathy in their later papers) occurred after exposure that was less intense (84 dB SPL) but much more prolonged (one week, continuous; Maison et al, 2013) and in guinea pigs (Lin et al, 2011). The degree of neuropathy found by Maison et al for mice with intact efferent systems was modest at best, and questionable when synaptic ribbon counts in exposed animals (84 dB SPL) were compared to those in unexposed controls across multiple studies (LePrell & Brungart, 2016).

These studies showed that large TTSs requiring more than 24 h to recover could not be considered safe, at least for mice and guinea pigs. However, it is important to note that in these animal models, not all TTSs, or even persistent TTSs, led to neuropathy. Specifically, Fernandez et al (2015) found neuropathy in mice exposed at 100 dB for 2 h (24 h TTS was over 40 dB), but not in mice exposed at 91 dB (24 h TTS averaged 30 dB).

Interpreting these new findings, Kujawa and Liberman (2015) stated that ''. . . noise is much more dangerous than we have previously thought.'' According to Maison et al (2013), ''. . . many common workplace and leisure exposures to noise are likely more dangerous to hearing health than current federal guidelines indicate.'' Truong and Cunningham (2011) concluded that ''. . . noise levels that had been considered as 'harmless' may actually represent a significant risk to hearing and public health.''

Jensen et al (2015) concluded that ''a re-examination of damage risk criteria may be required to prevent cochlear synaptopathy.'' Liberman and Kujawa (2014) stated: ''noise exposure guidelines should be re-evaluated, as they are based on the faulty premise that threshold audiograms are the most sensitive measures of noise damage.''

Our purpose in this commentary is to ask whether, as the above statements suggest, the neuropathy data indicate the need for revision of Occupational Safety and Health Administration (OSHA,

1974) regulations (we are unaware of any current OSHA deliberations regarding regulatory changes based on these studies). Specifically, OSHA's permissible exposure limit (PEL) is 90 dBA time-weighted average[1] (TWA); in addition, the PEL forbids exposures of 115 dBA or higher for more than one second. We focus on the OSHA regulations because they are less restrictive than those recommended by NIOSH (1998) or by most European nations (Suter, 2000). If compliance with the OSHA PEL is adequate to protect against noise-induced cochlear neuropathy, more restrictive regulations will be more than adequate.

There are three fundamental pitfalls in extrapolating the rodent neuropathy data to human exposure regulations:

1. Different species have different susceptibilities to noise damage;

2. After adjustment for inter-species audiometric differences in most sensitive frequency regions, but not for susceptibility, the exposures that have caused neuropathy in rodents already exceed the OSHA PEL; and

3. Rodent neuropathy occurred only after exposures that caused ''pathological'' TTS, which has been recognized as reflecting an unsafe exposure for decades and does not appear to occur in humans with broadband exposures below the OSHA PEL.

Species susceptibility

Some rodents suffer both OHC loss and hearing threshold shifts from noise exposures that would be harmless for humans. Chinchillas and gerbils appear to be the most noise-susceptible of commonly used laboratory animals (Drescher & Eldredge, 1974; Saunders & Tillney, 1982) and are much more susceptible than humans (Mills et al, 1979; Mills, 1988). Mice are more susceptible than guinea pigs (Burdick et al, 1978; Henry, 1982; Wang et al, 2002; Duan et al, 2008), although this varies across different strains of mice (Erway et al, 1996). Guinea pigs are, in turn, more susceptible than humans (Liang, 1992). These studies suggest that the levels and/or durations of noise required to cause cochlear neuropathy could be higher for humans than for guinea pigs, and much higher than for mice.

Of course, susceptibility might vary not only across species, but also across types of exposure (impulse vs continuous noise, for example) and outcomes (e.g. behavioural versus ABR versus otoacoustic emissions, OHC loss versus threshold shifts). In particular, rodents in the Eaton-Peabody lab experiments described above lost IHC synapses before losing OHCs and displaying permanent threshold shifts; humans and other primates might conceivably lose OHCs and suffer threshold shifts before losing IHC synapses.

A serendipitous pair of data points provides a gross estimate of the human-mouse susceptibility difference for noise-induced neuropathy. A recent mouse neuropathy experiment (Fernandez et al, 2015) and a human TTS experiment from 1960 (Ward, 1960) used exposures that were very similar in every respect except noise level. Both presented octave-band noise for 2 h, in frequency bands where the two species have sensitive hearing: 8–16 kHz for mice, 1.2–2.4 kHz for humans. Both exposures caused very large and persistent TTS; mean 24 h TTS was about 30 dB for mice, and 20–30 dB for most of Ward's subjects. The main difference was in

the noise levels required to cause a large and persistent TTS: 91 dB SPL for mice and 105 dB SPL for humans (Ward's human exposure had an 8 h TWA of 96 dBA and would have been illegal if OSHA had been in existence in 1960). To produce the same effect in humans as in mice required 14 dB higher noise levels (105 minus 91). The 91 dB noise level in mice in Fernandez et al did not show neuropathy; to cause neuropathy, they had to present noise at 100 dB SPL. If the species susceptibility difference were in fact 14 dB, it would take 114 dB SPL for 2 h to cause neuropathy in humans (the OSHA TWA would be 105 dBA). According to an experienced acoustical engineer (Dennis Driscoll, personal communication, 2/26/16), uninterrupted occupational exposures of that level and duration were never observed in over 10,000 noise surveys, and of course OSHA forbids such exposures without hearing protection.

Rodent exposures and OSHA PEL

Even ignoring species susceptibility differences, the exposures needed to cause neuropathy exceed OSHA PEL, after considering species differences in audiograms.

Mice hear best at about 16 kHz (Wang et al, 2002), while human sensitivity is best about 4 kHz, a two-octave difference. Neuropathic exposures for adult mice in the Eaton-Peabody lab were in the 8–16 kHz octave band, either 2 h at 100 dB SPL (Kujawa & Liberman, 2009) or 168 h at 84 dB SPL (Maison et al, 2013; as noted above, neuropathy from this exposure was modest and questionably significant). Comparable exposures from humans would probably be in the 2–4 kHz band. The OSHA TWA for a 100 dB SPL exposure in that band for 2 h (as in Kujawa & Liberman, 2009) would be 91 dBA, i.e. impermissible without hearing protection. The OSHA TWA for the 168 h 84 dB exposure in that band would reach 95 dBA at 32 h and 105 dBA at 128 h, again impermissible without protection.

Guinea pig audiograms are more similar to human than to mouse audiograms. For these rodents, cochlear neuropathy required 2 h exposures of 106 dB in the 4–8 kHz band (Lin et al, 2011). OSHA TWA for this exposure would be 96 dBA, well above the PEL.

"Pathological" TTS

TTS studies in humans over many decades, which contributed to the formulation of damage-risk criteria in various federal standards and guidelines over the years, focussed on the TTS *immediately following* exposure (typically TTS$_2$, as described above). For TTS$_2$ values less than 30 dB, recovery over time is typically exponential, i.e. linear in log time, with complete recovery expected by 16 h post exposure (Ward, 1963, 1969, 1973). However, for TTS$_2$ values of about 40 dB or more, the recovery process follows a different time course, typically delayed and linear over time. Synthesising about two decades of research on human TTS from noise exposures similar to those used by Kujawa and Liberman (2009), Ward (1969) cited six "...firmly established relations between noise and TTS" (pg. 41), with the relevant portion of the first relation as follows: "Moderate TTS also recovers exponentially in time, recovering completely within 16 h after exposure. However, when the TTS has reached 40 dB or more, recovery may become linear in time, with TTS requiring days or even weeks to disappear. This 40 or 50 dB TTS may represent some sort of

'critical TTS' that should not be exceeded if danger of permanent damage is to be avoided." (p. 41–42). In subsequent taxonomies of TTS, Ward often referred to the latter type of TTS with very high initial TTS$_2$ values and delayed recovery as "pathological" TTS (e.g. Ward, 1973). Similarly, Mills (1970) recommended avoiding exposures that lead to TTS requiring more than 16 h to recover because of the risk of permanent injury.

TTS$_2$ values for the laboratory mice in the study by Kujawa and Liberman (2009) were not reported. However, the average TTS values *at the earliest post-exposure measuring point of 24 h* were 30–40 dB, depending on the physiological measure used to establish threshold sensitivity. One can assume that the TTS$_2$ values for these same laboratory mice were considerably higher – probably 50 dB or more. Prolonged recovery lasting more than 16 h would be expected based on the human behavioural TTS data, as was clearly observed for their laboratory mice. This pattern of TTS results in humans would not be considered reflective of a "harmless" exposure, even if threshold sensitivity eventually returned to normal. This would be considered to be "pathological TTS" that would significantly increase the likelihood or danger of permanent damage, as noted by Ward (1963, 1969) and Mills (1970).

The demonstration by Kujawa and Liberman (2009) that changes to neural structures and physiology occur after "pathological" TTS in mice (and possibly in humans) is an important advance in our understanding of the effects of noise exposure, because this helps to identify possible mechanisms underlying such pathological TTS. While Kujawa and Liberman were the first to show the synaptic histopathology of pathological TTS, their physiological findings were foreshadowed by previous animal studies. Benitez et al (1972) found that chinchilla VIIIth nerve compound action potentials (CAPs; equivalent to wave I of the ABR) displayed large threshold shifts and markedly reduced maximum amplitude 48 h post-exposure, by which time a large TTS, as well as cochlear microphonics, had nearly returned to baseline. They attributed this to "dysfunction of synaptic mechanisms or in the primary neurons." They did not establish whether this neural dysfunction was permanent or would eventually resolve. A later study (Eldredge et al, 1973) addressed this question and showed, in a small group of chinchillas with very slow recovery of TTS, that CAP threshold shift and reduced amplitude persisted at least for 3–4 months, after behavioural thresholds had returned to baseline levels.

We know of only two human studies where exposures at or slightly below the OSHA PEL caused TTS of 40 dB. Ward and Sklar (1959) reported mean TTS of 42 dB at 4 kHz after exposure to a 2.4–4.8 kHz octave band noise at 100 dB SPL for 102 min (OSHA TWA would have been 90 dBA, precisely matching the PEL). In addition, Davis et al (1950) reported that TTS of 40 dB, for exposures to a 4 kHz pure tone, required 110 dB for 20 min; the TWA would have been 88 dBA. These exposures were different from typical real-world exposures in two ways that made them more hazardous: they were spectrally narrow and limited to the spectral region of greatest vulnerability for humans (around 4 kHz). In contrast, the same investigators found that to achieve a 40 dB TTS with broadband noise required much more intense exposures, well above the OSHA PEL: 119 dBA for 52 min (TWA = 103 dBA; Davis et al, 1950) or 106 dBA for 102 min (TWA = 95 dBA; Ward et al, 1958). We could find no evidence of human TTS persistent after 24 h from exposures below the OSHA PEL.

Most TTS events in humans are likely to be less extreme than those examined in the Eaton-Peabody Laboratory studies and would

therefore fall into the domain of normal ''physiological'' TTS (Ward, 1973). For example, TTS measured within minutes of unprotected concert exposure is typically less than 10 dB (Derebery et al, 2012; Opperman et al, 2006; Ramakers et al, 2016). Such TTS events (TTS_2 less than 30 dB in magnitude, recovering fully within 16 h) are, based on currently available evidence, likely to be harmless unless repeated frequently over a period of months or years. Do animal studies such as those of Kujawa and Liberman (2009) and their colleagues ''...represent a paradigm shift in our thinking about noise exposure'' (Truong & Cunningham, 2011), of a magnitude that would impact federal noise exposure standards? In our opinion, this would require demonstration of neuropathy after exposures producing moderate amounts of TTS_2 (≤ 30 dB) that recover exponentially within 16 h of exposure.

Summary and conclusions

The rodent neuropathy studies reported in recent years from the Eaton-Peabody Laboratory have demonstrated a new and important phenomenon in mammalian hearing: auditory nerve degeneration from noise exposures that cause no permanent threshold shifts or OHC loss. Future research may show whether this occurs in primates, including humans. Based on what is known to date, it would be premature to conclude that noise exposures below the OSHA PEL can cause cochlear neuropathy in humans. Specifically:

Humans are less susceptible than mice to noise-induced hearing loss, at least as measured by TTS;

Adjusting for inter-species audiometric differences in terms of frequency regions of best hearing, but not for susceptibility, exposures that have caused neuropathy in rodents already exceed the OSHA PEL established for humans; and

Rodent neuropathy occurred only after exposures that caused ''pathological'' TTS, an effect that since at least 1966 has been considered a sign of potentially hazardous exposure. Pathological TTS does not appear to have been shown to occur in humans with broadband exposures below the OSHA PEL.

Of course, it would be equally premature to conclude that such effects cannot occur. More research is needed to determine whether noise-induced cochlear neuropathy without NIPTS occurs in humans. If it does not occur after single exposures, such as those typically used in animal experiments, does it occur after repeated exposures that do not produce NIPTS? Does it occur after exposures that would be permissible under current OSHA regulations? Do noise-exposed people report poorer communication performance than audiometrically matched non-noise-exposed people (as might be expected if neuropathy were relatively more important for noise-induced than for age-related hearing loss)? Do they have worse speech recognition scores in difficult listening situations than audiometrically matched non-noise-exposed individuals? There are of course many other promising directions for future research. For example, the foregoing research questions focus on behaviourally measured differences in hearing or speech perception for those suspected to have noise-induced neuropathy, but establishing such performance differences will not be sufficient to establish the cause as synaptopathy of the first-order afferents. Additional electro-physiological measurements, including auditory brainstem responses, would be needed to better determine the site of lesion

underlying any observed decrements in behaviourally measured performance (LePrell & Brungart, 2016).

Even if deleterious effects of noise exposure permissible under current regulations cannot be documented in humans, it would be reasonable to assume that some workplace and leisure exposures that exceed the PEL (and are therefore already impermissible without hearing protection where OSHA regulations are in force) might cause worse damage than we have previously assumed. An appreciation of this risk could certainly motivate greater efforts to enforce current regulations, to extend regulatory oversight to less-regulated industry sectors such as agriculture and construction, and to educate young people about the risks of excessive noise exposure.

Acknowledgements

Note

1. Time_weighted average (TWA): the sound level (dBA) that, if constant over an 8 h exposure, is presumed to be equally hazardous as the exposure in question. The OHSA PEL uses a 5 dB exchange rate: a 5 dB increase in level is considered to increase hazard as much as a doubling of duration. For example, 90 dBA for 8 h is considered to pose the same hazard as 95 dBA for 4 h. For the literature reviewed in this commentary, we estimated TWA using two calculators available online at www.esion.com: A_WEIGHT, which converts octave band levels to dBA, and EXPOSURE, which converts dBA and duration to TWA.

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