PHARMACEUTICAL INTERVENTIONS FOR HEARING LOSS (PIHL)

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Temporary and Permanent Noise-Induced Threshold Shifts

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Definition of Temporary and Permanent Threshold Shifts

Hearing loss due to noise has been recognized in humans for centuries. However, it was only in the 20th century that the phenomenon of noise-induced hearing loss (NIHL) was rigorously investigated in animals, allowing a more accurate determination and definition of the disease. Such studies have demonstrated that exposure to excessive sound produces hearing loss (threshold sensitivity loss), with the magnitude of the initial shift and the degree of recovery depending on characteristics of the exposure in the level, time and frequency domains, and on characteristics of the individual, as noted below. Threshold shifts that recover to baseline levels in the hours, days or weeks following exposure are termed temporary threshold shifts (TTS). More injurious exposures can produce threshold sensitivity losses containing both temporary and permanent components, in which the majority of the TTS resolves but a measurable permanent threshold shift (PTS) has evolved (e.g. Eldredge et al., 1973; Ryan and Bone, 1976). Threshold shifts of up to ~50 dB immediately after a single noise exposure can recover completely, while more extensive immediate hearing losses are likely to result in permanent losses of hearing sensitivity (Ryan and Bone, 1976). Continuous or repeated exposures to noise that only induce a TTS, may evolve to a PTS if repeated (Lonsbury-Martin, 1987), as occurs in occupational noise exposure. Therefore, PTS can be defined as noise-induced threshold shift that persists after a period of recovery subsequent to the exposure. In animal models, recovery has been reported for periods extending up to 3 weeks, therefore it may be premature to define a threshold shift as temporary until at least 3 weeks post-exposure, when a permanent threshold shift arises.

While the smallest level of TTS or PTS that can be reliably measured in an individual has not been well defined given test-to-test variability in individuals, several standards have been set for what is considered a significant hearing loss or "standard threshold shift" (STS). The Occupational Safety and Health Administration (OSHA) states that an STS is a 10 decibel (dB) increase in hearing threshold averaged across 2000, 3000 and 4000 Hz in the same ear from an individual's baseline or recent annual audiogram (29 CFR 1910.95). An STS is a reportable work related injury once it has been reconfirmed with a retest within 30 days of the initial test and results in a hearing threshold of at least 25 dB in the affected ear. Therefore, most occupational hearing loss or PTS is under reported since OSHA only requires an STS to be reported.

The Department of Defense policy for the military's Hearing Conservation Program (HCP) and the American Speech-Language-Hearing Association (ASHA) similarly define STS by a 10 dB shift average using the same frequencies, "in either ear without age corrections" (DoDI 6055.12, 2010 [currently under revision]). In contrast, the National Institute of Occupational Safety and Health (NIOSH) recommended definition of an STS is "an increase of 15 dB in hearing threshold level (HTL) at 500, 1000, 2000, 3000, 4000, or 6000 Hz in either ear, as determined by two consecutive audiometric tests," with the second test required to reduce false-positive findings (NIOSH 1998). A significant negative STS (improved hearing) is further defined by the DoD as a decrease of 10 dB or greater change (improvement in hearing) for the average of 2, 3 and 4 kHz in either ear. An early warning shift STS (decrease in hearing) is defined as a 10 dB or greater change at 1, 2, 3 or 4 kHz in either ear. Therefore, a consistent measure between TTS and PTS involves a 10 dB shift from baseline hearing involving one or more frequencies in the same ear.

Characteristics of PTS

PTS is sensorineural and varies across frequencies, depending on characteristics of the exposure, the transmission characteristics of the external and middle ears, and the innate sensitivity of different regions of the cochlea to damage.

Noise damage is typically most extensive at frequencies above those of the exposure (Cody and Johnstone, 1981), a phenomenon well explained by nonlinearities in the cochlear mechanical response to sound (Robles and Ruggero, 2001). This is most apparent for TTS and for low levels of PTS. However, noises to which human ears are exposed often are broadband in frequency composition. These signals are shaped (some frequencies amplified, others reduced by filtering) by passage through the external and middle ears (Rosowski, 1991). Resonance in the ear canal produces amplification of acoustic frequencies whose wavelengths are approximately 4 times the length of the canal, which for humans results in enhancement of frequencies around 4 kHz. This contributes to an enhanced "notch" of PTS at 4-6 kHz for exposure to broad-band stimuli. Finally, as with many other forms of damage, the basal cochlea appears to be most vulnerable to noise. While the reason for this is not entirely clear, it may be related to higher levels of antioxidants in apical hair cells as well as higher rates

of metabolic activity in basal hair cells (Sha et al., 2001). This basal sensitivity results in a tendency for TTS and PTS to be more extensive at high frequencies.

Characteristics of TTS

TTS is a change in hearing threshold that recovers to pre-exposure levels (baseline) over time. The amount of time to recover to baseline may be relatively fast (minutes to hours) or slow (days to weeks). The severity of the initial insult, as well as the time course of the recovery, are dependent on a number of factors including: the type of insult or trauma, the intensity and duration of the insult (single vs repeated, short vs long exposures), and the stimulus type (impulse/impact sound or continuous noise including wide or narrow-band noise). Individual susceptibility is dependent on the use of hearing protective devices, the quiet time or rest between exposures, and the level of hearing loss prior to exposure. Individual susceptibility to TTS may also be influenced by age, sex, prior history or noise exposure, diabetes, genotype and other personal or environmental factors such as smoking and diet. While these factors are at play for PTS as well, unlike PTS, TTS is a change in hearing sensitivity which recovers to baseline or within test/retest criteria in minutes, hours, days or weeks with the upper limit being 30 days post exposure. TTS and PTS outcomes will vary as a function of the insult and individual factors.

Historically, TTS was largely thought to be a mechanical process that involved structures within the outer and middle ear including the ear drum, ossicular chain and middle ear muscles through the acoustic reflex. Extremely intense noise exposure is also known to mechanically damage the cochlea, disrupting the connections between the tectorial membrane and outer hair cell stereocilia, damaging the stereocilia themselves, breaching the integrity of the reticular lamina or even disrupting the basilar membrane.

However, recent work in several preclinical studies has demonstrated a significant involvement of several sensorineural inner ear structures including hair cells and their stereocilia, supporting cells within the organ of Corti, endothelial cells and fibrocytes within the stria vascularis and spiral ligament, and dendritic processes of the auditory nerve (Mulroy et al., 1990; Kujawa and Liberman, 2009). Molecular and biochemical changes have been identified that include pro-inflammatory and pro-apoptotic processes (Henderson et al., 2006). These changes have been shown to alter the normal function of several critical processes within the cochlea including the endolymphatic potential that drives hair cell depolarization (Yan et., al., 2013), cellular membranes and mitochondria responsible for hair cell and supporting cell activity, and neural innervation of the inner hair cell that conduct impulses to the auditory brainstem. In addition, changes in the activity or metabolism of neurons in the cochlear nucleus, superior-olivary complex and inferior colliculus have been observed (Ryan et al., 1992). In support of this noise-induced change in inner ear biology and pharmacology and its relevance in establishing the TTS, several preclinical studies have demonstrated a significant reduction in TTS when the animals were administered otoprotective compounds or drugs immediately prior to noise exposure (Siedman et al., 1993; Attias et al., 2004; Yamasoba et al., 2005; Lynch and Kil, 2005; Kil et al., 2007).

Mechanisms of PTS

While intense sounds such as blast can damage the conductive apparatus of the outer and middle ears, producing permanent hearing loss through tympanic membrane rupture or ossicular dislocation, PTS is generally considered to be a sensorineural phenomenon restricted to the cells of the cochlea. The most recognized cause of PTS is damage to and loss of cochlear hair cells. The mechanisms by which this damage can occur are not known with certainty. However, there is extensive evidence implicating the generation of reactive oxygen species (ROS) within hair cells during and after overexposure (Henderson et al., 2006). This leads to the activation of stress signaling pathways such as the JNK MAP kinase cascade (Pirvola et al., 2000), which can in turn lead to cell damage, apoptosis and/or necrosis (Bohne et al., 2007). The biochemical pathways leading to hair cell damage/death are undoubtedly complex, and also appear to include competing survival pathways that attempt to rescue hair cells and restore their function. It is the balance of these competing pathways that determine the fate of the cell. The outer hair cells, responsible for the exquisite sensitivity and frequency and selectivity of the cochlea, are the most sensitive to damage (Eldredge et al., 1973; Ryan and Bone, 1976).

Noise also can target hair cell synapses and neurons directly, even when the hair cells themselves remain and recover normal function. The insult is seen acutely as a glutamate-like 'excitotoxicity' that includes swelling and retraction of afferent terminals from beneath inner hair cells (Robertson 1983). Recent work in animal models shows that noise-induced loss of synapses and afferent terminals is rapid and permanent (Kujawa and Liberman 2009; Lin et al 2011). Loss of spiral ganglion neurons is comparatively slow, and can be 'primary,' that is, occurring without noise-induced hair cell loss (Kujawa and Liberman 2006; 2009; Lin et al 2011) or 'secondary' to the loss of their inner hair-cell targets (Bohne, 1997; Puel, 1998). Such synaptic and neural loss can exacerbate the functional consequences of noise exposure by reducing the ability of the VIIIth nerve to encode auditory signals with fidelity, with or without loss of threshold sensitivity (Bharadwaj et al 2014). Thus lack of PTS does not imply that auditory function is normal.

It should be noted that our understanding of the mechanisms of NIHL remain incomplete. For example, many of the mechanisms that have been proposed to mediate hearing loss would take considerable time to develop. However impulse exposures, even those that do not result in PTS, produce hearing loss essentially instantaneously, without immediate loss of cells. Presumably this represents a disruption of cochlear cells at the microstructural and protein levels. In another example, it has recently been suggested that the initial 10-15 dB of TTS may serve as a mechanism to extend the dynamic range of hearing, rather than representing a damage mechanism (Housley et al., 2013). Further studies of NIHL mechanisms are clearly warranted.

Consequences of PTS

ASHA uses the following threshold-based definitions of hearing loss: none (normal hearing) (-10 to 15 dB), slight (16-24 dB), mild (25-40 dB), moderate (41-55 dB), moderately severe (56-70 dB) severe (71-90 dB) or profound (>91 dB). Thus 10 dB of PTS would have different consequences depending upon the initial level of hearing, for example leaving one individual with normal hearing (by definition) while increasing hearing loss from mild to moderate in another. One reasonable strategy may be to calculate the resulting hearing handicap as per the AAO-1979 criteria, or using the ASHA criteria, both of which incorporate a low fence of 25-dB HL. Key differences include the frequencies included in the calculation (AAO-1979: 0.5, 1, 2, and 3 kHz; ASHA: 1, 2, 3, and 4 kHz) and the growth rate for impairment for PTA thresholds above the low fence value (AAO-1979: 1.5% per dB; ASHA: 2% per dB). However, if PTA thresholds were below 25 dB HL after the exposure, the PTS would be "missed" using this scheme, as there is deemed to be no handicap below the low fence value. Moreover, functional losses that have no threshold change correlate would not be recognized using these strategies.

The consequences of threshold sensitivity loss have been well documented in animal studies of auditory physiology and psychophysical studies of human auditory function. Loss of 40 dB of hearing sensitivity is associated with a loss of outer hair cells, which as noted above are responsible for the lower ranges of hearing sensitivity, and for the sharply tuned responses of the cochlea to individual frequencies. The loss of these cells leads to a degraded ability to discriminate sounds, especially in noisy environments. More severe hearing loss is associated with the loss of inner hair cells, which transmit sensory information from the cochlea to the central auditory system. Loss of all inner hair cells from a cochlear region eliminates auditory responses, and loss from the entire cochlea results in total deafness.

Of course, the consequences of PTS are dependent upon the degree and frequency range of the loss, and total loss of hearing from noise exposure is rare. However, with PTS leading to moderate and especially severe hearing loss, many facets of life become extremely challenging (Arlinger, 2003). Communication is significantly impacted. This can lead to difficulty in performing military duties or in obtaining/retaining civilian employment. Social interactions are also heavily impacted, with the result that individuals with hearing loss can become withdrawn and isolated. This can in turn lead to depression and possibly cognitive decline (Arlinger, 2003). In the case of blast injury, hearing loss can exacerbate the effects of traumatic brain injury (TBI), even when TBI is mild (Lew et al., 2009). Another consequence of noise exposure is an increase in sensitivity to other forms of hearing loss, including ototoxicity (Bone and Ryan, 1978) and aging (Campo et al., 2011).

There is also a strong, positive correlation between the presence of noise-induced permanent hearing loss and tinnitus (Mazurek et al., 2010). While tinnitus can be a benign condition, a large fraction of individuals with tinnitus experience distress that can be extreme (e.g. Gomaa et al., 2013). A lesser correlation is observed for hyperacusis (e.g. Jansen et al., 2009), another negative sequela of PTS.

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