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Cellular mechanisms of noise-induced hearing loss

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ABSTRACT

Exposure to intense sound or noise can result in purely temporary threshold shift (TTS), or leave a residual permanent threshold shift (PTS) along with alterations in growth functions of auditory nerve output. Recent research has revealed a number of mechanisms that contribute to noise-induced hearing loss (NIHL). The principle cause of NIHL is damage to cochlear hair cells and associated synaptopathy. Contributions to TTS include reversible damage to hair cell (HC) stereocilia or synapses, while moderate TTS reflects protective purinergic hearing adaptation. PTS represents permanent damage to or loss of HCs and synapses. While the substrates of HC damage are complex, they include the accumulation of reactive oxygen species and the active stimulation of intracellular stress pathways, leading to programmed and/or necrotic cell death. Permanent damage to cochlear neurons can also contribute to the effects of NIHL, in addition to HC damage. These mechanisms have translational potential for pharmacological intervention and provide multiple opportunities to prevent HC damage or to rescue HCs and spiral ganglion neurons that have suffered injury. This paper reviews advances in our understanding of cellular mechanisms that contribute to NIHL and their potential for therapeutic manipulation.

1. Introduction

Hearing loss is a significant handicap, affecting communication and impacting quality of life. There are many causes of hearing loss. These include exposure to ototoxic compounds including drugs (Roland and Rutka, 2004), mutations in deafness genes (Vona and Haaf, 2016), infections such as labyrinthitis or prenatal cytomegalovirus (Furutate et al., 2011), and aging (Zhang et al., 2013). Exposure to excessive levels of sound, even for short time periods, can also produce loss of hearing sensitivity and auditory acuity. Noise can lead to temporary threshold shift (TTS) that fully recovers to normal. However, it can also produce losses that fail to return to pre-exposure levels. Such permanent threshold shift (PTS) can have a significant effect on communication and quality of life (World Health Organization, 2015; accessed 26/06/2016).

Intense sound is a significant cause of hearing loss in the general population, due to occupational and recreational acoustic overstimulation. In fact, noise is one of the most common occupational hazards in the United States. Noise-induced hearing loss (NIHL) significantly affects the military and veterans. Service in the armed forces often involves exposure to noise, and blast exposure has been an increasingly common hazard of military deployment (Bramble, 2009). Blast exposure substantially raises the risk for hearing loss (Muhr and Rosenhall, 2011; Wells et al., 2015; Yong and Wang, 2015). Veterans who served in the military during the period from 2001 to 2010 are four times more likely than age- and occupation-matched non-veterans to suffer severe hearing loss (Centers for Disease Control, 2011), and high numbers of active duty military and veterans suffer hearing loss due to service in Afghanistan and Iraq (Theodoroff et al., 2015). More than 775,000 veterans had significant hearing loss prior to 2009 (Fausti et al., 2009), and this number has certainly only increased. The impacts of hearing loss on quality of life, psychological status and employability discussed above are of profound importance to these veterans, impeding their return to civilian life (Theodoroff et al., 2015). NIHL also results in substantial disability and rehabilitation expenses.

Due to the impacts on quality of life, extensive attention has rightly been focused on devices that protect the ear from acoustic overstimulation. However, despite decades of efforts, the problem of NIHL continues to grow (e.g. Johansson and Arlinger, 2004), especially among those associated with the military (Bramble, 2009; Pearson, 2009; Wells et al., 2015; Yong and Wang, 2015). In part, this problem reflects the resistance of many individuals to wearing noise suppressors such as earplugs with noise-intensive recreation, as well as workplace and military operational

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constraints which may limit practical sound barrier use, such as combat conditions (Bramble, 2009).

It is therefore important to develop alternative means of NIHL prevention. NIHL primarily reflects damage to the sensorineural structures of the cochlea, especially the sensory hair cells (HCs), but also primary auditory neurons (Webster and Webster, 1981; Kujawa and Liberman, 2009).

There have been many significant advances in our understanding of the cellular processes that mediate the death and survival of HCs. These processes represent potential check-points in cochlear damage mechanisms, at which intervention should be protective. Pharmacological intervention to protect the cochlea therefore has considerable future potential for the protection of hearing from noise.

It is our purpose, in this paper, to review current knowledge relevant to the biology of HC damage and its prevention. To accomplish this, we first review cellular mechanisms that have been found to contribute to NIHL. We then describe protective pathways that act in opposition to these damage pathways. Finally, we review the potential of damage and survival mechanisms as targets for pharmacological intervention to prevent or ameliorate NIHL.

The various molecules discussed in the paper are presented in Table 1.

Table 1
Selected molecules relevant NIHL.

Damage mediators
Free radicals
Reactive oxygen species (ROS)
Reactive nitrogen species (RNS)
Intracellular free Ca^{2+}
Nicotoinamide adenine dinucleotide phosphate oxidase (NADPH oxidase)
Pro-inflammatory cytokines
Interleukin 1 beta (IL-1β)
Interleukin 6 (IL-6)
Tumor necrosis factor alpha (TNFα)
Damage signaling molecules
Nuclear Factor kappa B (NF-κB)
Focal adhesion kinase (FAK)
Src
Kirsten rat sarcoma viral oncogene homolog (kRas)
Ras-related C3 botulinum toxin substrate (Rac)
Cell division control protein 42 (Cdc42)
Mixed lineage kinases (MLKs)
Jun amino-terminal kinase (JNK)
Jun
Activator protein 1 (AP-1)
Apoptosis pathway molecules
Bcl2 Associated X (Bax)
Bcl2 Associated death promoter (Bad)
B cell lymphoma 2 (Bcl2)
Bcl2 related gene (Bclx)
Cytochrome C
Apoptotic protease activating factor 1 (APAF)
Caspase 1
Caspases 3,6,7
Protective molecules
Antioxidants
Growth factors (GFs)
Harvey rat sarcoma oncogene (hRas)
Phosphinositol 3 kinase (PI3K)
Protein kinase B (PKB or AKT)
Extracellularly regulated kinase (ERK)
Pharmacological protectants
N-acetyl cysteine (NAC) (antioxidant)
FTI-277 (inhibitor of KRas at 10 μM; hRas at 1 μM)
Adenosine A1 receptor agonist adenosine amine congener (ADAC)
D-JNKI-1 (peptide JNK inhibitor)
Etanercept (TNFα inhibitor)
Anti-IL-6-receptor antibody
Dexamethasone (steroid)

2. Mechanisms of sensorineural damage in the cochlea

2.1. Mechanisms of TTS

Temporary loss of hearing sensitivity is often viewed as a less severe form of the same changes that lead to permanent cochlear damage. However, recent evidence suggests that TTS may be mediated by distinct mechanisms. Housley et al. (2013) found that low-level TTS is mediated by ion channels that are activated by extracellular ATP, since mice deficient in a specific channel (P2RX2) do not experience TTS after noise exposure that normally causes about 15 dB of temporary sensitivity loss. This ATP receptor is a nonselective cation channel, expressed in cochlear HCs and epithelial cells lining the scala media. Noise is known to stimulate local ATP release in the cochlea (Telang et al., 2010). This ATP opens the P2RX2 channels, which then shunt endocochlear current away from the HC transduction channel (Thorne et al., 2004; Morton-Jones et al., 2015) and also activates longer-lasting sensitivity reduction via a yet uncharacterized mechanism. Both mice and humans (Housley et al., 2013; Yan et al., 2013) lacking the *P2rx2* gene that encodes this receptor exhibit increased sensitivity to PTS when exposed to higher levels of noise or long periods of moderate level noise exposure. These findings suggest that low-level TTS, largely arising from P2RX2 receptor activation, may reflect hearing adaptation that extends the intensity range of hearing, and protects the cochlea from damage.

However more extensive, TTS (up to 50 dB) can also recover to normal threshold levels over time (Ryan and Bone, 1978), if not to normal levels of synaptic contact between HCs and spiral ganglion neurons (Kujawa and Liberman, 2009). These higher levels of TTS are thus due to additional mechanisms. Nordmann et al. (2000) noted that uncoupling of the outer HC stereocilia from the tectorial membrane was the primary morphological feature associated with 43 dB of TTS in animals. Other investigators have noted swelling of the afferent endings underneath the inner HCs after noise exposure, suggestive of excitotoxicity due to the release of excessive glutamate from overstimulated HCs (Puel et al., 1998). Supporting this mechanism, Puel et al. (1998) found that pre-treatment with the glutamate antagonist kynurenate not only prevented this swelling, but also reduced the amount of TTS. This finding suggests that reversible excitotoxicity to cochlear afferent neurons can also contribute to TTS.

Other evidence suggests that metabolic overstimulation may also contribute to temporary changes in threshold after noise. Cheng et al. (2008) found that treatment with the antioxidant D-methionine protected animals from TTS, implicating the generation of reactive oxygen species (ROS) by mitochondria, perhaps in response to metabolic overload. They also found that activity of the ion transporters Na,K-ATPase and Ca-ATPase was decreased, while free radicals were increased, in the cochlear lateral wall after TTS-inducing noise. Given the role of these transporters in generating the endocochlear potential (Mori et al., 2009), the decreased activity suggests that reversible reductions in the endocochlear potential may partially mediate TTS.

2.2. Mechanisms of PTS

Given sufficient noise exposure, the ability of the cochlea to recover is overwhelmed, and hearing loss becomes irreversible. Such permanent changes in auditory thresholds have primarily been linked to cochlear HC damage and loss, although damage to neurons and the lateral wall can also mediate long-term loss of hearing (Schuknecht, 1993). Sufficiently intense overstimulation of the cochlea, as can occur with blast exposure, will produce mechanical damage to the cochlea. This damage includes direct