Hearing Loss and Its Pathophysiology

Subjects: Others

Contributor: Natalia Smith-Cortinez , A. Katherine Tan , Robert J. Stokroos , Huib Versnel , Louise V. Straatman

Sensorineural hearing loss is caused by damage to sensory hair cells and/or spiral ganglion neurons. In non-mammalian species, hair cell regeneration after damage is observed, even in adulthood. Although the neonatal mammalian cochlea carries regenerative potential, the adult cochlea cannot regenerate lost hair cells. The survival of supporting cells with regenerative potential after cochlear trauma in adults is promising for promoting hair cell regeneration through therapeutic approaches.

inner ear regeneration endogenous progenitor cells re-innervation

1. Introduction

Hearing loss is the most frequent sensory deficit in humans and is mainly caused by irreversible damage to cochlear sensory cells (hair cells) and/or their associated neurons (spiral ganglion neurons, SGNs). Irreversible hair cell loss is particularly caused by aging, noise exposure and ototoxic medication. In 2019, there were approximately 460 million individuals with disabling hearing loss, and according to the WHO, this number might increase to more than 900 million individuals by 2050 [1]. Hearing loss, which is often accompanied by tinnitus, results in high levels of morbidity, depression and social isolation, and it has been shown to significantly contribute to cognitive decline in the elderly [2][3][4][5][6][7][8]. While hearing aids and cochlear implants restore hearing in hearing-impaired and deaf individuals to a large extent, sounds are still perceived as distorted (for the sound of a cochlear implant, see [9] because the original cochlear function—in which the hair cells together with the basilar membrane play a key role—is not replaced.

To prevent hair cell loss, there are currently several otoprotectants that can potentially prevent damage after ototoxic or noise-induced trauma, including antioxidants to reduce oxidative stress (such as sodium thiosulfate, amifostine, N-acetylcysteine) or anti-inflammatory medication, such as dexamethasone (for review on ototoxicity see [10] and for review on noise-induced hearing loss (NIHL) see [11]). Regeneration of lost cochlear cells has potential as an alternative approach and can have significant clinical applications to restore hearing without the need for an electronic device. Studies on the regeneration of the avian cochlea or zebrafish lateral line have demonstrated spontaneous hair cell regeneration out of endogenous progenitor cells after damage, even in adult specimens [12][13]. In contrast, the mammalian adult inner ear possesses limited regenerative potential [14][15]. The vestibular organ shows scarce but spontaneous hair cell regeneration after damage, whereas the cochlea shows no spontaneous regeneration [16]. For non-genetic hearing loss, targeting the endogenous cochlear progenitor cells by manipulating signaling pathways to promote hair cell renewal might improve the regenerative capacity.

Previous studies on the mammalian cochlea have mainly evaluated the presence of endogenous progenitor cells in the neonatal cochlea or in a normal hearing condition [17][18][19][20][21][22][23]. The effects of trauma, such as ototoxicity or noise exposure, on regenerative capacity of the cochlea of adult mammals has been scarcely studied. Because the majority of patients with SNHL are adults, studying the regenerative capacity after hair cell ablation in the adult mammalian cochlea is the key to understanding its true therapeutic potential. Importantly, the pathways that regulate cochlear development in mammals and hair cell regeneration in non-mammalian vertebrates shed light on the steps needed to improve mammalian hair cell regeneration in the future.

2. Hearing Loss and Its Pathophysiology

2.1. Age-Related Hearing Loss

Age-related hearing loss (presbyacusis) is the most common sensory impairment in the elderly, and with aging of the population, the number of affected people is expected to rise rapidly [24]. Several age-related structural changes have been described, including age-related hair cell loss, SGN loss and atrophy of the stria vascularis [25]. Over the last decade, studies have also shown loss of inner hair cell (IHC) synapses and their afferent fibers [26][27].

Based on histopathology and patterns of hearing loss, Schuknecht et al. classified four main types of presbyacusis, including (1) sensory (hair cell loss at basal end of cochlea), (2) strial or metabolic (correlated to atrophy in the stria vascularis), (3) neural (as a result of loss of cochlear neurons), and (4) cochlear conductive or mechanical presbyacusis (due to stiffness of the basilar membrane) [27][28]. They concluded that the main contributing factor to presbyacusis was atrophy of the stria vascularis. Interestingly, more recently, it has been shown that presbyacusis is predominantly associated with damage to sensory cells, rather than age-related changes in stria vascularis [29].

The precise mechanism underlying age-related degeneration of different cochlear structures is unknown. Several contributing factors have been described, including inflammatory changes [30], genetic factors [31] and oxidative stress [32]. Although age-related changes are multifactorial, noise exposure is thought to be the major contributing factor of presbyacusis [29][33].

2.2. Noise-Induced Hearing Loss

NIHL mainly causes damage to and loss of outer hair cells (OHCs). Depending on the duration and intensity of the noise exposure, there may be IHC loss as well. Three mechanisms of noise-induced cochlear damage can be distinguished: (1) mechanical destruction by short exposure to extreme noise intensities causing direct trauma; (2) metabolic decompensation after noise exposure, which occurs over a longer period of time in high intensities; and/or (3) IHC synaptopathy leading to loss of SGNs [11][34][35]. Excessive noise stimulation causes the formation of free radicals or reactive oxygen species (ROS), as well as glutamate excitotoxicity, followed by activation of signaling pathways leading to cell death [36]. For an extensive review on cellular mechanisms involved in NIHL, see [34].

Apart from the loss of sensory cells, it has been widely investigated that noise exposure causes permanent damage to the ribbon synapses of the IHCs, also referred to as cochlear synaptopathy [35][37][38]. This leads to supra-threshold hearing loss, i.e., no measurable increase in hearing threshold but worse hearing at supra-threshold levels (including reduced speech perception in noise, hyperacusis) and tinnitus, also known as hidden hearing loss [35][38][39][40].

2.3. Ototoxicity

Ototoxicity is a pharmacological adverse reaction that causes irreversible damage to the hair cells in cochlear and vestibular tissue, leading to their functional loss. With over a million cases of profound ototoxicity-induced hearing loss annually worldwide, this is a major problem [41]. There are more than 600 categories of drugs registered with ototoxic side effects, and this number is still increasing [42]. The two most important ototoxic drugs are aminoglycosides (including gentamicin and kanamycin) and platinum-based antineoplastic agents (such as cisplatin, oxaliplatin and carboplatin). Numerous studies have been performed evaluating the effects of ototoxicity on the cochlea (for review, see [43]). Ototoxicity causes mainly OHC loss in a basal to apical gradient, thus associated with especially high frequency hearing loss. With higher concentrations or persistent exposure, ototoxic damage progresses to IHC loss as well. The mechanism by which ototoxic drugs affect the cochlea has not yet been fully elucidated. It has been suggested that oxidative stress induces apoptosis and necrosis in hair cells and marginal cells in the stria vascularis (for a review, see [44]). Ototoxins enter cells via active transport [45][46][47][48]. It has been recently shown that inflammation precedes oxidative stress and excessive production of ROS; therefore, it has been suggested that the inflammatory response triggers cell death [49]. After apoptosis of hair cells, the cell is extruded from the sensory epithelium and supporting cells phagocytize the remaining cell fragments. Supporting cells form a scar and preserve the epithelial cytoarchitecture and the integrity of the barrier of the organ of Corti [50][51][52]. Hair cell loss may occur rapidly (within days) after ototoxic exposure; following IHC loss, SGNs first become smaller and subsequently progressive SGN loss occurs [53]. The loss of SGNs has been associated with discontinued neurotrophic support from the organ of Corti [54][55].

Hair cell loss may occur rapidly (within days) after ototoxic exposure; following IHC loss, SGNs first become smaller and subsequently progressive SGN loss occurs [53]. Previous studies on ototoxicity have mainly focused on ototoxicity-induced hair cell loss and considered neuronal loss to be a secondary consequence caused by loss of trophic support [56][57][58][59][60][61]. However, as in NIHL, direct ototoxicity-induced damage to the synapse and SGNs may occur, as well as ototoxicity-induced swelling of the nerve [62][63][64][65].

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