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Protection, regeneration and replacement of hair cells in the cochlea: implications for the future treatment of sensorineural hearing loss

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Summary

In the last few years progress has been made in understanding basic mechanisms involved in damage to the inner ear and various potential therapeutic approaches have been developed. It was shown that hair cell loss mediated by noise or toxic drugs may be prevented by antioxidants, inhibitors of intracellular stress pathways and neurotrophic factors/neurotransmission blockers. Moreover, there is hope that once hair cells are lost, their regeneration can be induced or that stem cells can be used to build up new hair cells. However, although tremendous progress has been made, most of the concepts discussed in this review are still in the "animal stage" and it is difficult to predict which approach will finally enter clinical practice. In my opinion it is highly probable that some concepts of hair cell protection will enter clinical practice first, while others, such as the use of stem cells to restore hearing, are still far from clinical utility.

Key words: apoptosis; cochlea; hair cells; inner ear; regeneration; stem cells

Introduction

Scope of the problem

Hearing loss has a huge impact on the affected individual as well as on society. Not only is one baby out of 1000 born with hearing loss, but more than 50% of over-65s suffer from hearing loss. Hearing loss of adult onset is one of the ten leading causes of disability-adjusted life years globally [1]. It is estimated that 278 million persons worldwide (two-thirds of whom reside in developing countries) suffer from disabling hearing loss. The impact of hearing loss on health care costs will very probably increase in the future, bearing in mind the predicted improvement in life expectancy [2].

No conflict of interest to declare.

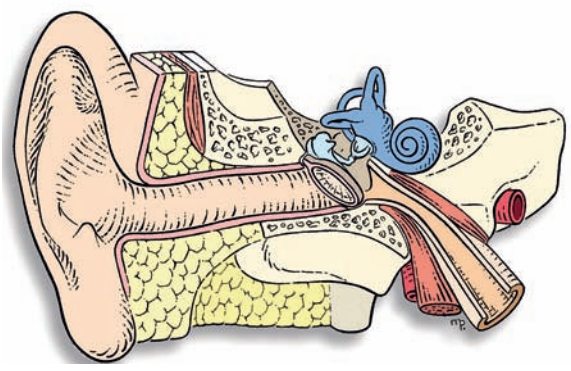


Figure 1

Overview of the ear, cochlea in blue.

Inner ear

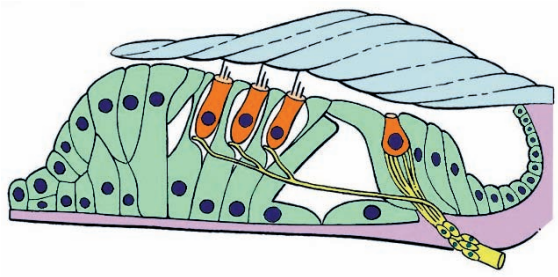
The complex architecture of the inner ear, named the labyrinth by early anatomists, houses the senses of hearing and balance. The main functions of the outer and the middle ear are transducing and amplification of sound, while the cochlea in the inner ear is the auditory sensory organ. The cochlea propagates mechanical signals as waves in fluid and membranes, and finally transduces them to nerve impulses. Its core component is the organ of Corti, which is distributed along the partition separating fluid chambers in the coiled tapered tube of the cochlea (fig. 1). The organ of Corti contains 16000 hair cells in each cochlea. The outer hair cells of the organ of Corti are mechanically active, while the inner hair cells of the same organ convert the stimulus into neuronal impulses via afferent synapses to the dendrites of primary auditory neurons (spiral ganglion neurons) (fig. 2).

Hearing loss causes

Hearing loss can be caused by damage to either external, middle or inner ear. Today, hearing loss caused by diseases of the external and the middle ear can be treated satisfactorily, while disorders affecting the inner ear cannot. Often, only prosthetic devices offer some help. For mild to

Figure 2

The organ of Corti, hair cells in orange.



moderate hearing loss conventional hearing aids are used, while for profound hearing loss cochlear implantation is the standard of care today.

Loss of or damage to hair cells and/or neuronal cells, which are the sensorineural elements of the inner ear, results in a so-called sensorineural hearing loss [3]. The neurons of the spiral ganglion are partially lost over a period of months and years, presumably due to lack of trophic support. However, the hair cells are the most vulnerable elements in the cochlea, and damage to them is the most common cause of sensorineural hearing loss. When the hair cells are lost from the adult organ of Corti, spiral ganglion dendrites retract and are possibly lost [4]. Total loss of hair cells can result in degeneration of some cochlear neurons.

Hair cell damage may result from a variety of causes, including genetic disorders, infectious diseases, overexposure to intense sound and certain drugs. As exposure to intense sound, drugs and diseases accumulates with aging, so the loss of sensorineural elements in the cochlea progresses with it, and many individuals experience noticeable hearing difficulty later in life [3].

Prevention of hearing loss?

Hearing loss due to sensorineural damage has been recognised for over a century and experiments to promote understanding of the phenomenon date from the early 1900s. Since cochlear hair cells of mammals, unlike those of fish and birds, do not regenerate, sensorineural hearing loss is often progressive and irreversible [5].

Until recently, damage to cochlear hair cells and neurons has been regarded as an inevitable consequence of age, genetic conditions or exposure to certain environmental stimuli. This made avoidance of potentially harmful stimuli the primary means of protecting sensorineural structures. However, in the last few years, progress has been made in the understanding of hair cell damage [6]. Research reports have implied involvement of several molecular mechanisms after exposure of hair cells to the most common causes of damage to them: noise (acoustic damage) and drugs (ototoxic damage). On this basis three major agents have been further investigated with a view to preventing hair cell loss: antioxidants, inhibitors of intracellular stress pathways and neurotrophic factors/neurotransmission blockers. It has been demonstrated that hair cells can be protected from acoustic and ototoxic damage by the use of some of these agents. In addition, it was suggested that under special conditions hair cells can be regenerated in the mammalian cochlea and that stem cells may be able to generate new hair cells in the damaged cochlea [6].

Protection of hair cells from noise damage

It is well known that loud noise can result in hearing loss. Hearing loss can result from sustained exposure to intermittent or continuous noise or from acoustic trauma. Acoustic trauma is due to a one-time brief exposure to a sound stimulus exceeding 140dB for less than 0.2 seconds. It is estimated that around 1.8% of American males suffer from handicapping noise-induced hearing loss. Data from animal studies show that the main organ affected is the cochlea [7]. Depending on the intensity of the noise, anatomical changes range from distorted stereocilia of the inner and outer hair cells to complete absence of the organ of Corti and rupture of intracochlear membranes. The primary site of injury appears to be the rootlets connecting the stereocilia to the top of the hair cells. With loss of stereocilia, hair cells die. Death of hair cells may result in partial degeneration of primary auditory nerve fibres. In a interesting study Kujawa et al. observed that mice exposed to noise displayed evidence of direct neuronal damage [8].

While for many years only devices such as ear plugs protected the auditory system, research has demonstrated that, at least in animal models, medical treatment may offer some remedy against noise-induced hearing loss.

As mentioned above, three major agents appear to be effective in preventing hair cell loss resulting from acoustic damage: antioxidants, inhibitors of intracellular stress pathways and neurotransmission blockers.

Reactive oxygen as a factor mediating noise damage

Numerous studies have shown that noise increases the level of reactive oxygen species within the auditory system, mainly in hair cells. Reactive oxygen species cause molecular and cellular damage. Interfering with this process using reactive oxygen species inhibitors/scavengers such as antioxidants may protect the delicate sensory elements within the cochlea. Different substances with reactive oxygen species inhibitor/scavenger

activity exhibit a protective effect against noise-induced hearing loss in rodents, e.g., N-acetylcysteine and acetyl-L-carnitine [9], vitamin C [10], ebselen [11], and T-817MA [12].

Intracellular stress pathways are involved in noise damage

Cellular stress such as that induced by noise activates stress pathways in cells of the inner ear. Consequently, inhibitors of such pathways may be capable of preventing noise-induced cell and hearing loss. This has been demonstrated for the Src protein tyrosine kinase signalling cascade in chinchilla [13] and for the JNK signalling pathway in mice and guinea pigs [14].

Glutamatergic neurotransmission is involved in noise damage

Glutamate is the most likely neurotransmitter at the synapse between the inner hair cells and its afferent neurons in the peripheral auditory system. Intense noise exposure may result in excessive glutamate release, binding to the post-synaptic receptors and leading to neuronal degeneration. Recently it has been demonstrated that glutamatergic neurotransmission may be involved in acoustic trauma-induced cochlear damage, and hence studies have demonstrated hearing preservation in rodents treated with the glutamatergic neurotransmission blocker riluzole [15] and the glutamate receptor antagonist caroverine [16].

Other factors with potential to rescue hair cells from noise-induced damage

In addition, several reports indicate that other substances may have the potential to rescue hearing from noise-induced damage. These are basic fibroblast growth factor in a mouse model [17], steroids in guinea pigs [18] and other substances.

Protection of hair cells from ototoxic drugs

Many agents have potentially toxic effects on the auditory system, including antibiotics such as aminoglycosides or anti-cancer drugs such as cisplatin. The last few years have brought progress in the understanding of the cellular events involved in ototoxicity. In addition to acoustic damage it has been demonstrated that ototoxic drugs often lead to generation of reactive oxygen species within the organ of Corti [19]. It has also been shown that intracellular stress pathways are activated in the organ of Corti after drug exposure (see below). Finally, it is likewise well known that neurotrophic factors play a highly important role in the development of the auditory system [20].

Thus, as is the case of acoustic damage, different approaches have been used to prevent ototoxicity: antioxidants, inhibitors of intracellular stress pathways leading to cell death, and neurotrophic factors.

Antioxidants and ototoxicity

Antioxidant substances such as salicylate and alpha-tocopherol have been effective in preventing cisplatin-induced ototoxicity in rodents [21, 22]. Alpha tocopherol has proved capable of preventing gentamicin ototoxicity in guinea pigs [23]. In addition, other reports in the literature show protection from ototoxicity in rodents using a variety of substances with antioxidant activities, such as sodium thiosulfate [24] and gingko extracts [25].

Stress pathways and ototoxicity

Different studies have shown that exposure of the organ of Corti to toxic substances activates stress pathways, ultimately resulting in cell death (apoptosis). Inhibitors of the apoptotic cell death machinery have therefore been evaluated as potential treatment for ototoxic-induced hair cell loss. It has been shown in rodents that inhibitors of the c-Jun N-terminal kinase signalling pathway, one of the intracellular stress pathways activated in hair cells upon aminoglycoside exposure, were capable of rescuing hair cells from ototoxicity [26, 27]. Stress pathway may eventually activate caspases, thus finally resulting in apoptotic cell destruction. It is therefore not surprising that inhibition of caspase activation may protect hair cells from aminoglycoside-induced cell death in chickens [28].

Neurotrophic factors and ototoxicity

Neurotrophic factors are small peptides which play an important role in tissue maintenance and cell survival. Different neurotrophic factors such as neurotrophin-3 and brain-derived neurotrophic factor are expressed by hair cells [29]. Both of these factors and a glial-derived neurotrophic factor have been found to be effective against trauma-induced hair cell loss in rodents [30].

Other mediators of ototoxicity?

To make all this even more complex, there appear to be other molecules involved in ototoxicity. One example is the NMDA receptor, a membrane protein activated upon glutamate binding. It is down-regulated in organ of Corti explants soon after aminoglycoside exposure. Combined application of an NMDA receptor agonist and neurotrophin-3, one of the above-mentioned neurotrophic factors, preserved hair cell morphology and decreased threshold shifts in auditory brainstem response in mice when given before noise or amikacin application, compared to control animals [31].

It is noteworthy that specific mutations in the mitochondrial genome render an individual more susceptible to aminoglycoside toxicity [32]. It has been speculated that the altered protein biosynthesis results in this phenomenon, although the exact molecular mechanisms are still unclear.

Hair cell survival pathways

One concept of apoptosis is that cells are thought to exist in a finely tuned balance between survival and cell death. There are pathways that signal cell survival whereas other pathways promote cell death. Under physiological conditions, cell survival pathways are active and keep the cells alive, while cell death-promoting pathways are inactive. Cell stress disrupts this balance, and if the stress is severe apoptosis-promoting pathways predominate and cell death occurs. Survival-signalling pathways have recently been described in the inner ear. We have demonstrated that in immature hair cells of rats NF-kappaB is constitutively active and keeps the cells alive: inhibition of NF-kappaB therefore results in rapid hair cell loss [33].

Regeneration of hair cells

Mammalian hair cells show no regeneration: hearing loss is therefore irreversible. Interestingly, hair cells can regenerate in birds, and it would be of great interest to induce regeneration of lost hair cells in the mammalian inner ear as well. Recently there have been exciting discoveries concerning hair cell regeneration. It has been shown that the transcription factor Math1 is essential for generation of hair cells [34]. Over-expression of Math1 in cultures of immature rat cochleas resulted in the production of ectopic hair cells [35]. Additionally, it has been shown that delivery of an adenoviral vector encoding Math1 into a mature deaf guinea pig resulted in regeneration of hair cells and improved the hearing thresholds of the animals treated [36].

Another research group has demonstrated that conditional tissue-specific deletion of the cell cycle regulator retinoblastoma gene in a mouse model results in generation of large numbers of new hair cells [37]. However, the hair cells in these animals displayed increased levels of apoptosis and showed alteration in stereociliary bundle morphology [38]. In addition, it has been shown that gene disruption of a cyclin-dependent kinase inhibitor (p27) leads to ongoing cell proliferation in postnatal and adult mouse organ of Corti [39]. These observations suggest that regulation of the cell-cycle is key in attempts to regenerate lost hair cells from the organ of Corti.

Replacement of hair cells by stem cells

Stem cells have the ability to develop into different cell types depending on their origin and local environmental cues. Therefore they have been used in inner ear research in the hope that they will ultimately differentiate into hair cells and auditory neurons.

Some types of adult tissue harbour their own endogenous stem cells, which provide regenerative capacity by their ability to self-renew and differentiate and therefore replace lost cells. However, the regenerative capacity of such endogenous cells is sometimes limited or that function is "off". Exogenous stem cells are stem cells from other sources than the target tissue into which they are transplanted, and they often possess a higher regenerative capacity than endogenous stem cells: however, there are other limitations on their use.

Interestingly, the inner ear of mice appears to contain endogenous stem cells, which were identified by neurosphere formation and their expression of the inner ear markers [40]. The existence of these endogenous stem cells in the mammalian inner ear suggests a new approach to repair of damaged cochlea: these cells may be directed towards a hair cell or a neuronal phenotype, to replace degenerated hair cells and neurons and finally restore inner ear function. First promising results have shown that these stem cells from mice can differentiate *in vitro* into hair cell-like cells [40].

Exogenous stem cells have been used in a variety of studies in different animal models to replace lost cochlear hair cells and neurons. Different types of stem cells have been used in these studies: embryonic stem cells [41], marrow-derived stem cells [42] and neural progenitor cells [43], to name but a few. These stem cells have demonstrated the capacity to differentiate into hair cells and auditory neurons, depending on the experimental setting. For example, bone-marrow mesenchymal stem cells from mice developed into hair cell-like cells in vitro when in contact with embryonic chick inner ear cells [44]. In a similar experiment adult mouse olfactory precursor cells differentiated into hair cell-like cells when co-cultured with cochlear cells and/or cochlear supernatant [45]. In a study by Corrales et al. embryonic stem cell-derived neural progenitor cells developed into neuronal cells and their neurites

grew in fasciculating bundles into the organ of Corti [46]. Thus stem cells appear to be suitable candidates to replace lost hair cells and neurons within the cochlea.

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