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Review Article

PROTECTION OF THE HAIR CELLS FROM THE OTOTOXIC EFFECT OF STREPTOMYCIN

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ABSTRACT

Ototoxicity is the property of being toxic to the ear (oto-), specifically the cochlea or auditory nerve and sometimes the vestibular system; it is commonly medication-induced. It has long been known that the major irreversible toxicity of aminoglycosides is ototoxicity. In many developing countries, where drugs such as the aminoglycosides are frequently prescribed to treat pneumonia, diarrhoea, and tuberculosis, the incidence of ototoxicity is high. Physicians in practice need to recognize that ototoxic drugs can cause significant auditory and in many instances, poorly recognized, vestibular toxicity.

Aminoglycosides can cause eighth cranial nerve damage, resulting in vestibular and/or auditory toxicities. Aminoglycosides appear to generate free radicals within the inner ear, with subsequent permanent damage to sensory cells and neurons, resulting in permanent hearing loss. Two mutations in the mitochondrial 12S ribosomal RNA gene have been previously reported to predispose carriers to aminoglycoside-induced ototoxicity.

As aminoglycosides are indispensable agents both in the treatment of infections and Meniere's disease, a great effort has been made to develop strategies to prevent aminoglycoside ototoxicity.

Efforts have been made against streptomycin toxicity using corticosteroid and Caffeic acid phenethyl ester. Chemicals are being evaluated for their ability to prevent ototoxicity and that might be prescribed in tandem with ototoxic drugs in the future. Investigators are also studying methods of hair-cell and nerve-cell regeneration.

KEYWORDS: Ototoxicity, Cause of ototoxicity, Symptoms, Efforts in hair cell protection, Treatment for ototoxicity

INTRODUCTION

Ototoxicity is, quite simply, ear poisoning (oto = ear, toxicity = poisoning), which results from exposure to drugs or chemicals that damage the inner ear or the vestibulo-cochlear nerve (the nerve sending balance and hearing information from the inner ear to the brain). Because the inner ear is involved in both hearing and balance, ototoxicity can result in disturbances of either or both of these senses. The parts of the brain that receive hearing and balance information from the inner ear can also be affected by poison, but this is not technically considered ototoxicity and won't be covered in this information sheet (Poisoning of the brain is classified as neurotoxicity).[1]

The occurrence and degree of inner ear poisoning depends upon the drug involved as well as other factors such as heredity. Ototoxicity can be temporary or permanent. The effect of certain drugs is often temporary, while other drugs typically produce permanent changes to the ear. Some drugs can cause either temporary or permanent problems. It is important to note here that the broad majority of people who experience ototoxicity have a temporary or reversible form that does not result in a major or long-term disruption in their lives.[2]

With cochleotoxicity, hearing loss or the start or worsening of tinnitus (ringing in the ears) can occur through damage to the cochlea (the hearing apparatus) or the cochlear branch of the vestibulo-cochlear nerve. Vestibular ototoxicity or vestibulotoxicity are terms used to describe ototoxicity that affects the balance

organs or the vestibular branch of the vestibulo-cochlear nerve.[2]

It is important to note that no drug is known to cause Ménière's disease, benign paroxysmal positional vertigo, or any other vestibular disorder causing fluctuating function.[2]

How common is ototoxicity?[3]

No one knows how many people suffer from ototoxicity each year or the percentage of vestibular disorders caused by ototoxicity. What is known is that when permanent and extensive ototoxicity occurs, the effects can take a terrible toll on a person's ability to function.

Cause of ototoxicity

Scientific studies are required to confirm whether a drug is ototoxic. Unfortunately, such research often involves years of study. When assessing the safety of a drug prior to releasing it on the market, the U.S. Food and Drug Administration does not require testing of inner ear function or examination of the inner ear structures. This is one reason it is almost impossible to say with confidence how many and which drugs cause ototoxicity and how many or which people are affected by it.

Problems with a particular drug are usually only discovered after enough people have suffered the consequences and when physicians or other health care professionals can see a probable connection between the symptoms or problems and a drug. This was the case with aspirin and quinine centuries ago, with the antibiotic streptomycin in the 1940s, and more recently with some anti-cancer drugs. Since then, scientific studies have shown that these drugs cause ototoxicity in animals and people. Other, newer drugs have been implicated as ototoxic as well, but solid scientific proof is often lacking.[4]

Many chemicals have ototoxic potential, including over-the-counter drugs, prescription medications, and environmental chemicals. The information below includes substances thought to cause ototoxicity. The discussion is incomplete because of the limited research thus far.

Note: if you are taking drugs on the advice of your physician, DO NOT STOP TAKING THEM just because you see them listed here! Speak with your doctor about your concerns to determine the best choice in your own unique situation.

Aspirin and quinine Aspirin (acetylsalicylic acid, ASA) and quinine are well known to cause temporary ototoxicity resulting in tinnitus. They may also reduce hearing, particularly when given at high doses. Quinine products can also temporarily reduce balance ability. Once aspirin or quinine is stopped, the ototoxicity generally disappears. Some quinine products include:[5,6]

- chloroquine
- quinidine
- quinine (including Q-vel)
- tonic water

Loop diuretics are a specific family of "water pills" that is known to occasionally cause temporary ototoxicity. These drugs cause ringing in the ears or decreased hearing that reverses when the drug is stopped.

An increased probability of ototoxicity is thought to occur with loop diuretics when they are administered during the same time period that an aminoglycoside antibiotic (see next section) is given. The loop diuretics include:[6,7]

- bumetanide (Bumex)
- ethacrynic acid (Edecrin)
- furosemide (Lasix)
- torsemide (Demadex)

Note: Hydrochlorothiazide (HCTZ) and Maxide diuretics commonly prescribed to people with Ménière's disease or other forms of endolymphatic hydrops are not loop diuretics.

Aminoglycoside antibiotics All members of the aminoglycoside antibiotic family are well known for their potential to cause permanent ototoxicity if they enter the inner ear. Some of these drugs are more likely to cause hearing loss; others are more likely to cause vestibular loss. Others can cause either problem.

A higher risk for aminoglycoside antibiotic induced ototoxicity occurs when a person receives concurrent ototoxic drugs (such as a loop diuretic or another antibiotic vancomycin), has insufficient kidney function or is receiving a drug that causes insufficient kidney function, or has a genetic vulnerability.

The risk of ototoxicity also increases with an increasing amount of the drug that enters the blood stream, the longer the drug is in the body, and the duration of time the drug is taken.

Aminoglycoside antibiotics can enter the inner ear through the blood system or via diffusion from the middle ear into the inner ear. They enter the blood stream in largest amounts when given

intravenously (by IV) and in the least amounts by pill. Inhaled drugs also enter the blood stream; an example of this is the use of inhaled tobramycin for long-term treatment of cystic fibrosis.

Can ear drops containing aminoglycosides be problematic? If they find their way into the middle ear in large enough quantities, such ear drops can diffuse into the inner ear and cause damage. Physicians do not agree about how often and under what circumstances this occurs. Many papers in medical journals address this argument.

Members of the aminoglycoside family include:[7,8,9,10]

- amikacin
- netilmicin
- dihydrostreptomycin
- ribostamycin
- gentamicin
- streptomycin
- kanamycin
- tobramycin
- neomycin

Anti-neoplastics (anti-cancer drugs)

Anti-cancer drugs work by killing cancer cells. Unfortunately some can also damage or kill cells elsewhere in the body, including the ears. **Cisplatin** is well known to cause massive and permanent hearing loss. **Carboplatin** is also known to be ototoxic.[9,10]

Environmental chemicals have long been implicated in ototoxicity. Little research has been done to substantiate their precise effect on ears, but most are associated with hearing disturbances that may be permanent. In addition, mercury has also been linked to permanent balance problems. These include:[9,10]

- butyl nitrite
- mercury
- carbon disulfide
- styrene
- carbon monoxide
- tin
- hexane
- toluene
- lead
- trichloroethylene
- manganese
- xylene

What damage occurs?[11,12]

Two areas can be damaged or destroyed through ototoxicity: the hair cells within the inner ear, and the vestibulo-cochlear nerve that links the inner ear to the brain. When damage occurs, any degree and combination of hearing loss and balance disruption are possible depending upon the part(s) affected.

Hair cells are located in both the cochlea and the vestibular areas of the inner ear. They are composed of a cell body with a hair-like attachment. When these "hairs" are normally bent with sound vibrations or movement, they send electrical signals to the brain about hearing or balance function. In ototoxicity, these hairs can be damaged to the point that they no longer stand up, thus reducing the auditory and/or balance signals sent to the brain.

Symptoms of ototoxicity[13]

Cochleotoxicity symptoms range from mild tinnitus to total hearing loss, depending upon each person and the form and level of exposure to the ototoxin. They can include one-sided or two-sided hearing loss and constant or fluctuating tinnitus.

Vestibulotoxicity symptoms range from mild imbalance to total incapacitation. Symptoms of a vestibular or balance function loss depend upon the degree of damage, if the damage occurred rapidly or slowly, if it's one-sided or two-sided, and how long ago the damage occurred. A slow one-sided loss might not produce any symptoms, while a rapid loss could produce enough vertigo, vomiting, and nystagmus (eye jerking), to keep a person in bed for days. Most of the time, the symptoms slowly pass, allowing a person to return to normal activities.

A two-sided loss in vestibulotoxicity typically causes headache, a feeling of ear fullness, imbalance to the point of being unable to walk, and a bouncing and blurring of vision (oscillopsia) rather than intense vertigo, vomiting, and nystagmus. It also tends to produce inability to tolerate head movement, a wide-based gait (walking with the legs farther apart than usual), difficulty walking in the dark, unsteadiness or the sensation of unsteadiness, lightheadedness, and significant fatigue. If the damage is severe, symptoms such as oscillopsia

and problems with walking in the dark or with the eyes closed will not diminish with time.

Ototoxicity and mechanism of hair cell damage

Susceptibility and Genetic Predisposition for Aminoglycoside Ototoxicity

While AGs preferentially target the bacterial ribosome, the inner ear and kidney are known to receive collateral damage in many patients receiving treatment[14,15]. However, a meta-analysis comparing once versus multiple-daily regimens of different AGs could not determine a statistical significant correlation between ototoxicity and treatment regimens[16]. One main susceptibility factor (17%–33% of patients with reported ototoxic damage[17]) is the genetic predisposition to AG ototoxicity[18]. The fact that this increased susceptibility was inherited maternally suggested mitochondrial involvement[18]. This is compelling in light of the endosymbiotic theory as mitochondrial ribosomes demonstrate more similarities to prokaryotic ribosomes than cytosolic ribosomes [19,20]. Therefore, the small subunit of the mitochondrial ribosome is one of the primary targeting sites for AGs[21,22]. Several mutations in mitochondrial DNA are linked to increased susceptibility to AG ototoxicity [17,23,24]. Exposure to AG leads to impairment of RNA translation within mitochondria through interaction with binding sites on mitochondrial 12S rRNA[23]. This interaction was mapped to an adenine-to-guanine mutation at nucleotide 1555 in the 12S rRNA gene[23]. Of additional note, bacterial resistance mutations are described at this locus[25,26]. This mutation increases structural similarity of mitochondrial rRNA to bacterial rRNA[23], which promotes binding of AG to mutated mitochondrial 12S rRNA[26,27]. As a result, damage can result from decreased protein synthesis[26].

Although no direct evidence exists to link ototoxicity to an inhibition of mitochondrial protein synthesis, inhibition of mitochondrial protein synthesis potentiates AG toxicity[28]. Also, electron microscopy reveals mitochondrial disruption following AG treatment[29]. This susceptibility mutation has been reported in 17%– 33% of patient with reported AG ototoxicity[17]; in the general population of the European Union, it is estimated to be 1 : 500[30,31]. Other mutations leading to increased AG susceptibility have also been described, including C1494T[24]. The C1494T mutations have varying degrees of penetrance[32], are less common than the A1555G mutation[33], and are sporadic with multiple origins[34]. In sum, the prevalence of the most common mutations across varying ethnic backgrounds is 0.9%–1.8%[33,35], of which 5%-6% are sporadic[19,36,37].

Although this genetic susceptibility is present in all organs, the mitochondrial mutations target the cochlea but not the vestibular organs or the kidneys[39]. This is intriguing as this selective cochleotoxicity also occurs with preferably vestibulotoxic AGs such as streptomycin[39]. One proposed explanation for this phenomenon is that AGs cause misreading in mitochondrial protein synthesis rather than direct inhibition of protein synthesis[39] such that tissues rich in mitochondria would be predominately affected[38].

Exposure to AGs would decrease mitochondrial ATP synthesis resulting in compromised ion pump activity[38,39]. Reduced ion pump activity in strial intermediate cells could ultimately lead to a progressive decrease of the endocochlear potential[38]. This scenario conceivably explains the slow progression of hearing loss after exposure to AGs observed in patients with increased genetic susceptibility. The strial impairment, furthermore, would explain the little effect on vestibular function in these patients[38]. Interestingly, the stria vascularis demonstrates extensive degeneration in syndromal mitochondrial diseases[40]. This further supports the hypothesis of the stria vascularis as the cochlear cells targeted by the mitochondrial mutations in patients with increased genetic susceptibility to AG ototoxicity. An alternative simple explanation is that susceptibility to the mitochondrial disease is a function of metabolic demand so that hair cells operating at higher frequencies will be more susceptible to a reduced mitochondrial function than lower frequency cells, that is, cochlea versus vestibular, basal versus apical, and type I versus type II. Similarly the highly metabolically active strial cells would also have increased sensitivity.

In genetically susceptible individuals, it is postulated that a single injection of AG can cause ototoxic damage[41], implying that genetic factors can reduce the threshold concentration at which AGs cause damage[17]. At higher concentrations or more frequent doses of AG, the incidence of ototoxic damage exceeds the prevalence of genetic predispositions[33,38,42]. Although *in vitro*, a clear relationship between damage and AG concentration is observed, the extent of ototoxic damage *in vivo* does not seem to correlate with

AG concentration in targeted tissues[43]. This discrepancy requires further evaluation.

Apoptotic Pathways of Ototoxic Hair Cell Death

Inside the hair cell, AGs cause damage, either directly or indirectly, by first inducing disarray of stereocilia and ultimately ending with apoptotic cell death[44–47]. The presence of AGs within hair cells leads to increased formation of reactive oxygen species (ROS) or free radicals[48–51]. A common mechanism for the formation of ROS is the Fenton reaction:

$$Fe2+ + H2O2 \longrightarrow Fe3+ + HO\bullet + HO-.$$

When gentamicin combines with iron salts, the gentamicin-iron complex enhances iron-catalyzed oxidations and, thereby, directly promotes the formation of ROS[48]. This requires electrons for which unsaturated fatty acids can act as electron donors. In return, those fatty acids, predominantly arachidonic acid, are oxidized to lipid peroxides[51].

The mechanism of involvement of mitochondrial mutations in ototoxic hair cell death is not completely understood. Exposure to AG leads to impairment of RNA translation and inhibition of protein synthesis within mitochondria[23,26,52]. It is further suggested that inhibition of mitochondrial protein synthesis leads to a decrease in ATP. With the decrease of energy production, the mitochondrial integrity is compromised and predispose to a leakage of Cytochrome C and subsequent activation of the apoptotic cascades.

Another group of mediators of apoptotic hair cell death is the stress-activated protein kinases, including the mitogen-activated protein (MAP) kinases (Figure 2)[46]. A particular group of MAP kinases are c-jun N-terminal kinases (JNK). These JNKs are located in the cytoplasm and regulated by c-Jun-interacting protein-1 (JIP-1)[55,56]. In response to cellular insults, JIP-1 facilitates the phosphorylation and thus activation of JNK[57–60]. Activated JNK in turn phosphorylates and thereby activates the transcription factors c-Jun, c-Fos, ELK-1, and activated transcription factor 2 (ATF-2) in the nucleus and Bcl-2 in mitochondria[46]. After AG treatment, increases in JNK, c-Jun, c-FOS, and Bcl-2 have been reported in hair cells[46,54,60,61]. Activation of the JNK signaling pathway appears to precede the release of mitochondrial Cytochrome C, which then activates caspases[54,62]. Caspases execute cell death in apoptosis[53].

Reactive oxygen species (ROS), stress kinases, and the caspase family of proteases are activated and mediate hair cell degeneration caused by aminoglycoside exposure, whereas overexpression of Bcl-2 protects against caspase activation and hair cell lose. Aminoglycosides damage the mitochondria and can result in generation of ROS and activation of stress kinases. Both ROS and stress kinases can cause cell death directly as well as amplify insults targeting the mitochondria. The balance between pro-apoptotic and anti-apoptotic Bcl-2 family membrane determines the integrity of the mitochondria. Cytochrome c leaking out of damaged mitochondria leads to caspase-9 activation, which in turn activates caspase-3 to execute cell death.

Efforts in hair cell protection

With increasing understanding of ototoxic cell death, a myriad of therapeutic efforts have been proposed to target various steps of the complex cascades to hair cell death. Those strategies include inhibition of apoptosis, neutralization of ROS, and administration of neurotrophic factors. A detailed overview of relevant studies including applied drugs, dosage, and outcome is presented in a table at the end of each subchapter.

Inhibition of Apoptotic Enzymes[63]

Caspase inhibitors conferred significant protection against hair cell damage from AG, preserving hair cell morphology as well as function *in vitro* and *in vivo*. Agents targeting upstream stress kinases in the apoptotic cascades also prevented AG-induced hair cell death. Targeting the Bcl-2 family as the upstream key mediator of apoptosis also prevented AG-induced hair cell loss.

Neutralization of Reactive Oxygen Species[64]

Aminoglycosides form complexes with iron, thereby, catalyzing the formation of ROS. Competitive blocking of the Fenton reaction involved by iron chelators, thus, is a reasonable approach to avoid oxidative damage from the beginning. Therefore, much efforts aiming at prevention of AG-induced hair cell death have focused on iron. Administration of the iron chelators deferoxamine and 2,3-dihydroxybenzoate before AG exposure significantly attenuated hearing threshold shifts and protected from hair cell loss *in vivo*.

Acetylsalicylate (ASA) is another iron chelator with additional direct antioxidant properties. ASA prevents cleavage of PKC zeta, a

key regulator of NF$\kappa\beta$ activated by exposure to amikacin. N-Acetylcysteine (NAC) is another drug commonly used in patients. Beside its mucolytic effect, NAC is also a known antioxidant.

Alternative Otoprotective Strategies[65-74]

There exist a number of alternative approaches to protect against AG ototoxicity. One intriguing approach is moderate exposure to ototoxic stimuli with the intent to increase intrinsic antioxidant mechanisms within the ear. Exposure to low doses of amikacin or gentamicin for 30 days and consecutive high-dose treatment for another 10 to 12 days resulted in significantly less morphologic and functional hair cell damage. However, this bears the undesirable risk of increased bacterial resistance and, thereby, undermines the primary antimicrobial purpose of the AG application. Exposure to moderate noise also protects from gentamicin ototoxicity in gerbils (Table 3). As this does not allow for immediate application of AG in therapeutic doses, applicability in human patients appears difficult. Other studies successfully target NMDA receptors to protect auditory nerves. However, the NMDA receptor antagonists dizocilpine and ifenprodil exist as maleate and tartrate salts, which carry intrinsic metal chelating properties. Their vehicle, dimethyl sulfoxide (DMSO), can also act as a radical scavenger. Therefore, the results of Basile and coworkers were challenged by Sha and Schacht. Nonetheless, NMDA antagonists do interact with receptors of afferent auditory nerve fibers. Thus, targeting the auditory nerve appears reasonable as AGs interact with certain nerve synapses. AGs can aggravate myasthenia gravis and cause postoperative respiratory suppression suggesting a direct neuromuscular blockade. Presynaptically, AGs interfere with the calcium internalization essential for acetylcholine release. At the postsynaptic level, streptomycin directly blocks the acetylcholine receptor primarily, whereas neomycin affects the open probability of the ion channel of the acetylcholine receptor. Also, in rat and mouse cochlear cultures, fluorescently tagged gentamicin accumulates in the afferent auditory nerve fibers in addition to the hair cells.

This direct interaction with the auditory nerve also might explain therapeutic effects by neurotrophic growth factors. Ciliary neurotrophic factor (CDNF), glial-cell-line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (NT-3) demonstrated partial protective effects against AG ototoxicity. The contribution of neurotrophic growth factors in preventing AG ototoxicity suggests an involvement of the auditory nerve. However, there is evidence that the effects of neurotrophic growth factors are short term. Local application of BDNF (62.5 μg/mL, 0.25 μL/h over 28 d) to guinea pigs exposed to kanamycin (400 mg/kg, single dose, s.c.) and furosemide (100 mg/kg, single dose, i.v.) demonstrated initial protection from ototoxicity. Cessation of the therapy, however, resulted in an accelerated neuronal degeneration and after another 14 d, the survival of BDNF treated auditory neurons did not differ from the deafened, untreated control animals. Ethacrynic acid (EA) is a diuretic which increases AG ototoxicity when administered simultaneously.

Delayed co-treatment with application of EA 12–18 hr after gentamicin injections in guinea pigs resulted in significantly protected hair cell function and morphology. The authors suggest that EA disrupts the blood-labyrinth barrier, thus creating a gradient promoting efflux of AG from the inner ear fluids back into the bloodstream. However, the protective effects are time dependent and could not be found when EA was injected 20 hr after the AG. Moreover, simultaneous AG and EA in patients resulted in ototoxic damage after a single treatment, thereby excluding EA as a treatment option. Overall, prevention of apoptotic hair cell death following AG exposure has been targeted effectively on various levels. Direct inhibition of apoptotic cascades resulted in functional and morphological preservation of hair cells. Neutralization of free radicals by antioxidants prevented activation of apoptotic enzymes. Furthermore, application of NMDA-receptor antagonists, neurotrophic growth factors, and sound conditioning have prevented ototoxic hair cell damage from AG. However, these protective results are mainly based on acute studies and the sustainability of therapeutic potential and safety remains to be evaluated inchronic exposure scenarios or in clinical trials.

Potential targets for hair cell protection[75]

The most effective target sites involve the mitochondrial rRNA as well as AG entry into the inner ear fluids and hair cells. On the level of the MET channel, at least two possibilities of preventing AG entry exist. The first one involves a reversible block of the MET channel. The process of hearing requires depolarization of the inner hair cell through the MET channel. Blocking of the MET channel would then prevent hair cell depolarization and, therefore pause hearing

function. Thus, the MET channel block has to be temporary. MET channel blockers have been tested successfully *in vitro*. The narrowest part of the MET channel pore has been estimated to be 1.25 nm. As dihydrostreptomycin is capable of blocking the MET channel, the difference in the dimensions of the MET channel and certain AGs appears to be small. Therefore, widening of the AG diameter by binding of inert molecules on sites irrelevant for antimicrobial activity appears a promising strategy to prohibit passage of AGs through the MET channel into the hair cells. As the passage through the bacterial membrane is self-promoting and depends on the relative positive charge of the AG, the intended increase of size should not affect bacterial uptake of the AG as long as the polarity and the charge of the new AG molecule remains the same. Another target lies in preventing AG from entering the inner ear fluids. AGs enter the inner ear fluids through the stria vascularis.

How is ototoxicity diagnosed?[76]

The diagnosis is based upon the patient's history, symptoms, and test results. There is no specific test for ototoxicity; this makes a positive history for ototoxin exposure crucial to the diagnosis. Some of the tests that may be used to determine how much hearing or balance function have been lost involve the vestibular autorotation test (VAT), vestibulo-ocular reflex testing equipment (VORTEQ), electronystagmography (ENG), computerized dynamic posturography (CDP), rotary chair (SHAT), head-shaking, electrocochleography (EcoG), auditory brainstem response (ABR), otoacoustic emissions, pure tone audiometry, speech discrimination, and most other tests often used to identify and quantify inner ear problems.

What is the treatment?[77]

At present there are no treatments that can reverse the damage. Currently available treatments focus on reducing the effects of the damage and rehabilitating function. Specifically, individuals with hearing loss may be helped with hearing aids; those with profound bilateral (two-sided) hearing loss have been shown to benefit from cochlear implants. In fact, many early recipients of cochlear implants were victims of ototoxicity. When a loss of balance function has occurred, physical therapy can help the brain become accustomed to the altered balance signals coming from the inner ear. Physical therapy can also assist an individual in developing other ways to maintain balance such as emphasizing the use of vision and proprioception the sensation felt by the soles of the feet, the ankles, knees, and hips and structuring a program of general physical conditioning and exercises designed to strengthen and tone muscles.

The effect of corticosteroid against streptomycin ototoxicity[77]

The aim of this experimental study was to determine the possible protective role of corticosteroid in prevention of streptomycin-induced ototoxicity. Twenty-eight adult Wistar albino rats were divided into 4 groups: control (n = 7), streptomycin (n = 7), corticosteroid (n = 7), and streptomycin + corticosteroid (n = 7). Rats were tested with distortion product otoacoustic emissions (DPOAEs) in the beginning and at the end of the study. The animals in all groups were killed under general anesthesia on the 45th day after the last DPOAE measurements. Hearing results were analyzed statistically to determine differences in amplitudes of DPOAE. In addition, the cochleas of each rat were evaluated by histopathologic and immunohistochemical examination. Significant difference was not observed in cochlear hair cells in the control and corticosteroid groups, whereas severe degeneration of hair cells and increased apoptotic cells were observed in the streptomycin group. Moderate degeneration was observed in the streptomycin + corticosteroid group. The hair cells were partially intact. DP-gram of the streptomycin and streptomycin + corticosteroid groups was significantly deteriorated ($P < 0.05$). The co-administration of steroids with streptomycin, which has a serious ototoxic effect, did not lead to a limitation of this harmful effect.

The protective role of caffeic acid phenethyl ester against streptomycin ototoxicity[78]

Caffeic acid phenethyl ester treatment attenuated hair cells injury in the inner ear, possibly via its antioxidant effect. Prophylactic administration of CAPE for streptomycin ototoxicity ameliorated hearing deterioration in rats.

Long-term goals[79]

The major long-term goals include continuing with conditioning activities to improve balance function, protecting the other systems involved with maintaining balance, and preventing further ototoxic damage.

Protection of other components of balance vision and proprioception is essential. Good vision is crucial in the face of a severe vestibular loss. Yearly ophthalmological examinations that include a glaucoma check

should become routine. Use of ultraviolet (UV) eye protection in the sun and eye protection in the wind (such as goggles or sunglasses) should be considered.

Protecting proprioception involves taking precautions such as avoiding walking barefooted on any surface that could injure or damage the soles (such as on a macadam road surface), not wearing clothing that restricts circulation to the legs and feet (such as a tight girdle), and taking off excess body weight that can cause knee and hip difficulties.

Avoidance of ototoxic substances is also very important because individuals who have suffered from ototoxicity have a higher likelihood of experiencing it again, if exposed. A medic alert tag might be helpful for warning health care professionals about the need to avoid prescribing ototoxic medications unless needed to save your life. Such tags might also serve to flag an existing reduction in balance and/or hearing function.

A look at the future[80]

Ongoing related research addresses prevention and treatment. Chemicals are being evaluated for their ability to prevent ototoxicity and that might be prescribed in tandem with ototoxic drugs in the future. Investigators are also studying methods of hair-cell and nerve-cell regeneration. In the distant future, it may be possible to stimulate the ear into growing replacement hair cells and to repair damaged nerve fibers.

Endnote[80]

Most of the drugs listed in this document appear because strong evidence exists to show that they cause or probably cause ototoxicity. This evidence includes at least one of the following criteria:

- Large numbers of isolated reports about particular drugs or chemicals
- Experiments showing that animals develop ototoxicity when given the drug
- Multiple post-mortem studies that demonstrate changes in the ear that are linked to ototoxins in people who took certain drugs and who subsequently developed symptoms of ototoxicity. (Such ear damage can only be observed after death, when the ears can be examined fully.) An example of this type of research is Zheng et al, 2001.
- Scientific reports about groups of people tested before (if possible), during, and after their use of a drug, some of whom were found to develop ototoxicity while taking the drug. An example of this type research is Black et al, 2001.

DISCUSSION

It is now well known that the aminoglycoside antibiotics act synergistically with some drugs, thus increasing the incidence of ototoxicity. For example, the use of aminoglycoside antibiotics with loop diuretics can produce an unexpectedly high incidence of ototoxicity. This has been extensively documented in human case reports as well as in animal studies. Ethacrynic acid, an ototoxic loop diuretic, has been shown to increase the permeability of the stria vascularis, facilitating the diffusion of the aminoglycoside into the endolymph. Finally, it has been found that diuretics given prior to the administration of aminoglycosides are less damaging than if done in the reverse . Most recently noted is a similar response to aminoglycoside antibiotics and the use of metronidazole .

It is unclear at this time if antiviral and protease inhibitors are responsible for the anecdotal reporting of neuro-sensory hearing loss in patients with human immunodeficiency virus. Prospective studies are needed to confirm whether nucleoside analog reverse transcriptase inhibitor or antiviral agents cause hearing loss in this patient population. The use of chemoprevention measures as described in animal studies show promise, but so far no prospective clinical trials have been performed and the authors are not aware of any medical centers with protocols to address this issue at this time.

CONCLUSION

Streptomycin is still recommended as first line drug for tuberculosis, Inspite of its potential to cause ototoxicity, clinician could use it with caution and with the aid of well designed system for early monitoring and early discontinuation.

Hearing loss due to ototoxicity is generally irreversible but avoidable in most instances, given preventive action through rational use of drugs in the health care system and by the consumers.

There are situations in which potentially ototoxic drugs must be administered. Under such

circumstances, the following should be observed: (i) proper dosage and duration of therapy; (ii) an appropriate route of drug administration; (iii) a continuous monitoring of the patient, with particular attention to audiometric values and serum drug level where feasible.

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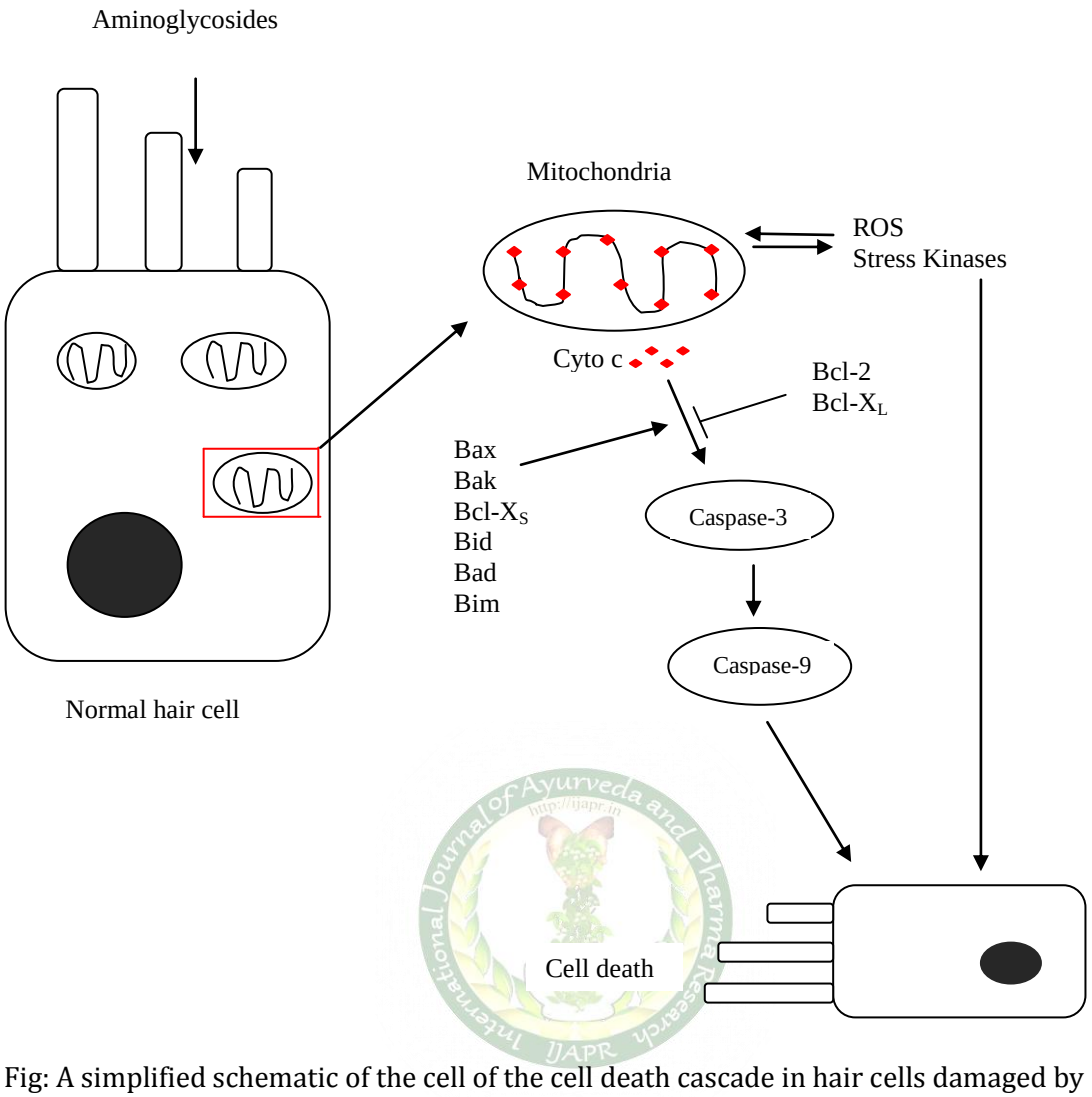

Fig: A simplified schematic of the cell of the cell death cascade in hair cells damaged by aminoglycosides