Purpose: This review article summarizes our current understanding of the mechanisms underlying acquired hearing loss from hospital-prescribed medications that affects as many as 1 million people each year in Western Europe and North America. Yet, there are currently no federally approved drugs to prevent or treat the debilitating and permanent hearing loss caused by the life-saving platinum-based anticancer drugs or the bactericidal aminoglycoside antibiotics. Hearing loss has long-term impacts on quality-of-life measures, especially in young children and older adults. This review article also highlights some of the current knowledge gaps regarding iatrogenic causes of hearing loss.

Conclusion: Further research is urgently needed to further refine clinical practice and better ameliorate iatrogenic drug-induced hearing loss.

In 2018, the consensus of the Ototoxicity Working Group of Pharmaceutical Interventions for Hearing Loss, 2018 defined ototoxicity as damage to the inner ear, targeting cochlear and vestibular structures and sensory function, due to exposure to certain pharmaceuticals, chemicals, and/or ionizing radiation (i.e., iatrogenic hearing loss). This review article will focus primarily on hospital-based medications: aminoglycoside antibiotics and cisplatin. Aminoglycosides are typically used for serious bacterial and mycobacterial infections, including gentamicin for meningitis and sepsis, tobramycin or amikacin for respiratory infections in individuals with cystic fibrosis, and kanamycin for tuberculosis. Cisplatin- and platinum-based derivatives like carboplatin and oxaliplatin provide efficacious treatment for solid (e.g., testicular and ovarian) tumors, head and neck cancers, and glioblastomas in the brain.

Other ototoxins include solvents and jet fuels (Davis et al., 2002; Fechter et al., 2007; Steyger, 2009), metals such as lead (Counter & Buchanan, 2002; Jamesdaniel et al., 2018), and cyclodextrins, which is a primary component of drug formulations that, at high doses, can sequester membrane cholesterols (Crumling et al., 2017). Ototoxicity is primarily considered a peripheral, inner ear phenomenon; however, ototoxic agents can also affect central neural (or auditory) pathways and are then considered to be neurotoxic (Gopal et al., 2012; Hinduja et al., 2015). Ototoxins can also cause kidney damage and associated renal dysfunction (i.e., nephrotoxicity; Humes, 1999; Jiang et al., 2017; Karasawa & Steyger, 2015).

Adults that lose their exquisite sense of hearing invariably have diminished interactions via spoken language with loved ones, friends, and colleagues, and reduced awareness of environmental sounds with a corresponding loss of safety (Centers for Disease Control and Prevention, 2004; Monson et al., 2019). The clinical consequences of uncorrected or maladaptation to hearing loss can include isolation, depression, and loss of self-esteem that can lead to declining cognitive ability and social withdrawal (Lin et al., 2013). UnCorrected congenital or acquired hearing loss in infants can lead to delayed acquisition of listening and spoken language skills expected of their peers with typical hearing, with concomitant delays meeting academic, linguistic, and psychosocial milestones (Dedhia et al., 2013; Gurney et al., 2007). Loss of vestibular function is also debilitating and can lead to depression and cognitive decline (Smith & Darlington, 2013; Smith & Zheng, 2013). In addition, there is a socioeconomic cost > $1.5 million over the lifetime of each deafened child and > $375,000 for each adult in the United States (extrapolated into 2019 values from Mohr et al., 2000).

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Incidence of Iatrogenic Drug-Induced Hearing Loss and Vestibular Disorders

In preclinical models, aminoglycoside-induced hearing loss is typically dose dependent (Wu et al., 2001). The prevalence of clinical aminoglycoside dosing in the United States has decreased from several million in the 1980s due to the use of β-lactams in the 1980s and 1990 to a few hundred thousand during the current era of antibiotic stewardship (Pitiriga et al., 2017; Whelton, 1984). The incidence of hearing loss in humans after aminoglycoside treatment remains unclear due to variable dose stratification regimens and limited pure-tone testing that does not always include frequencies above 8 kHz in audiometric assays; nonetheless, the incidence of hearing loss may occur in 20%–63% of those receiving aminoglycosides for multiple days (Elson et al., 2020; Fausti, Frey, et al., 1992; Fausti, Henry, et al., 1992; Garinis, Cross, et al., 2017; Garinis, Liao, et al., 2017). Patients often report vestibular (and tinnitus) issues before any awareness of aminoglycoside-induced hearing loss (Van Hecke et al., 2017); however, the incidence of aminoglycoside-induced elevations of vestibular thresholds for motion detection (Shayman et al., 2018) is likely underreported due to the widespread absence of clinical apparatus (away from major academic medical centers) for determining vestibular function.

Platinum-based drugs, like cisplatin, have long been known to be cochleotoxic in humans and preclinical models (Brock et al., 2012). Cisplatin is clinically very effective in reducing the mass of solid or central nervous system tumors, yet the incidence of hearing loss is cumulatively dose dependent (Callejo et al., 2015; Knight et al., 2005, 2007; Paken et al., 2016). Cisplatin has recently been reported to dose-dependently induce loss of vestibular hair cells and vestibular function in preclinical models (Callejo et al., 2017). Although there are fewer reports of cisplatin-induced vestibular dysfunction, this is more likely due to geographic limitations in determining human vestibular thresholds for motion detection (Prayuenyong et al., 2018), and lack of routine clinical assessments, as for aminoglycosides.

Trafficking of Aminoglycosides and Cisplatin Into the Inner Ear

The trafficking of these ototoxins into the inner ear and hair cells are generally similar, although more details are known for aminoglycosides. The blood–labyrinth barrier (BLB) separates cochlear cells and fluids from the bloodstream, akin to the blood–brain barrier. The endothelial cells of cochlear blood vessels are typically coupled together by tight junctions to form the primary BLB and prevent macromolecules and blood cells from entering the cochlea (Nyberg et al., 2019). Within the cochlea, perilymph has an ionic composition typical of other extracellular fluids (i.e., high in Na⁺, low in K⁺, and millimolar Ca²⁺) and the larger fluid volume (Wangemann, 2006). Although systemically administered aminoglycosides and cisplatin can enter the perilymphatic space surrounding the basolateral membranes of hair cells from the bloodstream (Hellberg et al., 2013; Tran Ba Huy et al., 1986), aminoglycosides do not easily enter hair cells from this domain (Li & Steyger, 2011).

In contrast, endolymph bathes the apical surfaces of hair cells and has a unique extracellular ionic composition in the mammalian body (i.e., high in K⁺, low in Na⁺, and ~20-µM Ca²⁺). Cochlear, but not vestibular, endolymph has a highly positive potential of ~ +80 mV relative to blood or perilymph that is crucial for sensitive hearing. Tight junction–coupled epithelial cells surround the smaller endolymphatic volume (relative to perilymph) to prevent fluid mixing with perilymph (and hearing loss). The endolymphatic potential and its ionic composition are generated by the highly metabolically active cells of the vascularized stria vascularis (see Figure 1) in the lateral wall of the cochlea (Wangemann, 2006). Systemically administered aminoglycosides cross the BLB of the stria vascularis more rapidly than into the adjacent spiral ligament in the perilymphatic domain (Dai & Steyger, 2008). Surprisingly, systemically administered aminoglycosides also enter hair cells more rapidly than when aminoglycosides are directly infused into the perilymphatic compartment that surrounds the basolateral membranes of hair cells (Li & Steyger, 2011). Systemic inflammation and noise, both of which are associated with vasodilation of the blood vessels in the stria vascularis, enhance cochlear uptake of aminoglycosides (Koo et al., 2015; Li et al., 2015). The cellular

Figure 1. Main cochlear trafficking routes for systemically administered aminoglycosides and cisplatin. Both blood-borne drugs enter the cochlea primarily from the capillaries in the stria vascularis. Aminoglycosides enter endolymph through as-yet-unidentified ion channels or transporters, although several candidates exist (e.g., transient receptor potential [TRP] vanilloid subtype 1 [TRPV1] and TRP vanilloid subtype 4 [TRPV4]). Cisplatin also enters endolymph potentially trafficking via organic cation transporters-2 (OCT2) and copper-like transport-1 (CTR1) transporters in the marginal cells. From the endolymph, these ototoxins enter hair cells across their apical membranes. Adapted with permission from Figure 1 in the study of Kros and Steyger (2019), copyright © Cold Spring Harbor Laboratory Press.
and molecular mechanisms by which aminoglycosides cross the BLB (i.e., endothelial cells) into the stria vascularis and transverse the tight junction–coupled marginal cells into endolymph remain unknown, and they likely include one or more ion channels, transporters, exchangers, or transcytosis (Koo et al., 2015).

Less is known about how systemically administered aminoglycoside traffic to vestibular hair cells, although the transitional and dark cells more readily take up aminoglycosides than hair cells and their surrounding supporting cells (Liu et al., 2015). Vestibular endolymph is maintained by dark cells in the vestibule (Wangemann, 2006), akin to the stria vascularis and suggestive of similar mechanisms in trafficking aminoglycosides into endolymph. Intratympanic injection of aminoglycosides also led to more prominent uptake by type I hair cells as well as the crypt cells at the base of vestibular ampullae. It has not been determined in vivo if this was via trafficking into vestibular endolymph, prior to into hair cells and crypt cells (Lyford-Pike et al., 2007; Zhang et al., 2013). Strikingly, intratympanically administered aminoglycosides are taken up by auditory afferent neurons and vestibular efferent neurons from perilymph and transported into the brainstem. Whether this phenomenon has any functional consequences has yet to be established (Zhang et al., 2012).

Several lines of evidence suggest that cisplatin preferentially enters the cochlea via the stria vascularis (Breglio et al., 2013; Chu et al., 2016; van Ruijven et al., 2005) before entering hair cells, presumptively from endolymph (Brock et al., 2012). The putative cisplatin transporters copper-like transport-1 (CTR1) and organic cation transporter-2 (OCT2) are expressed by cells in the stria vascularis but not in the spiral ligament, suggestive of potential trafficking mechanisms for cisplatin transport across the BLB into the endolymph (Ciarimboli et al., 2010; More et al., 2010; Waissbluth & Daniel, 2013). Trafficking of cisplatin into vestibular cells remains largely unexplored, yet in preclinical models, cisplatin can cause loss of vestibular hair cells and sensory function in all five vestibular end organs (Sergi et al., 2003; Takimoto et al., 2016).

Entry of Aminoglycosides and Cisplatin Into Sensory Hair Cells

Permanent drug-induced cochleotoxicity typically requires these ototoxins to enter hair cells (Hiel et al., 1993). The mechanically gated transmembrane channel-like protein-1 (TMC1) nonselective cation channels at the tips of most (but not all) hair cell stereocilia (see Figure 2A) that transduce sound or motion into electrical signals are readily permeable to the polyvalent aminoglycosides (Alharazneh et al., 2011; Marcotti et al., 2005; Pan et al., 2018). The +80-mV potential of endolymph electrochemically drives cations through the TMC channels into hair cells with their −40- to −70-mV resting potential adding to this electrochemical flux. Aminoglycosides transiently bind to the open-channel pore and are permeant blockers of TMC channels (Marcotti et al., 2005). Aminoglycoside permeation of these large, nonselective cation channels can be blocked by polyvalent cations, including magnesium and calcium (see Figure 2B), as well as organic compounds like curare and quinine (Alharazneh et al., 2011; Coffin et al., 2009). Once in hair cells, aminoglycosides appear unable to readily escape (Hiel et al., 1992; Leitner et al., 2011; Marcotti et al., 2005; Zhai et al., 2013).

Other aminoglycoside-permeant cation channels are also expressed by hair cells, particularly transient receptor potential (TRP) channels, individually activated by various physical or chemical stimuli (Nilius & Szallasi, 2014). TRP vanilloid subtype 1 (TRPV1) and TRP vanilloid subtype 4 (TRPV4) expressed on the apical membranes of hair cells are also aminoglycoside-permeant channels (see Figure 2C), and both are also expressed in the stria vascularis (see Figure 1; Jiang et al., 2019; Karasawa et al., 2008; Myrdal & Steyger, 2005; Zheng et al., 2003). Hair cell expression of TRPV1 is upregulated in the cochlea during inflammation that, in vivo, increases aminoglycoside entry into vestibular hair cells (Jiang et al., 2019; Qian et al., 2020). The TRP ankyrin 1 (TRPA1) channel is another aminoglycoside-permeant channel that is presumptively expressed on the basolateral membranes of outer hair cells (OHCs; see Figure 2D). Activation of TRPA1 by reactive oxygen species enhanced the cellular uptake of fluorescently tagged gentamicin (Stepanyan et al., 2011). This suggests that endogenous signals (e.g., pro-inflammatory cytokines and reactive oxygen species) during inflammation or noise can activate aminoglycoside-permeant TRP channels cochlear stress (e.g., noise and infection) to increase hair cell uptake of aminoglycosides (Goncalves et al., 2020; Kaewpitak et al., 2020).

Another entry route into hair cells is via non-receptor-mediated endocytosis at the apical and synaptic membranes of hair cells and trafficking toward lysosomes (see Figure 2E). However, blocking endocytosis (see Figure 2F) or impeding intracellular trafficking of aminoglycoside-laden endosomes does not prevent hair cell death (Alharazneh et al., 2011; Hailey et al., 2017; Hashino et al., 2000; Qian et al., 2020; Vu et al., 2013).

Defining the mechanisms by which cisplatin enters hair cells remains challenging, as cisplatin can enter cultured cells (see Figure 3A) across the cell membrane via passive diffusion (Hall et al., 2008). In zebrafish neuromasts, hair cells with functional TMC1 channels (see Figure 3B) are more susceptible to cisplatin-induced cytotoxicity (Thomas et al., 2013). Cellular uptake of cisplatin can be enhanced by the expression of putative cisplatin transporters, and two (i.e., CTR1 and OCT2) are expressed by cochlear hair cells (see Figure 3C; Ciarimboli et al., 2010; Hall et al., 2008; More et al., 2010; Waissbluth & Daniel, 2013). Systemic administration of cimetidine, an OCT blocker, genomic loss of both OCT1/2, or local administration of copper sulfate all ameliorate cisplatin-induced cochleotoxicity, demonstrating an as-yet-to-be specified (trafficking or hair cell uptake) role for these putative cisplatin transporters in the cochlea (Ciarimboli et al., 2010; More et al., 2010). However, zebrafish hair cells do not express the putative
Figure 2. Entry of aminoglycosides into hair cells. Aminoglycosides preferentially enter hair cells across their apical membranes, predominantly via the transmembrane channel-like protein-1 (TMC1) channel complex, consisting of two TMC subunits (purple), each with a permeation pore (A). Entry of aminoglycosides can be blocked by curare, quinine, and high polyvalent cation levels among others (B). Other aminoglycoside-permeant cation channels on the apical membrane of hair cells include transient receptor potential (TRP) vanilloid subtype 1 (TRPV1) and TRP vanilloid subtype 4 (TRPV4) channels (C), and TRP ankyrin 1 (TRPA1) channels on the basolateral membranes of outer hair cells (D). (E) Nonspecific endocytosis also traffics aminoglycosides into hair cells and to lysosomes. (F) Blocking endocytosis does not prevent hair cell death when aminoglycosides can enter hair cells via the TMC1 channel.

Figure 3. Entry of cisplatin into hair cells. Cisplatin has multiple potential entry routes, for which the relative importance has not been established. Neutral cisplatin can enter cells across the plasma membrane via diffusion and, once in the cytoplasm, is readily aquated into the more toxic form of cisplatin to form adducts with proteins and deoxyribonucleic acid. Uptake of (likely) aquated cisplatin is most dependent on a functional, mechanically gated transmembrane channel-like (TMC) channel complexes. Cellular uptake of the aquated form of cisplatin may also occur via copper-like transport-1 (CTR1) and organic cation transporter-2 (OCT2) transport proteins. TMC1 = transmembrane channel-like protein-1.
cisplatin transporters CTR1 or OCT2 (Thomas et al., 2013), leaving open the mechanically gated TMC transduction channels as a primary candidate for cisplatin entry into hair cells. Once in the cochlea and hair cells, cisplatin is retained for at least 12–18 months (Breglio et al., 2017).

Patterns of Cochlear Hair Cell Death

Systemically administered aminoglycosides initially induce hair cell death in the outer cells of the basal, high-frequency region of the cochlea. Continued dosing leads to OHC death at lower frequencies in more apical regions of the cochlea, and inner hair cells begin to also die (Forge & Schacht, 2000). Systemically administered cisplatin also initially leads to OHC death in the basal, high-frequency region of the cochlea before affecting hair cells at more apical, lower frequency regions. Increasing cumulative dosing of either ototoxin consistently leads to an increasing risk of permanent hearing loss in humans (Brock et al., 2012; Garinis, Cross, et al., 2017). The apices of dying hair cells are severed from their cell bodies by the expanding phalangeal plates of surrounding supporting cells to form a “scar” and maintain the structural integrity of the reticular lamina, that is, the apical tight junctions between adjacent cells of the organ of Corti facing the scala media. This phenomenon maintains optimal responsiveness in surviving, functional hair cells by preventing the equilibration of endolymphatic and perilymphatic fluids. These “scar” formations are characterized by distinct reticular patterns of junctional and cytoskeletal proteins at the site of the missing hair cell (Leonova & Raphael, 1997; Steyger et al., 1997). The hair cell bodies are typically phagocytosed by adjacent supporting cells and resident macrophages (Monzack et al., 2015). In the vestibule, the preferential uptake of aminoglycosides by a majority of type I hair cells may underlie their pharmacological and physiological sensitivity to aminoglycosides compared with the extra-striolar type II hair cells (Lyford-Pike et al., 2007; Sultemeier & Hoffman, 2017).

Multiple Mechanisms of Ototoxicity

Once inside hair cells, aminoglycosides and cisplatin cause multiple mechanisms of hair cell death that are reviewed in more detail elsewhere (Jiang et al., 2017; Karasawa & Steyger, 2015; Kros & Steyger, 2019). Highlighted here are peripheral mechanisms of ototoxicity that illustrate multiple (yet incompletely) characterized mechanisms of cytotoxicity and pathophysiology induced by aminoglycosides and cisplatin.

Following entry via ion channels into the cytoplasm, aminoglycosides bind to hundreds of proteins (Karasawa et al., 2010, 2011), yet for most protein binding to aminoglycosides, the downstream consequences are not known. Aminoglycosides also bind to the phosphatidylinositol family of lipids, particularly phosphatidylinositol 4,5-bisphosphate (PIP2), that, in mammalian hair cells, blocks voltage-gated, outwardly rectifying potassium channels on the basolateral membranes of OHCs. This blockade prevents the rapid repolarization of hair cells crucial for hair cell survival (Leitner et al., 2011; Schacht et al., 1977). In zebrafish neuromast hair cells, aminoglycosides dysregulate the endoplasmic reticulum that leads to calcium flux into mitochondria and the generation of cytotoxic levels of reactive oxygen species in zebrafish neuromast hair cells (Esterberg et al., 2013, 2014, 2016). Intracellular aminoglycosides have been implicated in the degradation of presynaptic ribbons in hair cells (Liu et al., 2013; Oishi et al., 2015) that may underlie the reported loss of auditory function in cochlear regions despite the presence of many surviving hair cells (Koo et al., 2015; Nicol et al., 1992). Vestibular synaptopathy also occurs after aminoglycoside dosing (Sultemeier & Hoffman, 2017).

Mammalian sensory hair cells do not undergo cell division, avoiding the primary toxic effect of cisplatin binding to deoxyribonucleic acid (DNA) that initiates apoptotic signaling in proliferating cells (Eastman, 1999). Cisplatin affects many other intracellular pathways and binds to hundreds of proteins that could potentially dysregulate cells and lead to cell death (Karasawa et al., 2013; Karasawa & Steyger, 2015). For cochlear cells, uptake of cisplatin triggers the transcription factor, signal transducer, and activator of transcription 1 (STAT1) to activate the TRPV1 and NADPH oxidase 3 (NOX3) signaling pathways that generate toxic levels of reactive oxygen species that ultimately induce cell death (Mukherjea et al., 2008, 2011).

Ototoxicity can occur in nonsensory cochlear or vestibular cells that have crucial homeostatic functions essential for sensitive hair cell function, that is, cisplatin-induced cytotoxicity in intermediate and marginal cells of the stria vascularis responsible for generating the endolymphatic potential (Laurell et al., 2007; McAlpine & Johnstone, 1990). Aminoglycosides can structurally damage marginal and intermediate cells in the stria vascularis, yet this does not appear to have a major effect on stria generation of the endolymphatic potential (Forge et al., 1987; Ono & Tachibana, 1990; Xiong et al., 2011). More transiently, the medial olivocochlear reflex that protects hair cells from loud sounds is dysregulated by aminoglycosides binding to the efferent synapses at the base of OHCs (Avan et al., 1996; Blanchet et al., 2000).

Factors Enhancing the Risk of Hearing Loss

Exacerbation of Aminoglycoside-Induced Cochleotoxicity

Experimentally induced sepsis (via parenteral injection of lipopolysaccharides [LPS]) potentiates the degree of aminoglycoside-induced hearing loss in mice (Jiang et al., 2019; Koo et al., 2015), and likely vestibulotoxicity (Qian et al., 2020). Pilot data suggest that inflammation (and fever) also increases the risk of aminoglycoside-induced hearing loss (Cross et al., 2015; Henry et al., 1983). Aminoglycosides lyse bacteria and increase blood levels of bacterial immunogens (e.g., LPS) that enhance the severity of inflammatory responses, a phenomenon known as the Jarisch–Herxheimer reaction (Kaplanski et al., 1998; Shenep & Mogan, 1984). Thus, the very patients with infection-induced inflammation and treated with aminoglycosides are likely
to be at higher risk of ototoxic-induced hearing loss (Koo et al., 2015), such as individuals with systemic lupus erythematosus, or with cystic fibrosis.

Other clinical risk factors that enhance the risk of aminoglycoside-induced hearing loss include the following: concomitant renal insufficiency that decreases clearance of aminoglycosides from blood (Zager, 1992); increasing age and the decreased glomerular filtration rate associated with aging (Gatell et al., 1987; Manian et al., 1990; McClure, 1992; Trigg & Charles, 1999); depletion of endogenous antioxidants (or poor nutritional status) to counter the aminoglycoside-induced toxic generation of reactive oxygen species (Lautermann, McLaren, et al., 1995); fever (higher-than-normal body temperature); and transient ischemia/hypoxia (Lin et al., 2011). Aminoglycoside dosing in rats during inactive hours (i.e., daytime rest phase for many rodents) has also been associated with greater hearing loss than when administered during active, nighttime hours for these rodents (McKinney et al., 2015; Soulban et al., 1990). How the circadian rhythm modulates ototoxicity is still to be determined.

A variety of mitochondrial mutations in ribosomal ribonucleic acid (RNA; e.g., A1555G and C1494T) have a higher affinity for binding to aminoglycosides. This leads to mistranslation of messenger RNA and inaccurate protein synthesis resulting in greater susceptibility to aminoglycoside-induced hearing loss (Hobbie et al., 2008; Matt et al., 2012; Qian & Guan, 2009). While several genomic polymorphisms have been thought to increase the risk of cisplatin-induced hearing loss (see below), none have yet been described to increase (or decrease) susceptibility to aminoglycoside-induced hearing loss, although several studies are underway.

Concomitant dosing with specific therapeutics synergistically enhances aminoglycoside ototoxicity and co-administration should be avoided whenever possible. These cotherapeutics include the loop diuretics in hypertensive individuals (Bates et al., 2002; Mathog & Klein, 1969; Rybak, 1993), and vancomycin, a glycopeptide antibiotic commonly prescribed in the neonatal intensive care unit (Brummett et al., 1990; Rubin et al., 2002). Loop diuretics co-administered with neuromuscular blocking agents (e.g., pancuronium bromide or vecuronium bromide) for patients requiring respiratory assistance (via intubation and ventilation) or surgical procedures that also induce cochleotoxicity (Cheung et al., 1999; Masumoto et al., 2007).

Since the late 1960s and 1970s, loud sound exposures have been known to readily enhance aminoglycoside-induced hearing loss (Brown et al., 1978; Darrouzet, 1963; Gannon & Tso, 1969; Gannon et al., 1979; Vernon et al., 1978). Subototoxic dosing of aminoglycosides becomes ototoxic in the presence of noise that is greater than either insult alone (Collins, 1988). Loud sound exposures up to 2 months prior to aminoglycoside dosing appears to enhance the ototoxicity observed compared with aminoglycoside exposure alone. However, if noise exposure occurs 4 weeks (or more) after aminoglycoside dosing, little or no ototoxic synergy is present. Noise exposure within 3 weeks after aminoglycoside will increase ototoxicity, although with decreasing severity over time compared with simultaneous noise plus aminoglycoside exposure (Ryan & Bone, 1978, 1982). These data will be relevant to those operating in noisy conditions where there is an increased risk of injury and/or infection subsequent to exposure that may require pharmacotherapy with aminoglycosides (e.g., surgery and burns).

**Exacerbation of Cisplatin-Induced Cochleotoxicity**

Experimentally induced sepsis (via LPS) also potentiates the degree of cisplatin-induced hearing loss in mice (Oh et al., 2011). LPS-induced inflammation in subjects treated with cisplatin occurs when the gastrointestinal tract is irradiated, killing commensal bacteria that then increase blood levels of LPS (Paulos et al., 2007). LPS typically binds to Toll-like receptor 4 (TLR4) that also recognizes endogenous damage-associated molecular patterns including DNA, heat shock proteins, and immunogens from injured cells to induce a sterile inflammatory response (Bhattacharyya et al., 2017; Oblak & Jerala, 2011) that can enhance the ototoxicity of cisplatin or other ototoxic chemotherapeutics. Other risk factors that enhance the ototoxicity of cisplatin include those that potentiate aminoglycoside-induced ototoxicity, including renal insufficiency and dehydrogenase (Gandara et al., 1991), malnutrition that depletes antioxidant levels (Lautermann et al., 1997; Lautermann, Song, et al., 1995), and the use of blood–brain barrier disruption protocols that also disrupt the BLB (Neuwelt et al., 1996). Specific genomic mutations may predispose individuals to cisplatin-induced hearing loss, including gene variants for DNA adduct repair enzymes like ERCC2 and XPC (Caronia et al., 2009; Turan et al., 2019); antioxidant enzymes; and drug efflux or membrane pumps ABCC3, COMT, and TPMT (Ross et al., 2009; Xu et al., 2015).

However, the predictive value in identifying these genomic variants in predisposing individuals for cisplatin-induced ototoxicity is currently poor (Langer et al., 2020; Tserga et al., 2019). Enhanced cisplatin-induced hearing loss also occurs when co-administered with ototoxic therapeutics, including aminoglycosides, loop diuretics, and cranial radiation (Clemens et al., 2016; McAlpine & Johnstone, 1990; Miller et al., 2009; Paulino et al., 2010). Although conflicting data can also be found in the literature, there are many differences in experimental design and treatment that could mitigate against these outcomes. Prior or low dosing with cisplatin (preconditioning) can synergize with subsequent cisplatin dosing to enhance ototoxicity (Harrison et al., 2015). Cisplatin dosing in rats during inactive hours (i.e., daytime) is also associated with greater hearing loss (Bielefeld et al., 2018). Noise exposure also increases cisplatin-induced hearing loss (Bokemeyer et al., 1998; Gratton & Kamen, 1990; Gratton et al., 1990; Laurell, 1992).

An additional phenomenon that exacerbates preexisting hearing loss has been identified in patients treated with cisplatin. Those with existing hearing loss at higher frequencies prior to treatment are more likely to experience hearing loss at lower frequencies that extend into the conventional hearing range and important for speech discrimination (Dille et al., 2012), affecting their ability to hear posttreatment compared with pretreatment baselines. The development of...
predictive ototoxicity modeling can enable pretreatment counseling to prepare for rehabilitating iatrogenic hearing loss (Deutsch et al., 2021; Dille et al., 2012).

**Gaps in the Current Ototoxicity Knowledge Base**

While the identity of several predisposing factors like aging, renal insufficiency, inflammation, genetic variants, or co-therapeutics are known to enhance the risk of ototoxicity, their interaction with each ototoxin is rarely well characterized, especially in human populations. The prevalence and incidence of these predisposing factors remain to be determined clinically, and this is typically complicated by the variability of each subject’s medical history in a clinical population. These individual interactions with each ototoxin can also affect the impact of other predisposing factors and pose an overwhelming challenge to better predict the ototoxic impact of prescribed aminoglycosides and cisplatin, although innovative studies now provide a framework to incorporate additional data points particularly for cisplatin-induced hearing loss (Deutsch et al., 2021; Dille et al., 2012; Hong et al., 2020; Konrad-Martin et al., 2010, 2014; Zhou et al., 2014). To enable better prediction of the risk of ototoxicity, much progress must first be made in better characterizing the key data points for individual medical settings that influence the risk of ototoxicity. Examples of key questions that need answers include the following.

1. Which molecular mechanisms enable ototoxins to cross the BLB and enter/traverse cochlear cells before entering hair cells?
2. What are the multiple molecular mechanisms of cytotoxicity for each ototoxin?
3. Which factors potentiate ototoxin trafficking, cellular entry, and cytotoxicity during inflammation?
4. What is the threshold for key inflammatory biomarkers to be associated with enhanced drug trafficking across the BLB and inflammation-enhanced drug-induced cochleotoxicity or vestibulotoxicity?
5. Are these biomarkers the same for inflammatory responses arising from different etiologies (i.e., bacterial, viral, drug-induced, and tumor- or radiation-derived inflammation)?
6. Are inflammatory responses from different etiologies (e.g., Gram-positive or Gram-negative bacterial species, and viral) equally potent in driving inflammation-enhanced ototoxicity?

These questions can also be rephrased by replacing inflammation with any exacerbating factor. The identification of prognostic, genomic, or diagnostic biomarkers of cochlear damage is an area of intense focus (Landegger et al., 2019; Lassaletta et al., 2019; Schmitt et al., 2018). It will be important for systemic biomarkers (i.e., molecular assays) or noninvasive functional (auditory or vestibular) assessments to efficaciously predict the risk of ototoxicity, especially with the growing list of predisposing factors interacting with the ototoxins. The identification of these biomarkers will require better characterization of these predisposing factors in preclinical models that then must be validated in human studies to be used clinically. Thus, much research lies ahead to provide new insights into iatrogenic ototoxicity. This research will ultimately lead to the identification of druggable targets to preserve or restore hearing during/after iatrogenic ototoxicity. Furthermore, otoprotectants must also efficaciously preserve or restore hearing and/or vestibular function in medical settings that include inflammation, exposure to other ototoxic agents including renal insufficiency, aging, and/or noise.

Finally, additional insights into cochleotoxicity and vestibulotoxicity will come from widespread ototoxicity monitoring, improved objective, data-driven measures of hearing loss (rather than blunt categories of relative hearing deficits), and widespread adoption of extended higher frequency audiometry, potentially via use of tablet-based audiometers.

**Brief Resume for Peter Steyger**

At 3 years old, Peter Steyger attended The University of Manchester, United Kingdom, to learn to listen and speak following drug-induced hearing loss acquired as a consequence of aminoglycoside treatment for bacterial meningitis. He subsequently obtained a bachelor’s degree in Zoology at The University of Manchester in 1984, followed by a PhD degree in Communications and Neuroscience at Keele University, United Kingdom. After postdoctoral training in vestibular neurosciences in San Antonio, Texas, and the Neurological Sciences Institute in Portland, Oregon, Peter joined the Oregon Hearing Research Center at Oregon Health & Science University in 1997 and rose through the professorial ranks. In June 2019, he moved to Creighton University School of Medicine to become the inaugural director of the Translational Hearing Center in the Department of Biomedical Sciences chaired by Dr. Jian Zuo. He has published more than 70 peer-reviewed original research articles and topic reviews. He has two current R01 awards that focus on (a) identifying mechanisms of aminoglycoside-induced ototoxicity and (b) translating that gained knowledge to clinical populations that may lead to refined clinical care guidelines to better ameliorate or prevent the degree of lifelong drug-induced hearing loss (cochleotoxicity).

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