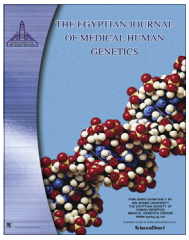
The Egyptian Journal of Medical Human Genetics (2016) 17, 287–293

HOSTED BY

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com



REVIEW

Aminoglycoside induced ototoxicity associated with mitochondrial DNA mutations

Joseph Foster II, Mustafa Tekin *

Dr. John T. Macdonald Foundation Department of Human Genetics and John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA

Received 20 October 2015; accepted 5 June 2016
Available online 16 June 2016

KEYWORDS

Aminoglycosides;
Genetics;
Mitochondrial mutation;
Ototoxicity

Abstract Despite the risk of permanent ototoxic effects, aminoglycosides remain commonly utilized antibiotics worldwide due to low cost and efficiency in treating severe infections. Over the last two decades, mitochondrial mutations have been shown to enhance the likelihood of ototoxic injury. In particular the 1555A > G mutation in the mitochondrial gene *MTRNR1* has been strongly associated with the onset of aminoglycoside-induced deafness; though pinning down the exact mechanism of action has thus far been elusive. Clinically aminoglycoside-induced deafness has been characterized by variation in the degree of hearing loss, which has prompted an investigation into genetic modifiers. To date, several putative mutations have been categorized as contributing factors to the onset of deafness with no single variation being sufficient to bring about hearing loss. Meanwhile current methods to mitigate the risk of ototoxic injury are in various stages of development. Efforts to alter the molecular structure of aminoglycosides have shown a potential path to reducing ototoxicity while preserving antibacterial properties, but these drugs are not clinically available. On the other hand, application of preemptive audiometry provides the most readily available method to both monitor and reduce the extent of aminoglycoside-induced deafness.

Contents

* Corresponding author at: 1501 NW 10th Avenue, BRB-610 (M-860), Miami, FL 33136, USA. Tel.: +1 305 243 2381.
E-mail address: mtekin@miami.edu (M. Tekin).
Peer review under responsibility of Ain Shams University.

http://dx.doi.org/10.1016/j.ejmhg.2016.06.001

1. Introduction

Hereditary hearing loss is the most common sensory problem, affecting 1 and 1000 newborns [1]. While around half of congenital deafness is explained genetically, hearing loss has also been linked to environmental factors such as *in utero* contraction of cytomegalovirus and antibiotics [2]. Originally developed in the 1940's aminoglycosides (AG) have been effective in treating gram-negative bacterial infections [3]. Unfortunately though, systemic administration of AGs can lead to both nephrotoxicity and ototoxicity [4,5]. In populations where AGs were commonly prescribed familial inheritance of ototoxicity became evident. Matrilineal inheritance of aminoglycoside-induced deafness (AID) was a defining characteristic in several of these families, which suggested mitochondrial involvement [6].

Currently the genetic mutations most strongly associated with AID are 1555A > G and 1494C > T in the mitochondrial gene *MTRNR1*, which codes for the mitochondrial 12S ribosomal subunit [7,8]. These mitochondrial positions map to the corresponding 1409–1491 base pairing in bacteria, which are the AG binding sites on the 16S ribosome subunit [9]. Several additional variations in mitochondrial tRNA genes have been associated with AID and non-syndromic hearing loss [10–12], though biochemical analysis of these variations suggests many are not sufficient to generate the hearing loss phenotype. While the effect of systemic AG administration in individuals carrying a mitochondrial tRNA gene mutation is not well established, it is clear that genetic defects in the mitochondrial *MTRNR1* gene at positions 1555 and 1494 facilitate AG-induced deafness [13].

Modifiers in the nuclear genome may provide an explanation for familial cases of non-syndromic deafness involving the 1555A > G mitochondrial mutation and absence of AG treatment. The nuclear gene *TRMU* has been identified as one such modifier, as a missense mutation in *TRMU* was shown to compromise tRNA metabolism. Reduction of tRNA metabolism in combination with the reduction of accurate protein synthesis caused by the 1555A > G mutation may be sufficient to cause the hearing loss phenotype, though this is yet to be fully elucidated [14].

As AGs continue to be prescribed to treat common infections around the world, reducing or removing the potential for ototoxicity holds significant clinical value. While concomitant treatment of AGs and antioxidants yields moderate protective properties, recent research on structurally unique AGs shows promise in reducing ototoxicity [15–18]. Increasing the size of AGs prohibits entry to the cytosol of cochlear hair cells while maintaining its potent antibacterial properties. As the physical properties of the cationic channels of hair cells are further characterized, these data may lead to improvements in AG alteration, potentially removing the concern of ototoxicity.

2. Mechanism of aminoglycoside ototoxicity

Localization of aminoglycosides to hair cells begins by crossing the blood-endolymph barrier [19]. Once in the endolymph AGs transverse the apical membrane of hair cells via the mechanoelectrical transducer (MET) channel or other cationic channels [20–23]. AG entrance through the MET channel was initially proposed after the detection of AGs at the tip of the stereocilia prior to observing AG in the cytosol of hair cells [24]. Further investigation revealed the opening of the channel measures 1.25 nm in diameter which is sufficient for the passage of AGs [25]. Alharazneh et al. has also shown that AGs reduce the transduction current pointing to the involvement of the MET channel [21]. Moreover, various concomitant factors have been shown to potentiate AID. Noise induces the open state of the MET channel leading to an increased concentration of AGs in the hair cell cytosol [26]. Hirose et al. reports the combined administration of aminoglycosides with loop diuretics exacerbates ototoxic injury in mice when compared with controls and mice injected only with aminoglycosides [27]. Cochlear uptake of aminoglycosides is also increased by endotoxemia-induced inflammation [28]. The unidirectional MET channel compounds the effect of these additional potentiating factors, as AGs are unable to move back to the endolymph leading to higher concentration in the hair cell cytosol [23].

Once in hair cell cytosol AGs interact with mitochondrial 12S ribosomal subunit causing inaccurate translation of mitochondrial proteins. The downstream implication of faulty protein synthesis is eventual cell death either through caspase-mediated or non-caspase-mediated apoptosis [22]. Additionally, AG interaction with iron species has been shown to produce reactive oxygen species (ROS), which also leads to cell death through apoptosis [29]. Previous *in vitro* experiments have shown an alteration in antioxidant defense system in melanocytes induced by aminoglycosides, which may be an additional contributing factor in the onset of ototoxicity [30]. Rizzi et al. has also shown a clear progression of hair cell death originating at the basal turn and moving toward apical turn of the cochlea [31]. This progression moves in line with the onset of deafness, as high frequency loss is observed before the loss of lower frequencies.

3. Increased susceptibility to aminoglycoside ototoxicity due to mitochondrial mutations

The baseline incidence of cochleotoxic effects following the administration of systemic AGs has previously been reported between 2% and 25%, and has been known to fluctuate depending on the drug administered [31,32]. Amikacin, Gentamicin, and Tobramycin produce ototoxic effects at a rate of 5%, 8%, and 14% respectively [32]. The incidence of AID increases to 17–33% in cases involving genetic variations [22]. In particular the 1555A > G and 1494C > T mutations in the *MTRNR1* gene have been shown to facilitate the binding of AGs to the 12S ribosomal subunit [13].

Prezant et al. initially sequenced the mitochondrial genome in three families with maternally inherited AID revealing the 1555A > G variation in the mitochondrial *MTRNR1* gene [7]. Over the last two decades 1555A > G has been identified as