Antibiotics 2018: Aminoglycoside antibiotics and hearing loss - Maria Rosa Chaig - Universidad Nacional de Cordoba

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Among potentially ototoxic therapeutics, the aminoglycoside antibiotics are of critical clinical importance. They cause sensorineural hearing loss in patients, a side effect that can be reproduced in experimental animals. Hearing loss is primarily in damage to outer hair cells, beginning in the basal turn of the cochlea. In addition, aminoglycosides might affect the vestibular system. Mitochondrial DNA (mtDNA) mutations have been found to be associated with sensorineural hearing loss. As part of genetic screening program for hearing loss, we studied 40 patients with sensorineural deafness, whose cause might have been after aminoglycoside (ATB-AG), treatment. The affected and control subject's DNA fragments spanning the 12S rRNA gene or tRNASer(UCN) gene, that are associated with both aminoglycoside-induced and non-Syndromic hearing loss, were amplified and studied by PCR-RFLP. Homoplasmic 7444G> A mutation in three families have the in the tRNAser (UCN) gene, the analysis of the mitochondrial genome in three family members did not detect any other pathology mutation.

The clinical history shows one syndromic phenotype for matrilineal family. In the first family the muscle biopsy findings in the proband (III-5) and her mother (II5), show in the electronic microscopy (EM) and in the light microscopy (LM) multiple mitochondrial abnormalities in the striated muscle. These findings have been correlated with the values from Citocromo Oxidase/Citrate Synthase ratio, which indicated poor activity of the Citocromo Oxidase. The matrilineal pedigree clinical feature, and the molecular, biochemical and morphological studies, might indicate that this is a novel syndromic presentation of the 7444G>A mutation in Córdoba - Argentina. In the fourth family, the report of the clinical, genetic, and molecular characterization in two of their members, revealed the variable phenotype of hearing impairment including audiometric configuration. mtDNA mutation Anlysis in these pedigrees showed the presence of non syndromic homoplasmic 12S rRNA A827G mutation, which has been associated with hearing impairment. The A827G mutation is located at the A-site of mitochondrial 12S rRNA gene which is highly conserved in mammals.

Aminoglycosides, likewise, promote the formation of ROS, albeit not necessarily the same species and by the same reactions. ROS and their reaction products have been observed in explanted tissues as well as in vivo and both non-enzymatic and enzymatic mechanisms have been suggested for their generation.

Gentamicin may act as an iron-chelator, forming a redox-active complex by stabilizing iron intermediates and thereby reducing molecular oxygen to superoxide radicals using electrons provided by available polyunsaturated fatty acids.
ROS may also be generated by enzymatic pathways, akin to the stimulation of NADPH by cisplatin. Aminoglycosides affect signaling pathways linked to Rho-GTPases, which in turn may lead to activation of the NADPH oxidase complex. Mitochondrial dysfunction had also been speculated as an element in aminoglycoside ototoxicity, based on the A1555G mitochondrial mutation that conveys hyper susceptibility. A recent study now demonstrates that apramycin, a structurally unique aminoglycoside used in veterinary medicine, shows little activity toward eukaryotic ribosomes, even toward hybrid ribosomes genetically engineered to carry the mitochondrial A1555G allele. The drug, despite being a potent antibacterial, causes only little ROS formation and hair cell damage in cochlear explants and much less hearing loss in guinea pigs in vivo than other aminoglycosides.

These data strongly support the idea that mitochondrial dysfunction migh Aminoglycosides, in like manner, advance the development of ROS, but not really similar species and by similar responses. ROS and their response items have been seen in explanted tissues just as in vivo and both non-enzymatic and enzymatic systems have been recommended for their age. Gentamicin may go about as an iron-chelator, framing a redox-dynamic complex by balancing out iron intermediates and along these lines lessening atomic oxygen to superoxide radicals utilizing electrons gave by accessible polyunsaturated unsaturated fats. ROS may likewise be produced by enzymatic pathways, likened to the incitement of NADPH by cisplatin. Aminoglycosides influence flagging pathways connected to Rho-GTPases, which thusly may prompt enactment of the NADPH oxidase complex. Mitochondrial brokenness had likewise been hypothesized as a component in aminoglycoside ototoxicity, in view of the A1555G mitochondrial change that passes on hyper defenselessness. An ongoing report currently exhibits that apramycin, a basically extraordinary aminoglycoside utilized in veterinary medication, shows little action toward eukaryotic ribosomes, even toward cross breed ribosomes hereditarily built to convey the mitochondrial A1555G allele. The medication, in spite of being a powerful antibacterial, causes just little ROS arrangement and hair cell harm in cochlear explants and significantly less hearing misfortune in guinea pigs in vivo than different aminoglycosides.

This information emphatically bolster the possibility that mitochondrial brokenness may be connected to over the top arrangement of ROS and ototoxicity. Besides, the separation of antibacterial movement and ototoxicity may give a novel system to the advancement of less harmful aminoglycosides. Furthermore, the dissociation of antibacterial activity and ototoxicity may provide a novel framework for the development of less toxic aminoglycosides.

The alteration of the tertiary or quaternary structure of this rRNA by the A827G mutation may lead to mitochondrial dysfunction, thereby playing a role in the pathogenesis of hearing loss and aminoglycoside hypersensitivity may be possible. Although the 827A> G mutation in the 12S rRNA, is associated with haplogroup B, its prevalence ≥ 2%, does not eliminate its participation and association to ototoxicity by ATB-AG. In addition, it is necessary to know more about the mechanism by which ATB-AG induces hearing loss, in the presence of the 7444 G>A mutation in the tRNAser (UNC).