8. MOLECULAR ASPECTS OF AMINOGLYCOSIDE OTOTOXICITY

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Introduction. Aminoglycosides are a class of antibiotics widely used in pediatric clinical practice due to their effectiveness against gram-negative bacterial infections. Despite this, they are known to have cochleotoxicity and vestibulotoxicity, which can occur as tinnitus and/or sensorineural hearing loss or vertigo, nausea, nystagmus, ataxia.

Aim of study. A wide range of 2% to 57% of the neonates treated with aminoglycosides develop bilateral profound hearing loss in a dose-dependent manner, aminoglycoside type, genetic constitution of the patient and the physiology of the renal system.

Methods and materials. Utilizing the repositories of Medline, PubMed, Google Scholar, a comprehensive review of the literature was made to find actual and relatable papers on "aminoglycoside ototoxicity ".

Results. The mechanism of aminoglycoside-induced ototoxicity is complex and involves changes in the outer hair cells, perilymph and neural pathways. Firstly, the drugs entering the cells disrupt ionic homeostasis, whereas inside the cell they inhibit voltage gated K+channels, causing a prolonged depolarization and apoptosis. Secondly, due to bacterial lysis with releasing proapoptotic factors and oxidative enzymes inside the cells are generated reactive oxygen species with endoplasmatic reticulum stress and mitochondrial Ca2+ influx. Aminoglycosides are also ribotoxic, by binding to cytosolic Rrna and blocking protein synthesis. Moreover, in the perilymph aminoglycosides block the postsynaptic nicotinic-like cholinergic receptors interrupting the olivocochlear reflex. In addition, there are risk factors for developing aminoglycoside-induced hearing loss: prematurity, renal impairment, local inflammation, poor nutritional state, circadian time of daily administration, co-medication with cisplatin, noise exposure, prolonged therapy regimens, severe inflammatory response syndrome, and genetic susceptibility. Septic conditions lead to systemic accumulation of lipopolysaccharides and activation of toll-like receptor 4 which upregulate cochlear expression of aminoglycoside-permanent channels. Mutations in the mitochondrial 12S rRNA MT-RNR1 gene: 1555A>G, 1494C>T, m.1095T>C result in higher affinity of aminoglycosides to outer hair cells and influence codon interaction, compromise mitochondrial protein synthesis and reduce by 30% mitochondrial ATP synthesis. 100% of the patients carrying named mutations develop moderate to profound, bilateral, irreversible, one dose-dependent hearing loss.

Conclusion. Aminoglycosides ototoxicity remains a high-priority challenge. By studying the molecular basis, we can gain a better understanding of how it happens and what factors increase the risk. Since no therapy is currently available to reverse the ototoxic damage, the focus is on developing targeted otoprotective drugs and setting up a genetic testing policy in families with acquired deafness history.