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INHIBITION OF NFAT IN COMBINATION WITH ANTIOXIDANTS PROVIDES AUDITORY HAIR CELL PROTECTION FROM AMINOGLYCOSIDE TOXICITY

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Aminoglycosides generate free radicals within the inner ear, resulting in permanent damage to sensory cells and neurons, followed by hearing loss. Decreasing aminoglycoside-induced reactive oxygen species (ROS) production was shown to be beneficial. Based on author's previous study, preventing nuclear factor of activated T cells (NFAT) nuclear accumulation preserves auditory hair cells from gentamicin toxicity. They addressed hair cell protection from two angles by using NFAT inhibitor 11R-VIVIT and one of the well-described antioxidants L-carnitine (LCAR) or N-acetylcysteine (NAC). Organs of Corti (OCs) from 5-day old mice were exposed to gentamicin +/- 11R-VIVIT, NAC or LCAR *in vitro*, followed by phalloidin based detection and counting of hair cells. Combined treatment with 11R-VIVIT and LCAR in the presence of gentamicin resulted in higher protection compared to single component culture treatment. 11R-VIVIT combined with NAC provided practically full protection (>98%) of the hair cells compared to single component treatment in the presence of gentamicin. Relative gene expression determined by qPCR revealed decrease in Casp9 after exposure to 11R-VIVIT and increase Hmox1 after exposure to NAC, compared to gentamicin treated OC cultures. In a caspase assay, combination of 11R-VIVIT and LCAR when compared to single component treatments was shown to be less effective in decreasing apoptotic signals than the 11R-VIVIT combined with NAC. Similar results were observed on heme oxygenase-1 western blot signals, where NAC combination showed to be more effective than LCAR. Selective NFAT inhibition by 11R-VIVIT appears to be a good strategy in preventing hair cell damage caused by gentamicin. L-carnitine and N-acetylcysteine with their ROS reducing properties could contribute to the observed synergistic effectiveness with 11R-VIVIT through decrease of ROS induced NFAT translocation. Our data suggest that combined approach of NFAT inhibition together with the presence of antioxidant like N-acetylcysteine could be promising in the treatment and/or prevention of hearing loss.



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