Transient cochlear ischemia enhances antibiotic ototoxicity

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Aminoglycoside ototoxicity is a common cause of drug-induced hearing loss. Toxicity is dose-related, but some patients may still develop hearing loss even under safe dosage. Apart for genetic idiosyncrasy, indirect evidences imply that ischemia may increase the aminoglycoside ototoxic sensitivity because common clinical situations associated with cochlear ischemia such as noise, sepsis, shock are known to augment the development of aminoglycoside ototoxicity. At present a direct interaction of cochlear ischemia and aminoglycoside ototoxicity is still lacking. This study demonstrated a direct evidence of increased gentamicin ototoxic sensitivity in chronic guinea pig models of transient cochlear ischemia. No permanent auditory changes were observed after single dose of gentamicin (125mg/kg) or after transient cochlear ischemia for 30 min. Cochlear hair cells and spiral ganglion neurons are the major regions affected. Apoptosis contributes to hair cell death during acute interaction of ischemia and gentamicin ototoxicity. Increased apoptotic cell death also was depicted when gentamicin cross-reacted with hypoxia *in vitro*, using cochlear cell lines. Generation of reactive oxygen species, loss of mitochondrial membrane potential, calcium release and caspase-dependent apoptotic cell death were shown during the interaction of hypoxia and gentamicin ototoxicity *in vitro*. This synergistic ototoxicity may be critical to aminoglycoside-induced hearing loss in clinical scenarios. Results should improve our understanding of the interacting mechanism and potential preventive strategy to aminoglycoside ototoxicity.

Keywords: ischemia, hypoxia, aminoglycoside, ototoxicity