Elucidation of ROS effects on auditory transmission impairment

Lin Chen, Hiroaki Mouri, Naoaki Saito, Takehiko Ueyama

Biosignal Research Center., Kobe Univ

【BACKGROUND】The NADPH oxidase (NOX) family consists of seven enzymes that produce reactive oxygen species (ROS). NOX4 is expressed in various cells and tissues, and functions in many signaling pathways. ROS reportedly contributes to the development of several types of sensorineural hearing loss, such as age-related, drug-induced, and noise induced hearing loss. Cisplatin (CDDP) is a platinum-based anti-cancer drug. It is well known as the side effect on hearing via damaging outer hair cells (OHCs), spiral ganglion neurons, and the stria vascularis. We have reported transgenic mice of NOX4 (NOX4-TG) that overproduce ROS without phenotypes in hearing loss under baseline conditions; however, they show hearing function vulnerability after noise exposure.【PURPOSE】In the present study using NOX4-TG mice, we examined the effects of ROS on the ribbon synapse, which is a neuronal synaptic structure localized at the pre-synaptic zone of cochlear HCs (both inner HCs (IHCs) and OHCs), and OHC loss in aging (from 1 to 12 month old mice) and in CDDP treatment (2 month old mice).【RESULTS】In DNA microarray obtained from P6 cochleae, we found cochleae in NOX4-TG mice showed lower mRNA levels of ribbon synapse constituent proteins than those in WT mice. Furthermore, the number of ribbon synapses immunostained by CtBP2 in IHCs was decreased with age compared to age-matched WT mice. After CDDP treatment, the decreased number of ribbon synapses and the number of OHC loss in the basal turn of cochleae were larger in NOX4-TG mice compared to WT mice.【SUMMARY】This study showed that ROS accumulated by aging and CDDP treatment induced decreased number of ribbon synapses in IHCs, that is synaptopathy, and OHC loss. These results suggest that impairment in ribbon synapses induced by ROS may be a preceding pathology before HC loss.