G6PD Overexpression Protects from Oxidative Stress and Retard Age-related Hearing Loss Progression

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Ageing of the auditory system is associated with the incremental production of reactive oxygen species (ROS) and the accumulation of oxidative-derived damage in macromolecules, which contribute to cellular malfunction, compromise cell viability and, finally, causes functional decline. The cellular detoxi¿cation power partially relies in NADPH production, which is a cofactor for major cellular antioxidant enzymes. NADPH is mainly produced by glucose-6-phosphate dehydrogenase (G6PD), an enzyme that catalyzes the rate-limiting step in the pentose phosphate pathway. We show here that the transgenic mouse G6PD-Tg, which shows enhanced NADPH production along life, maintains lower auditory thresholds than wild type mice during ageing. G6PD overexpression preserved inner (IHC) and outer hair cells (OHC), OHC innervation and number of synapses per IHC. Transcripts for antioxidant enzymes were increased whereas levels of pro-apoptotic proteins were reduced in 3-month-old G6PD-Tg. Consequently, nitration of proteins, mitochondrial damage and TUNEL+ apoptotic cells were reduced in 9-month-old G6PDTg compared to wild type mice. Unexpectedly, G6PD overexpression triggered low grade inÀammation that was effectively resolved in young mice, as shown by the absence of cochlear cellular damage and macrophages in¿ltration. In conclusion, we propose here that NADPH overproduction from an early stage is an ef¿cient mechanism to maintain the balance between the generation of ROS and the cell detoxi¿cation power along ageing and, therefore to prevent hearing loss progression.

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