Alterations in outer hair cell and auditory neuron in aged mouse models with a hearing phenotype akin to humans

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Age-related hearing loss (ARHL), also known as presbycusis, is prevalent in mammalian aging and is the most common sensory disorder in the elderly and as such, is a major social and health challenge. Currently, there is no treatment for ARHL. One of the problems is that auditory neurons do not regenerate in mammals, and the loss of these long-lived neurons leads to permanent hearing impairment. We investigated auditory neuron structure and function in aged CBA/CaJ mice, whose age of onset of ARHL has been evaluated and is comparable to an equivalent human age. We discovered systematic and profound changes in hair cells and auditory neuron structure and functions.

We investigated mitochondrial structure and function in aged OHCs using three-dimensional electron microscopy (3DEM) supported by key functional assays in CBA/CaJ mice. We found that aging increased the auditory brainstem response (ABR) and distortion product otoacoustic emissions (DPOAE) thresholds indicating OHC malfunction, which correlated to clear-cut pathology. We discovered that mitochondria were depolarized in 24-month OHCs and had altered size and number, which led us to determine that the number of dynamin-related protein (Drp1) RNA molecules (mitochondrial fission), but not optic atrophy 1 (Opa1) RNA molecules (mitochondrial fusion) was significantly reduced in old compared to young OHCs indicating a down-regularization of mitochondrial fission. Interesting, mitochondria were found to be tethered to the subsurface cisternae (SSC) by short, thin filaments and both cristae and crista junctions were polarized towards the SSC at all ages. The crista and crista junction densities were lower, yet the crista junction polarization had increased in aged mitochondria. These findings suggest that mitochondria close to the SSC may calibrate their ATP-generating capacity by efficiently sensing increased calcium levels due to their cristae and crista junction polarization. SSC stress and lowered modeled mitochondrial energy production in aged OHCs may contribute to functional cellular stress and the observed death of OHCs in CBA/CaJ mice. Additionally, there were profound changes in auditory neuron myelination and functional properties along the tonotopic axis of the cochlea. We will describe in detail, the morphological and functional changes in auditory neurons, and propose functional alterations that may retard the progression of ARHL.

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