Mechanisms Underlying Presbycusis: Age-Related Changes of Na, K-ATPase in the Cochlear Stria Vascularis

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The endocochlear potential (EP) is critical for normal hearing and its dysfunction has been implicated in a number of types of hearing loss and deafness. Na, K-ATPase is one of the key ion channels responsible for generating the EP and is composed of four α subunits and three β subunits. It is not clear that whether alteration of subunit isoforms in the cochlear lateral wall could contribute to age-related hearing loss or deafness since this phenomenon has not been previously investigated. The present report aimed to examine subunit alterations with age in the mouse cochlear lateral wall. To avoid inconsistent and non-specific detection (for example, relying only on immunohistochemistry method or gene expression detection alone) we combined real time reverse transcriptase polymerase chain reaction (RT-PCR), western blot and immunocytochemistry methodologies. Out of 7 subunit isoforms, only significant expression levels of α1, β1 and β2 subunit isoforms were detected in the lateral wall in CBA/CaJ mice. Immunoprecipitation assays showed that the α1-β1 heterodimer is the selective preferential heterodimer over the α1-β2 subunit isoform heterodimer. Interestingly, in vitro pathway studies utilizing cultured SV-K1 cells (cochlear marginal cells, SV), indicated that no change was found in mRNA and protein expression levels of the α1, β2 and β3 subunit isoforms under Na,K-ATPase activity inhibition (induced by ouabain), but this inhibition did disrupt the α1-β1 heterodimer interaction. Secondly, the association between the α1 and β1 subunit isoforms was present in the cochlea of young adult mice, but this interaction could not be detected in the old mice. Our preliminary data showed that the inhibition of Na, K-ATPase activity leads to down-regulation of stability in the α1 subunit with decreased activity of Na, K-ATPase in the SV-K1 cell line. In addition, we also found that Na, K-ATPase activity is lower in the lateral wall of old mice (31 month) compared to young adult mice (3 month). Taken together with previous report of no protein and mRNA expression changes under the treatment of Na, K-ATPase activity inhibitor ouabain in vitro, these data suggest that protein stability related Na,K-ATPase activity may contribute to a specific, functionally-selective assembly of Na, K-ATPase subunit isoforms in SV, which is disrupted and down-regulated with age; and this alteration may play a role in regulation of the function of SV in the aged cochlear. Prevention of this age-linked ion channel disruption could be part of a biotherapeutic intervention to treat hearing loss.

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