学位論文抄録

Hearing impairment in *SMS1* deficient mice
(*SMS1*欠損マウスにおける難聴)

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Abstract of the Thesis

Background and Purpose: Sphingomyelin (SM) is a sphingolipid reported to function as a structural component of plasma membranes and to participate in signal transduction. The role of SM metabolism in the process of hearing remains controversial. Here, we examined the role of SM synthase (SMS), which is subcategorized into the family members SMS1 and SMS2, in auditory function.

Methods: Both SMS1 and SMS2 knockout mice were used in the study. We first assessed the hearing ability using an association learning paradigm and measurements of the auditory brainstem response. To investigate the cochlear function, we first examined the endocochlear potentials (EPs) and endolymph K^+ concentration, and then distortion product otoacoustic emissions (DPOAE). Next we made cochlear sections to examine the structure of the stria vascularis (SV), and further performed and F-actin staining to visualize the marginal cells and outer hair cells in a flat-mount preparation. For evaluating pigmentations in the SV, brightfield images of flat-mount SV were also acquired. Finally, the expression of KCNQ1 on marginal cells was examined by fluorescent immunostaining and western blotting.

Results: We found that the hearing ability of *SMS1*$^{-/-}$ mice was impaired at low frequency range. As a possible mechanism for this impairment, we found that the SV in these mice exhibited atrophy and had disorganized marginal cells. Consequently, *SMS1*$^{-/-}$ mice exhibited significantly smaller EPs. As a possible mechanism for EP reduction, we observed altered expression patterns and a reduced level of KCNQ1 protein in the SV of *SMS1*$^{-/-}$ mice. These mice also exhibited reduced levels of DPOAE. Quantitative comparison of the SV atrophy, KCNQ1 expression, and outer hair cell density at the cochlear apical and basal turns revealed no location-dependence. But more macrophage invasion into SV was observed in the apical region than the basal region, suggesting a role of cochlear location-dependent oxidative stress in producing the frequency-dependence of hearing loss in *SMS1*$^{-/-}$ mice. Elevated ABR thresholds, decreased EPs, and abnormal KCNQ1 expression patterns in *SMS1*$^{-/-}$ mice were all found to be progressive with age. Mice lacking SMS2, however, showed neither detectable hearing loss nor changes in their EPs.

Conclusions: our results suggest that hearing impairments occur in *SMS1*$^{-/-}$ mice, but not in *SMS2*$^{-/-}$ mice. Defects in the SV with subsequent reductions in EPs together with hair cell dysfunction may account, at least partially, for the hearing impairments in *SMS1*$^{-/-}$ mice.