論 文 要 旨

Reduced Autophagy in Aged Trigeminal Neurons Causes Amyloid β Diffusion

（ 老化した三叉神経細胞におけるオートファジーの減少が アミロイドβの拡散を引き起こす ）

園田　怜美

The relationship between oral health and the development of Alzheimer's disease (AD) in the elderly is not yet well understood. In this regard, the association between aging or neurodegeneration of the trigeminal nervous system and the accumulation of amyloid-β Aβ(1-42) $(Aβ)_{42}$ oligomers in the pathogenesis of Alzheimer's disease (AD) is unknown. We focused on selective autophagy in the trigeminal mesencephalic nucleus (Vmes) and the diffusion of $Aβ_{42}$ oligomers with respect to aging of the trigeminal nervous system, and whether the degeneration of Vmes neurons affects the diffusion of $Aβ_{42}$ oligomers. We used female 2–8-month-old transgenic 3×Tg-AD mice and App^{NL-G-F} knock-in mice, and immunohistochemically examined aging-related changes in selective autophagy and $Aβ_{42}$ oligomer processing in the trigeminal mesencephalic nucleus (Vmes), which exhibits high Aβ expression. We induced degeneration of Vmes neurons by extracting the maxillary molars and examined the changes in $Aβ_{42}$ oligomer kinetics. Autophagosome-like membranes, which stained positive for Aβ, HO-1, and LC3B, were observed in Vmes neurons of 3×Tg-AD mice, while there was weak immunoreactivity of the membranes for intra-neuronal Aβ in App^{NL-G-F} mice. By contrast, there was strong immunopositivity for extracellular $Aβ_{42}$ oligomers with the formation of $Aβ_{42}$ oligomer clusters in App^{NL-G-F} mice. The expression of Rubicon, which indicates age-related deterioration of autophagy, increased with the age of Vmes neurons. Tooth extraction increased the extracellular immunopositivity for $Aβ_{42}$ oligomers in App^{NL-G-F} mice. These results suggest that autophagy maintains homeostasis in Vmes neurons, and that deterioration of autophagy due to aging or neurodegeneration leads to the diffusion of $Aβ_{42}$ oligomers into the extracellular space and possibly the development of AD.