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学位論文の題名	Tooth Loss Induces Memory Impairment and Gliosis in App Knock-in Mouse Models of Alzheimer's disease （歯の喪失はアルツハイマー病モデルマウスである APP ノックインマウスで記憶障害とグリオーシスを誘発する） Journal of Alzheimer's Disease, 80(4):1687-1704, 2021
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Abstract

Background: Epidemiological studies have shown that tooth loss is associated with Alzheimer's disease (AD) and dementia. However, the molecular and cellular mechanisms by which tooth loss causes AD remain unclear.

Objective: We investigated the effects of tooth loss on memory impairment and AD pathogenesis in $App^{NL\text{-}G\text{-}F}$ mice.

Methods: Maxillary molar teeth on both sides were extracted from 2-month-old $App^{NL\text{-}G\text{-}F}$ mice, and the mice were reared for 2 months. The short- and long-term memory functions were evaluated using a novel object recognition test and a passive avoidance test. Amyloid plaques, amyloid-β (Aβ) levels, glial activity, and neuronal activity were evaluated by immunohistochemistry, Aβ ELISA, immunofluorescence staining, and Western blotting. The mRNA expression levels of neuroinflammatory cytokines were determined by qRT-PCR analysis.

Results: Tooth loss induced memory impairment via an amyloid-cascade-independent pathway, and decreased the neuronal activity, presynaptic and postsynaptic protein levels in both the cortex and hippocampus. Interestingly, we found that tooth loss induced glial activation, which in turn leads to the upregulation of the mRNA expression levels of the neuroinflammation cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1β in the hippocampus. We also found that tooth loss activated a stress-activated protein kinase, c-Jun N-terminal kinase (JNK) and increased heat shock protein 90 (HSP90) levels in the hippocampus, which may lead to a glial activation.

Conclusions: Our findings suggest that taking care of teeth is very important to preserve a healthy oral environment, which may reduce the risk of cognitive dysfunction.