Systemic Exposure to Lipopolysaccharide from Porphyromonas gingivalis Induces Bone Loss-Correlated Alzheimer's Disease-Like Pathologies in Middle-Aged Mice

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論 文 名　：Systemic Exposure to Lipopolysaccharide from *Porphyromonas gingivalis* Induces Bone Loss-Correlated Alzheimer's Disease-Like Pathologies in Middle-Aged Mice

（Middle-Aged マウスへの Porphyromonas gingivalis 由来リポポリサッカライドの全身投与は骨喪失を伴うアルツハイマー病様症状を引き起こす）

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論 文 内 容 の 要 旨

Background: Alzheimer's disease (AD) and bone loss are clinically exacerbated. However, the mechanism of exacerbation remains understood.
Objective: We tested our hypothesis that periodontitis is involved in the exacerbation, contributing to AD pathologies.
Methods: The bone, memory, and inflammation in bone and brain were examined in 12-month-old mice after systemic exposure to lipopolysaccharide from *Porphyromonas gingivalis* (*Pg*LPS) for 3 consecutive weeks.
Results: Compared with control mice, bone loss in tibia (26% decrease) and memory decline (47% decrease) were induced in mice with a positive correlation after exposure to *Pg*LPS ($r = 0.7378$, $p = 0.0011$). The IL-6 and IL-17 expression in tibia was negatively correlated with the bone volume/total tissue volume ($r = –0.6619$, $p = 0.0052$; $r = –0.7129$, $p = 0.0019$), while that in the cortex was negatively correlated with the memory test latency ($r = –0.7198$, $p = 0.0017$; $p = 0.0351$, $r = –0.5291$). Furthermore, the IL-17 expression in microglia was positively correlated with Aß42 accumulation in neurons ($r = 0.8635$, $p < 0.0001$). In cultured MG6 microglia, the *Pg*LPS-increased IL-6 expression was inhibited by a PI3K-specific inhibitor (68% decrease), and that of IL-17 was inhibited by IL-6 antibody (41% decrease). In cultured N2a neurons, conditioned medium from *Pg*LPS-stimulated microglia (MCM) but not *Pg*LPS increased the productions of AßPP, CatB, and Aß42, which were significantly inhibited by pre-treatment with IL-17 antibody (67%, 51%, and 41% decrease).
Conclusion: These findings demonstrated that chronic systemic exposure to *Pg*LPS simultaneously induces inflammation-dependent bone loss and AD-like pathologies by elevating IL-6 and IL-17 from middle age, suggesting that periodontal bacteria induce exacerbation of bone loss and memory decline, resulting in AD progression.

Keywords: Alzheimer's disease, amyloid-ß, bone loss, interleukin-6, interleukin-17,

lipopolysaccharide from *Porphyromonas gingivalis*, memory decline, microglia, systemic inflammation