

Lipopolysaccharides from *Porphyromonas gingivalis* indirectly induce neuronal GSK3 β -dependent synaptic defects and cause cognitive decline in a low-A β -concentration environment in Alzheimer's disease

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論 文 名 : Lipopolysaccharides from *Porphyromonas gingivalis* indirectly induce neuronal GSK3 β -dependent synaptic defects and cause cognitive decline in a low-A β -concentration environment in Alzheimer's disease

(ポルフィロモナス・ジンジバリス由来リポ多糖は、アルツハイマー病の低 A β 濃度環境において、ニューロンの GSK3 β 依存性シナプス障害を間接的に誘導し、認知機能低下を引き起こす)

区 分 : 甲

論 文 内 容 の 要 旨

Background: Lipopolysaccharides from *Porphyromonas gingivalis* (*P.g*LPS) are involved in the pathology of Alzheimer's disease (AD). However, the effect of *P.g*LPS on synaptic defects remains unclear. **Objective:** In this study, we tested our hypothesis that *P.g*LPS induces synaptic defects in a low-amyloid-beta (A β)-concentration environment. **Methods:** MG6 microglia or N2a neurons was treated with *P.g*LPS (0.1 μ g/mL), soluble A β ₄₂ (0.1 μ M) or AL (combined *P.g*LPS and soluble A β ₄₂ at 0.1 μ M). **Results:** In cultured MG6 microglia, increased the mRNA expression of TNF- α , IL-1 β and IL-6 and the TNF- α release in parallel with increased NF- κ B activation. In cultured N2a neurons, treatment with A β ₄₂, *P.g*LPS, and AL did not affect the mRNA expression of synapsin1 (SYN1) or post-synaptic density protein-95 (PSD-95). However, the treatment with conditioned medium from AL-exposed MG6 microglia (AL-MCM) significantly reduced the mRNA and protein expression of SYN1, PSD-95, and nuclear translocation of repressor element-1 silencing transcription factor (REST), but significantly increased the mRNA expression of TNF receptor type I (at 48 h) and glycogen synthase kinase (GSK)3 β (at 24 h). TWS119 pretreatment (5 μ M), a GSK3 β specific inhibitor, significantly reversed the AL-MCM-induced reduction in the mRNA expression of SYN1 and PSD-95 and nuclear translocation of REST in cultured N2a neurons. In APP^{NL-F/NL-F} mice, the immunofluorescence intensity of SYN1 and PSD-95 in cortical neurons was positively correlated with the index of the memory test but negatively correlated with that of TNF- α -positive microglia. **Conclusions:** These observations demonstrate that *P.g*LPS induces neuronal GSK3 β -dependent synaptic defects in a low-A β concentration environment via microglial activation.