# 学 位 論 文 の 要 旨

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主論文の題名

Selective Toll-Like Receptor 4 Antagonists Prevent Acute Blood-Brain Barrier Disruption After Subarachnoid Hemorrhage in Mice

主論文の要旨

Toll-like receptor 4 (TLR4) activation in subarachnoid hemorrhage (SAH) may result in blood-brain barrier (BBB) disruption. The purpose of this study was to examine if TLR4 antagonist prevents BBB disruption after SAH in mice and if the TLR4 signaling involves mitogen-activated protein kinases (MAPKs). C57BL/6 male mice underwent sham or endovascular perforation SAH operation, randomly followed by an intracerebroventricular infusion of vehicle or two dosages (117 or 585 ng) of a selective TLR4 antagonist IAXO-102 at 30 min post-operation. The effects were evaluated by survival rates, neurological scores, and brain edema at 24–72 h and immunoglobulin G immunostaining and Western blotting at 24 h post-SAH. IAXO-102 significantly prevented post-SAH neurological impairments, brain edema, and BBB disruption, resulting in improved survival rates. IAXO-102 also significantly suppressed post-SAH activation of MAPK c-Jun N-terminal kinase (JNK) and matrix metalloproteinase-9 as well as periostin induction and preserved tight junction protein zona occludens-1. Another selective TLR4 antagonist TAK-242, which has a different binding site from IAXO-102, also showed similar effects to IAXO-102. This study first described that TLR4 signaling is involved in post-SAH acute BBB disruption mediated at least partly by JNK activation. TLR4-targeted therapy may be promising to reduce post-SAH morbidities and mortalities.