学 位 論 文 の 要 約

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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

（選択的 Toll 様受容体 4 阻害薬はマウスくも膜下出血後の血液脳関門破綻を抑制する）

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主論文の要約

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a cerebrovascular disease with devastating consequences. Recent studies have suggested that early brain injury (EBI) is the primary determinant of poor outcomes after SAH. Blood-brain barrier (BBB) disruption is one of the important pathological manifestations of EBI, and post-SAH BBB disruption allows inflammatory substances and plasma components to enter into the brain parenchyma, causing further aggravation of neuroinflammation and brain injuries. Neuroinflammation is a well-recognized consequence of SAH and possibly implicated in EBI including BBB disruption after SAH.

Background

Toll-like receptor 4 (TLR4), innate immune receptor is activated by post-SAH secondary products, and possibly plays a critical role in initiating inflammatory reactions after SAH leading to EBI. However, there are no direct evidences showing the linkage between TLR4 and BBB disruption after SAH.

Objectives

The purpose of this study was to examine if selective blockage of TLR4 prevents BBB disruption after SAH in mice and if the TLR4 signaling involves mitogen-activated protein kinases (MAPKs).

Methods

One hundred and fifty-one 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 postoperation. The effects were evaluated by survival rates, neurological scores, and brain water content at 24–72 h and immunoglobulin G immunostaining and Western blotting at 24 h post-SAH.

Results

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 a major isoform of MAPK p46 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 provided the evidence that TLR4 signaling is involved in post-SAH acute BBB disruption and that the signaling is mediated at least partly by JNK activation.

Consideration

The novel findings in the present study were as follows: (1) a selective TLR4 antagonist IAXO-102 improved survival rates and neurological scores in endovascular perforation SAH mice; (2) two kinds of selective TLR4 antagonists suppressed post-SAH BBB disruption as measured by IgG extravasation; and (3) selective blockage of TLR4 also prevented JNK activation, **matrix metalloproteinase-9 activation**, and periostin induction after SAH. This is the first study demonstrating the direct linkage between TLR4 and BBB disruption after SAH, as well as the involvement of TLR4/MAPK signaling in post-SAH BBB disruption.

Conclusion

TLR4-targeted therapy may be promising to reduce post-SAH morbidities and mortalities.