学 位 論 文 の 要 旨

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主論文の題名

Tenascin-C Induces Prolonged Constriction of Cerebral Arteries in Rats

主論文の要旨

Tenascin-C (TNC), a matricellular protein, is induced in association with cerebral vasospasm after subarachnoid hemorrhage. The aim of this study was to assess the vasoconstrictive effects of TNC and its mechanisms of action on cerebral arteries in vivo. Two dosages (1 and 10 μg) of TNC were administered intracisternally to healthy rats, and the effects were evaluated by neurobehavioral tests and India-ink angiography at 24, 48, and 72 hours after the administration. Western blotting and immunohistochemistry were performed to explore the underlying mechanisms on constricted cerebral arteries after 24 hours. The effects of toll-like receptor 4 (TLR4) antagonists (LPS-RS), c-Jun N-terminal kinase (JNK), and p38 inhibitors (SP600125 and SB203580) on TNC-induced vasoconstriction were evaluated at 24 hours. Higher dosages of TNC induced more severe cerebral arterial constriction, which continued for more than 72 hours. TNC administration also upregulated TLR4, and activated JNK and p38 in the smooth muscle cell layer of the constricted cerebral artery. LPS-RS blocked TNC-induced TLR4 upregulation, JNK and p38 activation, and vasoconstrictive effects. SP600125 and SB203580 abolished TNC-induced TLR4 upregulation and vasoconstrictive effects. TNC may cause prolonged cerebral arterial constriction via TLR4 and activation of JNK and p38, which may upregulate TLR4. These findings suggest that TNC causes cerebral vasospasm and provides a novel therapeutic approach against it.