トロンビン誘発脳組織障害における Heme oxygenase-1 の関与

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Heme oxygenase-1 contributes to pathology associated with thrombin-induced striatal and cortical injury in organotypic slice culture

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ABSTRACT: A blood coagulation factor thrombin that leaks from ruptured vessels initiates brain tissue damage after intracerebral hemorrhage. We have recently shown that mitogen-activated protein kinases (MAPKs) activated by thrombin exacerbate hemorrhagic brain injury via supporting survival of neuropathic microglia. Here we investigated whether induction of heme oxygenase (HO)-1 is involved in these events. Zinc protoporphyrin IX (ZnPP IX), a HO-1 inhibitor, attenuated thrombin-induced injury of cortical cells in a concentration-dependent manner (0.3 - 3 μM), and tended to inhibit shrinkage of the striatal tissue at 0.3 μM. HO-1 expression was induced by thrombin in microglia and astrocytes in both the cortex and the striatum. The increase of HO-1 protein was suppressed by a p38 MAPK inhibitor SB203580, and early activation of p38 MAPK after thrombin treatment was observed in neurons and microglia in the striatum. Notably, concomitant application of a low concentration (0.3 μM) of ZnPP IX with thrombin induced apoptotic cell death in striatal microglia and significantly decreased the number of activated microglia in the striatal region. On the other hand, a carbon monoxide releaser reversed the protective effect of ZnPP IX on thrombin-induced injury of cortical cells. Overall, these results suggest that p38 MAPK-dependent induction of HO-1 supports survival of striatal microglia during thrombin insults. Thrombin-induced cortical injury also may be regulated by expression of HO-1 and resultant production of heme degradation products such as carbon monoxide.

抄録　脳内出血時のニューロン障害性ミクログリアの生存維持における抗酸化酵素 heme oxygenase (HO)-1 の関与について解析を行った。培養脳組織切片において凝固系セリンプロテアーゼであるトロンビンは、p38 MAPK (mitogen-activated protein kinase) 活性化を介してグリア細胞に HO-1 を誘導した。HO-1 阻害薬である zinc (II) protoporphyrin (ZnPP) IX は、ミクログリアにアポトーシス性細胞死を惹起し、脳組織障害を減弱した。

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