

## トロンビン誘発脳組織障害における Heme oxygenase-1 の関与

大西正俊、香月博志\*、畝村和宏\*\*、泉 安彦\*\*、  
久米利明\*\*、高鳥（高田）悠記\*\*\*、赤池昭紀\*\*

*Brain Research*, **1347**, 170-178 (2010)

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

Masatoshi Ohnishi, Hiroshi Katsuki\*, Kazuhiro Unemura\*\*, Yasuhiko Izumi\*\*,  
Toshiaki Kume\*\*, Yuki Takada-Takatori\*\*\*, Akinori Akaike\*\*

**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  $\mu$ M), and tended to inhibit shrinkage of the striatal tissue at 0.3  $\mu$ M. 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  $\mu$ M) 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。

\* Department of Chemico-Pharmacological Sciences, Graduate School of Pharmaceutical Sciences, Kumamoto University

熊本大学大学院生命科学研究部

\*\* Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Kyoto University

京都大学大学院薬学研究科

\*\*\* Department of Pharmacology, Faculty of Pharmaceutical Sciences, Doshisha Women's College

同志社女子大学薬学部