Cytotoxic effects of metal protoporphyrins in glioblastoma cells: roles of albumin, reactive oxygen species, and heme oxygenase-1

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摘要

Abstract

We investigate the cytotoxic effect of metal protoporphyrins including ferric protoporphyrin (FePP; hemin), cobalt protoporphyrin (CoPP), and tin protoporphyrin (SnPP) in glioblastoma cells C6 and GBM8401. Data of MTT assay show that FePP and CoPP, but not SnPP, significantly reduce the viability of glioma cells C6 and GBM8401 in the absence of serum. In the condition with fetal bovine serum (FBS) or bovine serum albumin (BSA), the cytotoxic effect of FePP and CoPP was completely inhibited. Binding of FePP, CoPP, and SnPP with BSA was examined via spectrophotometer analysis, and the protective effect of serum against FePP and CoPP-induced cell death was abolished by BSA depletion. A loss in the integrity of DNA with an occurrence of apoptotic events including DNA ladders, caspase 3 and PARP protein cleavage, and chromatin-condensed cells is observed in FePP-treated or CoPP-treated C6 cells. An increase in intracellular peroxide level was examined in FePP, but not CoPP, -treated C6 cells, and N-acetyl-l-cysteine (NAC) addition significantly protected C6 cells from FePP, but not CoPP, -induced cell death with reducing FePP-stimulated reactive oxygen species (ROS) production. Activation of extracellular regulated kinases (ERKs) and c-Jun-N-terminal kinases (JNKs) with an increase in the heme oxygenase-1 (HO-1) protein was observed in FePP-treated or CoPP-treated C6 cells in the absence of FBS or BSA, and adding JNKs inhibitor SP600125 (SP), but not ERKs inhibitor PD98059 (PD), significantly attenuated FePP-induced or CoPP-induced HO-1 protein expression in accordance with reducing JNKs protein phosphorylation. However, PD98059, SP600125, or transfection of C6 cells with antisense HO-1 oligonucleotides show no effect on the cytotoxicity elicited by FePP and CoPP in C6 cells. Effect of serum and BSA on the cytotoxicity of metal protoporphyrins in glioma cells is first demonstrated in the present study, and the roles of ROS, MAPKs, and HO-1 were elucidated.

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