Baicalein inhibition of hydrogen peroxide-induced apoptosis via ROS-dependent heme oxygenase 1 gene expression

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摘要

Abstract

In the present study, baicalein (BE) but not its glycoside, baicalin (BI), induced heme oxygenase-1 (HO-1) gene expression at both the mRNA and protein levels, and the BE-induced HO-1 protein was blocked by adding cycloheximide (CHX) or actinomycin D (Act D). Activation of ERK, but not JNK or p38, proteins via induction of phosphorylation in accordance with increasing intracellular peroxide levels was detected in BE-treated RAW264.7 macrophages. The addition of the ERK inhibitor, PD98059, (but not the p38 inhibitor, SB203580, or the JNK inhibitor, SP600125) and the chemical antioxidant, N-acetyl cysteine (NAC), significantly reduced BE-induced HO-1 protein expression by respectively blocking ERK protein phosphorylation and intracellular peroxide production. Additionally, BE but not BI effectively protected RAW264.7 cells from hydrogen peroxide (H(2)O(2))-induced cytotoxicity, and the preventive effect was attenuated by the addition of the HO inhibitor, SnPP, and the ERK inhibitor, PD98059. H(2)O(2)-induced apoptotic events including hypodiploid cells, DNA fragmentation, activation of caspase 3 enzyme activity, and a loss in the mitochondrial membrane potential with the concomitant release of cytochrome c from mitochondria to the cytosol were suppressed by the addition of BE but not BI. Blocking HO-1 protein expression by the HO-1 antisense oligonucleotide attenuated the protective effect of BE against H(2)O(2)-induced apoptosis by suppressing HO-1 gene expression in macrophages. Overexpression of the HO-1 protein inhibited

H(2)O(2)-induced apoptotic events such as DNA fragmentation and hypodiploid cells by reducing intracellular peroxide production induced by H(2)O(2), compared with those events in neo-control (neo-RAW264.7) cells. In addition, CO, but not bilirubin and biliverdin, addition inhibits H(2)O(2)-induced cytotoxicity in macrophages. It suggests that CO can be responsible for the protective effect associated with HO-1 overexpression. The notion of induction of HO-1 gene expression through a ROS-dependent manner suppressing H(2)O(2)-induced cell death is identified in the present study.