YC-1 increases cyclo-oxygenase-2 expression through protein kinase G- and p44/42 mitogen-activated protein kinase-dependent pathways in A549 cells.

許準榕
Chang MS;Lee WS;Teng CM;Lee HM;Sheu JR;Hsiao G;Lin CH

Abstract

YC-1, an activator of soluble guanylate cyclase (sGC), has been shown to increase the intracellular cGMP concentration. This study was designed to investigate the signaling pathway involved in the YC-1-induced COX-2 expression in A549 cells. YC-1 caused a concentration- and time-dependent increase in COX activity and COX-2 expression in A549 cells. Pretreatment of the cells with the sGC inhibitor (ODQ), the protein kinase G (PKG) inhibitor (KT-5823), and the PKC inhibitors (Go 6976 and GF10923X), attenuated the YC-1-induced increase in COX activity and COX-2 expression. Exposure of A549 cells to YC-1 caused an increase in PKC activity; this effect was inhibited by ODQ, KT-5823 or Go 6976. Western blot analyses showed that PKC-alpha, -iota, -lambda, -zeta and -mu isoforms were detected in A549 cells. Treatment of A549 cells with YC-1 or PMA caused a translocation of PKC-alpha, but not other isoforms, from the cytosol to the membrane fraction. Long-term (24 h) treatment of A549 cells with PMA down-regulated the PKC-alpha. The MEK inhibitor, PD 98059 (10 - 50 microM), concentration-dependently attenuated the YC-1-induced increases in COX activity and COX-2 expression. Treatment of A549 cells with YC-1 caused an activation of p44/42 MAPK; this effect was inhibited by KT-5823, Go 6976, long-term (24 h) PMA treatment or PD98059, but not the p38 MAPK inhibitor, SB 203580. These results indicate that in human pulmonary epithelial cells, YC-1 might activate PKG through an upstream sGC/cGMP pathway to elicit PKC-alpha activation, which in turn, initiates p44/42 MAPK activation, and finally induces COX-2 expression.