YC-1 Increases Cyclooxygenase-2 Expression through a Protein Kinase G-Dependent Pathway in Human Pulmonary Epithelial Cells: Involvement of Activation of Protein Kinase G- and p44/42 Mitogen-Activated Protein Kinase.

李文森

Ming-Shyan Chang;Wen-Sen Lee;Che-Ming Teng;Horng-Mo Lee;Joen-Rong Sheu;George Hsiao;and Chien-Huang Lin.

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-α, -ι, -λ, -ζ and -μ isoforms were detected in A549 cells. Treatment of A549 cells with YC-1 or PMA caused a translocation of PKC-α, but not other isoforms, from the cytosol to the membrane fraction. Long-term (24h) treatment of A549 cells with PMA down-regulated the PKC-α.

The MEK inhibitor, PD 98059 (10–50μM), 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 (24h) 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-α activation, which in turn, initiates p44/42 MAPK activation, and finally induces COX-2 expression.