Celecoxib Induces Heme Oxygenase-1 Expression in Glomerular Mesangial Cells via c-Jun-N-terminal kinase and Phosphatidylinositol 3-kinase dependent pathways.

李宏謨

Kao SH;Hung SL;Chen TS;Lee HM

摘要

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used as analgesics. They inhibit cyclooxygenases (COX), preventing the formation of prostaglandins, including prostacyclin and thromboxane. A serious side effect of COX-1 and COX-2 inhibitors is renal damage. To investigate the molecular basis of the renal injury, we evaluated the expression of the stress marker, heme oxygenase-1 (HO-1), in celecoxib-stimulated mesangial cells. We report here that a COX-2 selective NSAID, celecoxib, induced a concentration- and time-dependent increase of HO-1 expression in glomerular mesangial cells. Celecoxib-induced HO-1 protein expression was inhibited by actinomycin D and cycloheximide, suggesting that de novo transcription and translation are required in this process. N-acetylcysteine, a free radical scavenger, strongly decreased HO-1 expression, suggesting the involvement of reactive oxygen species (ROS). Celecoxib-induced HO-1 expression was attenuated by pretreatment of the cells with SP 600125 (a specific JNK inhibitor), but not SB 203580 (a specific p38 MAPK inhibitor), or PD 98059 (a specific MEK inhibitor). Consistently, celecoxib activated c-Jun N-terminal kinase (JNK) as demonstrated by kinase assays and by increasing phosphorylation of this kinase. N-acetylcysteine reduced the stimulatory effect of celecoxib on stress kinase activities, suggesting an involvement of JNK in HO-1 expression. On the other hand, LY 294002, a phosphatidylinositol 3-kinase (PI-3K)-specific inhibitor, prevented the enhancement of HO-1 expression. This effect was

correlated with inhibition of the phosphorylation of the PDK-1 downstream substrate Akt/protein kinase B (PKB). In conclusion, our data suggest that celecoxib-induced HO-1 expression in glomerular mesangial cells may be mediated by ROS via the JNK-PI-3K cascade.