p38 Mitogen-Activated Protein Kinase

RAW 264.7 -2

Involvement of p38 Mitogen-Activated Protein Kinase in Advanced Glycosylation End Products-Induced Cyclooxygenase-2 Expression in RAW 264.7 Macrophages

(advanced glycosylation end products, AGEs)

RAW 264.7 poly-L-lysine (PLL)-AGEs -2 (cyclooxygenase-2, COX-2) (arachidonic acid) E2 (prostaglandin E2, PGE2) PLL-AGEs RAW 264.7 -2 PLL-AGEs -2 -1 (cyclooxygenase-1, COX-1) Gamma-glutamylcysteine synthetase －L-buthionine-[S, R]-sulfoximine (BSO) glutathione －L-nitro-acetyl-cysteine (L-NAC) PLL-AGEs -2 PLL-AGEs -2 -2 (nitric oxide synthase, NOS) －L-gamma-nitro-L-arginine methyl ester (L-NAME) (lipopolysacchride, LPS) －polymyxin B Tyrosine kinase －genistein tyrphostin AG 126 p38 mitogen-activated protein kinase (MAPK) －SB 203580 PLL-AGEs -2 Ras －FPT II MEK －PD 98059 PLL-AGEs -2 PLL-AGEs RAW 264.7 p38 MAPK genistein SB 203580 protein tyrosine kinase p38 MAPK PLL-AGEs -2

Advanced glycosylation end products (AGEs) have been implicated in the structural and functional alterations of proteins that occur during aging and long-term diabetes. In the present study, murine RAW 264.7 macrophages were incubated with poly-L-lysine (PLL)-AGEs to examine cyclooxygenase-2 (COX-2) protein expression. Treatment of RAW 264.7 cells with PLL-AGEs caused a dose-dependent increase in

COX activity as reflected by PGE2 secretion (measured in the presence of exogenous arachidonic acid). Furthermore, treatment of RAW 264.7 cells with PLL-AGEs induced COX-2 but not COX-1 expression. The induction was affected by neither L-buthionine-[S, R]-sulfoximine (BSO), a gamma-glutamylcysteine synthetase inhibitor, nor by L-nitro-acetyl-cysteine (L-NAC), a known glutathione precursor, suggesting that AGEs-induced COX-2 expression is not due to reactive oxygen species. Moreover, COX-2 expression was affected by neither N-gamma-nitro-L-arginine methyl ester (L-NAME), a competitive inhibitor of nitric oxide synthase (NOS), nor polymyxin B, a lipopolysaccharide (LPS) inhibitor, suggesting that COX-2 induction is not secondary to iNOS induction or LPS contamination. The tyrosine kinase inhibitor, genistein and tyrphostin AG 126, and the p38 mitogen-activated protein kinase (MAPK) inhibitor, SB 203580, inhibited PLL-AGEs-induced COX-2 expression, while the Ras inhibitor, FPT inhibitor II, and the MEK inhibitor, PD 98059, had no effect on PLL-AGEs-induced COX-2 expression. Incubation of RAW 264.7 cells with PLL-AGEs resulted in activation of p38 MAPK, and this activation was suppressed by genistein and SB 203580. Taken together, our results suggest that activation of protein tyrosine kinase and p38 MAPK is involved in AGEs-induced COX-2 expression in RAW 264.7 macrophages.