

Bradykinin B2 receptor mediates NF-kB activation and cyclooxygenase-2 expression via the Ras/Raf/ERK pathway in human airway epithelial cells

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摘要

Abstract

In this study, we investigated the signaling pathways involved in bradykinin (BK)-induced NF-kappaB activation and cyclooxygenase-2 (COX-2) expression in human airway epithelial cells (A549). BK caused concentration- and time-dependent increase in COX-2 expression, which was attenuated by a selective B2 BK receptor antagonist (HOE140), a Ras inhibitor (manumycin A), a Raf-1 inhibitor (GW 5074), a MEK inhibitor (PD 098059), an NF-kappaB inhibitor (pyrrolidine dithiocarbamate), and an IkappaB protease inhibitor (L-1-tosylamido-2-phenylethyl chloromethyl ketone). The B1 BK receptor antagonist (Lys-(Leu8)des-Arg9-BK) had no effect on COX-2 induction by BK. BK-induced increase in COX-2-luciferase activity was inhibited by cells transfected with the kappaB site deletion of COX-2 construct. BK-induced Ras activation was inhibited by manumycin A. Raf-1 phosphorylation at Ser338 by BK was inhibited by manumycin A and GW 5074. BK-induced ERK activation was inhibited by HOE140, manumycin A, GW 5074, and PD 098059. Stimulation of cells with BK activated IkappaB kinase alphabeta (IKKalphabeta), IkappaBalph phosphorylation, IkappaBalph degradation, p65 and p50 translocation from the cytosol to the nucleus, the formation of an NF-kappaB-specific DNA-protein complex, and kappaB-luciferase activity. BK-mediated increase in IKKalphabeta activity and formation of the NF-kappaB-specific DNA-protein complex were inhibited by HOE140, a Ras dominant-negative mutant (RasN17), manumycin A, GW 5074, and PD 098059. Our results demonstrated for the first time that BK, acting through B2 BK receptor, induces activation of the Ras/Raf-1/ERK pathway, which in turn initiates

IKKalpha and NF-kappaB activation, and ultimately induces COX-2 expression in human airway epithelial cell line (A549).