

Cyclooxygenase-2 Induction by Bradykinin in Aortic Vascular Smooth Muscle Cells

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Abstract

Vascular smooth muscle cell proliferation and migration play an important role in the pathophysiology of several vascular diseases, including atherosclerosis. Prostaglandins that have been implicated in this process are synthesized by two isoforms of cyclooxygenase (COX), with the expression of the regulated COX-2 isoform increased in atherosclerotic plaques. Bradykinin (BK), a vasoactive peptide increased in inflammation, induces the formation of prostaglandins through specific receptor activation. We hypothesized that BK plays an important role in the regulation of COX-2, contributing to the increase in production of prostaglandins in vascular smooth muscle cells. Herein we examined the signaling pathways that participate in the BK regulation of COX-2 protein levels in primary cultured aortic vascular smooth muscle cells. We observed an increase in COX-2 protein levels induced by BK that was maximal at 24 h. This increase was blocked by a B2 kinin receptor antagonist but not a B1 receptor antagonist, suggesting that the B2 receptor is involved in this pathway. In addition, we conclude that the activation of mitogen-activated protein kinases p42/p44, protein kinase C, and nitric oxide synthase is necessary for the increase in COX-2 levels induced by BK because either of the specific inhibitors for these enzymes blocked the effect of BK. Using a similar approach, we further demonstrated that reactive oxygen species and cAMP were not mediators on this pathway. These results suggest that BK activates several intracellular pathways that act in combination to increase COX-2 protein levels. This study suggests a role for BK on the evolution of the atheromatous plaque by virtue of controlling the levels of COX-2.

Keywords: Atherosclerosis, signal transduction, antioxidants.