METHODS AND FINDINGS

IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY

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CO-20 SINERGISTIC EFFECTS OF ANGIOTENSIN II AND INTERLEUKIN-1β ON COX-2 EXPRESSION IN ADVENTITIAL FIBROBLASTS

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Adventitial layer plays a critical role in the regulation of vascular function and structure. Angiotensin II (Ang II) has been implicated in the pathophysiological processes that occur in hypertension through its significant proinflamatory actions in the vascular wall, including the production of inflammatory cytokines. Cyclooxygenase-2 (COX-2) and prostaglandin E synthase-1 (mPGES-1) are induced by several proinflammatory agents like cytokines. The purpose of the present study was to evaluate if Ang II alter the effect of Interleukin-1β (IL-1β) on COX-2 and mPGES-1 expression in rat aortic fibroblasts. IL-1β (10 ng/ml, 24h) increased COX-2 and mPGES-1 mRNA levels, COX-2 protein expression and PGI2 and PGE2 production. Incubation of cells with Ang II (0.1 μM, 24 h) did modify neither COX-2 and mPGES-1 expression nor prostaglandin levels but enhanced COX-2 expression and PGI2 production induced by IL-1β; however Ang II did not change mPGES-1 mRNA levels and PGE2 production after treatment with IL-1β for 24 hours. The potentiator effect of Ang II was inhibited by losartan (10 μM), suggesting that the effect was mediated by activation of AT1 receptor signaling pathway. IL-1β (10 ng/ml 5-60 min) increased p38 and ERK 1/2 MAP kinases phosphorylation; after coincubation with Ang II, this increase was higher and more sustained. The respective inhibitors of p38 and ERK 1/2, PD98059 (10 μM) and SB203580 (10 μM) disminished COX-2 expression in cells treated with IL-1β or with the combination of IL-1β plus Ang II. These results suggest that Ang II participate in the vascular inflamatory response not only through the increase of cytokines levels but also through the increase of cytokine effects on expression of some proinflammatoy enzymes such as COX-2, but not mPGES-1. This additional effect is thought to be caused by signaling pathways in which p38 and ERK 1/2 MAP kinases are involved.

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