



# METHODS AND FINDINGS

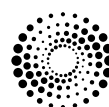
IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY

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SUPPLEMENT A

SEPTEMBER 2009

XXXI CONGRESS OF THE SPANISH SOCIETY OF PHARMACOLOGY



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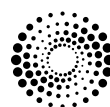
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**THOMSON REUTERS**

**CO-20 SINERGISTIC EFFECTS OF ANGIOTENSIN II AND INTERLEUKIN-1 $\beta$  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 proinflammatory 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-1 $\beta$  (IL-1 $\beta$ ) on COX-2 and mPGES-1 expression in rat aortic fibroblasts. IL-1 $\beta$  (10 ng/ml, 24h) increased COX-2 and mPGES-1 mRNA levels, COX-2 protein expression and PGI<sub>2</sub> and PGE<sub>2</sub> production. Incubation of cells with Ang II (0.1  $\mu$ M, 24 h) did modify neither COX-2 and mPGES-1 expression nor prostaglandin levels but enhanced COX-2 expression and PGI<sub>2</sub> production induced by IL-1 $\beta$ ; however Ang II did not change mPGES-1 mRNA levels and PGE<sub>2</sub> production after treatment with IL-1 $\beta$  for 24 hours. The potentiator effect of Ang II was inhibited by losartan (10  $\mu$ M), suggesting that the effect was mediated by activation of AT<sub>1</sub> receptor signaling pathway. IL-1 $\beta$  (10 ng/ml 5-60 min) increased p38 and ERK 1/2 MAP kinases phosphorylation; after coinubation with Ang II, this increase was higher and more sustained. The respective inhibitors of p38 and ERK 1/2, PD98059 (10  $\mu$ M) and SB203580 (10  $\mu$ M) diminished COX-2 expression in cells treated with IL-1 $\beta$  or with the combination of IL-1 $\beta$  plus Ang II. These results suggest that Ang II participate in the vascular inflammatory response not only through the increase of cytokines levels but also through the increase of cytokine effects on expression of some proinflammatory 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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