



Inhibition of the Angiotensin Type 1 Receptor and Differential Regulation of Inflammatory Genes in Human Vascular Endothelial Cells

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Abstract

Background: Angiotensin II may contribute to the pathogenesis of atherosclerosis through activation of the endothelial inflammatory response. These effects may be inhibited in part by blockade of the angiotensin type 1 (AT₁) receptor. We wished to investigate the effect of angiotensin II receptor blockade on the regulation of inflammatory genes such as mitogen activated protein (MAP) kinases and adhesion molecules in human vascular endothelial cells.

Methods:

- 1) Human coronary artery endothelial cells (HCAEC, available from Clonetics, San Diego USA), at no greater than the fourth passage, were pretreated with the AT₁ receptor inhibitor losartan (LOS, 100 nM) + the AT₂ receptor inhibitor PD123319 (100 nM) for 24 hours. The cells were then exposed to the cytokine TNF- α (100 U/ml) for one hour.
- 2) Utilizing Western blot analysis, we determined the phosphorylation of the following MAP kinases: p38, ERK1, and ERK2.
- 3) Using ELISA technique, we determined the gene expression of the inflammatory molecules vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1).

Discussion: Pretreatment of HCAEC with losartan significantly and selectively, reduced the activity of oxidation sensitive genes (i.e. mRNA of VCAM-1 but not ICAM-1) and phosphorylation of MAP kinases (p38 and JNK but not ERK-1 or ERK-2). This suggests the strong anti-inflammatory and anti-oxidant effect of blockade of the AT₁ receptor.

Since oxidative stress within the vasculature has been clearly identified as a key player in the progression of atherosclerosis, this study aimed at looking for any cardiovascular benefit that could be achieved by specifically investigating oxidation in conjunction with AT₁ receptor blocker therapy. In this study, AT₁ receptor inhibitors may demonstrate vascular benefit by acting on the oxidation state at multiple levels within the vasculature thereby demonstrating a targeted area of benefit in relation to atherogenesis.

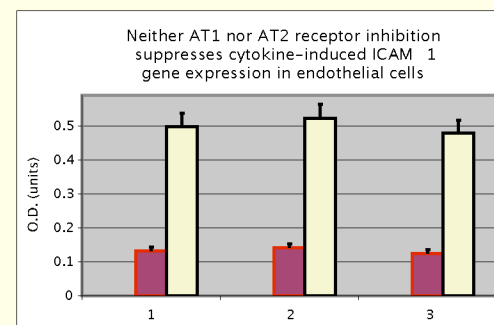
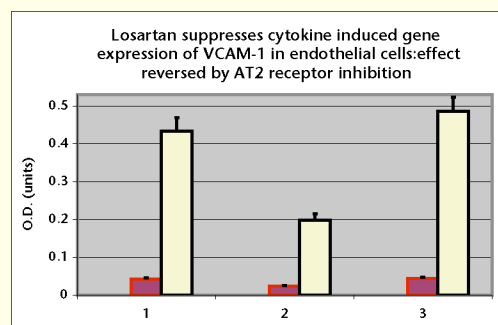
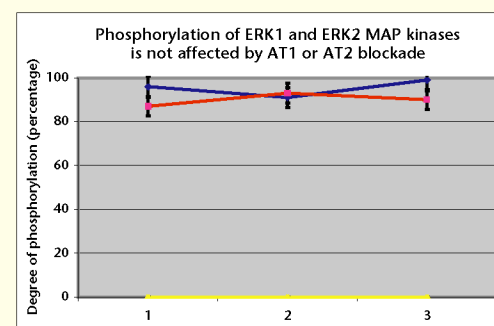
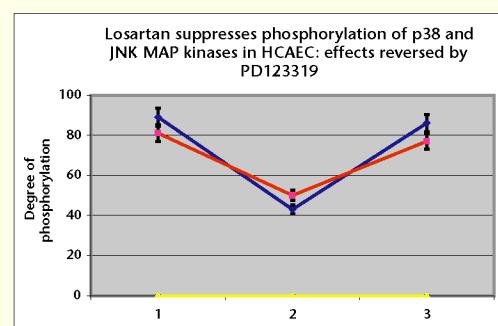
Conclusions: These findings suggest that there is differential regulation of MAP kinases and inflammatory genes by AT₁ blockade in human vascular endothelial cells. Furthermore, these results suggest the presence of AT₂ receptors in HCAEC and that inhibition of the AT₁ receptor activates AT₂ receptors in human vascular endothelial cells.

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