METHODS AND FINDINGS

IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY

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P-122 PPARγ ACTIVATION IMPROVES OXIDATIVE STRESS AND DOWNREGULATES COX-2 EXPRESSION IN VASCULAR CELLS

R. Palacios,[1] J.V. Pérez-Girón,[1] A. Martín,[1] R. Hernanz,[1] A. Briones,[2] M. Salaices,[2] M.J. Alonso[1,2]

[1]Depto. Ciencias de la Salud III, Universidad Rey Juan Carlos, Alcorcón, Spain; [2]Depto. Farmacología, Universidad Autónoma de Madrid, Madrid, Spain

Introduction: The increased renin-angiotensin system (RAS) activity seems to contribute to the pathophysiology of hypertension by the increase in reactive oxygen species (ROS) levels and proinflammatory mediators. Endothelin-1 (ET-1) has been proposed to explain the cardiovascular damage induced by angiotensin II (AngII). Moreover, peroxisome proliferator activated receptor γ (PPARγ) agonists have anti-inflammatory actions by interference with redox-sensitive transcription factors, such as NFkB or AP-1, involved in the transcription of proinflammatory genes including cyclooxygenase-2 (COX-2).

Aim: To analyze if AngII contributes to the increased COX-2 levels in vascular smooth muscle cells (VSMC) from spontaneously hypertensive (SHR) rats by mechanisms dependent of ROS and ET-1 production and whether PPARγ activation regulates this effect.

Methods: Aortic VSMC from SHR were stimulated with AngII in the absence and the presence of different drugs. mRNA levels were measured by qRT-PCR and protein expression by Western blot. Aortic segments from SHR and Wistar-Kyoto (WKY) rats untreated and treated with losartan (15 mg/Kg/day, 12 weeks) were also used.

Results: COX-2 mRNA levels were greater in segments from SHR than WKY; the treatment with losartan reduced COX-2 levels in SHR. In VSMC from SHR, AngII (0.1 μM, 2 h) induced COX-2, ET-1 and NOX-1 mRNA levels; this effect was reduced by losartan (10 μM). AngII-induced COX-2 protein expression was also reduced by the NADPHox inhibitor apocynin (30 mM). The antagonist of the ET_A receptor BQ 123 (1 μM), but not of the ET_B receptor BQ 788 (1 μM), also reduced COX-2 and NOX-1 mRNA levels after AngII. The proteasome inhibitor lactacystin (20 μM) did not modify the ET-1 mRNA levels but inhibited those of NOX-1 and COX-2. AngII also increased c-jun expression; this expression was reduced by losartan but not by BQ 123. Moreover, the PPARγ activator pioglitazone (10 μM) decreased AngII-induced COX-2 and NOX-1 mRNA levels in VSMC from SHR.

Conclusions: 1) The RAS activation contributes to the increased vascular COX-2 expression in hypertension. 2) AngII-induced COX-2 expression in VSMC is related with NOX-1 induction and NFkB and AP-1 activation. 3) AngII-induced ET-1 production and ET_A activation contributes, at least partially, to the increased NOX-1 and COX-2 expression. 4) PPARγ activation inhibits AngII-induced COX-2 expression by reducing NOX-1 levels; we suggest that transrepression mechanisms on NFkB and/or AP-1 can play an important role in this inhibitory effect of PPARγ activation.

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