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ANGIOTENSIN CONVERTING ENZYME ACTIVITY AND LYMPHO-PROLIFERATIVE RESPONSE DURING ENALAPRIL AND LOSARTAN ADMINISTRATION IN MEN

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Objective. To evaluate the long-term effects of the angiotensin converting enzyme inhibitor enalapril and of the angiotensin II type 1 receptor antagonist losartan on the angiotensin converting enzyme activity in T-lymphocytes and on the proliferation of peripheral blood mononuclear cells (PBMC) in patients with essential hypertension.

Design. Randomised, placebo-controlled, double-blind, cross-over design.

Methods. Nine patients with sitting blood pressure ≥ 95 mm Hg and ≤ 105 mm Hg at the end of a 4-week placebo run-in period entered the double-blind phase of the study, which consisted of three 6-week periods during which patients were treated with placebo, enalapril 20 mg o.d. or losartan 50 mg o.d. The angiotensin converting enzyme activity in T-lymphocytes was measured as the activity of the degradation of the substrate Hippuril-His-Leu and as the appearance of the dipeptide His-Leu, which was quantified spectrophotometrically. The de novo synthesis of DNA, RNA and protein in PBMC was measured by, respectively, [3H]thymidine, [3H]uridine or [3H]leucine incorporation.

Results. Enalapril but not losartan suppressed (P ≤ 0.01) the angiotensin converting enzyme activity in plasma, while it stimulated (P ≤ 0.05) the angiotensin converting enzyme activity in circulating T-lymphocytes. Neither enalapril nor losartan affected the proliferation of PBMC measured as de novo synthesis of DNA, RNA and protein.

Conclusions. Our data show that during angiotensin converting enzyme inhibition with enalapril the angiotensin converting enzyme activity was decreased in plasma and increased in T-lymphocytes, while the proliferation of PBMC was not affected. Angiotensin II receptor type 1 antagonism losartan had no effect on these variables.

Key Words: Angiotensin converting enzyme, Enalapril, Losartan

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EFFECT OF TELMISARTAN ON ANGIOTENSIN II-MEDIATED COLLAGEN GEL CONTRACTION BY ADULT RAT CARDIAC FIBROBLASTS

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The possible contributions of the angiotensin receptor subtypes 1 (AT_1) and 2 (AT_2) on the angiotensin II-induced collagen gel contraction by adult rat cardiac fibroblasts were studied using the specific angiotensin receptor AT_1 and AT_2 antagonists telmisartan and P-186, respectively. Cardiac fibroblasts (from normal male adult rats) from passage 2 were cultured to confluency and added to a hydrated collagen gel, with or without angiotensin II (ANGII), angiotensin II plus telmisartan or angiotensin II plus P-186. Addition of telmisartan but not by the specific AT_2-receptor antagonist P-186 completely blocked the ANGII-induced increase in collagen secretion and production. Addition of telmisartan and P-186 does not affect the collagen secretion and production in basal fibroblasts.

Our data demonstrate that the effects of ANGII on collagen secretion and production in adult rat cardiac fibroblasts in culture are AT_1-receptor mediated because they were abolished by the specific AT_1-receptor antagonist telmisartan but not by the specific AT_2-receptor antagonist P-186.

Key Words: Fibroblasts, Angiotensin II, Collagen

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ANGIOTENSIN II-INDUCED STIMULATION OF COLLAGEN SECRETION AND PRODUCTION IN CARDIAC FIBROBLASTS IS MEDIATED VIA ANGIOTENSIN II SUBTYPE 1 RECEPTOR

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The possible contributions of the angiotensin receptor subtypes 1 (AT_1) and 2 (AT_2) on the angiotensin II-induced changes in collagen secretion and production were studied using the specific angiotensin receptor AT_1 and AT_2 antagonists telmisartan and P-186, respectively. Cardiac fibroblasts (from normal male adult rats) from passage 2 were cultured to confluency and incubated in the presence of angiotensin II (ANGII) in a concentration range of 10^{-10} to 10^{-6} M for 24 hours in Dulbecco’s MEM medium. The collagen production and secretion were assayed by [3H]-Proline incorporation, the non-collagen production and secretion were also also calculated.

ANGII dose-dependently increases the collagen secretion and production in rat adult cardiac fibroblasts in culture. The non-collagen secretion and production were also concentration-dependently increased by ANGII. Addition of 100 nmol/l ANGII increases (p < 0.01) the collagen secretion and production by 75 ± 6 (SEM) % and 113 ± 23 %, respectively and the non-collagen secretion and production by 65 ± 6 % and 57 ± 16 %, respectively.

Pretreatment of cardiac fibroblasts with telmisartan completely blocks the ANGII-induced increase in collagen secretion (p < 0.001) and production (p < 0.05) and in non-collagen secretion (p < 0.01) and production (p < 0.01). P-186 has no effect on the ANGII-induced increase in collagen secretion and production. Addition of telmisartan and P-186 does not affect the collagen secretion and production in basal fibroblasts.

Our data demonstrate that the effects of ANGII on (non)collagen secretion and production in adult rat cardiac fibroblasts in culture are AT_1-receptor mediated because they were abolished by the specific AT_1-receptor antagonist telmisartan but not by the specific AT_2-receptor antagonist P-186.

Key Words: Collagen, Angiotensin II, Fibroblasts

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A FUNCTIONAL ANALYSIS OF ANGIOTENSIN II TARGETS THROUGH GENOME WIDE SURVEYS

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The mitogen Angiotensin II (AII) that binds to specific G-protein coupled receptors, plays an important role in human disease as the distal effector of the renin-angiotensin system. AII is mitogenic in adrenal, liver epithelial, and vascular smooth muscle cells. Many of the known biological actions of AII including enhanced DNA synthesis are mediated by stimulation of the AT1 receptor which is a member of the G protein-coupled seven transmembrane spanning receptor family. AT1 receptor activation through phospholipase C initiates a rapid release of inositol...