subjects (128 ± 23%) with significant overexpression in hypertensive patients (229 ± 28%). c-fos protein expression and activity of AP-1 binding activity were enhanced in hypertensives. PD98059, a specific inhibitor of the ERK1/2 pathway, attenuated Ang II-stimulated effects and normalized responses in hypertensives. Ang II-induced expression of c-myc and c-jun were similar in normotensives and hypertensives. Ang II increased DNA synthesis, with responses increased (p < 0.01) in hypertensives. PD98059 decreased (p < 0.05) Ang II-stimulated effects. Ang II-stimulated c-fos expression and 3H-thymidine incorporation were reduced (p < 0.05) in cells transfected with antisense oligonucleotide compared with sense oligonucleotide. Thus vascular remodeling in human hypertension is associated with augmented growth of VSMCs that is mediated via increased ERK1/2 activation. This amplification leads to upregulation of c-fos, but not c-myc or c-jun gene expression and enhanced AP-1 binding activity. Our findings suggest a signal transduction pathway through which Ang II influences VSMC growth and vascular remodeling in human hypertension.

Key Words: Signal transduction; angiotensin II; essential hypertension; vascular remodeling

**RETINOIC ACIDS INHIBIT ANGIOTENSIN II-DEPENDENT EFFECTS IN VASCULAR SMOOTH MUSCLE CELLS: ROLE OF AP-1**

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Angiotensin II-driven stimulation of vascular smooth muscle cell (VSMC) growth determines the response of the vascular wall to hypertension. We, therefore, examined the effects of retinoids, powerful anti-proliferative and anti-inflammatory agents on the actions of angiotensin II and their mechanism of interaction in VSMC primary culture.

VSMCs express both RXRα and RARα protein. All-trans RA inhibited angiotensin II-induced i) cell proliferation during long-term exposure dose-dependently and ii) DNA- and protein synthesis as indicated by prolin- and thymidine incorporation. RA reversed Ang II-dependent morphological changes back to a „neural-like“ phenotype and completely blocked Ang II stimulation of TGFβ1 mRNA. RA inhibition of VSMC growth was mediated both via RAR- and RXR-dependent pathways as shown by synthetic receptor-specific retinoids. Transfection experiments revealed that RA inhibits Ang II actions via AP-1 but not via SRE or Cre. RARα cotransfection alters the anti-AP-1 effect of RA in a dose-dependent manner. AP-1 mediated inhibition was equipotent after cotransfection with either RARα or RXRα-construts.

Our findings demonstrate that retinoids are potent inhibitors of the proliferative actions of angiotensin II in vascular smooth muscle cells. This suggest that retinoids influence vascular changes in response to hypertension also in vivo.

Key Words: Angiotensin II; Retinoids; AP-1; vascular

**MECHANISMS OF INCREASED SUSCEPTIBILITY TO ANGIOTENSINII-INDUCED APOPTOSIS IN CARDIOMYOCYTES FROM SPONTANEOUSLY HYPERTENSIVE RATS**

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Previous findings show that hypotensive doses of losartan normalize the excess of apoptosis present in the hypertrophied left ventricle of adult SHR. This study was designed to determine whether angiotensin II is directly involved in stimulation of apoptosis in ventricular cardiomyocytes isolated from adult SHR. Primary cultures of ventricular cardiomyocytes from 30-week-old normotensive Wistar-Kyoto rats (WKY) and SHR were exposed to 10⁻⁹ M angiotensin II, for 24 h. Apoptotic cells were assessed by terminal deoxynucleotidyl transferase assay and confirmed by Annexin V detection. The expression of Bax-α mRNA was assessed by Northern blot and Western blot. The expression of proteins p53, Bax-α, procaspase 3 and caspase 3 was assessed by Western blot. Angiotensin II resulted in stimulation of apoptosis and Bax-α protein in cardiomyocytes from the two strains of rats, these effects being higher (P < 0.05) in SHR cells than in WKY cells. The caspase 3: procaspase 3 ratio (an index of caspase 3 activation) was increased (P < 0.05) in a similar extent in cells from the two strains incubated with angiotensin II. No changes in Bax-α mRNA and p53 were observed in cardiomyocytes incubated with angiotensin II. Losartan inhibited (P < 0.05) angiotensin II-induced apoptosis, Bax-α protein expression and caspase 3 activation in cells from the two strains of rats. These results indicate that cardiomyocytes from the left ventricle of adult SHR exhibit increased susceptibility to the ability of angiotensin II to induced apoptosis via the AT1 receptor. The mechanisms of this abnormality involve changes in the post-transcriptional processing of Bax-α that result in accumulation of the protein and the subsequent stimulation cell death effectors different from caspase 3.

Key Words: Apoptosis; Bax; Caspase 3; Angiotensin II; Spontaneously hypertensive rats; Losartan