178A ASH XIV ABSTRACTS

C005
ANGIOTENSIN IV ACTIVATES NUCLEAR TRANSCRIPTION FACTOR-KAPPA B (NF-ßB) AND ACTIVATOR PROTEIN-1 (AP-1) IN VASCULAR SMOOTH MUSCLE CELLS
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Angiotensin (Ang II) activates several transcription factors in vascular smooth muscle cells (VSMC), including NF-ßB and AP-1. In our study, we investigated whether Ang IV, an Ang II metabolite with a non-peptide structure, could activate NF-ßB and AP-1, as well as the receptor subtypes involved in this process. Growth-inactivated VSMC were incubated with Ang IV (10^{-7} to 10^{-5}M) for increasing periods of time, and compared to Ang II. After 6h of treatment, Ang IV caused a dose-related NF-ßB activation (maximal at 10^{-5}M). In controls, no effect was seen on Ang II stimulation.

C006
ANG II-INDUCED PROTO-ONCOGENE EXPRESSION IS ALTERED IN VASCULAR SMOOTH MUSCLE CELLS FROM ESSENTIAL HYPERTENSIVE PATIENTS: IMPLICATIONS IN VASCULAR REMODELING.
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We previously demonstrated that Ang II-induced vascular smooth muscle cell (VSMC) growth is augmented in cells from hypertensive patients. To investigate the molecular mechanisms underlying this phenomenon, we examined the effects of Ang II on expression of c-fos, c-myc and c-jun. A role in cellular growth responses. VSMC (passages 4-6) derived from subcutaneous gluteal biopsies of normotensive (n=3) and hypertensive subjects (n=4) were studied. Cells from normotensive subjects, Ang II (10^{-7} mol/L) increased c-fos expression (138 % of control) but had no effect on expression of c-myc or c-jun. In cells from hypertensive patients, Ang II increased expression of c-fos (333 % of control) and c-myc (230 % of control) but had little effect on c-jun. Ang II-stimulated NF-ßB activation, a dose-related NF-ßB activation, Ang II-stimulated nuclear translocation of p50/p65 heterodimers. By Western blot, c-jun degradati,w was increased up to 18h, similar to Ang II. To determine which transcription factor was involved in NF-ßB activation, we investigated whether Ang II-stimulated c-fos expression contributes to enhanced cell growth in hypertensio, cells from hypertensive patients were transfected with antisense c-fos oligonucleotides. Ang II-stimulated 3H-thymidine incorporation (index of VSMC hyperplasia) was reduced (p<0.05).

C007
SEVERE HYPERTENSION IS ASSOCIATED WITH REDUCED ENDOTHELIAL FUNCTION IN THE RESISTANCE ARTERIES INDEPENDENTLY OF METABOLIC DISTURBANCES.
A. LIFE STUDY.
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The objective of the study was to investigate whether endothelial function in patients with hypertension and left ventricular hypertrophy was related to increased blood pressure or metabolic disturbances. In 42 patients with essential hypertension and left ventricular hypertrophy on ECG we measured after two weeks of placebo treatment blood pressure value of 82 mmHg maximal acetylcholine-induced vasodilatation, Insulin resistance and plasma lipids.

C008

An association of endothelial dysfunction with enhanced production of superoxide has been reported in the aorta of SHR. It has been shown that Ang II induces superoxide production, by upregulating expression of p22phox, a component of the NADPH/NADH oxidase. To investigate the regulation of endothelial dysfunction in hypertension we studied the expression of p22phox mRNA in the aorta of 16-week old Wistar Kyoto rats (WKY) and SHR, 16-week old SHR (SHR, 30-week old SHR (SHR) and 30-week old SHR treated during 14 weeks with ibesimine (SHR)). Systolic blood pressure (SBP) was measured by the tail-cuff method. The expression of p22phox mRNA was assessed by competitive reverse transcription-polymerase chain reaction. We observed that p22phox mRNA expression and endothelium-dependent relaxations were analyzed in normotensive rats treated with acetycholine, In SHR, no differences were found in p22phox mRNA level and endothelium-dependent relaxations to Ach between WKY rats and SHR. As compared to WKY, p22phox mRNA exhibited increased (p<0.01) in SHR, a decrease in (p<0.01) and endothelium-dependent relaxations to Ach. The chronic administration of ibesimine was associated with normalization of p22phox mRNA expression and endothelium-dependent relaxations to Ach. The SHR exhibited reduced expression of mRNA, increased levels of SBP above those reported in WKY rats. These results suggest that the association exists between endothelial dysfunction and p22phox mRNA overexpression in the aorta of adult SHR. Despite a non complete correction of hypertension, chronic blockade of AT, receptors prevents p22phox mRNA overexpression and corrects endothelial dysfunction in the aorta of treated SHR. It can be proposed that the functional activity of AT, receptors may be involved in endothelial dysfunction of SHR via translocation of p50/p65 heterodimers. By Western blot, c-jun degradati,w was increased up to 18h, similar to Ang II.