critical factor both in cardiovascular physiology and pathophysiology. Therefore, we investigated the effect of chronic consumption (16 weeks and 78 weeks) of various concentrations of ethanol (0, 6, 12, 18%, v/v) on ACE metabolism in the rat (n=5/group).

There was a significant dose-dependent decrease in plasma ACE activity in rats at 78 weeks not observed at 16 weeks. In addition, myocardial ACE activity was also decreased dose-dependently at 78 weeks, while myocardial protein and mRNA for ACE were both increased. These changes were not observed at the earlier time point. There were no changes in blood pressure between groups at either time point. These findings indicate that ethanol, or a metabolite, is a direct inhibitor of ACE. Our finding of a decrease in ACE activity associated with chronic ethanol consumption provides new insights into the influence of ethanol consumption on various disease processes.

Key Words: Ethanol, Chronic Consumption, ACE Inhibition

P-501
ROLE OF OXIDATIVE STRESS AND CARDIAC CALCINEURIN IN ANGIOTENSIN II-INDUCED HYPERTENSION
Ming-Sheng Zhou, Leopoldo Raji, Nephrology and Hypertension Division/Vascular Biology Institute, University of Miami School of Medicine and Miami VAMC, Miami, FL, United States.

In the present study we investigated the relationship between superoxide anion O$_2^-$ generation and end-organ damage in angiotensin II (Ang II)-induced hypertension. Sprague-Dawley rats received Ang II (0.7 mg/kg/day, n=7) or vehicle (n=7) SC for 5 days by mini-pump. We determined O$_2^-$ production by lucigenin chemiluminescence and laser-confoocal fluorescence microscope (LCM) in the aorta and heart (left ventricle [LV]) and by the assay of NADPH/NADH oxidase activity in the kidney and LV. The Ang II rats developed hypertension (183±3 vs. 138±2 mm Hg; P<0.05), aortic and LV hypertrophy (8% and 10%, respectively; P<0.05) and proteinuria (21.4±0.5 vs 5.1±0.3 mg/24 h; P<0.05). In Ang II rats, we did not detect any increase in O$_2^-$ production in the LV by lucigenin, LCM or NADPH/NADH oxidase assay. However, O$_2^-$ production significantly increased by lucigenin (1799±176 vs. 1213±181 cpm/mg; P<0.05) and LCM (1969±158 vs. 1474±154 pixels, P<0.05) in the aorta and by NADPH oxidase assay in the kidney (51217±5233 vs. 35017±6985 cpm/mg, P<0.05). Studies in cultured cardiac myocytes have shown that Ang II increases calcineurin activity. In Ang II rats, calcineurin, which has been associated with LV hypertrophy, was significantly increased (52±8 vs 33±5 pmol/mg/min, P<0.05). These studies suggest that in the aorta and the kidney the effects of Ang II are linked to O$_2^-$ whereas in the heart Ang II-induced hypertrophy may be associated with calcineurin. Our studies may have important therapeutic implications.

Key Words: Angiotensin, Superoxide Anion, End Organ Damage

P-502
THE ROLE OF JAK/STAT PATHWAY IN THE REGULATION OF ANG GENE EXPRESSION
Yueling Guo, Eduardo Mascarenho, M.A.Q. Siddiqui, Anatomy and Cell Biology, State University of New York Downstate Medical Center, Brooklyn, NY, United States.

Recent work in our lab has demonstrated that janus kinase 2 (JAK2) and signal transducers and activators of transcription (STATs) pathway is involved in the activation and maintenance of the heart tissue autocrine renin and angiotensin system (RAS). The aim of the present study is to analyze whether the Jak/STAT pathway is also involved in the transcription regulation of angiotensinogen (ANG) gene in the liver.

A 688 bp 5'-flanking sequence of the ANG gene was fused to the luciferase cDNA reporter and expressed in the liver cell line (HepG2 cell) along with a constitutively active JAK2 expression plasmid in a transient transfection assay. The results showed that Jak2 activated the ANG promoter activity in a concentration-dependent manner. The activation was dependent upon Jak2 phosphorylation, as administration of tyrosine kinase inhibitor AG490, a selective inhibitor of Jak2 phosphorylation, reduced ANG promoter activity to the basal level. Mutations in the Stat domain, the target site for STAT proteins, caused loss of Jak2-mediated activation of ANG gene. Gel mobility shift assay using antibodies against STATs proteins showed that STAT5 and STAT6 are the activated proteins that interact with Stat domain. Strong protein-Stat domain DNA complex formation occurred with HepG2 cells or rat liver nuclear extracts, but not in heart tissue or cardiomyocyte extracts. When tyrphostin AG490 was injected into the rat intraperitoneally, Stat binding activity decreased significantly with a concomitant loss in the ANG mRNA level.

Taken together, these results suggest that the activation of the systemic RAS, as that of heart tissue localized RAS, is mediated by the Jak/STAT signaling via transcriptional regulation of ANG gene.

Key Words: Transcription Regulation, Angiotensionogen, JAK/STAT Pathway

P-503
CHANGES IN LDL-CHOLESTEROL DURING COMPLETE BLOCKADE OF THE ANGIOTENSIN SYSTEM IN PATIENTS WITH DIABETES AND HYPERTENSION
Giovanni Gaudio, Pietro Margaroli, Alberto Schizzarotto, Pietro M. Bossi, Attilio Cristallo, Marco Scaltritti, Ivano Cosini, Franco Rotolo, Adriano Daverio, Sergio Masnaghetti, Luigina Giusti. Internal Medicine, Bellini Hospital, Somma Lombardo, Italy; Laboratory Unit, Bellini Hospital, Somma Lombardo, Italy; Internal Medicine, University of Insubria, Varese, Italy.

Experimental evidence has suggested a possible relationship between LDL-cholesterol metabolism and the angiotensin converting enzyme system. Hypertension and diabetes-associated dyslipidemia contribute to enhance the cardiovascular risk in the diabetic population. The aim of this study was to investigate whether the complete blockade of the renin-angiotensin system (combination therapy with ACEi plus ARBs) in diabetic patients could modify the LDL plasma levels.

Sixty-two patients (pts) with type 2 diabetes on treatment with Enalapril 10 mg/day and Sulphonylurea or Metformin were submitted to clinical evaluation (body-mass index -BMI-, blood pressure -BP-, 24-h ambulatory BP monitoring and to blood sampling for metabolic profile including HbA1c, LDLc and ApoB. Afterwards, in 50/62 pts, Valsartan 80 mg/day was added and the clinical parameters, BP and metabolic profile were re-evaluated after 3 months.

In the 50 pts, at the first evaluation, the clinical BP was: 148±29/82±15 mmHg, pulse pressure (PP): 65±17 mmHg. The ambulatory BP was: 142±26/76±14 mmHg. The HbA1c was: 7.2±2 %. The lipid profile was: Total cholesterol 216±54 mg/dl, LDLc 132±40 mg/dl, HDL 49±16, triglycerides 175±111 mg/dl, ApoA 136±32, ApoB 112±34. At the second evaluation, after 3 months of combination therapy, the PP was significantly reduced, as expected (133±29/74±16; PP: 59±18 mmHg; 24-BP: 137±24/74±12 mmHg (p<.01). The LDLc and the ApoB showed a significant reduction (paired t test: p<.002 and p<.005, respectively), in presence of unchanged BMI and HbA1c.

The control group of 12 pts who did not agree to assume the combination therapy, no significant change was observed in BP or metabolic parameters.

In conclusion, in hypertensive pts with type 2 diabetes, after three months of anti-hypertensive treatment achieving the complete block of the angiotensin system, a LDLc reduction was observed in the absence of changes in BMI or glycemic parameters. These results may suggest a possible influence of the angiotensin system on lipid metabolism in humans.

Key Words: Angiotensin System, Diabetes, LDL-Cholesterol