P3.13: ROLE OF THE SEMICARBAZIDE-SENSITIVE AMINE OXIDASE (SSAO) IN CELL DIFFERENTIATION: CONSEQUENCES IN ATHEROSCLEROSIS


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enzyme, with anti-oxidative and anti-inflammatory properties, results in protection against atherogenesis. We investigated whether oxidative stress affects HO-1 induction differentially uremic or control conditions.

Methods: HOAEs were conditioned in 30% human serum conditions (pooled from 40 hemodialysis patients or 10 healthy volunteers) for 72h, followed by exposure to increasing concentrations of peroxynitrite (0.1-1mM) for 10 minutes in 100mM phosphatebuffer, pH 7.5. Additionally, HOAEs were incubated with 100mM Hemin during 6h. Cell viability was measured by MTT assay, 30 minutes after peroxynitrite exposure with or without hemin (50mM for 6h).

HO-1 expression was evaluated by RT-PCR, Western blot and ELISA.

Results: Equal cell viability was found when conditioned in uremic or control serum. Hemin treatment did not affect cell viability, but peroxynitrite treatment reduced cell viability by 23% and 43% in control and uremic serum (P<0.05 vs. control). Hemin induced a 250-fold increase in HO-1 expression in both conditions. Consistent with mRNA induction, WB and ELISA confirm the induction of HO-1 by hemin in uremic and control conditions.

Conclusion: Although uremia is considered pro-oxidative, pro-inflammatory state, uremic serum per se does not affect cell viability. Oxidative stress however affects endothelial cell viability to a larger extent in uremic conditions compared to control. More work will be needed to determine whether the induction of HO-1 by hemin is capable of abrogating oxidative-stress-induced processes, implicated in atherogenesis, in cells exposed to uremic toxins in the circulation.

P3.12 A MONOCLONAL ANTIBODY TO THE ENDOGENOUS NA/K-ATPASE LIGAND, MARINOBUFAGINEN, REDUCES PROFIBROTIC GENE EXPRESSION AND REVERSES CARDIOVASCULAR FIBROSIS IN SALT-SENSITIVE HYPERTENSION

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Salt-sensitive hypertension is accompanied by elevated levels of an endogenous Na/K-ATPase inhibitor, marinobufagenin (MBG). Because MBG is implicated in cardiac fibrosis in experimental uremic cardiomyopathy (Hypertension 2007:99:215-24), we hypothesized that immunoneutralization of heightened levels of MBG in hypertensive Dahl salt-sensitive rats (DS) with monoclonal antibody may affect the profibrotic gene expression and cardiac remodeling. We studied the following groups (n = 6 each): (a) DS on a low salt (0.3% NaCl) diet (LS); (b) DS on a high salt (8% NaCl) diet for 7 weeks (HS); (c) DS on a high salt diet for 7 weeks, followed by monoclonal anti-MB antibody treatment for 5 days (HSAB). Levels of MBG and of proteins implicated in pro-fibrotic signalling, and mRNA expression (microarray analysis) in left ventricles (LV) and aortae were assessed.

In HS vs. LS, BP increased by 74 mmHg (p<0.01), plasma MBG doubled (p<0.05), renal MBG excretion increased 6-fold (p<0.01), tissue weights increased (LV: 2.37±0.05 vs. 1.62±0.04 kg/g bw, p<0.01; aorta: 4.44±0.17 vs. 3.01±0.06 mg/mm²/kg bw, p<0.01), and LV collagen rose 3.5-fold. In HSAB, BP was reduced by 35 mmHg (p<0.01), collagen-1 and LV and aortic weights were reduced (p<0.01 vs. HS group). In hypertensive DS there was a tissue-specific pattern of up-regulation of expression of genes, implicated in TGF-β signaling (LV: TGFβ1, -3, MAKP3, CTGF, SMADs, collagen-1; aorta: TGFβ1, -3, PDGF, fibronectin, SNAI1, PCOLCE, collagens), that was down-regulated following immunoneutralization of MBG. Thus, immunoneutralization of MBG produces an anti-remodeling effect associated with down-regulation of genes implicated in TGFβ-induced fibrosis initiated by MBG in salt-sensitive hypertension.