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Atrial Natriuretic Peptide Prevented Lipid-Induced Kidney Injuries by Inhibiting Endoplasmic Reticulum Stress

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Objectives: The purpose of the present study was to investigate whether atrial natriuretic peptide (ANP) prevented lipid-induced injury through inhibiting endoplasmic reticulum (ER) stress and apoptosis in the kidney.

Methods: Western Blot, Real-time PCR, Immunofluorescence were performed

Results: In human proximal tubule HK2 cells, saturated fatty acid palmitic acid (PA) treatment (0.4mM) for 24h markedly increased protein abundance of two ER stress makers BiP (370% of controls) and CHOP (520% of controls), which was associated with upregulated cleaved-caspase 3 expression (320% of controls) and decreased ratio of Bcl2/Bax (76% of controls), two markers of apoptosis. ANP treatment (10pM) markedly decreased protein abundance of BiP (280% of controls), CHOP (370% of controls), and cleaved-caspase 3 (170% of controls), and increased the ratio of Bcl2/Bax (120% of controls) in HK2 cells treated by PA. Co-treatment with ANP and LBQ657, a neprilysin inhibitor preventing hydrolysis of ANP, showed better protective effects than ANP treatment alone in HK2 cells treated with PA. ANP is known to stimulate intracellular cGMP-PKG signaling pathway, roles of cGMP and PKG in ANP-induced protection were thus investigated. Sildenafil (an inhibitor of phosphodiesterase) and exogenous 8-Br-cGMP markedly suppressed PA-induced ER stress and apoptosis, whereas KT-5823, a selective cGMP-dependent PKG inhibitor, blocked protective effects of ANP or cGMP in HK2 cells treated with PA. Compared with controls, in mice fed with high-fat diet for 8wk, the protein expression of BiP and CHOP in the kidney cortex showed 2.8-fold and 2.3-fold increases, respectively, which was markedly prevented by sildenafil (15mg/kg·BW/day, gavage).

Conclusions: In conclusion, our data demonstrated that ANP inhibited lipid-induced ER stress and apoptosis likely via activating the cGMP-PKG signaling pathway, and it may be a potentially therapeutic target for lipid-induced kidney injury.