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Heterozygous Overexpression of Preproendothelin-1 in Endothelial Cells Enhances Thromboxane-Prostanoid Receptor-Induced Contractions in the Renal Artery of Obese Mice

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Circulating levels of the endothelium-derived peptide endothelin-1 (ET-1) are elevated in human obesity, and ET-1 mediated vascular tone is increased. The renal artery is important in controlling intrarenal blood flow and is highly sensitive to ET-1. Whether or not ET-1 affects renal artery tone in obesity is unknown. To investigate the role of endogenous ET-1, a mouse model with *tie-1* promoter-driven endothelium-restricted heterozygous overexpression of preproendothelin-1 was used (TET+/-). Obesity was induced in TET+/- and WT littermates by feeding a high fat diet for seven months; lean controls were kept on standard chow. The main renal arteries were studied in wire myographs testing contractions (in the presence of L-NAME) to ET-1, serotonin (5-HT), and U46619, targeting ET_A, 5-HT_2, and TP receptors, respectively. Contractions to ET-1 were comparable between groups (PD_2 8.29±0.05, n=6-8); 5-HT-induced responses were facilitated at lower concentrations in obese mice leading to a shift in PD_2 (lean 7.08±0.02 vs. obese 7.23±0.07, n=5-8, P<0.01). Responses to U46619 were significantly shifted to the left in renal arteries of obese animals (PD_2 8.57±0.06 vs. lean 8.21±0.05, n=5-8, P<0.001), and the area under the curve was significantly different between lean and obese TET+/- mice (AUC 418±23 vs. lean 319±25, n=5, P<0.05). Thus, TET+/- had no effect on responses in lean animals. By contrast, in obesity heterozygous overexpression of ppET-1 enhanced TXA_2-mediated, but not 5-HT or ET-1 induced contractions of the renal artery.

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The Effect of Proteinuria-Mediated Endothelin-1 Downregulation of PKCα Signalling in Proximal Tubular Cells and Its Successul Treatment is Measurable Using microRNA15a as Biomarker in Vitro and in Vivo

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In proteinuric diseases, stimulation of proximal tubule cells (RPTECs) by protein and endothelin-1 result in the activation of different signal pathways, ultimately causing renal insufficiency. Therapeutic interventions are hampered by the lack of specific and easily detectable markers. We described a regulatory pathway in which nuclear migration of protein kinase C α controls the release of pri-miRNA15a. After endothelin-1 stimulation the migration of PKCα is inhibited, and mature miRNA15a is made. Using qRT-PCR we detect miRNA15a in the urine of adult and pediatric patients with membranous or mimimal change nephropathy. By laser-microdissection this miRNA is predominantly located in the proximal tubules. In cell culture, human RPTECs produce the highest miRNA15a levels after ET-1 stimulation. In rats after 5/6 nephrectomy, miRNA15a is increased in the urine. By graded sieving and qRT-PCR, the highest amount of miRNA15a is found in the tubular fraction. Selegiline treatment upregulates PKCα in vitro and in the murine adriamycin model, significantly downregulating ET-1 induced miRNA15a production. Thus measuring urinary miRNA15a levels: i) indicates the regulation of a signal pathway in RPTECs in vivo in proteinuric conditions; ii) allows for the first time to control the effectiveness of a therapy aiming to protect proximal tubules.