Session 3: Renal Diseases

The role of endothelin in glomerular diseases: Cellular culprits, cellular targets
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The lecture will review experimental and clinical evidence for an involvement of the endothelin system in promoting glomerular dysfunction and damage. We will propose a network of pathophysiological interactions involving paracrine effects of ET-1 in the distinct glomerular cells. At last, the lecture will tease out specific pathophysiological contexts where clinical development are expected to bring fruits and would meet therapeutic needs.

We will focus on experimental evidence for a regulatory role of ET-1 in podocyte function and hypothesize non-exclusive pathophysiological involvement of the ET-1 system in different glomerular diseases with podocyte injury. First, ET-1 produced by injured glomerular or pregglomerular endothelium could be freely filtered through the filtration barrier and act on podocyte ETRs. This is expected to occur in severe hypertension, hemolytic uremic syndrome (HUS) and thrombotic microangiopathy (TMA), sickle cell disease, diabetic nephropathy (DN), connective tissue diseases and vasculitis. We will briefly review evidences for increased ET-1 activity in the vasculature in IgA nephropathy (IgAN) where vascular lesions are frequent and of prognostic value. Second, ET-1 may be produced de novo by mesangial cells. We will review the current evidence for ET-1 production by mesangial cells, in particular in DN and IgAN. Third, scarce evidence suggest that podocytes and glomerular parietal epithelial cells produce ET-1 that affects podocyte phenotype in a paracrine and autocrine fashion in vitro. In this regard we will examine the current evidences in focal and segmental glomerulosclerosis (FSGS) and crescentic glomerulonephritis. This review and further studies may assist clinicians in optimally designing clinical trials for patients at increased risk for CKD.


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 1-NMMA) to ET-1, serotonin (5-HT), and U46619, targeting ETA, 5-HT2, and TP receptors, respectively. Contractions to ET-1 were comparable between groups (PD2 8.29 ± 0.05, n = 6–8); 5-HT-induced responses were facilitated at lower concentrations in obese mice leading to a shift in PD2 (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 (PD2 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 TXA2-mediated, but not 5-HT or ET-1 induced contractions of the renal artery.


The effect of proteinuria-mediated endothelin-1 downregulation of PKCα signalling in proximal tubular cells and its successful 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