Molecular changes in proximal tubule function in diabetes mellitus

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Our studies focus on the changes in the tubulointerstitum (proximal tubule, cortical fibroblast and endothelial cells) that occur when exposed to a 'diabetic environment', i.e. high glucose, low density lipoproteins and cytokines implicated in the pathogenesis of diabtic nephropathy. The current discussion focuses on the specific changes in proximal tubule function that occur following exposure to high glucose. In the normal kidney, the proximal tubule plays a crucial role in the reabsorption of 50-70% of the filtered Na^+ and the receptor mediated uptake of the protein that crosses into the filtrate from the glomerulus. Diabetic nephropathy is frequently associated with increased Na^+ retention, proteinuria and thickening of the tubular basement membrane is the earliest histological abnormality.

Using experimental models, which include both primary cultures of human proximal tubule (hPTC) cells as well as immortalised cell lines, we found initially that high glucose increases the activity of Na^+-H^+ exchanger 3 (NHE3), the key transporter that mediates Na^+ uptake in the proximal tubule. This increase is paralleled by an increase in the mRNA for NHE3. There is also a similar increase in the activity and protein levels of the V-H^+-ATPase, which plays a role in HCO_3^- reabsorption. In a recent study we have shown that the activity of NHE3 is upregulated by exposure to albumin. NHE3 and V-H^+-ATPase are also known to be critical in the endocytosis of albumin, and indeed further studies confirmed that tubular exposure to high glucose increased albumin uptake. These data suggest a possible mechanism linking defective Na^+ reabsorption and protein handling in the kidney in diabetes mellitus.

One of the key regulators of proximal tubule function implicated in the pathogenesis of diabetic nephropathy is angiotensin II (AngII), We have shown that tubular production of AngII is increased significantly following exposure to high glucose. As AngII is also known to increase the activity of both NHE3 and V-H^+-ATPase this may underlie the abnormalities in transport and tubular protein reabsorption in diabetic nephropathy. The profibrotic cytokine transforming growth factor beta (TGFβ) has been shown to be upregulated in animal models of diabetic nephropathy and normalised by blockade of the renin-angiotensin system. We have demonstrated that high glucose induces TGFβ mRNA within 30 minutes of exposure. TGFβ in turn induces both collagen and non-collagen matrix production in the proximal tubule, an effect that is facilitated by the autocrine production of CTGF.

Thus our data provide further insights into the mechanisms by which high glucose induces tubular pathology in the human kidney and are consistent with the deleterious effects of high glucose being mediated at least in part by elevated intrarenal AngII and downstream cytokine production.