Chronic endothelin-1 infusion in rats increases glomerular permeability to albumin and proximal tubular albumin uptake as determined by intravital microscopy

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Animal and human studies demonstrate the ability of ETA receptor blockade to rapidly reduce albuminuria and proteinuria suggesting an active effect of ET-1 to control glomerular permeability. Chronic infusion of endothelin-1 (ET-1) in rats increases glomerular permeability to albumin (Palb) in an ETA dependent manner; however, ET-1 had no effect on albuminuria or arterial pressure. Therefore, we utilized in vivo intravital 2-photon microscopy to determine whether ET-1 increases glomerular albumin filtration are accompanied by an increase in albumin uptake via the proximal tubule (PT). Simonsen Munich-Wistar rats were surgically prepared for in vivo imaging (n=3). Rats were placed on the microscope stage with the exposed kidney placed in a coverslip-bottomed dish bathed in warm isotonic saline. Serum albumin conjugated to Alexa568 (AA) was acutely infused i.v. to visualize glomeruli and associated S1 segments before and after 2 wk of chronic ET-1 (2 pmol/kg/min; i.v. osmotic minipump). AA was observed to enter capillaries of superficial glomeruli, move into Bowman's space, bind to the PT cell brush border and reabsorbed across the apical membrane. Glomerular-sieving coefficient (GSC) was calculated as the ratio of AA within the glomerular capillary vs. that in Bowman's space. GSC was significantly increased in rats following chronic ET-1 infusion (0.039 ± 0.001 vs. 0.028 ± 0.001, $p<0.05$). Mean fluorescence intensity for AA in PTs was increased by ET-1: 118 ± 6 vs. 76 ± 3 pixel intensity ($p<0.05$). These findings provide direct in vivo evidence that chronic ET-1 in a non-diabetic rat increases Palb and that albuminuria is prevented by increased PT albumin uptake. (NIH P-30 O'Brien Center for Advanced Renal Microscopy)