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ANG II CONTRIBUTES PROXIMAL TUBULE REMODELING IN TRANSGENIC REN2 RATS

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Abstract

Background/Aims: Activation of the renin-angiotensin system (RAS) and subsequent elevations of tissue angiotensin (Ang) II contribute to the development of proteinuria and progressive kidney disease. Recent work suggests that proximal tubule injury contributes to development of proteinuria in addition to glomerular contributions. Thereby, the aim of this study was to determine the impact that Ang II has on renal proximal tubular cell (PTC) function in a transgenic rodent model of hypertension and nephropathy, the transgenic TG(mRen2)27 rat.

Methods: Young Ren2 (R2-T) and SD (SD-T) rats were treated with an Ang type 1 receptor (AT_1R) blocker telmisartan (2mg•kg-1•day-1) or vehicle (R2-C; SD-C) for 3 weeks and glomerular and PTC structure and function were tested.

Results: R2 rats displayed increases in systolic blood pressure and proteinuria with parallel increases in NADPH oxidase and reactive oxygen species formation. R2 rats further displayed increases in podocyte foot process effacement on ultrastructural analysis with TEM and loss of the podocyte specific protein nephrin as well as proximal tubule specific megalin. There were additional findings of proximal tubule injury with increased kidney injury molecule-1, Ser^{2448} phosphorylation of mTOR, total mTOR and downstream S6K1. Findings were temporally related to tubolinterstitial fibrosis and loss of the adhesion molecule N-Cadherin. Collective findings were improved with AT_1R blockade.

Conclusions: These observations support that Ang II contributes to both glomerular and proximal tubule contributions to proteinuria as a result of NADPH oxidase-dependent oxidative stress. Further, that Ang II contributes to proximal tubule injury and tubulointerstitial fibrosis through mTOR-dependent loss of N-cadherin.