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Balancing the Renin-Angiotensin System: A Strategy to Prevent Tubular Injury in Early Diabetic Kidney Disease

Abstract:

Diabetic Kidney Disease (DKD) is a life-threatening, progressive chronic kidney disease associated with higher rates of mortality and morbidity worldwide. DKD is a major risk factor for kidney disease progression and complete organ failure. In the early stages of DKD, the development of tubulointerstitial injury and proteinuria occurs, mainly associated with dysfunction in tubular protein reabsorption. However, the molecular mechanisms underlying these processes are still poorly understood. One possibility is the involvement of components of the Renin-Angiotensin System (RAS). Interestingly, increased levels of angiotensin II (Ang II), an octapeptide from the classical RAS, and reduced levels of angiotensin-(1-7) [Ang-(1-7)], a heptapeptide from the alternative RAS, have been observed in kidney tissues in various kidney diseases. In addition, angiotensin receptor blockers (ARBs), inhibitors of the classical RAS, have been extensively used due to their anti-proteinuric effects and their ability to improve outcomes in patients with CKD. However, it remains unclear how the interaction between these peptide pathways occurs in early DKD. Herein, we discuss how RAS peptides modulate tubular protein reabsorption dysfunction and the development of tubulointerstitial injury in early DKD. Our findings show that blocking the effects of Ang II using ARBs or increasing systemic Ang-(1-7) levels—through both pharmacological means (using an oral formulation containing Ang-(1-7) included in hydroxypropyl-β-cyclodextrin) and genetic tools (the L-3292 transgenic rat strain)—leads to amelioration of tubular proteinuria and tubular injury in animal models of DKD. These results suggest that the imbalance between the classical and alternative arms of RAS could be a key mediating mechanism. Overall, these findings expand our understanding of the involvement of RAS components in the development of tubular injuries, opening new therapeutic strategies to prevent or at least slow the progression of DKD.

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Keywords: diabetic kidney disease, renin-angiotensin system, tubular protein reabsorption, tubulointerstitial injury, angiotensin II, angiotensin-(1-7)

Biography

Dr. Diogo B. Peruchetti is a pharmacist having master (2011) and PhD (2015) degrees in physiology at Carlos Chagas Filho Biohysics Insitute from Federal University of Rio de Janeiro (UFRJ, Brazil). He also trained at Department of Physiology / School of Medicine from Johns Hopkins University (USA, 2011-2013) and a post-doc fellow in renal physiology at UFRJ (2015-2022). Nowadays, Dr. Peruchetti is associate professor at Department of Physiology and Biophysics-Insitute of Biological Science from Federal Universtity of Minas Gerais (UFMG, 2022-) and leader of ReMPhy - Renal Molecular Physiology Research Group.