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Cyclo(His-Pro) prevents against oxidative stress-induced renal injury through activating Nrf2-mediated pathway.

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Objectives: Apoptosis is a key feature of the pathogenicity associated with glomerular and tubulo-interstitial injury of acute kidney injury (AKI) and chronic kidney disease (CKD). Cyclo(His-Pro) (CHP) is an endogenous cyclic dipeptide that exerts cellular protective effects against oxidative damages. Here, we show that treatment with exogenous (recombinant) CHP prevented renal structural and functional injury triggered by experimental ischemia-reperfusion injury (IRI) model in mice as well as 5/6 nephrectomy (Nx) model in rat.

Methods: In this study, to investigate the effect of CHP on AKI, we used IRI mice model and hypoxia-induced in vitro models with cultured human tubular epithelial cells (TECs). In addition, 5/6 nephrectomy rat model and TGFβ- and hydrogen peroxide (H₂O₂)-induced apoptosis models with cultured human podocytes were employed.

Results: Exogenous CHP pre-treatment prevented kidney function and accompanied by a significant reduction in ischemia-induced tubular injury, apoptosis, and inflammatory cell infiltration on renal IRI model. In vitro stimulation of TECs with hypoxia, CHP-mediated renal protection was associated with reduced IL-11, IL-18, reactive oxygen species (ROS) and the proportion of dead cells. Compared with control-treated 5/6 Nx rat, CHP-treated 5/6 Nx rat also restored kidney function and decreased proteinuria and pathologically decreased glomerulosclerosis, tubule-interstitial fibrosis in the remnant kidney of 5/6 nephrectomized rat. The administration of exogenous CHP significantly reduced not only ROS production via Nrf2-dependent pathway, but also the resultant apoptosis induced by H₂O₂ in cultured human podocytes. Microarray analysis highlights a cascade of specific gene expression patterns related to kidney injury, repair, and innate immunity. Notably, tubular epithelial cell and podocytes cell cycle arrest in G2/M mediates oxidative stress after injury.

Conclusions: This study has uncovered a major protective role of CHP in renal IRI and 5/6 nephrectomy through TECs and podocytes regeneration that could be potentiated as a therapeutic strategy.