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**A novel drug development to attenuate the progression of kidney fibrosis:
Cyclo (Histidine-Proline).**

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Objectives: Apoptosis is a key feature of the pathogenicity associated with glomerular and tubulo-interstitial injury of chronic kidney disease (CKD). Cyclo(His-Pro) (CHP) is an endogenous cyclic dipeptide that exerts cellular protective effects against oxidative damages.

Methods: We developed a synthetic CHP that could be treated exogenously by oral intake. To determine whether the exogenous CHP treatment might reduce kidney fibrosis, a mouse model of kidney fibrosis disease induced by unilateral ureteral obstruction (UUO) was introduced and subsequently validated with fibrosis induced primary cultured podocytes with hydrogen peroxide (1 μ M). To investigate the therapeutic effects of the novel drug, CHP was treated in a various time point both in in vivo and in vitro models; pre- and post-treatment of CHP was administrated 2 days before and after UUO operation and 1 hour before and after H₂O₂ injury, and CHP was treated on the day of UUO operation or with H₂O₂, respectively.

Results: Two weeks after UUO, renal fibrosis was extensive; however exogenous CHP treatment (20mg/kg) showed significant reduction in tubular injury, apoptosis, and kidney fibrosis. The protein expression of fibronectin and phospho-form p65 was suppressed and Nrf2 was increased after CHP administration. In vitro stimulation of podocytes with H₂O₂, CHP-mediated renal protection was associated with reduced mRNA expression of p53, p21, reactive oxygen species (ROS) and the proportion of dead cells. The administration of exogenous CHP induced Nrf2 and ZO-1 gene expressions. These reno-protective effect showed consistently regardless of the timing of CHP treatment. Collectively, we suggest that the mechanisms driving renal protective effect in response to CHP treatment is the anti-oxidant effect via Nrf2 pathway activation.

Conclusions: This study demonstrated a major protective role of CHP on renal fibrosis. The novel drug might have not only a protective role but also as a therapeutic option which could be used in CKD patients.