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Dehydropeptidase-I inhibitor reduces tacrolimus-induced kidney injury by anti-oxidative and anti-apoptotic effect

Kang LUO, Jian JIN, Long JIN, Sun woo LIM, Byung ha CHUNG, Hyeon seok HWANG, *Chul woo YANG

Transplant Research Center, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea, Korea,South

Objectives : Cilastatin is an inhibitor of dehydropeptidase-I which enhances the antibacterial activity of imipenem. Dehydropeptidase I is associated with not only the metabolism of the enzyme but also the formation of possible renal toxic products. At present, role of cilastatin in chronic Tacrolimus (TAC) nephropathy still unclear.

Methods : Chronic TAC nephropathy was induced by administering TAC (1.5 mg/kg/day, subcutaneously) to rats on a low-salt diet (0.05%) with cilastatin (75 or 150 mg/kg/day, intraperitoneal injection) for 4 weeks. The effects of cilastatin on TAC-induced renal injury were evaluated in terms of renal function, tubulointerstitial inflammation and fibrosis. As a possible mechanism, we evaluated the effect of cilastatin on TAC-induced oxidative stress and apoptosis.

Results : Chronic TAC nephropathy was confirmed with impaired renal function and typical striped interstitial fibrosis. Combined treatment of TAC and cilastatin attenuated TAC-induced kidney dysfunction (serum creatinine, blood urea nitrogen, creatinine clearance, urine microalbumin) and interstitial fibrosis and maker of profibrotic cytokine (α-smooth muscle actin, transforming growth factor β1). Also, cilastation treatment decreased TAC-induced interstitial inflammation, demonstrated by decreased the ED-1-positive cells and pro-inflammatory cytokine (osteopontin) expression. Oxidative stress, a common mechanism of calcinurin inhibitor nephrotoxicity, was decreased with cilastatin treatment, demonstrated by decreased 8-OHdG and increased manganese superoxide dismutase. The increased number of TUNEL-positive cells and pro-apopptic active caspase-3 and decreased antiapoptotic Bcl-2 expression by TAC was reversed with cilastatin treatment.

Conclusions : Cilastatin has anti-oxidative and anti-apoptotic properties and this may be responsible for protection of TAC-induced nephrotoxicity.

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