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Cilastatin preconditioning attenuates oxidative stress and apoptosis through hypoxia inducible factor-1α activation in renal ischemia-reperfusion injury

Yu Ah Hong[1], So Young Jung[2], Keum Jin Yang[2], Jung Ho Kim[1], Yoon Kyung Chang[1], Cheol Whee Park[3], Chul Woo Yang[3], Suk Young Kim[1], Dai Sig Im[4], Hyeon Seok Hwang[5]
[1]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of
[2]Department of Clinical Research Institute, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Republic of
[4]Department of Department of Chemistry, College of Natural Sciences, Soonchunhyang University College of Medicine, Korea, Republic of
[5]Department of Internal Medicine-Nephrology, Kyung Hee University School of Medicine, Korea, Republic of

Objectives: Cilastatin is a specific inhibitor of renal dehydrodipeptidase-1 (DHP-1). We investigated whether cilastatin preconditioning attenuates apoptosis via hypoxia inducible factor-1α (HIF-1α) activation in renal ischemia-reperfusion (IR) injury.

Methods: *In vitro*, human proximal tubular cell line (HK-2) was exposed to ischemia by mineral oil monolayer. *In vivo*, Male C57BL/6 mice were subjected to 23 min of bilateral kidney ischemia and 24 h reperfusion. The effects of cilastatin preconditioning were investigated in IR injury models.

Results: In HK-2 cells, HIF-1α expression was most highly increased at 200 μg/ml and 6 h after cilastatin preconditioning. Cilastatin increased HIF-1α translation via phosphorylation of Akt and mTOR expression followed by increases of EPO and VEGF expression in a time-dependent manner. Cilastatin did not affect the expression of HPD and pVHL expression, but the ubiquitination of HIF-1α expression was significantly decreased after cilastatin preconditioning. Cilastatin prevented the HK-2 cell death induced by IR injury. This protective effect of cilastatin in IR-exposed cells was offset by YC-1 or HIF-1α small interfering RNA. In consistent with *in vitro* study, HIF-1α expression and its upstream and downstream signaling were significantly increased by cilastatin in a time dependent manner. Cilastatin preconditioning further increased HIF-1α expression and decreased HIF-1α ubiquitination in mice kidney with IR injury. Cilastatin decreased serum creatinine level and tubular necrosis were decreased in mice kidney with IR injury. Cilastatin decreased tissue MDA levels, expression of Bax/Bcl-2 and TUNEL-positive cells in mice kidney with IR injury.

Conclusions: Cilastatin preconditioning attenuates oxidative stress and apoptosis through HIF-1α activation induced by activating Akt-mTOR signaling and inhibiting ubiquitination of HIF-1α in renal IR injury.