PARICALCITOL PRETREATMENT ATTENUATES APOPTOSIS AND INFLAMMATION IN RENAL ISCHEMIA-REPERFUSION INJURY VIA PROSTAGLANDIN E2 RECEPTOR EP4

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Introduction and Aims: The protective mechanism of paricalcitol remains unclear in renal ischemia-reperfusion (IR) injury. We investigated whether paricalcitol attenuates apoptosis and inflammation in renal IR injury through the prostaglandin E2 (PGE2) receptor EP4.

Methods: Human proximal tubular cells (HK-2) were exposed to ischemia and LPS treatment. Male C57BL/6 mice were subjected to 23 min of bilateral kidney ischemia and 24 h reperfusion. The effects paricalcitol pretreatment with or without EP4 antagonist was investigated in both in vitro and in vivo models.

Results: Paricalcitol treatment upregulated the expression of cyclooxygenase-2, PGE2 and EP4 in HK-2 cells. Paricalcitol pretreatment prevented the HK-2 cell death induced by IR and LPS exposure, and the cotreatment of EP4-specific antagonist offset these cell-protective effects. The phosphorylation of Akt and CREB protein increased after paricalcitol pretreatment in IR-exposed cells. EP4 antagonist blunted the phosphorylation of these cell survival signals and inhibited the suppressive effects of paricalcitol on p65 NF-κB activation in LPS-exposed cells. In mice kidneys with IR injury, EP4 antagonist restored serum creatinine elevation and tubular necrosis, which was improved by paricalcitol pretreatment. Decreased TUNEL-positive cells, decreased Bax, and increased Bcl-2 expression were observed in paricalcitol-treated kidneys with IR injury, and the infiltration of inflammatory cells and the production of proinflammatory cytokines were also attenuated. The cotreatment with EP4 antagonist abolished all of these anti-apoptotic and anti-inflammatory effects.

Conclusions: EP4 plays a pivotal role in the anti-apoptotic and anti-inflammatory effects of paricalcitol pretreatment in renal IR injury.