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Acute Kidney Injury

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Paricalcitol pretreatment attenuates apoptosis and inflammation in renal ischemia-reperfusion injury via EP4 pathway

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Background: We investigated whether paricalcitol attenuates apoptosis and inflammation in renal ischemia reperfusion (IR) injury through the prostaglandin E_2 receptor (PGE_2) EP4.

Methods: HK-2 cells were exposed to ischemia and lipopolysaccharide (LPS) treatment. Male C57BL/6 mice were subjected to bilateral kidney ischemia for 23 min and reperfusion for 24 h. The effects of paricalcitol pretreatment with and without EP4 blockade were investigated.

Results: Paricalcitol upregulated the expression of cyclooxygenase-2, PGE_2, and EP4 in HK-2 cells. Cellular membrane expression of EP4 was increased in paricalciol-treated cells with and without IR exposure. Paricalcitol pretreatment prevented cell death induced by IR and LPS exposure, and EP4 antagonist co-treatment offset these protective effects. Paricalcitol increased the phosphorylation of Akt and cyclic AMP-responsive element binding protein (CREB) in IR-exposed cells and suppressed nuclear factor-κB (NF-κB) activation in LPS-exposed cells. EP4 antagonist and small interfering RNA against EP4 blunted these cell survival signals and inhibited the suppressive effects of paricalcitol on nuclear translocation of p65 NF-κB. *In vivo* studies showed that paricalcitol pretreatment improved renal dysfunction and tubular necrosis after IR injury, and co-treatment with EP4 antagonist inhibited the protective effects of paricalcitol. Phosphorylation of Akt increased and nuclear translocation of p65 NF-κB decreased in paricalcitol-treated mice kidney with IR injury. Paricalcitol pretreatment decreased terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeled (TUNEL)-positive cells, increased protein expression of B cell leukemia/lymphoma 2 (Bcl-2), and decreased expression of BCL-2-associated X (Bax), and attenuated the infiltration of inflammatory cells and production of proinflammatory cytokines after IR injury. Co-treatment with EP4 antagonist abolished all of these anti-apoptotic and anti-inflammatory effects.

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

Keywords: Apoptosis, EP4, Inflammation, Ischemia-reperfusion injury, Kidney, Paricalcitol