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Effects of Paricalcitol on Cisplatin-induced Renal Injury in Rats

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Since paricalcitol (19-nor-1,25-dihydroxyvitamin D2) has been known by its renoprotective effects, we tested whether it can blunt renal dysfunction and fibrosis in a rat model of cisplatin-induced nephropathy. Male Sprague-Dawley rats were treated with either vehicle, single intraperitoneal injection of cisplatin (6 mg/kg) or cisplatin plus paricalcitol (0.2 μg/kg/d, s.c.), for 5 days. The expression of transforming growth factor (TGF)-β1, Smad/Mitogen-activated protein (MAP) kinase signaling, apoptotic markers and epithelial-to-mesenchymal transition (EMT) markers were assessed by Western blot analysis and/or immunohistochemistry. Renal expression of tumor necrosis factor (TNF)-α, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 was determined by RT-PCR. Cisplatin increased plasma creatinine levels and decreased creatinine clearance, which were ameliorated by paricalcitol co-treatment. Cisplatin significantly increased the expression of TNF-α, ICAM-1 and VCAM-1, which were reduced by paricalcitol co-treatment. Paricalcitol also suppressed the cisplatin-induced increases of TGF-β1 expression and Smad -2, -3 and -4 signaling. Cisplatin decreased the expression of E-cadherin, increased that of α-smooth muscle actin and increased that of vimentin, which were attenuated with paricalcitol co-treatment. In HK-2 cells, paricalcitol attenuated the cisplatin-induced increases of phosphorylated extracellular signal-regulated kinase (ERK) 1/2 levels. Furthermore, paricalcitol effectively prevented TGF-β1-induced EMT processes. Paricalcitol also ameliorated the cisplatin-induced increases of fibronectin and connective tissue growth factors in HK-2 cells. Paricalcitol decreased the number of tubular epithelial cells containing TUNEL-positive nuclei and reduced the expression of pro-apoptotic markers such as bad, bax and cleaved caspase-3 in cisplatin-treated HK-2 cells. These results suggest that paricalcitol appears to attenuate cisplatin-induced nephropathy through the suppression of inflammatory, fibrogenic and apoptotic factors, of which underlying mechanisms may include an inhibition of TNF-α, Smad and ERK signaling pathways.

Key Words : Cisplatin, Paricalcitol, 급성신손상
Cisplatin; Paricalcitol; Acute Kidney Injury