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Paricalcitol Attenuates Cisplatin-Induced Renal Injury by Suppressing Apoptosis and Proliferation

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Background: Cisplatin is one of widely used chemotherapeutic agents. However, approximately one-third of patients experience renal injury with cisplatin treatment. Paricalcitol is an active vitamin D analog that is renoprotective in various experimental nephropathy models. We investigated the efficacy of paricalcitol in preventing the progression of cisplatin-induced kidney injury.

Methods: Male Sprague-Dawley rats were treated with vehicle (n=12), cisplatin (n=12, 6 mg/kg/day, i.p.), or cisplatin+paricalcitol (n=12, 0.2 μg/kg/day, s.c.) for 4 days. In another series of experiment, HK-2 cells were treated with cisplatin (50 μM), either with or without paricalcitol (0.2 ng/ml), and were examined of their expression of mitogen-activated protein kinases (MAPKs), epithelial-to-mesenchymal transition (EMT), and apoptotic factors.

Results: Paricalcitol counteracted the cisplatin-induced decline in renal function. Paricalcitol also suppressed the expression of TGF-β1, Smad signaling, and the subsequent EMT process in cisplatin-treated rats. Accordingly, renal expression of BMP-7 decreased significantly, which was reversed by paricalcitol. Cisplatin induced the expression of TNF α, which was also attenuated by paricalcitol. The number of tubular epithelial cells containing TUNEL-positive nuclei was decreased by paricalcitol. In addition, paricalcitol augmented the expression of p27kip1 and decreased the number of PCNA-positive cells. It reduced the expression of CDK2/cyclin E. H&E staining revealed increased cisplatin-induced tubulointerstitial damage and vimentin staining confirmed EMT, which were reversed by paricalcitol. In HK-2 cells, paricalcitol suppressed the cisplatin-induced increases in MAPKs phosphorylation and in fibronectin/CTGF expression. Paricalcitol co treatment also reduced cisplatin-induced over expression of p53, which coincided with a decrease in pro-apoptotic markers such as Bad, Bax, and total/cleaved caspase-3.

Conclusion: These results suggest that paricalcitol may attenuate cisplatin-induced renal injury by suppressing apoptotic and proliferative factors. Its underlying mechanisms may include inhibition of TGF-β1, MAPK signaling pathways, p53-induced apoptosis, and augmentation of p27kip1 over expression.

Key Words: Cisplatin, Paricalcitol, Apoptosis, Proliferation