한국쿄와하코기린 신진연구비

Paricalcitol Attenuates 4-hydroxy-2-hexenal-induced Inflammation and Epithelial-mesenchymal Transition in Human Renal Proximal Tubular Epithelial Cells

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4-Hydroxy-2-hexenal (HHE), the aldehyde product of lipid peroxidation, may be responsible for the pathogenesis of progressive renal disease. Recently, paricalcitol (19-nor-1,25-dihydroxyvitamin D2) was shown to be renoprotective through its anti-inflammatory and antifibrotic effects in various experimental nephropathy models. In this study, we investigated the effects of paricalcitol on inflammation and epithelial-mesenchymal transition (EMT) after HHE-induced renal tubular epithelial cell injury. To investigate the molecular mechanisms underlying HHE-induced renal tubular cell injury, the human proximal tubular epithelial (HK-2) cells cultured with 10 μM HHE in the presence or absence of paricalcitol. In HK-2 cells, paricalcitol attenuated the HHE-induced expression of extracellular signal-regulated kinase, c-Jun N- terminal kinase, and p38 mitogen-activated protein kinase, and prevented nuclear factor-κB (NF-κB) activation. The expression of the inflammatory proteins inducible nitric oxide synthase and cyclooxygenase-2 was attenuated by paricalcitol pretreatment. In addition, HHE increased the expression of the transforming growth factor (TGF)-β/Smad signaling proteins and fibrotic proteins, such as α-smooth muscle actin and connective tissue growth factor; this inducible expression was suppressed by pretreatment with paricalcitol. Treatment with HHE resulted in the activation of the β- catenin signaling pathway, and paricalcitol pretreatment reduced the expression of β-catenin in HHE-treated HK-2 cells. Coimmunoprecipitation shows that paricalcitol induced vitamin D receptor (VDR)/β-catenin complex formation in HK-2 cells. Also immunofluorescence staining revealed that co- localization of VDR and β-catenin in the nuclei. ICG-001, an inhibitor of β-catenin, decreased the expression of TGF-β1 and attenuated HHE-induced tubular EMT. These results show that paricalcitol attenuated HHE-induced renal tubular cell injury by suppressing inflammation and EMT process through inhibition of the NF-κB, TGF-β/Smad, and β-catenin signaling pathways.

Key Words: HHE, HK-2 cells, Paricalcitol