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다낭신에서 유발되는 낭포와 신장섬유화에 Paricalcitol의 효과

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Paricalcitol Attenuated Cyst Formation and Phenotype Transition of Renal Tubular Cells in Polycystic Kidney

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Introduction and aims: Recent data demonstrated the reno-protective effect of vitamin D analogs via anti-inflammatory, immunomodulatory and anti-fibrotic effects. Polycystic kidney disease (PCK) is the most common inherited disease characterized by multiple cysts formation accompanied by renal fibrosis. There have been no studies investigating whether vitamin D imposes any effect on cyst formation, growth & renal fibrosis in PCK. We examined the effect of paricalcitol on in-vitro and in-vivo cyst formation and phenotype transition or renal tubular cells.

Methods: 3D culture system of forskolin-treated Madin-Darby Canine Kidney (MDCK) cells was used to examine the effect of paricalcitol (20 nM) on cyst development. Effect of paricalcitol on TGF-β (10 ng/ml)-induced phenotype transition of cyst-lining epithelial cells (WT9-12 cell) was evaluated with an assessment of phosphorylation of B-Raf, ERK1/2 MAPK, GSK-3β, nuclear translocation of β-catenin and the expression of cyclic adenosine monophosphate (cAMP). In in-vivo experiment, paricalcitol (50 ng/kg/day, intraperitoneal) was administered in 3-week-old juvenile cystic kidney (jck) mouse for 3 weeks with an assessment of renal function and pathology at 6 weeks.

Result: Paricalcitol significantly inhibited both forskolin-induced cyst formation, cAMP and growth of MDCK cells with an attenuation of B-Raf, ERK1/2 MAPK activation. Paricalcitol also inhibited TGF-β-induced increase of vimentin and fibronectin in WT9-12 cells with an amelioration of p38- and ERK1/2 MAPK activation, GSK-3β phosphorylation and nuclear translocation of β-catenin. In paricalcitol-treated jck mice, kidney weight/body weight, serum creatinine, cyst size and interstitial fibrosis score were significantly lower compared to vehicle-treated mice. Altered expression of E-cadherin and α-smooth muscle actin in 6-week-old jck mice was alleviated in paricalcitol-treated mice.

Conclusion: Paricalcitol ameliorated cyst formation and pro-fibrotic phenotype transition of renal tubular cells in renal tubular cells and animal model of PKD, which can be one of the therapeutic options targeting early and late mechanisms of renal disease progression in PKD.

Key Words: 다낭신
Polycystic kidney disease, Paricalcitol