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The Effect of Targeted Rho-kinase Inhibition on Cyclosporine-induced Nephrotoxicity in Rats

전남대학교 의과대학 내과학교실[1], 전남대학교 의과대학 생리학교실[2]

박정우[1] · 박천훈[2] · 김인진[2] · 배은희[1] · 마성권[1] · 이종은[2] · 김수완[1]

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Jeong Woo Park[1], Cheon Hoon Park[2], In Jin Kim[2], Eun Hui Bae[1]
Seong Kwon Ma[1], JongUn Lee[2], Soo Wan Kim[1]

Department of Internal Medicine[1] Chonnam National University Medical School
Department of Physiology[2] Chonnam National University Medical School

The aim of this study was to evaluate a protective efficacy of fasudil, a Rho kinase (ROCK) inhibitor, in CsA-induced renal injury. Male Sprague-Dawley rats were treated with vehicle, CsA (20 mg/kg/d, s.c.), or CsA plus fasudil (3 mg/kg/d, i.p.) for 28 days. The expression of transforming growth factor (TGF)-β1, Smad/Mitogen-activated protein (MAP) kinase signaling, nitric oxide synthase (NOS), apoptotic markers and epithelial-to-mesenchymal transition (EMT) markers were assessed by Western blot analysis and/or immunohistochemistry. Renal expression of inflammatory markers and adhesion molecules were analyzed by real-time PCR. The mean blood CsA level was not significantly altered with fasudil co-treatment. Following the CsA treatment, creatinine clearance decreased and plasma creatinine levels increased. Urine osmolality was decreased, and albumin excretion increased. Accordingly, CsA increased the infiltration of ED-1-expressing monocyte/macrophages and the expression of inflammatory cytokines, which were attenuated by fasudil. Fasudil suppressed the expression of transforming growth factor (TGF)-β1 and Smad signaling in CsA-induced nephropathy. In addition, fasudil restored the CsA-induced decreases of endothelial NOS (eNOS), increases of inducible NOS (iNOS) and 3-nitrotyrosine. Fasudil also effectively prevented the TGF-β1-induced EMT process. CsA-induced decreases of E-cadherin, increases of α-smooth muscle actin (SMA) and increases of vimentin expression were attenuated by fasudil. In HK-2 cells, fasudil attenuated the CsA-induced increases in phosphorylated extracellular signal-regulated kinase (p-ERK) 1/2, phosphorylated c-Jun N-terminal kinase (p-JNK), and phosphorylated p38 (P-p38) and nuclear factor kappa B (NF-kB) levels. Fasudil also ameliorated the increase of fibronectin and connective tissue growth factor (CTGF) in CsA-treated HK-2 cells. In addition, fasudil 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 CsA-treated HK-2 cells. These results suggest that ROCK inhibitor appears to attenuate CsA-induced nephropathy through the suppression of inflammatory, apoptotic and fibrogenic factors, the underlying mechanism of which may include an inhibition of Smad, MAPK and NO signaling pathways.

Key Words : Cyclosporine, Fasudil, 신손상
Cyclosporine, Fasudil, Kidney Injury