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# Fasudil Prevents Cyclosporine-induced Kidney Injury by Inhibition of Smad, MAPKs, and Nitric Oxide Signaling Pathway

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## Fasudil Prevents Cyclosporine-induced Kidney Injury by Inhibition of Smad, MAPKs, and Nitric Oxide Signaling Pathway

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Rho-kinase (ROCK), an effector of Rho protein, leads to phosphorylation of downstream targets such as myosin light chain and myosin light chain phosphatase. In the kidney, an inhibition of Rho/ROCK pathway has been shown to prevent tubulointerstitial fibrosis and to ameliorate renal function without affecting systemic blood pressure. The present study was aimed to examine a protective efficacy of fasudil, a ROCK inhibitor, in cyclosporine (CsA)-induced nephropathy which includes tubulointerstitial inflammation, apoptosis, and tubular epithelial cell fibrosis. Fasudil attenuated the CsA-induced increases in inflammatory cell infiltration and inflammatory cytokine expression, consistent with the restoration of the CsA-induced decline in renal function. CsA-induced decreases of endothelial nitric oxide synthase (NOS) and increases of inducible NOS and 3-nitrotyrosine were ameliorated by fasudil cotreatment. Fasudil also reduced CsA-induced expressions of p53, which coincided with a decrease in pro-apoptotic markers in the HK-2 cells. Additionally, fasudil augmented p27kip1 expression and decreased the number of PCNA-positive cells in CsA-treated rat kidneys. It also suppressed the expression of transforming growth factor-β1, Smad signaling, and the subsequent epithelial-to-mesenchymal process in CsA-induced nephropathy. In HK-2 cells, fasudil suppressed the CsA-induced increases in mitogen-activated protein kinase (MAPK) phosphorylation. These results suggest that an inhibition of Rho/ROCK pathway attenuates CsA-induced nephropathy through suppressing inflammatory, apoptotic, and fibrogenic factors, in association with inhibition of Smad, MAPKs, and nitric oxide signaling pathways.

**Key Words:** Cyclosporine, Fasudil, 신독성
Cyclosporine, Fasudil, Renal toxicity