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Cyclosporine 신독성 쥐 모델에서 oleanolic acid가 항섬유화를 유도하는 기전에 대한 연구

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Oleanolic Acid–induced Nrf2 Activation Attenuates Renal Oxidative Stress and Tubulointerstitial Fibrosis in Chronic Cyclosporine Nephropathy

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Background: Cyclosporine (CsA)-induced kidney injury is characterized by renal dysfunction with inflammatory cell infiltrations, apoptosis and fibrosis. Nuclear factor erythroid-2-related factor-2 (Nrf2) is known to confer protection against tissue injury by orchestrating antioxidant and detoxification responses to oxidative stress. This study investigated whether upregulation of Nrf2-depedent antioxidative signaling by OA would attenuate renal inflammation fibrosis in CsA-induced kidney injury.

Methods: Male ICR mice fed a low-sodium diet were divided into four treatment groups: control, control+OA, CsA, CsA+OA. In the OA-treated groups, 25 mg/kg/day of OA was administrated by intraperitoneal injection for last 1 week of experimental period. Renal inflammation and fibrosis, markers of oxidative stress, and changes in Nrf2 signaling were subsequently evaluated at the end of 4 weeks.

Results: Following the CsA treatment, kidney function and urine osmolality were decreased, and urine volume and urinary albumin were increased. However, these findings were attenuated by OA treatment. Administration of OA decreased tubulointerstitial fibrosis score that was increased in CsA-treated mice. Increased apoptotic cell death and a high ratio of Bax to Bcl-2 expression in CsA-treated mice were also significantly ameliorated with OA treatment. Furthermore, OA treatment was attributed with the increased levels of total and nuclear content of Nrf2, and heme oxygenase (HO)-1, resulted in ameliorating oxidative stress, as reflected by decrease in urinary 8-OHdG concentrations. There were no changes in the expression of total Nrf2 and Kelch-like ECH-associated protein 1 (Keap1), indicating that oleanolic acid enhanced nuclear translocation of Nrf2.

Conclusion: Our results suggest that OA may have beneficial effects on inflammation and oxidative stress through activation of Nrf2-HO-1 signaling in the chronic cyclosporine nephropathy.

Key Words: Nrf2, 산화 스트레스, Cyclosporine 신병증
Nrf2, Oxidative stress, Cyclosporine 신병증