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만성 사이클로스포린 신독성 쥐 모델에서 Histone deacetylase의 발현

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Expression of Histone Deacetylase in a Rat Model of Chronic Cyclosporine Nephrotoxicity

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Background: It is well known that histone deacetylase (HDAC) is associated with the fibrosis of organ in pathologic state. This study was conducted to investigate the expression of HDAC in chronic cyclosporine (CsA) nephrotoxicity model and to confirm its relevance to the progression of renal fibrosis.

Methods: Chronic CsA nephrotoxicity was induced in Sprague-Dawely rats by subcutaneous injection of CsA (15 mg/kg) under the low salt diet (0.05%) for 28 days. Renal function was examined with measurement of concentrations of blood urea nitrogen (BUN) and serum creatinine, and the degree of tubulointerstitial fibrosis (TIF) was expressed as TIF score. Expression level of Acetyl-H3 protein was determined by Western blot assay, and HDAC1 and HDAC2 expression was evaluated with immunohistochemistry and Western blot. ELISA was employed to measure 8-OHdG in 24-hour urine samples, which reflects the degree of oxidative damage. The relationship between HDAC expression, interstitial fibrosis or oxidative damage was investigated.

Results: The concentrations of BUN and serum creatinine were significantly increased in the CsA group compared to the control group, and the TIF score was also significantly increase in the CsA group. Immunoreactivity of HDAC1 was observed in the distal tubule and connecting tubule and collecting duct, and its expression was significantly increased in the CsA group compared to the control (291 ± 15 vs. 100 ± 6%, $p<0.01$). The expression pattern of HDAC2 was similar to that of HDAC1. The urinary 8-OHDG was significantly higher in the CsA group than in the control group (61.2 ± 7.9 vs. 39.1 ± 4.7 ng/day, $p<0.01$), The expression of HDAC was well correlated with urinary 8-OHdG concentration ($r=0.709$, $p<0.05$) and TIF score ($r=0.895$, $p<0.01$).

Conclusion: Upregulation of HDAC by CsA-induced renal injury is closely associated with the fibrosis and that oxidative stress may be involved in this process.

Key Words: Histone deacetylase, 산화성손상, CsA
Histone deacetylase, 8-OhdG, CsA