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만성 사이클로스포린 신독성 모델에서 관찰된 오토파지의 특징

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Chronic Cyclosporine Nephropathy is Characterized by Excessive Autophagosome Formation and Decreased Autophagic Clearance

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Background: The study was performed to investigate the influence of cyclosporine (CsA)-induced renal injury on autophagy in an experimental model of chronic CsA nephropathy.

Methods: Three doses of CsA (7.5, 15, 30 mg/kg/day) were administered to mice for 4 weeks. The formation of autophagosomes was measured with LC3-II and beclin-1, and the ability of autophagic clearance was examined with sequestosome-1 (p62). Autophagic vacuoles were visualized and counted using electron microscopy (EM). Double immunolabeling of LC3-II and active caspase-3 was performed to evaluate the association between autophagy and apoptosis. Oxidative stress was evaluated by measuring urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) excretion, demonstrating oxidative DNA damage. Antioxidative drugs, pravastatin and N-acetylcysteine, were employed to evaluate the role of CsA-induced oxidative stress on autophagy.

Results: CsA treatment increased the expression of LC3-II and beclin-1 in kidney in a dose-dependent manner. The number of p62-positive cells was also significantly increased in a CsA dose-dependent manner. EM revealed excessive autophagic vacuoles in the CsA group compared with the vehicle group. Expression of active caspase-3 was increased in a CsA dose-dependent manner, and was colocalized with LC3-II in the injured area of CsA-treated kidneys. Concurrent pravastatin or N-acetylcysteine treatment reduced urinary excretion of 8-hydroxy-2'-deoxyguanosine, and subsequently decreased LC3-II expression and the number of p62-positive cells compared with the CsA group.

Conclusions: Chronic CsA nephropathy is a state of excessive autophagic vacuoles and decreased autophagic clearance. Oxidative stress may play an importation role in the induction of autophagy.

Key Words: 사이클로스포린, 오토파지, 산화성스트레스
Cyclosporine A, Autophagy, Oxidative stress