

사이클로스포린에 의해 유도된 Endoplasmic Reticulum Stress가 아포프토시스에 의한 세포사에 미치는 영향

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Purpose : It is well known that cyclosporine (CsA)-induced apoptotic death involves mitochondrial pathway, but role of endoplasmic reticulum (ER) in CsA-induced apoptotic cell death is undetermined. This study was performed to evaluate the influence of CsA-induced renal injury on ER stress using animal model of chronic CsA nephropathy.

Methods : Sprague-Dawley rats were used. Chronic CsA nephropathy was induced by administering CsA (15 mg/kg per day) subcutaneously for 7 or 28 days. Apoptotic cell death by CsA was evaluated TUNEL-staining, and activation of ER stress was evaluated with expression of ER-stress related molecules (Bip, GADD153, eIFalpha, caspase 12, caspase 3 and bcl-2 protein). Electron microscopic (EM) finding of ER was compared between the VH and CsA group.

Results : TUNEL-positive cells were not significantly increased at 1 week treatment of CsA, but 4 weeks treatment of CsA significantly increased TUNEL-positive cells compared with the VH group. The Bip mRNA and protein in CsA-treated rat kidney was maximally increased at 1 week and gradually decreased. On the other hand, GADD153 mRNA and protein was gradually increased and maximally expressed at 4 weeks. Caspase 12 protein was maximally increased at 1 week but gradually decreased. On the other hand, caspase 3 and eIF alpha proteins were significantly increased at 4 weeks treatment of CsA, and bcl-2 protein was significantly decreased at 4 weeks treatment of CsA. The EM finding revealed severe structural injury of ER in CsA-treated rat kidney compared with the VH group.

Conclusion : CsA-induced renal injury is compensated in early period by inducing ER stress, but persistent activation of ER stress may lead to apoptotic cell death in chronic CsA nephropathy.