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겐타마이신으로 유발된 급성신부전에서 소포체 스트레스의 역할

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Role of ER Stress in Gentamicin-induced Acute Kidney Injury (AKI)

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Introduction : Aminoglycoside nephrotoxicity is one of the most common causes of AKI, which accounts for 10-20% of AKI, however there are still controversies in its pathogenetic mechanisms. Recent data suggested that ER stress may play a role in the development of AKI and progression of renal disease. ER stress is a cellular stress pathway induced by the accumulation of unfolded proteins in the ER which is initially a defense mechanism of cells against various stressful environment to adaptation, however cell apoptosis develops with prolonged activation of ER stress. To understand the role of ER stress in aminoglycoside nephrotoxicity, we investigated whether gentamicin (GM) induced ER stress in the kidney with an assessment of therapeutic potential of ER stress preconditioning in GM nephropathy.

Methods : Cellular ER stress was evaluated by measurement of the expression of glucose-regulated protein 78/Grp94 and the phosphorylation of eukaryotic initiation factor (eIF2-α) by Western blotting and immunohistochemistry, and X box-binding protein (XBP-1) splicing by RT-PCR in cultured HK-2 cells. Markers of ER stress were also evaluated in the kidney of rats in which GM (100 mg/kg.day, ip, N=12) was administered for 10 days. To investigate the effect of ER stress preconditioning, tunicamycin (25 □g/kg, ip, N=12) was administered 4 days before the 1st GM injection. BUN, creatinine and proteinuria were evaluated on day 10 with histologic evaluation of the kidney. Cellular oxidative stress was evaluated by release of ROS by DCF-DA staining and FACscan analysis.

Results : GM increased the activation of eIF2-α and the expression of GRP 78/94 in NRK cells at 10 minutes and 3 hours of stimulation. Renal cortical expression of GRP and eIF2-α was also significantly increased in rats with GM nephrotoxicity from day 1 to day 10 of GM administration whereas XBP-1 splicing was comparable to control rats. Pre-treatment of tunicamycin resulted in an amelioration of proteinuria and tubular necrosis at day 10. Pre-treatment of HK-2 cells with tunicamycin (0.01 □mol/mL) for 4hrs resulted in a decreased ROS generation in GM-treated HK-2 cells.

Conclusion : Our study showed that GM-induced AKI was associated with ER stress. ER stress preconditioning protected the kidney from AKI via the mechanism of reduction of oxidative stress, suggesting that an induction of ER stress is not an epiphenomenon, but plays a key role in the pathogenesis of aminoglycoside nephrotoxicity.

Key Words : 겐타마이신, 급성신부전, 소포체 스트레스
ER stress, Gentamicin, Acute Kidney Injury