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당뇨조건하에서 kallikrein-kinin계가 족세포의 세포사멸에 미치는 영향

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Kallikrein-kinin System is Involved in Podocyte Apoptosis Under Diabetic Conditions

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Background : Previous study has shown that proteinuria and glomerulosclerosis are markedly enhanced in diabetic mice lacking the bradykinin (BK) B2 receptor. In addition, bradykinin is known to reduce mesangial cells proliferation under diabetic conditions. These findings suggest that kallikrein-kinin system (KKS) plays an important role in the pathogenesis of diabetic nephropathy (DN). However, it has never been explored whether KKS exists in podocytes and it is involved in podocyte injury under diabetic conditions.

Purpose : This study was undertaken to investigate the changes of KKS within podocytes and the functional role of BK in podocyte apoptosis under diabetic conditions.

Methods : In vivo, 32 Sprague-Dawley rats were injected either with diluent (n=16, C) or STZ IP (n=16, DM), and 8 rats from each group were treated with BK for 6 weeks. In vitro, immortalized mouse podocytes were exposed to media containing 5.6 mM glucose (NG), NG+24.4 mM mannitol (NG+M), NG+angiotensin II (NG+AII), and 30 mM glucose (HG) with or without BK. BK levels in sieved glomeruli and cell lysates were measured by ELISA. For the assessment of apoptosis, Western blot for Bax, Bcl-2, and cleaved caspase-3 were performed with sieved glomeruli and cell lysates. TUNEL assay and Hoechst 33342 staining were also performed with renal tissue and cultured podocytes.

Results : Urinary albumin excretion was significantly increased in DM rats and this increase was significantly inhibited by BK treatment. BK levels were significantly lower in DM compared to C glomeruli. HG and AII also significantly reduced BK levels in cultured podocytes. The ratios of Bax/Bcl-2 protein expression were 2.1-fold higher in DM relative to C glomeruli and 1.9- and 2.3-folds higher in podocytes exposed to HG or AII, respectively, compared to NG cells, and these increases were abrogated by the administration of BK. Western blot for cleaved caspase-3 protein showed a similar pattern to the ratios of Bax/Bcl-2 protein expression. The number of TUNEL positive-cells was significantly higher in DM relative to C glomeruli, and BK treatment significantly ameliorated the increase in apoptotic cells in DM glomeruli. Hoechst 33342 staining revealed that apoptotic cells were significantly increased in HG and NG+AII compared to NG cells, which were attenuated by BK treatment.

Conclusion : KKS seems to be involved in podocyte apoptosis under diabetic conditions and BK treatment may be beneficial in preventing DN.

Key Words : Kallikrein-kinin계, 족세포, 세포사멸
Kallikrein-kinin system, Podocyte, Apoptosis