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실험적 당뇨 백서에서 epidermal growth factor 수용체 차단제가 사구체내 세포사멸에 미치는 영향

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Epidermal Growth Factor Receptor (EGFR) Inhibitor Ameliorates Apoptosis in Experimental Diabetic Glomeruli

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Background : Kidney size is typically increased in diabetes primarily due to glomerular and tubular hypertrophy. In addition to hypertrophy, apoptosis has been documented in the course of diabetic nephropathy. To date, in spite of numerous studies on hypertrophy and apoptosis in diabetic nephropathy, little is known on the interrelationship between hypertrophy and apoptosis in diabetic glomeruli. To clarify the consequence of inhibiting hypertrophy on apoptosis in diabetic glomeruli, we examined the changes in glomerular expression of apoptosis-related molecules in experimental diabetic rats treated with a selective epidermal growth factor (EGF) receptor tyrosine kinase inhibitor, which was reported to abrogate hypertrophy in diabetic glomeruli.

Methods : Thirty-two male Sprague-Dawley rats were injected either with diluent (n=16, C) or STZ intraperitoneally (n=16, DM). After confirming diabetes, eight rats from each group were treated with 100 mg/kg/day of PKI 166 [4-(R)-phenethylamino-6-(hydroxyl)phenyl-7H-pyrrolo(2.3.d)pyrimidine] (PKI), a selective EGF receptor tyrosine kinase inhibitor. After 3 months, Western blot for apoptosis-related molecules (Bax, Bcl-2, and active caspase-3) was performed with sieved glomeruli and TUNEL staining with renal tissue. Glomerular volume was calculated according to the method of Weibel and total glomerular cell number by Exhaustive Count method.

Results : Twenty-four-hour urinary albumin excretion were significantly higher in DM compared to C rats, and PKI treatment significantly reduced albuminuria in DM rats. The mean glomerular volume in DM was 60.6% larger than in C rats, and PKI treatment for 3 months significantly prevented glomerular hypertrophy in DM rats. The ratio of Bax/Bcl-2 protein expression and active caspase-3 protein expression were significantly increased in DM compared to C glomeruli, and these changes in DM glomeruli were significantly abrogated by the administration of PKI. PKI treatment also significantly inhibited the increase in TUNEL-positive apoptotic cells within DM glomeruli. Compared to C rats, the number of total glomerular cells was significantly decreased in DM, and this decrement in DM rats was significantly ameliorated by PKI treatment.

Conclusion : PKI treatment attenuated apoptosis in diabetic glomeruli, suggesting that the inhibition of glomerular hypertrophy could inhibit glomerular cells apoptosis under diabetic conditions.

Key Words : 당뇨병성 신병증, 세포비후, 세포사멸
Diabetic nephropathy, Hypertrophy, Apoptosis