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당뇨 백서에서 신장내 산화질소 합성효소의 발현과 안지오텐진 전환효소 억제제의 조절

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Renal Nitric Oxide Synthase Expression and its Modulation by ACE Inhibitor in Streptozotocin (STZ) Induced Diabetic Rat

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Purpose : Alteration of intrarenal nitric oxide (NO) synthesis has been suggested in the pathophysiologic change of diabetic nephropathy. In the present study We tested short-term (2 weeks) and long-term effects (8 weeks) of hyperglycemia on tissue-specific endothelial NO synthase (eNOS) and inducible NOS (iNOS) expression in streptozotocin (STZ) induced diabetic rats and whether angiotensin converting enzyme inhibitor (ramipril 3 mg/kg) could modulate these changes.

Methods : Male Sprague-Dawley rats were injected with STZ and sufficient amount of insulin was provided. Systolic blood pressure, urinary albumin excretion rate and plasma and urine NOx concentration were measured. Cortical eNOS and iNOS expression were determined by the methods of RT-PCR, western blotting and immunohistochemisty at 2 and 8 weeks.

Results : In 2 weeks of hyperglycemia, diabetic rats had increased kidney weight and urinary volume. Urinary albumin excretion was markedly increased in the 8 weeks diabetic rats. Ramipril significantly ameliorated albuminuria without change of systolic blood pressure. Plasma NOx was not different between the diabetic and control rats at 2 weeks. However, plasma NOx was significantly increased at 8 weeks and it was effectively reduced by ramipril administration. Urinary NOx was not related to the change of plasma NOx. In both 2 weeks and 8 weeks, cortical expression of eNOS was not changed in diabetic rats, as compared with control rats. However, it was significantly increased in diabetic rats by 8-week ramipril administration. In the results of RT-PCR and Western blot analysis, cortical iNOS expression was not changed at 2 weeks, but it was significantly increased at 8 weeks. Ramipril administration significantly attenuated the increase of iNOS expression in RT-PCR and Western blot analysis. In immunohistochemistry, iNOS expression was not found in controls, but it was weakly stained in proximal and distal tubular cells at 2 weeks of diabetic rats. Cortical iNOS expression was markedly increased at 8 weeks in renal tubules and glomeruli, as compared with that of control rats, whereas it was significantly decreased by ramipril administration.

Conclusions : eNOS and iNOS expression was differentially affected with the development of diabetic nephropathy, and the ACEi could modify renal NOS system in STZ induced diabetic rats.