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아드리아마이신 신증에서 sitagliptin의 항산화 및 항염증 효과

한양의대 신장내과

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The Effects of Sitagliptin on NADPH-oxidase 2 in Rat Kidneys with Doxorubicin-induced Nephrosis

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Purpose: NADPH-oxidase 2 (NOX2, also termed gp91phox) binds the respective homologues, p47phox and p67phox, and NOX2-derived ROS may be proinflammatory in renal tissue. Sitagliptin, an inhibitor of the enzyme dipeptidyl peptidase-IV, has been reported to have an antiinflammatory action especially in diabetes mellitus. In this study using an animal model of nephrotic syndrome, we investigated whether NOX2 is activated in kidneys and if so, whether the upregulation of NOX2 can be reversed by sitagliptin in nondiabetic kidney disease.

Methods: Male Sragues-Dawley rats were uninephrectomized and randomly divided into vehicle-treated controls (VC, n=5) and doxorubicin-treated rats. Doxorubicin was intravenously given into the femoral vein as a single bolus (5 mg/kg BW), and 3 days later the doxorubicin-treated rats were again randomly divided into doxorubicin-treated controls (DC, n=5), and doxorubicin- and sitagliptin-treated rats (DS, n=5). Sitagliptin (10 mg/kg/d) was daily administered to DS by oral gavage for 6 weeks. Urine protein and serum creatinine were determined at 2, 4 and 6 weeks, and kidneys were harvested for quantitative PCR analysis at the end of animal experiment.

Results: Although remarkable proteinuria and azotemia was induced by doxorubicin treatment, DC and DS had no significant differences in proteinuria (727+74 vs. 769+30 mg/d) and serum creatinine (0.77+0.14 vs. 0.67+0.08 mg/dL) at 6 weeks. Quantitative PCR analysis revealed that compared with VC, DC had higher mRNA expression levels ($p<0.05$) of gp91phox (8.1±0.4 fold), p47phox (5.6±0.3 fold) and p67phox (8.1±1.0 fold). Notably, the increase of gp91phox was significantly reduced in DS (4.6±0.4 fold, $p<0.05$). Compared with VC, DC also had higher mRNA expression levels ($p<0.05$) of TGF-β (10.7±0.4 fold), TNF-α (1.9±0.2 fold), IkB-α (2.2±0.2 fold), MCP1 (5.8±0.8 fold), and RANTES (1.7±0.1 fold). Among these, the increase of RANTES was significantly reduced in DS (1.0±0.1 fold, $p<0.05$).

Conclusion: Inflammatory responses are associated with NOX2 upregulation in rat kidneys with doxorubicin-induced nephrosis, and the NOX2-activated RANTES production could be prevented by sitagliptin. However, the antioxidant and antiinflammatory action of sitagliptin may be insufficient to reverse heavy proteinuria and renal failure.

Key Words: DPP4, NOX2, Doxorubicin
Dipeptidyl peptidase-IV, NADPH-oxidase 2, Doxorubicin