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제2형 당뇨병성신증에서 안지오텐신수용체차단제와 알도스테론차단제의 병합효과에 대한 연구

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Additive Amelioration of Glomerulosclerosis and Molecular Alterations by Combined Aldosterone and Angiotensin Receptor Antagonist in Type II Diabetic Rat

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Aldosterone blockade showed beneficial effect in various animal models of renal injury and recent data suggested the possibility that inhibition of aldosterone system may have additional beneficial effect independent of renin-angiotensin blockade in diabetic nephropathy. In this study, we investigated the effect of combined therapy with aldosterone blockade and ACE inhibitor compared with monotherapy with each drug on renal function in animal model of type II diabetic nephropathy. Otsuka Long-Evans Tokushima Fatty (OLETF) rats were treated with spironolactone (20 mg/kg/day) or Irbesartan (50 mg/kg/day) or both of drugs starting at 20 weeks of age. Compared with the control (Long-Evans Tokushima Otsuka, LETO) rats, OLETF rats showed higher glucose concentration than controls. There was no significant difference in body weight, kidney weight, serum creatinine concentration and blood glucose level among each group. However, urinary ACR was significantly decreased in the treatment group (LETO, 28.11±11.46; OLETF, 497.65±196.44; OLETF+Spironolactone, 332.81 ±107.12; OLETF+Irbesartan, 292.38±45.7; OLETF+Spironolactone+Irbesartan, 200.95±45.4 ug/mgCr, $p<0.05$). Although spironolactone did not induce any significant change in blood pressure, Irbesartan and combination group showed significantly lower level of blood pressure (LETO, 101±14; OLETF, 150±14; OLETF+Spironolactone, 139±11; OLETF+Irbesartan, 134±6; OLETF+Spironolactone+Irbesartan, 129±10 mmHg, $p<0.05$). Interestingly, glomerulosclerosis was markedly improved in the treatment group(LETO, 0.025±0.002; OLETF, 0.348± 0.05; OLETF+Spironolactone, 0.164±0.047; OLETF+Irbesartan, 0.184±0.032; OLETF+Spironolactone+Irbesartan, 0.024±0.001, $p<0.05$). In accordance with these findings, renal expression and protein synthesis of profibrotic molecules such as TGFβ1, type IV collagen and PAI-1 also markedly decreased in the treatment group, and most dramatic improvement was observed in the combination group. Furthermore, urinary excretion of big-h3, which is an biologic marker of TGFβ activation also showed that it was decreased in the treatment group and most dramatic decrease in the combination group. From these results, aldosterone receptor antagonism may provide additional benefit to RAS blockade in preserving renal function and associated with improvement of tissue fibrosis in type 2 diabetic nephropathy.