

db/db mice에서 알도스테론 만성주입이 심장과 신장 합병증에 미치는 영향

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Chronic Administration of Aldosterone Further Aggravates Diabetic Cardio-Renal Complication in db/db Mice

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We evaluated the role of aldosterone (ALD) as a mediator of cardio-renal complication in db/db mice using ALD infusion and the selective ALD blocker, eplerenone. The db/db mice were randomized to receive treatment for 90 days: vehicle infusion (control); 0.15 ug/hour ALD subcutaneous infusion; or ALD infusion plus 200 mg/kg/day oral dose of eplerenone (EPL). ALD infusion increased blood pressure and microalbuminuria compared with controls, which were attenuated by EPL. There were no changes in serum creatinine, glucose concentration, HbA1c, glucose tolerance after ALD and EPL treatment. Db/db mice receiving ALD plus EPL had elevated PRA, serum potassium and ALD levels, compared with db/db mice receiving ALD. Renal expression of ALD synthase and MR in db/db mice were increased compared with nondiabetic (db/m) mice and ALD synthase was decreased by ALD infusion. Renin, renin receptor, AT1, AT2 expressions did not differ between db/m mice and all three db/db mice group. Decreased %FS and increased LVMI in echocardiography were observed in db/db mice compared with db/m mice. These parameters were not changed by ALD infusion, but it was significantly ameliorated by EPL. ALD infusion increased urinary level of VEGF and renal/cardiac expression of MCP- 1, PAI- 1, TGF β 1 and type IV collagen compared with controls. EPL cotreatment completely blocked these effects. In db/db mice, serum total cholesterol and triglyceride, renal expressions of HMG- CoA reductase and SREBP- 2 were increased and FXR, fatty acid synthase, ABCA- 1 expressions were not changed compared with db/m mice. ALD infusion in db/db mice decreased SREBP- 2 and HMG- CoA reductase expressions, which were attenuated by EPL. FXR, fatty acid synthase, ABCA- 1 expressions in ALD- infused db/db mice were not different compared with controls, and were increased in EPL- cotreated db/db mice. To define the direct effect of ALD, we performed in vitro experiment using cultured MCs. In cultured MCs, ALD treatment increased VEGF transcriptional activity in a dose-dependent manner. Furthermore, ALD induced VEGF mRNA and protein synthesis. In addition, administration of ALD increased various profibrotic molecules including TGF β 1, PAI- 1 and collagen synthesis in cultured MCs. These results suggest that long- term administration of ALD may induce cardio-renal injury, inflammation and fibrosis and the protective effect of EPL in ALD- infused db/db mice may be associated with altered renal lipid metabolism, irrespective of RAAS

Key Words : 알도스테론, 지질, 당뇨병성신증
Aldosterone, Lipid, Diabetic nephropathy