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새로 개발된 plasminogen activator inhibitor-1 억제제인 TM5275가 당뇨병성 신손상에 미치는 효과

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Effect of a Novel Inhibitor of Plasminogen Activator Inhibitor-1 on Diabetic Renal Injury

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Aims : Diabetes is the leading cause of end-stage renal disease worldwide. Plasminogen activator inhibitor-1 (PAI-1) is increasingly recognized as a profibrotic factor. We previously reported that diabetic renal injury in PAI-1 KO mice was attenuated compared to WT mice. TM5275, a novel inhibitor of PAI-1 developed through virtual screening by docking simulations and subsequent structure-activity relationship study, has antithrombotic benefits devoid of bleeding effect in rats and nonhuman primates. The present study examined the therapeutic effect of TM5275 on diabetic nephropathy.

Methods : 5-week-old male Sprague-Dawley rats and 6-week-old male C57BL/6 mice were utilized. Diabetes was induced by i.p. injection of streptozotocin (STZ) 70 mg/kg and 150 mg/kg into rats and mice, respectively. Control animals were injected with an equivalent volume of sodium citrate. TM5275 was administered orally for 4 and 16 weeks in rats and mice, respectively.

Results : At 4 weeks after the injection of STZ, diabetic rats showed increased plasma glucose, total cholesterol, and triglyceride. TM5275 (10 mg/kg/day) effectively prevented hypercholesterolemia and hypertriglyceridemia without effect on hyperglycemia. STZ-induced diabetic rats showed increased renal expression of active TGF-β1 and MCP-1 mRNA, which was inhibited by TM5275 treatment. At 16 weeks after the injection of STZ, diabetic mice showed increased plasma glucose, creatinine, triglyceride, kidney weights, and urinary albumin excretion. Treatment with TM5275 (50 mg/kg/day) improved hypertriglyceridemia and albuminuria in diabetic mice without significant effect on plasma glucose.

Conclusion : Oral administration of TM5275, a novel inhibitor of PAI-1, effectively inhibited dyslipidemia, albuminuria, and upregulation of renal TGF-β1 and MCP-1 in STZ-induced diabetic rats and mice.

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Diabetic nephropathy, PAI-1 inhibitor, Dyslipidemia