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db/db 마우스에서 VEGF 수용체1,2를 개별 혹은 동시적으로 차단하였을 때 당뇨병성 신증을 악화시키는 기전에 대한 연구

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Effects of VEGFR-1 or VEGFR-2 or Both VEGF-1 and VEGFR-2 Inhibition in the Early Stage of Diabetic Nephropathy in db/db Mice

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Introduction : Interventions to manipulate vascular endothelial growth factor (VEGF)-VEGF receptors (VEGFRs) axis may be promising therapeutic tools in diabetic nephropathy. In the early stage of diabetes, VEGF and VEGFRs are upregulated in experimental animals and humans with type 1 and 2 diabetes with relation to renal hypertrophy, hyperfilatration and increased urinary protein excretion. Therefore, we examined the renal effects of anti-flt 1 hexamer (GNQWFI; VEGFR-1 inhibitor) or anti-flk 1 heptamer (ATWLPPR; A7R, VEGFR-2 inhibitor) or both of them in db/db mice.

Methods : We treated with GNQWFI or A7R peptide or both of them for 12 wks from 8 wks of age in male db/m and db/db mice.

Results : There were no differences in fasting blood sugar and HbA1c levels in all db/db groups. Diabetes significantly suppressed the VEGFR-1 and increased VEGFR-2 expressions in the kidneys. VEGFR-1 and VEGFR-2 expressions were completely inhibited by GNQWF1 and A7R, respectively. In db/db mice treated with GNQWF1 or A7R, albuminuria, glomerular mesangial matrix expansion and inflammatory cell infiltration, and profibrotic growth factors' expressions were more prominent than those of diabetic control db/db mice. They also exhibited increases in the number of apoptotic glomerular cells with no change in Ki-67 positive cells. 24 hour urinary 8-isoprostane and 8-OH-deoxyguanosine concentrations increased in db/db mice treated with GNQWF1 or A7R compared with those of diabetic control db/db mice. Interestingly, more severe albuminuria and renal lesions were noted in db/db mice treated with both of them compared with those of db/db mice treated with either GNQWFI or A7R. By contrast, GNQWFI- and A7R-induced albuminuria and histopathological changes were not observed in any db/m groups.

Conclusion : The blockade of VEGFR-1 or VEGFR-2 or both using GNQWF1 or A7R peptide caused glomerular injury related to the oxidative stress-induced apoptosis. Our results show that the inhibition of VEGF-VEGFR system can aggravate renal damage in type 2 diabetic nephropathy.

Key Words : 혈관내피성장인자, 혈관내피성장인자 수용체, 당뇨병
Vascular endothelial growth factor, VEGF receptor, Diabetes