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혈관내피성장인자 수용체 1, 2를 개별 혹은 동시 차단 시 제 2형 당뇨병성 신증에 대한 영향

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정성진, 임지희, 김민영, 양근석, 홍유아, 신석준, 김형욱, 김용수, 장윤식, 박철휘

Simultaneous or Separate Inhibition of Vascular Endothelial Growth Factor Receptors 1 and 2 Aggravates Diabetic Nephropathy in db/db Mice

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Introduction: It is a still controversy over manipulating vascular endothelial growth factor (VEGF) receptors (VEGFRs) may be promising therapeutic tools in diabetic nephropathy. Therefore, we examined the renal effects of anti-flt 1 hexamer (VEGFR1 inhibitor) or anti-flk 1 heptamer (VEGFR2 inhibitor) or both of them in db/db mice treating for 12 wks in male db/db mice.

Methods: Male db/db amd db/m mice were treated with VEGFR1 inhibitor and VEGFR2 inhibitor simultaneously or separately for 12 weeks from 8 weeks of age.

Results: Induction of diabetes suppressed the VEGFR1 and increased VEGFR2 expressions in kidneys. In the db/db mice with VEGFR1 or VEGFR2 inhibition, albuminuria, glomerular mesangial matrix expansion, and inflammatory cell infiltration were more prominent than those of control db/db mice although there were no differences in blood glucose levels in all db/db groups. They exhibited an increase in the number of apoptotic glomerular cells without cell proliferation and increased 24-h urinary 8-OH-deoxyguanosine concentrations. Interestingly, more severe albuminuria and renal lesions were noted in the db/db mice with both VEGFR1 and VEGFR2 inhibition compared with either VEGFR1 or VEGFR2 inhibition. All of these changes were associated with the inactivation of renal PI3K-Akt-eNOS-NO pathway. In contrast, VEGFR1 or VEGFR2 blockade-induced renal phenotypes were not observed in any db/m groups. In glomerular endothelial cells, high-glucose media containing VEGFRs inhibitors, especially media with both VEGFR1 and VEGFR2 inhibition, induced more apoptotic cell death and oxidative stress than did high-glucose media associated with an inactivation of both the PI3K-Akt-eNOS pathway and SOD1 and SOD2.

Conclusion: Our results reveal that the blockade of VEGFR1 or VEGFR2 or both VEGFR1 and VEGFR2 caused severe renal injury related to the inactivation of the PI3K-Akt-eNOS pathway resulting in the oxidative stress-induced apoptosis in type 2 diabetic nephropathy.

Key Words: 혈관내피성장인자 수용체, 당뇨병성 신증, 산화 스트레스
VEGF, Diabetic nephropathy, Oxidative stress