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Vascular Endothelial Growth Factor-Receptor 1 Inhibition Aggravates Diabetic Nephropathy through eNOS Signaling Pathway in db/db Mice

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The manipulation of vascular endothelial growth factor (VEGF)-receptors (VEGFRs) in diabetic nephropathy is still controversial. Most of the cellular actions of VEGF in experimental diabetic nephropathy are predominantly regulated by VEGF-A and VEGFR2. In contrast, VEGF-A, -B and placenta growth factor bind to VEGFR1 with high affinity. Therefore, we investigated whether selective VEGFR1 inhibition using GNQWFI hexamer in db/db mice aggravates and progresses diabetic nephropathy. Diabetes suppressed VEGFR1 and increased VEGFR2 expressions in the glomerulus. In db/db mice with VEGFR1 inhibition, albuminuria, mesangial matrix expansion, inflammatory cell infiltration and greater numbers of apoptotic cells in the glomerulus, and oxidative stress were more prominent than in control db/db mice. All of these changes were related to the suppression of diabetes-induced increases in PI3K activity and Akt phosphorylation and the aggravation of endothelial dysfunction associated with the inactivation of FoxO3a and eNOS-NOx. In cultured human glomerular endothelial cells (HGECs), high-glucose media with VEGFR1 inhibition induced more apoptotic cells and oxidative stress than did high-glucose media along, which were associated with the suppression of PI3K-Akt phosphorylation, independently of the activation of AMP-activated protein kinase, and inactivation of FoxO3a and eNOS-NOx pathway. In addition, transfection with VEGFR1 siRNA in HGECs also suppressed PI3K-Akt-eNOS signaling. In conclusion, the specific blockade of VEGFR1 with GNQWFI caused severe renal injury related to profound suppression of the PI3K-Akt, FoxO3a and eNOS-NOx pathway, resulting in the oxidative stress-induced apoptosis of glomerular cells in type 2 diabetic nephropathy.

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