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Inhibition of PCSK9 attenuates renal lipotoxicity by activating the AMPK-PGC-1a-FoxO3a signaling in diabetic kidney disease

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Objectives : Lipotoxicity has been implicated in the pathophysiology of diabetic kidney disease. Proprotein convertase subtilisin kexin 9 (PCSK9) plays an important role in regulating low-density lipoprotein (LDL) receptor degradation and is a novel therapeutic target to reduce hyperlipidemia. We aimed to examine whether inhibition of PCSK9 ameliorates diabetic kidney disease by reducing lipotoxicity through activation of AMP-activated protein kinase (AMPK).
Methods : Male C57BLKS/J db/m control and db/db mice at 8 weeks of age were divided four groups, and PCSK9 inhibitor (SBC-115076, 1.5 mg/kg) was daily administered to db/m control and db/db mice via subcutaneous injection for 8 weeks. Phenotypic changes and target molecules with associated cellular signaling pathways were investigated in the mice kidneys.
Results : PCSK9 inhibitor significantly reduced urine albumin/creatine ratio, serum and urine kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin levels in db/db mice. PCSK9 inhibitor also improved mesangial matrix expansion, and decreased collagen IV, and transforming growth factor-β1 staining, and reduced serum and intra-renal LDL cholesterol and serum free fatty acid levels. At the molecular level, PCSK9 inhibitor induced the increases in LDL receptor, phosphorylation of liver kinase B1 (LKB1) and AMPK expressions and activation of PPARγ co-activator 1α (PGC-1α). The protective effects of PCSK9 inhibitor were attributed to inhibited sterol regulatory element-binding protein (SREBP)-1 expressions and subsequently increased expressions of carnitine palmitoyl transferase 1 (CPT1) and acyl-CoA oxidase 1 (ACOX1). PCSK9 inhibitor decreased the phosphorylation of Akt and forkhead box O3a (FoxO3a), increasing the B cell leukaemia/lymphoma 2 (BCL-2)/ BCL-2-associated X protein (BAX) ratio in the kidnyes. Consequently, PCSK9 inhibitor recovered from kidney apoptosis and oxidative stress, as reflected by 8-OHdG and TUNEL staining and malondiadehyde assay in db/db mice.
Conclusions : Inhibition of PCSK9 improves lipotoxicity via activation of AMPK-PGC-1α-FoxO3a signaling, showing potential as a therapeutic modality to treat diabetic kidney disease.