Frontier in Nephrology

AMP-activated Protein Kinase in Diabetic Nephropathy

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Each cell has the ability to recognize and response to nutrient fuel substrates, such as glucoe, lipids, and amino acids, to ensure their efficient use. These nutrient-sensing pathways appear critical for cellular homeostasis for making nutrient balance. These pathways also represent important regulators of cell growth and proliferation, motility, mitochondrial function, autophage, and survival. The best known of these pathways include mTOR, AMP-activated protein kinase (AMPK), and sirtuins (SIRT). Under low-energy conditions, AMPK and SIRT are activated by increases in intracellular AMP and NAD+ levels, respectively. In excessive nutrient conditions, mTOR is activated. AMPK is activated by upstream kinases such as CaMKK and LKB1 as well as metformin, thiazolidinediones, PPARα agonist fenofibrate. In addition, many of the effects of resveratrol are consistent with the activation of AMPK-SIRT1-PGC-1α, which play key roles in the regulation of lipids and glucose homeostasis, and in the control of oxidative stress. *db/db* mice treated with resveratrol displayed decreased albuminuria. Resveratrol ameliorated glomerular matrix expansions and inflammation. Resveratrol also lowered the non-esterified fatty acid and triacylglycerol contents in the kidney related to increases in the phosphorylation of AMPK and activation of SIRT1-PGC-1α signaling, and one of the key downstream effecters, the PPARα-ERR-1α-SREBP1 expressions in *db/db* mice. Furthermore, resveratrol decreased the activity of PI3K-Akt phosphorylation and FoxO3a phosphorylation, which resulted in a decrease in Bax and increases in Bcl-2, SOD1 and SOD2 expressions. Consequently, resveratrol reversed the increased renal apoptotic cells and oxidative stress, as reflected by the renal 8-OH-dG and urinary 8-OH-dG and isoprostane concentrations. Resveratrol prevented high glucose-induced oxidative stress and apoptosis in cultured mesangial cells due to the phosphorylation of AMPK and activation of SIRT1-PGC-1α signaling and their downstream effecters, the PPARα-ERR-1α-SREBP.

The results suggest that resveratrol prevented diabetic nephropathy in db/db mice by the phosphrylation of AMPK and activation of SIRT1-PGC-1α signaling, which seems to prevent lipotoxicity-related apoptosis and oxidative stress in the kidney.