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SIRT3 activation with viniferin treatment ameliorates features of diabetes induced tubular injury through restoration of mitochondrial function

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Objectives: Oxidative stress and mitochondrial dysfunction are key factors inducing diabetic nephropathy. SIRT3, a potent deacetylase, has been found to regulate mitochondrial activity and cell survival. However, whether SIRT3 is involved in the process of diabetic nephropathy development is not well-known. In this study, the role of SIRT3 in diabetes-induced tubular injury was investigated. In addition, the effect of viniferin treatment, inducing SIRT3 activation, on improvement of tubular injury was assessed.

Methods: *In vitro,* NRK-52E cells treated with TGF-β-were compared with controls after SIRT3-targeted lentivirus transfection and viniferin treatment to evaluate the effect of SIRT3 overexpression. In an animal study, viniferin was injected to *db/db* mice for 6 weeks and to C57BL/6 mice given with unilateral nephrectomy and intraperitoneal streptozotocin injection (UNXSTZ) for 4 weeks using osmotic pump, *db/m* mice and C57BL/6 mice served as controls, respectively. Expression of SIRT3 after mitochondrial isolation, mitochondrial dynamics and morphology, cell injury markers, and histological manifestations were examined.

Results: In NRK-52E cells, TGF-β treatment resulted in decreased expression of SIRT3, in parallel with increased intracellular reactive oxygen species production, and decreased mitochondrial mass, integrity, and respiration. In addition, increased fibrotic activities and apoptotic cell death index were observed in TGF-β-treated NRK-52E cells. These changes were accompanied by decreased PGC-1α and p-AMPK expressions. SIRT3 overexpression by lentiviral transfection improved mitochondrial dynamics and cell injury, and similar alterations were observed with the SIRT3 activation by viniferin treatment. In the kidney of *db/db* and UNXSTZ mice, diabetes induced downregulation of SIRT3, increased cellular oxidative stress, decreased expressions of mitochondrial dynamic-related genes, and cell injury. SIRT3 activation by viniferin treatment restored these alterations. Furthermore, tubular degeneration and fibrotic remodeling in diabetic kidney tissues were also ameliorated by viniferin treatment.

Conclusions: This study demonstrates that SIRT3 activation by viniferin treatment improves oxidative stress and impaired mitochondrial metabolism in diabetes-induced tubular injury.