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Sodium Glucose Cotransporter 2 inhibitor Canagliflozin Attenuates Renal Tubulointerstitial Fibrosis in rats with hyperuricemia nephropathy and its possible mechanisms

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Objectives: The pathogenesis of hyperuricemia-induced chronic kidney disease still remains unknown. In this study, we investigated whether sodium glucose cotransporter 2 (SGLT2) inhibitor would contribute to the development of hyperuricemic nephropathy (HN).

Methods: Nine male SD rats were randomly assigned to three groups: normal control, HN group, and HN treated with Canagliflozin (25 mg/kg) group. Rats were fed a mixture of adenine (0.1 g/kg) and potassium oxonate (1.5 g/kg) daily for 3 weeks and then killed. The kidneys were collected for protein analysis and histological examination.

Results: In a rat model of HN induced by feeding mixture of adenine and potassium oxonate, increased SGLT2 expression and severe renal interstitial fibrosis were found, in parallel with increased urine microalbumin excretion. Administration of canagliflozin, which is a selective inhibitor of SGLT2, improved renal function, decreased urine microalbumin and inhibited renal tubular epithelial cells mesenchymal transition as well as the accumulation of collagen 1 and fibronection. Canagliflozin also inhibited hyperuricemia-induced expression of multiple profibrogenic cytokines/chemokines in the kidney. Furthermore, canagliflozin inhibited phosphorylation of Smad3, a key mediator in transforming growth factor (TGF-β) signaling.

Conclusions: Thus, pharmacologic targeting of SGLT2 can alleviate HN via inhibiting epithelial-myofibroblast transdifferentiation (EMT), reducing accumulation of extracellular proteins, suppressing TGF-β signaling, and reducing inflammation responses.

renal HE staining

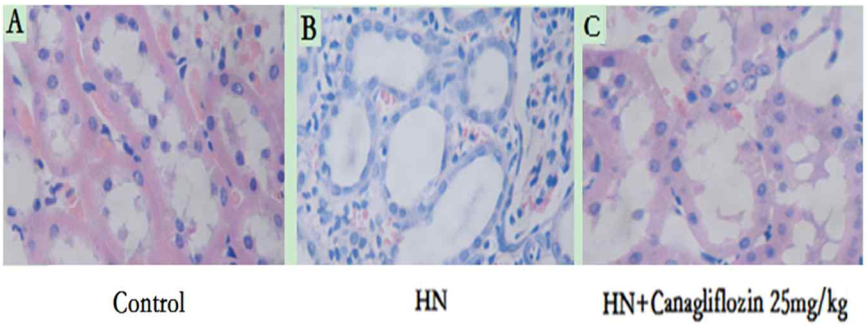

Figure. Canagliflozin alleviates EMT in hyperuricemic rats.