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Sirtuin 3 Activation by Honokiol Decreases Unilateral Ureteral Obstruction-Induced Renal Inflammation and Fibrosis via Regulation of Mitochondrial Dynamics and the Renal NF-κB-TGF-β1/Smad Signaling Pathway

Kyung Pyo Kang[1], Jixiu Jin[1], Ji-Hyun Yeom[2], Won Kim[1], Sik Lee[1], Sung Kwang Park[1]
[1]Department of Internal Medicine-Nephrology, Jeonbuk National University Medical School, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Jeonbuk National Universtiy Hospital, Korea, Republic of

Objectives: Renal fibrosis is a common feature of all progressive chronic kidney diseases. Sirtuin3 (SIRT3) is one of the mitochondrial sirtuins, and plays a role in the regulation of mitochondrial biogenesis, oxidative stress, fatty acid metabolism, and aging. Recently, honokiol (HKL), as a pharmaceutical SIRT3 activator, has been observed to have a protective effect against pressure overload-induced cardiac hypertrophy by increasing SIRT3 activity. In this study, we investigated whether HKL, as a SIRT3 activator, also has protective effects against unilateral ureteral obstruction (UUO)-induced renal tubulointerstitial fibrosis through SIRT3-dependent regulation of mitochondrial dynamics and the nuclear factor-κB (NF-κB)/transforming growth factor-β1 (TGF-β1)/Smad signaling pathway.

Methods: Renal fibrosis was induced by UUO in the six-week-old C57BL/6 mice for 10 days. Honokiol (5 mg/kg) was treated by intraperitoneal injection for 7 days before induction of renal fibrosis and continued for 10 days. Histologic examination and Western blot analysis for α-SMA, type I collagen were performed. We also evaluated cell adhesion molecule expression and TGF-β1/Smad signaling pathway after ureteral obstruction. *In vitro* experiments were performed using rat renal fibroblast cell line (NRK-49F cells). Cell proliferation and migration were evaluated by XTT assay and wound healing assay. TGF-β1-induced renal fibroblast activation was evaluated by Western blot analysis.

Results: We found that HKL decreased the UUO-induced increase in tubular injury and extracellular matrix (ECM) deposition in mice. HKL also decreased myofibroblast activation and proliferation in UUO kidneys and NRK-49F cells. Finally, we showed that HKL treatment decreased UUO-induced mitochondrial fission and promoted mitochondrial fusion through SIRT3-dependent effects.

Conclusions:

In conclusion, activation of SIRT3 via HKL treatment might have beneficial effects on UUO-induced renal fibrosis through SIRT3-dependent regulation of mitochondrial dynamics and the NF-κB/TGF-β1/Smad signaling pathway.