KSN 2017 Abstract

KSN-17-P210

HDAC1 inhibition by valproic acid attenuates TGF-β-induced renal fibroblast activation and extracellular matrix protein production in mouse UUO model

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Objectives : Tubulointerstitial fibrosis is a common final feature of kidney disease, irrespective of glomerular, tubular and capillary injury. These fibrotic processes are characterized by sustained inflammation and excessive extracellular matrix (ECM) accumulation and leads to organ dysfunction. A key mediator of fibrosis is myofibroblasts, which produce and secrete ECM after activation. VPA has anti-cancer activities through regulation of cell differentiation and apoptosis by inhibition of histone deacetylase (HDAC) activity and is considered a class I HDAC inhibitor. In this study, we investigate the effect of valproic acid on renal fibroblast activation in tubulointerstitial fibrosis model.

Methods : Renal fibrosis was induced by UUO in the six-week-old C57BL/6 mice for 14 days. Valproic acid (300 mg/kg) was treated by intraperitoneal injection for 5 days before induction of renal fibrosis and continued for 14 days. Histologic examination and Western blot analysis for α-SMA, vimentin, and fibronectin were performed. We also evaluated TGF-β1/Smad signaling pathway after ureteral obstruction.

Results : Renal tubular injury and fibrosis were increased after ureteral obstruction. After treatment of VPA, renal tubular injury and fibrosis were significantly attenuated. The number of fibroblast (FSP-1 positive cells) and proliferating myofibroblast (α-SMA and Ki67 double positive cells) was significantly decreased after VPA treatment in UUO kidney. In Western blot analysis, extracellular matrix such as type I collagen and fibronectin were significantly decreased after VPA treatment in UUO kidney. Finally, VPA was suppressed UUO-induced increase of renal TGF-β1 levels and UUO-induced increase of phosphorylation of Smad2 and Smd3.

Conclusions : These results suggest that VPA has a beneficial effect on UUO-induced renal fibrosis by inhibition of myofibroblast proliferation through modulation of renal TGF-β1/Smad signaling pathway.

Keywords : fibrosis, HDAC1, valproic acid, extracellular matrix