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Febuxostat inhibits ER stress and renal fibrosis through activation of SIRT1, followed by induction of AMP-activated protein kinase, heme oxygenase-1, and thioredoxin

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Objectives : Because endoplasmic reticulum (ER) stress has been increasingly recognized as a modulator of fibrosis, blocking ER stress may serve as a promising therapeutic strategy for the reduction and prevention of fibrosis. Febuxostat is a novel, potent inhibitor of xanthine oxidase (XO). Although the renoprotective role of XO inhibitors is convincing, whether and how febuxostat suppresses ER stress are largely unknown. Silent information regulator 1 (SIRT1), AMP-activated protein kinase (AMPK), heme oxygenase-1 (HO-1), and thioredoxin have been implicated as modulators of ER stress. Therefore, we postulated that febuxostat would suppress ER stress via interactions with SIRT1, AMPK, HO-1, or thioredoxin.

Methods : The effects of febuxostat on ER stress induced by the chemical inducer, tunicamycin (TM), and non-chemical inducers in tubular HK-2 cells were examined. The in vivo effects of febuxostat with or without sirtinol (inhibitor of SIRT1) and compound C (inhibitor of AMPK) were further examined in a mouse model of unilateral ureteral obstruction (UUO).

Results : Febuxostat suppressed TM-induced ER stress in tubular epithelial cells, as indicated by inhibition of TM-induced up regulation of GRP78 and p-eIF2α. The inhibitory effect of febuxostat was mediated through the activation of SIRT1, followed by induction of AMPK, HO-1, and thioredoxin. Febuxostat also inhibited ER stress induced by angiotensin II, aldosterone, high glucose, and albumin. In UUO mice, febuxostat reduced the UUO-induced tubular expression of GRP78 and also increased the expression of HO-1 and thioredoxin, which were abolished by pretreatment with sirtinol and compound C. Febuxostat also reduced UUO-induced renal fibrosis.

Conclusions : Our results provide new insights into renoprotective effects of febuxostat and suggest that the induction of SIRT1, AMPK, HO-1, and thioredoxin may have a clinical therapeutic potential in kidney diseases under excessive ER stress condition.

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Keywords : ER stress, febuxostat, SIRT1, AMPK, HO-1, thioredoxin