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The Inhibition of Xanthine Oxidoreductase by Febuxostat Ameliorates Oxidative Stress in Contrast Induced Nephropathy through the AMPK-NOXs-HIF-1 α Signaling in Mice

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Objectives: Serum uric acid is an independent predictor of contrast induced nephropathy (CIN). Febuxostat, a uric acid lowering agent, has been reported to reduce reactive oxygen species by the inhibition of xanthine oxidoreductase. We hypothesized that febuxostat would attenuates oxidative stress via the activation of AMP-activated protein kinase (AMPK) in CIN.

Methods: C57BL/6 mice were pretreated with 50 mg/kg of febuxostat via oral gavage before iohexol administration and scarified after 24 hr. Human kidney-2 (HK-2) cells were pretreated with febuxostat for 1 hr and then exposed to iohexol for 48 hrs. We investigated whether febuxostat attenuates oxidative stress in CIN mice and iohexol-induced tubular cell damage.

Results: Serum creatinine and renal tubular injury increased significantly after iohexol treatment, and febuxostat co-treatment attenuated the renal injury. Febuxostat treatment markedly decreased serum and kidney xanthine oxidase and xanthine dehydrogenase levels in CIN mice. Febuxostat was accompanied with the activation of AMPK and the inhibition of NOX1 and NOX2 in mice with CIN. Hypoxia inducible factor-1 α (HIF-1 α) and heme oxygenase-1 (HO-1) expressions were increased by iohexol, and significantly decreased in febuxostat-treated CIN mice. Cell survival decreased after iohexol exposure and febuxostat reduced cell death induced by iohexol in HK-2 cells. Febuxostat increased AMPK phosphorylation and decreased NOX1 and NOX2 expressions in iohexol-exposed HK-2 cells. These processes resulted in reduction of oxidative stress both *in vivo* and *in vitro* experiments. AMPK inhibition using AMPK α 1 and AMPK α 2 siRNA blunted the protective effects of febuxostat in iohexol-treated HK-2 cells.

Conclusions: Febuxostat attenuated CIN by modulating renal oxidative stress through activation of AMPK-NOXs-HIF-1 α signaling.