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Xanthine oxidase inhibitor ameliorates high glucose-induced oxidative stress by activating AMPK via the activation of purine salvage pathway in glomerular endothelial cells

Keum-Jin Yang[2], Won Jung Choi[1], Yoon-Kyung Chang[1], Cheol Whee Park[3], Suk Young Kim[1], **Yu Ah Hong[1]**
[1]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of
[2]Department of Clinical Research Institute, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Republic of

Objectives: Oxidative stress plays a crucial role in the pathogenesis of diabetic nephropathy (DN). Xanthine oxidase (XO) contribute to reactive oxygen species (ROS) production, and XO inhibitor, febuxostat has been reported to the protection of kidney diseases. However, the mechanism of renoprotective effects for febuxostat remained unclear. We investigated the renoprotective mechanism associated with purine salvage pathway of febuxostat against DN

Methods: Glomerular endothelial cells (GEnCs) exposed to high glucose (HG) were treated with or without febuxostat for 72 hours, and then the changes of purine salvage pathway and the phosphorylation of 5' AMP-activated protein kinase (AMPK) and its related signaling pathway were evaluated.

Results: Cell survival was significantly decreased in HG-treated GEnCs, and febuxostat treatment enhanced cell survival in a dose-dependent manner. The expressions of xanthine/hypoxanthine, and the levels of xanthine oxidoreductase were significantly increased in HG-treated GEnCs, and these findings were attenuated by febuxostat. The AMP/ATP ratio was inhibited in in HG-treated GEnCs and enhanced by febuxostat treatment. Febuxostat treatment enhanced phosphorylation of AMPK, peroxisome proliferator-activated receptor (PPAR)-gamma coactivator (PGC)-1α, PPARα, and dephosphorylation of the Forkhead box O (FoxO)3a in HG-treated GEnCs. Febuxostat treatment also suppressed NADPH oxidase expressions and increased supreoxide dismutase (SOD) activities in HG-treated GEnCs. AMPK inhibition using small interfering RNA blunted the antioxidative effects of febuxostat and suppressed hypoxanthine phosphoribosyltransferase 1 mRNA expressions in HG-treated GEnCs.

Conclusions: Febuxostat attenuated HG-induced oxidative stress through the activation of purine salvage pathway and AMPK–PGC-1α–NADPH oxidase signaling.