KSN 2021
FULLY VIRTUAL MEETING
September 02 (Thu) - 05 (Sun)

Abstract Submission No. : 2258

Xanthine oxidase inhibitor attenuates renal oxidative through the inhibition of VEGF-NADPH oxidases in diabetic nephropathy

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Objectives: Xanthine oxidase (XO) is one of major source of reactive oxygen species, and a XO inhibitor, febuxostat has been reported to the protection of kidney diseases. We investigated whether febuxostat exerts renoprotective effects against diabetic nephropathy (DN).

Methods: Eight-week Male C57BL/6 mice were divided into four groups: Control group (Cont), Febuxostat control group (FEB), streptozotocin treated group (STZ) and a febuxostat and STZ-treated diabetes group (STZ+FEB). STZ was used to induce diabetes (50 mg/kg/day, 5 days), and 5 mg/kg of febuxostat was treated to experimental mice for 8 weeks.

Results: STZ-treated diabetic mice were significantly decreased in serum and kidney XO levels, serum cystatin C and albuminuria by febuxostat treatment. Febuxostat treatment decreased renal hypertrophy and mesangial matrix expansion in STZ-treated diabetic mice. Febuxostat treatment suppressed the expression of vascular endothelial growth factor (VEGF)1 and 3, NADPH oxidase (NOX)1, 2, and 4, and the levels of their catalytic subunit mRNA in in STZ-treated diabetic mice. Febuxostat treatment was accompanied by the downregulation of Akt phosphorylation, followed by the suppression of transcription factor forkhead box O3a phosphorylation and the enhancement of endothelial nitric oxide synthase. Finally, febuxostat improved oxidative stress and resulted in decreased 8-hydroxy-2'-deoxyguanosine and kidney malondialdehyde levels, and increased superoxide dismutase activity in STZ-treated diabetic mice.

Conclusions: Febuxostat attenuates DN by modulating oxidative stress through VEGF–NADPH oxidase signaling pathway.