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페북소스테트의 스트렙토조토신 유발 당뇨쥐에 신보호 효과

가천대학교 동인천길병원 신장내과[1], 경희대학교 의과대학 신장내과[2]

이홍주[1], 문주영[2], 이상호[2], 임천규[2], 정경환[2], 이태원[2]

Febuxostat Attenuates Kidney Injury in Streptozotocin Induced Diabetic Rats

Hong Joo Lee[1], Ju Young Moon[2], Sang Ho Lee[2], Chun Gyoo Ihm[2], Kyung Hwan Jeong[2], Tae Won Lee[2]

Gachon University Dongincheon Gil Hospital Division of Nephrology[1]
Kyung Hee University School of Medicine Division of Nephrology[2]

Oxidative stress and inflammation are known to play a central role in the development of diabetic nephropathy. Febuxostat (Fx) is a novel nonpurine xanthine oxidase (XO)-specific inhibitor for treating hyperuricemia. In this study, we investigated whether Fx could ameliorate diabetic nephropathy and impart renoprotective effects, including anti-oxidative stress and anti-inflammatory mechanisms.

Male Sprague-Dawley rats were divided into three groups: normal, vehicle-treated diabetes (DM), and febuxostat-treated diabetes (DM+Fx). We administered 5mg/kg of Fx to experimental rats for 7 weeks. We evaluated clinical and biochemical parameters such as the ratio of kidney weight to body weight, serum creatinine and albuminuria. We also examined renal histopathology and morphologic change in extracted kidneys from rats as well as XO and xanthine dehydrogenase (XDH) activity in hepatic tissue. Urine 8-hydroxy-2-deoxyguanosine (8-OHdG) concentration was used to measure oxidative stress, while immunohistochemistry of ED-1 and mRNA expression of the inflammatory mediator TGF-β1 were evaluated to measure the degree of inflammation.

Diabetic rats (DM and DM+Fx groups) had higher blood glucose, higher kidney weight relative to body weight, and lower creatinine clearance compared to normal rats. Blood glucose, kidney to body weight ratio, and uric acid were not different significantly between DM rats and DM+ Fx rats; however, urinary albuminuria was significantly reduced, and creatinine clearance was improved in Fx-treated diabetic rats. We observed no differences in renal histopathology between the three groups. Quantitative analysis showed that hepatic XO and XDH activity was increased in the DM group but reduced after treatment with Fx. Urine 8-OHdG concentrations also indicated reduced oxidative stress in the DM+Fx group relative to the DM group. We also observed a greater number of ED-1 stained cells in the glomerulus and tubule of diabetic renal tissue compared to normal; after administration of Fx, ED-1 stained cell count decreased. Finally, diabetic rats showed increased mRNA expression of genes related to inflammation. Among these genes, E-selectin, VCAM-1, and TGF-β1 mRNA expression decreased significantly in renal tissue of Fx-treated rats. Renoprotective effects of Fx may attenuate the inflammatory and oxidative stress mechanisms of renal damage in diabetes by inhibiting XO and XDH activity.

Key Words: 당뇨병성신증, 페북소스테트, 크산틴 산화제 억제
Diabetic nephropathy, Febuxostat, Xanthine oxidase inhibitor