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## Effects of Empagliflozin on solitary rat kidneys producing doxorubicin-induced nephrotic syndrome

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**Objectives :** The effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors on lowering blood pressure are well characterized in diabetic animals and humans. Besides, empagliflozin, an Inhibitor of SGLT2 was reported to have anti-inflammatory effects on experimental diabetic nephropathy. However, it is unclear whether SGLT2 inhibitors may have beneficial effects on non-diabetic kidney disease. This study was undertaken to test our hypothesis that empagliflozin may relieve hypertension in non-diabetic proteinuric kidney disease via exerting anti-inflammatory renoprotective action.

**Methods :** Male Sprague-Dawley rats were randomly divided into uni-nephrectomized controls (NX, n=5), uni-nephrectomy plus doxorubicin-treated rats (NXD, n=5), and uni-nephrectomy plus doxorubicin/empagliflozin-cotreated rats (NXDE, n=5). Doxorubicin was administered via femoral vein in a single bolus (5 mg/kg) after 7 days of right nephrectomy. Empagliflozin (20 mg/kg/d) was daily given in food slurry. Systolic blood pressure (SBP), plasma creatinine, and urine data were weekly measured. After 5 weeks of empagliflozin administration, kidneys were harvested for immunoblotting of sodium transporters and quantitative PCR analysis of inflammatory markers.

**Results :** At baseline (Day 0, immediately before doxorubicin treatment), SBPs were not different between groups: NX, 120 ± 1; NXD, 120 ± 1; and NXDE, 119 ± 3 mmHg. From Day 7 (NX, 127 ± 1; NXD, 163 ± 3; and NXDE, 155 ± 1 mmHg) through Day 35 (NX, 130 ± 1; NXD, 172 ± 1; and NXDE, 160 ± 1 mmHg), remarkable hypertension was induced by doxorubicin and significantly relieved by empagliflozin cotreatment ($P<0.01$). Significant proteinuria was produced from Day 14 and increased thereafter by doxorubicin but not decreased by empagliflozin cotreatment. Osmotic diuresis was evident from Day 7 (NXDE 40.7 ± 1.3 vs. NXD 21.7 ± 1.1 mosmoles/d, $P<0.01$) through Day 35 (NXDE 52.3 ± 4.0 vs. NXD 27.9 ± 1.7 mosmoles/d, $P<0.01$), in parallel with natriuresis and glycosuria. Immunoblot analysis from the kidney showed that compared with NXD, NXDE had decreased protein abundance of Na-K-2Cl cotransporter-2 (100 ± 31 vs. 40 ± 8%, $P<0.05$) and Na-K-ATPase alpha1 subunit (100 ± 13 vs. 51 ± 13%, $P<0.05$) but no change in Na/H exchanger-3

(100 ± 12 vs. 104 ± 13%). Notably, quantitative PCR analysis revealed that the increased mRNA expression of NLRP3, ASC, IL-1beta, MCP1, and RANTES in NXD were not reversed by empagliflozin cotreatment in NXDE.

Conclusions : We show that hypertension in non-diabetic proteinuric kidney disease may be controlled by empagliflozin treatment. The antihypertensive effect was associated with osmotic diuresis and natriuresis, but not with proteinuria reduction. Activation of NLRP3 inflammasome in doxorubicin nephropathy was not ameliorated by empagliflozin treatment.

Keywords : empagliflozin, blood pressure, proteinuria, inflammasome, osmotic diuresis, natriuresis.