

Abstract Submission No. : IL-9022

Sodium-glucose cotransporter 2 (SGLT2) inhibitor, dapagliflozin, does not ameliorate non-diabetic renal injury

Young Sun Kang
Korea University Ansan Hospital, Korea, Republic of

Introduction

The sodium-glucose cotransporter 2 (SGLT2) inhibitors were shown to have their protective effect on diabetic kidney disease and heart failure. It targets SGLT2 in renal proximal tubules and promotes glycosuria in type 2 diabetic mellitus, resulting in lowering blood glucose. However, its role remains uncertain in non-diabetic kidney disease. In this study, we investigated the effects of SGLT2 inhibitor, dapagliflozin (DAPA), on a mouse model of adriamycin (ADX)-induced nephropathy and adult zebrafish injury model.

Methods

ADX induced nephropathy model resulted in severe proteinuria and progressive glomerulosclerosis. Seven week old Balb/c mice were divided in five groups; 1) control with vehicle, 2) control with DAPA 3mg, 3) ADX (11.5mg/kg) control, 4) ADX (11.5mg/kg) +DAPA 1mg, 5) ADX (11.5mg/kg) + DAPA 3mg. With ADX injection, DAPA was administered via gavage for 2 weeks.

Adult zebrafish were injected 40mg/kg of gentamicin (GM) or/and 3ug of DAPA via intraperitoneal injection. Dextran filtration assay was performed and by in situ hybridization, *slc52a*, *wt1b*, *pax2a*, *lhx1a*, and *fgf8a* gene expressions were evaluated over kidney injury and regeneration.

Results

When compared to ADX control mice group, administration of DAPA did not alleviate proteinuria in ADX-induced nephropathy. In the kidney, ADX injection induced significant glomerular and interstitial injury, and SGLT2 inhibition did not attenuate the extent of renal injury. Gene and protein expressions of ED1, the macrophage marker in the kidney were significantly increased in the ADX control group. DAPA administration in ADX groups decreased macrophage infiltration in the renal medulla compared to ADX control group, whereas no significant difference was observed in the renal cortex. SGLT2 expressions were decreased in DAPA administration groups as expected.

In adult zebrafish, GM-induced tubular injury was confirmed after 1 day and regeneration after 4 days by dextran filtration assay. Over this duration, *slc5a2* gene expression was disappeared after 1 day and recovered after 5 days. *wt1b* and *pax2a* gene expressions were increased after 5 days of GM. *wt1b* and *pax2a* gene expressions were increased after 1 day of DAPA. DAPA did not recover *slc5a2* gene expression after 5 days of GM injection and did not change *wt1b* and *pax2a* gene expressions during the regeneration.

Conclusion

From the results, dapagliflozin had no protective effect on ADX-induced kidney injury in mice model and GM-induced zebrafish injury model. However, interestingly DAPA improved renal medullary injury although it had no effect on renal cortex injury.