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Dapagliflozin Improves Glycemic Control, Hypertension and is Neutral on Severe Renal Impairment in Uni-nephrectomized SDT fatty rat, a 10-week Model of Advanced Renal Complications and Glomerular Filtration Rate Decline.

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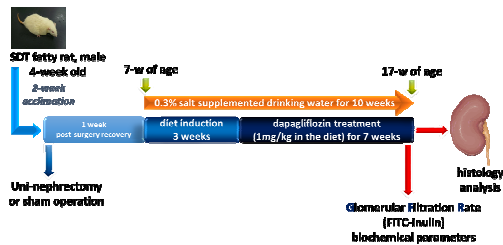
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BACKGROUND & OBJECTIVES

Sodium glucose cotransporter 2 inhibition (SGLT2i) represents a promising new class of glucose lowering drugs but may not be recommended in type 2 diabetic patients with severe renal impairment. To investigate the effects of SGLT2i, later in the course of diabetic nephropathy, dapagliflozin (DAPA) was evaluated in uni-nephrectomized Spontaneously Diabetic Torii (SDT) fatty rat. This novel hypertensive, obese, type 2 diabetic model, develops advanced renal complications and >50% glomerular filtration rate (GFR) decline within 10 weeks.

METHODS



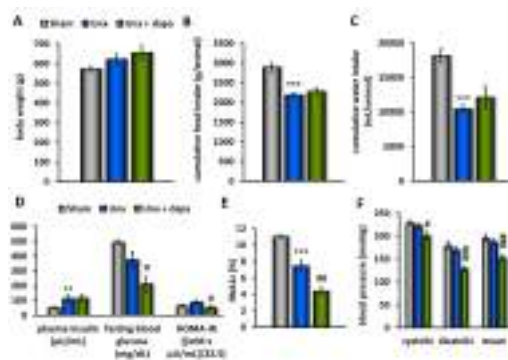
Male, 6-week old SDT fatty rats underwent unilateral nephrectomy (Unx; n=16) or sham operation (Sham; n=8). After a 1-week recovery, rats had free access to Purina 5008 chow diet and drinking water supplemented with 0.3% salt for 10 weeks. After 3 weeks of diet to enhance kidney complications, 8 Unx rats were treated with DAPA 1mg/kg/day for 7 weeks.

At the end of the treatment period, blood pressure was measured using tail-cuff plethysmography. Blood samples were taken and urine was collected over 24 hours to measure biochemical parameters. Glomerular Filtration Rate was assessed after FITC-inulin injection. Kidney was collected for histology analysis (Periodic Acid Schiff (PAS), Sirius Red staining, and ED1 immunostaining).

Data are presented as mean \pm SEM. Statistical analysis was performed using either an unpaired, 2 tailed Student t-test, Mann-Whitney test or a 2-way ANOVA + Bonferroni post-test. A $p < 0.05$ was considered significant.

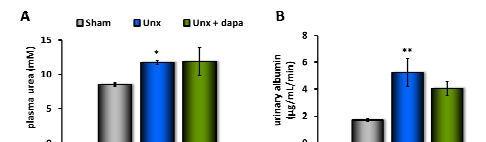
RESULTS

1. Dapagliflozin reduces hyperglycemia and hypertension in Unx SDT fatty rat under 0.3% salt



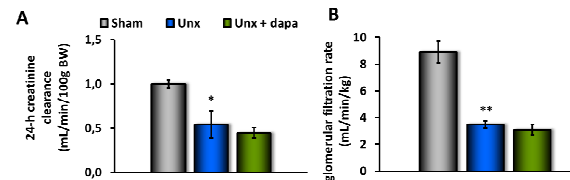
Body weight (A), food intake (B), water intake (C), fasting plasma insulin, blood glucose and HOMA-IR index of insulin resistance (D), HbA1c (E) and blood pressure (F) in Sham, Unx and Unx+dapagliflozin rats after 7 weeks of treatment. ** $p < 0.01$ and *** $p < 0.001$ Unx vs. Sham, ## $p < 0.01$ and ### $p < 0.001$ Unx+dapa vs. Unx.

2. Dapagliflozin does not alter the increased plasma urea and albuminuria in Unx SDT fatty rat under 0.3% salt



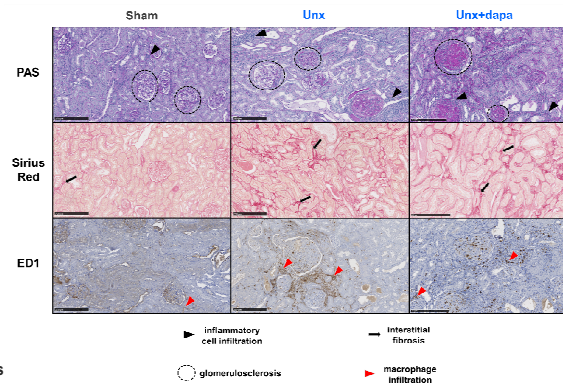
Plasma urea (A) and albuminuria in Sham, Unx and Unx+dapagliflozin rats after 7 weeks of treatment. * $p < 0.05$, ** $p < 0.01$ Unx vs. Sham.

3. Dapagliflozin has neutral effect on creatinine clearance and the >50% GFR decline in Unx SDT fatty rat under 0.3% salt

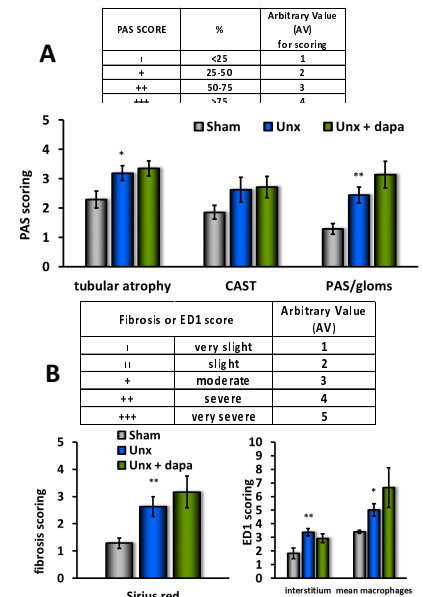


24-hour creatinine clearance (A) and glomerular filtration rate (GFR) measured after FITC-inulin injection in Sham, Unx and Unx+dapagliflozin rats after 7 weeks of treatment. * $p < 0.05$ and ** $p < 0.01$ Unx vs. Sham.

4. Dapagliflozin does not alter the advanced glomerulosclerosis, inflammation and fibrosis in Unx SDT fatty rat under 0.3% salt



5. Dapagliflozin has neutral effect on advanced kidney disorders in Unx SDT fatty rat under 0.3% salt



PAS scoring (A), fibrosis and ED1 scoring (B) in Sham, Unx and Unx+dapagliflozin rats after 7 weeks of treatment. * $p < 0.05$ and ** $p < 0.01$ Unx vs. Sham.

CONCLUSION AND PERSPECTIVES

•Unilateral nephrectomy and salt supplementation in SDT fatty rat expedite renal complications resulting in a >50% GFR decline in only 10 weeks.

•Our data suggest that SGLT2i with DAPA has no detrimental effect in uni-nephrectomized SDT fatty rat with advanced renal complications and >50% GFR decline.

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