**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.**

François Briand1, Masami Shinohara2, Emmanuel Brousseau1, Yasushi Kageyama2, Thierry Sulpice1

1Physiogenex, Labège, France; 2CLEA Japan Inc. Meguro-ku, Tokyo, Japan

**BACKGROUND & OBJECTIVES**

Sodium glucose cotransporter 2 inhibition (SGLT2) 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 SGLT2 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 ± 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

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

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

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

**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.

**Authors disclosures:** FB, EB and TS are employees of Physiogenex. MS and YK are employees of CLEA Japan Inc.