10-WEEK, BUT NOT 7-WEEK, DAPAGLIFLOZIN TREATMENT IMPROVES SEVERE RENAL IMPAIRMENT IN UNI-NEPHRECTOMIZED SDT FATTY RAT, A 10-WEEK MODEL OF ADVANCED RENAL COMPLICATIONS AND GLOMERULAR FILTRATION RATE DECLINE.

François Briand[1], Masami Shinohara[2], Emmanuel Brousseau[1], Takeshi Ohta[3], Yasushi Kageyama[2], Thierry Sulpice[1]

[1]Physiogenex, Labège, France; [2]CLEA Japan Inc. Meguro-ku, Tokyo, Japan, [3]Central Pharmaceutical Research Institute, Japan Tobacco Inc., Osaka, Japan

BACKGROUND

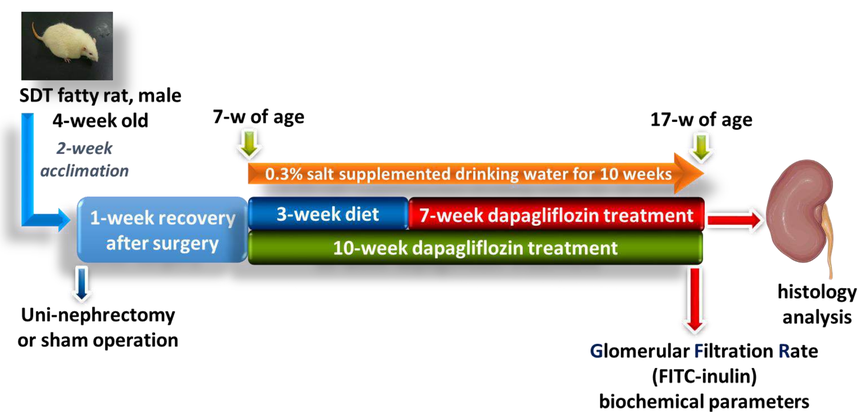
Sodium glucose cotransporter 2 inhibition (SGLT2i) represents a promising new class of glucose lowering drugs but may not be recommended in type 2 diabetic patients with severe renal impairment. Here we evaluated the effects of dapagliflozin (DAPA) treatment in uni-nephrectomized Spontaneously Diabetic 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

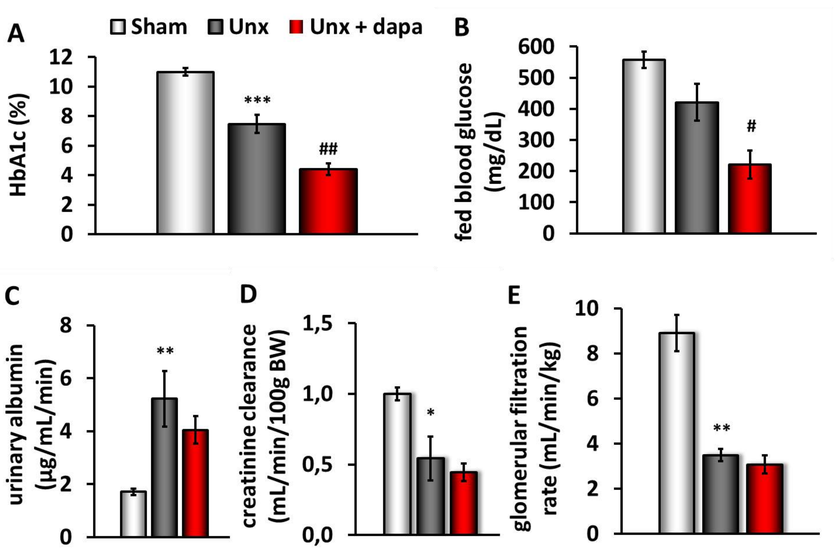
Male, 6-week old SDT fatty rats underwent unilateral nephrectomy (Unx). After a 1-week recovery, rats were put on a salt-supplemented diet (Purina 5008 chow diet and drinking water supplemented with 0.3% salt) for 10 weeks. Rats were treated without or with DAPA 1mg/kg/day in the chow diet either upon diet start (10-week treatment) or after 3 weeks of diet to enhance kidney complications (7-week treatment). A group of control/sham operated rats was included to evaluate kidney complications induced by nephrectomy and salt supplementation.

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

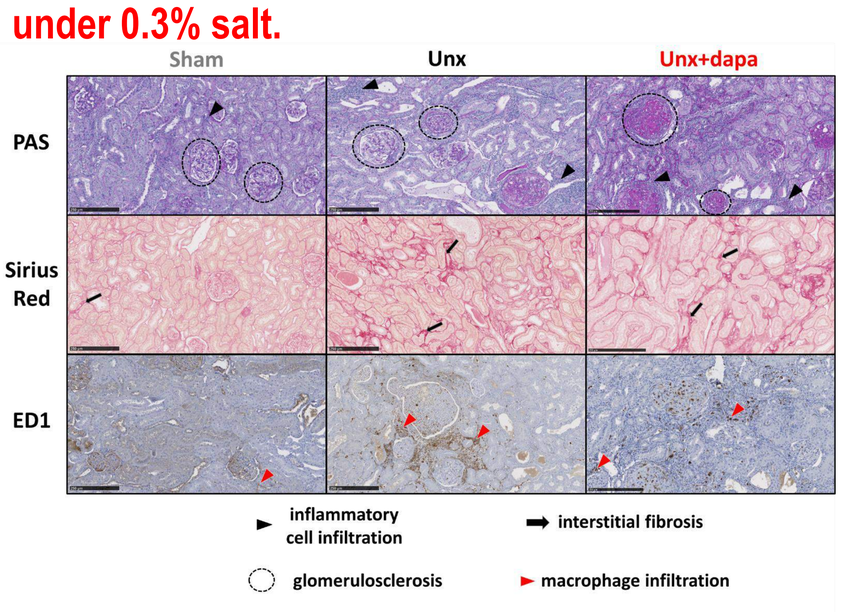


1. Dapagliflozin treatment for 7 weeks improves glycemic control but not kidney dysfunction in Unx SDT fatty rat under 0.3% salt.



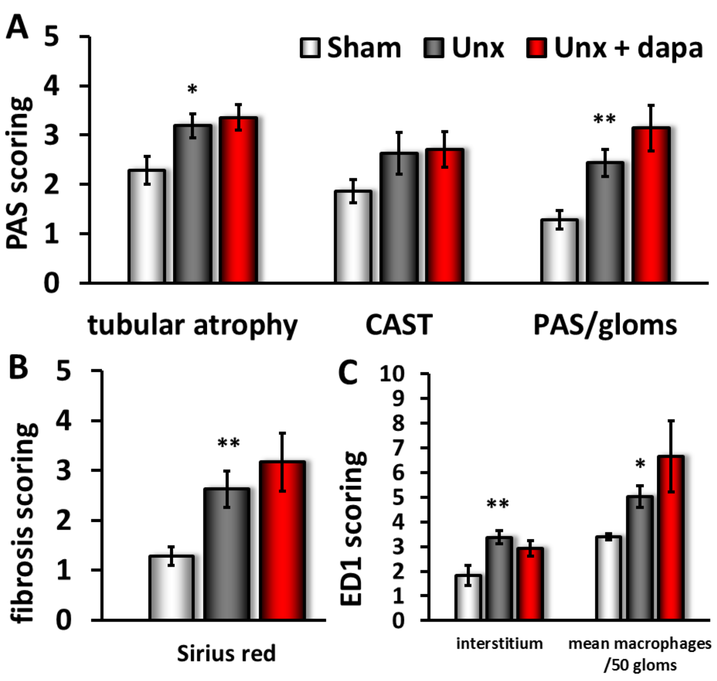
HbA1c (A), fed glycemia (B), albuminuria (C), 24-hour creatinine clearance (D) and glomerular filtration rate (E) measured after FITC-inulin injection in Sham, Unx and Unx+dapagliflozin rats after 7 weeks of treatment. *p<0.05, **p<0.01 and ***p<0.001 Unx vs. Sham, #p<0.05 and ##p<0.01 Unx vs. Unx+dapa.

2. Dapagliflozin treatment for 7 weeks does not alter kidney complications in Unx SDT fatty rat under 0.3% salt.



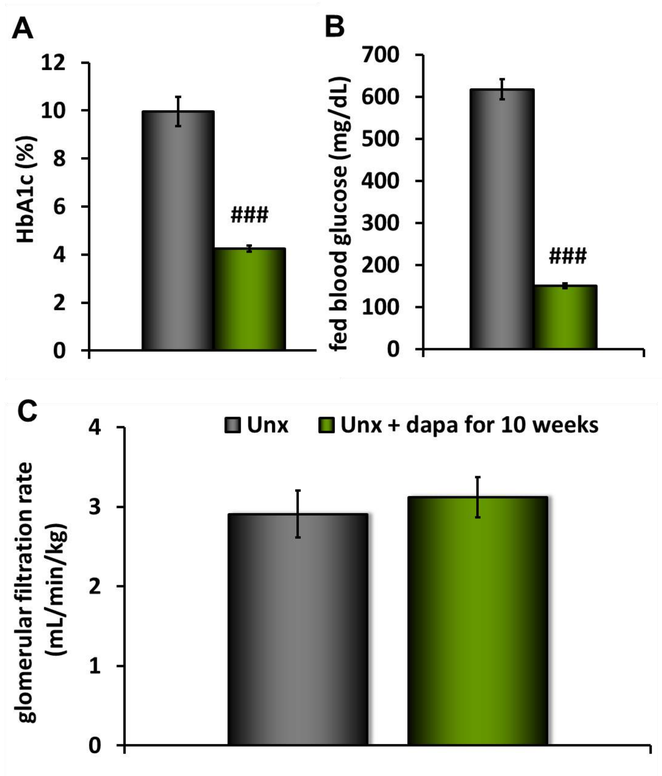
Histopathological features (PAS, Sirius Red and ED1) staining in Sham, Unx and Unx+dapagliflozin rats after 7 weeks of treatment.

3. Dapagliflozin treatment for 7 weeks does not change kidney histopathology scoring in Unx SDT fatty rat under 0.3% salt.



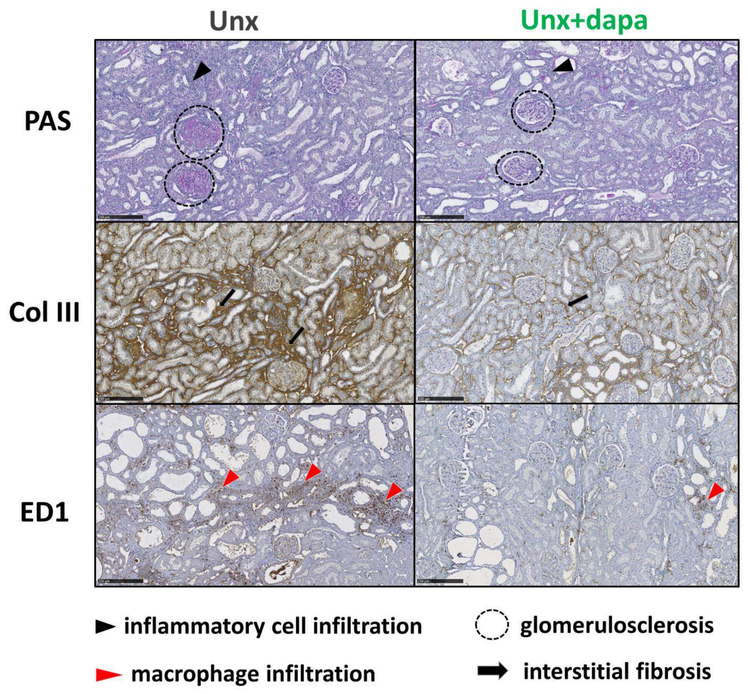
PAS (A), fibrosis (B) and ED1 scoring (C) in Sham, Unx and Unx+dapagliflozin rats after 7 weeks of treatment. *p<0.05 and **p<0.01 Unx vs. Sham.

4. Dapagliflozin treatment for 10 weeks improves glycemic control but not GFR in Unx SDT fatty rat under 0.3% salt.



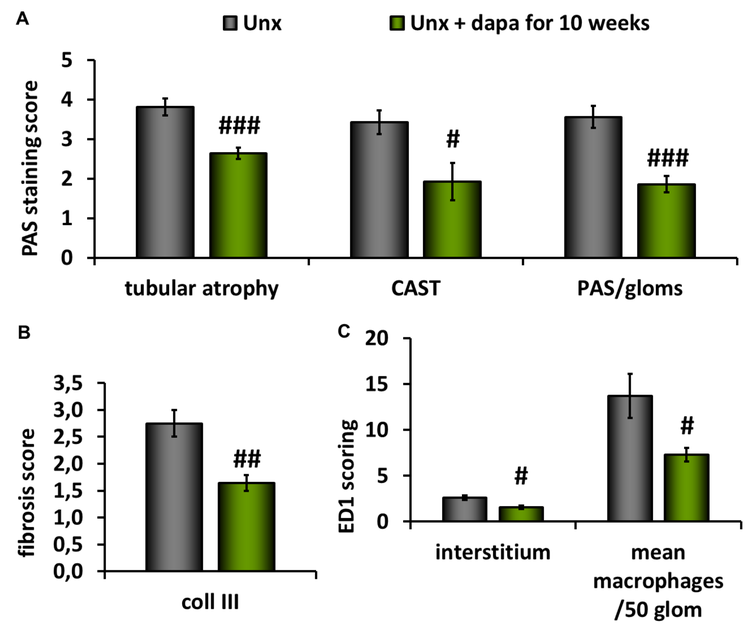
HbA1c (A), fed glycemia (B) and glomerular filtration rate (C) measured after FITC-inulin injection in Unx rats and Unx+dapagliflozin rats after 10 weeks of treatment. ##p<0.01 vs. Unx.

5. Dapagliflozin treatment for 10 weeks improves kidney complications in Unx SDT fatty rat under 0.3% salt.



Histopathological features (PAS, Collagen III and ED1) staining in Sham, Unx rats and Unx+dapagliflozin rats after 10 weeks of treatment.

6. Dapagliflozin treatment for 10 weeks improves kidney histopathology scoring in Unx SDT fatty rat under 0.3% salt.



PAS (A), fibrosis (B) and ED1 scoring (C) in Unx and Unx+dapagliflozin rats after 10 weeks of treatment. #p<0.05, ##p<0.01 and ###p<0.001 vs. Unx.

CONCLUSION

- Dapagliflozin for 10 weeks, but not 7 weeks, significantly prevents advanced renal complications in Unx SDT fatty rats.
- Long-term SGLT2i may be beneficial against kidney complications in the context of type 2 diabetes.

PHYSIOGENEX SAS - 516 Rue Pierre et Marie Curie –31670 Labège – France - business@physiogenex.com - www.physiogenex.com

CLEA Japan Inc., 1–2–7 Higashiyama, Meguro-ku, Tokyo 153-8533, JAPAN - export@clea-japan.com - www.clea-japan.com/en/