Dapagliflozin Alone or Combined with Ramipril Improves Hyperglycemia, Hypertension, and Prevents Kidney Complications and GFR Decline in the Nephrectomized SDT Fatty Rat Model of Diabetic Nephropathy.

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]Japan Tobacco Inc., Osaka, Japan

CLEA Japan, Inc.

Physiogenex
THE METABOLIC DISEASES EXPERTS

BACKGROUND & OBJECTIVES

Combination of sodium glucose cotransporter 2 inhibitor (SGLT2i) and angiotensin converting enzyme inhibitor (ACEi) represents a potential therapeutic strategy to prevent diabetic nephropathy progression to end stage renal disease (ESRD). Here we evaluated SGLT2i dapagliflozin (DAPA) alone or combined with ACEi ramipril (RAMI) in the uni-nephrectomized Spontaneously Diabetic Torii (SDT) fatty rat. This 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. 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. Rats were treated without (CTRL) or either with DAPA 1mg/kg/day alone or with DAPA + RAMI both at 1mg/kg/day, in the diet, upon diet start (10-week treatment; n=7 per group).

Glomerular Filtration Rate (GFR) was assessed using FITC-inulin i.v. injection at different timepoints: before and 1-week after unilateral nephrectomy (treatment start), then at 5 and 10 weeks of treatment.

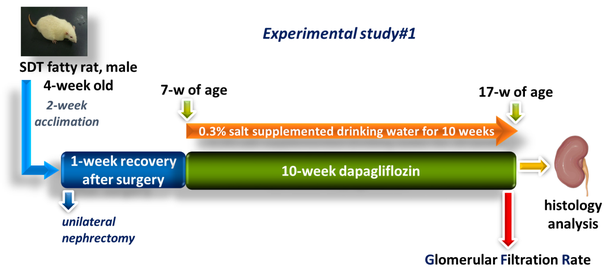
At the end of the treatment period, blood pressure (tail-cuff plethysmography) and biochemical parameters from blood, plasma and urine samples, were measured.

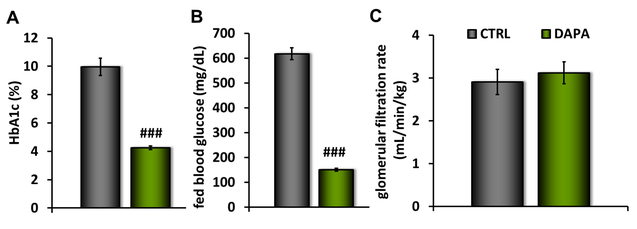
Kidney was collected for histology analysis (Periodic Acid Schiff (PAS), Coll III and ED1 immunostaining prior to a blinded histopathology scoring.

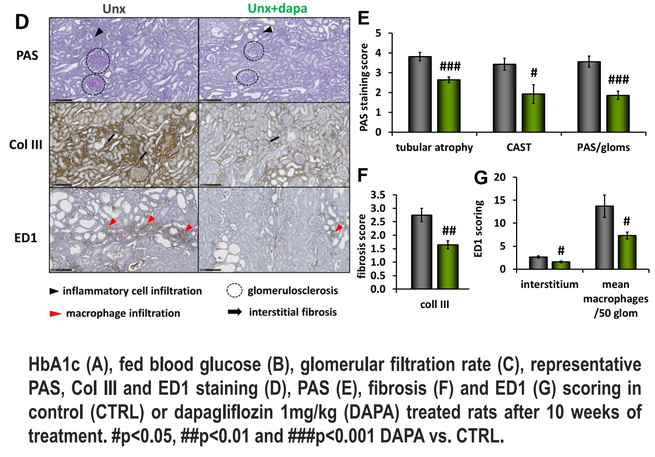
Data are presented as mean ±SEM. Statistical analysis was performed using either an unpaired, 2 tailed Student t-test, Mann-Whitney test or a 1-way ANOVA + Bonferroni post-test. A $p<0.05$ was considered significant.

RESULTS

1. A 10-week dapagliflozin treatment does not alter GFR but significantly improves kidney complications in Unx SDT fatty rat under 0.3% salt.

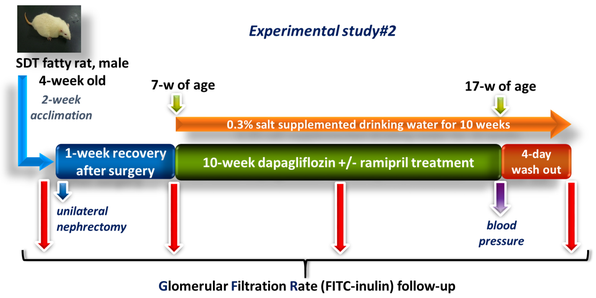


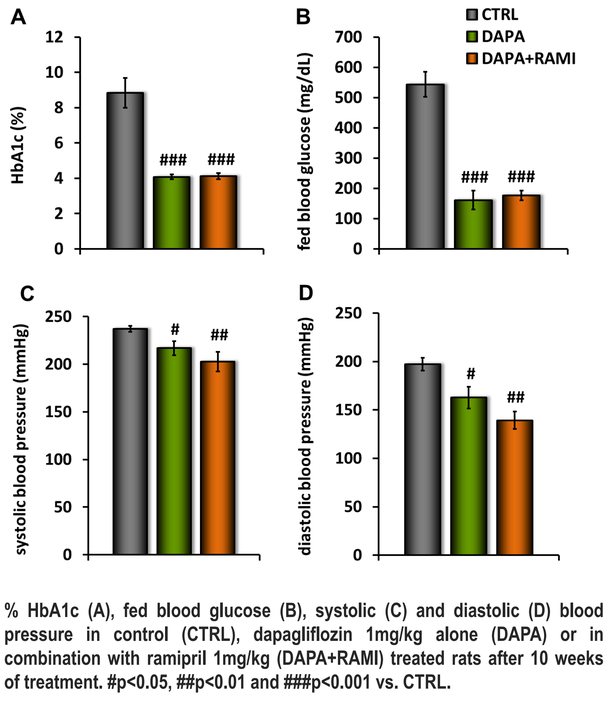




HbA1c (A), fed blood glucose (B), glomerular filtration rate (C), representative PAS, Col III and ED1 staining (D), PAS (E), fibrosis (F) and ED1 (G) scoring in control (CTRL) or dapagliflozin 1mg/kg (DAPA) treated rats after 10 weeks of treatment. #p<0.05, ##p<0.01 and ###p<0.001 DAPA vs. CTRL.

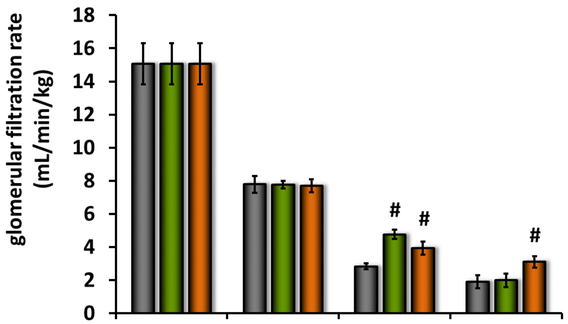
2. Dapagliflozin in combination with ramipril for 10 weeks results in similar glycemic control but further reduces hypertension compared to dapagliflozin alone.





% HbA1c (A), fed blood glucose (B), systolic (C) and diastolic (D) blood pressure in control (CTRL), dapagliflozin 1mg/kg alone (DAPA) or in combination with ramipril 1mg/kg (DAPA+RAMI) treated rats after 10 weeks of treatment. #p<0.05, ##p<0.01 and ###p<0.001 vs. CTRL.

3. Dapagliflozin in combination with ramipril for 10 weeks better prevents severe GFR decline than dapagliflozin alone.



Glomerular filtration rate, before nephrectomy, at treatment start, and at 5 weeks and 10 weeks of treatment (after a 4-day wash out) in control (CTRL), dapagliflozin 1mg/kg alone (DAPA) or in combination with ramipril 1mg/kg (DAPA+RAMI) treated rats. #p<0.05 vs. CTRL.

CONCLUSION AND PERSPECTIVES

- **In the 10-week Unx SDT fatty rat under 0.3% salt, DAPA alone prevents kidney complications, while the combination with RAMI adds benefits by better delaying GFR decline.**
- **Our data suggest that SGLT2i/ACEi combination prevents progression to ESRD.**

DISCLOSURES

FB, EB and TS are employees of Physiogenex.
MS and YK are employees of CLEA Japan Inc.
TO is an employee of Japan Tobacco Inc.

Kidney Week 2017 October 31st - November 5th, 2017, New-Orleans, LA, USA

PHYSIOGENEX - 516 Rue Pierre et Marie Curie –31670 Labège Cedex – France Phone: +33 561 287 040 - 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/

This work has been funded by Physiogenex and CLEA Japan Inc.