Unilateral Nephrectomy and Salt Supplementation in Spontaneously Diabetic Torii Fatty Rat Expedites Renal Complications and Glomerular Filtration Rate Decline within 10 weeks

Francois Briand¹, Masami Shinohara², Emmanuel Brousseau¹, Katsuhiro Miyajima³, Takeshi Ohta⁴, Yasushi Kageyama², Thierry Sulifice⁵
¹Physiogenex SAS, Labège, France; ²CLEA Japan Inc., Tokyo, Japan; ³Tokyo University of Agriculture, Tokyo, Japan; ⁴Japan Tobacco Inc., Osaka, Japan.

OBJECTIVES

Evaluation of drugs targeting diabetic nephropathy requires suitable diabetic animal models developing renal complications and a 50% glomerular filtration rate (GFR) decline within a short period of time. Although the Spontaneously Diabetic Torii (SDT) Fatty Rat rapidly develops obesity, type 2 diabetes, hypertension with age, advanced kidney disorders are only observed around 40 weeks of age. We therefore developed a novel experimental procedure expediting renal complications within 10 weeks fitting the mandatory needs for preclinical drug development.

METHODS

Male, 6-week old SDT fatty rats underwent unilateral nephrectomy (Unx; n=8) 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. The salt % was selected from preliminary studies performed by Dr. Miyajima (Tokyo University of Agriculture) and Dr. Ohta (Japan Tobacco Inc.). At the end of the 10-week diet period, glomerular filtration rate was measured using FITC-inulin i.v. injection, urine was collected over 24 hours and blood samples were collected for biochemical parameters measured with a Horiba Pentra 400. Rats were then sacrificed and kidney was collected to perform histology analysis (Periodic acid-Schiff, Sirius Red staining, ED1 immuno-staining) and scoring. Data are expressed as mean ± SEM. Unpaired 2-tailed Student t-test were used for statistics.

RESULTS

1. Unx SDT fatty rat under 0.3% salt for 10 weeks are obese, hyperglycemic and hypertensive.

2. Unx SDT fatty rat under 0.3% salt for 10 weeks have increased plasma urea levels and albuminuria.

3. Unx SDT fatty rat under 0.3% salt for 10 weeks show reduced creatinine clearance and >50% GFR reduction.

4. Unx SDT fatty rat under 0.3% salt for 10 weeks develop advanced glomerulosclerosis, inflammation and fibrosis.

5. Unx SDT fatty rat under 0.3% salt for 10 weeks show advanced kidney disorders.

CONCLUSION

- Unilateral nephrectomy and salt supplementation in SDT fatty rat expedite renal complications resulting in a >50% GFR decline in only 10 weeks.
- The SDT fatty rat therefore represents a robust model to evaluate drugs targeting diabetic nephropathy.
- Anti-diabetic SGLT2 inhibitor dapagliflozin and anti-hypertensive ACE inhibitor ramipril are currently under evaluation.