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

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OBJECTIVES

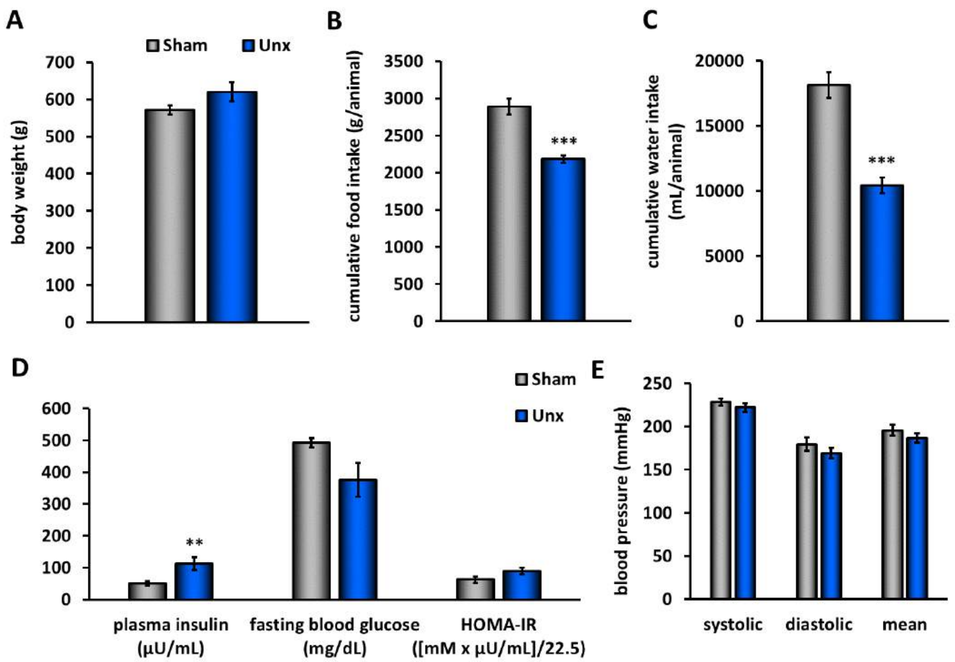
Evaluation of drugs targeting diabetic nephropathy requires suitable diabetic animal models developing renal complications and a 50% glomerular filtration rate (GFR) decline within a short period of time. Although the Spontaneously Diabetic Torii (SDT) Fatty Rat rapidly develops obesity, type 2 diabetes, 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.

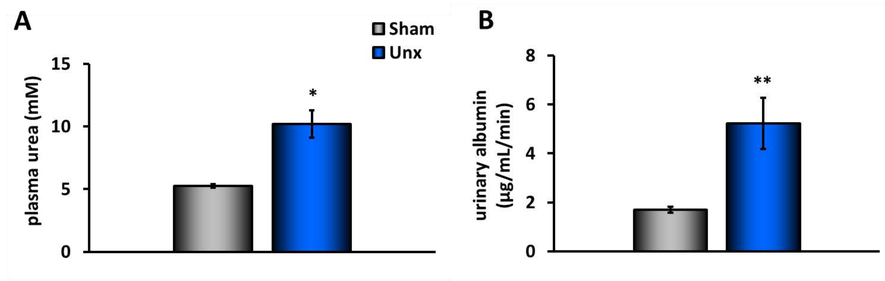
RESULTS

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



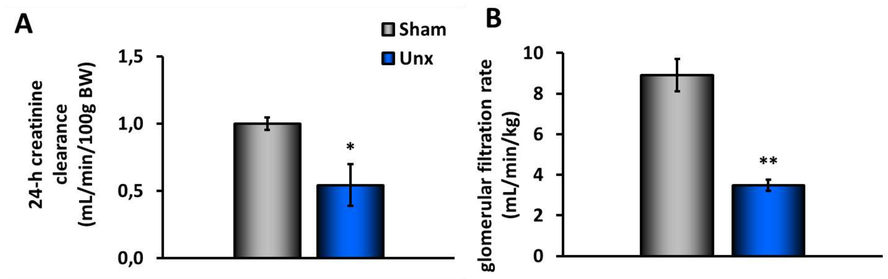
Body weight (A), cumulative food intake (B) and water intake (C), fasting plasma insulin, blood glucose and HOMA-IR index (D) and blood pressure (E) in Sham or Unx rats after 10 weeks of 0.3% salt supplementation. ***p<0.01 and ***p<0.001 vs. vehicle.*

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



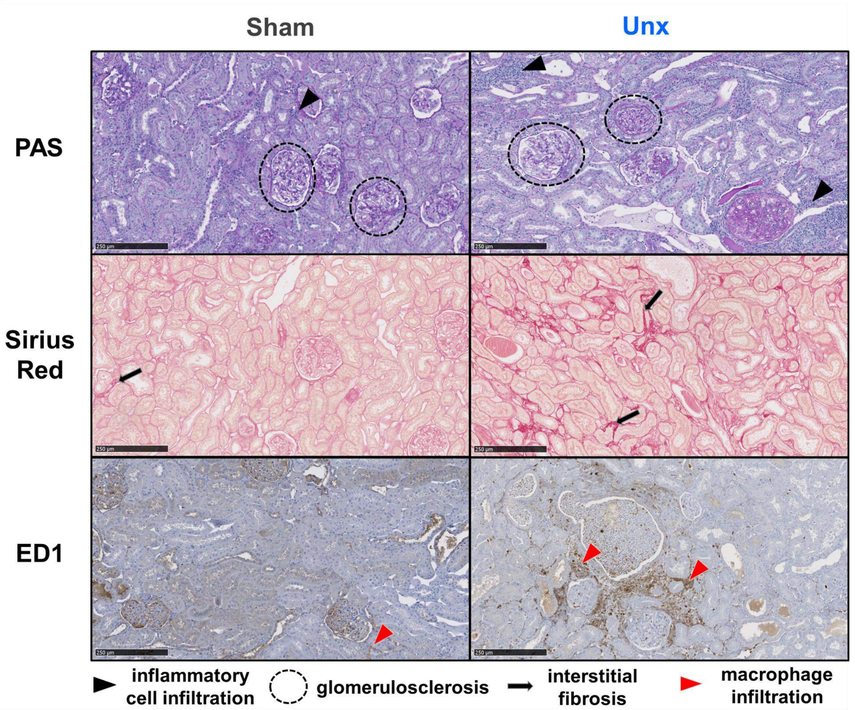
Plasma urea (A), and albuminuria (B) in Sham or Unx rats after 10 weeks of 0.3% salt supplementation. **p<0.05 and **p<0.01 vs. vehicle.*

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



Creatinine clearance (A), and glomerular filtration rate (B) in Sham or Unx rats after 10 weeks of 0.3% salt supplementation. **p<0.05 and **p<0.01 vs. vehicle.*

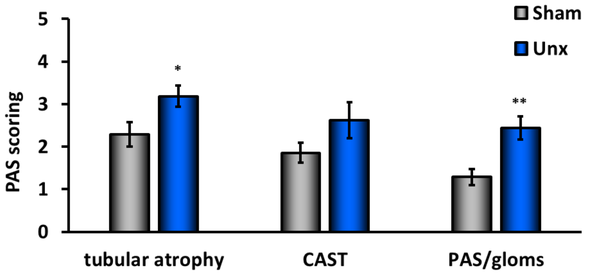
4. Unx SDT fatty rat under 0.3% salt for 10 weeks develop advanced glomerulosclerosis, inflammation and fibrosis.



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

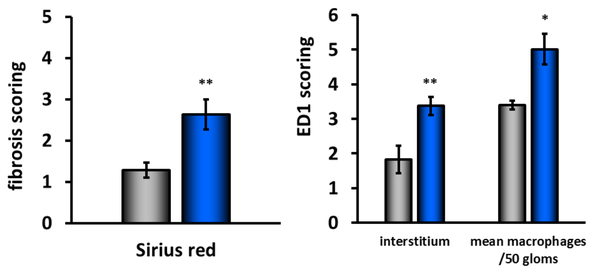
A

PAS SCORE	%	Arbitrary Value (AV) for scoring
ı	<25	1
+	25-50	2
++	50-75	3
+++	>75	4



B

Fibrosis or ED1 score		Arbitrary Value (AV)
ı	very slight	1
ıı	slight	2
+	moderate	3
++	severe	4
+++	very severe	5



PAS scoring (A), fibrosis and ED1 scoring (B) in Sham or Unx rats after 10 weeks of 0.3% salt supplementation. **p<0.05 and **p<0.01 vs. vehicle.*

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.**

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