

## BACKGROUND

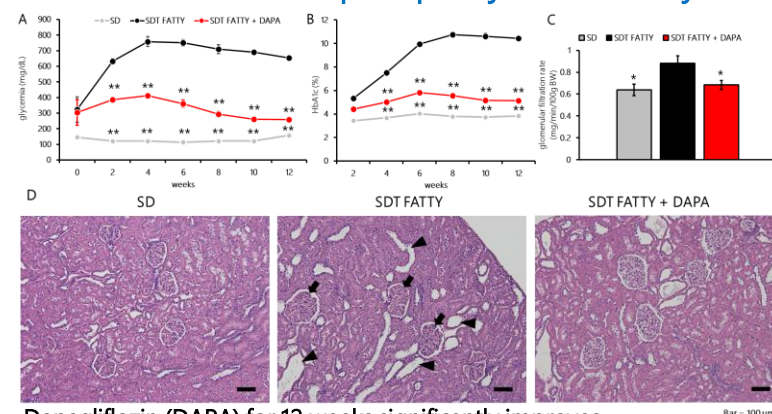
Our objective was to validate a type 2 diabetic rat model that would also develop both diabetic nephropathy and neuropathy. Therefore, we characterized the Spontaneously Diabetic Torii (SDT) fatty rat, a preclinical model of type 2 diabetes, and evaluated the effects of SGLT2 inhibitor dapagliflozin.

## METHODS

Nephropathy and neuropathy were characterized in SDT fatty male rats, without or with unilateral nephrectomy (Unx). In both models, dapagliflozin was evaluated at 1mg/kg/day for up to 12 weeks. Sprague Dawley rats were used as healthy controls.

## RESULTS

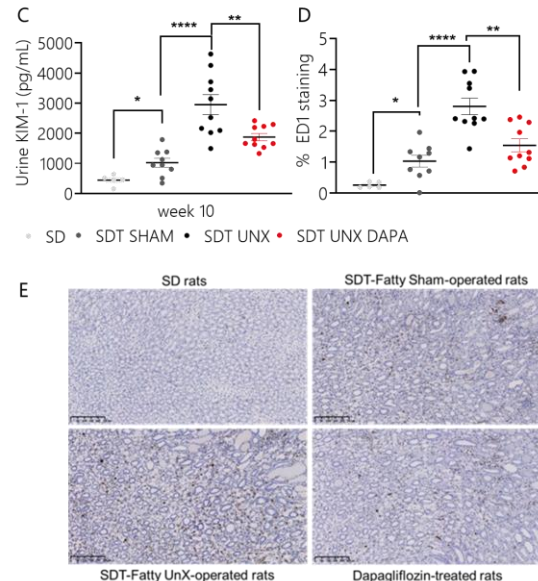
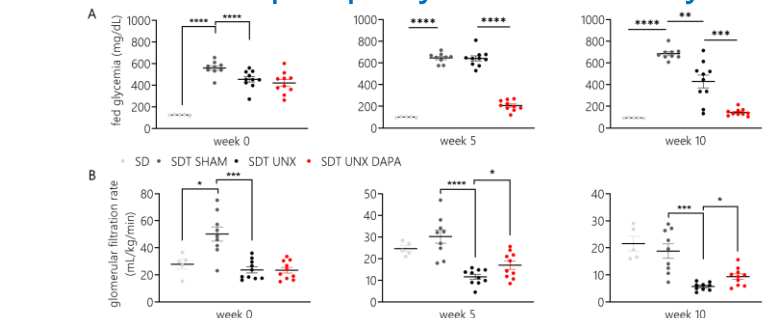
### 1 SGLT2 inhibition with dapagliflozin significantly improves glycemic control and diabetic nephropathy in SDT fatty rats



Dapagliflozin (DAPA) for 12 weeks significantly improves glycemia (A), %HbA1c (B), glomerular hyperfiltration (C) and renal tubules abnormalities (D) in SDT fatty rats. Arrows indicate greater glomerular size and arrow heads show tubular lesions including the dilation.

\* $p < 0.05$  and \*\* $p < 0.01$  vs. SDT Fatty

### 2 Dapagliflozin markedly improves glycemia and diabetic nephropathy in Unx SDT fatty rats



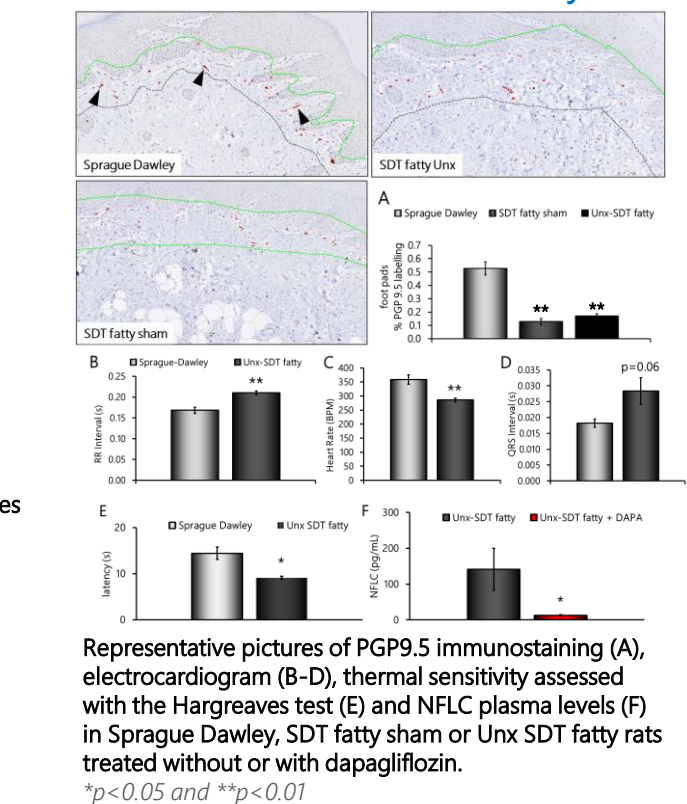
Dapagliflozin (DAPA) for 10 weeks significantly reduces glycemia (A) and prevents glomerular filtration rate decline (B). Dapagliflozin also reduces urine levels of KIM-1 (C), a biomarker of kidney injury, and kidney inflammation as shown by lower %ED1 staining (D). Representative ED1 staining pictures in SD, SDT fatty sham-operated or unilaterally nephrectomized (Unx) rats are shown in panel (E).

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  and \*\*\*\* $p < 0.0001$

## CONCLUSIONS

SGLT2 inhibition improves glycemic control, diabetic nephropathy and neuropathy in SDT fatty rats. Our experimental setting will help to evaluate novel therapies versus dapagliflozin as a reference drug.

### 3 Dapagliflozin lowers NFLC, a marker of neuropathy, another comorbidity observed in the Unx SDT fatty rat



Representative pictures of PGP9.5 immunostaining (A), electrocardiogram (B-D), thermal sensitivity assessed with the Hargreaves test (E) and NFLC plasma levels (F) in Sprague Dawley, SDT fatty sham or Unx SDT fatty rats treated without or with dapagliflozin.

\* $p < 0.05$  and \*\* $p < 0.01$