The Uni-Nephrectomized SDT Fatty Rat, a novel Type 2 diabetic model of Diabetic Nephropathy, develops features of diabetic retinopathy over 10 weeks

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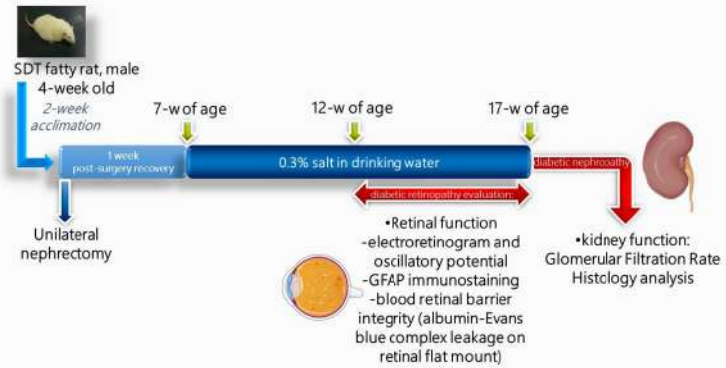
PURPOSE:

Animal models of spontaneous diabetes are still needed to mimic human diabetic retinopathy. We recently developed a novel model of diabetic nephropathy using the uni-nephrectomized Spontaneously Diabetic Torii (SDT) fatty rat. Fed a salt rich diet, this hypertensive/obese/type 2 diabetic rat develops advanced renal glomerulosclerosis, inflammation and fibrosis, and a >50% glomerular filtration rate decline within 10 weeks. Here we investigated whether this rat model would also develop features of diabetic retinopathy.

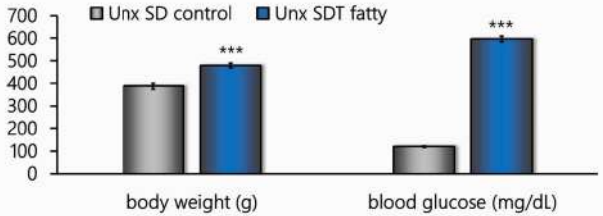
METHODS:

Two groups of 6-week old, male, Sprague Dawley (SD, control) rats and SDT fatty rats (n=10 per group) underwent unilateral nephrectomy. After a 1-week recovery period, rats were fed for 10 weeks a chow diet with 0.3% salt in drinking water (i.e. from 7 weeks to 17 weeks of age). Diabetic retinopathy was evaluated in terms of i) retinal function by electroretinogram and oscillatory potentials, ii) integrity of blood-retinal barrier by albumin–Evans blue complex leakage, iii) microscopy histopathologic studies by glial fibrillary acidic protein IHC.



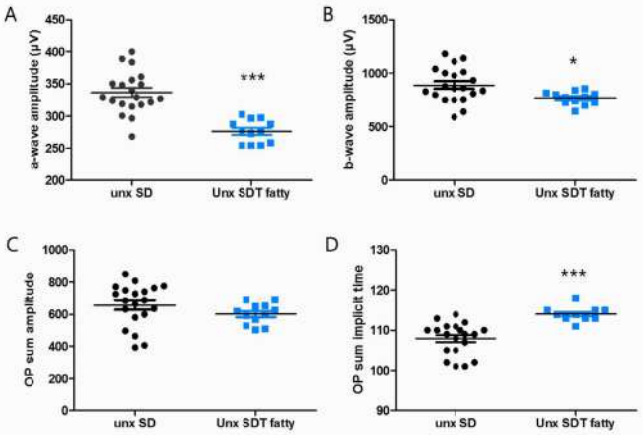
RESULTS:

1 SDT fatty rats under 0.3% salt exhibit obese and diabetic phenotype after unilateral nephrectomy



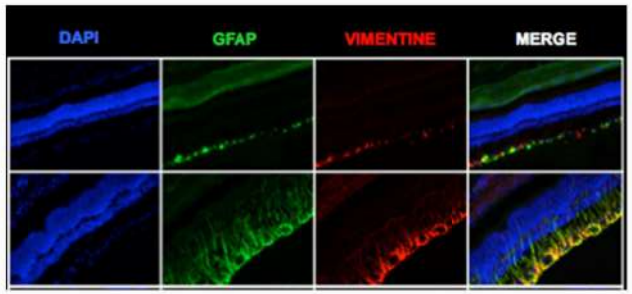
Body weight and fed blood glucose in Sprague Dawley (SD) control and SDT fatty rat at one week after unilateral nephrectomy. ****p<0.001 vs. Unx SD control.*

2 Electroretinography demonstrates retinal neurologic dysfunction in Unx SDT fatty rats from 12 weeks of age



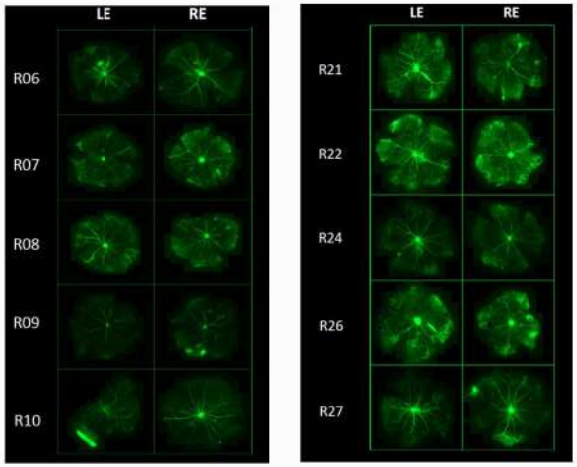
A-wave (panel A; photoreceptor response) and B-wave (panel B; inner retinal cells activity) during a standard scotopic ERG recording to a bright white flash (0 log cd s/m2). Amplitudes (panel C) and implicit times (panel D) of the oscillatory potentials (OPs, reflects inner retinal function) extracted from scotopic responses. **p<0.05 and ***p<0.001 vs. Unx SD control.*

3 Unx SDT fatty rats show reactive gliosis in retina at 17 weeks of age



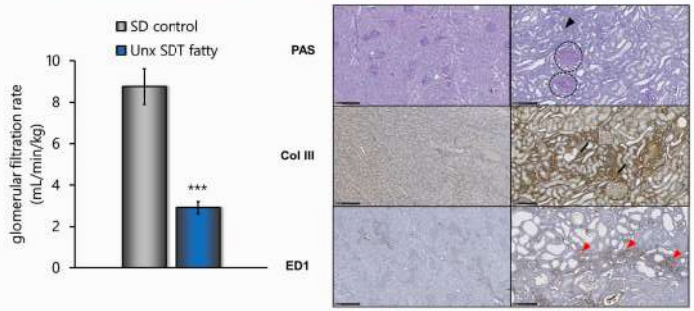
DAPI (4',6-diamidino-2-phenylindole; for nuclear acid staining), glial fibrillary acidic protein (GFAP) and vimentin (markers of Müller cells) immunoreactivity in sagittal retinal sections, assessed by fluorescence microscopy.
Upper and lower panels show representative pictures from a Unx SD rat and Unx SDT fatty rats, respectively, at 17 weeks of age.

4 Evans blue retinal flat-mount indicates vessel dilatation and tortuosity, without evidence of retinal vascular permeability, in 17-week old Unx SDT fatty rats



Evans blue retinal flat-mount of uni-nephrectomized SD rat (left panel) and SDT fatty rat (right panel) at 17 weeks of age.

5 17-week old Unx SDT fatty rats show advanced kidney complications and a >50% glomerular filtration rate decline.



Glomerular Filtration Rate (left panel) and representative histopathological features after PAS (glomerulosclerosis), collagen III (fibrosis) and ED1 (macrophage/inflammation) staining (right panel), in 17-week old SD control or Unx SDT fatty rats. Black and red triangles indicate inflammation and macrophages, respectively, black circles indicate glomerulosclerosis and black arrows indicate fibrosis. ****p<0.001 vs. control.*

CONCLUSION

- Uni-nephrectomized SDT fatty rats develop features of diabetic retinopathy in parallel with diabetic nephropathy.
- Our original data set suggests that this rat model is suitable to evaluate the effects of drugs on these type 2 diabetes co-morbidities.

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DISCLOSURES: F.B., F.B. and T.S. are employees of Physiogenex S.A., V.M., N.C., L.F. are employees fo Iris PharmaM.S. and Y.K. are employees of CLEA Japan Inc.; T.O. is employee of Japan Tobacco Inc.