Goto-Kakizaki (GK) rats

Model advantages:

The Goto-Kakizaki (GK) rat model is one of the best characterized animal model of spontaneous type 2 diabetes, generated by selecting and inbreeding hyperglycemic Wistar rats (produced byMetabrain Research). This non-obese diabetic rat presents many similarities with type 2 diabetic patients in term of pancreas dysfunction such as impaired glucose stimulated insulin secretion, reduction in beta-cell mass, perturbed islets microenvironment, and multiple beta-cell functional common defects. Furthermore, it also displays both bladder and sexual dysfunctions, complications commonly associated to diabetes type 2 in patients.

Pathophysiological features:

Metabolic features:

- Hyperglycemia
- Defective insulin secretion in response to glucose (figure 1)
- Decreased β cell mass (50%)
- Hepatic and peripheral insulin resistance
- Defects in lipid metabolism (mainly cholesterol)
- Inflammation, particularly in pancreatic islets

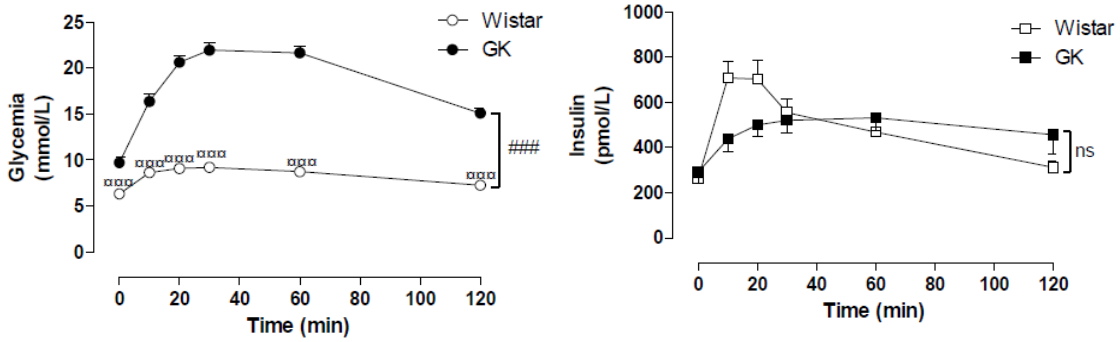

Figure 1: Plasma glucose and insulin levels in 18-weeks old GK rats and in age-matched Wistar rats before and 10, 20, 30, 60 and 120 min after oral glucose challenge (2g/kg body weight). (Pelvipharm, internal data).

Cardiovascular features:

- Defective cardiac function (heart hypertrophy, lower heart rate)
- Increased blood pressure

Genito-sexual features:

- Erectile dysfunction (ED)
  → only partially reversed by ED standard-of-care sildenafil (figure 2)
- Hypogonadism

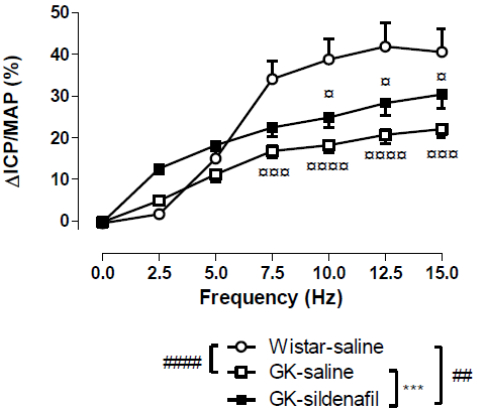

Figure 2: *Erectile responses elicited by cavernous nerve stimulation at increasing stimulation frequencies in anaesthetized Wistar rats (treated with saline) and GK rats (treated with saline or with sildenafil 0.3 mg/kg i.v.) reported as intracavernosal pressure/mean arterial pressure rise (ΔICP/MAP). (Pelvipharm, internal data).*

Bladder and urinary features:

- Diabetic bladder dysfunction (DBD) with detrusor overactivity, increased bladder capacity and micturition pressure
  → Bladder contraction parameters reversed by OAB standard-of-care solifenacin (figure 3)
- Proteinuria

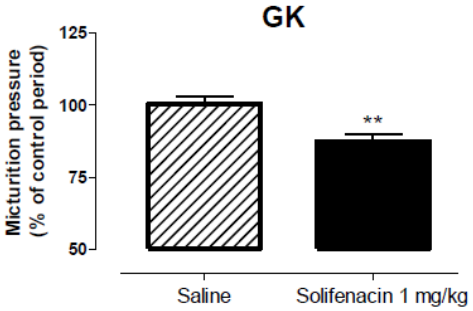

Figure 3: *Effect of i.v. solifenacin (1 mg/kg) or saline on micturition pressure parameter characterizing micturition contraction in GK rats. (Pelvipharm, internal data).*

Links to applicable experimental skills

- Administration routes / regimen
- Plasma / urine / tissue collection
- In vivo experiments – conscious animals
* Telemetry
* metabolic cages
* tail cuff
- Organ bath studies
* Rat tissues
- Biochemistry
* Spectrophotometric assays
* Protein expression and activity
- Histology/Morphometry
* Histomorphology
* Histomorphometry
- Immunohistologie/Immunofluorescence/Confocal microscopy
* Immunohistology
* Immunofluorescence
* Confocal microscopy