

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. 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, disturbed islets microenvironment, and multiple beta-cell functional common defects. Furthermore, it also displays both bladder and sexual dysfunctions, associated to endothelial dysfunction, complications commonly associated to type 2 diabetes 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

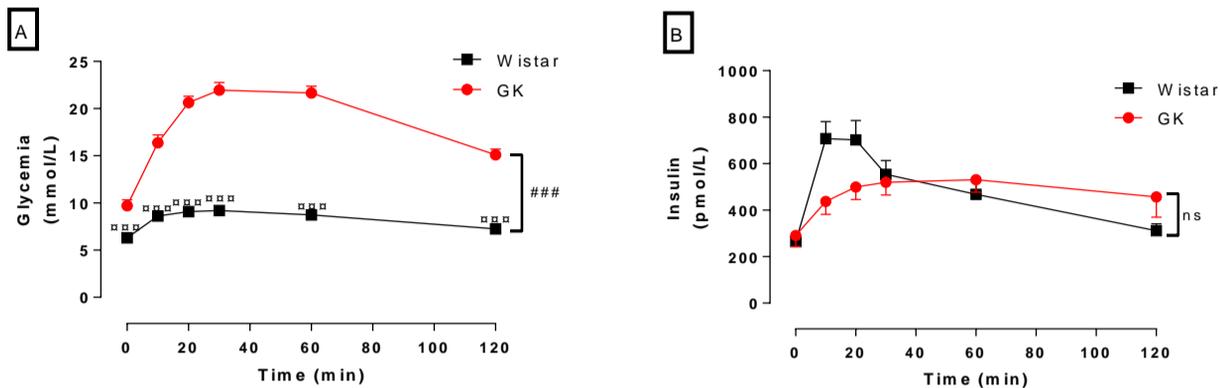


Figure 1: Plasma glucose [A] and insulin [B] levels in 18-week-old GK rats and in age-matched Wistar rats before and 10, 20, 30, 60 and 120 min after oral glucose challenge (2g/kg body weight). ns: non-significant, ### $p < 0.001$ two-way ANOVA followed by post hoc modified Student's test $***p < 0.001$ (From Oger-Roussel et al., 2014).

Cardiovascular features

- Defective cardiac function (heart hypertrophy, lower heart rate)
- Increased blood pressure
- Endothelial dysfunction
- Elevated oxidative stress biomarkers

Erectile dysfunction

- Erectile dysfunction (ED), only partially reversed by ED standard-of-care sildenafil (figure 2)
- Cavernosal endothelial dysfunction (figure 3)
- Penile fibrosis

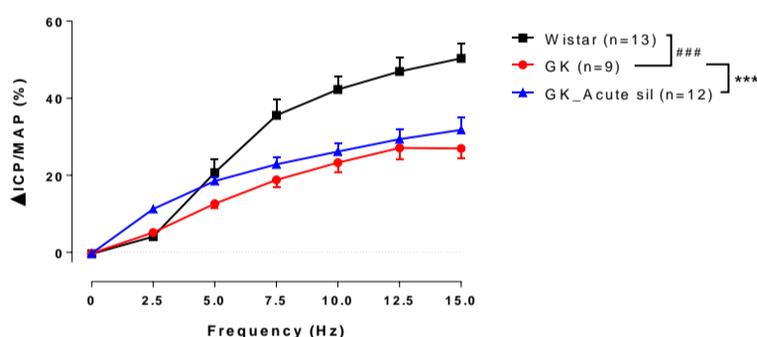


Figure 2: Erectile responses elicited by cavernous nerve stimulation at increasing stimulation frequencies in anaesthetized Wistar rats (treated with saline) and GK rats (treated with saline or with sildenafil 0.3 mg/kg i.v.) reported as intracavernosal pressure/mean arterial pressure rise (Δ ICP/MAP). ### $p < 0.001$ two-way ANOVA vs Wistar; *** $p < 0.01$ two-way ANOVA vs GK-saline (From Assaly-Kaddoum et al., 2016).

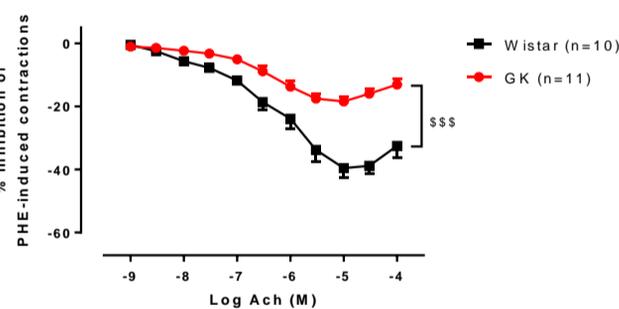


Figure 3: Endothelium-dependent relaxant responses to acetylcholine (Ach) on phenylephrine (PHE)-pre-contracted cavernosal strips from control Wistar and GK rats. CRC: concentration response curve \$\$\$ $p < 0.001$ two-way ANOVA (From Assaly et al., 2018).

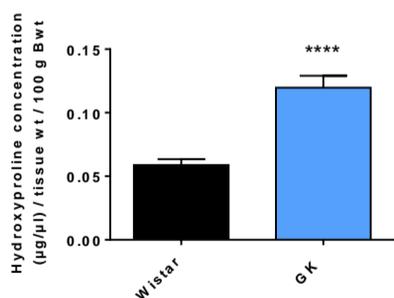


Figure 4: Quantitative assessment of cavernosal collagen by hydroxyproline assay in Wistar and GK rats. Data are mean \pm SEM. **** $p < 0.001$, Student's t-test (Pelvipharm, internal data).

Bladder dysfunction

- Diabetic bladder dysfunction (DBD) with detrusor overactivity, increased bladder capacity and micturition pressure, with some effect of solifenacin as an OAB standard-of-care treatment (figure 3).

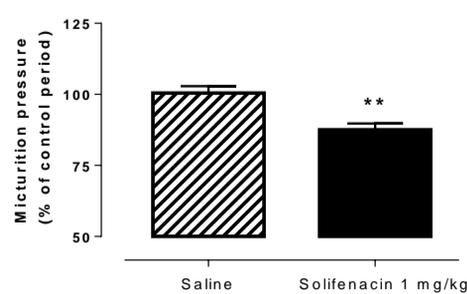


Figure 5: Effect of i.v. solifenacin (1 mg/kg) or saline on micturition pressure parameter characterizing micturition contraction in GK rats. (** $p < 0.01$ Student's t-test (From Oger-Roussel et al., 2014).

- Proteinuria

Related Pelvipharm bibliography:

Assaly R et al. **J sex med** (2018):15:1224-1234

Assaly-Kaddoum R et al. **J Urol** (2016):196:950-956

Oger-Roussel S et al. **Am J Physiol Regul Integr Comp Physiol** (2014):306:R108-17