Methods

Insulin Baseline and glucose-stimulated insulin response was assessed on separate days to minimize stress from tail bleeding. Animals were fasted for 6 hours prior to baseline assessment of insulin. Because of the difficulty in detecting an additive effect of the DPP-4 inhibitor and glucose on insulin levels in the control animals, plasma insulin was assessed at either 5 or 15 minutes after a glucose load (2g/kg).

Baseline levels of proglucagon derived product Blood was collected 5-6 hours into the light cycle in *ad lib* fed mice in heparinized syringes and placed in a tube with a mixture of DPP-4 inhibitor (Millipore, Burlington, MA, USA), heparin, EDTA, and aprotonin. Plasma was assayed for total GLP-1 using sandwich ELISA kits (K150JWC-1, Mesoscale Discovery, Rockville, MD, USA) and total mouse GIP using an ELISA (EZRMGIP, Millipore Sigma).

ESM Table 1

	Control	*Gcg*RA$^{\Delta PDXCre}$	*Gcg*RA$^{\Delta VilCre}$	*Gcg*RA$^{\Delta Null}$
Body Weight (g)	27.1 ± 2.4	27.8 ± 2.3	32.9 ± 1.8*	30.2 ± 2.8*
Fasted glucose (mmol/L)	9.5 ± 0.4	9.3 ± 0.3	9.6 ± 0.3	9.1 ± 0.4
Total GLP-1 (pM)	9.1 ± 4.1	5.2 ± 2.7	4.4 ± 1.6	undetectable
Total GIP (pM)	29.4 ± 19.6	32.3 ± 8.9	15.7 ± 5.0	48.1 ± 22.3

* $p<0.05$ compared to control and *Gcg*RA$^{\Delta PDX1Cre}$ groups. Mean ± STDEV.

ESM Figure 1

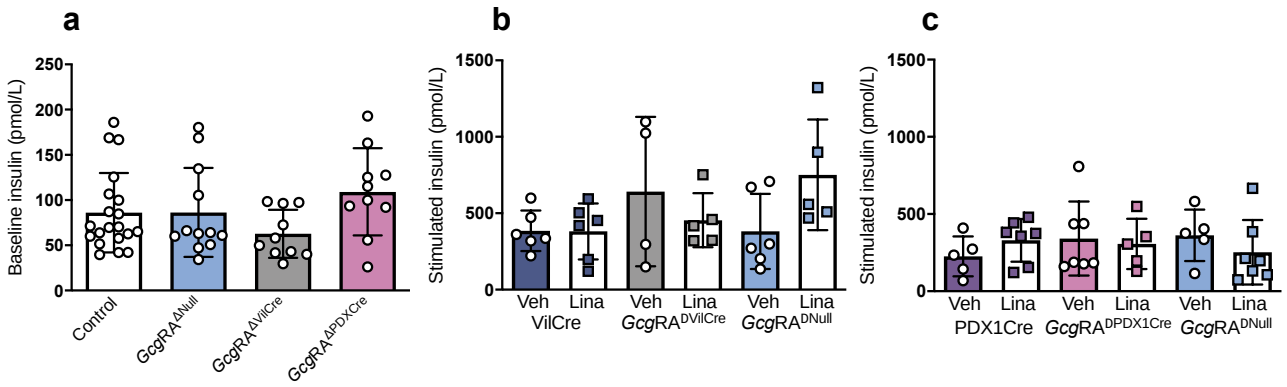
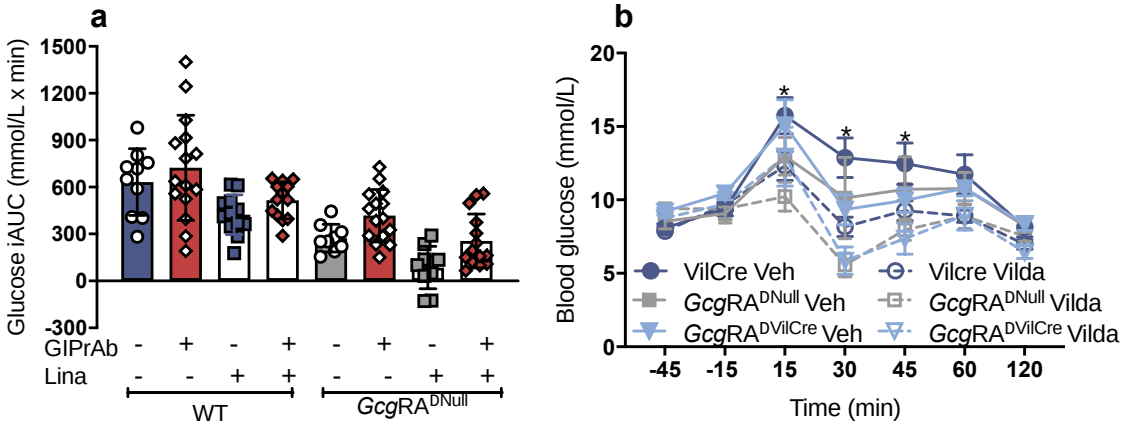


Fig 1. Insulin response to linagliptin. (a) Baseline insulin levels after a 6 hour fast in control (VilCre and PDX1Cre), *Gcg*RA$^{\Delta Null}$, *Gcg*RA$^{\Delta VilCre}$, and *Gcg*RA$^{\Delta PDX1Cre}$ mice. **(b)** Insulin levels 15 minutes after oral glucose (2g/kg) and 30 minutes after linagliptin (10mg/kg) in VilCre, *Gcg*RA$^{\Delta VilCre}$, and *Gcg*RA$^{\Delta Null}$ mice. **(c)** Insulin levels 5 minutes after oral glucose (2g/kg) and 30 minutes after linagliptin (10mg/kg) in PDX1Cre, *Gcg*RA$^{\Delta PDX1Cre}$, and *Gcg*RA$^{\Delta Null}$ mice.

ESM Figure 2



ESM Fig. 2. Data corresponding Fig 4. (a) iAUC corresponding to Figure 4a,b ($p<0.0001$, main effect of genotype; $p<0.0001$, main effect of linagliptin across genotypes; $p<0.001$, main effect of

GIPrAB across genotypes). **(b)** Glucose excursion line graph corresponding the iAUC graph in Fig **4c** ($p<0.0001$, time x genotype interaction; $^{*}p<0.05$, time x vildagliptin interaction across genotypes; n=5-7).