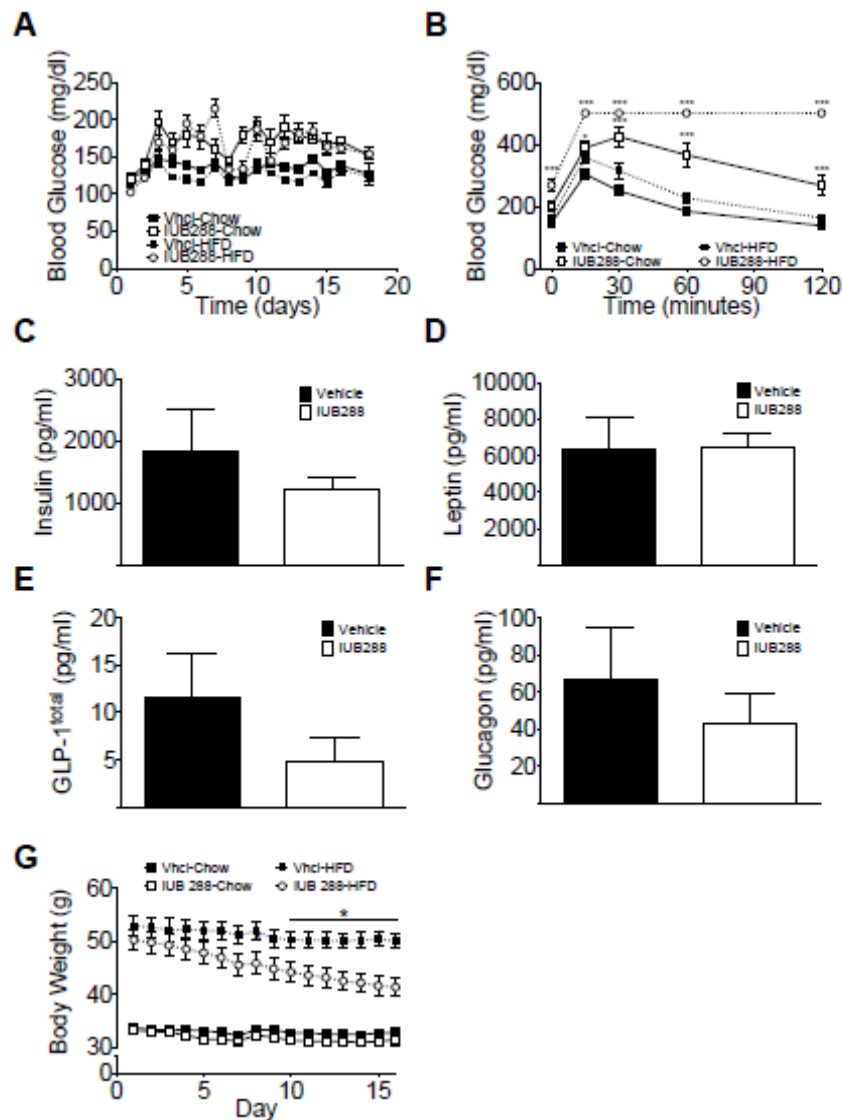


SUPPLEMENTARY DATA

**Supplementary Figure 1.** Glycemic effects of chronic GcgR activation: Ad lib blood glucose in standard chow- (circles) or HFD-fed (squares) C57Bl/6J mice during 16 d of chronic GcgR activation (10 nmol/kg/day IUB288, A). Glucose tolerance (B) as (assessed by 1.5 g/kg i.p. glucose challenge) following 17 d of vehicle (PBS, closed symbols) or 10 nmol/kg/day IUB288 (open symbols) treatment in standard chow- (circles) or HFD-fed (squares). Plasma insulin (C), leptin (D), GLP-1 (E), and glucagon (F) following 18 d of vehicle (PBS, closed bars) or 10 nmol/kg/day IUB288 (open bars) in 2-h fasted, HFD-fed mice. Absolute body weight (G) in response to 16 d of vehicle (PBS, closed symbols) or 10 nmol/kg/day IUB288 (open symbols) treatment in standard chow- (circles) or HFD-fed (squares) C57Bl/6J mice. All treatments conducted in 11-month-old male C57B6 mice maintained on standard chow or HFD for 9 months. All data are represented as mean +/- SEM. Panels A, B, & G; \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  vs. vehicle control, 2-way ANOVA w/ Bonferroni post hoc analysis,  $n = 8$  per treatment. Panels C-F \*  $p < 0.05$  vs. vehicle control, students unpaired t-test,  $n = 4-5$ .



SUPPLEMENTARY DATA

**Supplementary Figure 2.** GcgR activation in FGF21<sup>-/-</sup> mice: (A) Blood glucose excursion in response to an acute, IUB288 challenge (10 nmol/kg, open symbols) on day 0 in male WT (squares) and FGF21<sup>-/-</sup> (circles) mice (n=6-13). Absolute body weight (B) in response to 20 d of vehicle (PBS, closed symbols) or 10 nmol/kg/day IUB288 (open symbols) in male WT (squares) and FGF21<sup>-/-</sup> (circles) mice switched to HFD on Day 0 (n= 12-16). Hepatic FGF21 expression (C) and plasma FGF21 concentration (D) following 20 d of vehicle (PBS, closed bars) or 10 nmol/kg/day IUB288 (open bars) in 2-h fasted, male WT (squares) and FGF21<sup>-/-</sup> (circles) mice switched to HFD on day 0 (n= 3-5). All treatments conducted in 12-week-old male littermates maintained on standard chow diet until day 0. All data are represented as mean +/- SEM. \* *p* < 0.05; \*\* *p* < 0.01; \*\*\* *p* < 0.001 vs. genotype-specific vehicle control, 2-way ANOVA w/ Bonferroni post hoc analysis.

