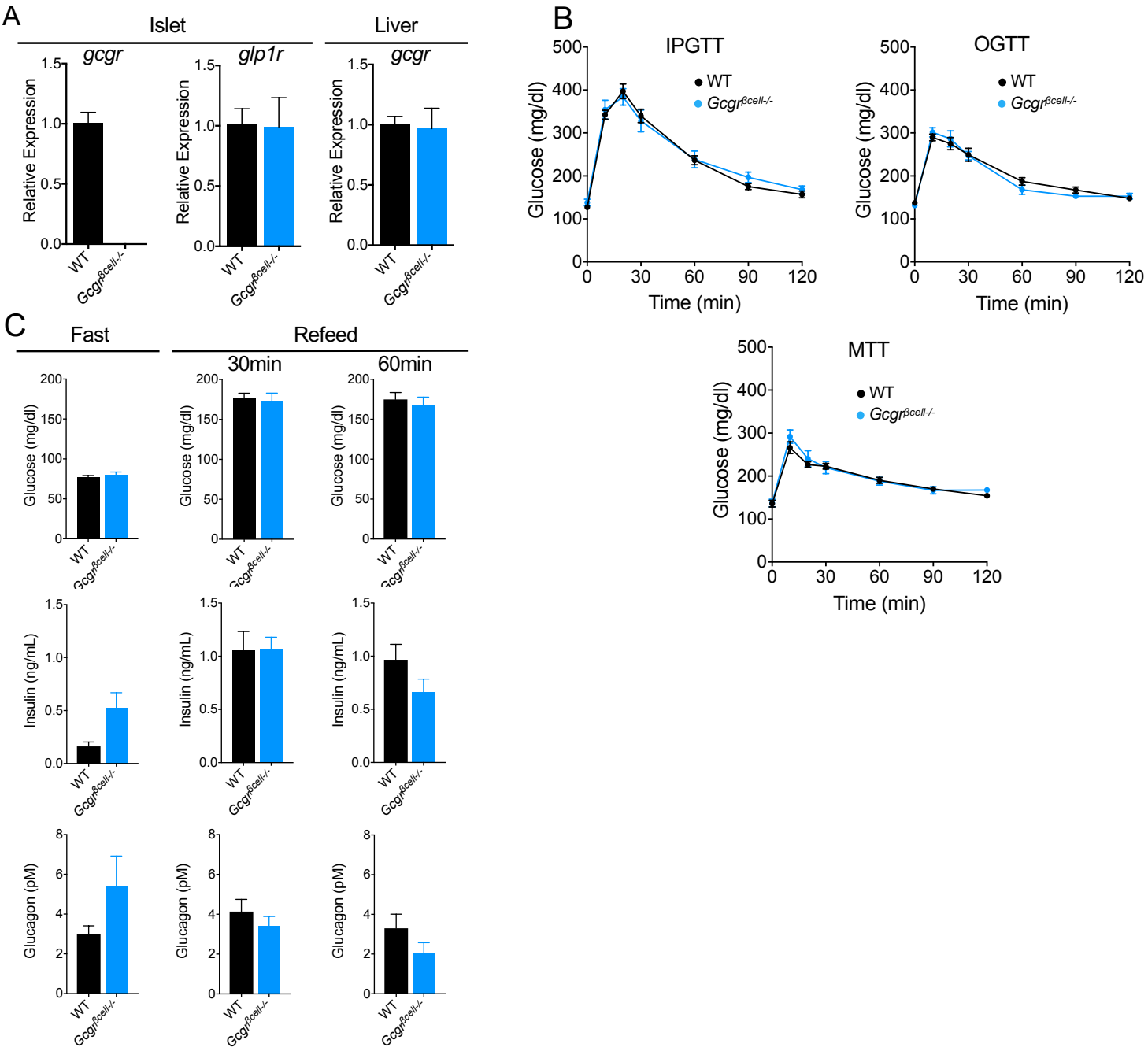
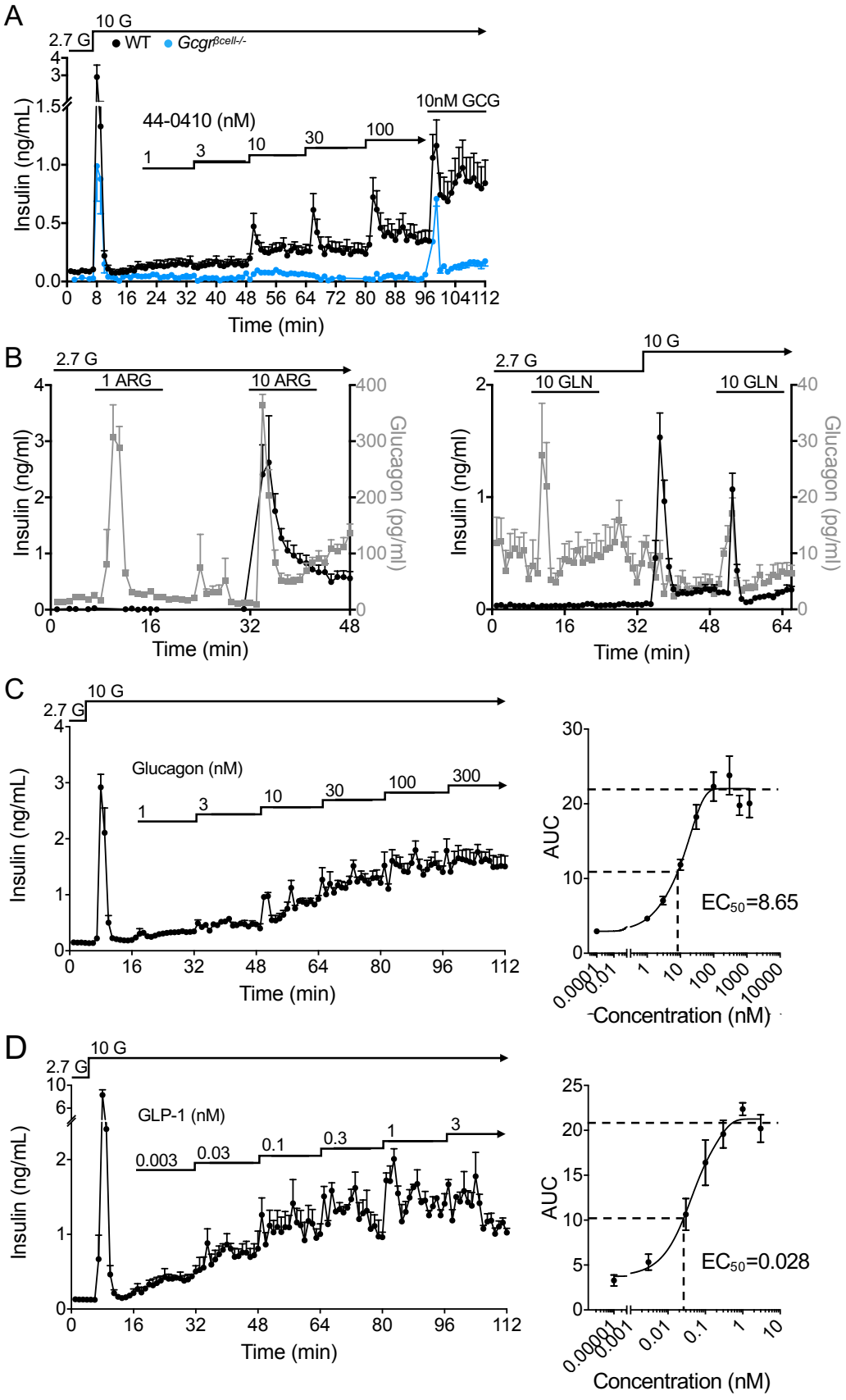
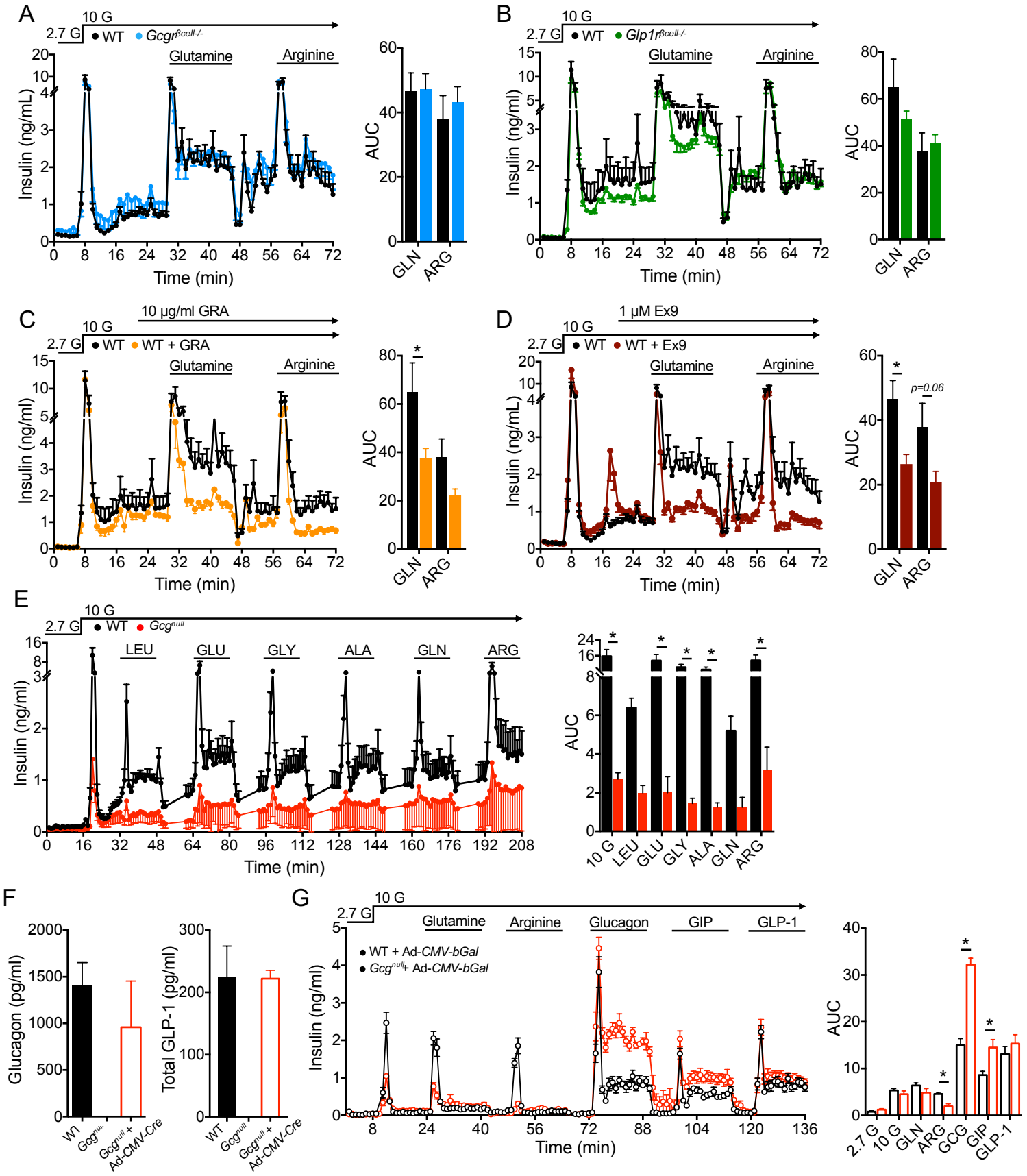


Supplemental Figure 1. Generation and validation of *Gcgr*$^{\beta cell-/-}$ (A) Islet (left) and liver (right) expression of *Gcgr* and islet expression of *Glp1r* (middle) in *Gcgr*$^{\beta cell-/-}$ **(B)** Intraperitoneal, oral, and meal tolerance test in 12-16 week old WT (n=10) or *Gcgr*$^{\beta cell-/-}$ (n=7) mice on chow diet. **(C)** Glucose (top), insulin (middle), and glucagon (bottom) levels after an overnight fast (left) or 30min and 60min after refeeding (right) in 12-16 week old WT (n=10) or *Gcgr*$^{\beta cell-/-}$ (n=7) mice on chow diet. Data are shown as mean ± SEM.



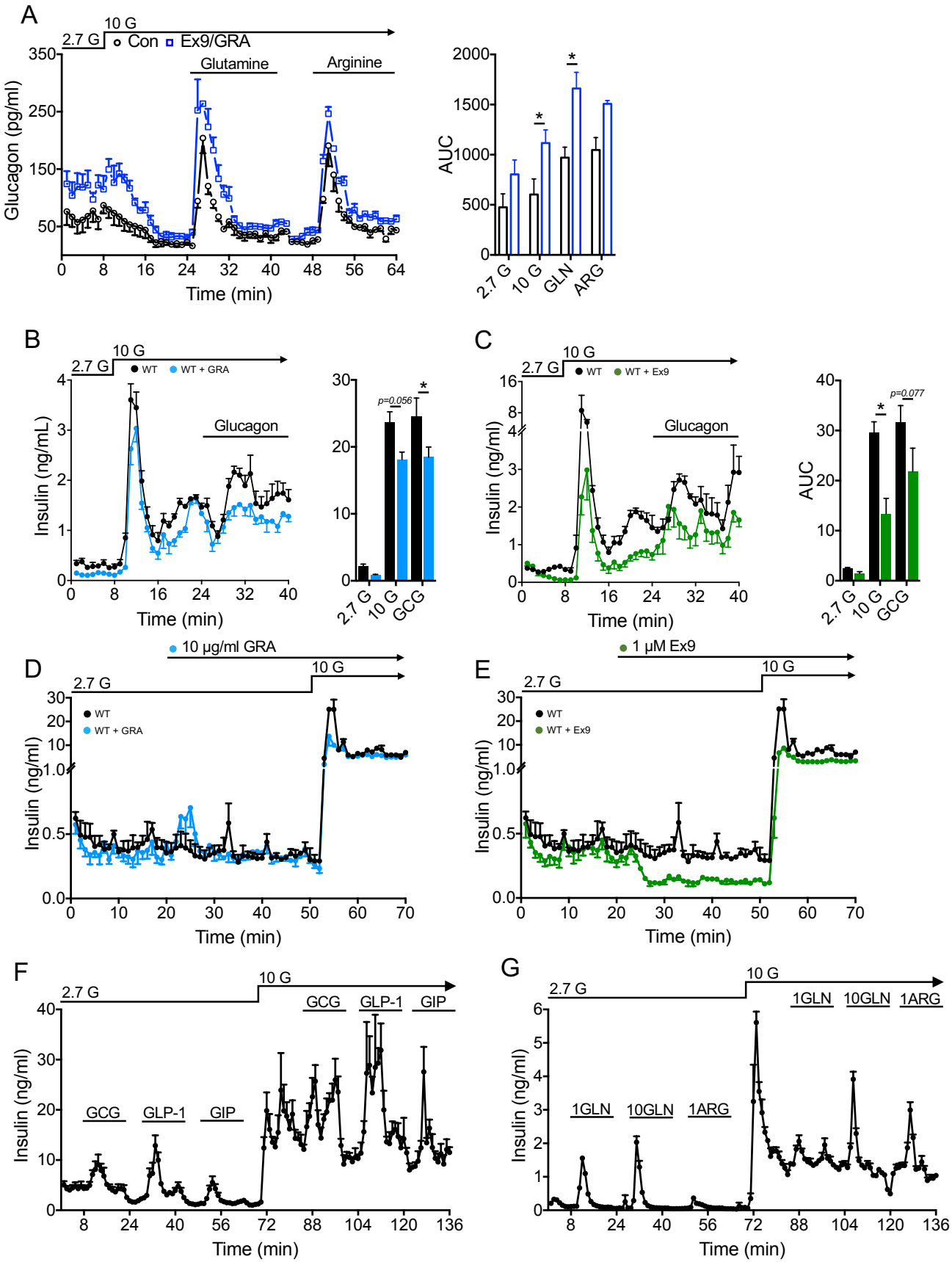
Supplemental Figure 2.

(A) Insulin secretion in response to a Gcgr specific agonist (44-0410) and glucagon in WT (n=2) and *Gcgr*$^{\beta cell-/-}$ (n=4) islets. **(B)** Insulin and glucagon secretion in WT islets (n=4). **(C-D)** Insulin secretion in WT islets in response to increasing concentrations of **(C)** glucagon or **(D)** GLP-1, and the dose-response relationships (n=6). Data are shown as mean ± SEM. Statistical tests used: two-tailed t-test.



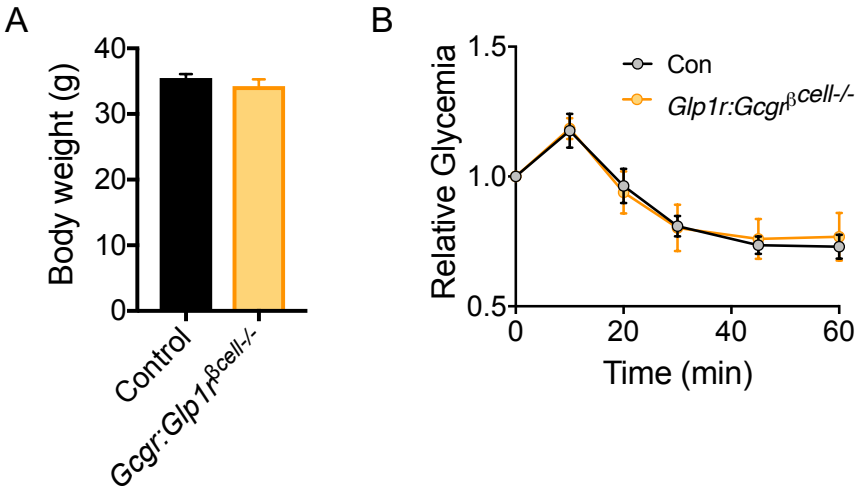
Supplemental Figure 3

(A-G) Insulin secretion in response to glucose, glutamine, or arginine in mouse islets were either (**A,C**) Gcgr or (**B,D**) Glp1r are blocked by either genetic knockout (**A,B**) or pharmacological antagonism **(C,D).** (n=4). (**E**) Insulin secretion in response to various amino acids in WT and *Gcg*$^{-/-}$ islets (n=6). (**F**) Glucagon and GLP-1 levels after *Ad-CMV-Cre* treatment of *Gcg*$^{-/-}$ islets. (n=3-6) (**G**) Insulin secretion in *Ad-CMV-bGal* treated WT and *Gcg*$^{-/-}$ islets (n=5). Data are shown as mean ± SEM. Statistical tests used: two-tailed t-test.



Supplemental Figure 4

(A) Glucagon secretion in human islets treated with Ex9/GRA (n=4). (**B-E**) Insulin secretion in response to glucose in human islets treated with either **(B,D)** GRA alone (n=4) or (**C,E**) Ex9 alone (n=4). **(F)** Insulin secretion in human islets in response to Gcg, GLP-1, and GIP at low and high glucose (n=4). **(G)** Insulin secretion in human islets in response to glutamine or arginine at low and high glucose (n=4). Data are shown as mean ± SEM. Statistical tests used: two-way ANOVA with Bonferonni post-hoc analysis.



Supplemental Figure 5

(A) Body weight in control and *Glp1r:Gcgr*$^{\beta cell-/-}$ mice on high-fat diet. (n=6-8) **(B)** Relative glycemia in response to an exogenous insulin bolus (0.5 U/kg) in control and *Glp1r:Gcgr*$^{\beta cell-/-}$ mice on high-fat diet. (n=6-8). Data are shown as mean ± SEM