SUPPLEMENTARY DATA

Supplementary Table 1. Analysis of perforated patch clamp data. Action potential frequency and membrane potential at low (2 mM) and high (14 mM) glucose for the experiments presented in figure 5D.

	Action Potential Frequency	Membrane potential 2 mM glucose	Membrane potential 14 mM glucose
Control	3.9 +/- 1.1 Hz	-74-2±1.3 mV	-52.0±2.6 mV
β-caPKA	4.1+/- 0.8 Hz	-72.0±3.2 mV	-51.2±1.4 mV

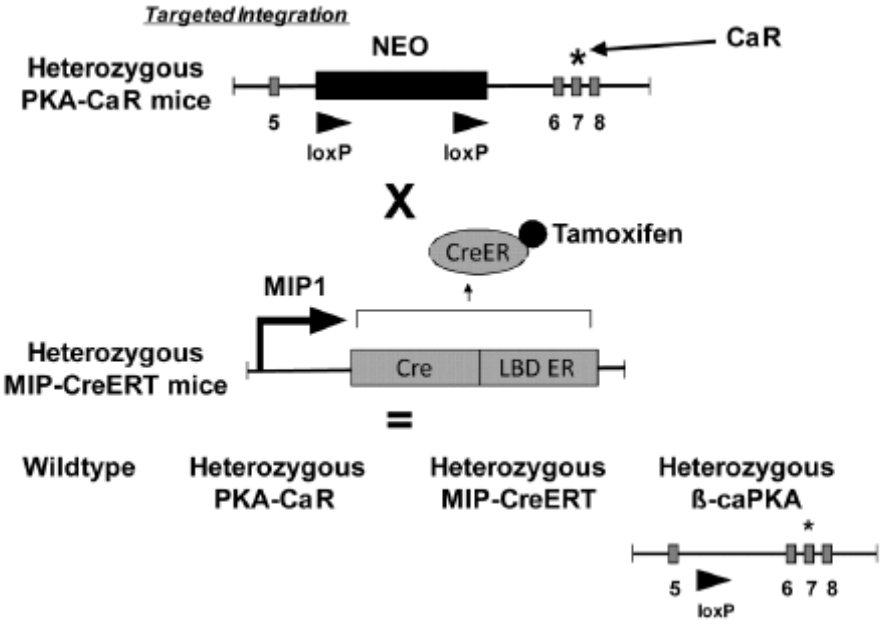
SUPPLEMENTARY DATA

Supplementary Table 2. Reagents used in the studies. The information in this table lists the reagents used, the supplier and the catalogue number. For antibodies, the dilution used is given in parentheses.

Reagent	Supplier	Catalogue number
Insulin antibody (1:1,000)	Linco	4010-01
Glucagon antibody (1:400)	Sigma	G2654
β-galactosidase Ab (1:400)	Abcam	9361
Snap25 anitbody (1:1,000)	Cell Signaling	5308
Snapin antibody (1:250)	Synaptic Systems	148002
PI 3 kinase-p85 Ab (1:2,000)	Millipore (Upstate)	06497
PKA-Cα (1:1000)	Cell Signaling	4782
PKA-RIα (1:2,000)	BDBioscience	610609
PKA-RIIα (1:1,000)	BDBioscience	612242
PKA-RIIβ (1:1,000)	BDBioscience	610625
Phosphoprotein columns	Qiagen	37101
fura 2-AM	Invitrogen	F1221
Mouse insulin ELISA	ALPCO	80-INSMSU
Exendin-4	American Peptide Co.	46-3-12A
Tamoxifen	Sigma	T-5648
Corn oil	Sigma	C-8267
Collagenase P	Roche	11213857001
Mouse Diet	Harlan Teklad	2018
Glucose meter	Abbott Laboratories	Freestyle

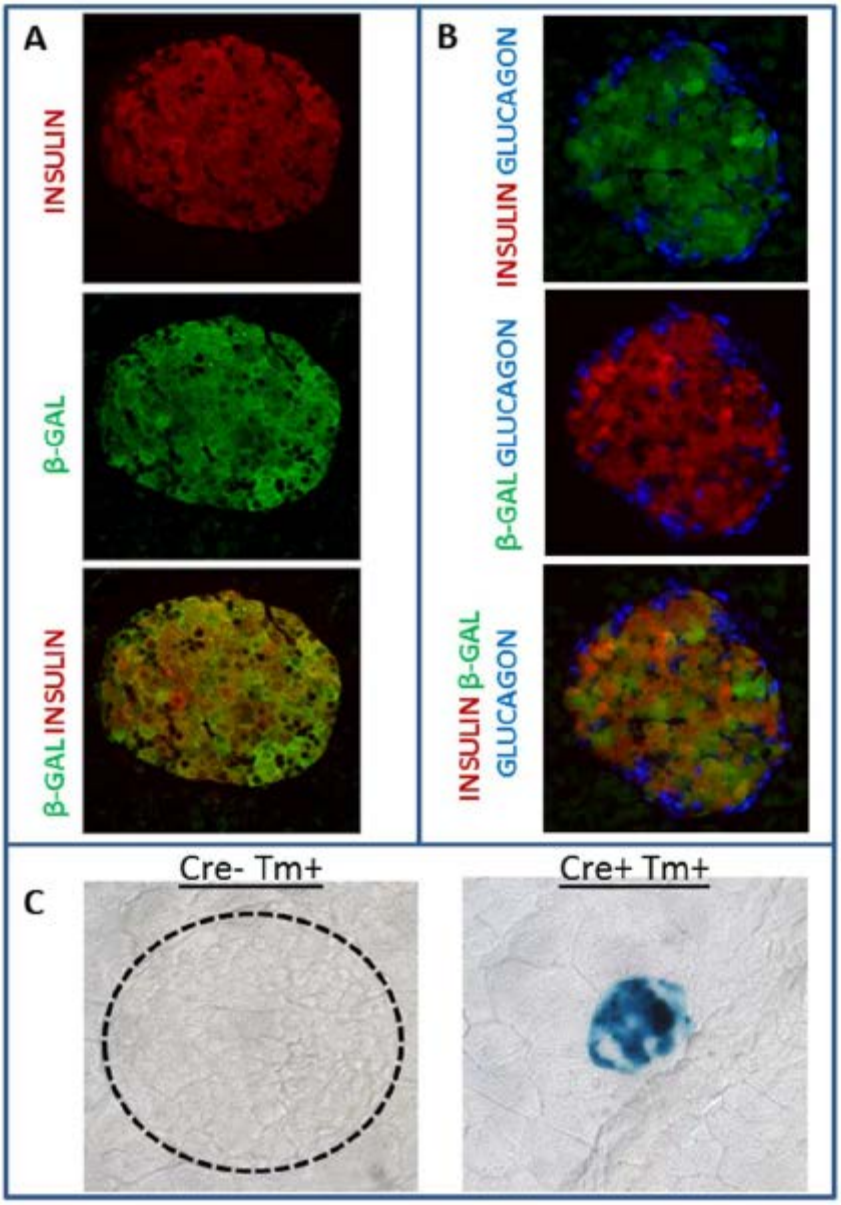
SUPPLEMENTARY DATA

Supplementary Figure 1. The β-caPKA Mouse Model of Increased β-cell PKA Activity**.** PKACαR mice carry a single allele in which a point mutation has been introduced to exon 7 of the endogenous PKA alpha catalytic subunit gene (PKA-Cα) using a knock-in strategy (18). This point mutation increases kinase activity of subunits expressed from this allele. A *loxP*-flanked neomycin (NEO) STOP cassette prevents expression of the mutated allele until Cre-recombinase mediates recombination. Cre-activity was delivered to the β-cells of these mice by crossing to the recently developed MIP-CreERT mouse line that expresses the tamoxifen-inducible Crerecombinase (CreERT) specifically in the islet β-cells (19). Expression of CreERT leads to retention of the Cre-recombinase in the cytosol, due to fusion to the estrogen receptor ligand binding domain (LBD ER), until tamoxifen is present to drive translocation to the nucleus and so permit recombination.



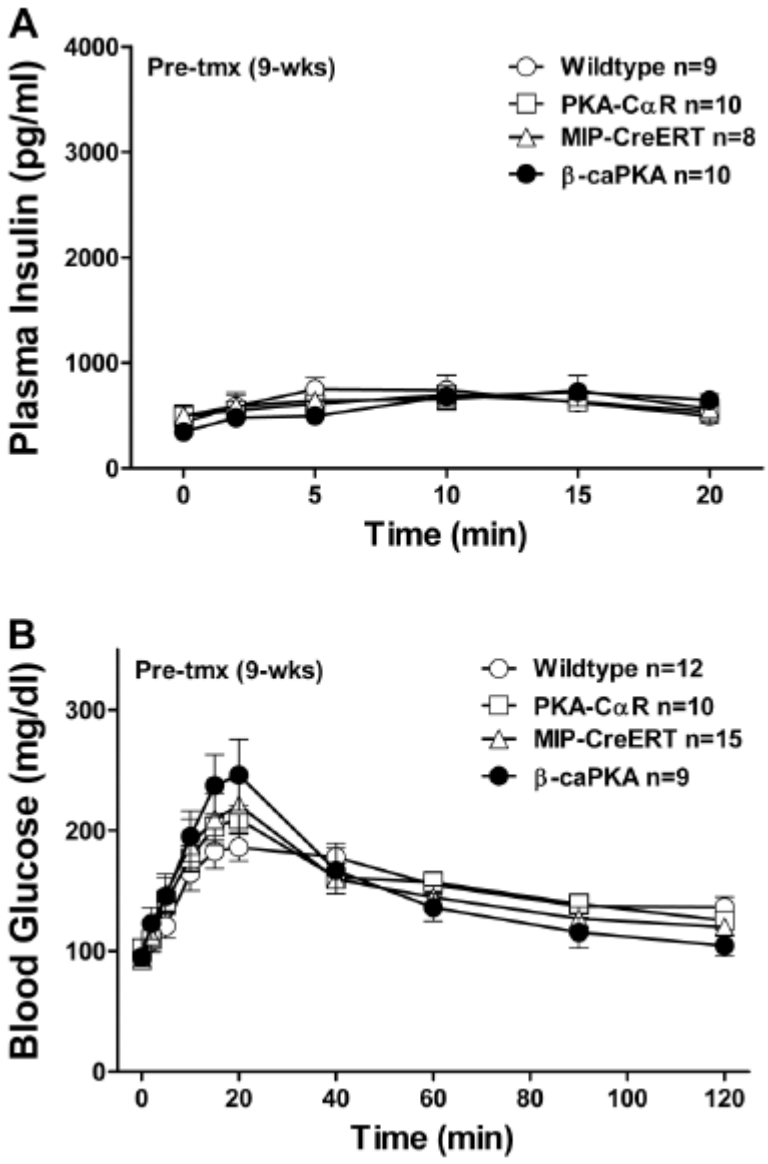
SUPPLEMENTARY DATA

Supplementary Figure 2. Cre-recombinase Activity in Islet β-cells. Pancreata from MIPCreERT+ mice carrying the Cre-inducible LacZ allele (B6.129S4-*Gt(ROSA)26Sortm1Sor*/J; Jackson Laboratories stock # 003474) were assayed for Cre-mediated induction of β-galactosidase. **A and B.** Sections of pancreata fixed in 4% paraformaldehyde and embedded in paraffin were stained for insulin and β-galactosidase (A), or insulin, β- galactosidase and glucagon (B). **C.** Frozen Sections of 2% paraformaldehyde fixed pancreata from Cre+ and Cre- tamoxifen (Tm) treated mice were incubated overnight at 37oC in the presence of 1.5 mg/ml X-gal. The dotted line in the Cre- Tm+ sample delineates an islet.



SUPPLEMENTARY DATA

Supplementary Figure 3. Pre-tamoxifen Intraperitoneal Glucose Tolerance Tests. At 9 weeks of age, prior to receiving tamoxifen to drive PKA activation in β-caPKA mice, all genotypes were subjected to i.p. glucose tolerance tests (1 g/kg glucose). Blood was collected from the tail vein for plasma insulin determination from 0-20 minutes and for blood glucose measurement from 0-120 minutes. Open circles, wildtype; open squares, PKA-CαR; open triangles, MIP-CreERT; closed circles, β-caPKA. 2-way ANOVA P>0.05 for A and B.



SUPPLEMENTARY DATA

Supplementary Figure 4. Enhanced snapin phosphorylation in response to constitutive PKA activity. Min6 immortalized β-cells were infected with a recombinant adenovirus expressing the constitutively active PKA-Cα subunit (caPKA) or were uninfected (Control). Lysates were prepared and phosphoproteins purified by passage through phosphoprotein purification columns. Eluted phosphoproteins were analyzed by immunoblotting for Snapin and Snap 25. Equal protein was loaded onto the column as indicated by the loading control, PI3 kinase p85 subunit, in the pre-column lysate.