Supplementary Figure 1. A: Representative PCR results showing detection of GLUCre+ and PTENfl/fl genes. B: Quantification of percent PTEN-positive glucagon-positive dispersed islet cells by immunofluorescent staining (n = 3 mice). C: Immunofluorescent co-staining of glucagon with PTEN in dispersed islet cells from GLUCre+ Ptenfl/fl mice (20X magnification; scale bars, 50 μm). D: Representative immunofluorescent costaining glucagon and PTEN of GLUCre+ Pten+/+ (+/+) and GLUCre+ Ptenfl/fl (-/-) mouse pancreas (20X magnification; scale bars, 80 μm). E: Representative western blot and quantification of PTEN in whole islets, hypothalamus, visceral adipose, muscle and liver tissue (n = 3). F: Serum active GLP-1 levels 0 and 10 minutes following oral glucose 3g/kg after a 4-h fast (n = 13-14). *p < 0.05 **p < 0.01.
**Supplementary Figure 2.** A-B: Serum corticosterone (n = 4) (A) and epinephrine (n = 12) (B) levels of GLUCre+ Pten+/+ and GLUCre+ Ptenfl/fl mice. *p < 0.05.

**Supplementary Figure 3.** Western blotting of PTEN in αTC and In-R1-G9 cells, and in isolated islets and negative control.
Supplementary Figure 4. A-B: Glucagon secretion of isolated islets from GLUCre+ Pten+/+ (+/+) and GLUCre+ Pten−/− (-/-) mice after incubation with glucose (A) and stimulation with L-arginine (B) (n = 3 mice). *p < 0.05.
Supplementary Figure 5. A-B: Blood glucose (A) and serum glucagon levels (B) during intraperitoneal insulin tolerance test (ITT) (n = 4). *p < 0.05.
**Supplementary Figure 6.** Representative Western blot and quantification of phospho-CREB (p-CREB) and total CREB (t-CREB) in liver from GLUCre+ Pten+/+ (+/+) and GLUCre+ Ptenfl/fl (-/-) mice on HFD (n=3). *p < 0.05.