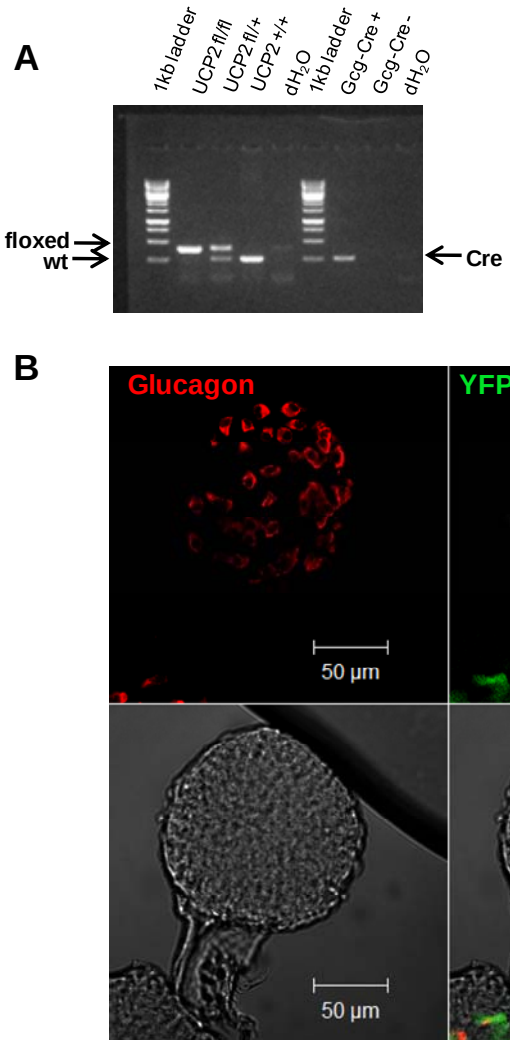
SUPPLEMENTARY DATA

**Supplementary Table 1.** Primers used for PCR and qPCR

| Primer Name | Accession Number | Fwd | Rev | Type of PCR |
|---|---|---|---|---|
| Cre | NC_005856 | GGCAGTAAAAACTATCCAGCAA | GTAAAGACCCCTAACGAATATTG | Standard PCR |
| *LoxUcp2* | | ACCAGGGCTGTCTCCAAGCAGG | AGAGCTGTTCGAACACCAGGCCA | Standard PCR |
| *Ucp2Δ exon3-4* | NM_011671.3 | GACACAGCCTTCTGCACTCCTGTGTT | GGCAGCTTTGAAGAACGAGAC | Standard PCR |
| *β-Actin* | NM_007393 | CTGAATGGCCCAGGTCTGA | CCCTGGCTGCCTCAACAC | qPCR |
| *Pepck* | NM_011044 | GTGAGGAAGTTCGTGGAAGG | TCTGCTCTTGGGTGATGATG | qPCR |
| *G6pc* | NM_008061 | TCTGTCCCGGATCTACCTTG | GTAGAATCCAAGCGCGAAAC | qPCR |
| *Fbp1* | NM_019395 | AGGAAGCACAAAGCCAAGTGAAGG | TGAGGATGAAGTGACCTTGGGCAT | qPCR |
| *Gck* | NM_010292 | GAGATGGATGTGGTGGCAAT | ACCAGCTCCACATTCTGCAT | qPCR |
| *Fasn* | NM_007988 | CTCTGATCAGTGGCCTCCTC | TGCTGCAGTTTGGTCTGAAC | qPCR |
| *Sod1* | NM_011434 | GTGATTGGGATTGCGCAGTA | TGGTTTGAGGGTAGCAGATGAGT | qPCR |
| *Sod2* | NM_013671 | TTAACGCGCAGATCATGCA | GGTGGCGTTGAGATTGTTCA | qPCR |
| *Sod3* | NM_011435 | CATGCAATCTGCAGGGTACAA | AGAACCAAGCCGGTGATCTG | qPCR |
| *Gpx1* | NM_008160 | CGCTTTCGTACCATCGACATC | GGGCCGCCTTAGGAGTTG | qPCR |
| *Gpx2* | NM_030677 | ACCGATCCCAAGCTCATCAT | CAAAGTTCCAGGACACGTCTGA | qPCR |
| *Gpx3* | NM_008161 | ACAATTGTCCCAGTGTGTGCAT | TGGACCATCCCTGGGTTTC | qPCR |
| *Gpx4* | NM_008162 | CCCGATATGCTGAGTGTGGTT | CCTGCCTCCCAAACTGGTT | qPCR |
| *Cat* | NM_009804 | TGAGAAGCCTAAGAACGCAATTC | CCCTTCGCAGCCATGTG | qPCR |
| *Ho1* | NM_010442 | CCTCACTGGCAGGAAATCATC | CCTCGTGGAGACGCTTTACATA | qPCR |
| *Ucp2* | NM_011671.3 | CAGCCAGCGCCCAGTACC | CAATGCGGACGGAGGCAAAGC | qPCR |
| *UCP2* | NM_003355 | AGGGGCCCCGAGCCTTCTAC | GGCAGCCATGAGGGCTCGTT | qPCR |
| *GCG* | NM_002054 | GGCAGCTGGCAACGTTCCCT | CTTGGGCACGCCTGGAGTCC | qPCR |
| *ACTB* | NM_001101 | TGAGCTGCGTGTGGCTCCC | AGGGATAGCACAGCCTGGATAGCA | qPCR |

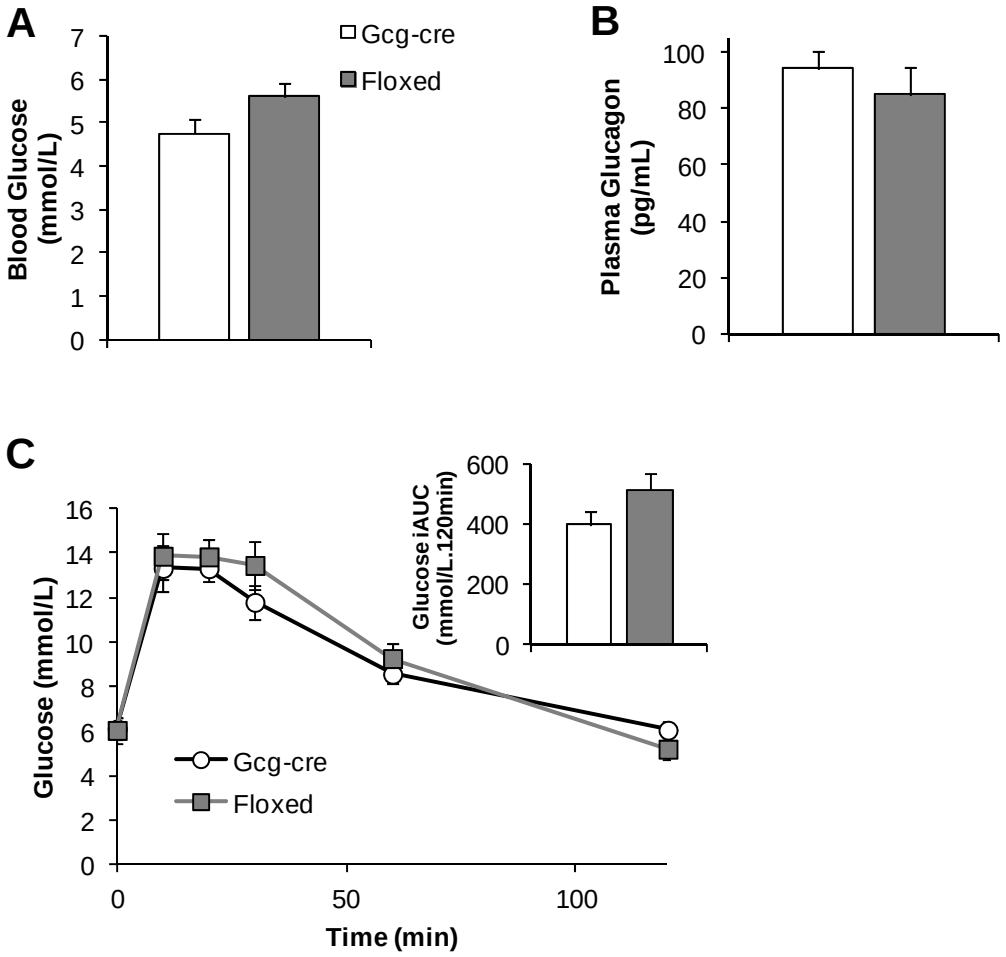
SUPPLEMENTARY DATA

**Supplementary Figure 1.** Genotyping of mice and efficiency of recombination/deletion using Gcg-cre mice. A. Genotyping results using PCR to detect floxed UCP2 and cre expression in loxUCP2 and Gcg-cre mice. B. Immunostaining for glucagon protein (red) (mouse anti-glucagon, Sigma Cat#G2654) and eYFP (green) (rabbit anti-GFP, Invitrogen Cat#A11122; also detects eYFP) in islets from Gcg-cre-YFP mice. Co-localization is indicated by yellow and was observed in 72 ± 10% of glucagon positive cells. N=3.



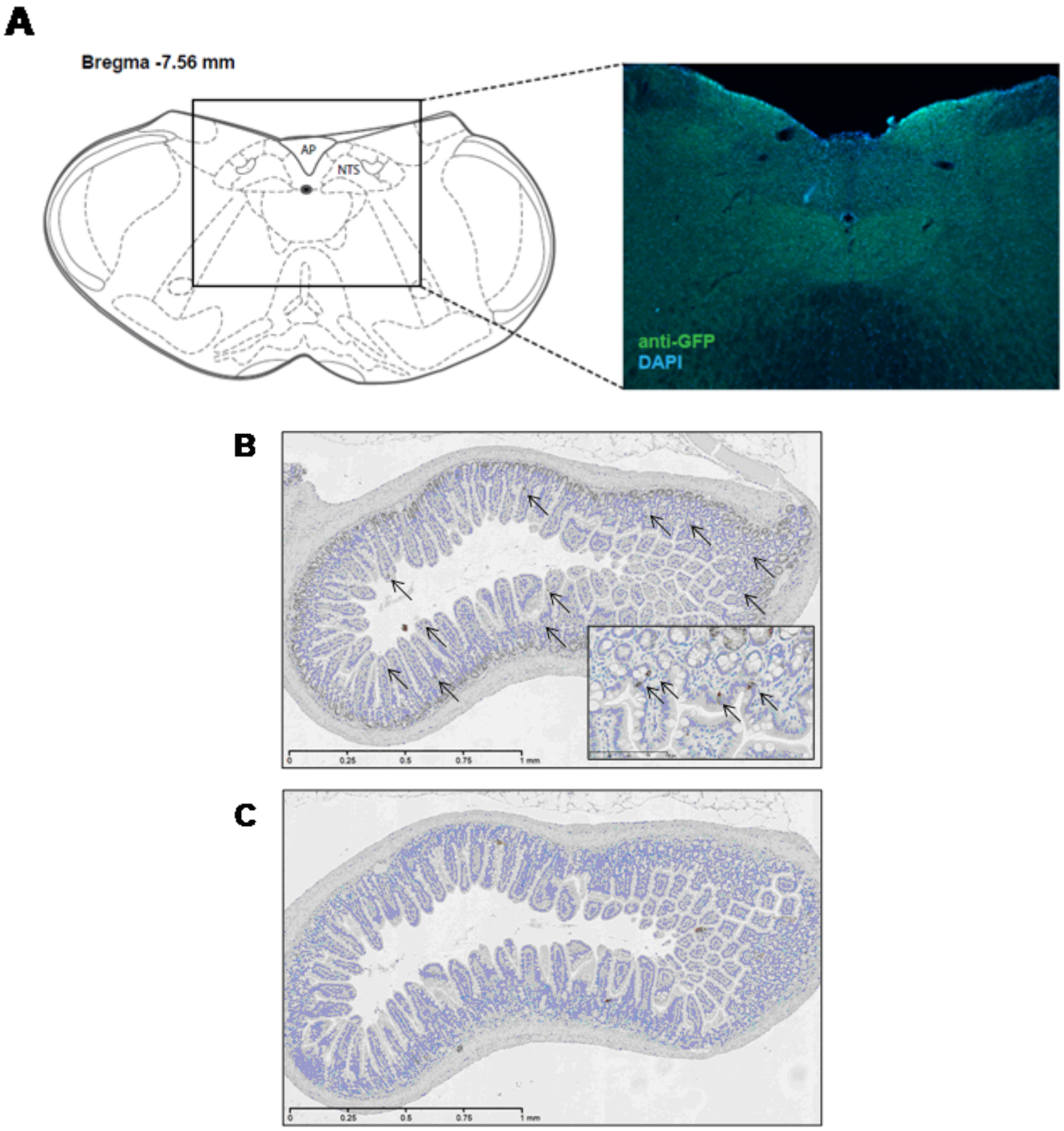
SUPPLEMENTARY DATA

**Supplementary Figure 2**. Phenotypical comparison of Gcg-cre and floxed UCP2 mice. 6-8 week old male Gcg-cre and floxed UCP2 mice were fasted overnight and then A. Blood glucose concentration and B. Plasma glucagon levels were measured. N= 9-23/genotype. C. Oral glucose tolerance test (OGTT) shows no difference in glucose tolerance between the two genotypes as the incremental area under the OGTT curve (iAUC) (inset) was similar. N= 7-9/genotype.



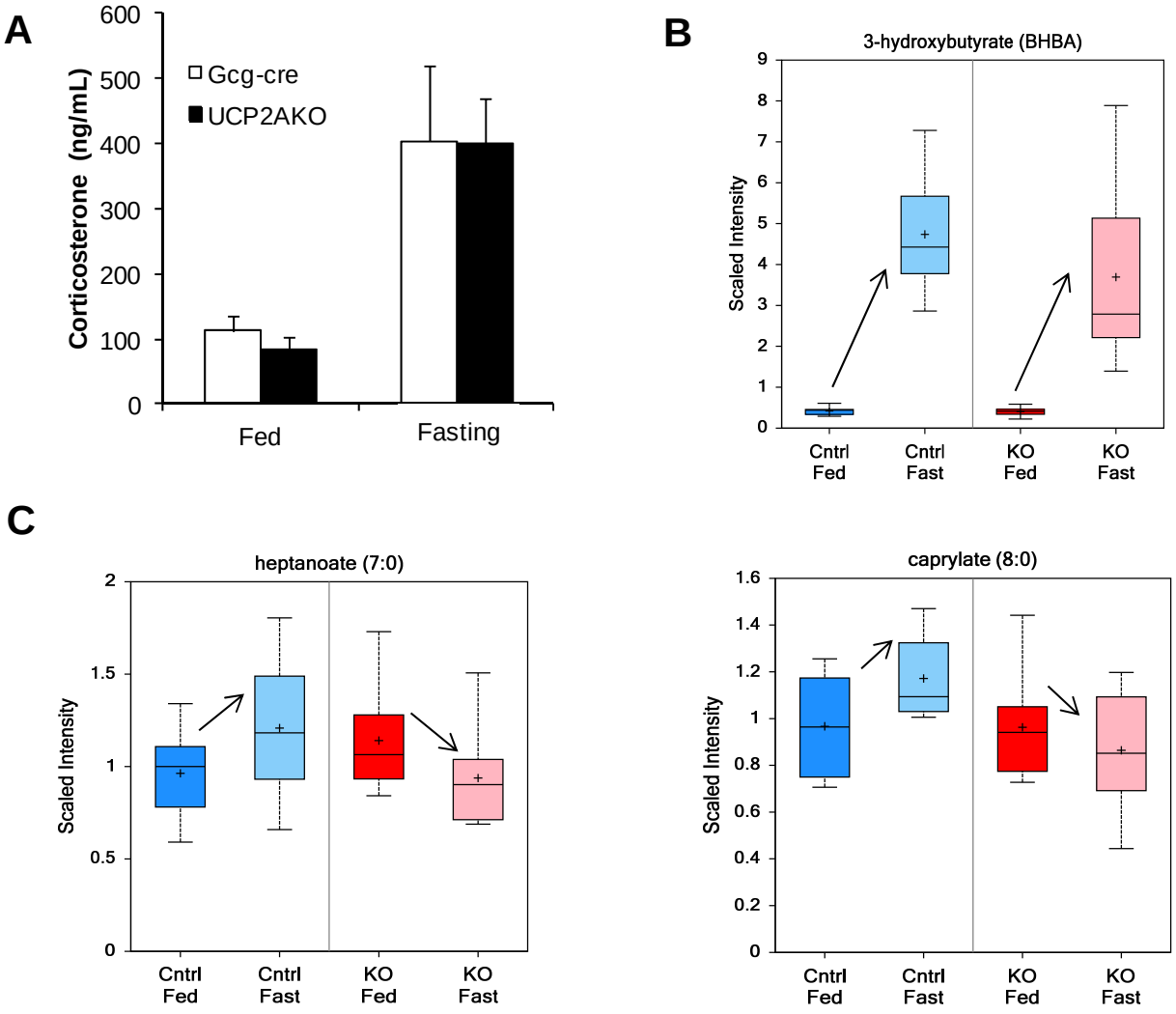
SUPPLEMENTARY DATA

**Supplementary Figure 3.** No ectopic expression of cre in the brainstem or distal ileum. A. Gcg-cre-YFP mice were perfused with 4% PFA by cardiac perfusion, the brains removed, sectioned and stained with a GFP antibody that detects eYFP (Millipore Cat# 06-696) and co-stained with DAPI. Images were acquired with a fluorescent microscope. There was eYFP staining in the nucleus of the solitary tract (n=2). B-C. The distal ileum was removed from Gcg-cre-YFP (not shown) and UCP2AKO-YFP (shown) mice, fixed with 4% PFA, embedded in paraffin blocks, sectioned and stained with either (B) a GLP-1 antibody (Abcam Cat#22625) which showed scattered staining throughout as indicated with the arrows (inset is higher magnification) or (C) a GFP antibody (Invitrogen Cat# A10262) which did not show any specific eYFP staining (n=3).



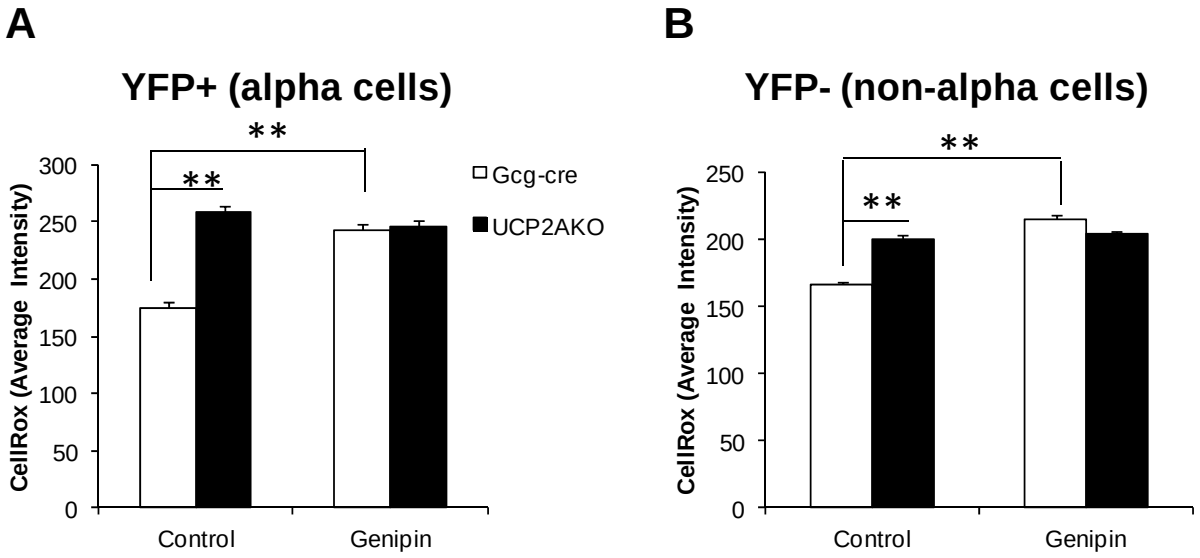
SUPPLEMENTARY DATA

**Supplementary Figure 4.** Corticosterone levels and 3-hydroxybutyrate were not different between Gcg-cre and UCP2AKO mice after a prolonged 24h fast but MCFA were significantly reduced in UCP2AKO mice. A. Corticosterone levels were measured in plasma before (Fed) and after a 24h fast (Fasting) using an RIA kit (MP Biomedicals, Canada). n = 7–8 mice in each group. B & C. A mass spectromic analysis of plasma metabolite levels was conducted on samples taken from fed and 24h fasted Gcg-cre (Cntrl) and UCP2AKO (KO) mice. B. The levels of 3-hydroxybutyrate was similarly increased in Gcg-cre and UCP2AKO mice upon fasting. C. Examples of 2 medium chain-length fatty acids (MCFA) (7:0 and 8:0) are shown that increased in Gcg-cre mice and decreased in UCP2AKO mice upon fasting (n=8 per genotype). Data are expressed as means ± SEM; **P*<0.05 genotype/fed state interaction.



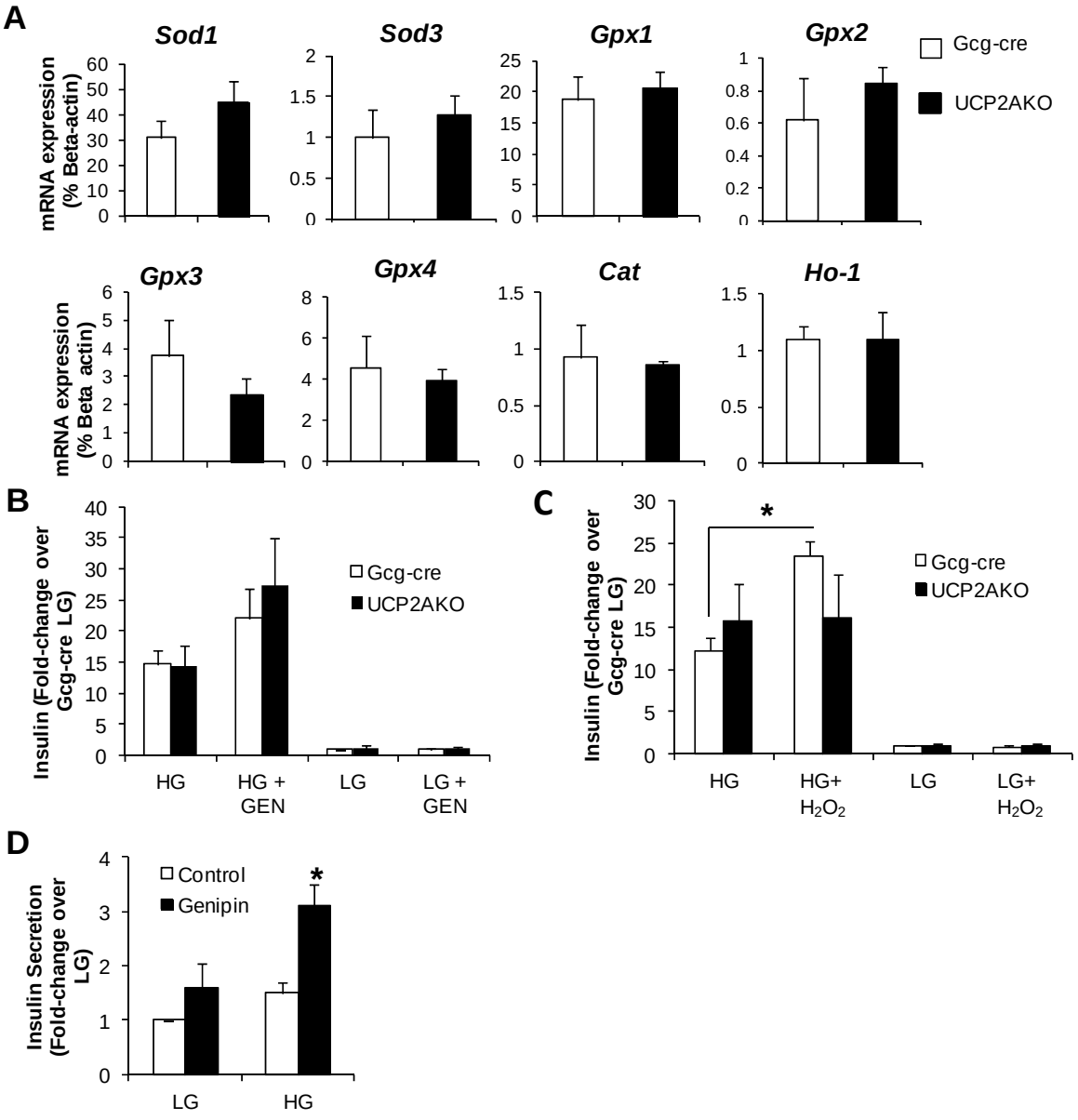
SUPPLEMENTARY DATA

**Supplementary Figure 5.** Dispersed UCP2AKO alpha cells have higher ROS levels. Islets isolated from Gcg-cre-YFP and UCP2AKO-YFP mice were cultured overnight and then dispersed and plated into a 96 well View Plate (Perkin-Elmer, Ontario, Canada). The following day islet cells were incubated with or without genipin (50µM) for 2h before being loaded with CellROX (2mM) and Hoechst (1mM) for 30min in complete media. The cells were then washed once with imaging buffer and then imaged on a Cellomics Array Scan (Thermo Fisher, Pittsburgh). Gcg-cre YFP+ cells = 1384; Gcg-cre YFP- cells = 7498; UCP2AKO YFP+ cells = 2150 UCP2AKO YFP- cells = 10, 092. **P<0.01.



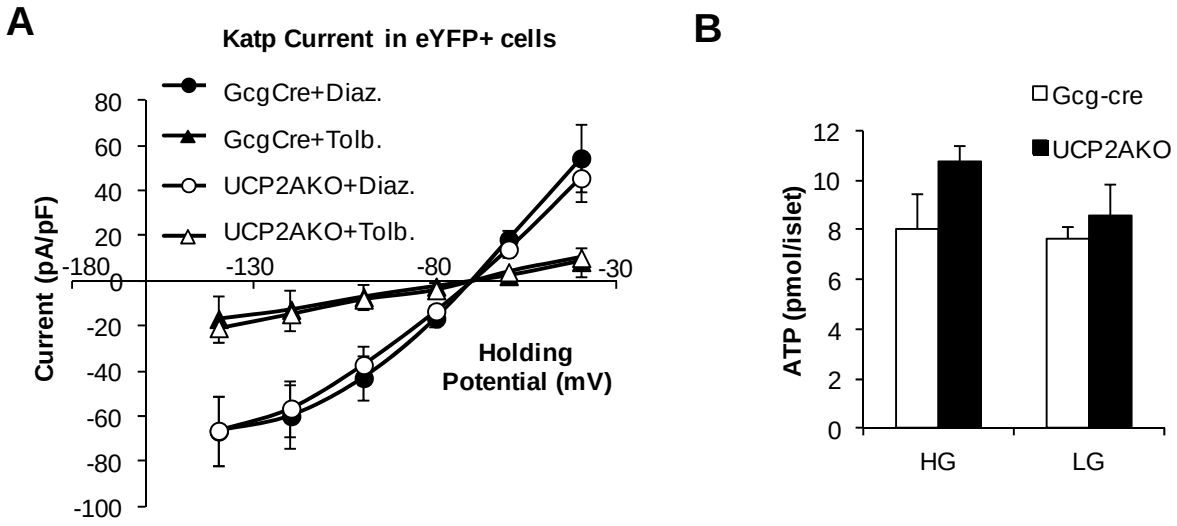
SUPPLEMENTARY DATA

**Supplementary Figure 6.** Alpha cell UCP2 deletion does not affect the expression of a series of antioxidant genes and insulin secretion was enhanced from Gcg-cre islets incubated with $H_2O_2$. A. Islet expression of the antioxidant enzymes superoxide dismutase 1 (*Sod1*), *Sod3,* Glutathione peroxidase 1 (*Gpx1*), *Gpx2, Gpx3, Gpx4,* catalase (*Cat*) and the cytoprotective Heme oxygenase 1 (*Ho-1*) genes were quantified by real-time PCR and normalized to beta-actin. n = 4-6/genotype Data are means ± SEM. B-C. Fresh isolated mouse islets were pre-incubated ± 50 µM genipin (GEN) (B) or 16 µM $H_2O_2$ (C) for 1h in 11mM RPMI before being incubated with high glucose (HG:20mM) for 15 min and then HG or low glucose (LG:1mM) during a 1h static secretion assay. N = 6-11 mice/genotype. D. GSIS from human islets pre-incubated ± Genipin (50 µM) during a half hour static secretion assay. N=6-7. **P*<0.05.



SUPPLEMENTARY DATA

**Supplementary Figure 7.** ATP sensitive $K^+$ current was similar in UCP2AKO and Gcg-cre alpha cells and islet ATP content was unchanged. A. Whole cell recordings of $K_{ATP}$ currents in YFP+ alpha cells. Average I/V curves were obtained by plotting the maximum current against the applied potential. Diazoxide (Diaz.:100 µmol/l) application produced a large $K_{ATP}$ current (N=14-16 cells) that was blocked by tolbutamide (Tolb.:250 µmol/l) N=8-10 cells, 5 mice/genotype. B. ATP content was measured in mouse islets after a static secretion assay protocol (HG = high glucose KRB (20mM) and LG = low glucose KRB (1mM)). N=3 mice/genotype.



SUPPLEMENTARY DATA

**Supplementary Figure 8.** Genipin and $H_2O_2$ reduce intracellular calcium but increase oscillations in Gcg-cre alpha cells. A-D Dispersed islets were pre-incubated with genipin (50µM) or $H_2O_2$ (16µM) for 1h in 11mM glucose RPMI. Cytosolic calcium uptake was measured in dispersed YFP+ alpha cells loaded with Fura2-AM in high glucose KRB (20mM). The effect of a switch to low glucose (1mM) and then the addition of HG + arginine (10mM) or KCl (30mM) were then determined. A family of 5 representative traces is shown per condition. N = 30-41 cells from 3 different mice/genotype. **E.** Quantification of oscillation frequency in YFP+ alpha cells in the presence of low glucose ± $H_2O_2$ (16µM) or genipin (GEN) (50µM).