Supplementary Figure 1. 10 mg/kg FKN-Fc improves glucose tolerance for 2 days in lean mice. GTTs in NCD WT mice at day 2. A single injection of 10 mg/kg FKN-Fc or vehicle was given to NCD WT mice at day 0 and, at day 2, glucose tolerance was measured without any further FKN-Fc administration. Mean+/-SEM. $^{*}p < 0.05$; n = 8 for both groups (result of 1 time experiment), two tailed unpaired t-test.

Supplementary Figure 2. Chronic FKN-Fc administration increases insulin secretion and decreases apoptosis in the islets of obese mice. (**A**) Insulin secretion activity in Min6 cells incubated in low glucose (2 mM) conditions with or without FKN-Fc treatment. (**B-C**) Islet insulin content. 10 week HFD mice were ip injected with FKN-Fc every other day for total 8 week and the islet was isolated for measure total insulin content per islet (**B**) and GSIS (**C**) activity per well. Mean+/-SEM. (**D**) Q-PCR analyses of mRNA expression in the islets of HFD mice treated with vehicle or FKN-Fc for 8 weeks. mRNA expression was measured by realtime RT Q-PCR. Mean+/-SEM, n = 4. $^{*}p<0.05$ versus lane 1; $^{\#}p<0.05$ versus lane 2; one way ANOVA. AU, arbitrary unit. (**E**) Oral GTTs in 15 week-old *ob/ob* mice treated with vehicle or FKN-Fc (30 mg/kg) for 7 weeks. Mean+/-SEM, n = 7-8.

*p<0.05; **p<0.01; two tailed unpaired t-test. (**F**) Caspase-3/7 activity assays in the islets from the *ob/ob* mice treated with vehicle or FKN-Fc (30 mg/kg) for 7 weeks. Mean+/-SEM, n = 4. *p<0.05; two tailed unpaired t-test. AU, arbitrary unit. (**G**) Q-PCR analyses in the islets from the *ob/ob* mice treated with vehicle or FKN-Fc (30 mg/kg) for 7 weeks. Mean+/-SEM, n = 4. *p<0.05 and **p<0.01 versus lane 1; #p<0.05 and ##p<0.01 versus lane 2; one way ANOVA.

Supplementary Figure 3. Chronic FKN-Fc administration ameliorates hepatic steatosis in obese mice. (**A-D**) Chronic FKN-Fc administration ameliorates hepatic steatosis in HFD mice. 10 week HFD mice were ip injected with vehicle or FKN-Fc (30 mg/kg) every other day. After 8 weeks of FKN-Fc treatment, mice were sacrificed and liver weight (**A**), epididymal adipose tissue weight (**B**), liver triglyceride (TG) content (**C**) and liver none-esterified fatty acid (NEFA) content (**D**) were measured. Mean+/-SEM, n = 8. *p<0.05; **p<0.01; two tailed unpaired t-test. (**E**) Liver and adipose tissue histology analyses in *ob/ob* mice. 8 week-old *ob/ob* mice were ip injected with FKN-Fc (30 mg/kg) every other day for 7 weeks. Liver (left row) and epididymal adipose tissue (right row)

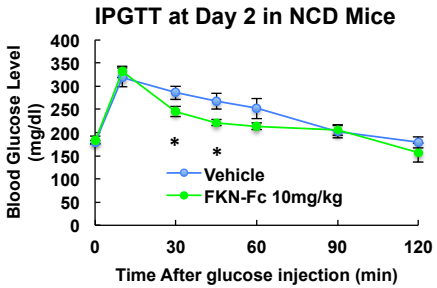
samples were harvested and fixed for histology analyses. Liver samples were stained with hematoxylin and eosin (H&E). Adipose tissue macrophages were assessed after staining with anti-F4/80 antibodies. (**F**) Serum adipokine levels in HFD mice treated with vehicle or FKN-Fc for 8 weeks. Mean+/-SEM, n = 4. (**G**) Gluconeogenic activity in NCD mouse hepatocytes. Conversion rate of ^{14}C-labeled pyruvate to glucose was measured in primary hepatocytes after 3 h incubation with glucagon (10 ng/ml), FKN and/or insulin (10 nM) in the presence or absence of MEK inhibitors, U0126 (200 nM) or PD98059 (10 μM). Mean+/-SEM. n = 4. *$p<0.05$ versus lane 1; #$p<0.05$ versus lane 3; one way ANOVA.

Supplementary Figure 4. Identification of primary alpha and beta cells in intact mouse islets. Functional characterization of beta and alpha cells in intact mouse islets. (**A**) Intact mouse pancreatic islets were isolated from transgenic mice expressed EGFP under the control of the mouse insulin 1 promoter. Epifluoresence and bright field images were obtained with a 20X objective lens and an inverted epifluorescence microscope (TE2000-U, Nikon) equipped with Evolve 512 EMCCD (Photometrics). The contrast and brightness of images were adjusted to improve the image quality with Image J software. (**B**) Membrane

currents elicited by a 5-ms depolarization from -70 mV to 0 mV using K^+-containing intracellular solution and the extracellular solution including 10 mM TEA-Cl. Ca^{2+} current is only shown in β cell (*left*) and transient inward current followed by TEA-resistance outward K^+ current is recorded in α cell (*right*). (**C**) Intracellular ATP levels in Min6 cells treated with or without FKN (100ng/ml), U0126 (200 nM) and/or PD98059 (10 μM) in low (left) or high (right) glucose conditions.

Supplementary Figure 5. FKN inhibit K_{ATP} activity in an ERK-dependent manner without changing cAMP levels in alpha cells. (**A**) K_{ATP} channel current activity before and after by FKN treatment in the presence or absence of U0126. A representative data was present from 5 (without U0126) or 6 (with U0126) separate cell measurements . $^*p<0.05$ versus control without FKN treatment; two-tailed unpaired t-test. (**B**) Intracellular cAMP levels in αTC1-6 cells after 1 hour incubation in 1mM glucose KRB with either: 100 nM insulin, 10 ng/ml mFKN, 100 ng/ml mFKN, 100 nM GLP-1, 10 ng/ml mFKN + 100 ng/ml pertussis toxin, 100 ng/ml mFKN + 100 ng/ml pertussis toxin or 25 mM glucose KRB. Data presented as means +/- SEM, data a combination of two experiments, n = 3-8. (**C**) Schematic model of FKN action mechanisms in alpha and beta cells and hepatocytes.

Supplementary Figure 1



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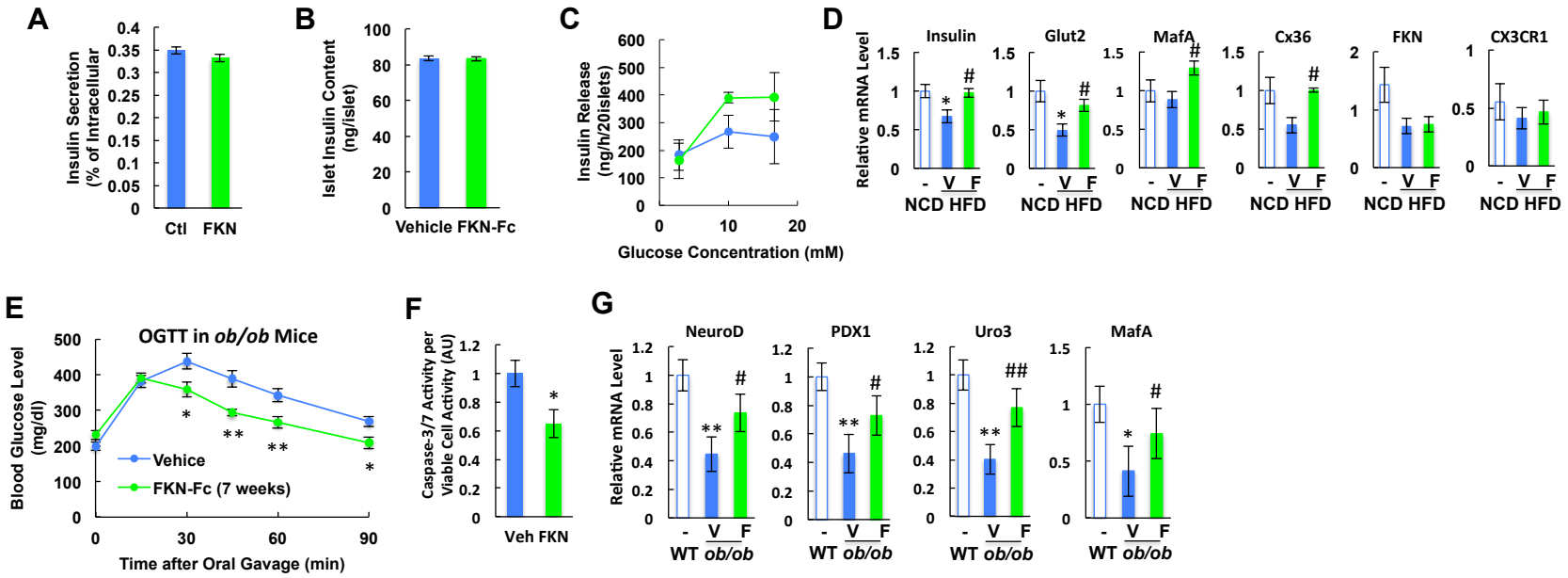

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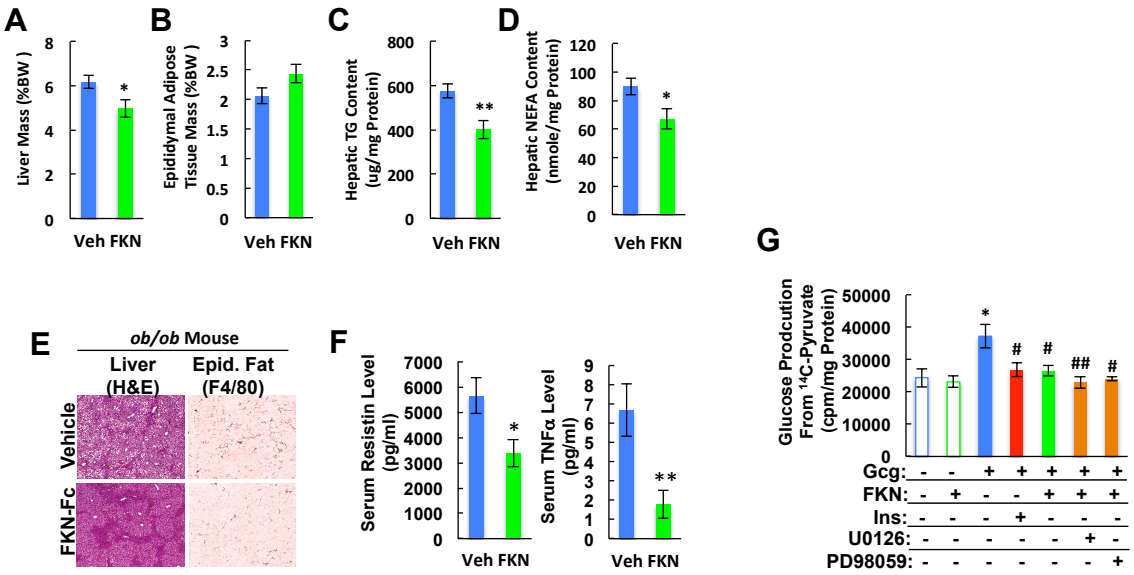
Supplementary Figure 2

Supplementary Figure 3



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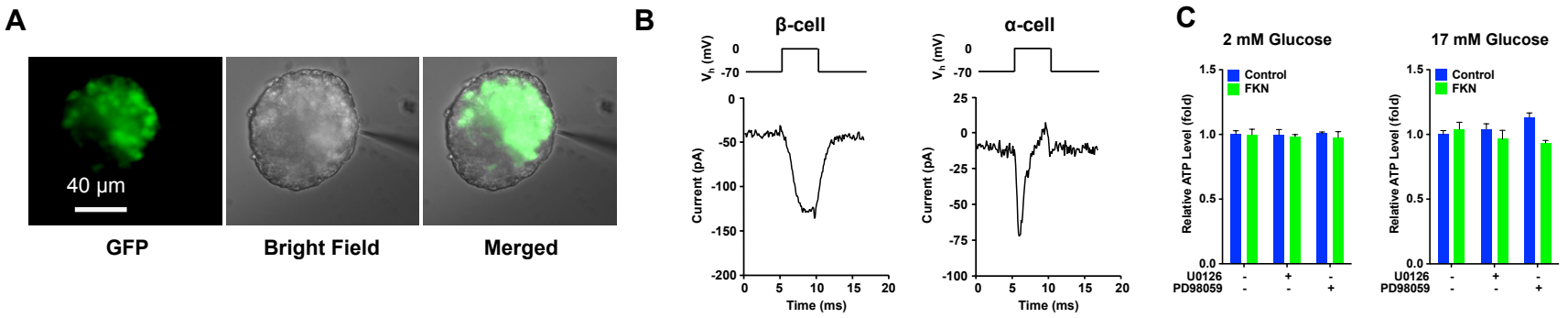

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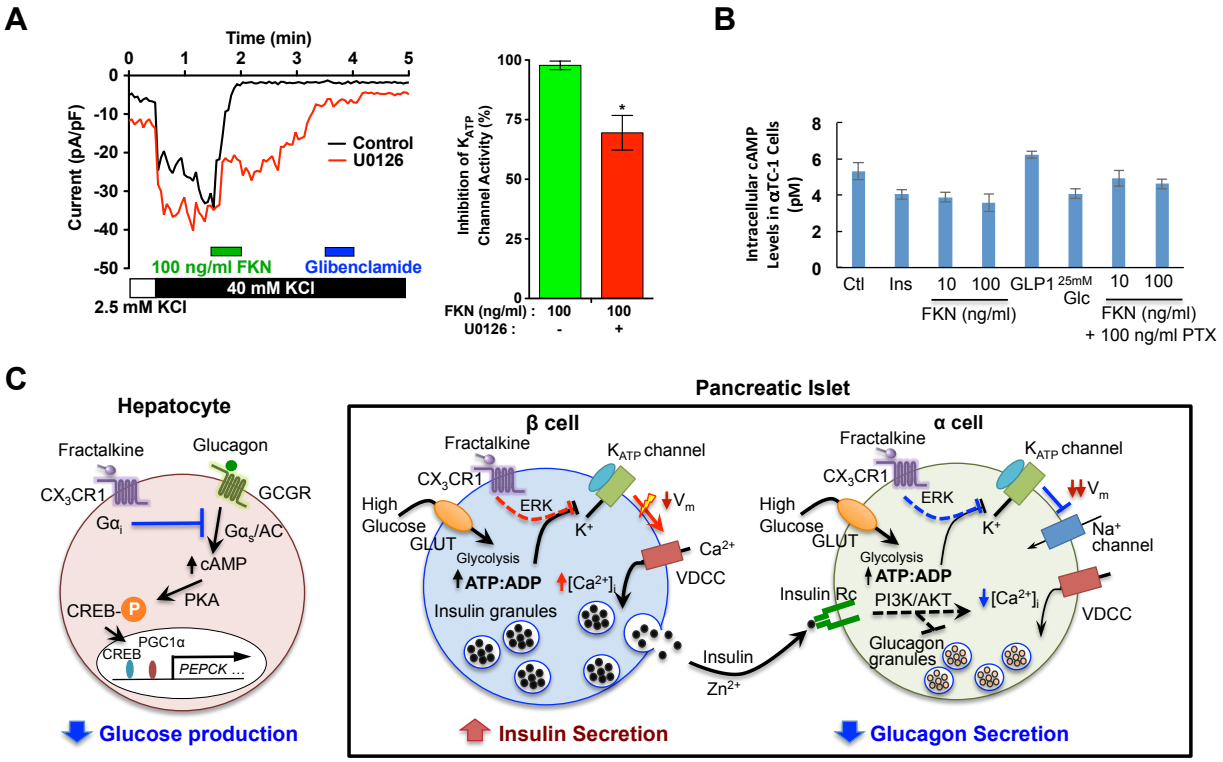
Supplementary Figure 4

Supplementary Figure 5



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Full unedited film for the Western blots in Figure 3 (Riopel et al.)