SUPPLEMENTARY DATA

Cholesterol Content Assays.
Plasma cholesterol concentrations were performed in triplicate by the Department of Clinical Laboratory, Xijing Hospital, The Fourth Military Medical University.

Intraperitoneal Glucose Tolerance Test (IPGTT).
After a 16-hour fast, alert mice were challenged with a glucose load of 1.5g/kg, administered via intraperitoneal injection. Tail blood was taken 0, 15, 60, and 120 minutes after the glucose load, and blood glucose levels were determined with a OneTouch II glucose meter (Lifescan, Milpitas, CA).

Insulin Tolerance Test (ITT)
After a 16-hour fast, insulin (0.5 IU/kg, Sigma, St. Louis, MO) was administered by intraperitoneal injection. Tail blood samples were collected at 0, 15, 30, 60, 90 and 120 minutes for the measurement of plasma glucose. Blood glucose levels were detected by a OneTouch II glucose meter (Lifescan, Milpitas, CA).

Detection of Plasma Insulin Levels.
Fasting blood insulin concentrations were detected with a mouse insulin ELISA kit (EMD Millipore, Billerica, MA) in accordance with the manufacturer's instructions.

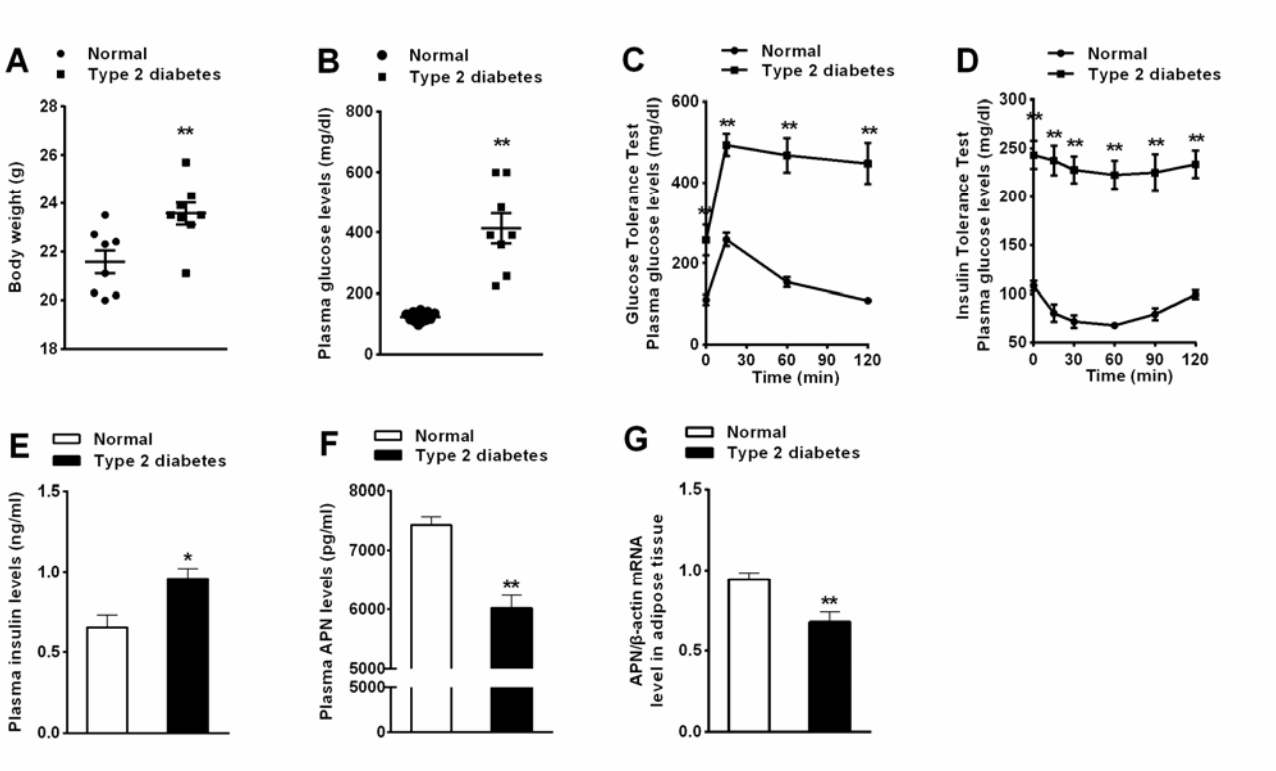
Determination of Plasma Total Adiponectin Concentrations.
Endogenous plasma adiponectin levels were determined with a mouse adiponectin ELISA kit (R&D Systems, Minneapolis, MN) in accordance with the manufacturer's instructions.

Cell Culture and BCKA Challenge.
AML12 mouse hepatocytes (ATCC, Manassas, VA) were cultured in DMEM medium (Invitrogen, Carlsbad, CA) containing 10% fetal bovine plasma (HyClone Waltham, MA). Experiments were carried out at 3 or 4 cell passages. After 5 hours of plasma-starvation (plasma-free growth medium incubation), hepatocytes were washed twice with PBS and incubated in DMEM medium (Invitrogen, Carlsbad, CA) which contained an additional mixture of all of the BCKA (Sigma, St. Louis, MO) at 2.5mM. Cell cohorts were randomized to receive one of the following treatments: vehicle (PBS), APN (10 μg/ml), APN (10 μg/ml) + AMPK inhibitor compound C (added 30 mins before APN treatment, 20 pmol/ml), AMPK activator AICAR (2 pmol/ml). After 30 mins, 1 hour, 3 hours, or 24 hours of treatment, cells and supernatants were collected for Western blotting, real-time RT-PCR and BCKA analysis.

RNA Preparation and Real-Time RT-PCR Analysis. Total RNA from mouse adipocytes, liver, and cultured hepatocytes were prepared with TRIzol (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. Total RNA was reverse transcribed into first-strand cDNA using the SuperScript First-Strand Synthesis Kit (TaKaRa, Otsu, Shiga). cDNA transcripts were quantified by the Step-One Plus RT-PCR System (Bio-Rad, Hercules, CA) using SYBR Green (TaKaRa, Otsu, Shiga). β-actin ((TaKaRa, Otsu, Shiga) served as an endogenous control. Each reaction was performed in triplicate and values were averaged to calculate relative expression levels. Primers sequences are available upon request.

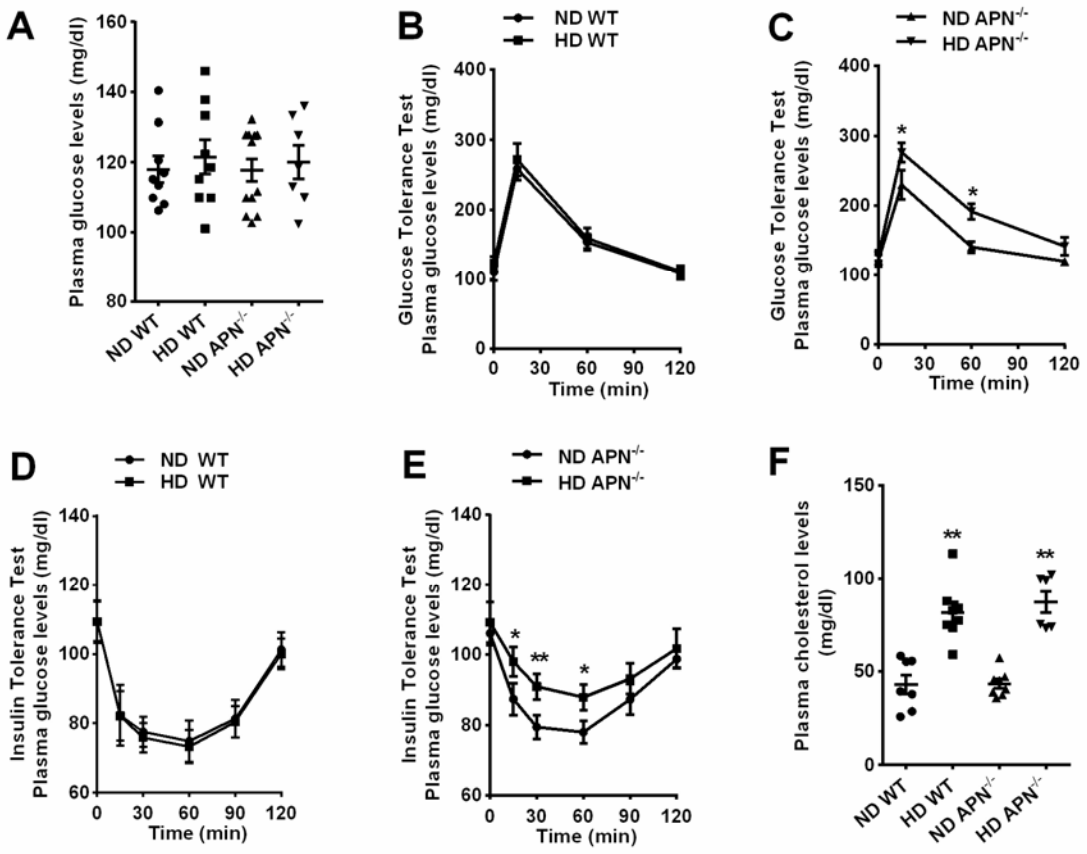
SUPPLEMENTARY DATA

Supplementary Figure 1. Adiponectin Is Reduced in Type 2 Diabetic Mice (Related to Figure 1, Figure 3 and Figure 4) (A) Body weight, (B) blood glucose concentrations, (C) glucose tolerance tested by IPGTT, (D) insulin tolerance tested by ITT and (E) fasting blood insulin levels in normal controls and type 2 diabetic mice. (F) APN concentrations in plasma and (G) APN mRNA levels in adipose tissue of type 2 diabetic mice and their controls. All results are presented as mean ± SEM. *****Significant difference between type 2 diabetic group and normal group. * $P < 0.05$, ** $P < 0.01$. n = 5 - 8.



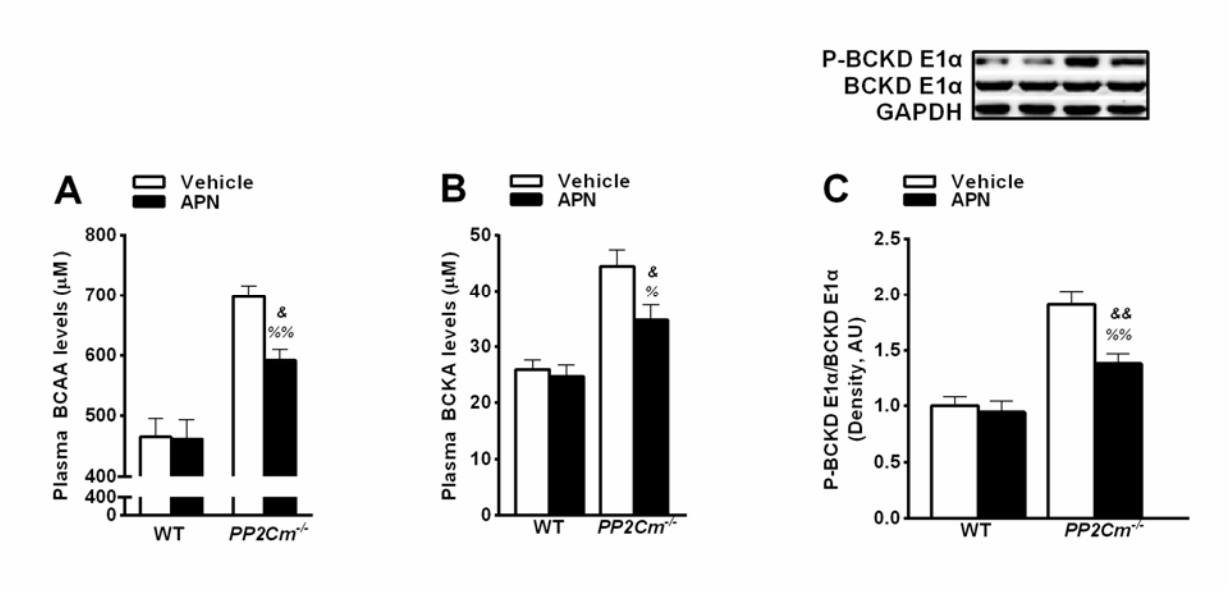
SUPPLEMENTARY DATA

Supplementary Figure 2. HD-fed Adiponectin Knockout Reveals Insulin Resistance (Related to Figure 2) (A) Blood glucose levels, (B and C) glucose tolerance tested by IPGTT, (D and E) insulin tolerance tested by ITT and (F) blood cholesterol levels in WT and *APN*$^{-/-}$ mice fed with normal diet (ND) or high fat diet (45% HD). All results are presented as mean ± SEM. *Significant difference between HD and ND fed group. * $P < 0.05$, ** $P < 0.01$. n = 6 - 8.



SUPPLEMENTARY DATA

Supplementary Figure 3. PP2Cm Deficiency Partially Inhibits Adiponectin-activated BCKD (Related to Figure 3) (A and B) Plasma BCAA and BCKA concentrations, (C) hepatic BCKD E1α phosphorylation levels in WT and *PP2Cm*$^{-/-}$ mice treated with vehicle or APN for 3 days. All results are presented as mean ± SEM. $^{\%}$Significant difference between APN and vehicle injected group. $^{\&}$Significant difference between APN treated WT and *PP2Cm*$^{-/-}$ mice. $^{\%\&}P < 0.05$, $^{\%\%\&\&}P < 0.01$. n = 5 - 8.



SUPPLEMENTARY DATA

Supplementary Figure 4. APN up-regulates PP2Cm expression and improves BCAA catabolism which depend on AMPK *in vitro* (Related to Figure 2, 3 and 4) (A) BCKA levels, (B) BCKD phosphorylation (E1α at Ser293), (C) PP2Cm protein and (D) PP2Cm mRNA levels in hepatocytes challenged with BCKA and treated with APN. Measurements by western blot were made at 30 mins (blot lane 1-4, lane 2 and 4 represent APN treated group); 1 hour (blot lane 5-8, lane 6 and 8 represent APN treated group); 3 hours (blot lane 9-12, lane 10 and 12 represent APN treated group); 24 hours (blot lane 13-16, lane 14 and 16 represent APN treated group). (E) Biochemical analysis of BCKA concentrations, (F) BCKD phosphorylation, (G) PP2Cm protein expression and (H) PP2Cm mRNA levels in BCKA challenged hepatocytes which treated with vehicle, APN, APN + CC or AICAR. Measurements were made at 1 hour. All results are presented as mean ± SEM. $^{\%}$Significant difference between APN and vehicle treated group. $^{\&}$Significant difference between APN and APN plus CC treated group. *Significant difference between AICAR and vehicle treated group. $^{\%\&*}P < 0.05$, $^{\%\%\&\&**}P < 0.01$. n = 6 - 12 wells. CC, compound C.