Supplemental Tables and Figures

	Normal (n=30)	T2DM (n=30)	*P* value
Age (year)	45.2±8.3	46.1±9.5	0.81
BMI (kg/m^2)	22.47±2.10	30.92±2.61	<0.001
HbA1c (%)	5.24±0.28	8.87±1.90	<0.001
Pregnenolone	0.41±0.29	0.47±0.63	0.67
Progesterone	0.20±0.37	0.078±0.04	0.13
17-hydroxy pregnenolone	2.52±1.32	1.71±1.45	0.041
17-OHP	0.76±0.34	1.27±0.55	<0.001
DHEAS	5.09±2.39	3.23±2.23	<0.01
Androstenedione	0.91±0.29	0.81±0.33	0.27
Testosterone	3.81±2.53	3.52±1.18	0.63
11deoxycortisol	0.30±0.24	0.32±0.24	0.74
Cortisol	121.15±36.76	109.78±58.63	0.39
Aldosterone	0.037±0.026	0.029±0.025	0.28
Deoxycorticosterone	0.071±0.041	0.063±0.047	0.57
Dihydrotestosterone	0.503±0.25	0.52±0.14	0.78
Corticosterone	5.39±4.01	4.19±1.39	0.18

Supplemental Table 1: Plasma steroid hormones measured by mass spectroscopy in normal subjects and diabetic patients (T2DM). n=30 per group. The unit of all steroid hormones in this table is ng/ml. Analysis of covariance was performed using general linear models to test the differences between groups.

Variables	r	*P value*
Body mass index (kg/m2)	0.41	0.016
Fasting plasma glucose (mmol/l)	0.24	0.19
Fasting plasma insulin (μU/ml)	0.42	0.019
HOMA-IR	0.47	0.009
Triglyceride(mmol/l)	0.40	0.011
Total cholesterol (mmol/l)	0.41	0.009
HDL cholesterol (mmol/l)	0.53	0.001
LDL cholesterol (mmol/l)	0.38	0.018
Systolic blood pressure (mmHg)	0.35	0.025
Diastolic blood pressure (mmHg)	0.29	0.064

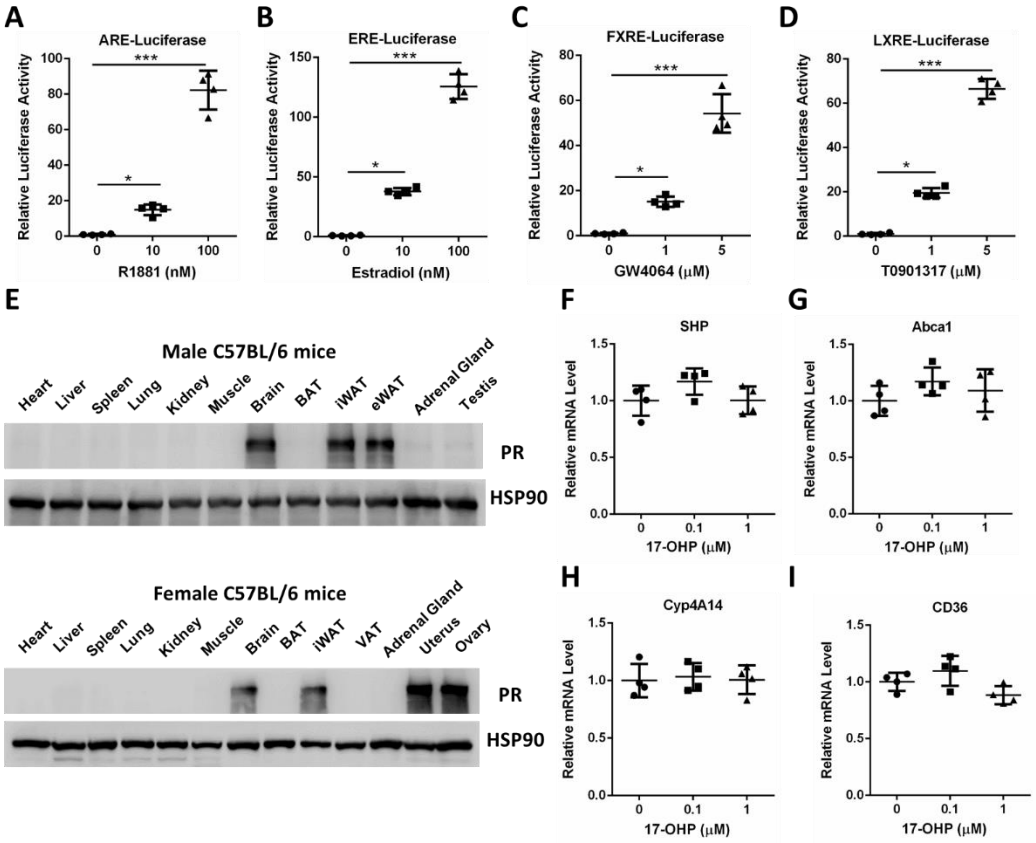
Supplemental Table 2: Univariate regression analysis with plasma 17-OHP levels as an independent variable in normal subjects and patients with congenital adrenal hyperplasia. n=30 per group.

Plasmid	Sequence 5'→3'
Mouse *AR*	Forward: GATCTCGAGCTCAAGCTTGCCACCATGTACCCC TACGACGTGCCCGACTACGCCGAGGTGCAGTTAGGGCTGGGAAG Reverse: GTGGCGACCGGTGGATCCTCACTGTGTGTGGAAATAGATGGG
Mouse *ERα*	Forward: GATCTCGAGCTCAAGCTTGCCACCATGTACCC TACGACGTGCCCGACTACGCCACCATGACCCTTCACACCAAAGC Reverse: GTGGCGACCGGTGGATCCTCAGATCGTGTTGGGGAAGCCCT
Mouse *FXR*	Forward: GATCTCGAGCTCAAGCTTGCCACCATGTACCCC TACGACGTGCCCGACTACGCCGTGATGCAGTTTCAGGGTTTAGAA Reverse: GTGGCGACCGGTGGATCCTCACTGCATCCCAGATCTCAC
Mouse *GR*	Forward: GATCTCGAGCTCAAGCTTGCCACCATGTACCCC TACGACGTGCCCGACTACGCCGACTCCAAAGAATCCTTAGC Reverse: GTGGCGACCGGTGGATCCTCATTTCTGATGAAACAGAAGCTTTTTG
Mouse *LXRα*	Forward: GATCTCGAGCTCAAGCTTGCCACCATGTACCC TACGACGTGCCCGACTACGCCTCCTTGTGGCTGGAGGCCTCAATG Reverse: GGCGACCGGTGGATCCTCACTCGTGGACATCCCAGATCTC

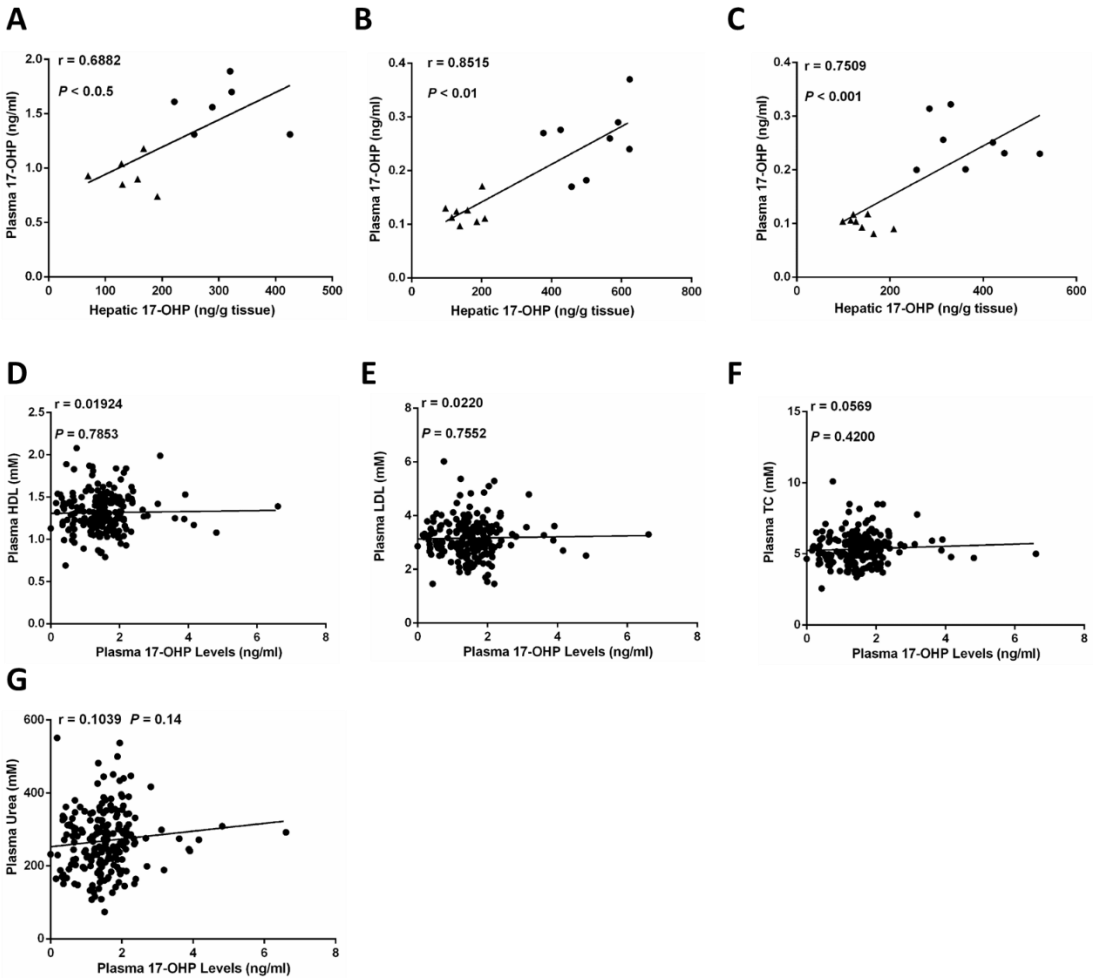
Supplemental Table 3. Plasmids construction primer sequences.

Gene	Sequence 5'→3'
Human *Cyp17A1*	Forward: CCGTAAGGGTATCGCCTTCG Reverse: CCATCCTTGAACAGGGCAAAG
Human *36B4*	Forward: GCAGCATCTACAACCCTGAAG Reverse: CACTGGCAACATTGCGGAC
Mouse *Cyp17A1*	Forward: GCCCAAGTCAAAGACACCTAAT Reverse: GTACCCAGGCGAAGAGAATAGA
Mouse *GR*	Forward: AGCTCCCCCTGGTAGAGAC Reverse: GGTGAAGACGCAGAAACCTTG
Mouse *PEPCK*	Forward: CTGCATAACGGTCTGGACTTC Reverse: CAGCAACTGCCCGTACTCC
Mouse *TAT*	Forward: AGCCGAATCCGAACAAAACC Reverse: GCCGATAGATGGGGCATAGC
Mouse *G6Pase*	Forward: CGACTCGCTATCTCCAAGTGA Reverse: GTTGAACCAGTCTCCGACCA
Mouse *SHP*	Forward: TGGGTCCCAAGGAGTATGC Reverse: GCTCCAAGACTTCACACAGTG
Mouse *Abca1*	Forward: AAAACCGCAGACATCCTTCAG Reverse: CATACCGAAACTCGTTCACCC
Mouse *Cyp4A14*	Forward: TTTAGCCCTACAAGGTACTTGGA Reverse: GCAGCCACTGCCTTCGTAA
Mouse *CD36*	Forward: ATGGGCTGTGATCGGAACTG Reverse: GTCTTCCCAATAAGCATGTCTCC
Mouse *36B4*	Forward: AGATTCGGGATATGCTGTTGGC Reverse: TCGGGTCCTAGACCAGTGTTC

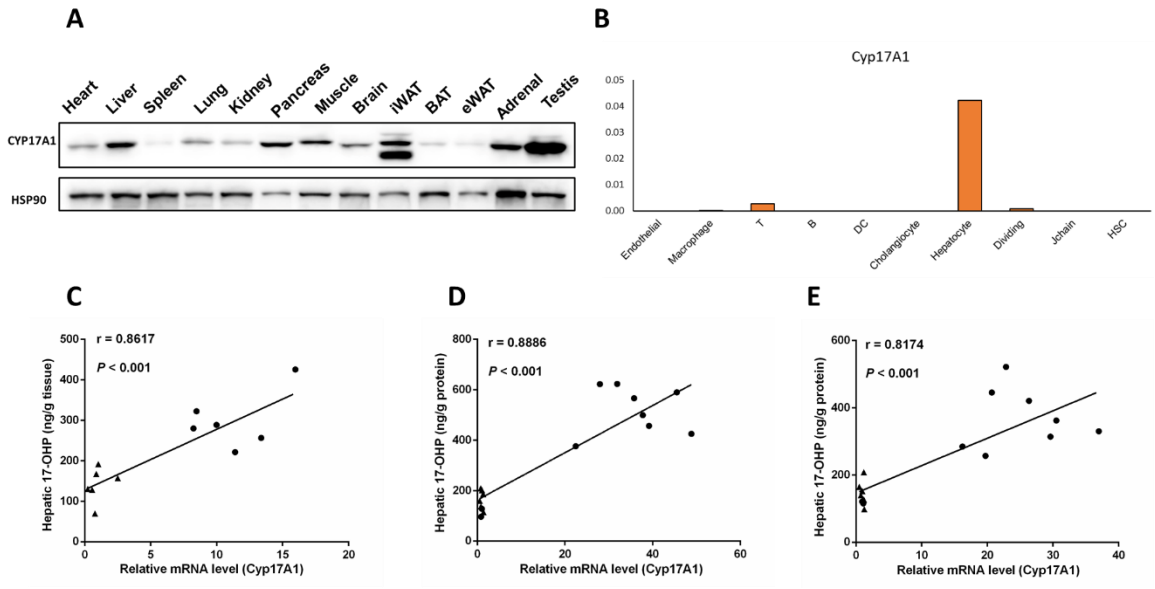
Supplemental Table 4: Primer sequences for quantitative real-time PCR.



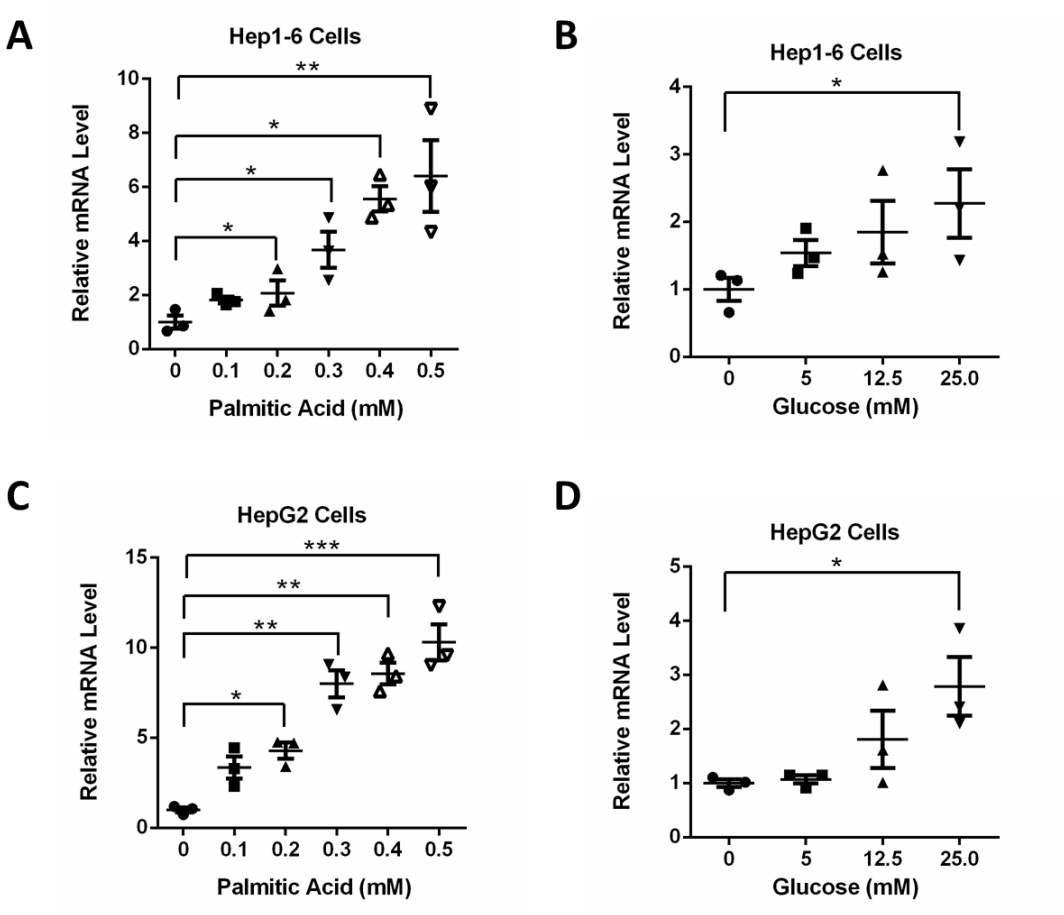
Supplemental Figure 1: (**A-D**) Luciferase assay for ARE (**A**), ERE (**B**), FXRE (**C**) and LXRE (**D**) activity in HepG2 cells. Cells were transfected with luciferase reporters and nuclear receptor expression plasmids for 24 h and then treated with the corresponding ligands for 24 h. n=4 per group. Data represent mean ± SD. * *P* <0.05, *** *P* <0.001, 1-way ANOVA followed by the Student-Newman-Keuls test. (**E**) Western blots showing PR protein expression in various tissues isolated from 9-week-old male and female C57BL/6 mice. (**F-I**) Relative mRNA levels of SHP (**F**), Abca1 (**G**), Cyp4A14 (**H**), and CD36 (**I**) in mouse primary hepatocytes treated with 17-OHP or vehicle control for 16 h. n=4 per group. Data represent mean ± SD. 1-way ANOVA followed by the Student-Newman-Keuls test.



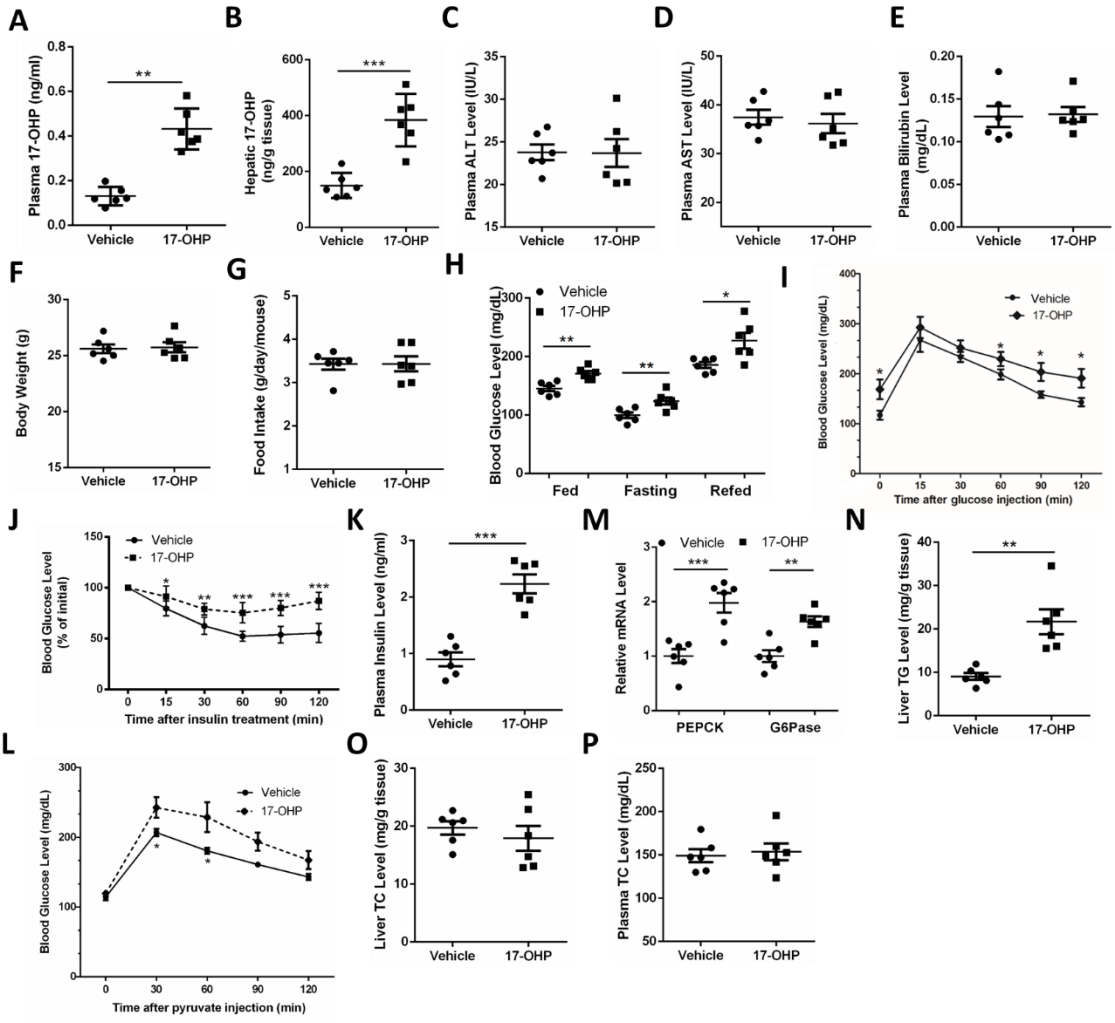
Supplemental Figure 2: (**A-C**) Pearson correlation analysis of hepatic 17-OHP concentrations and plasma 17-OHP levels in HFD (**A**, n=6 per group), *db/db* (**B**, n=8 per group), *ob/ob* (**C**, n=8 per group) and the corresponding control mice. (**D-G**) Pearson correlation analysis of plasma 17-OHP levels and HDL (**D**), LDL (**E**), total cholesterol (**F**) and urea (**G**) in human subjects. n=203 in total. HDL: high density lipoprotein, LDL: low density lipoprotein, TC: total cholesterol.



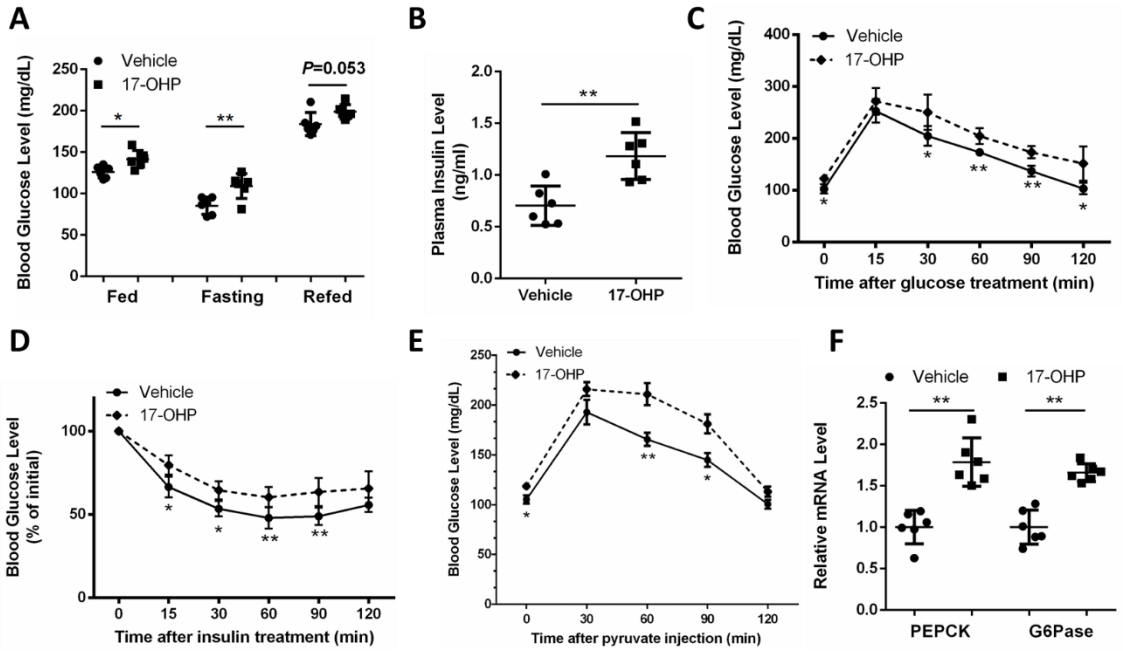
Supplemental Figure 3: (**A**) Western blots showing the protein expression of Cyp17A1 in various tissues of 9-week-old C57BL/6 male mice. (**B**) Cellular source of Cyp17A1 mRNA revealed by liver single cell RNA sequencing. (**C-E**) Pearson correlation analysis of hepatic 17-OHP concentrations and Cyp17A1 mRNA levels in the HFD (**C**, n=6 per group), *db/db* (**D**, n=8 per group), *ob/ob* (**E**, n=8 per group) and the corresponding control mice.



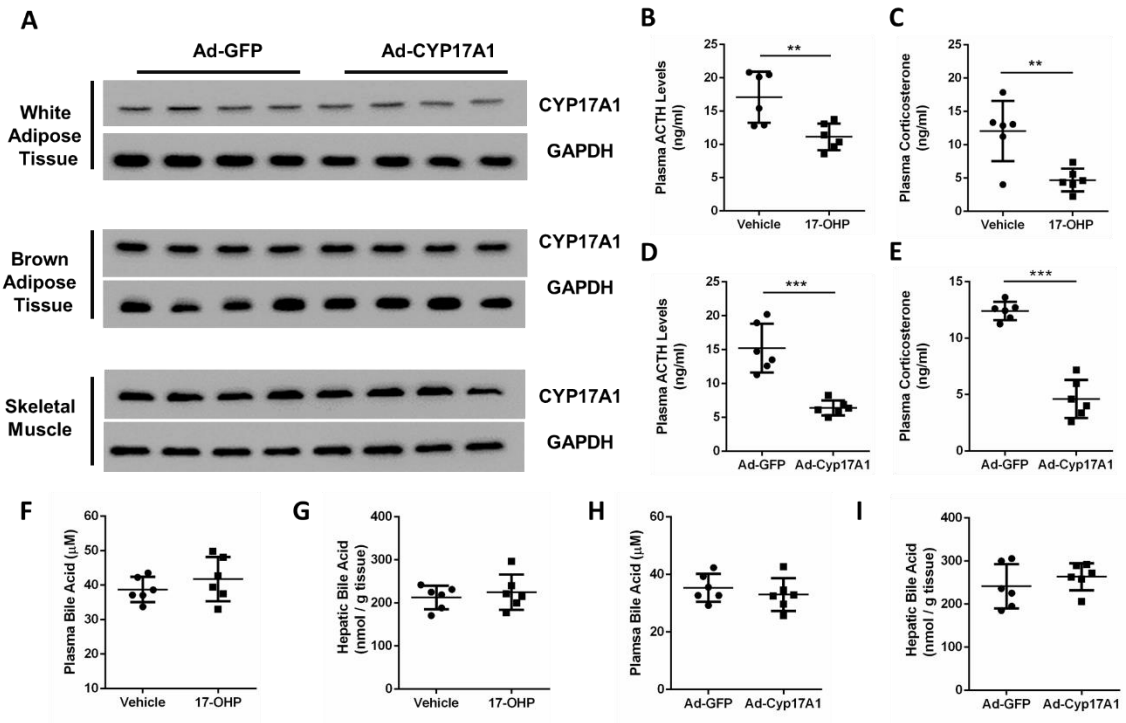
Supplemental Figure 4: (**A-B**) Relative mRNA levels of Cyp17A1 in HepG2 cells treated with different concentrations of palmitic acid (**A**) or glucose (**B**) for 24 h. (**C-D**) Relative mRNA levels of Cyp17A1 in Hep1-6 cells treated with different concentrations of palmitic acid (**C**) or glucose (**D**) for 24 h. n=3 per group. Data represent mean ± SD. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, (A-D) 1-way ANOVA followed by the Student-Newman-Keuls test.



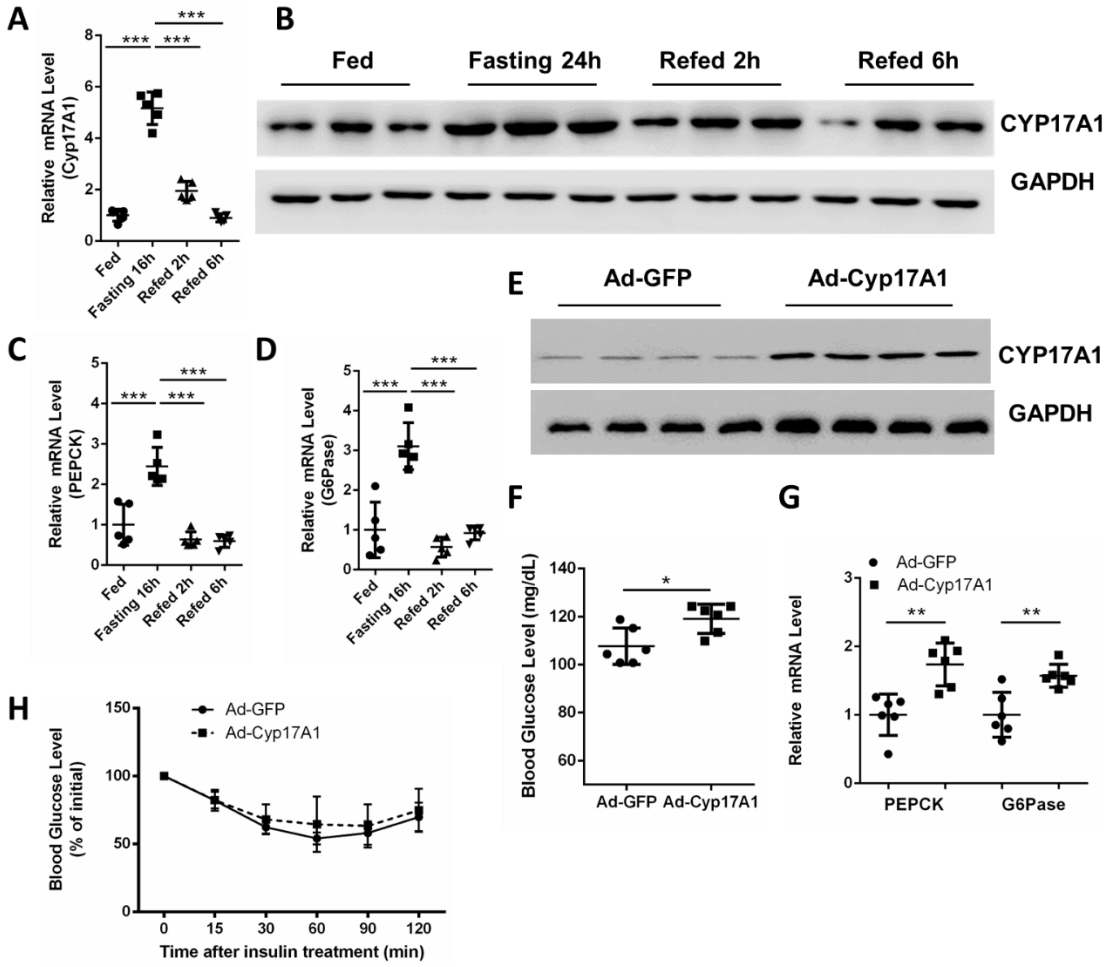
Supplemental Figure 5: (A-B) Plasma and hepatic 17-OHP concentrations in C57BL/6 mice treated with 17-OHP (50mg/kg) or vehicle control for 14 days. (**C-E**) Plasma ALT (**C**), AST (**D**), and bilirubin (**E**) levels two groups of mice. (**F-G**) Body weight and food intake in the two groups of mice. (**H**) Blood glucose levels on post-injection day 8. (**I-J**) Glucose and insulin tolerance tests on post-injection days 10 and 12, respectively. (**K**) Plasma insulin levels in the two groups of mice. (**L**) Pyruvate tolerance tests in mice on post-injection day 10. (**M**) Relative mRNA levels of gluconeogenic genes in mice. (**N-P**) Hepatic TG contents (**N**), hepatic and plasma total cholesterol (TC) contents (**O, P**) in mice. n=6 per group. C57BL/6 mice were given daily intraperitoneal injections of 50 mg/kg 17-OHP for 14 days or corn oil (vehicle control). Then, mice were sacrificed for analysis (A-E, I, K-P). This experiment was repeated in three independent groups with similar results. n=6 per each group. Data represent mean ± SD, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, (A-H, K, M-P) 2-tailed unpaired Student's *t* test. (I, J, L) 1-way ANOVA followed by the Student-Newman-Keuls test.



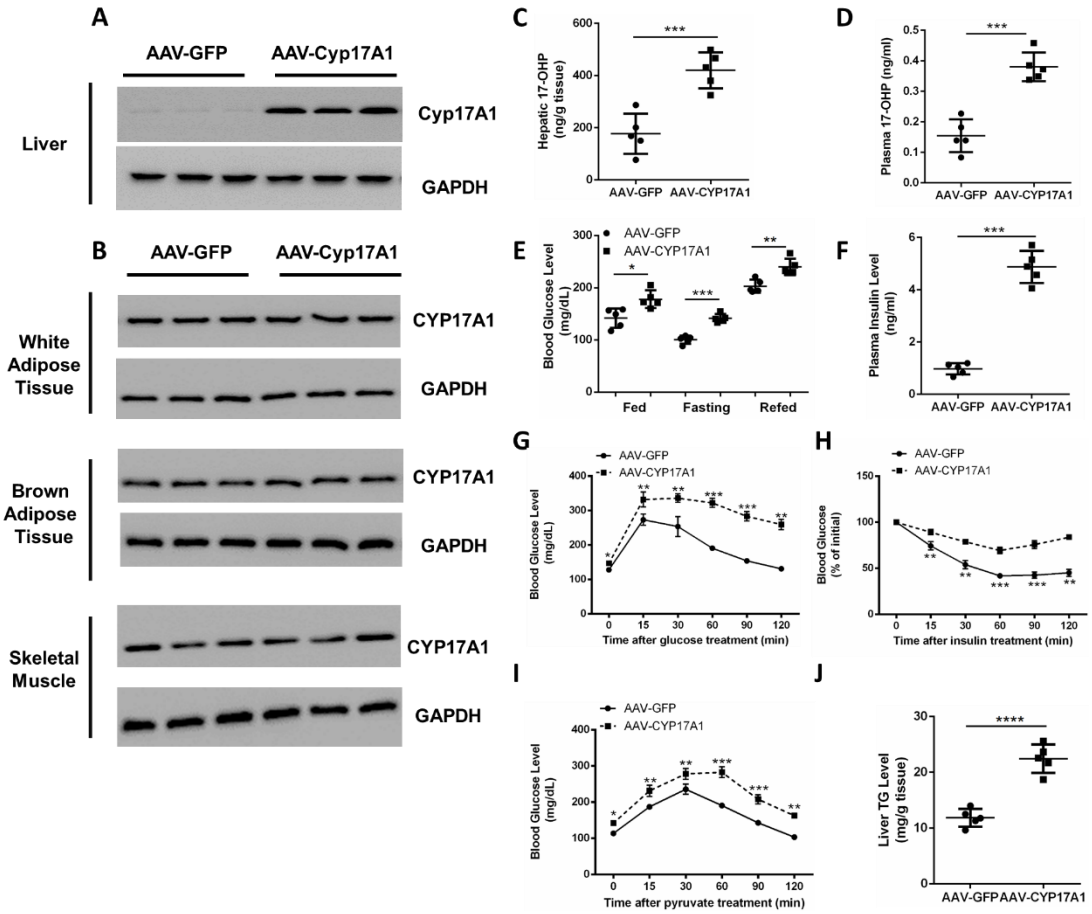
Supplemental Figure 6: C57BL/6 female mice aged 10 weeks were treated with 17-OHP (50 mg/kg) or vehicle control for 14 days (n=6 per group). (A) Blood glucose levels in the two groups of mice on post-injection day 8. (B) Plasma insulin levels in the two groups of mice. (C-D) Glucose and insulin tolerance tests on post-injection days 10 and 12, respectively. (E) Pyruvate tolerance tests in mice on post-injection day 10. (F) Relative mRNA levels of gluconeogenic genes in mice. This experiment was repeated in two independent groups with similar results. Data represent mean ± SD, * $P < 0.05$, ** $P < 0.01$, (A, B, F) 2-tailed unpaired Student's *t* test. (C-E) 1-way ANOVA followed by the Student-Newman-Keuls test.



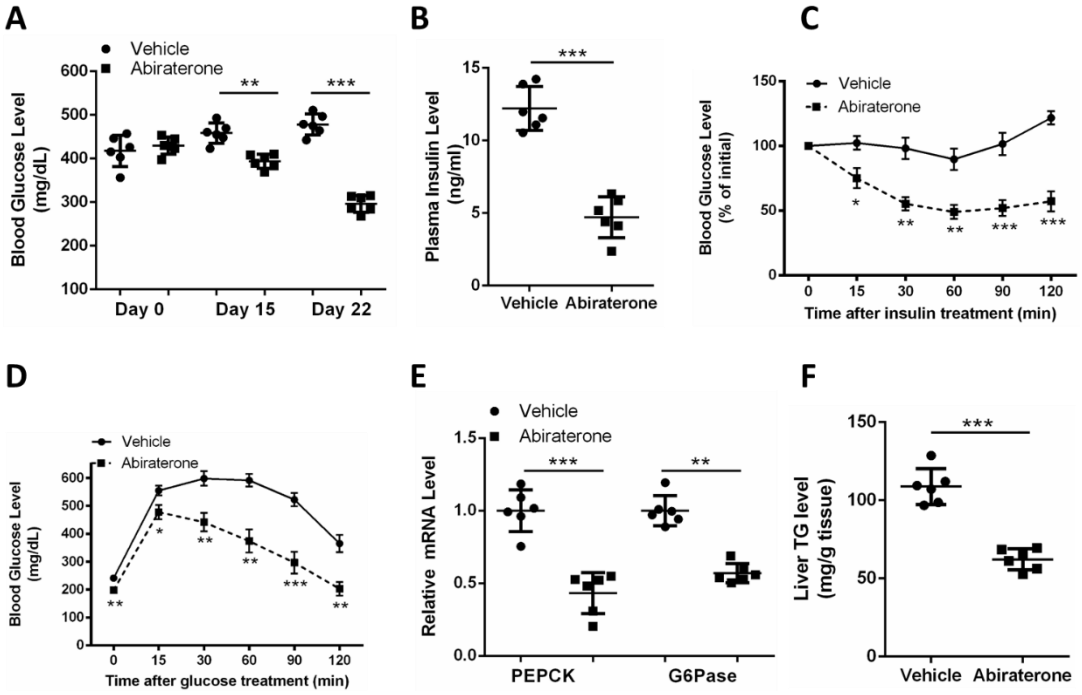
Supplemental Figure 7: (A) Western blots showing the protein contents of Cyp17A1 in the C57BL/6 mice infected with Ad-GFP or Ad-Cyp17A1. (**B-C**) Plasma ACTH and corticosterone levels in the C57BL/6 mice treated with 17-OHP or vehicle control. n=6 per group. (**D-E**) Plasma ACTH and corticosterone levels in the C57BL/6 mice overexpressing Cyp17A1 or GFP. n=6 per group. (**F-G**) Plasma and hepatic bile acid levels in the C57BL/6 mice treated with 17-OHP or vehicle control. n=6 per group. (**H-I**) Plasma and hepatic bile acid levels in the C57BL/6 mice overexpressing Cyp17A1 or GFP. n=6 per group. Data represent mean ± SD, ** $P < 0.01$, *** $P < 0.001$, (B-I) 2-tailed unpaired Student's *t* test.



Supplemental Figure 8: (**A**) Relative mRNA levels of Cyp17A1 in the liver of C57BL/6 mice under fed or 16-h fasted or 16-h fasted/2-h refed or 16-h fasted/6-h refed conditions. n=5 per group. (**B**) Western blots showing the protein levels of Cyp17A1. (**C-D**) Relative mRNA levels of PEPCK and G6Pase as in (**A**). n=5. (**E**) Western blots showing the protein levels of Cyp17A1 in C57BL/6 mice infected with Ad-GFP or Ad-Cyp17A1 (5×10^8 plaque-forming units per mouse). (**F**) Fasting blood glucose levels in mice on post-injection day 8. n=6 per group. (**G**) Relative mRNA levels of PEPCK and G6Pase as in (**E**). (**H**) Insulin tolerance test performed on post-injection day 11. Data represent mean ± SD, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. (A, C, D, H) 1-way ANOVA followed by the Student-Newman-Keuls test. (F, G) 2-tailed unpaired Student's *t* test.



Supplemental Figure 9: (**A**) Western blots showing the protein levels of Cyp17A1 in the livers of C57BL/6 mice transfected with adeno-associated virus (AAV) containing Cyp17A1 or GFP on post-injection day 35. (**B**) Western blots showing the protein levels of Cyp17A1 in the skeletal muscles, white adipose tissues and brown adipose tissues. (**C-D**) 17-OHP concentrations in the liver and plasma from mice overexpressing Cyp17A1 or GFP. (**E**) Blood glucose levels at fed, fasting (16 h), and refed (2 h) conditions on day 10 post-injection. (**F**) Plasma insulin levels on post injection day 15. (**G-I**) Glucose tolerance tests (**G**), insulin tolerance tests (**H**), and pyruvate tolerance tests (**I**) were performed on day 20, 24, and 30, respectively. (**J**) Liver triglyceride contents in the two groups of mice. C57BL/6 mice were administered with AAV-Cyp17A1 or AAV-GFP through tail vein injection. 35 days later, mice were sacrificed for analysis (A-D, F, J). n=5 per group. Data represent mean ± SED. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, (C, D, E, F, J) 2-tailed unpaired Student's *t* test. (G-I) 1-way ANOVA followed by the Student-Newman-Keuls test.



Supplemental Figure 10: Male *db/db* mice aged 10 weeks were daily treated with abiraterone (0.5 mmol/kg/day) or vehicle control (5% benzyl alcohol plus 95% olive oil mixture) by intraperitoneal injection for 30 days. n=6 per group. (**A**) Blood glucose measured at days 0, 15, and 22 as indicated. (**B**) Plasma insulin levels between the two groups of mice. (**C**-**D**) Insulin tolerance test and glucose tolerance test performed at days 18 and 26, respectively. (**E**) Relative mRNA levels of gluconeogenic genes (PEPCK and G6Pase) in the liver from the two groups of mice. (**F**) Liver triglyceride contents between the two groups of mice. Data represent mean ± SD. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, (A, B, E, F) 2-tailed unpaired Student's *t* test. (C, D) 1-way ANOVA followed by the Student-Newman-Keuls test.