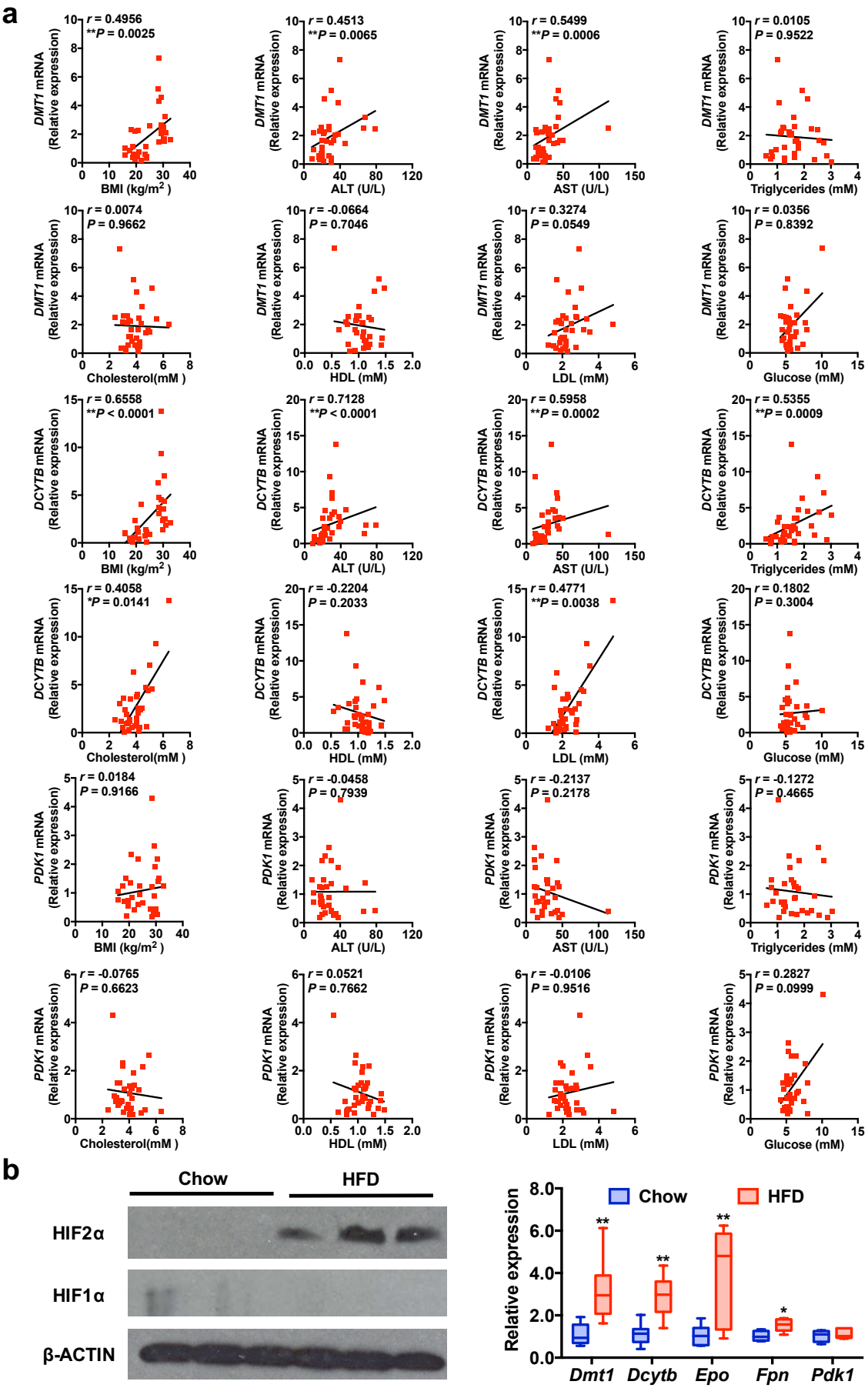

Nature Medicine: doi:10.1038/nm.4412

Supplementary Figure 1. Increased HIF2α signaling in human ileum biopsies is correlated with obesity. (**a**) Correlative analysis of ileum *DMT1, DCYTB, and PDK1* mRNA levels with BMI, ALT, AST, triglycerides, cholesterol, HDL, LDL, and glucose. $n = 35$. Correlations were assessed by nonparametric Spearman's test. (**b**) Western blot analysis of HIF2α and HIF1α protein expression ($n = 3$/group) and mRNA expression analysis of their target genes in small intestine from chow or HFD-fed mice (1 week). $n = 4$ for chow and $n = 5$ for HFD. For box plots, the midline represents the median; box represents the interquartile range (IQR) between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. $^{*}P < 0.05$, $^{**}P < 0.01$ versus chow, by two-tailed Student's *t*-test.

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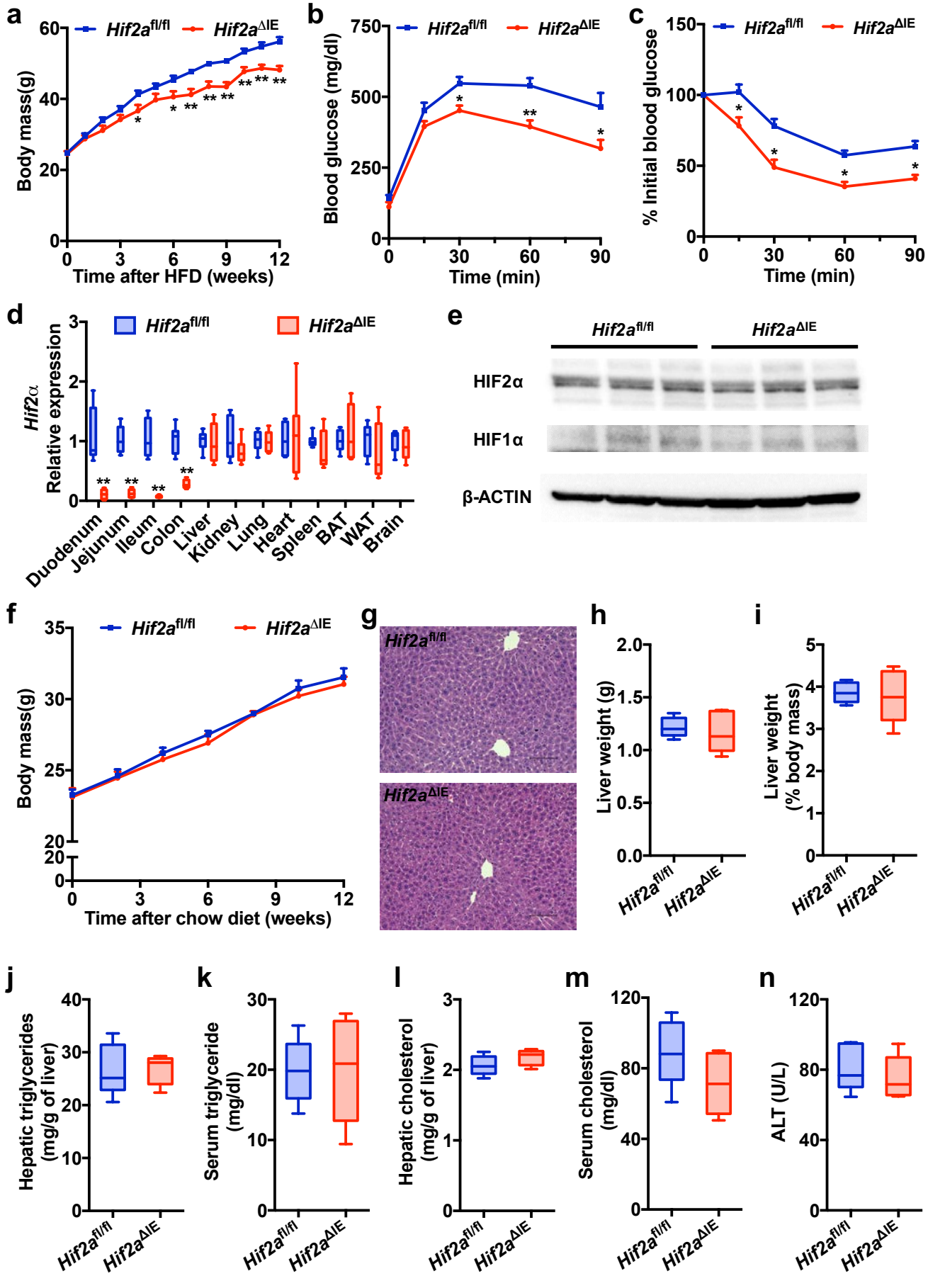

Nature Medicine: doi:10.1038/nm.4412

Supplementary Figure 2. Lack of intestinal HIF2α prevents HFD-induced obesity and improves metabolic homeostasis. (**a**) Growth curves of HFD-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**b**) Glucose tolerance testf HFD-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**c**) Insulin tolerance testf HFD-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**d**) *Hif2a* mRNA expression in different tissues from HFD-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**e**) Western blot analysis of liver HIF2α and HIF1α from f HFD-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice (n = 3/group). (**f**) Growth curves of chow-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**g**) Representative H&E staining of liver sections of chow-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice (n = 15, 3 images/mouse). Scale bars, 100 μm. (**h**) Liver weights of chow-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**i**) Liver weight to body weight ratios of chow-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**j, k**) Liver (**j**) and serum (**k**) triglyceride content of chow-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**l**,**m**) Liver (**l**) and serum (**m**) cholesterol content of chow-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**n**) Serum ALT levels of chow-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. n = 5/group. Data are presented as the mean ± sem. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. *$P < 0.05$, **$P < 0.01$ versus *Hif2a*$^{fl/fl}$ mice, by two-tailed Student's t-test.

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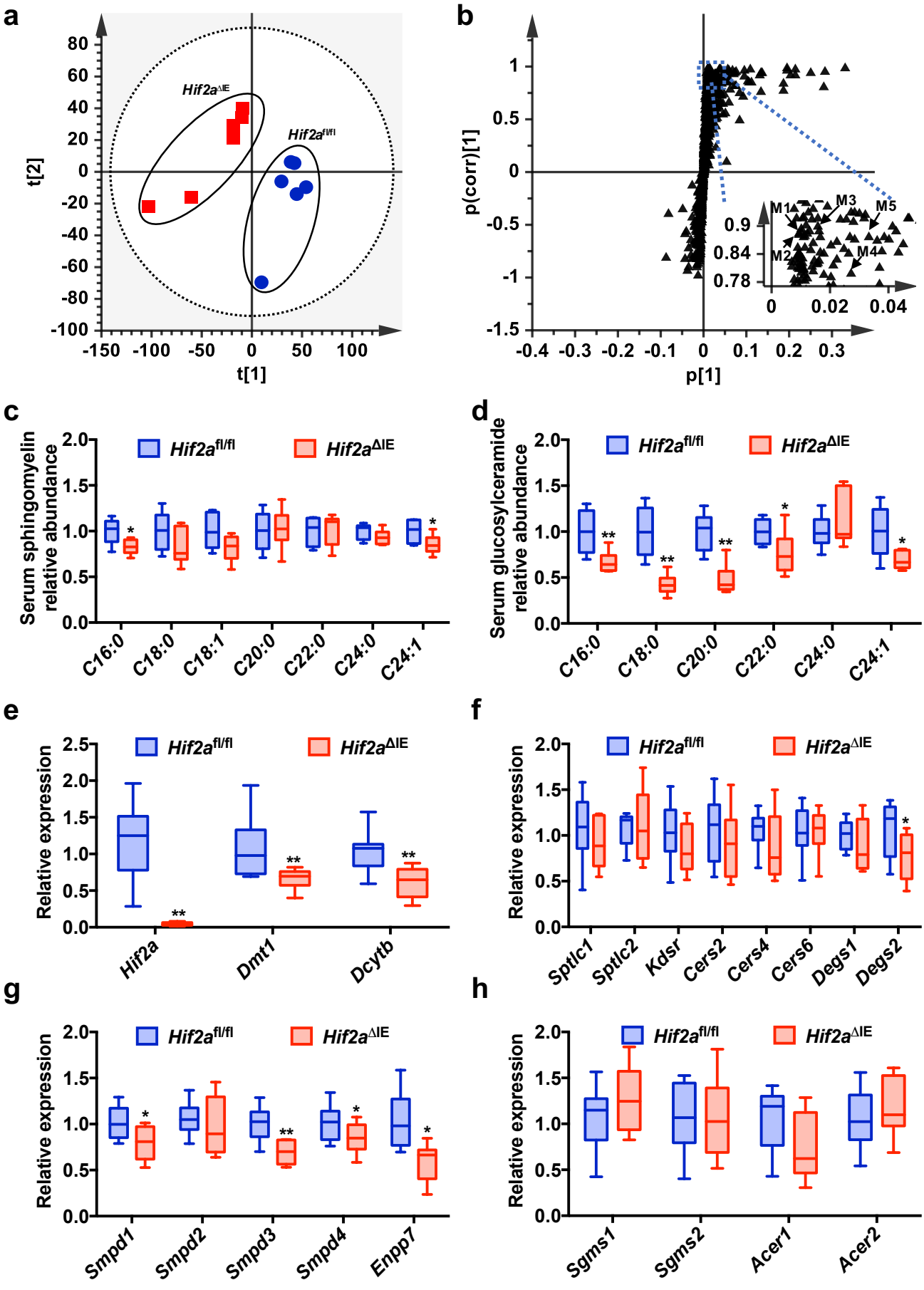
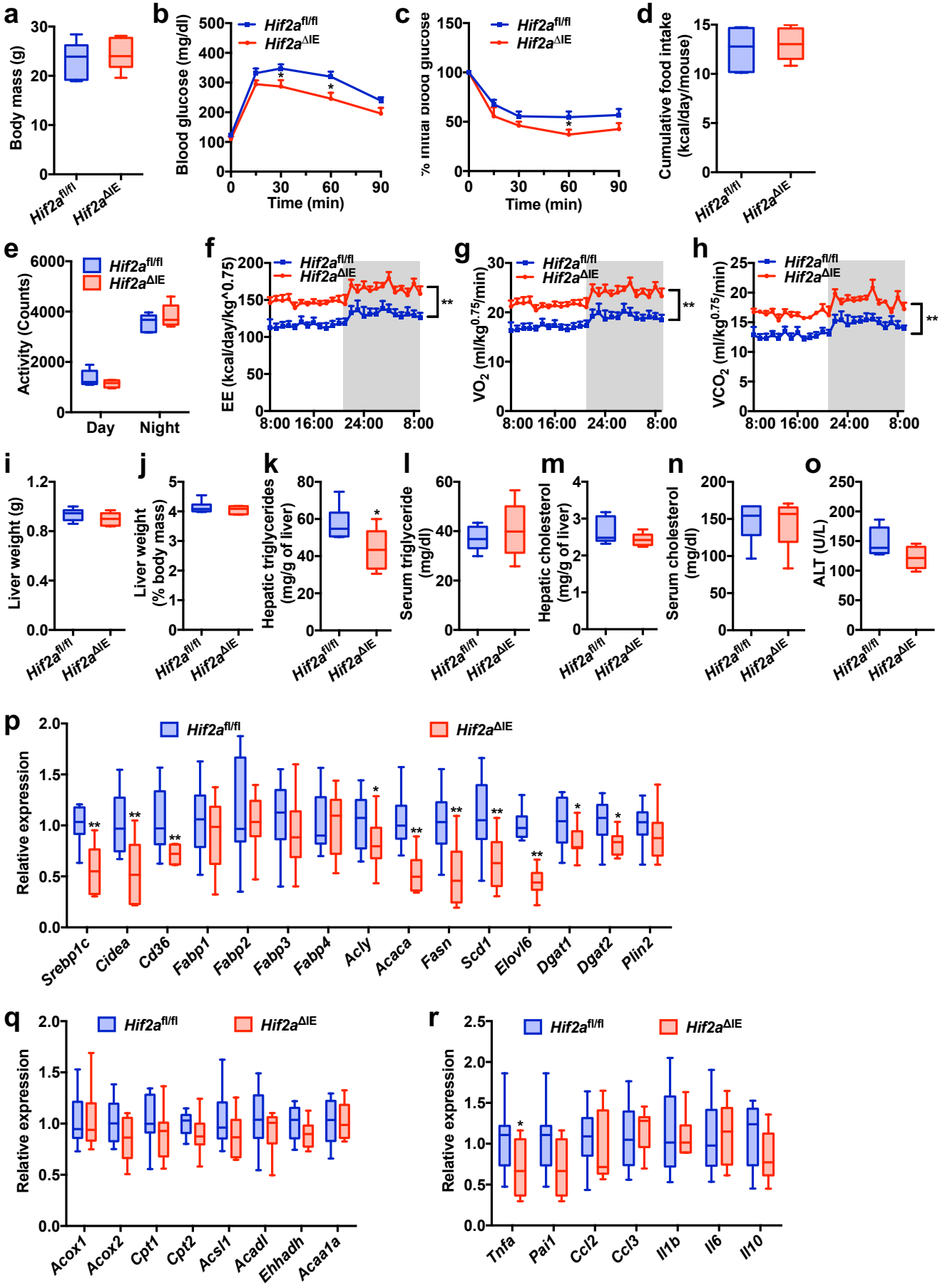


Nature Medicine: doi:10.1038/nm.4412

Supplementary Figure 3. Loss of HIF2α in the intestine affects ceramide metabolism in HFD-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**a**) Score scatter plot of a PCA model of the serum metabolites between *Hif2a*$^{fl/fl}$ (circle) and *Hif2a*$^{\Delta IE}$ (square) mice. (**b**) S-plot of an OPLS-DA model of the serum metabolites. (**c**,**d**) The relative levels of sphingomyelin (**c**) and glucosylceramide (**d**) in serum. (**e**) Expression of intestinal *Hif2a* mRNA and HIF2α target gene mRNAs. (**f**,**g**) Intestinal expression of mRNAs encoded by ceramide synthesis-related genes, including the *de-novo* pathway (**f**) and the sphingomyelinase pathway (**g**). (**h**) Intestinal expression of mRNAs encoded by ceramide catabolism-related genes. n = 6/group. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. *$P < 0.05$, **$P < 0.01$ versus *Hif2a*$^{fl/fl}$ mice, by two-tailed Student's *t*-test.



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Supplementary Figure 4. Inhibition of the intestinal HIF2α substantially increases the metabolic rate and decreases hepatic steatosis independent of body weight changes in HFD-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**a**) body weight. (**b**) Glucose tolerance test. (**c**) Insulin tolerance test. (**d**) Cumulative food intake. (**e**) Activity. (**f**) Energy expenditure. (**g**) Oxygen consumption rate. (**h**) Carbon dioxide production rate. (**i**) Liver weights. (**j**) Liver weight to body weight ratios. (**k**,**l**) Liver (**k**) and serum (**l**) triglyceride content. (**m**,**n**) Liver (**m**) and serum (**n**) cholesterol content. (**o**) Serum ALT levels (P = 0.08). (**p**) Hepatic expression of mRNAs encoding fatty acid transport and lipogenesis. (**q**) Hepatic expression of mRNAs encoding fatty acid oxidation-related enzymes. (**r**) Hepatic expression of mRNAs encoding inflammatory cytokines and chemokines. n = 6 for *Hif2a*$^{fl/fl}$ group and n = 5 for *Hif2a*$^{\Delta IE}$ group. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. *P < 0.05, **P < 0.01 versus *Hif2a*$^{fl/fl}$ mice, by two-tailed Student's t-test.

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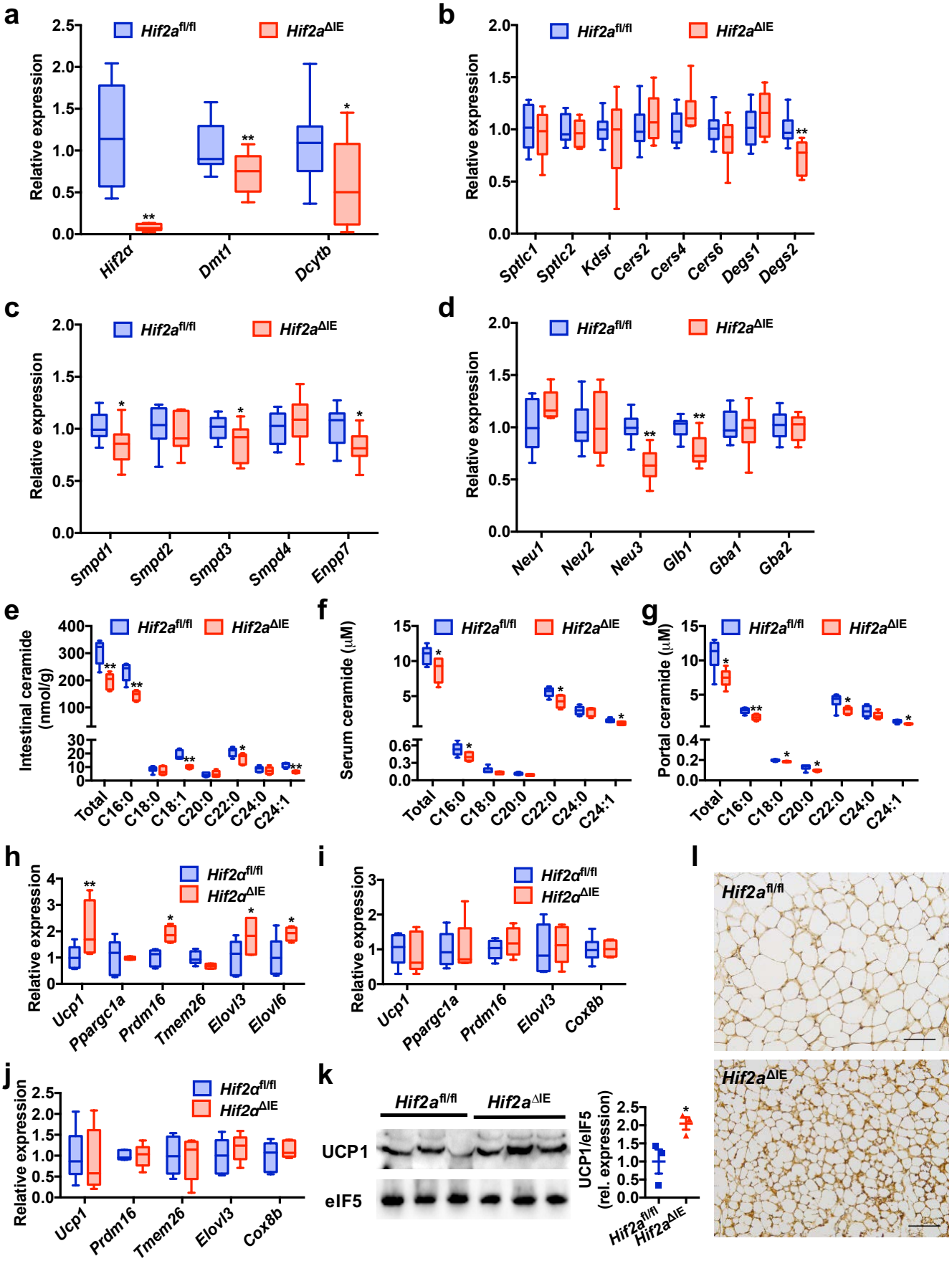

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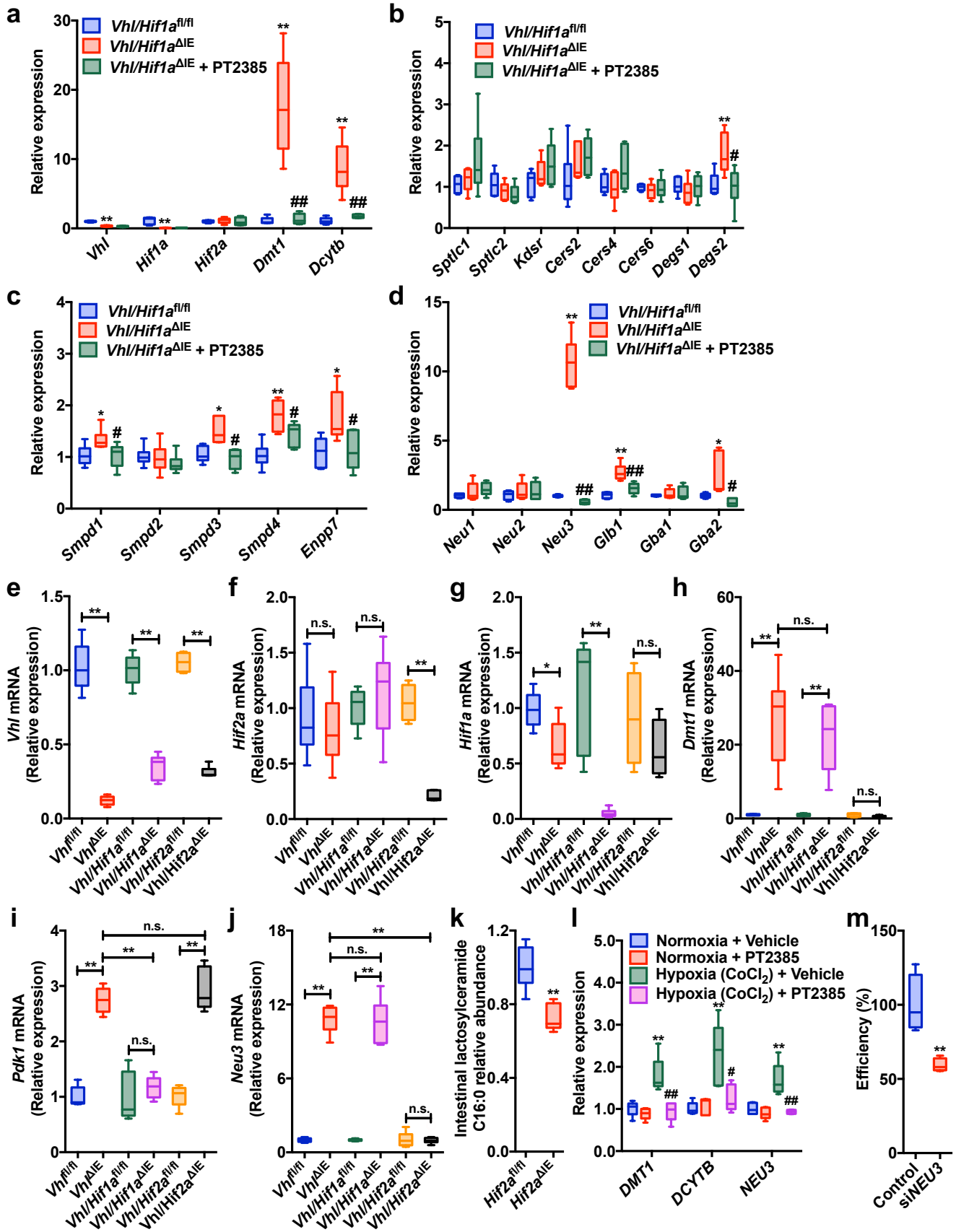
Supplementary Figure 5. Intestinal HIF2α deficiency reduces ceramide synthesis in the small intestine independent of body weight changes in HFD-fed *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**a**) Expression of intestinal *Hif2a* mRNA and HIF2α target gene mRNAs. (**b-d**) Intestinal expression of mRNAs encoded by ceramide synthesis-related genes, including the *de-novo* pathway (**b**), the sphingomyelinase pathway (**c**), and the salvage pathway (**d**). (**e**–**g**) Ceramide levels in the small intestine (**e**), systematic serum (**f**), and portal serum (**g**). (**h**–**j**) Thermogenic gene expression in scWAT (**h**), BAT (**i**), and eWAT (**j**). (**k**) Western blot analysis of UCP1 protein expression in scWAT (n = 3/group). Data are presented as the mean ± sem. n = 6 for *Hif2a*$^{fl/fl}$ group and n = 5 for *Hif2a*$^{\Delta IE}$ group. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. *$P < 0.05$, **$P < 0.01$ versus *Hif2a*$^{fl/fl}$ mice, by two-tailed Student's t-test. (**l**) Representative UCP1 immunohistochemistry staining of scWAT sections (n = 3 images/mice). Scale, 100 μm.



Supplementary Figure 6. HIF2α regulates the ceramide synthesis in the small intestine. (**a**) Intestinal expression of *Vhl*, *Hif1a*, *Hif2a*, *Dmt1* and *Dcytb* mRNAs. (**b**–**d**) Intestinal expression of mRNAs

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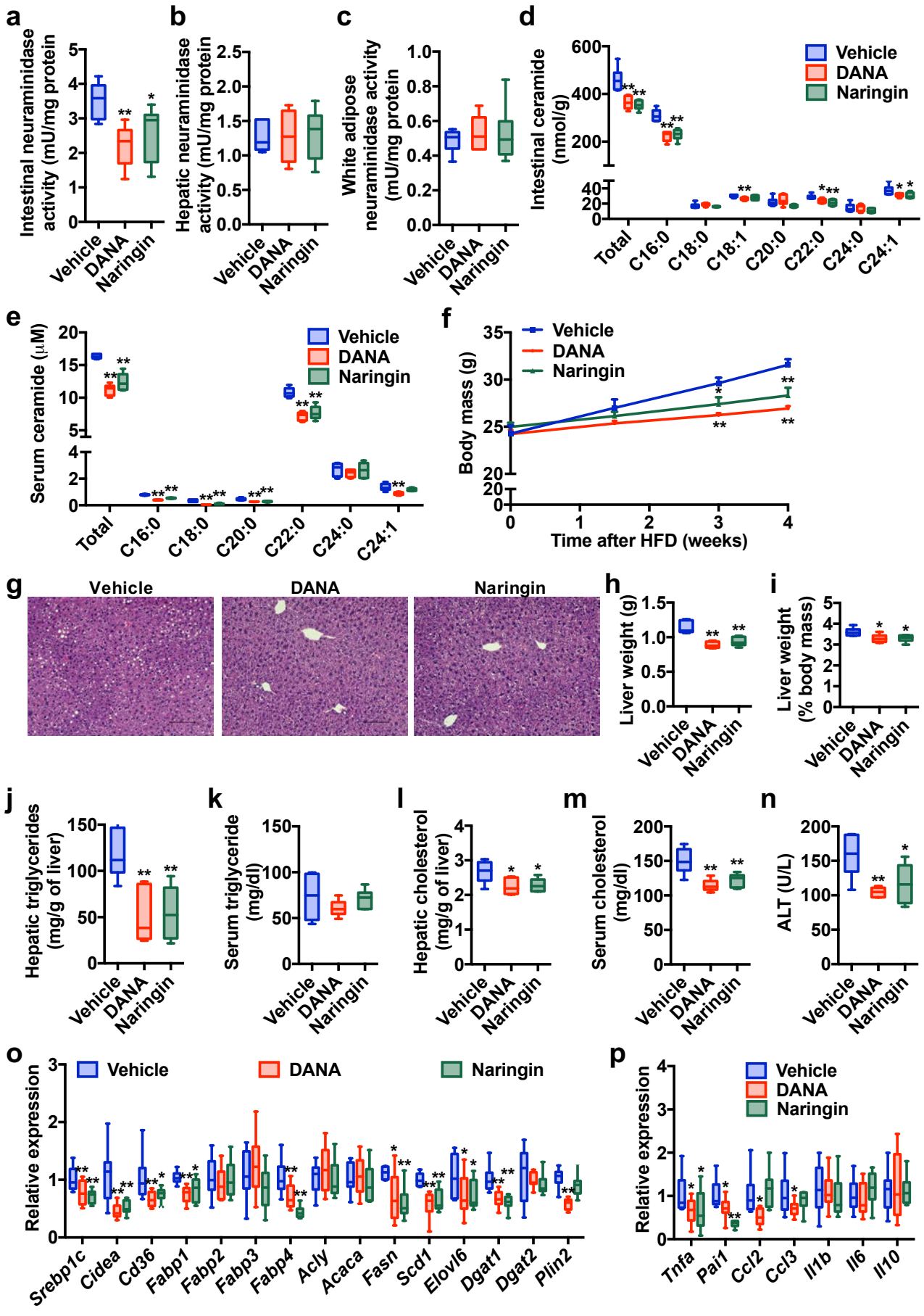
encoded by ceramide synthesis-related genes, including the *de-novo* pathway (**b**), the sphingomyelinase pathway (**c**), and the salvage pathway (**d**). Male *Vhl/Hif1a*$^{fl/fl}$ and *Vhl/ Hif1a*$^{\Delta IE}$ mice fed a chow diet were treated with or without PT2385 (20 mg/kg) for three consecutive days (n = 4 to 6/group). *$P < 0.05$, **$P < 0.01$ versus vehicle-treated *Vhl/Hif1a*$^{fl/fl}$ mice, #$P < 0.05$, ##$P < 0.01$ versus vehicle-treated *Vhl/Hif1a*$^{\Delta IE}$ mice, by one-way ANOVA with Tukey's correction. (**e-j**) Intestinal mRNA expression levels of *Vhl* (**e**), *Hif2a* (**f**), *Hif1a* (**g**), *Dmt1* (**h**), *Pdk1* (**i**), and *Neu3* (**j**) in *Vhl*$^{fl/fl}$, *Vhl*$^{\Delta IE}$, *Vhl/Hif1a*$^{fl/fl}$, *Vhl/Hif1a*$^{\Delta IE}$, *Vhl/Hif2a*$^{fl/fl}$, and *Vhl/Hif2a*$^{\Delta IE}$ mice fed a chow diet (n = 4 to 6/group). (**k**) The relative levels of lactosylceramide C16:0 in the small intestine from *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice fed a HFD for 12 weeks (n = 6/group). **$P < 0.01$ versus *Hif2a*$^{fl/fl}$ mice, by two-tailed Student's t-test. (**l**) mRNA expression of *DMT1*, *DCYTB*, and *NEU3* in HCT116 cells treated with vehicle or PT2385 and exposed to either vehicle or $CoCl_2$ (n = 5/group). **$P < 0.01$ versus Normoxia + Vehicle treatment, #$P < 0.05$, ##$P < 0.01$ versus Hypoxia ($CoCl_2$) + Vehicle treatment, by one-way ANOVA with Tukey's correction. (**m**) The knockdown efficiency of si*NEU3* in HCT116 cells. **$P < 0.01$, by two-tailed Student's t-test. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles.



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Supplementary Figure 7. NEU3 inhibitor DANA and naringin treatments protect mice from HFD-induced obesity and hepatic steatosis. (**a**–**c**) Neuraminidase activities in intestine (**a**), liver (**b**), and white adipose tissue (**c**). (**d**,**e**) Ceramide levels in the small intestine (**d**) and serum (**e**). (**f**) Growth curves. (**g**) Representative H&E staining of liver sections (n = 3 images/mouse). Scale bars, 100 μm. (**h**) Liver weights. (**i**) Liver weight to body weight ratios. (**j**,**k**) Liver (**j**) and serum (**k**) triglyceride content. (**l**,**m**) Liver (**l**) and serum (**m**) cholesterol content. (**n**) Serum ALT levels. (**o**) Hepatic expression of mRNAs encoding fatty acid transport and lipogenesis. (**p**) Hepatic expression of mRNAs encoding inflammatory cytokines and chemokines. n = 6/group. Data are presented as the mean ± sem. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. *$P < 0.05$, **$P < 0.01$ versus vehicle treatment, by two-tailed Student's t-test.

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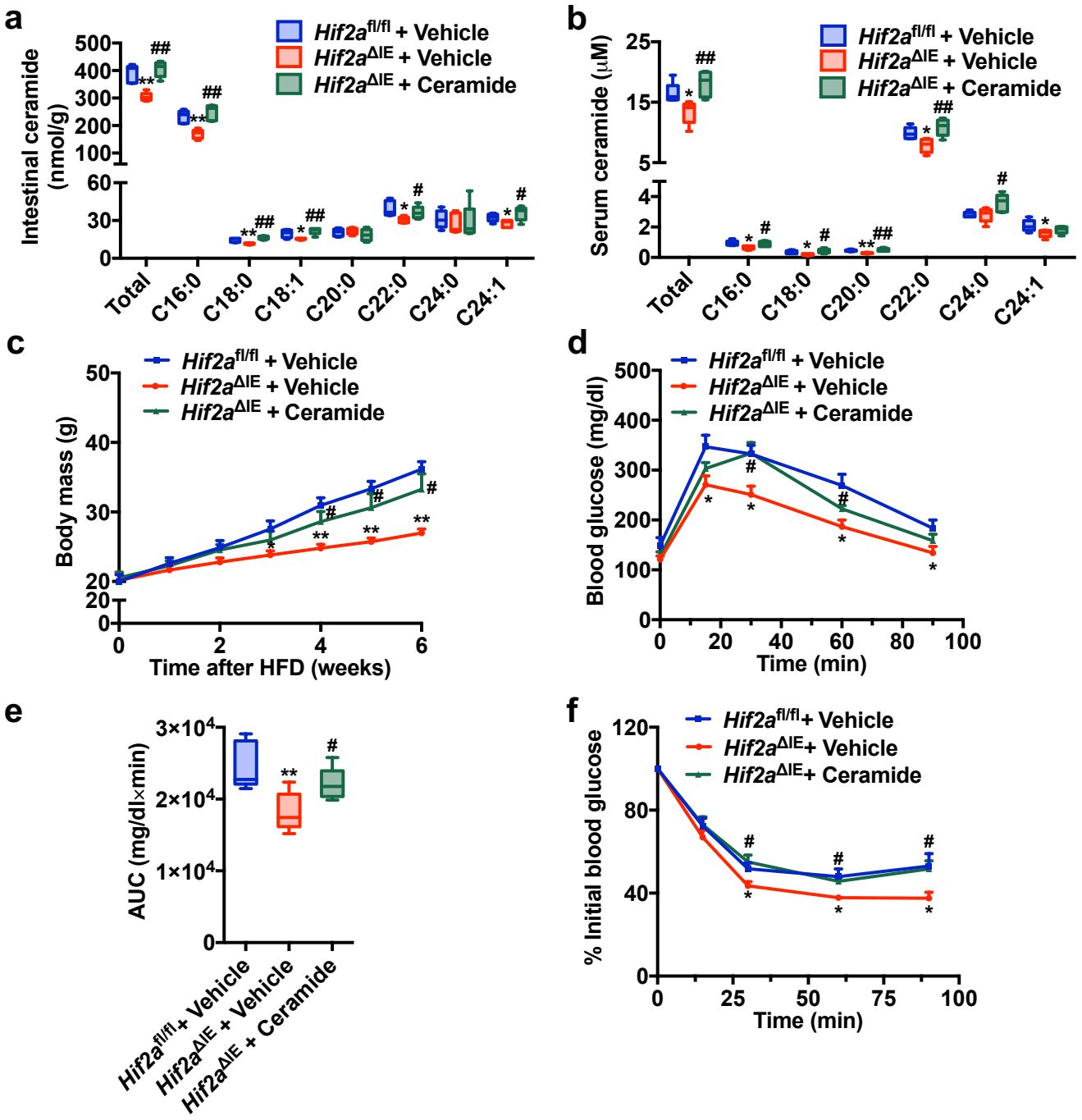

Supplementary Figure 8. Administration of ceramide reverses the protective effects of intestinal HIF2α inhibition on the HFD-induced obesity and insulin resistance in *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$. (**a**,**b**) Ceramide levels in the small intestine (**a**) and serum (**b**). (**c**) Growth curves. (**d**,**e**) Glucose tolerance test (**d**) and glucose AUC (**e**). (**f**) Insulin tolerance test. n = 5/group. Data are presented as the mean ± sem. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. *P < 0.05, **P < 0.01 versus vehicle-treated *Hif2a*$^{fl/fl}$ mice, #P < 0.05, ##P < 0.01 versus vehicle-treated *Hif2a*$^{\Delta IE}$ mice, by one-way ANOVA with Tukey's correction.

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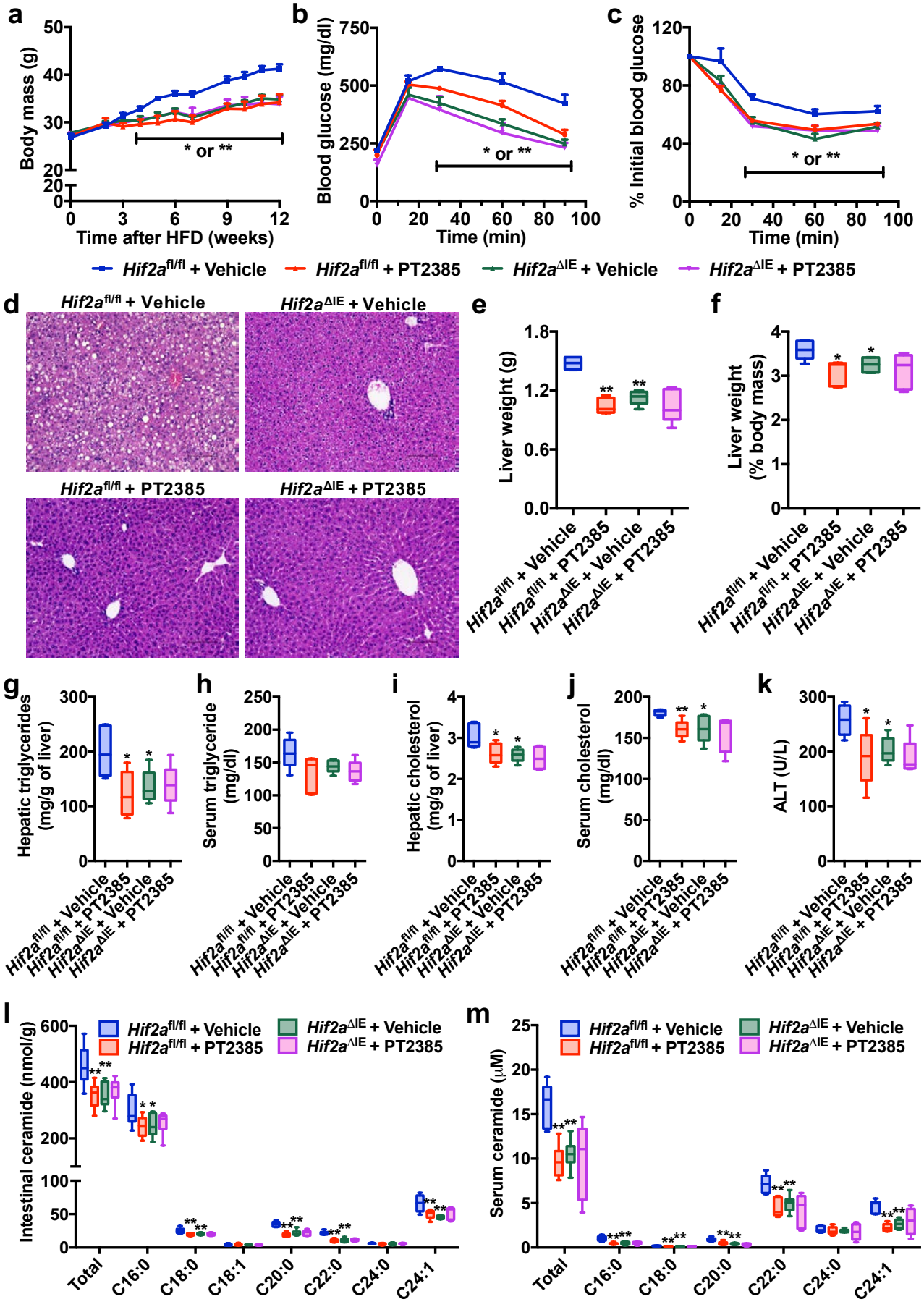

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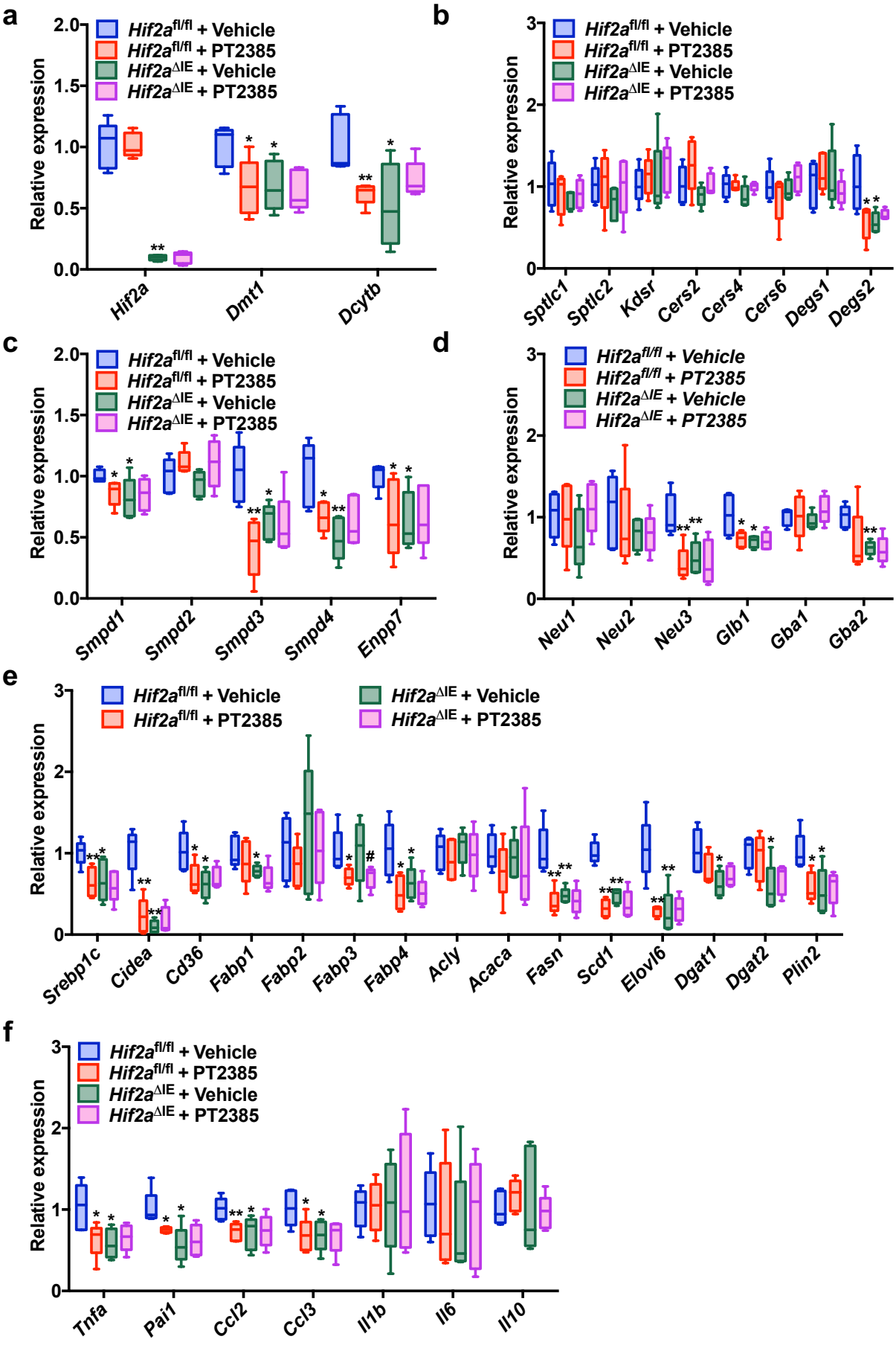
Supplementary Figure 9. PT2385 prevents mice from HFD-induced obesity and hepatic steatosis through inhibition of the intestinal HIF2α-ceramide axis in *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**a**) Growth curves. (**b**) Glucose tolerance test. (**c**) Insulin tolerance test. (**d**) Representative H&E staining of liver sections (n = 3 images/mouse). Scale bars: 100 μm. (**e**) Liver weights. (**f**) Liver weight to body weight ratios. (**g**,**h**) Liver (**g**) and serum (**h**) triglyceride content. (**i**,**j**) Liver (**i**) and serum (**j**) cholesterol content. (**k**) Serum ALT levels. (**l**) Quantitation of ceramide concentrations in the intestine. (**m**) Quantitation of ceramide concentrations in serum. n = 5/group. Data are presented as the mean ± sd. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. *$P < 0.05$, **$P < 0.01$ versus vehicle-treated *Hif2a*$^{fl/fl}$ mice, by one-way ANOVA with Tukey's correction.



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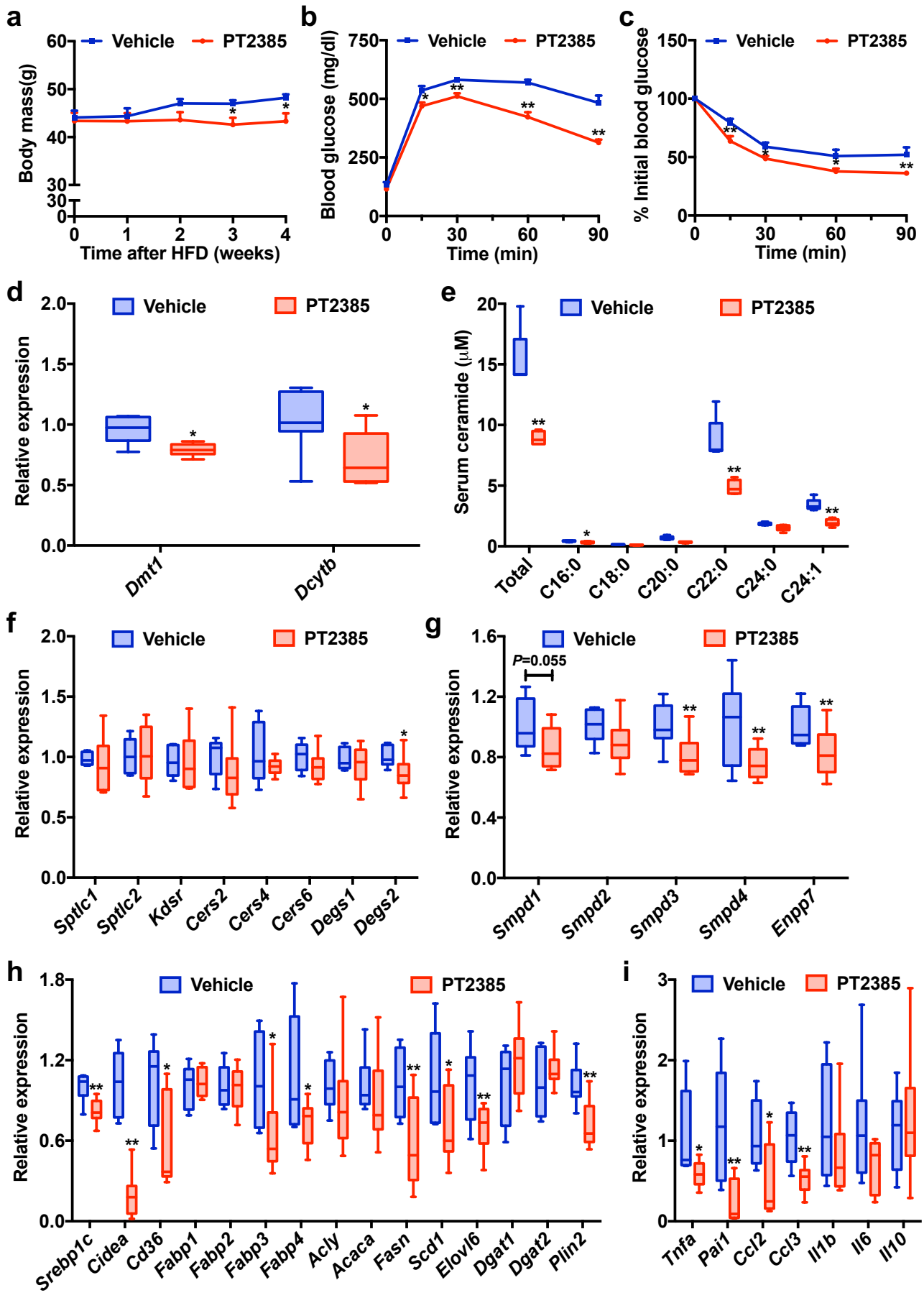
Supplementary Figure 10. PT2385 inhibits ceramide synthesis in the small intestine and alters fatty acid synthesis, metabolism, and inflammation in the liver dependent on intestinal HIF2α in *Hif2a*$^{fl/fl}$ and *Hif2a*$^{\Delta IE}$ mice. (**a**) Expression of *Hif2a* mRNA and its target gene mRNAs in the intestine. (**b–d**) Intestinal expression of mRNAs encoded by ceramide synthesis-related genes, including the *de-novo* pathway (**b**), the sphingomyelinase pathway (**c**) and the salvage pathway (**d**). (**e**) Hepatic expression of mRNAs encoding fatty acid transport and lipogenesis. (**f**) Hepatic expression of mRNAs encoding inflammatory cytokines and chemokines. $n = 5$/group. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. $^{*}P < 0.05$, $^{**}P < 0.01$ versus vehicle-treated *Hif2a*$^{fl/fl}$ mice, by one-way ANOVA with Tukey's correction.



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Supplementary Figure 11. PT2385 reverses metabolic dysfunctions in HFD-induced obese mice. (**a**) Growth curves. (**b**) glucose tolerance test. (**c**) Insulin tolerance test. (**d**) Expression levels of HIF2α target gene mRNAs in the intestine. (**e**) Quantitation of ceramide concentrations in serum. (**f**,**g**) Intestinal expression of mRNAs encoded by ceramide synthesis-related genes, including the *de novo* pathway (**f**) and the sphingomyelinase pathway (**g**). (**h**) Hepatic expression of mRNA encoding fatty acid transport and lipogenesis-related enzymes. (**i**) Hepatic expression of mRNAs encoding inflammatory cytokines and chemokines. $n = 4$ for vehicle group, $n = 5$ for PT2385 group. Data are presented as the mean ± sem. For box plots, the midline represents the median; box represents the IQR between the first and third quartiles, and whiskers represent the lowest or highest values within 1.5 times IQR from the first or third quartiles. $*P < 0.05$, $**P < 0.01$ versus vehicle treatment, by two-tailed Student's *t*-test.

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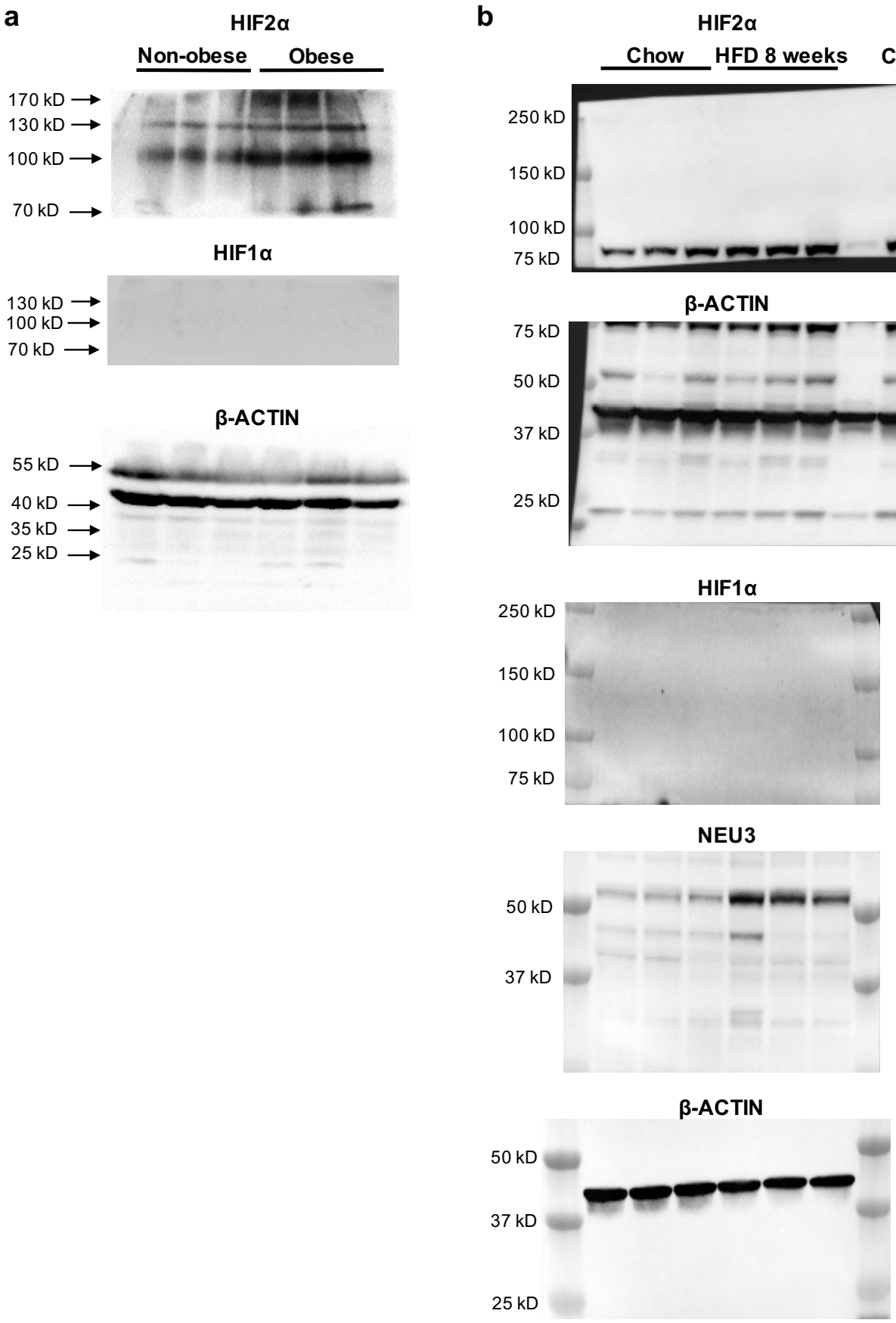

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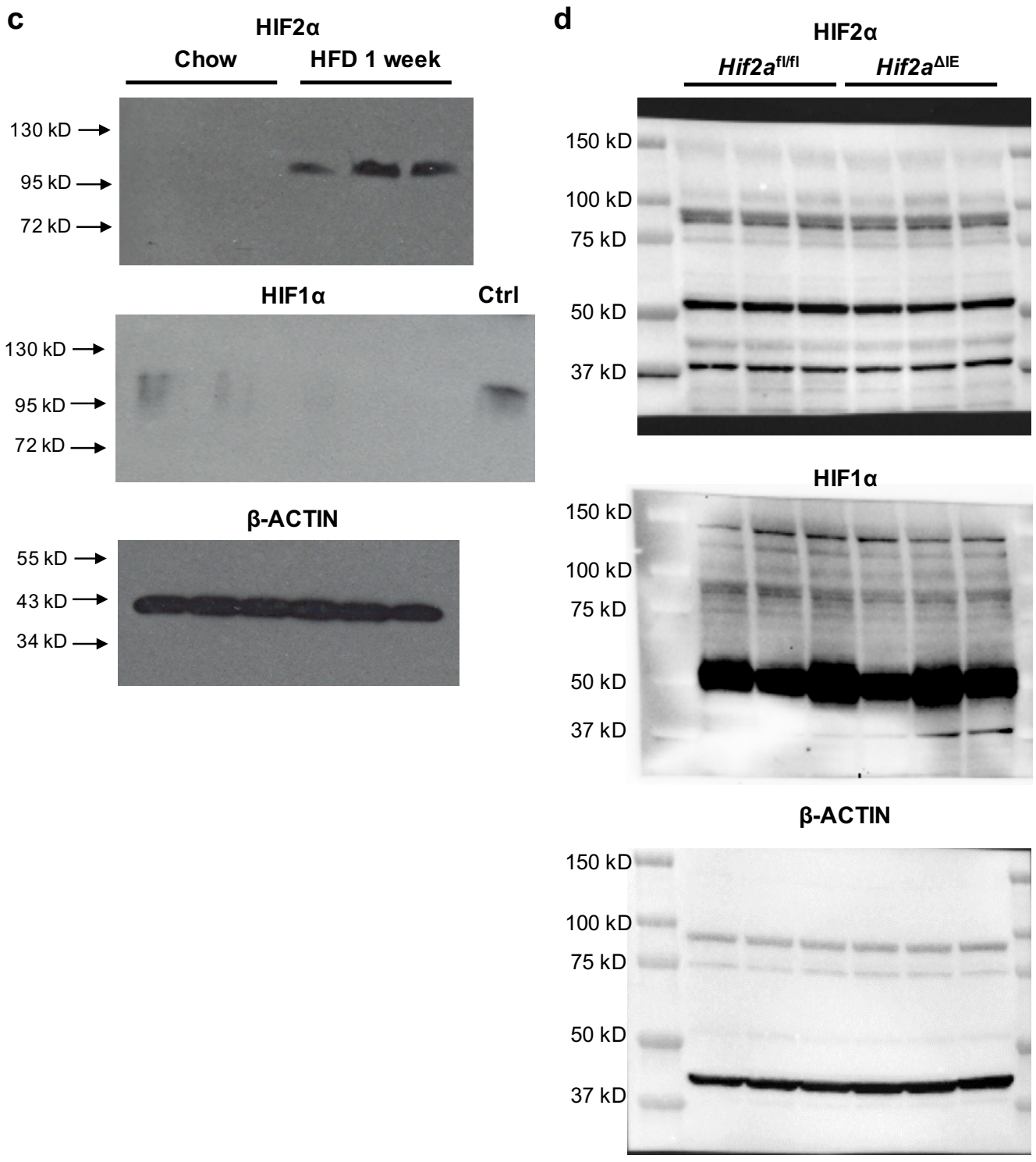

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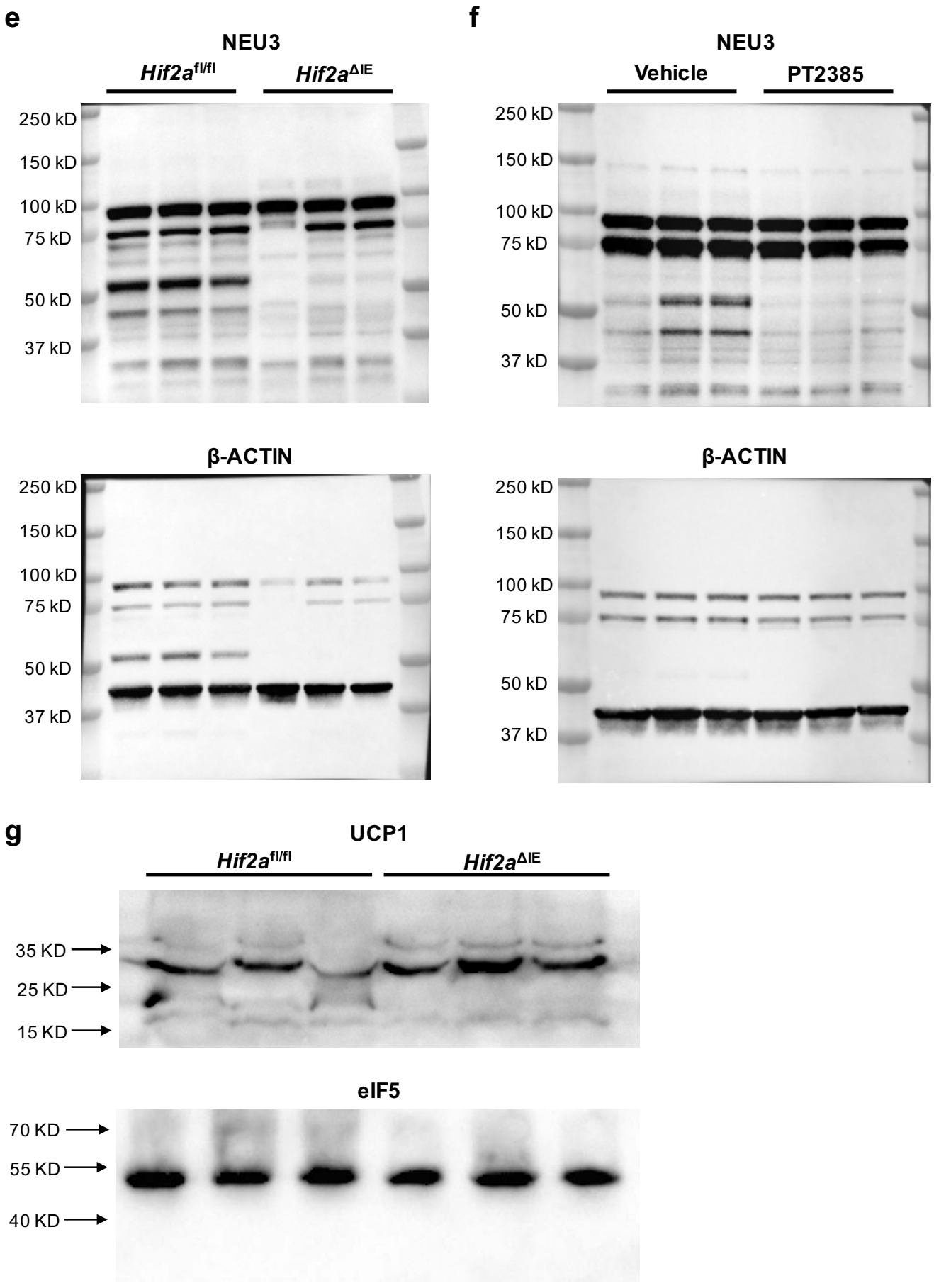

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Supplementary Figure 12. Full western blot gel panels. (**a-d**) HIF2α, HIF1α, NEU3 and β-ACTIN from which the data in **Figure 1b** (**a**), **Figure 1f** (**b**), **Supplementary Figure 1b** (**c**), **Figure 4g** (**b**) and **Supplementary Figure 2e** (**d**) were derived. (**e**, **f**) NUE3 and β-ACTIN from which the data in **Figure 4h** (**e**) and **Figure 6k** (**f**) were derived. (**g**) UCP1 and EIF5 from which the data in **Supplementary Figure 4v** were derived.

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Supplementary Table 1. Demographic characteristics of the subjects

Characteristics	Non-obese	Obese
Cohort 1 (*n* = 12)		
Gender, *n* (%)		
Male	4 (66.7)	4 (66.7)
Female	2 (33.3)	2 (33.3)
Age, *y*		
Mean (sem)	49.7 (4.8)	50.2 (6.0)
Range	29.0-61.0	23.0-63.0
Body weight, *kg*		
Mean (sem)	59.5 (2.4)	76.0 (3.2) **
Range	51.0-67.0	70.0-91.0
Body mass index, kg/m^2		
Mean (sem)	21.5 (0.6)	28.5 (0.8) **
Range	19.8-23.9	26.0-31.1
Cohort 2 (*n* = 35)		
Gender, *n* (%)		
Male	9 (50.0)	7 (41.2)
Female	9 (50.0)	10 (58.8)
Age, *y*		
Mean (sem)	57.4 (3.2)	54.7 (2.2)
Range	23.0-73.0	36.0-69.0
Body weight, *kg*		
Mean (sem)	55.7 (1.2)	82.1 (1.5) **
Range	49.0-65.0	72.0-90.0
Body mass index, kg/m^2		
Mean (sem)	20.4 (0.6)	29.8 (0.3) **
Range	15.8-25.0	28.1-32.8

**$P < 0.01$ versus Non-obese, by two-tailed Student's t-test.

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Supplementary Table 2. Clinical biochemistry of the subjects

Laboratory analytes	Non-obese	Obese	P value
Cohort 1 (*n* = 12)			
Liver enzymes, *U/L*			
ALT	13.2 (1.3)	25.0 (4.2)	0.0222
AST	17.5 (2.7)	30.3 (4.0)	0.0241
Lipids, *mM*			
Triglycerides	1.57 (0.33)	2.67 (0.44)	0.0755
Cholesterol	4.14 (0.46)	4.79 (0.32)	0.2695
HDL	1.25 (0.14)	0.99 (0.21)	0.3359
LDL	2.07 (0.45)	3.29 (0.36)	0.0615
Glucose, *mM*	5.35 (0.27)	5.39 (0.37)	0.9352
Cohort 2 (*n* = 35)			
Liver enzymes, *U/L*			
ALT	19.6 (1.4)	38.2 (4.2)	0.0001
AST	19.0 (1.4)	41.4 (4.8)	0.0001
Lipids, *mM*			
Triglycerides	1.45 (0.16)	1.79 (0.12)	0.1045
Cholesterol	3.63 (0.10)	4.22 (0.25)	0.0352
HDL	1.09 (0.04)	1.01 (0.06)	0.2630
LDL	1.99 (0.09)	2.67 (0.19)	0.0027
Glucose, *mM*	5.42 (0.18)	6.13 (0.36)	0.0798

Data are presented as mean (sem). Two-tailed Student's t-test.

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Supplementary Table 3. Primer list

Mouse primers	Sequence
β-Actin FWD	5'- GGCTGTATTCCCCTCCATCG -3'
β-Actin REV	5'- CCAGTTGGTAACAATGCCATGT -3'
Hif1a FWD	5'- ATAGCTTCGCAGAATGCTCAGA -3'
Hif1a REV	5'- CAGTCACCTGGTTGCTGCAA -3'
Hif2a FWD	5'- TGAGTTGGCTCATGAGTTGC -3'
Hif2a REV	5'- TATGTGTCCGAAGGAAGCTG -3’
Dmt1 FWD	5'- TGTTTGATTGCATTGGGTCTG -3’
Dmt1 REV	5'- CGCTCAGCAGGACTTTCGAG -3’
Dcytb FWD	5'- CATCCTCGCCATCATCTC -3’
Dcytb REV	5'- GGCATTGCCTCCATTTAGCTG -3’
Pdk1 FWD	5'- TTACTCAGTGGAACACCGCC -3’
Pdk1 REV	5'- GTTTATCCCCCGATTCAGGT -3’
Vhl FWD	5'- ACATCGTCAGGTCACTCTATGA -3’
Vhl REV	5'- CTCTTGGCTCAGTCGCTGTAT -3’
Sptlc1 FWD	5'- CGAGGGTTCTATGGCACATT-3'
Sptlc1 REV	5'- GGTGGAGAAGCCATACGAGT -3'
Sptlc2 FWD	5'- TCACCTCCATGAAGTGCATC -3'
Sptlc2 REV	5'- CAGGCGTCTCCTGAAATACC -3’
Kdsr FWD	5'- TCCAGTGGCATTGGGAAGTG -3’
Kdsr REV	5'- CTTCTCTTGTGCCTGCTTTATGA -3’
Degs1 FWD	5'- AATGGGTCTACACGGACCAG -3’
Degs1 REV	5'- TGGTCAGGTTTCATCAAGGAC -3’
Degs2 FWD	5'- AAGCCAATGGACCACAAACT -3’
Degs2 REV	5'- TGCTTGGAGAGCCCTTCTAAT -3’
Cers2 FWD	5'- AAGTGGGAAACGGAGTAGCG-3’
Cers2 REV	5'- ACAGGCAGCCATAGTCGTTC -3’
Cers4 FWD	5'- GGATTAGCTGATCTCCGCAC -3’
Cers4 REV	5'- CCAGTATGTCTCCTGCCACA -3’
Cers6 FWD	5'- AAGCCAATGGACCACAAACT -3’
Cers6 REV	5'- TGCTTGGAGAGCCCTTCTAAT -3’
Smpd1 FWD	5'- GTTACCAGCTGATGCCCTTC -3’
Smpd1 REV	5'- AGCAGGATCTGTGGAGTTG -3’
Smpd2 FWD	5'- AGCAGGATCTGTGGAGTTG -3’
Smpd2 REV	5'- CTCCAGCCATGAAGCTCAAC -3’
Smpd3 FWD	5'- CCTGACCAGTGCCATTCTTT -3’
Smpd3 REV	5'- AGAAACCCGGTCCTCGTACT -3’

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Smpd4 FWD	5'- ACCTGGCCCTCAATCCATTTG -3’
Smpd4 REV	5'- ATAGGCACAGTCCGAAGTACG -3’
Enpp7 FWD	5'- AAGCCCAGTATATGACTCCTGC -3’
Enpp7 REV	5'- ACCGTGCTGGTGGTATTGTAG -3’
Neu1 FWD	5'- GGACCGCTGAGCTATTGGG -3’
Neu1 REV	5'- CGGGATGCGGAAAGTGTCTA -3’
Neu2 FWD	5'- CACAGGCGTCCATGCTTACA -3’
Neu2 REV	5'- CTGCGTGCTCATCCGTCTT -3’
Neu3 FWD	5'- ATGGAGGCCACATTACCTGG -3’
Neu3 REV	5'- TCTGGCACCTCTCAGTAACAT -3’
Glb1 FWD	5'- GCACGGCATCTATAATGTCACC -3’
Glb1 REV	5'- GTATCGGAATGGCTGTCCATC -3’
Gba1 FWD	5'- GCCAGGCTCATCGGATTCTTC -3’
Gba1 REV	5'- CACGGGGTCAAGAGAGTCAC -3’
Gba2 FWD	5'- GGCTGTGCCGAAAGAGATTC -3’
Gba2 REV	5'- ATCCTGGGGTCCACTATCCTC -3’
Galc FWD	5'- CGCCTACGTGCTAGACGAC -3’
Galc REV	5'- ACGATAGGGCTCTGGGTAATTT -3’
Srebp1c FWD	5'- GGAGCCATGGATTGCACATT-3'
Srebp1c REV	5'- GCTTCCAGAGAGGAGGCCAG -3'
Cidea FWD	5'- TGACATTCATGGGATTGCAGAC -3'
Cidea REV	5'- GGCCAGTTGTGATGACTAAGAC -3'
Cd36 FWD	5'- AGATGACGTGGCAAAGAACAG -3’
Cd36 REV	5'- CCTTGGCTAGATAACGAACTCTG -3’
Fabp1 FWD	5'- ATGAACTTCTCCGGCAAGTACC -3’
Fabp1 REV	5'- CTGACACCCCCTTGATGTCC -3’
Fabp2 FWD	5'- GTGGAAAGTAGACCGGAACGA -3’
Fabp2 REV	5'- CCATCCTGTGTGATTGTCAGTT -3’
Fabp3 FWD	5'- GTGGAAAGTAGACCGGAACGA -3’
Fabp3 REV	5'- CCATCCTGTGTGATTGTCAGTT -3’
Fabp4 FWD	5'- AAGGTGAAGAGCATCATAACCCT -3’
Fabp4 REV	5'- TCACGCCTTTCATAACACATTCC -3’
Acly FWD	5'- ACCCTTTCACTGGGGATCACA -3’
Acly REV	5'- GACAGGGATCAGGATTTCCTTG -3’
Acaca FWD	5'- ATGGGCGGAATGGTCTCTTTC -3’
Acaca REV	5'- TGGGGACCTTGTCTTCATCAT -3’
Fasn FWD	5'- AAGTTGCCCGAGTCAGAGAACC -3'
Fasn REV	5'- ATCCATAGAGCCCAGCCTTCCATC -3'
Scd1 FWD	5'- TTCTTGCGATACACTCTGGTGC -3’

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Scd1 REV	5'- CGGGATTGAATGTTCTTGTCGT -3’
Elovl6 FWD	5'- GAAAAGCAGTTCAACGAGAACG -3'
Elovl6 REV	5'- AGATGCCGACCACCAAAGATA -3'
Dgat1 FWD	5'- GACGGCTACTGGGATCTGA -3'
Dgat1 REV	5'- TCACCACACACCAATTCAGG -3'
Dgat2 FWD	5'- CGCAGCGAAAACAAGAATAA -3'
Dgat2 REV	5'- GAAGATGTCTTGGAGGGCTG -3'
Plin2 FWD	5'- GACCTTGTGTCCTCCGCTTAT -3'
Plin2 REV	5'- CAACCGCAATTTGTGGCTC -3'
Acox1 FWD	5'- GGGCACGGCTATTCTCACAG -3’
Acox1 REV	5'- CATCAAGAACCTGGCCGTCT -3’
Acox2 FWD	5'- ACGGTCCTGAACGCATTTATG -3’
Acox2 REV	5'- TTGGCCCCATTTAGCAATCTG -3’
Cpt1 FWD	5'- GAACACAAATGTGCAAGCAGC -3’
Cpt1 REV	5'- GCCATGACCGGCTTGATCTC -3’
Cpt2 FWD	5'- CAGCACAGCATCGTACCCA -3’
Cpt2 REV	5'- TCCCAATGCCGTTCTCAAAAT -3’
Acsl1 FWD	5'- CGATGGCTGTTGGACTTTGC -3’
Acsl1 REV	5'- CACCCAGGCTCGACTGTATC -3’
Acadl FWD	5'- TCTTTTCCTCGGAGCATGACA -3’
Acadl REV	5'- GACCTCTCTACTCACTTCTCCAG -3’
Ehhadh FWD	5'- CGGTCAATGCCATCAGTCCAA -3’
Ehhadh REV	5'- TGCTCCACAGATCACTATGGC -3’
Acaa1a FWD	5'- AGGCTTCAAGAACACCACCC -3’
Acaa1a REV	5'- GGCTCCTGGCTCAAGAACAT -3’
Tnfa FWD	5'- AGGGTCTGGGCCATAGAACT -3’
Tnfa REV	5'- CCACCACGCTCTTCTGTCTAC -3’
Pai1 FWD	5'- TTCAGCCCTTGCTTGCCTC -3’
Pai1 REV	5'- ACACTTTTACTCCGAAGTCGGT -3’
Ccl2 FWD	5'- TTAAAAACCTGGATCGGAACCAA -3’
Ccl2 REV	5'- GCATTAGCTTCAGATTTACGGGT -3’
Ccl3 FWD	5'- TTCTCTGTACCATGACACTCTGC -3’
Ccl3 REV	5'- CGTGGAATCTTCCGGCTGTAG -3’
Il1b FWD	5'- AAGAGCTTCAGGCAGGCAGTATCA -3’
Il1b REV	5'- TGCAGCTGTCTAGGAACGTCA -3’
Il6 FWD	5'- TAGTCCTTCCTACCCCAATTTCC -3’
Il6 REV	5'- TTGGTCCTTAGCCACTCCTTC -3’
Il10 FWD	5'- GCTCTTACTGACTGGCATGAG -3’
Il10 REV	5'- CGCAGCTCTAGGAGCATGTG -3’

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Human primers	**Sequence**
GAPDH FWD	5'- GGAGCGAGATCCCTCCAAAAT -3'
GAPDH REV	5'- GGCTGTTGTCATACTTCTCATGG -3'
HIF1A FWD	5'- GAACGTCGAAAAGAAAAGTCTCG -3'
HIF1A REV	3'- CCTTATCAAGATGCGAACTCACA -3'
HIF2A FWD	5'- CGGAGGTGTTCTATGAGCTGG -3'
HIF2A REV	5'- AGCTTGTGTGTTCGCAGGAA -3'
DMT1 FWD	5'- GCTCTCATACCCATCCTCACATT -3'
DMT1 REV	5'- TCCATTGGCAAAGTCACTCATT -3'
DCYTB FWD	5'- GGTGTTTTCGTAAATACGCTTGG -3'
DCYTB REV	5'- ATTGCGGTCTGGTGACTATCC -3'
PDK1 FWD	5'- CTGTGATACGGATCAGAAACCG -3'
PDK1 REV	5'- TCCACCAAACAATAAAGAGTGCT -3'
NEU3 FWD	5'- AAGTGACAACATGCTCCTTCAA -3'
NEU3 REV	5'- TCTCCTCGTAGAACGCTTCTC -3'
ChIP primers	**Sequence**
NEU3 FWD	5'- TGTCAAGAGGGGCCTTTTCC -3'
NEU3 REV	5'- ACAATCACACGCAAGGACCA -3'
Construct primers	**Sequence**
Neu3 promoter *FWD*	5'- AACTCGAGCACAGACGCTGAAACGAACCC -3'
Neu3 promoter *REV*	5'- AAGGTACCTGCTGCAGTGTGTCAAGAGGG -3'
Neu3 promoter$^{\Delta HRE1}$ *FWD*	5'- CGCGCAGTCTGTGGAAGGTATCACCGCC -3'
Neu3 promoter$^{\Delta HRE1}$ *REV*	5'- TTCCACAGACTGCGCGGTGAAGGGGC -3'
Neu3 promoter$^{\Delta HRE2}$ *FWD*	5'- GAATCCATATCCCATTCTTCCCCACCTAC -3'
Neu3 promoter$^{\Delta HRE2}$ *REV*	5'- AATGGGATATGGATTCAGTACTTGGTGACAG -3'