ESM Table 1. Immunoblot antibodies.

Primary Antibody	Supplier	Dilution
Akt	Cell Signaling Technology	1:1000
Phosphorylated Akt (Ser 473)	Cell Signaling Technology	1:1000
PKCε	Cell Signaling Technology	1:1000
Na/K ATPase	Abcam Inc.	1:2000
GAPDH	Santa Cruz Biotechnology	1:3000
β-Actin	Sigma	1:5000

ESM Table 2. Quantitative PCR primer sequences.

Gene	Forward	Reverse	Ref
TBP (H)	CACAGTGAATCTTGGTTGTAAACTTGA	AAACCGCTTGGGATTATATTCG	
ANGPTL8 (H)	CTGGGCCCTGCCTACCGAGA	CCGATGCTGCTGTGCCACCA	[1]
β-actin (*Actb*) (R)	CCAGATCATGTTTGAGACCTTC	CATGAGGTAGTCTGTCAGGTCC	
Angptl8 (R)	CAGAGCCGGCCCAATATGAA	GTGCTTGGTCAAAAAGGCCC	
Cd68 (R)	CACCTGGACCTGCTCTCCCTGA	CTGGCGCAAGAGAAGCATGGC	
Angptl3 (R)	GCACCAAGAACTACTCCCCC	AAATGGCAGAGCAGTCAGCA	
Angptl4 (R)	CCTCCGAGGGGACCTTAACT	AGATTGGAATGGCTGCAGGT	
Apoc3 (R)	GAACAAGCCTCCAAGACGGT	GGGATTTGAAGCGATTGTCC	
Apoe (R)	AGTGCCCCTGGAGAATCAA	CACCTGGCTGGTCATGGAT	[2]
Apoc1 (R)	CTGATCGTGGTCGTAGCCAT	GGTAAGCTCTCCATTGCGCT	
Apoa5 (R)	GCCTGGGAAGGAGCCTCCTCGGC	GCTCCATCAGCTCGACCGTGTAGGG	[3]
Hepatic Lipase (*Lipc*) (R)	GAACACAGTGCAGACCATAATGCT	TTCAGGTCACATTTCACGAAGACTT	[4]
β-actin (*Actb*) (M)	CCAGATCATGTTTGAGACCTTC	CATGAGGTAGTCTGTCAGGTCC	
Angptl8 (M)	AGCTGACCCTGCTCTTTCAC	TGCTCTGTCATAGAGGCCCA	

ANGPTL8: Angiopoeitin-Like 8; TBP: TATA-Binding Protein; ANGPTL3: Angiopoeitin-Like 3; ANGPTL4: Angiopoeitin-Like 4; (H): Human; (R): Rat; (M): Mouse.

ESM Table 3. Additional rat WAT variables. Data are the mean ± SEM of n = 6 (plasma leptin groups), n =7 (plasma adiponectin groups), n=8 (*Cd68* expression groups).
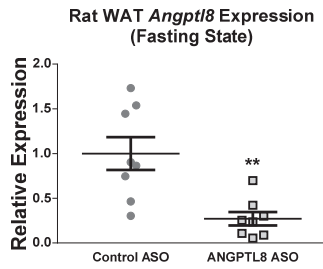
	Control ASO	ANGPTL8 ASO	*p*
Fasting Leptin (ng/mL)	1.5 ± 0.4	1.1 ± 0.4	0.51
Fasting Adiponectin (ng/mL)	12 ± 2	11 ± 2	0.78
Adipose *Cd68* Expression (Relative Expression)	1.00 ± 0.11	1.35 ± 0.12	0.05

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[2]   Yamagata K, Nakayama C, Suzuki K (2013) Dietary beta-carotene regulates interleukin-1beta-induced expression of apolipoprotein E in astrocytes isolated from stroke-prone spontaneously hypertensive rats. Neurochem Int 62: 43-49

[3]   Nowak M, Helleboid-Chapman A, Jakel H, et al. (2005) Insulin-mediated down-regulation of apolipoprotein A5 gene expression through the phosphatidylinositol 3-kinase pathway: role of upstream stimulatory factor. Molecular and cellular biology 25: 1537-1548

[4]   Mello T, Nakatsuka A, Fears S, et al. (2008) Expression of carboxylesterase and lipase genes in rat liver cell-types. Biochemical and biophysical research communications 374: 460-464

ESM Figure 1

a

Rat WAT *Angptl8* Expression (Fasting State)

b

Rat Hepatic *Angptl8* Expression · *Angptl3* · *Angptl4* · *Apoc3* · *Apoe* · *Apoc1* · *Apoa5* · *Lipc*
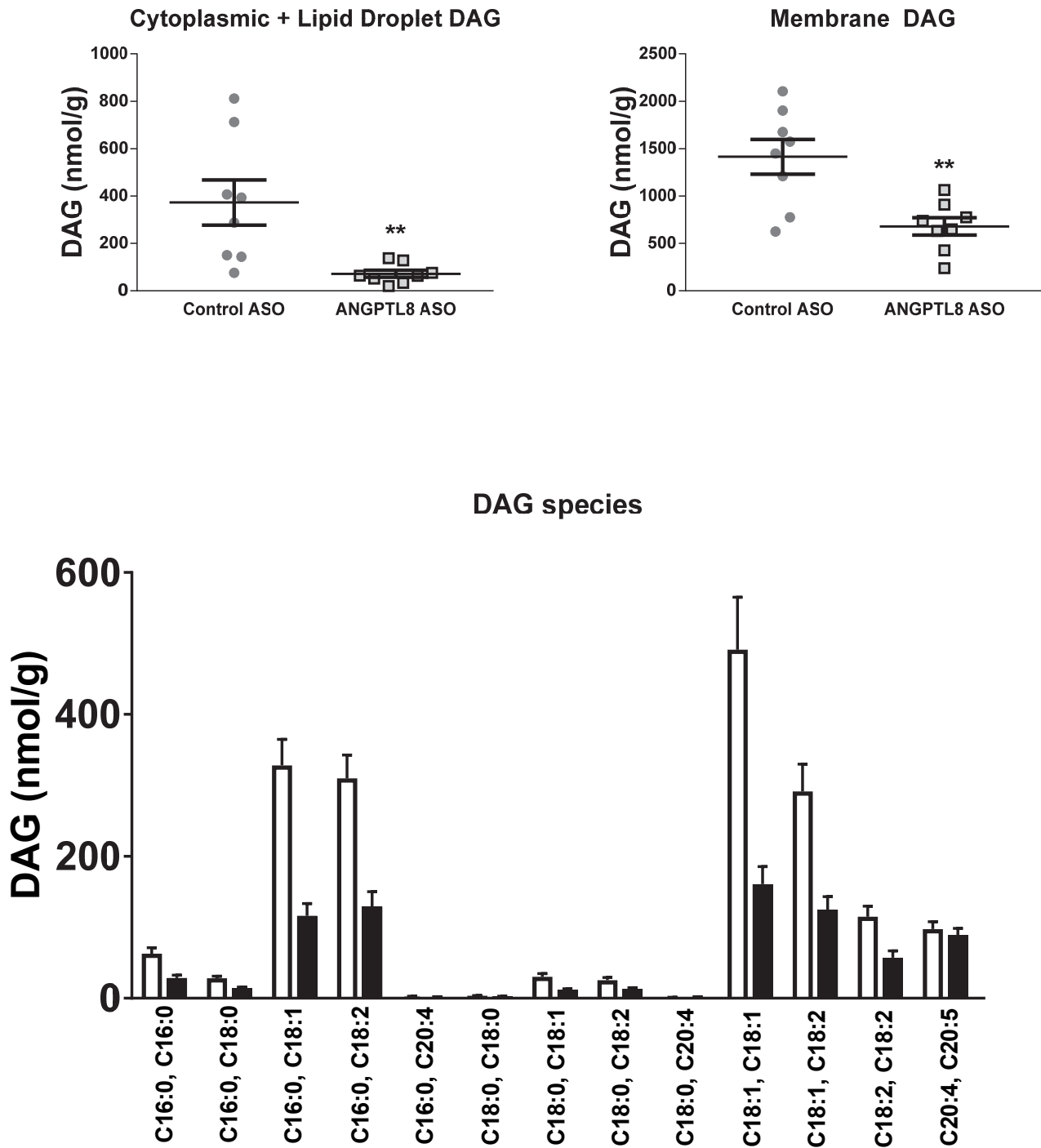
c

Body Weight
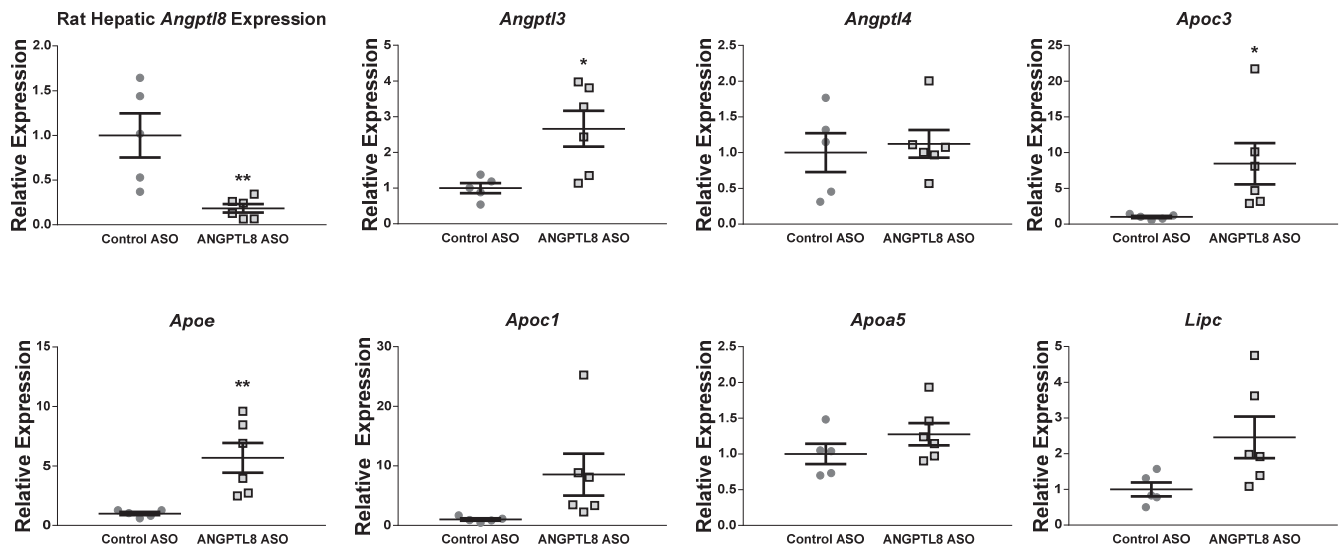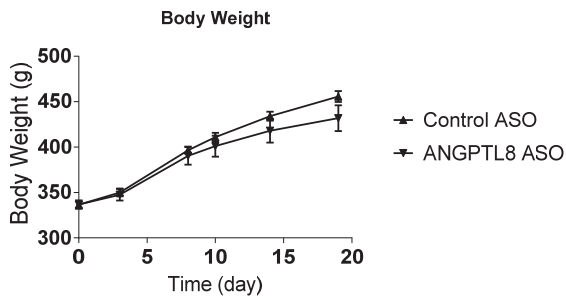
ESM Figure 1. a. Expression of *Angptl8* in rat epididymal adipose tissue assessed by qPCR. b. Rat hepatic expression of *Angptl8*, *Angptl3*, *Angptl4*, *Apoc3*, *Apoe*, *ApoC1*, *ApoA5*, and *Lipc* (Hepatic Lipase) assessed by qPCR. c. Growth curves assessed on HFD with ASO treatment. Data are the mean ± SEM of n = 5-8. * $p < 0.05$; ** $p < 0.01$.

ESM Figure 2

ESM Figure 2. **Hepatic diacylglycerol content by subcellular compartment and DAG species.** Assessed by LC-MS. For DAG species, white bars = control ASO, black bars = ANGPTL8 ASO. Data are the mean ± SEM of n = 8 (all groups).

ESM Figure 3

C16 Ceramide

C18 Ceramide

C20 Ceramide

C22 Ceramide

C24:1 Ceramide
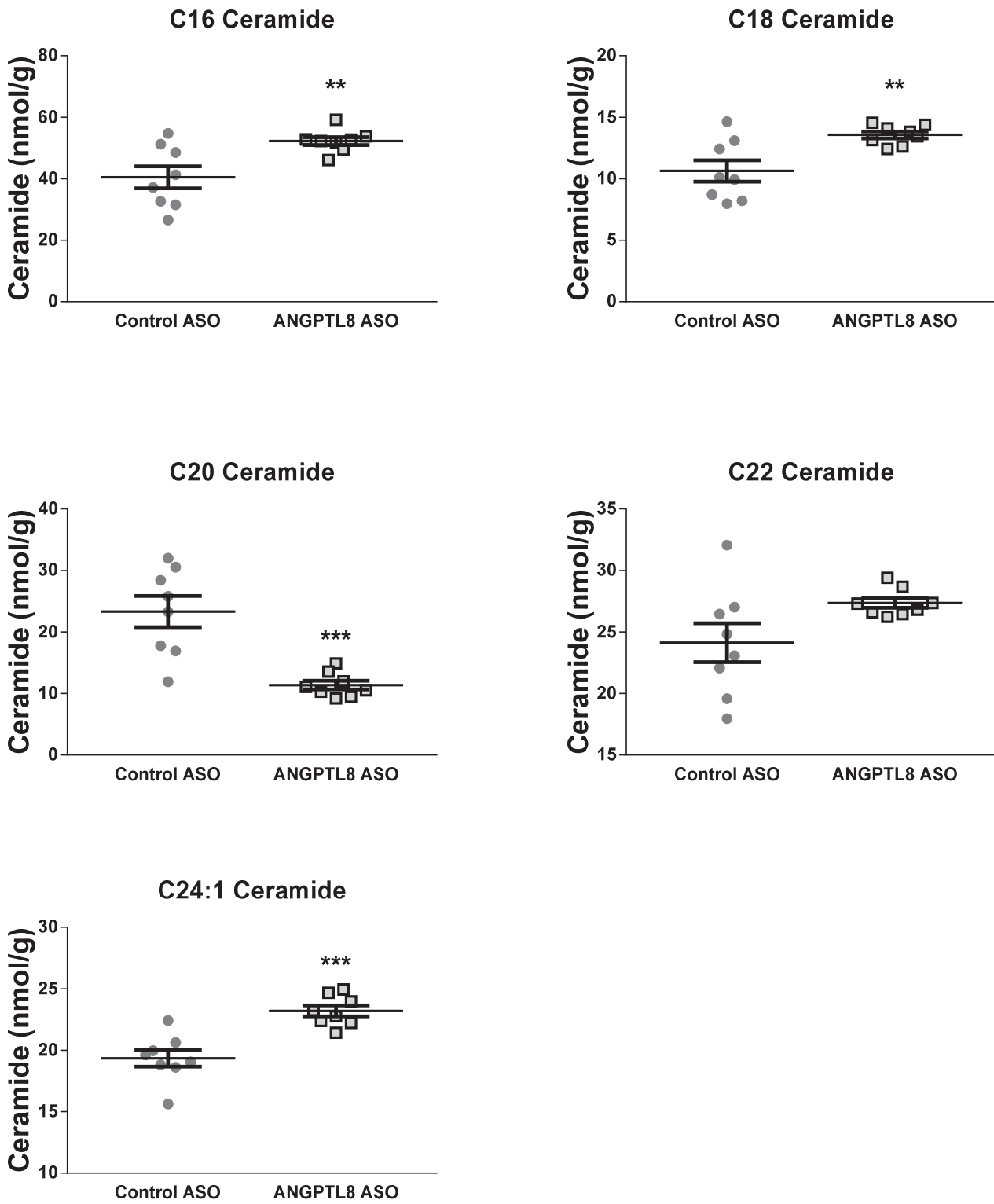
ESM Figure 3. Hepatic ceramide species. Assessed by LC-MS. Data are the mean ± SEM of n = 8 (all groups). ** $p < 0.01$; *** $p < 0.001$.

ESM Figure 4

a

**Adipose *Angptl8* Expression
Regular Chow Fed MMTT Rats**

**Adipose *Angptl8* Expression
HFD Fed MMTT Rats**

b

**Adipose *Angptl8*
Expression (Fasting State)**
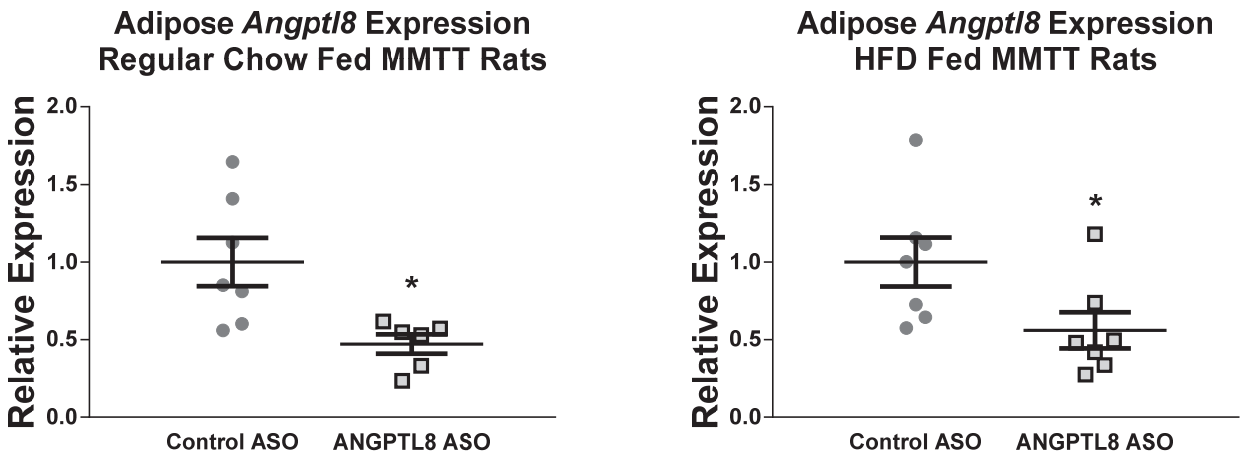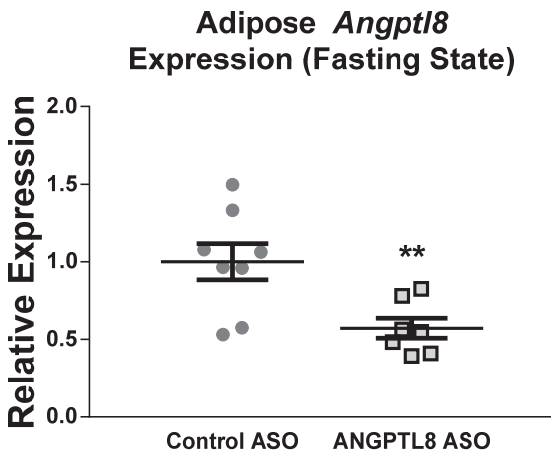
ESM Figure 4. Adipose *Angptl8* expression. a. Rat epididymal adipose *Angptl8* expression after one week ASO treatment, as assessed by qPCR. Data collected from rats studied in mixed meal tolerance tests. Data are the mean ± SEM of n = 7 (Regular Chow fed Control ASO, both groups HFD fed) or n = 6 (Regular Chow fed ANGPTL8 ASO). b. Expression of *Angptl8* in mouse epididymal adipose tissue assessed by qPCR. Data are the mean ± SEM n = 8 (control ASO) or mean ± SEM of n = 7 (ANGPTL8 ASO). * $p < 0.05$; ** $p < 0.01$.
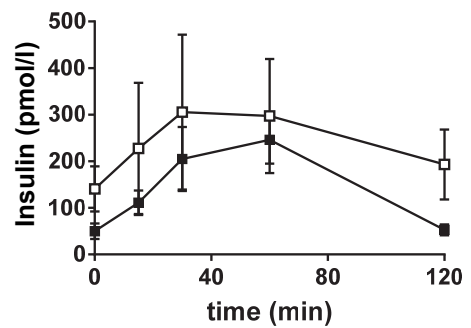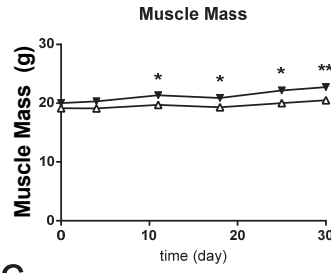
ESM Figure 5
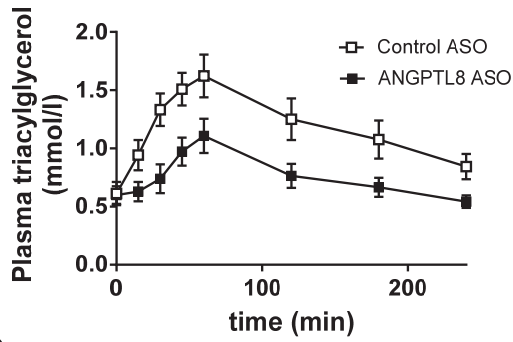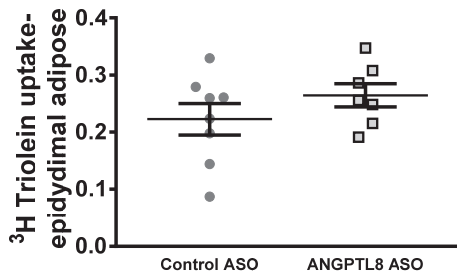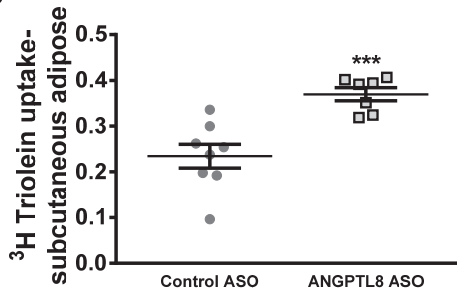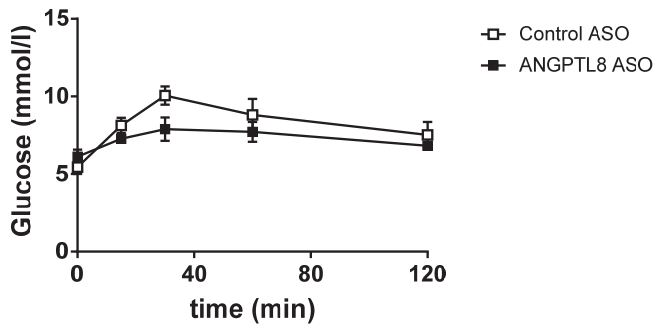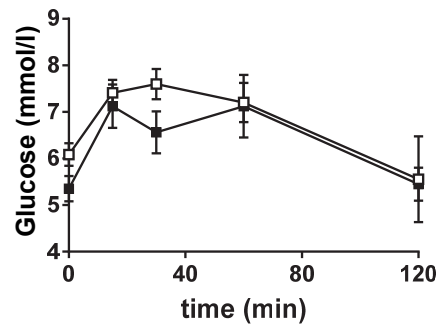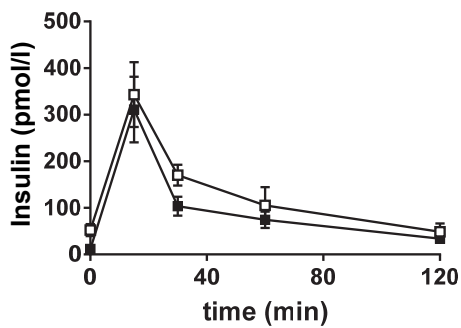
ESM Figure 5. Mixed meal tolerance test (MMTT) tissue triacylglycerol uptake. Tissue lipid uptake assessed four hours after delivery of mixed meal. Adipose tissue triacylglycerol uptake (counts per milligram tissue) is normalized to hepatic triacylglycerol uptake (counts per milligram tissue). a. Plasma triacylglycerol concentration during the MMTT in regular chow fed rats. b. Epididymal adipose and c. subcutaneous adipose triacylglycerol uptake after MMTT in regular chow fed rats. d. Plasma glucose and e. insulin concentrations during the MMTT in regular chow fed rats. f. Plasma glucose and g. insulin concentrations during the MMTT in high fat diet fed rats. Tissue triacylglycerol uptake data are the mean ± SEM of n =7-8; plasma glucose and insulin data are the mean ± SEM of n = 4-7. *** $p < 0.001$.
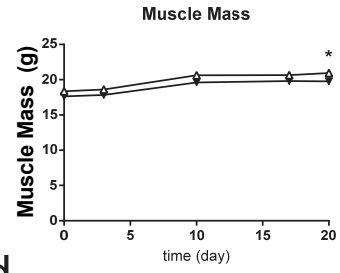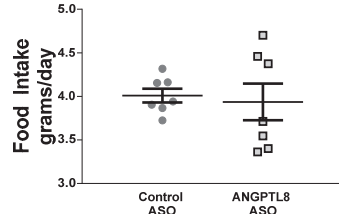
ESM Figure 6

Regular Chow Fed

High Fat Fed

a

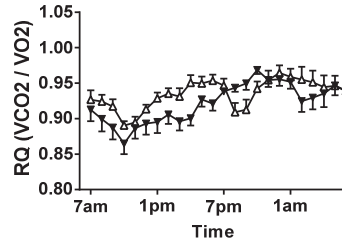**Muscle Mass**
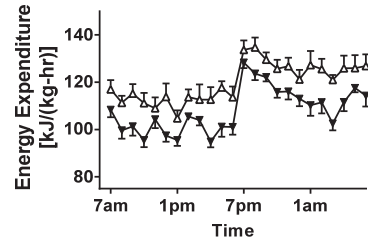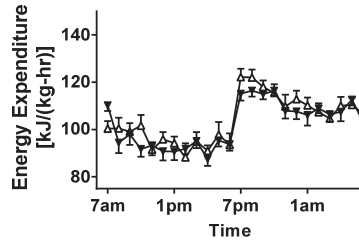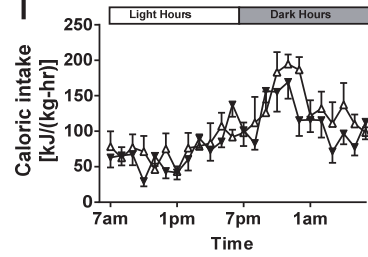
b

Muscle Mass

c

d
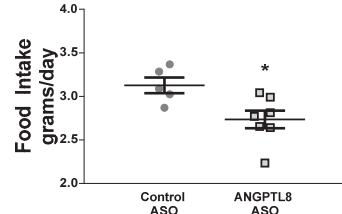
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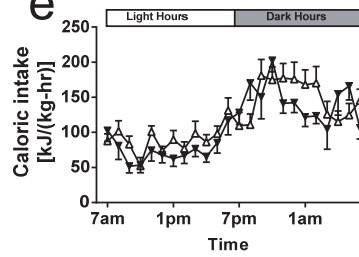
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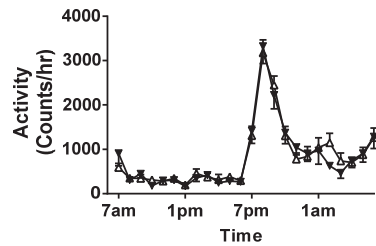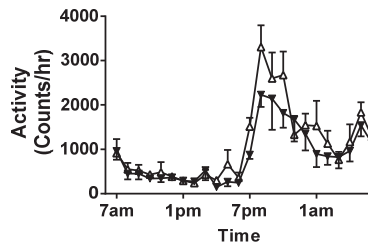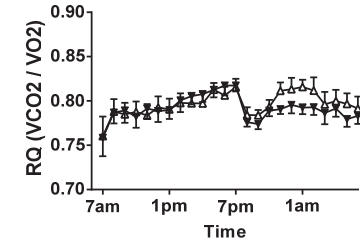
ESM Figure 6. Additional data regarding murine growth curves and energy homeostasis. Open triangles = Control ASO; Filled triangles = *Angptl8* ASO. a+b. Growth curve reproduced from Figure 6 in the main text. Muscle mass growth curve calculated from ^{1}H MRS assessment of fat mass. c+d. Averaged hourly metabolic cage data normalized to lean mass, including food intake, energy expenditure, respiratory quotient, and activity. Daily averages of food intake, energy expenditure, and Rq are represented in Figure 6. For RC fed growth curves, energy expenditure, and Rq data are the mean ± SEM of n = 8 in both groups. For HFD fed growth curves, data are the mean ± SEM of n = 7 (control ASO) or mean ± SEM of n = 8 (*Angptl8* ASO). For RC fed food intake, and HFD fed energy expenditure and Rq data are the mean ± SEM of n = 7 in both groups. For HFD fed food intake, data are the mean ± SEM of n = 5 (control ASO) or mean ± SEM of n = 7 (*Angptl8* ASO). * $p < 0.05$; ** $p < 0.01$.