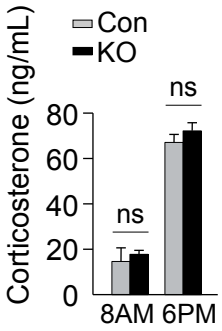


**Fig. S1**

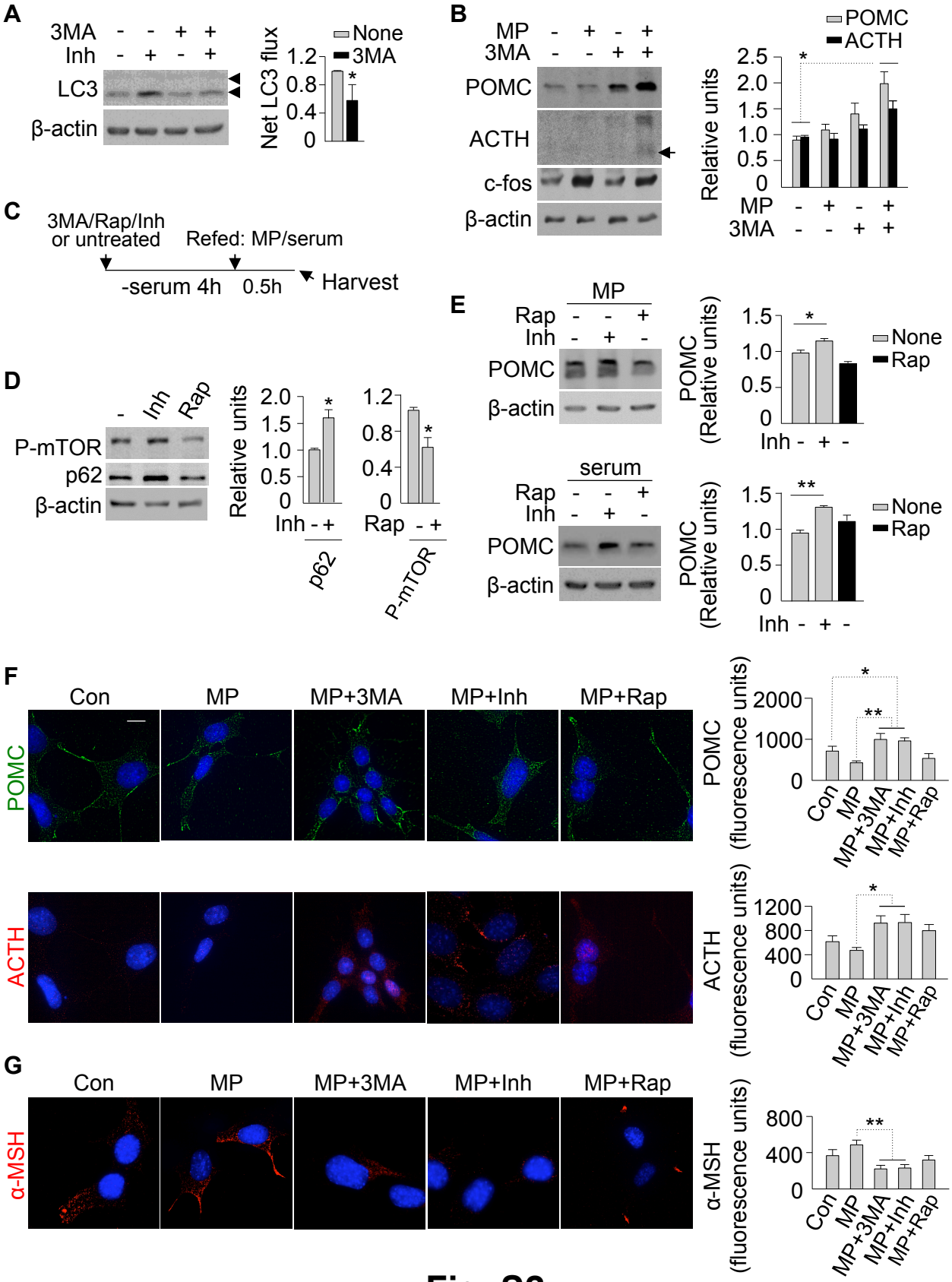
A
3MA - - + +
Inh - + - +
LC3
β-actin
Net LC3 flux
None
3MA
B
MP - + - +
3MA - - + +
POMC
ACTH
c-fos
β-actin
Relative units
C
3MA/Rap/Inh or untreated
Refed: MP/serum
-serum 4h
0.5h
Harvest
D
P-mTOR
p62
β-actin
Relative units
Inh
Rap
E
MP
Rap - - +
Inh - + -
POMC
β-actin
POMC (Relative units)
None
Rap
serum
F
Con
MP
MP+3MA
MP+Inh
MP+Rap
POMC
ACTH
(fluorescence units)
G
α-MSH

**Fig. S2**

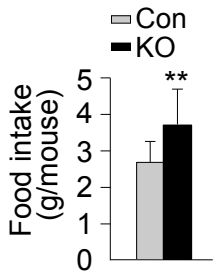


**Fig. S3**

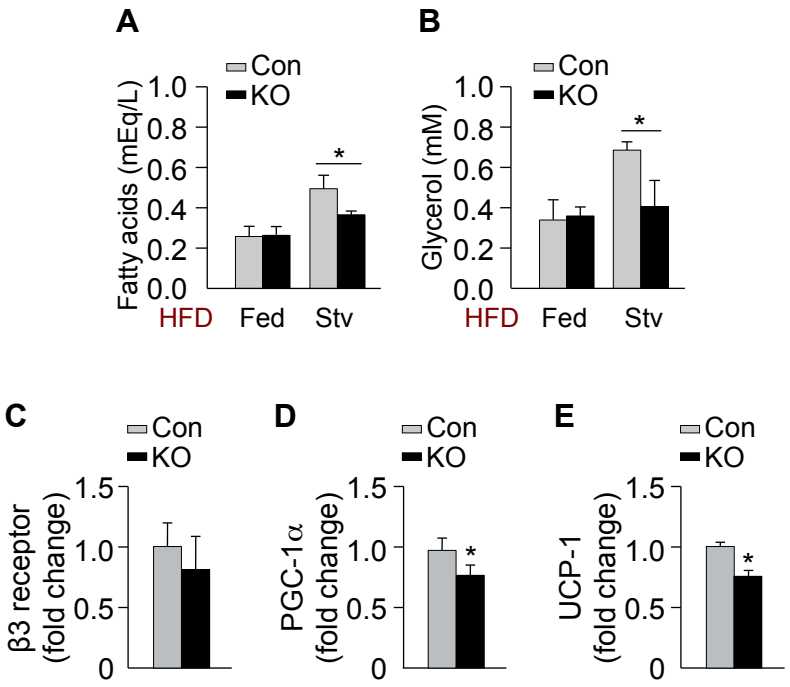
A
Con
KO
Fatty acids (mEq/L)
1.0
0.8
0.6
0.4
0.2
0.0
*
HFD
Fed
Stv
B
Con
KO
Glycerol (mM)
1.0
0.8
0.6
0.4
0.2
0.0
*
HFD
Fed
Stv
C
Con
KO
β3 receptor (fold change)
1.5
1.0
0.5
0
D
Con
KO
PGC-1α (fold change)
1.5
1.0
0.5
0
*
E
Con
KO
UCP-1 (fold change)
1.5
1.0
0.5
0
*

**Fig. S4**

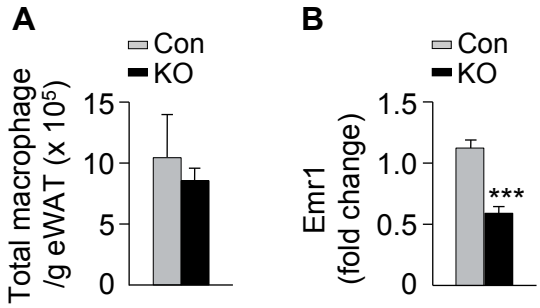
A
Con
KO
Total macrophage /g eWAT (x 10^5)
15
10
5
0
B
Con
KO
Emr1 (fold change)
1.5
1.0
0.5
0
***

**Fig. S5**

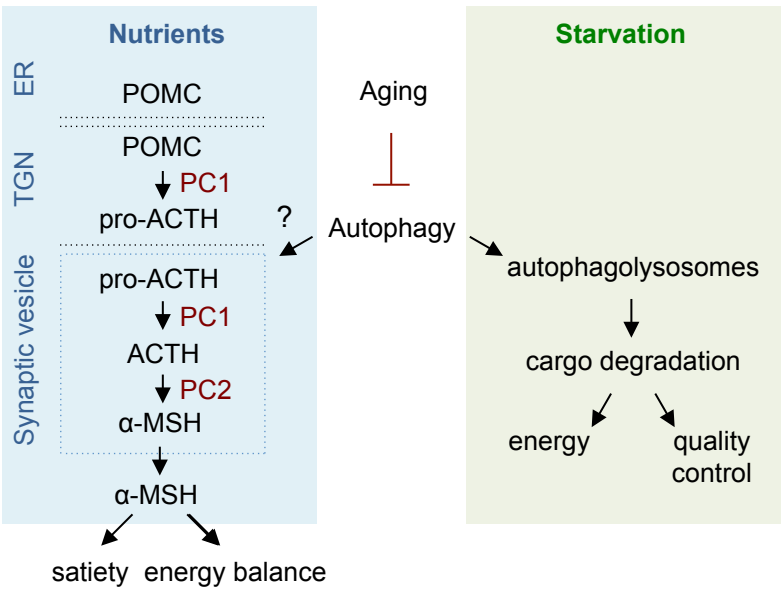
Nutrients
ER
TGN
Synaptic vesicle
POMC
POMC
PC1
pro-ACTH
?
pro-ACTH
PC1
ACTH
PC2
α-MSH
α-MSH
satiety
energy balance
Aging
Autophagy
Starvation
autophagolysosomes
cargo degradation
energy
quality control

**Fig. S6**

**Supplementary Information**

**Fig S1** Corticosterone levels in 8AM and 6PM plasma samples from 4mo old RD-fed control (Con) and KO mice, (n=5-6). Values are mean±SEM. *P* values are as compared to diet- and age-matched controls. ns, not statistically significant.

**Fig S2** (A) LC3 immunoblots in 3-methyladenine (3MA)-treated or -untreated N41 hypothalamic cells cultured in presence or absence of lysosomal inhibitors, ammonium chloride and leupeptin (Inh), (n=3). *P* value is as compared to 3MA-untreated sample; **P*<0.05. (B) Immunoblotting for POMC, ACTH, and c-fos in lysates from N41 cells pretreated with 3MA or none and exposed to methylpyruvate (MP) (n=3), as depicted in Fig S2C. *P* value is as compared to untreated control; **P*<0.05. (C) General scheme for experiments in Fig S2B, S2E, S2F, and S2G. (D) Immunoblotting for P-mTOR, and p62 in N41 cells exposed to rapamycin (Rap) or Inh, (n=3). *P* value is as compared to Inh-untreated or Rap-untreated control; **P*<0.05. (E) Immunoblotting for POMC in serum-starved N41 cells refed MP or serum following pretreatment with Rap or Inh (n=3), as shown in Fig S2C. *P* value is as compared to Inh-untreated cells; **P*<0.05, ***P*<0.01. (F) Indirect immunofluorescence for POMC, and ACTH in serum-starved N41 cells refed MP following pretreatment with 3MA, Rap or Inh (n=3), as in Fig S2C. *P* value is as compared to untreated or MP-treated cells; **P*<0.05, ***P*<0.01. (G) Indirect immunofluorescence for α-MSH in serum-starved N41 cells (n=3), with treatments as indicated in Fig S2C. All values for Fig S2 are mean±SEM. *P* values are as compared to MP-treated cells; ***P*<0.01.

**Fig S3** Food intake over 24h by Con and KO mice on RD (n=29-34). Values are mean±SEM. *P* values are as compared to diet- and age-matched controls; ***P*<0.01.

**Fig S4** (A) Serum fatty acids, and (B) glycerol from fed or 6h-fasted Con and KO mice on HFD for 10mo (n=7-9). (C) Messenger RNA (fold change) for β3-adrenergic receptor, (D) PGC-1α**,** and (E) UCP-1 in eWAT from 4mo old RD-fed Con and KO mice (n=4). Values are mean±SEM. *P* values are as compared to diet- and age-matched controls; **P*<0.05.

**Fig S5 (A)** Total macrophage count, and (B) relative mRNA (fold change) for *Emr1* in eWAT from 4mo old RD-fed Con and KO mice (n=4). Values are mean±SEM. *P* values are as compared to diet- and age-matched controls; ****P*<0.001.

**Fig S6** POMC precursor is processed to generate α-MSH via successive steps in the endoplasmic reticulum (ER), trans-golgi network (TGN) and in synaptic vesicles, and requires a number of peptidases, including proprotein convertases-1 (PC1), and -2 (PC2). Nutrient signals may initiate an unconventional form of autophagy in POMC neurons wherein autophagy components are functionally diverted toward POMC processing and α-MSH production, and possibly, α-MSH

secretion to generate satiety, whereas starvation activates the canonical autophagy pathway resulting in turnover of cellular contents.

**Supplementary Methods**

**Body composition**

Body composition was determined by an ECHO magnetic resonance spectroscopy instrument (Echo Medical Systems, Houston, TX, USA).

**Food intake measurements**

Mice were housed in individual cages and allowed to adjust for 1 week, following which daily food consumption was measured.

**Protein oxidation analysis**

Adipose protein oxidation was determined by the Oxyblot kit (Millipore, Billerica, MA, USA) as per the manufacturer's instructions. Oxyblot membranes (Whatman, Dassel, Germany) were exposed to secondary antibodies (Millipore), and signals detected using chemiluminescence (PerkinElmer, Waltham, MA, USA).

**Stromal vascular fraction preparation and Flow cytometry**

Finely minced adipose tissues were placed in HEPES-buffered DMEM containing low fatty acid bovine serum albumin (10mg/ml) (US Biological, Swampscott, MA, USA) and then centrifuged to precipitate erythrocytes and additional blood cells. Samples were treated with Liberase (0.05mg/mL) (Roche, Indianapolis, IN, USA), incubated at 37°C for 20min, and then passed through a sterile 250μm mesh (Sefar America Inc., Depew, NY, USA). Suspensions were then centrifuged, and the precipitated cells were collected as the stromal vascular fraction (SVF). The SVF cell pellets were resuspended in erythrocyte lysis buffer. These were then centrifuged, and pellets resuspended in FACS buffer. For flow cytometry, cells were treated with anti-mouse CD16/32 and then stained with APC-labeled anti-mouse F4/80 and APC-Cy7-labeled anti-mouse CD11c. 7-AAD was used to exclude dead cells.

**Biochemical analyses**

Blood glucose levels were determined using an Ascensia Contour glucometer (Bayer, Pittsburgh, PA, USA). Serum insulin levels were detected by radioimmunoassay as described previously [1]. Commercial kits from Wako (Richmond, VA, USA) and Sigma Aldrich were used to measure serum free fatty acids and glycerol, and liver triglycerides, respectively. Serum corticosterone levels were measured by a commercial kit from Cayman Chemicals (Ann Arbor , MI).

**Supplementary References**

1. Singh R *et al* (2009) Autophagy regulates adipose mass and differentiation in mice. *The Journal of clinical investigation* **119:** 3329-3339