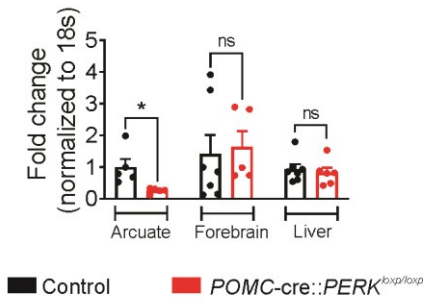
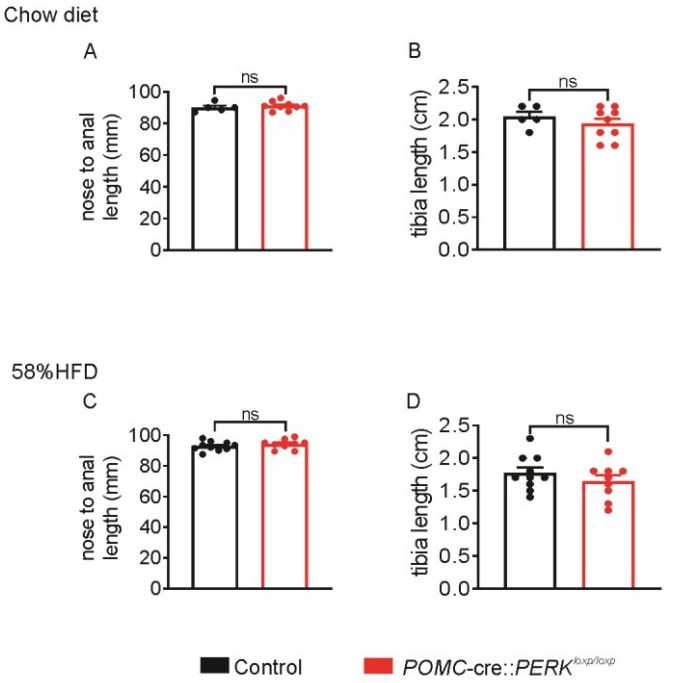


Supplement Figure 1

Figure S1: qPCR validation of PERK specific deletion in arcuate POMC neurons

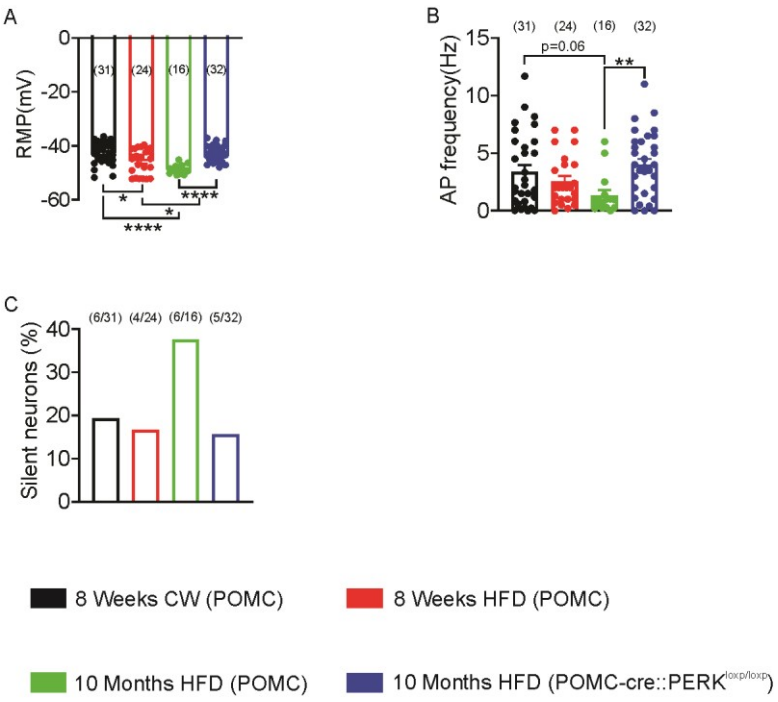
(A) qPCR detection of PERK mRNA expression in the arcuate nucleus of hypothalamus, forebrain, and liver, of mice with POMC neuron-specific deficiency of PERK (POMC-cre::PERK$^{loxp/loxp}$) and littermate controls (POMC-cre::PERK$^{+/+}$). Black bars: littermate control mice. Red bars: POMC-cre::PERK$^{loxp/loxp}$ mice. Data are from male mice (n=5-7, per group) analyzed using unpaired t-test and are expressed as mean ± SEM; *$p < 0.05$.



Supplement Figure 2

Figure S2: Body length of male POMC-cre::PERK$^{loxp/loxp}$ mice

(A) Body length of male POMC-cre::PERK$^{loxp/loxp}$ mice on a chow diet at 48 weeks. (B) Tibia length of male POMC-cre::PERK$^{loxp/loxp}$ mice on a chow diet at 48 weeks. (C) Body length of male POMC-cre::PERK$^{loxp/loxp}$ mice on a 58% HFD at 48 weeks. (D) Tibia length of male POMC-cre::PERK$^{loxp/loxp}$ mice on a 58% HFD at 48 weeks (Black bars: WT mice. Red bars: POMC-cre::PERK$^{loxp/loxp}$ mice, n = 5-10, per group). Data are from male mice are expressed as mean ± SEM. Unpaired t-test.

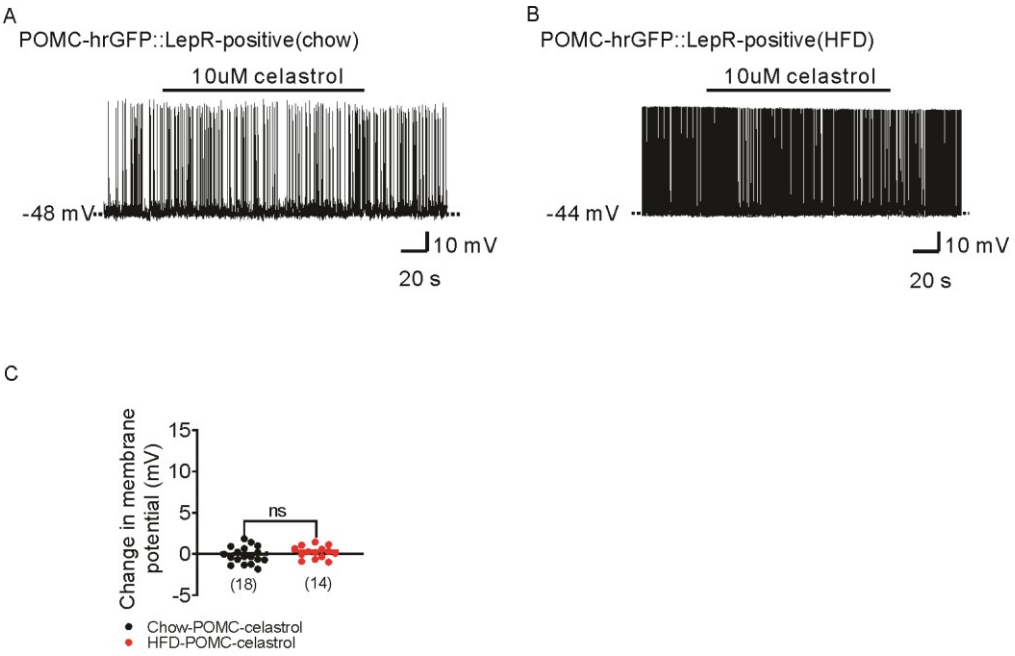


Supplement Figure 3

Figure S3: PERK deletion in POMC neurons depolarized resting membrane potential and activated POMC cells from mice on HFD

Histogram shows the resting membrane potential (A), action potential frequency (B) and percentage silent neurons; F < 0.5 Hz (C) of POMC neurons from POMC-cre::PERK$^{loxp/loxp}$::tdtomato mice and LepR-expressing POMC neurons control mice (Black: LepR-expressing POMC neurons from control mice fed chow diet for 8 weeks, n=31, Red: LepR-expressing POMC neurons from control mice fed HFD for 8 weeks, n=24, Green: LepR-expressing POMC neurons from mice fed HFD for 10 months, n=16, Blue: POMC-

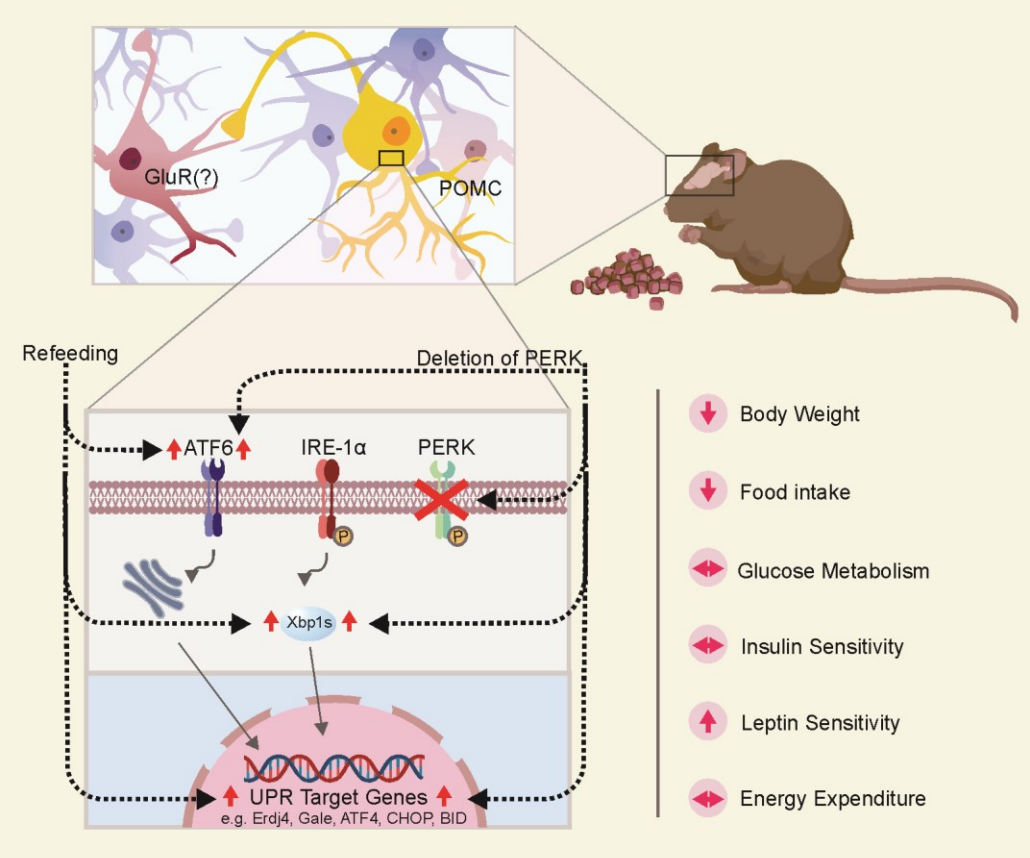
cre::PERK$^{loxp/loxp}$::tdtomato mice fed HFD for 10 months, n=32). Data are expressed as mean ± SEM, Unpaired t-test, **p<0.01; ****p<0.0001.



Supplement Figure 4

Figure S4: Acute Celastrol administration fails to alter POMC activity.

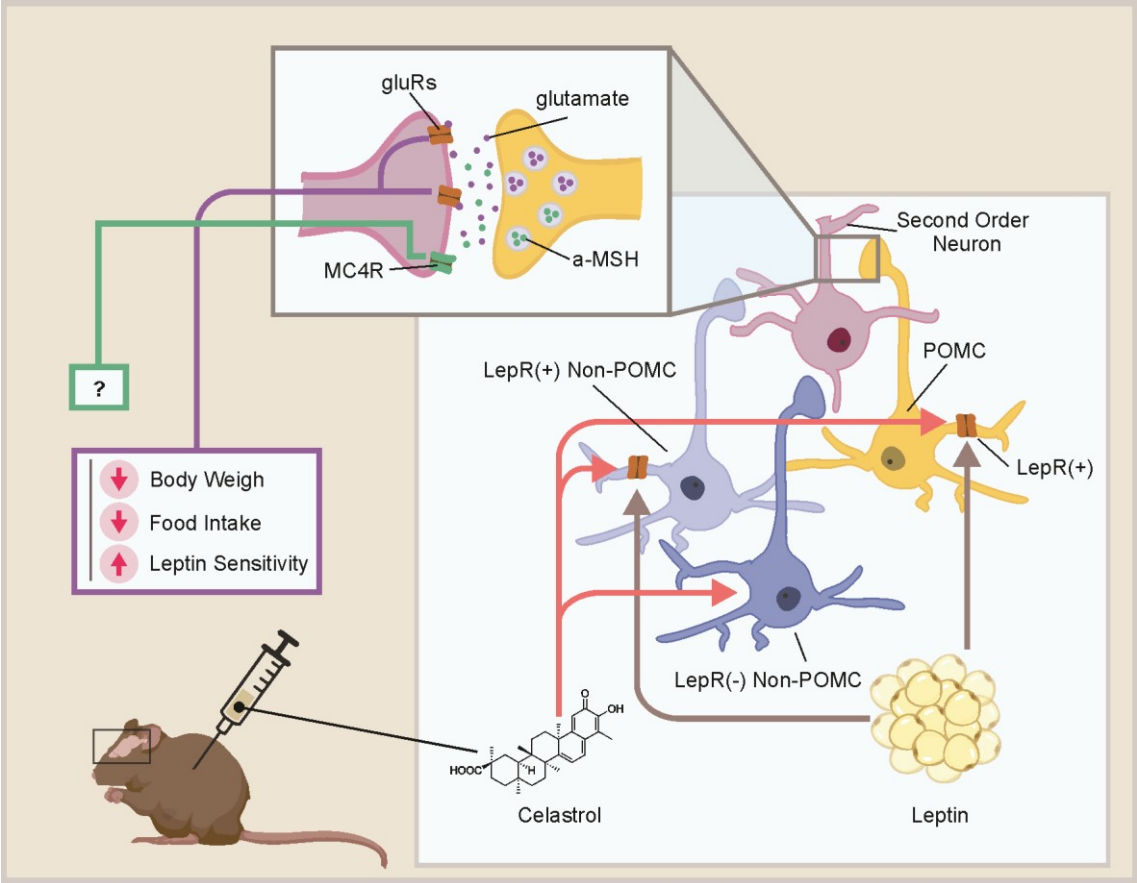
(A and B) Electrophysiological recordings demonstrate acute Celastrol (10uM) application fails to alter the resting membrane potential of LepR-expressing POMC neurons from either chow diet (A) or HFD (B) fed mice. (C) Histogram summarizing the acute effect of Celastrol (10uM) on the membrane potential of LepR-expressing POMC neurons from either chow or HFD fed mice (black dots: Celastrol application on LepR-expressing POMC neurons from chow fed mice, n=18; red dots: Celastrol application on LepR-expressing POMC neurons from HFD fed mice, n=14). Data are from male mice expressed as mean ± SEM. Unpaired t-test.



Supplement Figure 5

Figure S5: Physiological requirement of PERK in POMC neurons

Celastrol selectively inhibits the phosphorylation of PERK within the hypothalamus independent of other ER stress/UPR pathways (17). In the current study, we found that selective deficiency of PERK within POMC neurons, alone, mimics this effect of Celastrol. In particular, mice deficient for PERK in POMC neurons exhibited a lowered body weight largely dependent upon decreased food intake and increased systemic leptin sensitivity. Deletion of PERK from POMC neurons also resulted in a transcriptional program that was reminiscent of a post-prandial state, which may also contribute to the improvements in metabolism.



Supplement Figure 6

Figure S6: Pharmacological requirement of PERK in POMC neurons

In the current study, we found that Celastrol required PERK in POMC neurons, at least in part to mediate its beneficial effects on metabolism. PERK in POMC neurons was also required for the Celastrol-induced improvements of leptin sensitivity, both at the cellular and systems level. This highlights an important role of POMC neurons, mediating certain beneficial effects of Celastrol. Interestingly, the Celastrol-induced improvements in energy balance occur independent of MC4R and possibly LEPR signaling (33). Although Celastrol may work independent of MC4R receptors (33), these data cannot exclude the possibility of other receptors, such as receptors

for glutamate (gluRs), in mediating these observed effects downstream of POMC neurons. It is important to note that these data also do not preclude the possibility of other cell populations in this response, as PERK in POMC was partially required for these effects. Thus, based on previous and current experimental results we provide the current model for Celastrol action via PERK activity.

Supplemental Table 1: Primer sequences used for real-time quantitative polymerase chain reaction

Gene	Primer sequence	Ascension #
PEPCK - phosphoenolpyruvate carboxykinase 1 (Pck1)	5'TGACAACTGTTGGCTGGCTC 5'GACATACATGGTGCGGCCTT	NM_011044
G6P - Glucose-6- phosphatase (G6pc)	5'GGCGCAGCAGGTGTATACTA 5'ATGCCTGACAAGACTCCAGC	NM_008061
HNF4α - Hepatic nuclear factor 4, alpha (Hnf4a)	5'GCATGGATATGGCCGACTAC 5'TGTGGTTCTTCCTCACGCTC	NM_008261
Pyruvate carboxylase (Pcx)	5'GTGAGATTGCCATCCGAGTG 5'TCTGCTCGCTCTGAGAGGAA	NM_008797
Fox01- Forkhead box protein 01	5'GTGAACACCATGC 5'CACAGTCCAAGCG	NM_019739
Eif2aK3 - Eukaryotic Translation Initiation Factor 2AK3, PKR-like endoplasmic reticulum (ER) kinase (PERK)	5'TGGAATGACATGAAGTACTCAGG ATAC 5'CCACCACGACCCATGCA	NM_010121
Xbp1 - X-box binding protein 1	5'ACATCTTCCCATGGACTCTG 5'TAGGTCCTTCTGGGTAGACC	NM_013842
s-Xbp1 – spliced- X-box binding protein 1	5′GGTCTGCTGAGTCCGCAGCAGG 5′GAAAGGGAGGCTGGTAAGGAAC	NM_0133842

Erdj4 - heat shock protein family (Hsp40) member B9 (Dnajb9)	5’CTTAGGTGTGCCAAAGTCTGC 5’GGCATCCGAGAGTGTTTCATA	NM_013760
GalE - UDP-galactose-4-epimerase	5’CCATAACGCCATT 5’TCCAGAGGCTTCT	NM_001356493.1
Atf4 - activating transcription factor 4	5′CATGCCAGATGAGCTCTTGA 5′GCCAATTGGGTTCACTGTCT	NM_009716.2
Atf6 - activating transcription factor 6	5'CAGAAGTATGGGTTCGGATATCG 5'TGGCCTCCAGTCCTAGCAT	NM_001081304
Chops - CCAAT-enhancer-binding protein homologous protein, DNA-damage inducible transcript 3 (Ddit3)	5’ATATCTCATCCCCAGGAAACG 5’TCTTCCTTGCTCTTCCTCCTC	NM_007837
Bip – Binding immunoglobulin Protein, heat shock protein 5 (Hspa5)	5’GCTTCCGATAATCAGCCAACTG 5’GATTGTCTTTTGTTAGGGGTCG	NM_022310
EDEM1 - ER degradation enhancer, mannosidase alpha-like 1	5′TCTCTCCTGGTGGAATTTGG 5′AATGGCCTGTCTGGATGTTC	NM_138677

18s - 18S ribosomal RNA	5' ACCGCAGCTAGGAATAATGGA 5' GCCTCAGTTCCGAAAACCA	X00686, M10098

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