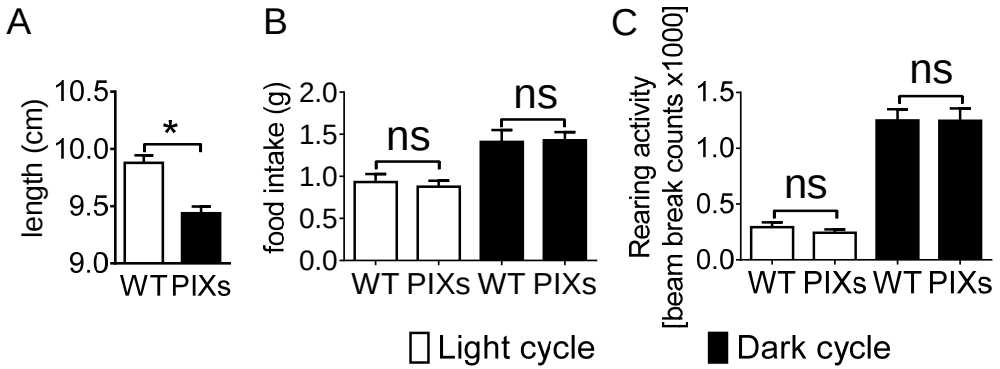
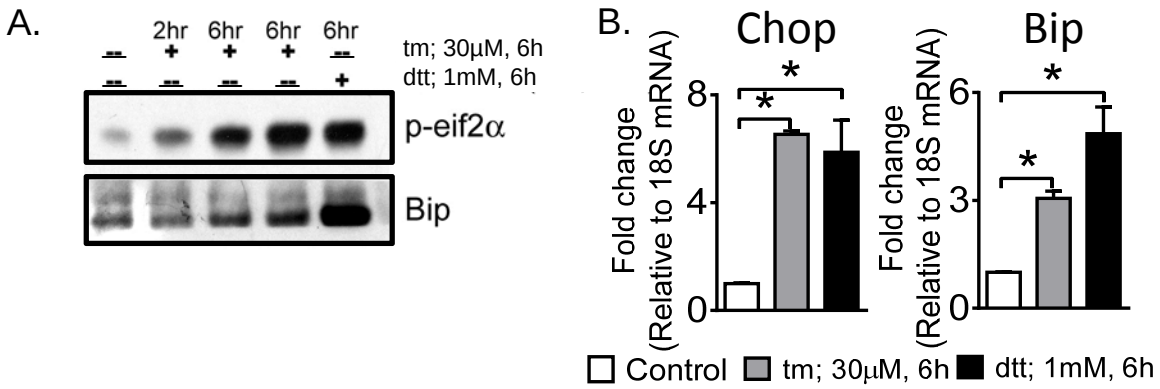
Supplementary Figure 1 (related to Figure 1). Metabolic assessment of *PIXs* mice (A) Snout-anus length in 25-week-old male anaesthetized mice (male wt, n = 7; *PIXs*, n = 6; $p < 0.05$). (B) Food intake was measured in 8-week-old weight matched male wild-type (n = 14) and *PIXs* (n = 14) for a week and is expressed here as 24 hr food intake. (C) Rearing activity as measured by beam break counts. *$P < 0.05$ compared with control. Error bars indicate SEM.



Supplemental Figure 1

Supplemental Figure 2 (related to Figure 6). Activation of ER stress blunts multiple signaling cascades activated by leptin. A. Slices were treated with saline (6h), tunicamycin (30μM; 2h or 6h), or dtt (1mM; 6h). Protein extracts were examined for expression of phospho-eif2α and Bip, known targets of the UPR. B. Relative mRNA expression of *Bip* and *Chop* in organotypic slices following pretreatment with tm (30μM; 6h), or dtt (1mM; 6h). *P < 0.05. Error bars indicate SEM.



Supplemental Figure 2

Supplemental Figure 3 (related to Figure 7). ER stress blunts acute leptin and insulin signaling in *Pomc* neurons from organotypic hypothalamic slices. Whole-cell recordings were performed on organotypic hypothalamic slices containing *Pomc*-GFP neurons within the arcuate nucleus. A. Histogram demonstrating the average cell size (as measured by whole cell capacitance) and whole cell input resistance between identified *Pomc* neurons from an organotypic and acute hypothalamic slice preparation. The resting membrane potential, whole-cell input resistance, and average cell size as measured by whole cell capacitance were not altered in *Pomc* neurons from organotypic slices as compared to *Pomc* neurons from an acute slice preparation. B. Plot demonstrates the resting membrane potential of *Pomc* neurons from organotypic and acute hypothalamic slices were similar. Moreover the leptin-induced activation of arcuate *Pomc* neurons was observed in the two preparations. Leptin (100nM) superfusion resulted in a similar depolarization of arcuate *Pomc* neurons from an acute hypothalamic slice preparation compared to the organotypic slice preparation. C. Plot shows that chemical activation of ER stress with tm (30μM, 6h) or tg (15μM, 6h) blunts the leptin induced depolarization of arcuate *Pomc* neurons. Pretreatment with tm (30μM, 6h; $t_{(12)} = 7.799$) and tg (15μM, 6h; $t_{(16)} = 9.305$) blunted the acute effects of leptin on arcuate *Pomc* neurons from organotypic hypothalamic slices. D. Histogram demonstrates (30μM, 6h) or tg (15μM, 6h) blunts the insulin-induced hyperpolarization of arcuate *Pomc* neurons. *$P < 0.05$. Error bars indicate SEM. Insulin (50nM) superfusion resulted in a similar hyperpolarization of arcuate *Pomc* neurons from an acute hypothalamic slice preparation compared to the organotypic slice preparation. Pretreatment with tm (30μM, 6h; $t_{(9)} = 5.474$) and tg (15μM, 6h; $t_{(8)} = 5.043$) also prevented the insulin-induced hyperpolarization of arcuate *Pomc* neurons from organotypic hypothalamic slices.

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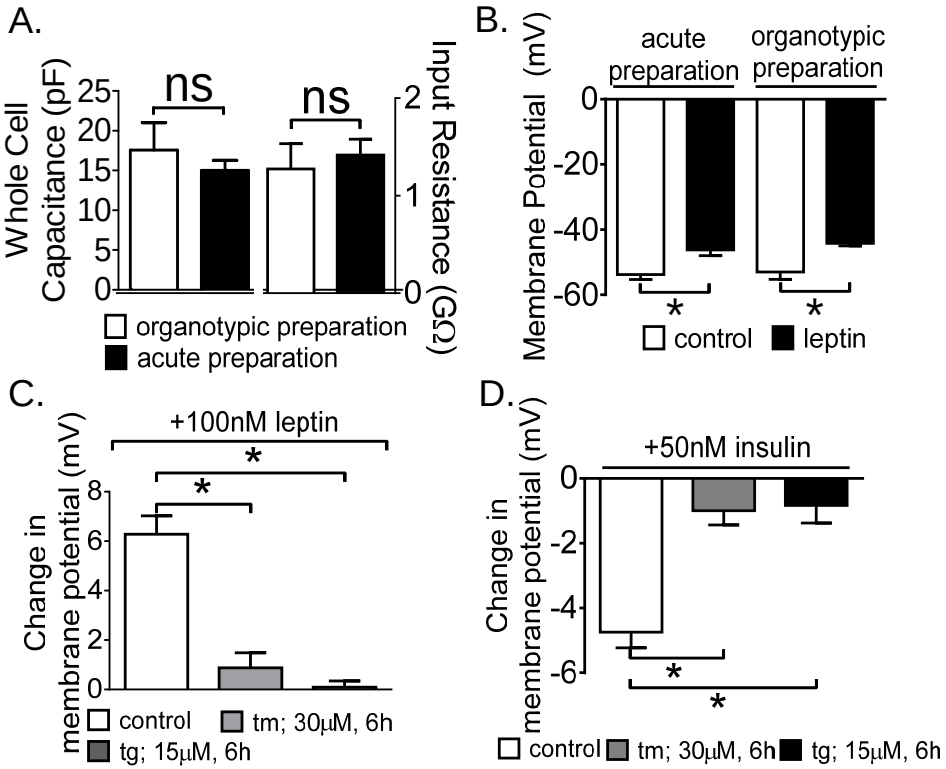

Supplemental Figure 3