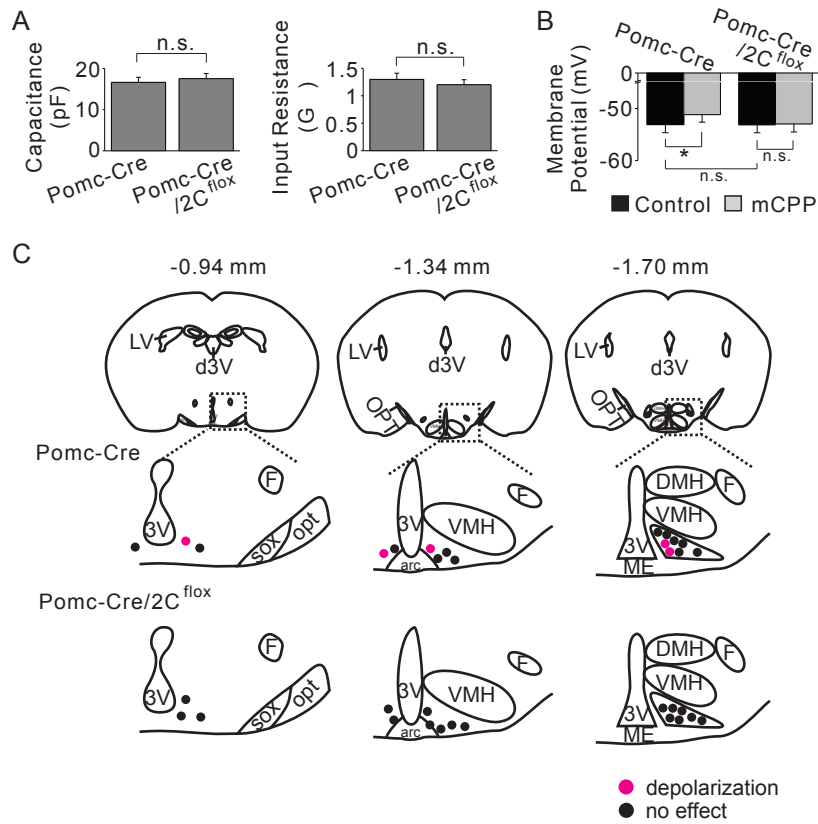
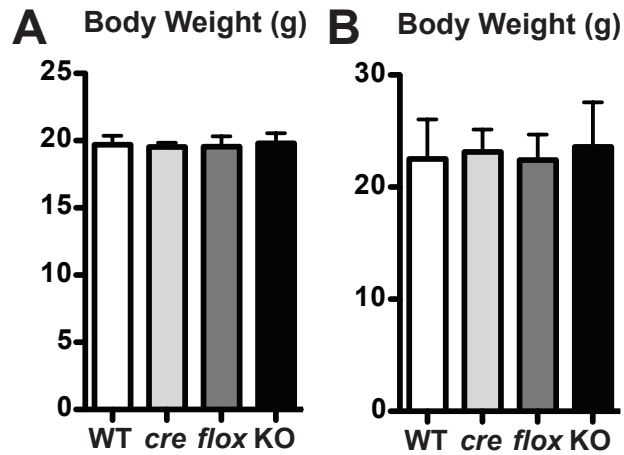


# Supplementary Figure 1



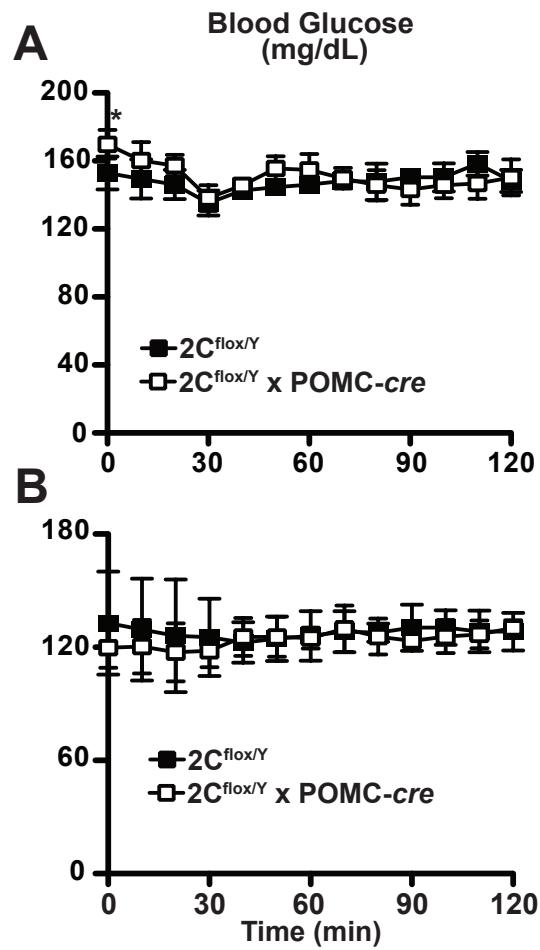
Supplementary Figure 1 – Electrophysiological validation of mice lacking 5-HT2CRs in pro-opiomelanocortin (POMC) neurons. 6-8 week-old male mice lacking 5-HT2CRs in pro-opiomelanocortin (POMC) neurons that co-express the fluorescent reporter tdTomato were functionally validated using treatment with the 5-HT2CR agonist mCPP (4 $\mu$ M) during electrophysiological recordings. Basal capacitance and input resistance are shown in A. Basal and m-chloro-phenylpiperazine (mCPP)-stimulated membrane potential is shown in B. Anatomical mapping is noted in C. n = 5 POMC-cre (controls) and 17 2C<sup>flox</sup>/Y x POMC-cre (2C<sup>flox</sup> x POMC-cre) littermate mice in panels E-I. Results are shown as mean  $\pm$  SEM. \* indicates  $p < 0.05$  versus other genotype assessed using student t-tests.

## Supplementary Figure 2



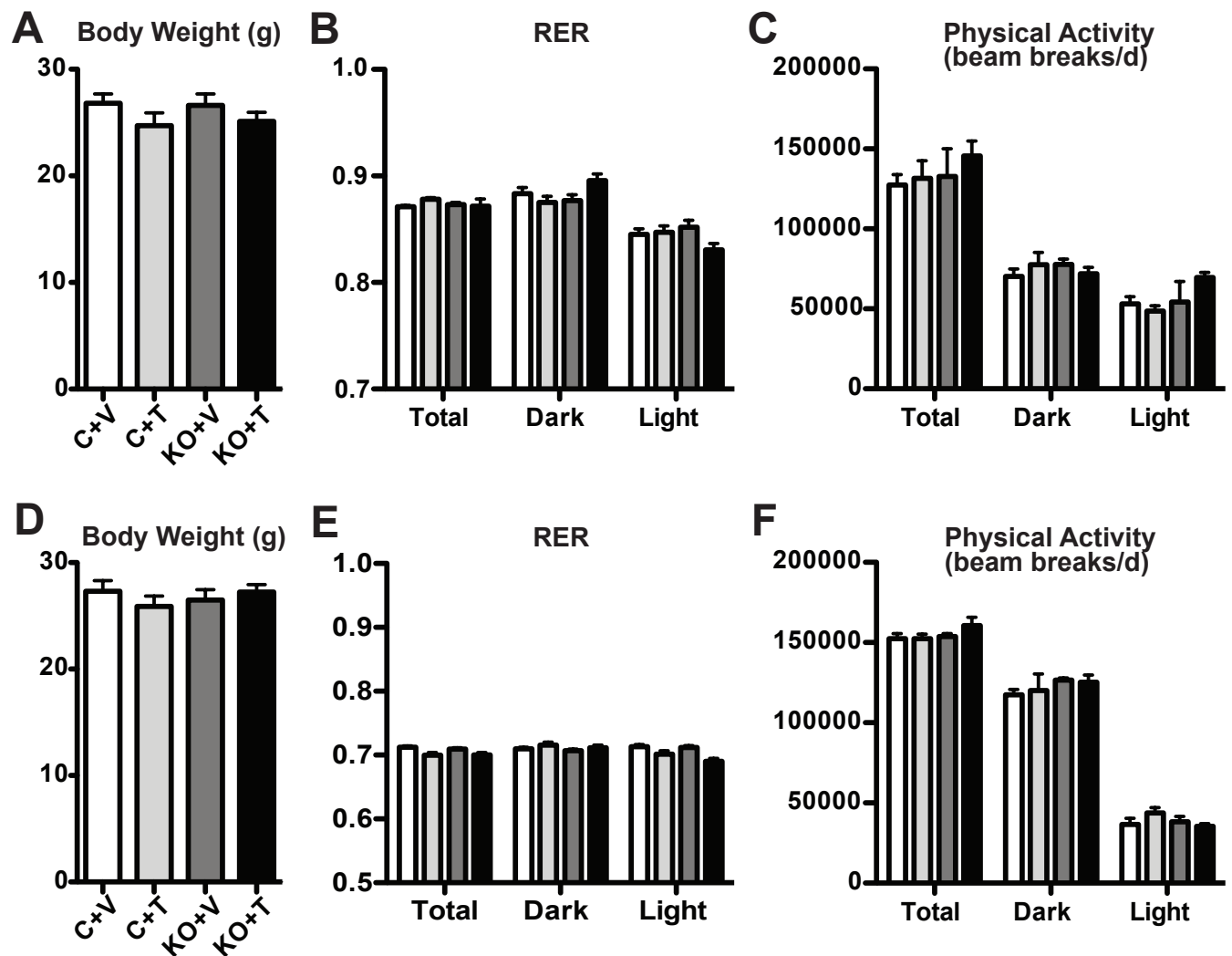
Supplementary Figure 2 – Body weight during metabolic cage studies in mice lacking 5-HT<sub>2</sub>CRs in pro-opiomelanocortin (POMC) neurons. Body weight in chow-fed groups prior to metabolic cages studies is noted in A. Body weight after one week of high-fat/high-sugar diet is noted in B. Results are shown as mean  $\pm$  SEM.

# Supplementary Figure 3



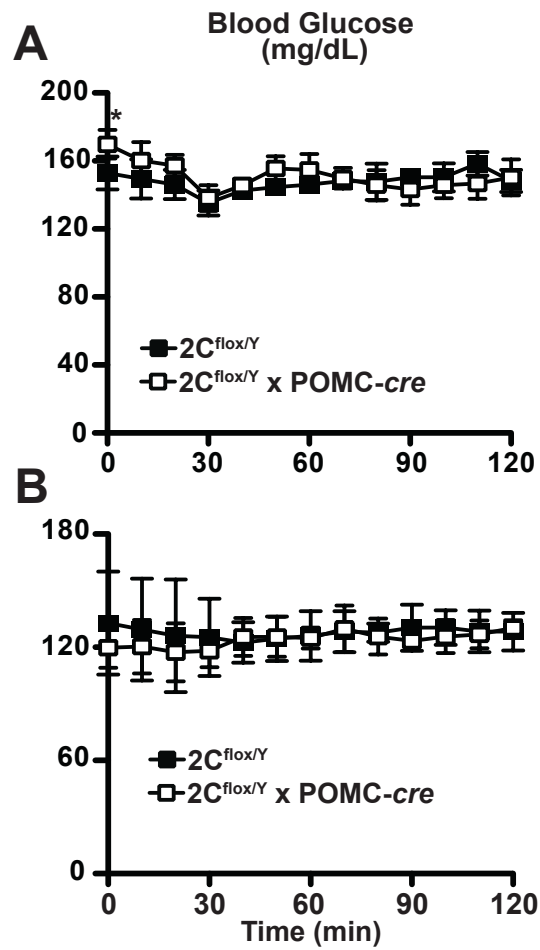
Supplementary Figure 3 – Blood glucose during 120 min hyperinsulinemic (4 mU/kg/min)-euglycemic (150 mg/dL) clamps. Blood glucose assessed from the cut tail in 4-5h morning fasted mice is shown in A. Similar values from mice fasted overnight for 12h (2100h-0900h) is noted in B. Results are shown as mean  $\pm$  SEM.

# Supplementary Figure 4



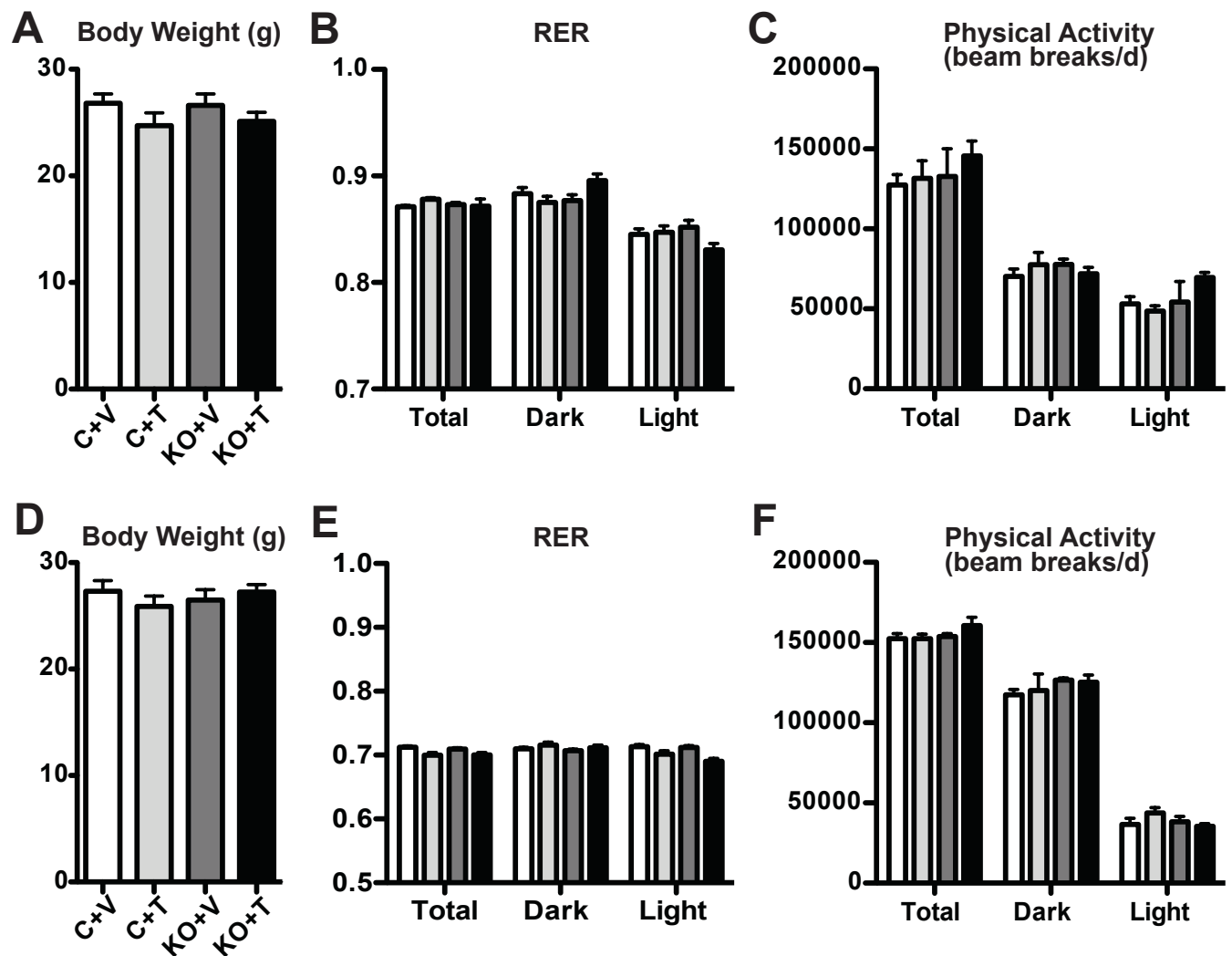
Supplementary Figure 4- Inducible deletion *Htr2c* (*2C*) in pro-opiomelanocortin (POMC) neurons of adult mice dysregulates energy homeostasis. Male chow-fed POMC-*cre:ERT2* (C) and *2C<sup>flox/Y</sup>* x POMC-*cre:ERT2* (KO) littermate mice were treated with TX (T) or vehicle (V) at 11 weeks of age and then placed in metabolic cages one week later (n=7-9 per genotype). Body weight, RER, and physical activity are shown in A-C. Male POMC-*cre:ERT2* (WT) and *2C<sup>flox/Y</sup>* x POMC-*cre:ERT2* (*2C<sup>flox/Y</sup>*) littermate mice were then fed a high-fat/high-sugar diet (HFHS) diet to capture acute changes using metabolic cages (n=7-9 per genotype). These data are noted in D-F. Results are shown as means  $\pm$  SEM.

# Supplementary Figure 5



Supplementary Figure 5 – Blood glucose during 120 min hyperinsulinemic (4 mU/kg/min)-euglycemic (150 mg/dL) clamps. Blood glucose assessed from the cut tail in 4-5h morning fasted mice is shown in A. Similar values from mice fasted overnight for 12h (2100h-0900h) is noted in B. Results are shown as mean  $\pm$  SEM.

# Supplementary Figure 6



Supplementary Figure 6 - Inducible deletion of 5-HT<sub>2</sub>CRs in pro-opiomelanocortin (POMC) neurons of adult mice dysregulates energy homeostasis. Male chow-fed POMC-cre:ERT2 (C) and 2Cflox/Y x POMC-cre:ERT2 (KO) littermate mice were treated with TX (T) or vehicle (V) at 11 weeks of age and then placed in metabolic cages one week later (n=7-9 per genotype). Body weight, RER, and physical activity are shown in A-C. Male POMC-cre:ERT2 (WT) and 2Cflox/Y x POMC-cre:ERT2 (2Cflox/Y) littermate mice were then fed a high-fat/high-sugar diet (HFHS) diet to capture acute changes using metabolic cages (n=7-9 per genotype). These data are noted in D-F. Results are shown as means  $\pm$  SEM.