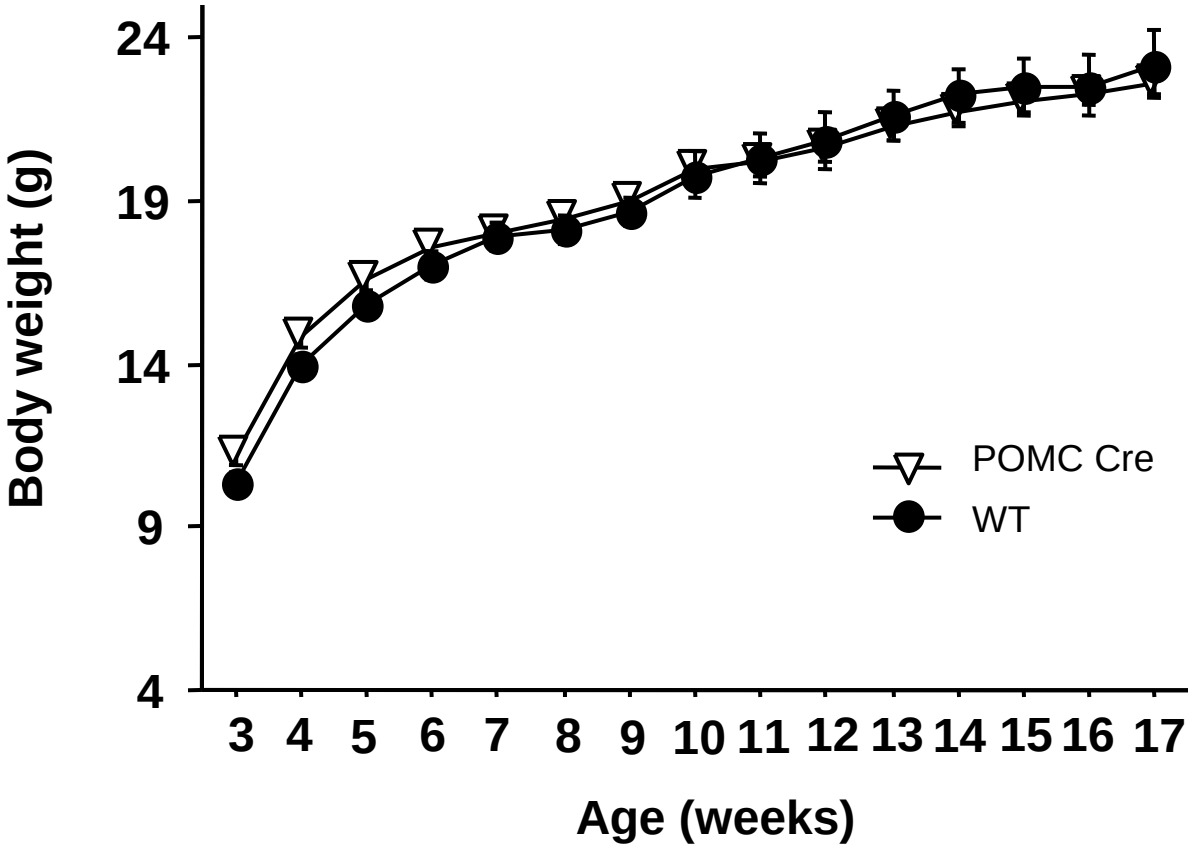
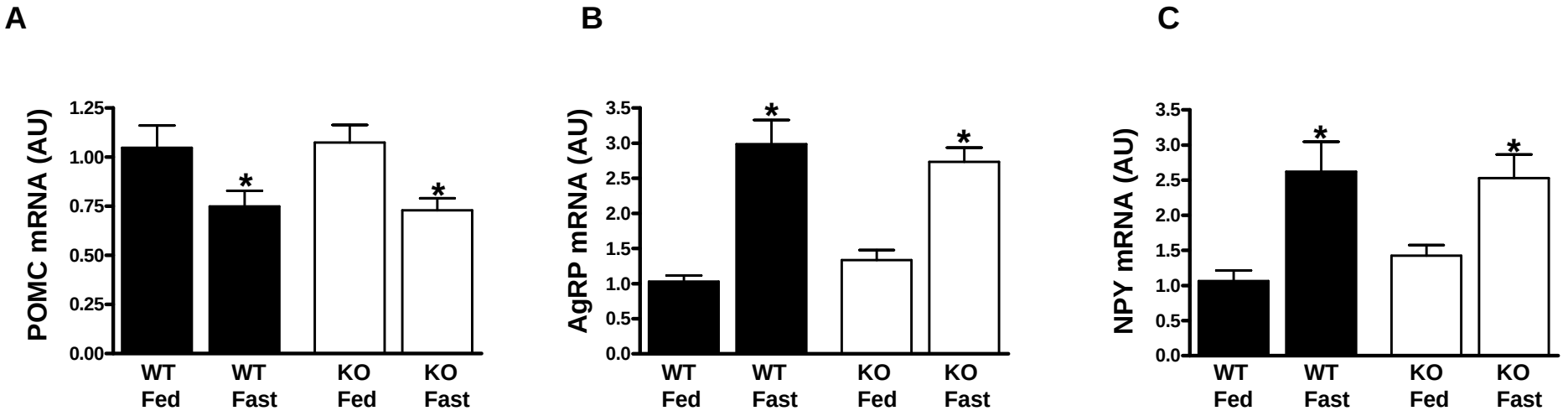
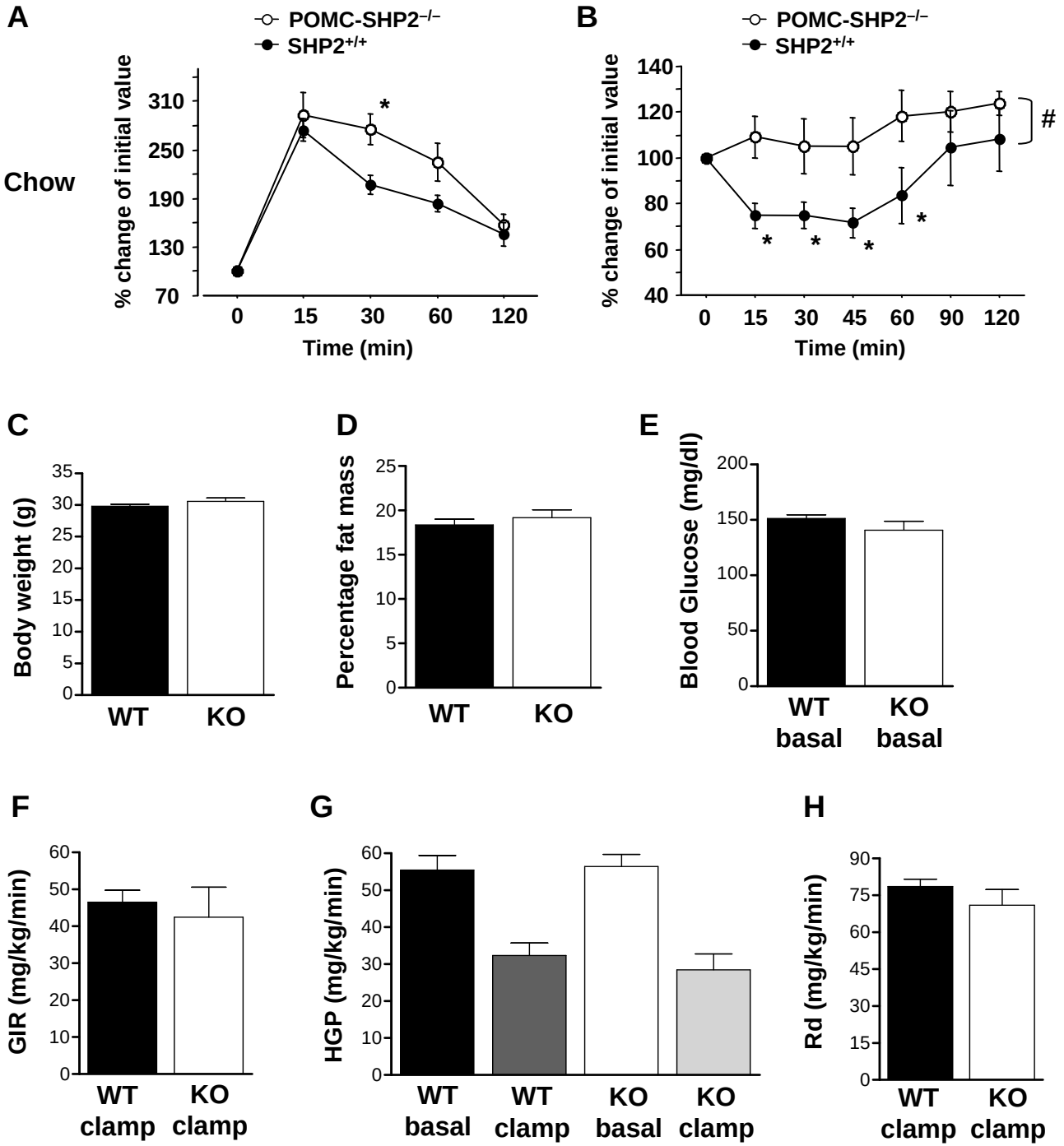


Supplemental Figure 1. POMC-Cre mice show similar body weight gain compared to WT mice.
Body weights of female POMC-Cre mice (n = 11) versus C57Bl/6 littermate controls (WT; n = 9) on high-fat diet from weaning.



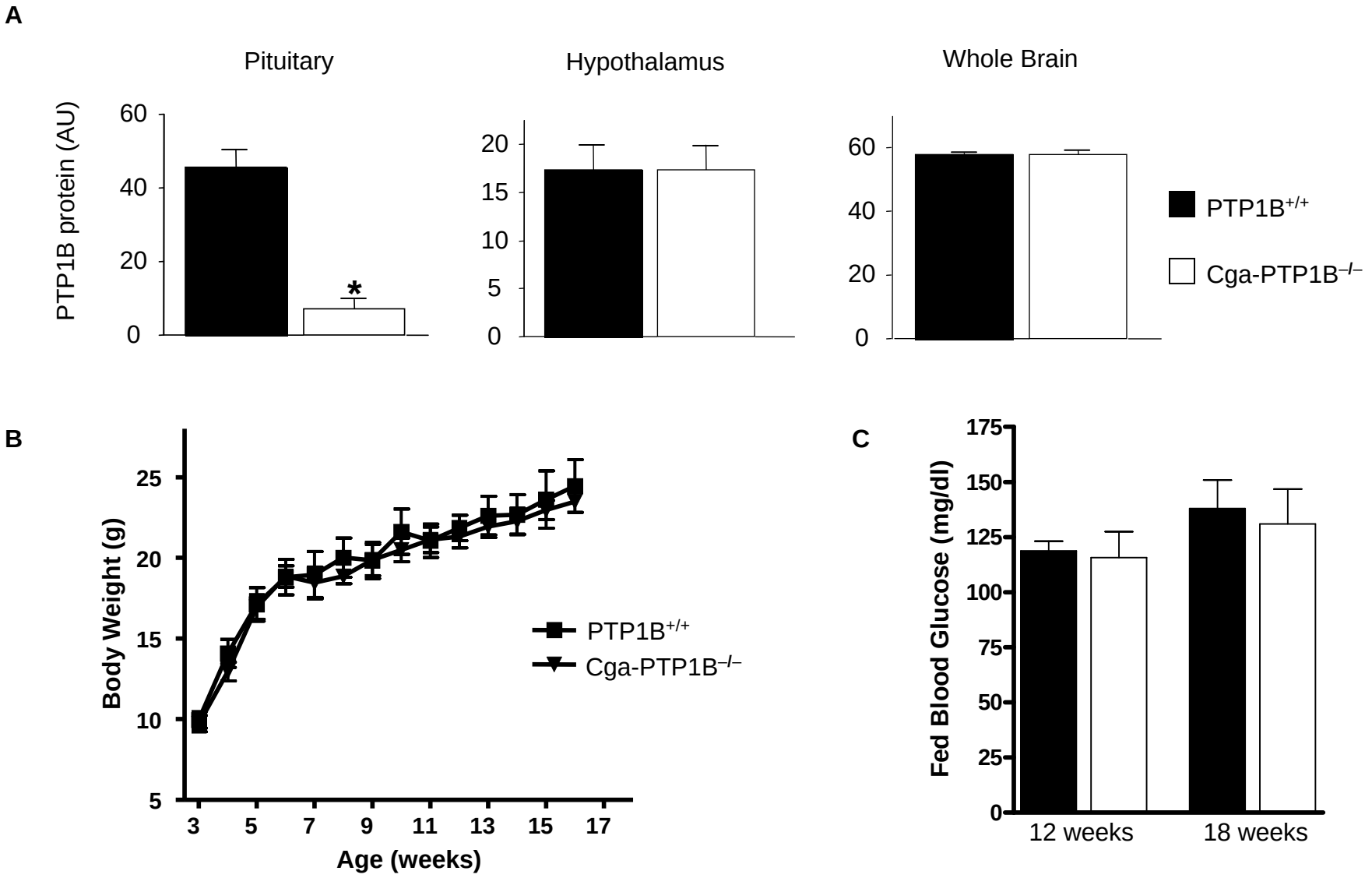
Supplemental Figure 2. Hypothalamic neuropeptide gene expression in POMC-PTP1B$^{-/-}$ mice.

Hypothalamic expression of genes encoding neuropeptides POMC (**A**), AgRP (**B**), and NPY (**C**) in POMC-PTP1B$^{-/-}$ mice (KO) versus PTP1B$^{+/+}$ controls (WT). All mice were male mice in either the fed state or 24 hour-fasted state, and on high-fat diet for 14-16 weeks; n=6-8 per genotype. All values are mean ± SEM. ***** $p < 0.05$ Fed vs. Fasted within genotype by two-tailed Student's *t*-test.



Supplemental Figure 3. Insulin sensitivity and glucose homeostasis in POMC-SHP2$^{-/-}$ mice.

(**A**) Glucose tolerance test (GTT) for POMC-SHP2$^{-/-}$ mice and SHP2$^{+/+}$ control mice on chow diet (12 weeks old). (**B**) Insulin tolerance test (ITT) for POMC-SHP2$^{-/-}$ mice and SHP2$^{+/+}$ control mice on chow diet (22 weeks old). Male mice, n=8/genotype, were used for GTT and ITT experiments.
(**C-H**) Hyperinsulinemic-euglycemic clamp analysis of male POMC-SHP2$^{-/-}$ (KO) and SHP2$^{+/+}$ control (WT) mice. Mice were 8 months of age on chow diet (n = 6/genotype) and matched for body weight (**C**) and fat mass by NMR analysis (**D**) prior to the clamp. POMC-SHP2$^{-/-}$ mice have normal insulin sensitivity as shown by similar basal blood glucose (**E**), glucose infusion rate (GIR) (**F**), hepatic glucose production (HGP) (**G**), and glucose disposal rate (Rd)(**H**), compared to SHP2$^{+/+}$ controls. All values are mean ± SEM. *$p < 0.05$ SHP2$^{+/+}$ vs. POMC-SHP2$^{-/-}$ by two-tailed Student's *t*-test; # $p < 0.05$ SHP2$^{+/+}$ vs. POMC-SHP2$^{-/-}$ by AUC.



Supplemental Figure 4. Mice with deficiency of PTP1B in the anterior pituitary (Cga-PTP1B$^{-/-}$ mice) have similar body weights on high-fat diet and similar blood glucose levels compared to PTP1B$^{+/+}$ controls. Deficiency of PTP1B was shown to be specific to the pituitary by immunoblotting with mPTP1B polyclonal antibody. Blots were quantified and PTP1B protein content is expressed in arbitrary units (**A**). Female Cga-PTP1B$^{-/-}$ mice and PTP1B$^{+/+}$ littermates were placed onto high-fat diet at weaning and weighed weekly (**B**); n=10-12 mice per genotype. Fed blood glucose levels were similar between genotypes at 12 and 18 weeks of age on high-fat diet (**C**); n=4-5 mice per genotype. * p<0.05 by two-tailed Student's *t*-test.