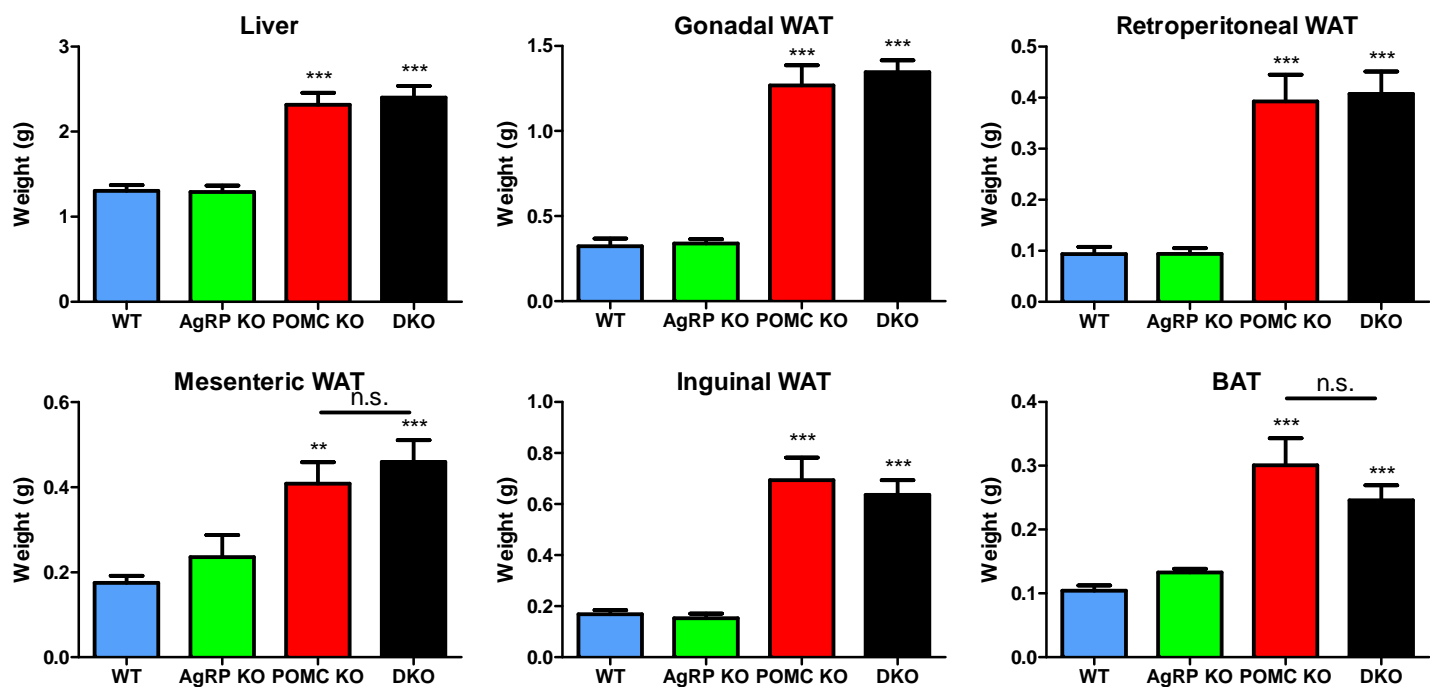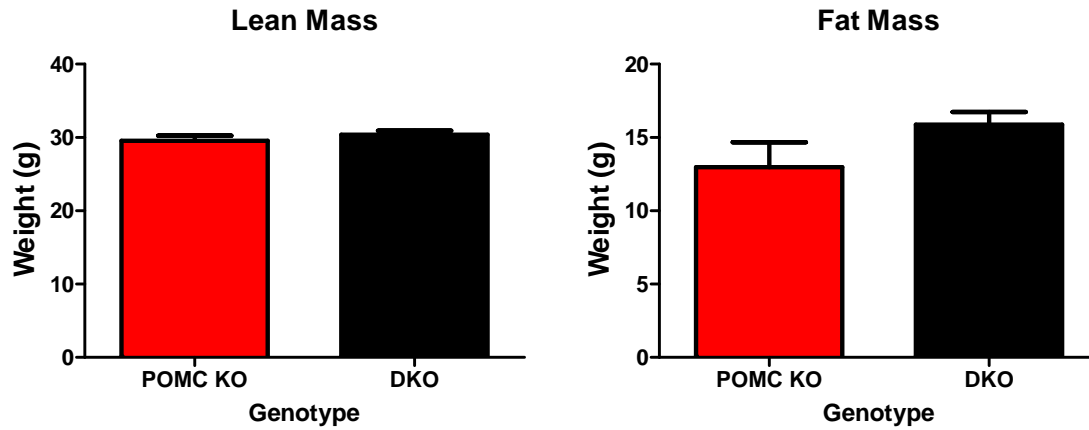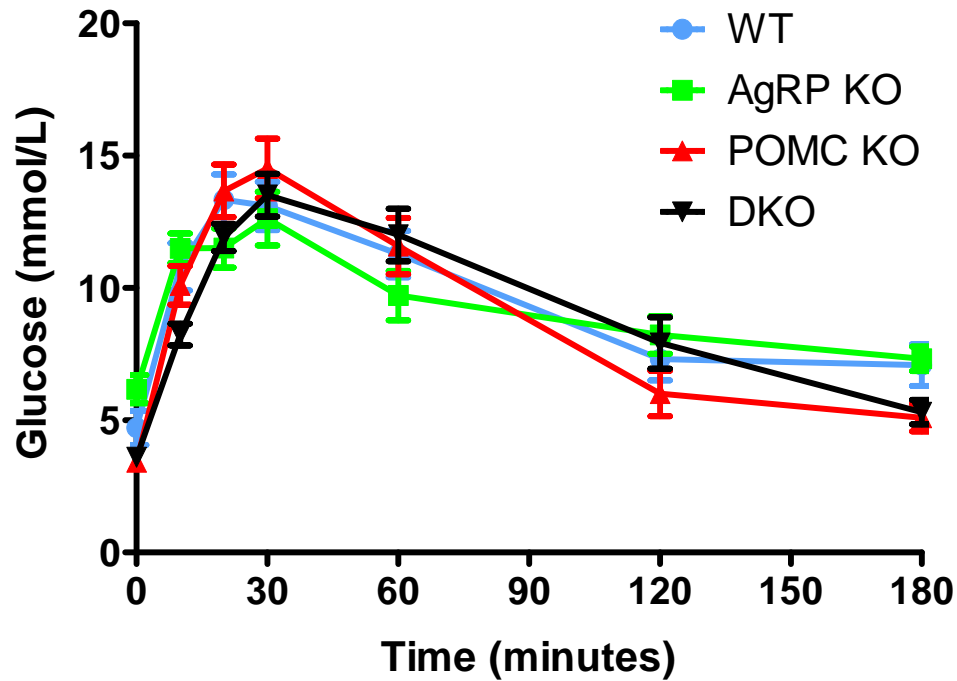Supplemental Figure 1: Hypothalamic mRNA expression of key neuropeptides and receptors in DKO mice. Expression of *Agrp, Pomc, Npy, Mc3r, Mc4r,* and *Crh* as determined by RT-qPCR of whole hypothalamic blocks of male mice. Data normalised to beta-actin (*Actb*) expression and expressed as mean±SEM. *p<0.05, **p<0.01, ***p<0.001 vs wild-type mice. Abbreviations: n.s., not significant. WT (*Pomc*$^{+/+}$/*Agrp*$^{+/+}$) n=9, AgRP KO (*Pomc*$^{+/+}$/*Agrp*$^{-/-}$) n=8, POMC KO (*Pomc*$^{-/-}$/*Agrp*$^{+/+}$) n=9, DKO (*Pomc*$^{-/-}$/*Agrp*$^{-/-}$) n=11.
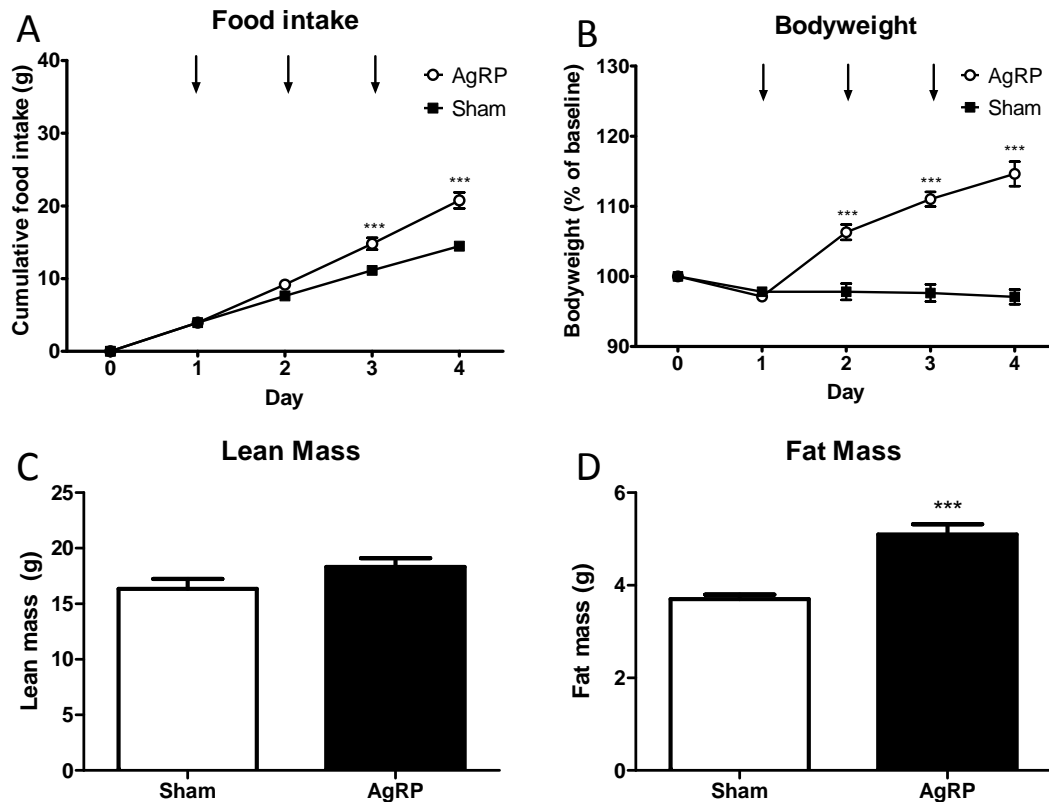
Supplemental Figure 2: Adipose depots of DKO mouse. Adipose depot weights as determined by dissection of 4-5 month old male mice. Abbreviations: White adipose tissue, WAT; Brown adipose tissue, BAT. Data represents mean±SEM. **$p<0.01$, ***$p<0.001$ vs WT mice. WT (*Pomc*$^{+/+}$/*Agrp*$^{+/+}$) n=9, AgRP KO (*Pomc*$^{+/+}$/*Agrp*$^{-/-}$) n=8, POMC KO (*Pomc*$^{-/-}$/*Agrp*$^{+/+}$) n=9, DKO (*Pomc*$^{-/-}$/*Agrp*$^{-/-}$) n=11.

Supplemental Figure 3: Late-onset phenotype of DKO mice. Body composition of male mice aged 6-7 months as determined by dual-energy x-ray absorptiometry (DEXA). Data represents mean ± SEM. POMC KO ($Pomc^{-/-}/Agrp^{+/+}$) n=7, DKO ($Pomc^{-/-}/Agrp^{-/-}$) n=15.

Supplemental Figure 4: Glucose homeostasis of DKO mice. Glucose homeostasis as determined by an intra-peritoneal glucose tolerance test. Data represents mean ± SEM. WT (*Pomc*^{+/+}/*Agrp*^{+/+}) n=9, AgRP KO (*Pomc*^{+/+}/*Agrp*^{-/-}) n=8, POMC KO (*Pomc*^{-/-}/*Agrp*^{+/+}) n=9, DKO (*Pomc*^{-/-}/*Agrp*^{-/-}) n=11.

Supplemental Figure 5: Central administration of AgRP to wild-type mice. (A) Cumulative food intake, (B) body weight, (C) lean mass and (D) fat mass of 10-16 week old wild-type female mice following icv administration of 2nmol AgRP or saline. Data represents mean±SEM for food intake and mean body weight as percentage of baseline ±SEM. ***$p<0.001$ vs control treated mice. AgRP n=8, control n=6