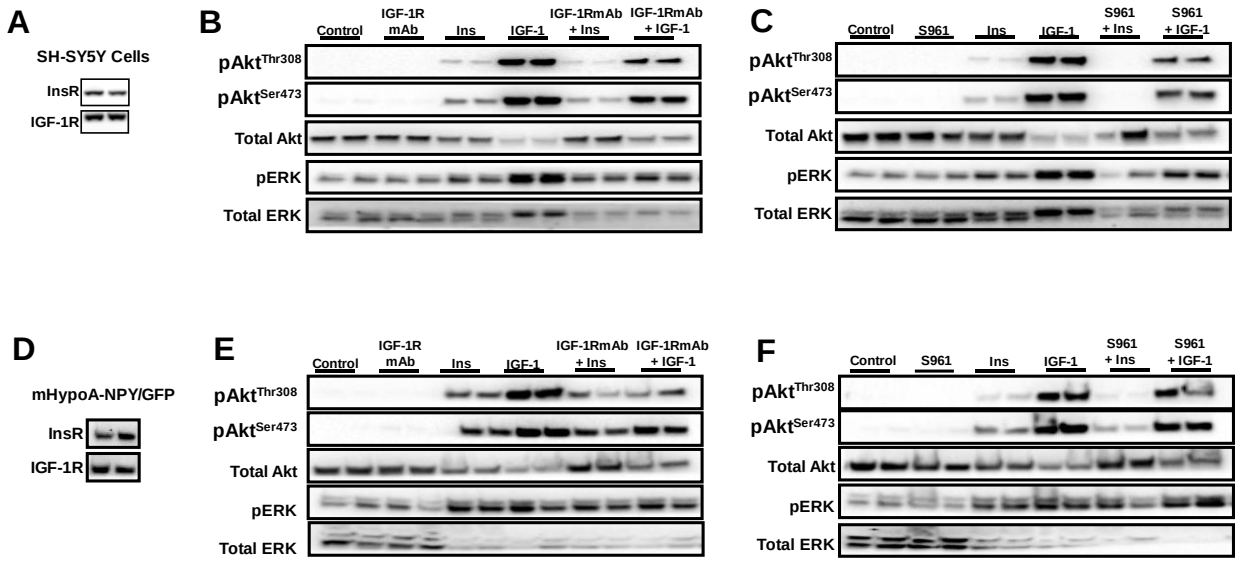
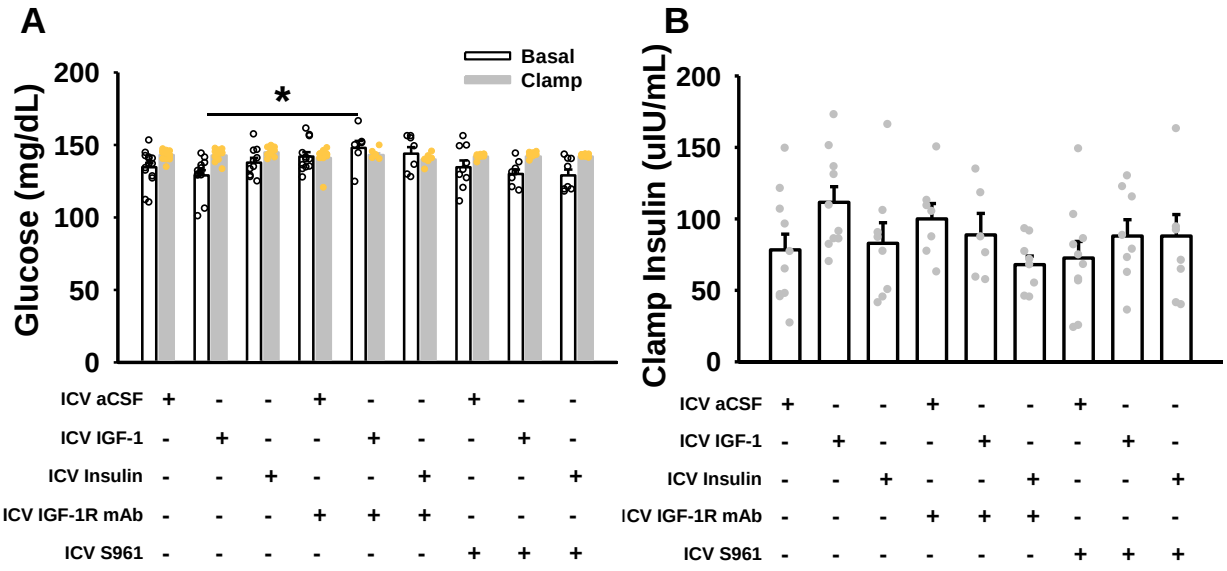
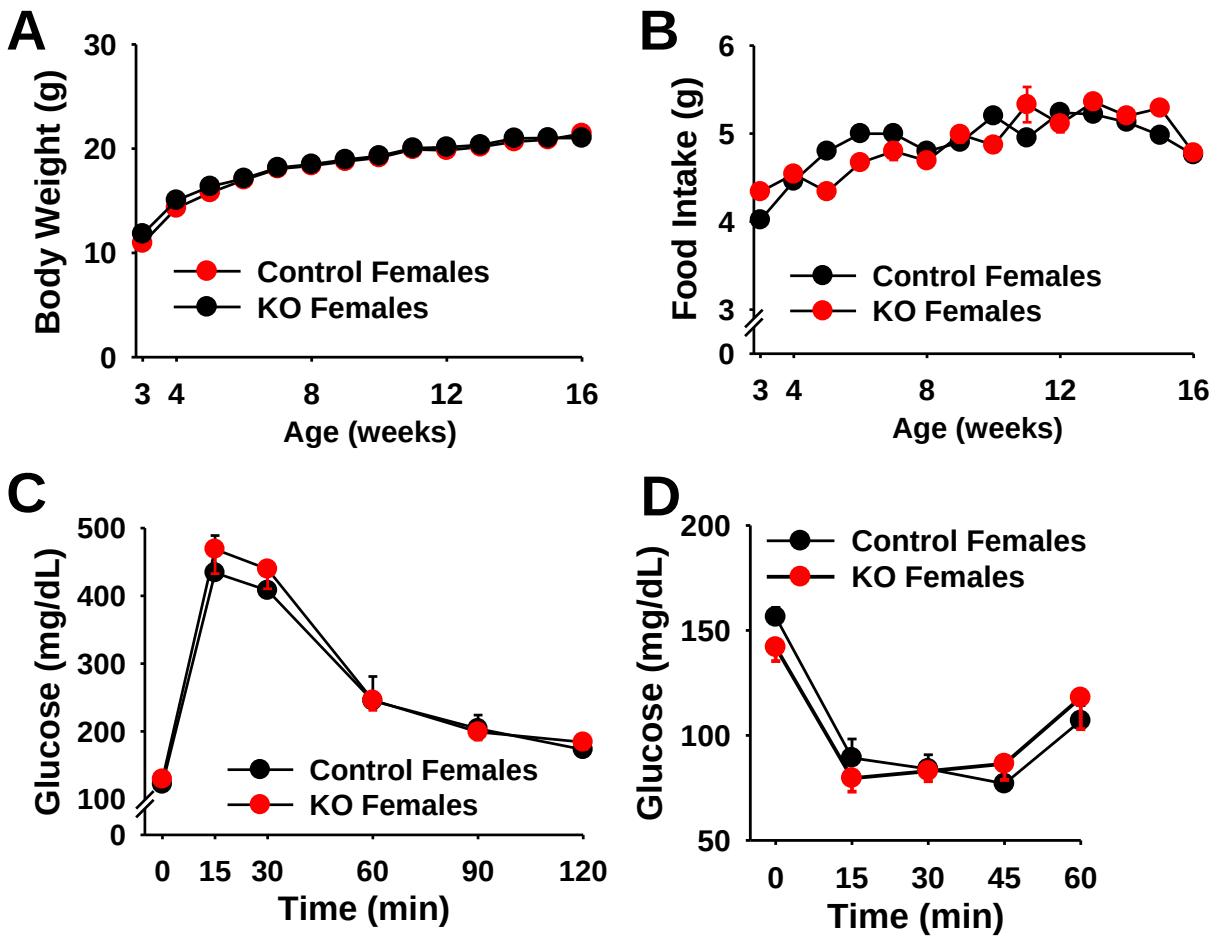


Supplementary Figure 1. Pharmacological inhibition of IGF-1R and InsR *in vitro A*: The SH-SY5Y cell line expresses both InsR and IGF-1R. *B*: Phosphorylation of downstream targets pAkt(Thr308), pAkt(Ser473) and pERK, were increased in SH-SY5Y cells after treatment with equimolar concentrations of Insulin or IGF-1, although IGF-1 seemed to be more potent in these cells. Pre-emptively treating SH-SY5Y cell with an IGF-1R antagonist mAb 30 min prior to ligand exposure, specifically reduced pAkt and pERK via IGF-1 treatment. *C*: Similarly, pre-emptively treating cells with S961 for 30min reduced expression of phosphorylated downstream targets via insulin. Treatment with this inhibitor also modestly reduced pAkt and pERK activation via IGF-1, perhaps due to interfering with collateral activation of the InsR by IGF-1. *D*: The mHypoA-NPY/GFP cell line expresses both InsR and IGF-1R. *E*: Phosphorylation of Akt and ERK was increased in mHypoA-NPY/GFP cells after treatment with equimolar concentrations of Insulin or IGF-1. Pre-emptively treating the cells with IGF-1RmAb for 30min, reduced the expression of pAkt and pERK in response to IGF-1. *F*: Pre-emptive treatment of cells with an InsR small molecule inhibitor, S961 for 30min, reduced expression of phosphorylated downstream targets in response to insulin. All i*n vitro* experiments were run as biological duplicates.

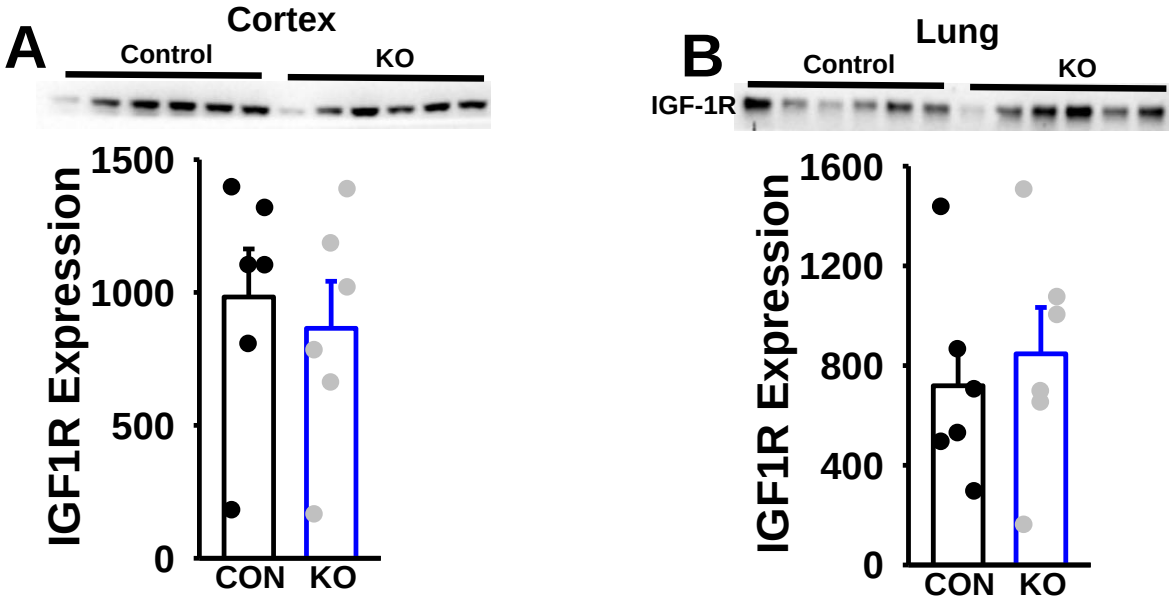


Supplementary Figure 2. Plasma glucose and insulin levels in FBN rats during the *in vivo* clamp study. *A*: Average plasma glucose levels under basal (white bar) and clamp conditions (gray bar) in rats. Under basal conditions, ICV IGF-1R mAb tended to raise basal glucose which was significant between ICV IGF-1 and ICV IGF-1+ICV mAb groups (aCSF Controls *n*=15, ICV IGF-1 *n*=12, ICV Insulin *n*=10, ICV IGF-1R mAb only *n*=12, ICV IGF-1+IGF-1R mAb n=6, ICV Insulin+IGF-1R mAb *n*=7, ICV S961 only *n*=10, ICV S961+IGF1 *n*=8, ICV S961+Insulin *n*=8). **P*<0.05, †*P*<0.01, ‡ *P*<0.001 versus aCSF Control after Dunnett posthoc adjustment.. However, there were no significant differences in clamp glucose levels (targeting ~140-145mg/dL) among groups. *B*: Although some inherent variation was observed for clamp insulin levels among individual animals within groups, there were no significant differences among groups. Measurements were made in a pooled sample that included the 330, 340, 350 and 360 min sample draws. Bar graphs indicate means ± standard error (SE) and circles indicate individual data points. **P*<0.05 after Tukey posthoc adjustment.



Supplementary Figure 3. *Metabolic phenotype of female mice lacking IGF-1R in AgRP neurons*

A-B: Body weight and food intake levels (*n*=11 Controls, *n*=12 KO) were not significantly different in female KO animals, as compared to controls. *C-D*: Similarly, no differences were seen between groups during glucose (GTT) or insulin (ITT) tolerance tests (*n*=8 Controls, *n*=8 KO). Data is represented as means ±SE. There were no significant differences between groups.



Supplementary Figure 4. *IGF-1R expression levels in tissue sites outside of hypothalamus in control and knockout mice.* IGF-1R levels were assessed via Western blot in (*A)* cortex and (*B)* lung tissue between Control (*Igf1r*$^{flox/flox}$) and mice lacking IGF-1Rs in AgRP neurons (n=6 per group). No significant differences were observed in IGF-1R levels between groups at either of these sites.