**Supplemental Information**

**Supplementary Figures Legends**

**Figure S1: DIO mice do not respond to centrally delivered leptin after 12 weeks of HF – related to Figure 1**

(A) Weekly BW measurement of mice fed with control diet or HFD for 12 weeks. Mice fed with HFD for 12 weeks display a significantly increased BW (two-way ANOVA followed by Bonferroni’s post-hoc test; n=10 mice per group; \*\*\*\*p<0.0001). (B) Representative photomicrographs (10X) showing pSTAT3-labelled cells (red) 30 min following 1g of leptin or aCSF icv injection (scale bar 150m). Leptin injection in the LV induces STAT3 activation in control diet mice compared to aCSF injection. No increase in pSTAT3 expression is seen in DIO mice after leptin icv injection compared to aCSF-injected DIO mice. (C) Graph representing the mean number of pSTAT3-labelled cells per hemi-section in the ARH of control and DIO mice in basal conditions (two-tailed unpaired t-test; n=3-5 mice per group; \*\*\*p<0.001). All data are represented as mean $\pm $ SEM. (D) Representative photomicrographs (10X) to illustrate where insulin-responsive cells are observed in the hypothalamus. Neurons expressing pAkt-alone (green) following an ip injection of insulin are mainly located in the ARH (scale bar 75m).

**Figure S2: Supplementary information related to figures 1, 3 and 4 - Leptin and insulin signalling in ARH neurons of control and DIO mice**

(A) Part of a whole graph representing the mean number of neurons displaying pSTAT3-alone, pAkt-alone and double pSTAT3/pAkt labelling in the ARH following saline, leptin (45min) and insulin (10min) i.p injections in DIO mice. (B) Part of a whole graph representing the mean number of neurons displaying pSTAT3-alone, pAkt-alone and double pSTAT3/pAkt labelling in the ARH of control and DIO mice following LAN icv injection. (C) Part of a whole graph representing the mean number of neurons displaying pSTAT3-alone, pAkt-alone and double pSTAT3/pAkt labelling in the ARH of control mice following insulin (10min) ip injection and in the ARH of DIO mice following LAN icv (30min) and insulin (10min) ip injections. All data are represented as mean, n=4-5 mice per group.

**Figure S3: Supplementary material on immunohistochemistry quantification method**

(A) Photomicrographs (20X) of single color channels (top row) after quantification on Image J software using the point tool (yellow dots for AgRP, green dots for pAkt, red dots for pSTAT3). (B) Image showing the superposition of the 3 single channel pictures displayed individually on the top row panels with their respective quantification dots. The pictures are set at 40% level of transparency and merged on Illustrator software. Co-localizations, pAkt-alone and pSTAT3-alone are indicated by arrowheads.