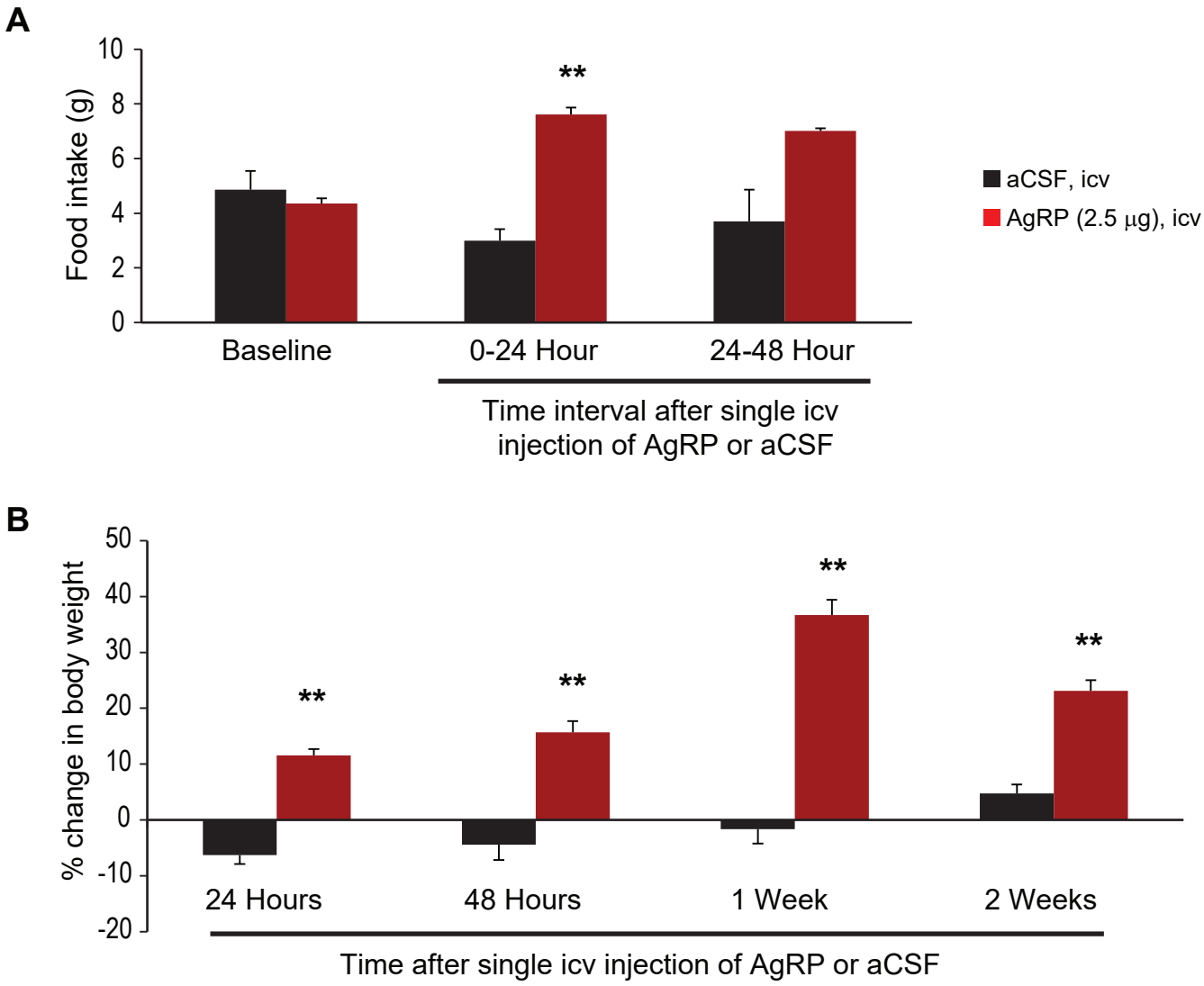
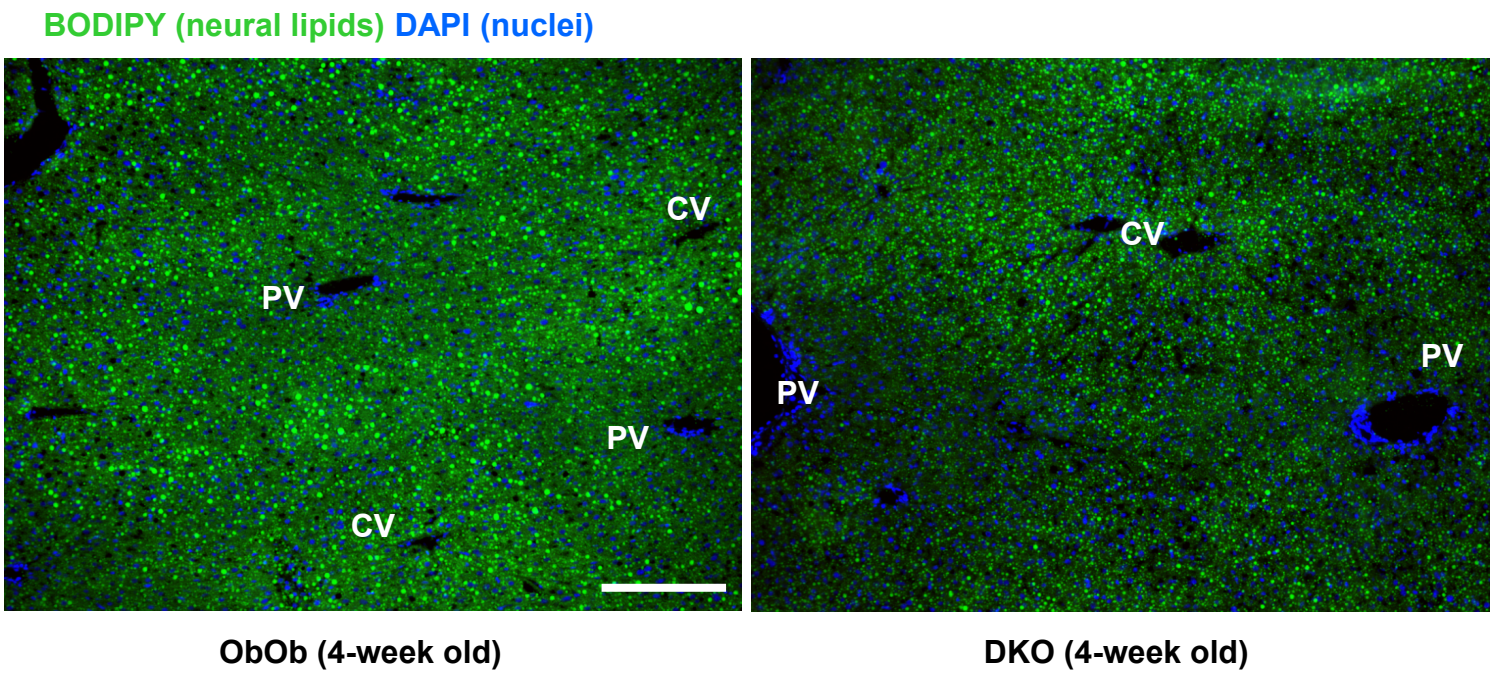
Supplementary Figure 1



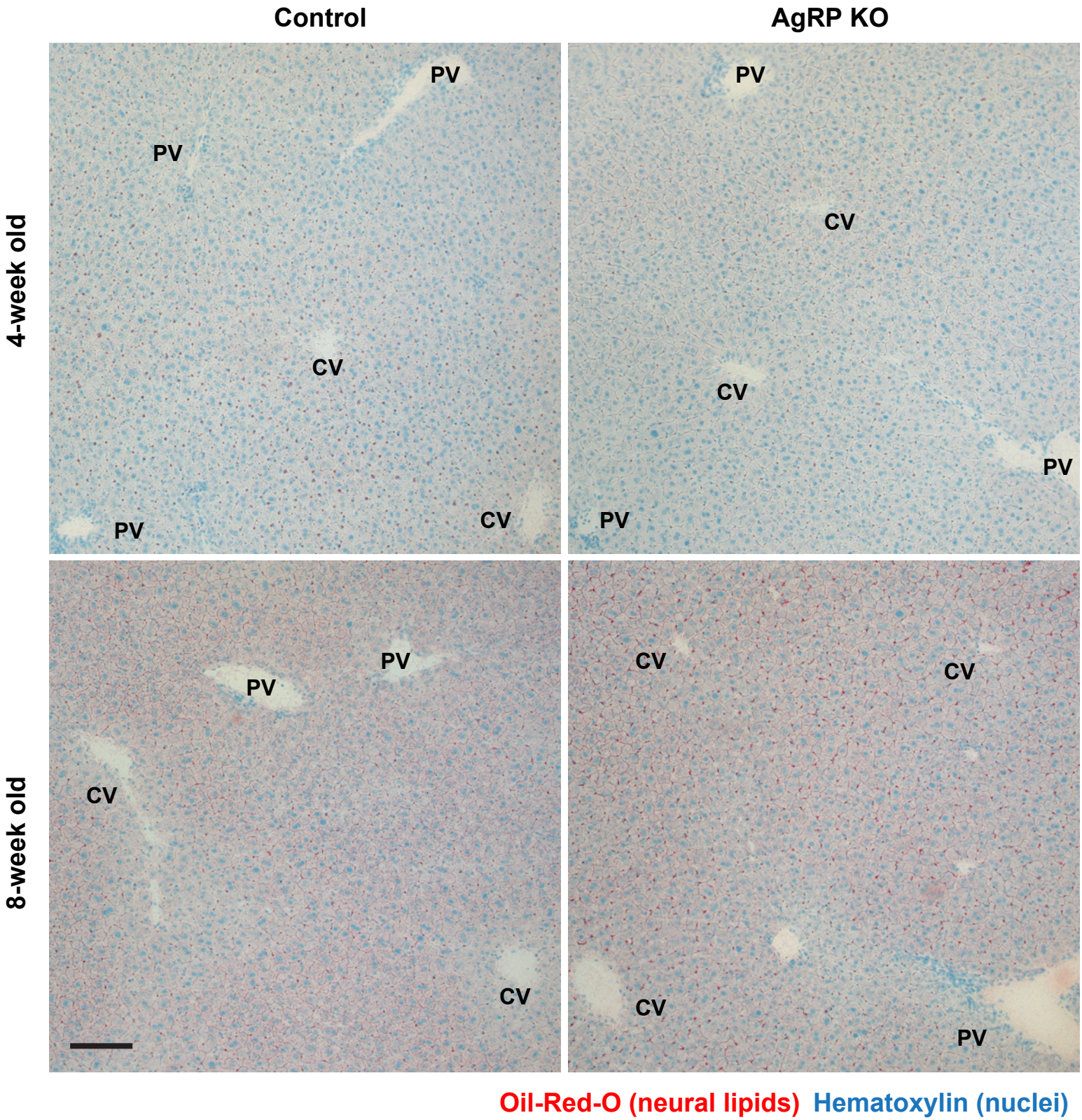
Supplementary Figure 1: A single injection of AgRP peptide into the brain leads to sustained weight gain.
One single injection of 2.5 µg of mouse AgRP peptide (82-131 amide, Phoenix Pharmaceutical, Inc) into the lateral ventricle of *Agrp*$^{-/-}$ mice via guide cannula resulted in increased feeding (**A**), and sustained weight gain (**B**). n=4-6 per group. ** P<0.01 compared between AgRP and aCSF group by two-way ANOVA with repeated measures.

Supplementary Figure 2



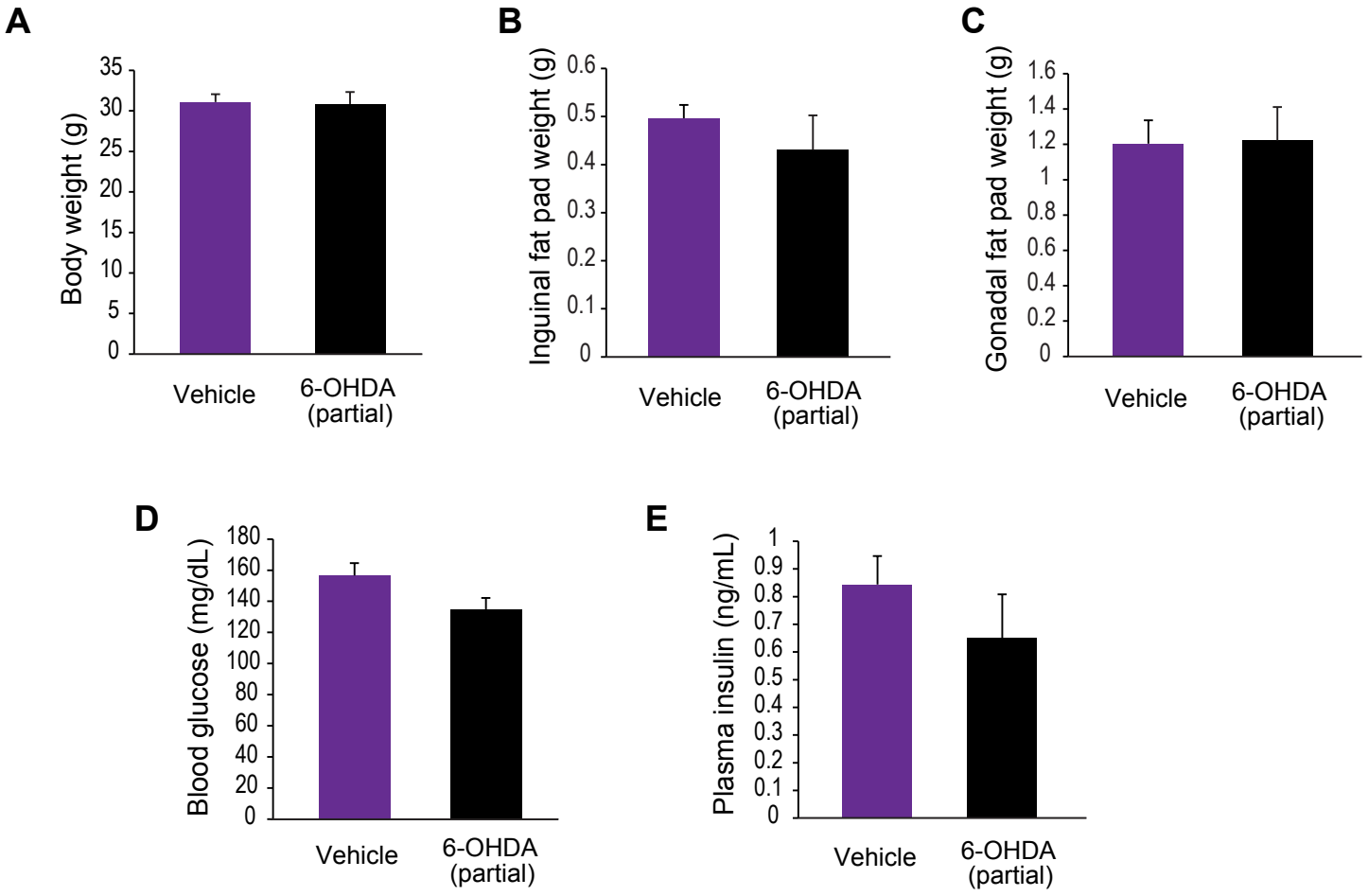
Supplementary Figure 2: Absence of AgRP function in 4-week-old prediabetic leptin-deficient mice alters their zonal distribution in the liver lobules.
A representative image showing lipid sparing around the periportal regions of 4-week-old ObOb (*Lep*$^{ob/ob}$, *Agrp*$^{+/+}$; or *Lep*$^{ob/ob}$, *Agrp*$^{+/-}$) and DKO (*Lep*$^{ob/ob}$, *Agrp*$^{-/-}$) mice. PV: portal vein. CV: central vein. Scale bar: 200 μm.

Supplementary Figure 3



Supplementary Figure 3: Abundance and distribution of neutral lipids in control and AgRP-deficient livers. Representative images showing Oil-red-O staining (red) in control ($Agrp^{+/+}$, $Agrp^{-/-}$) and AgRP-deficient mice. Nuclei were counter-stained with hematoxylin (blue). PV: portal vein. CV: central vein. Scale bar: 200 μm.

Supplementary Figure 4



Supplementary Figure 4: Terminal body weight, blood glucose and insulin levels in mice 3 weeks after 6-OHDA or vehicle treatment . Weight-matched 11-14 week-old male B6 mice were treated with 6-OHDA or vehicle (n=7 per group). Mice were then placed on a high-fat diets for 3 weeks, after which tissues were collected. (**A**) terminal body weight; (**B-C**) fat pad weights; (**D-E**) fasting (6h) blood glucose and insulin levels.