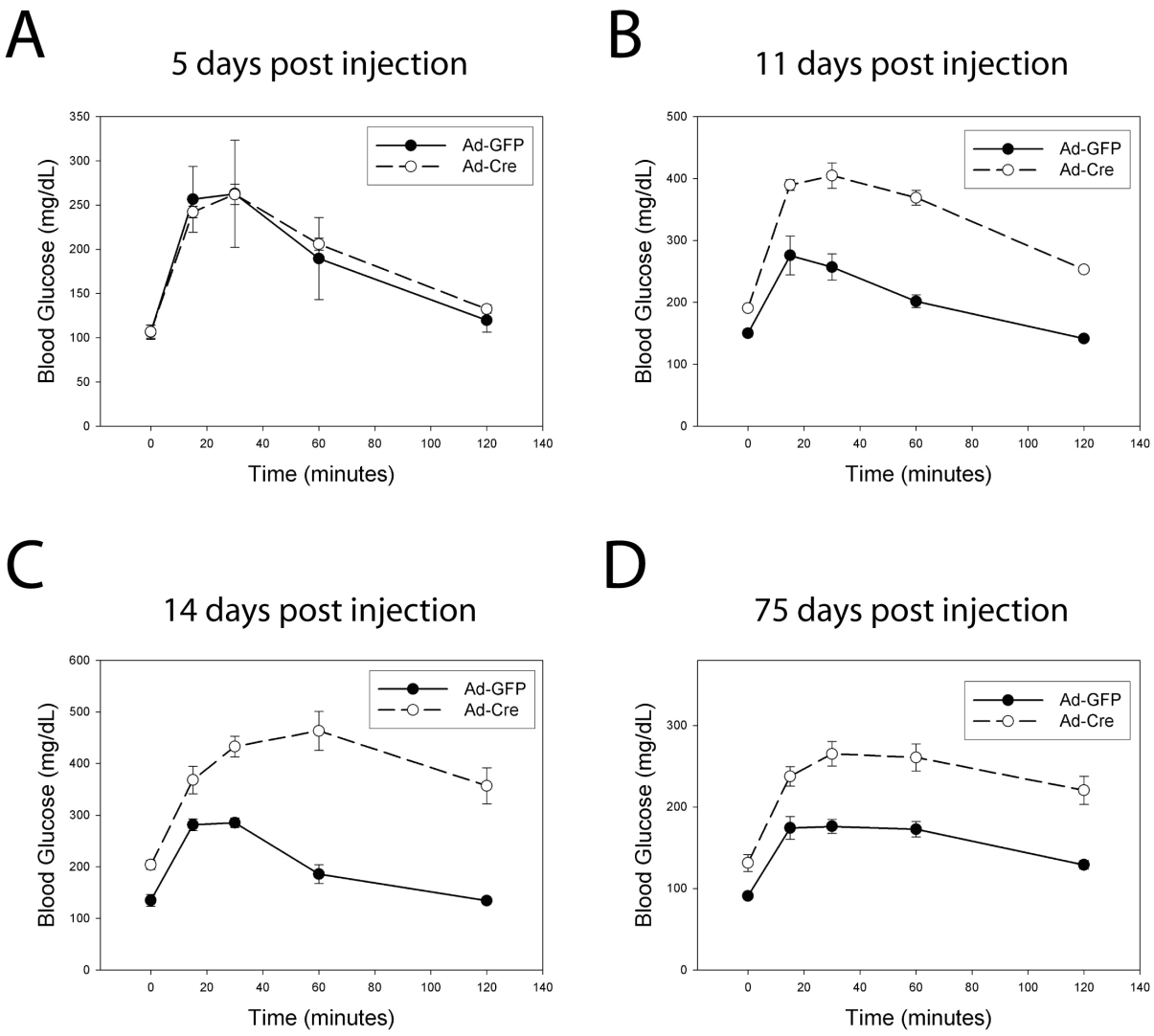
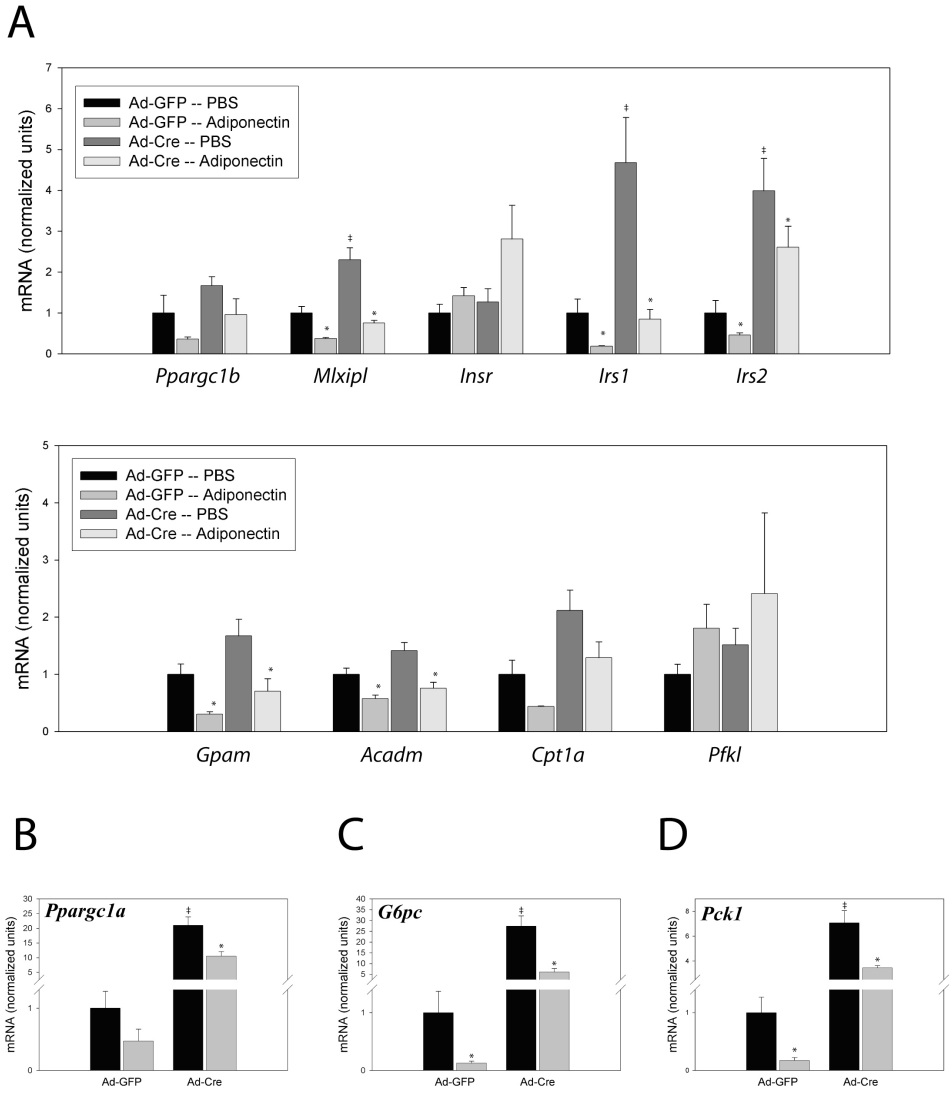
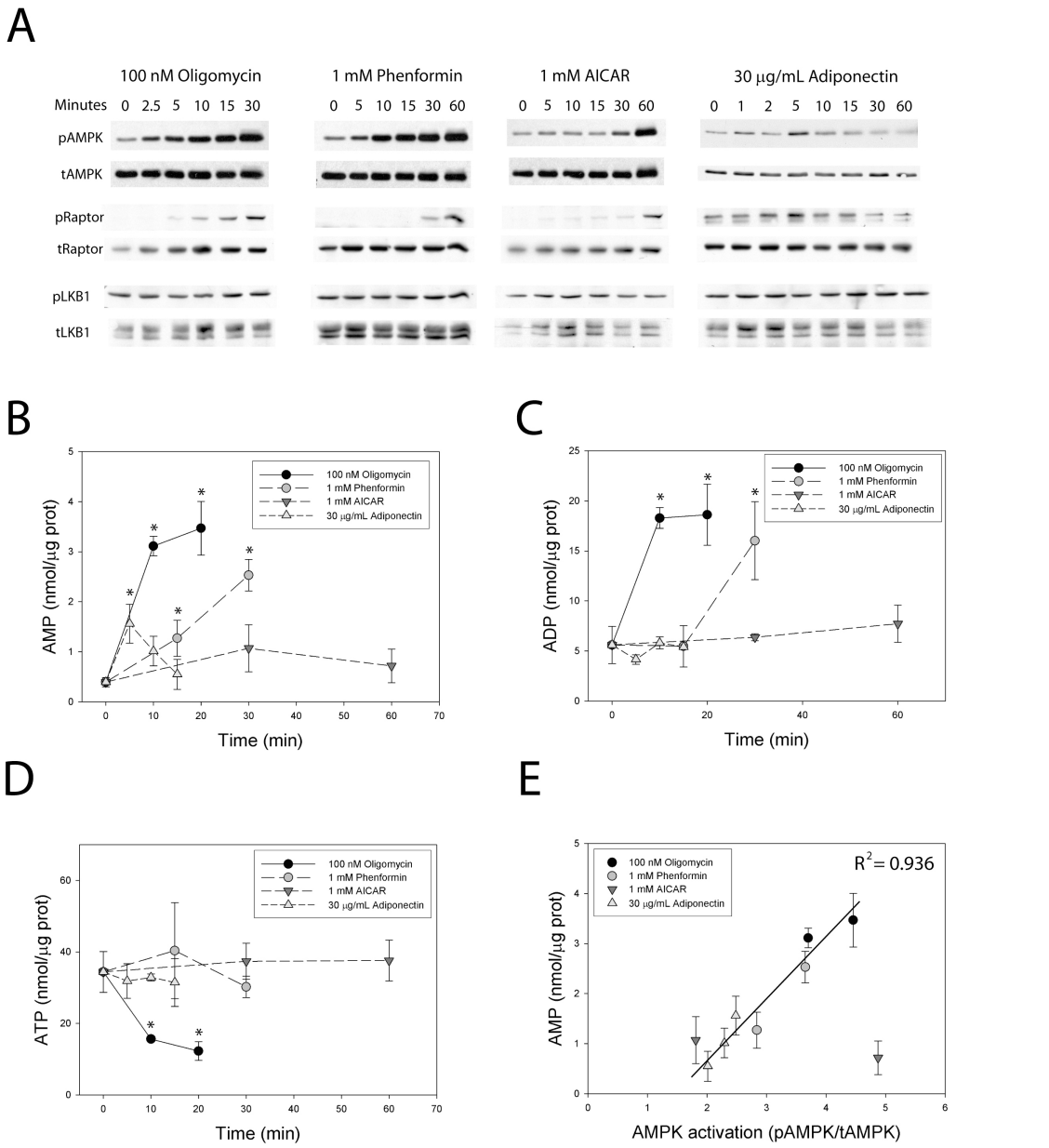


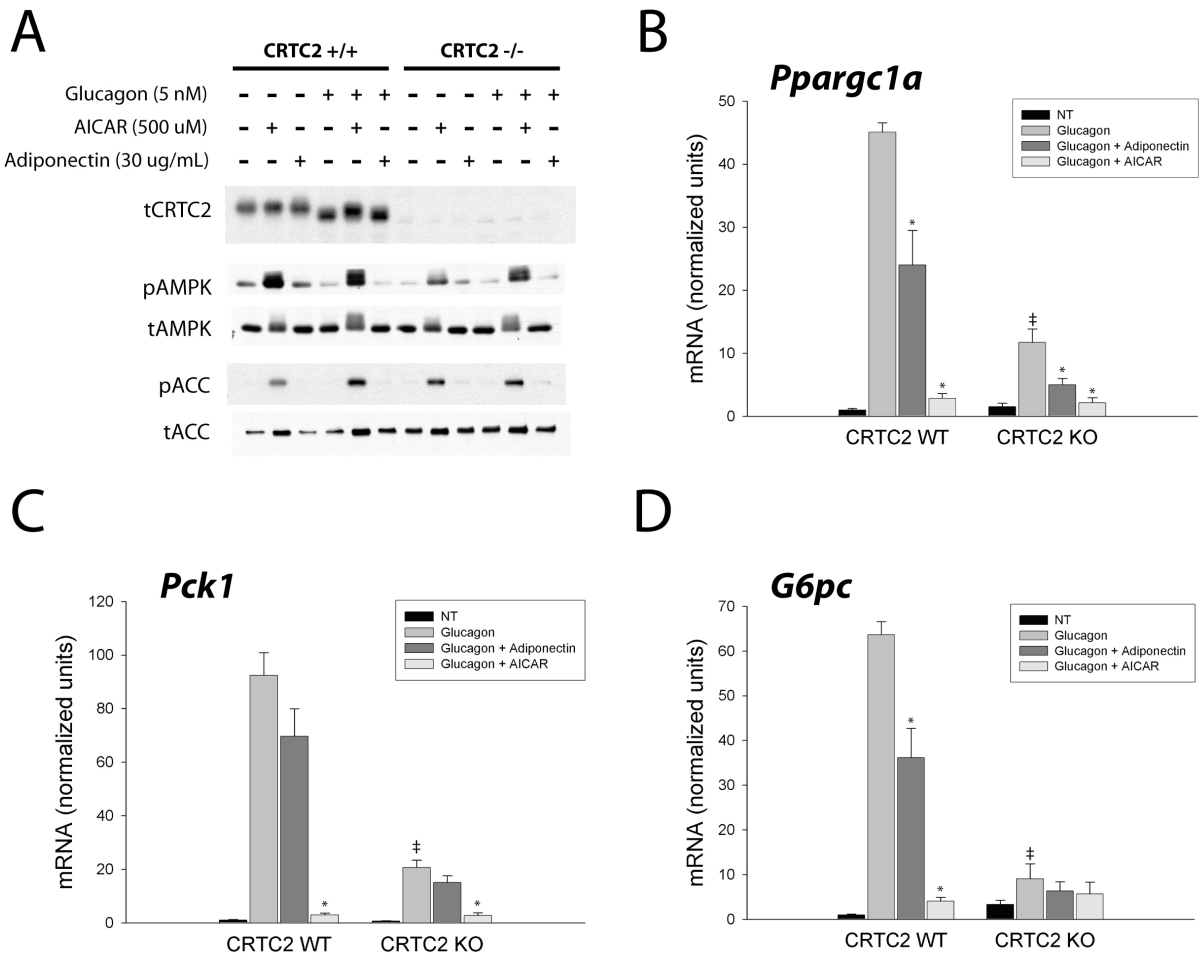
Supplemental Figure 1. Glucose tolerance tests in virus-infected *LKB1*$^{lox/lox}$ mice. *LKB1*$^{lox/lox}$ mice were infected with either Ad-GFP or Ad-Cre and after the indicated times were fasted for 6 hours and injected with 1 g/kg bw glucose. Blood glucose was followed for 2 hours.



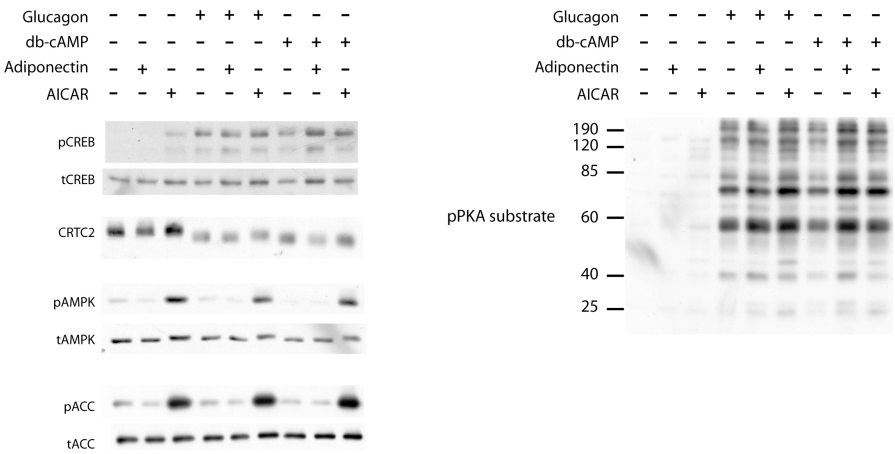
Supplemental Figure 2. Adiponectin induced gene expression following adiponectin tolerance test is not LKB1 dependent. A. Adenovirus infected *LKB1*$^{lox/lox}$ mice were injected intraperitoneally with PBS or 34 μg/g body weight adiponectin and 6 hours later their livers were collected for RNA analysis. The indicated mRNAs were quantified and expressed relative to *Tbp* mRNA levels. The data are represented normalized to the GFP-infected, PBS-injected group. **B-D.** Adenovirus infected *LKB1*$^{lox/lox}$ mice were clamped at euglycemia as indicated in Methods section, and infused with either PBS or 50 ng/min/g body weight of adiponectin. Following experiment, livers were collected for mRNA analysis. **B.** *Ppargc1a*, **C.** *G6pc*, and **D.** *Pck1* mRNA were quantified and expressed relative to *Cypa1* mRNA levels. The data are represented normalized to the GFP-infected, PBS-injected group. For **D.-F.** the inset bar shows the effect of adiponectin regulation on Ad-GFP treated mice.* = $p<0.05$ PBS vs adiponectin, ‡= $p<0.05$ GFP vs Cre



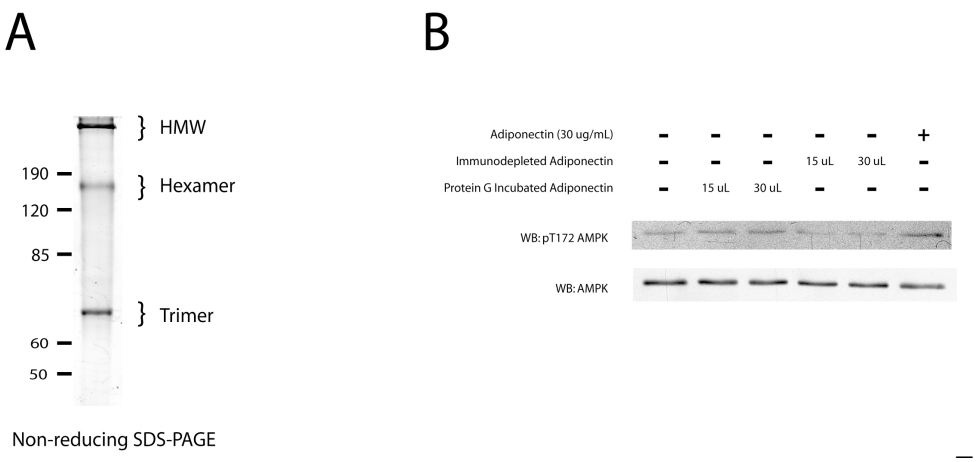
Supplemental Figure 3. Adiponectin-stimulated AMPK phosphorylation parallels increases in total cellular AMP. Western blots of phosphorylated (T172) and total AMPK, phosphorylated (T428) and total LKB1, and phosphorylated (S792) and total Raptor, showing the time course following addition of 100 nM Oligomycin, 1 mM Phenformin, 1mM AICAR, or 30 μg/mL adiponectin. **B-D.** Quantification of total cellular **B.** AMP, **C.** ADP, and **D.** ATP from wild type primary hepatocytes treated with the indicated concentrations of AMPK activators. **E.** Comparison of cellular AMP levels and quantification of pT172 AMPK/total AMPK shows an apparent linear correlation between all activators tested except AICAR, which is mediated through ZMP production and not AMP. * = $p<0.05$ vs. untreated hepatocyte nucleotide levels.



Supplemental Figure 4. Adiponectin signaling in *CRTC2* null primary hepatocytes. **A.** Primary hepatocytes isolated from CRTC2 +/+ and CRTC2 -/- mice were treated with 30 μg/mL adiponectin, 500 μM AICAR, and 5 nM glucagon for 6 hours and probed for CRTC2 (tCRTC2), phosphorylated and total AMPK (pAMPK and tAMPK), and phosphorylated and total ACC (pACC and tACC). **B-D.** Primary hepatocytes isolated from CRTC2 +/+ and CRTC2 -/- mice were treated with 30 μg/mL adiponectin, 500 μM AICAR, and 100 μM dibutyryl cAMP for 6 hours and total RNA was isolated and **B.** *Ppargc1a*, **C.** *Pck1*, and **D.** *G6pc* mRNA was quantified and expressed relative to Cyclophilin A mRNA and normalized to basal mRNA from GFP infected hepatocytes. * = $p<0.05$ vs glucagon, ‡= $p<0.05$ CRTC2 +/+ vs CRTC2 -/-



Supplemental Figure 5. Western blot showing adiponectin and AICAR do not inhibit db-cAMP or glucagon induced PKA activity. Primary hepatocytes were isolated from fed mice and plated on collagen coated 6 well plates in M199 media over night. Cells were stimulated with 5 nM Glucagon, 50 μM db-cAMP, 30 μg/mL Adiponectin, or 250 μM AICAR for 4 hours. Total protein was isolated and probed by western blot for phosphorylated and total CREB, phosphorylated and total AMPK, phosphorylated and total ACC, and proteins reactive with the phosphoPKA substrate antibody.



Supplemental Figure 6. Molecular composition of recombinant adiponectin. A. A representative adiponectin preparation was electrophoresed under non-reducing SDS-PAGE conditions to determine the molecular weight forms present in preparations used for all studies. **B.** Immunodepletion of adiponectin with anti-adiponectin antibody removes AMPK-activating ability.