SUPPLEMENTARY DATA

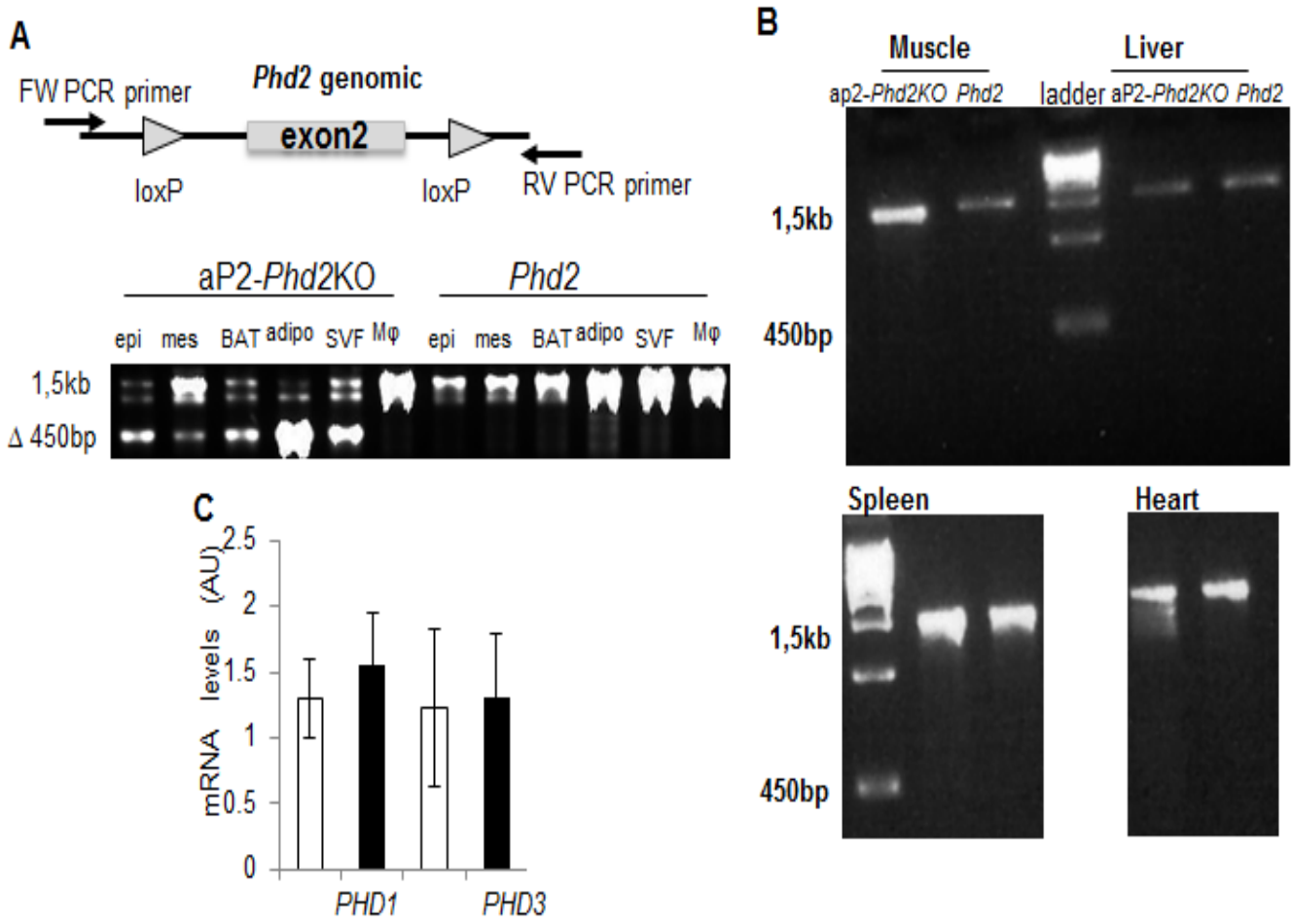
Supplemental Table 1. Plasma NEFA and liver triglyceride levels in aP2-*Hif1a*KO and aP2-*Hif2a*KO mice under control and high fat diets.

	Hif1a **CD (n=6)**	**aP2-*Hif1a*KO CD (n=6)**	***Hif2a*** **CD (n=4)**	**aP2-*Hif2a*KO CD (n=4)**	***Hif1a*** **HFD (n=5)**	**aP2-*Hif1a*KO HFD (n=5)**	***Hif2a*** **HFD (n=4)**	**aP2-*Hif2a*KO HFD (n=4)**
Plasma NEFA mmol/L (5h fast)	1.0±0.07	0.9±0.08	0.8±0.02	1.0±0.05	1.1±0.1	1.1±0.04	0.8±0.05	0.8±0.03
Liver TAG mmol/L corrected for protein	0.4±0.07	0.3±0.07	0.2±0.03	0.2±0.05	1.3±0.05	1.2±0.07	1.1±0.16	1.2±0.15

Data are mean±SEM. CD, control chow diet. HFD, high fat diet (58% kcal fat). NEFA, non-esterified fatty acids and TAG, triglycerides.

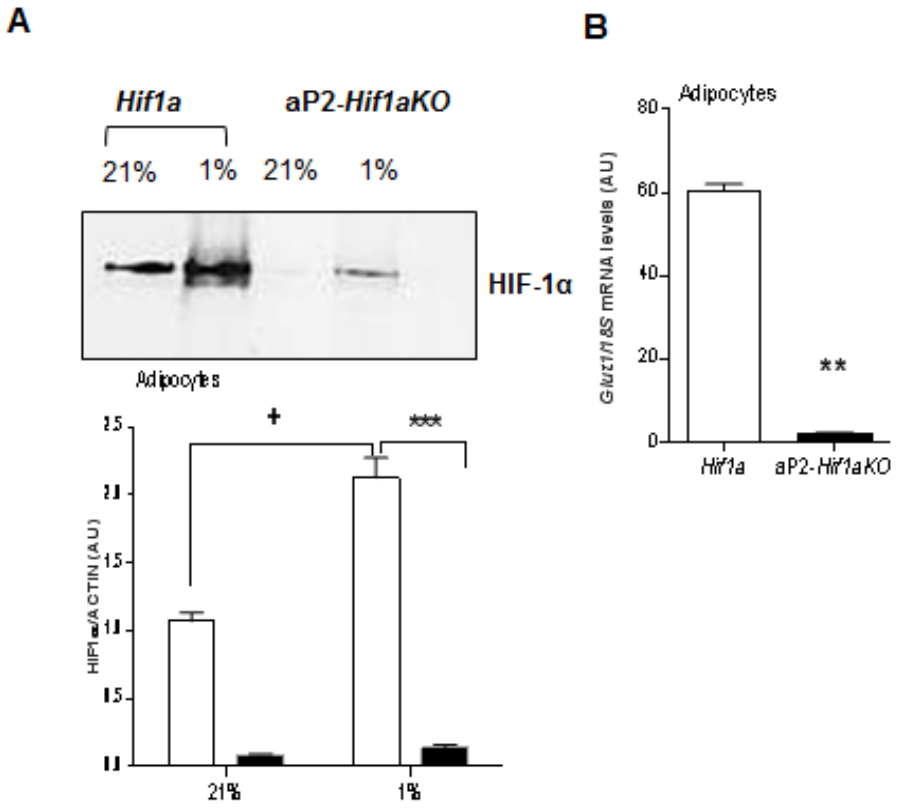
SUPPLEMENTARY DATA

Supplementary Figure 1. *Phd2* levels were not affected by adipocyte-specific *Phd2* deletion in other tissues. ***(A)*** A schematic view (upper panel) of the genomic PCR used to detect the recombined *Phd2* allele (450bp)and agarose gel (lower panel) showing recombination in white adipose tissue depots (epi; epididymal, mes; mesenteric), brown adipose tissue (BAT) and isolated adipocytes (adipo). Note recombination in the stromovascular fraction (SVF) but not in isolated peritoneal macrophages (Mφ) in aP2-*Phd2*KO mice. ***(B)*** Recombination PCR gels show that there is no recombination (Cre-mediated excision) present in muscle, liver, spleen or heart in aP2-*Phd2*KO tissues. **(C)** Adipose *Phd2* deficiency (black bars) did not affect adipose *Phd1* or *Phd3* mRNA levels.



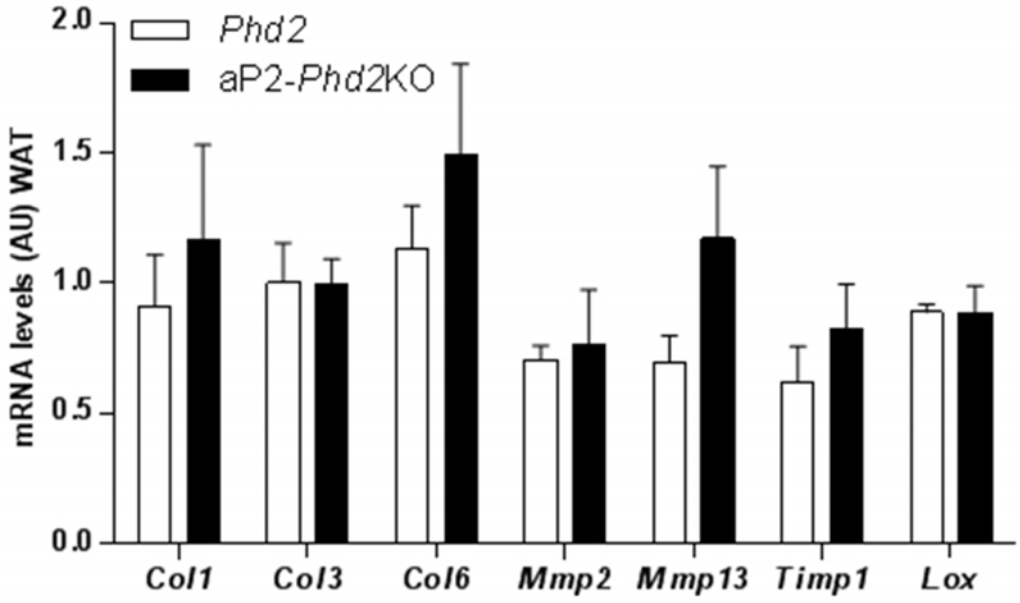
SUPPLEMENTARY DATA

Supplementary Figure 2. *Hif1a* deficient adipocytes do not respond to hypoxic stimulus and have reduced HIFα target genes. ***(A)*** Adipocytes from aP22-*Hif1a*KO mice (black bars, n=3) and *Hif1a* controls (white bars, n=3) were isolated and cultured in 21% O_2 or 1% O_2 for 6 hours. Cells were then lysed and probed with a HIF1α antibody. Representative blot (upper panel) and quantification graph (lower panel) showing significantly ablated HIF1α response in hypoxia in aP2-*Hif1a*KO adipocytes. ***(B)*** *Glut1* mRNA levels in isolated aP2-*Hif1a*KO adipocytes (black bars) are ~24 fold lower compared to control *Hif1a* adipocytes (white bars), n=3/group. mRNA levels are corrected for 18S and protein for beta ACTIN levels. AU; arbitrary units. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ comparisons between genotypes. $^{+}p<0.05$ comparison of the effect of hypoxia within genotype.



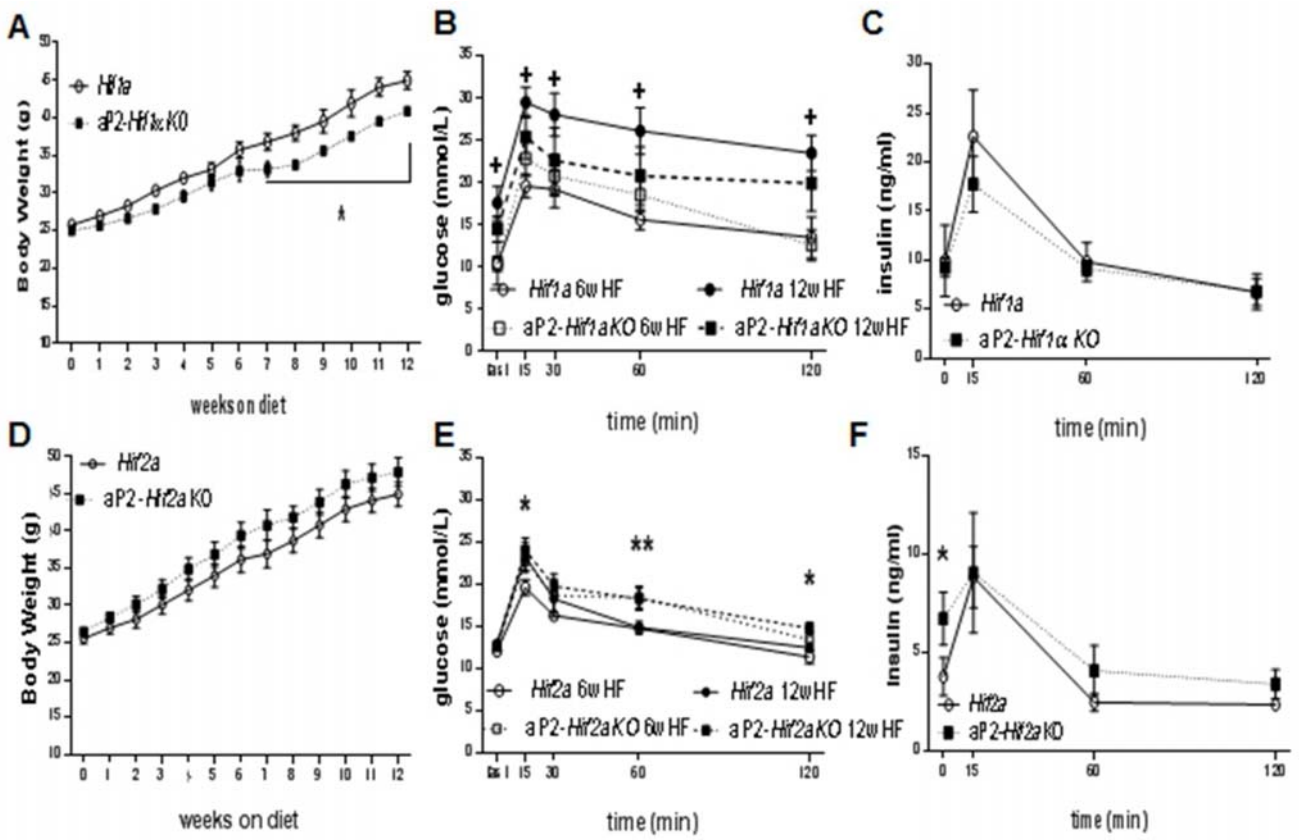
SUPPLEMENTARY DATA

Supplementary Figure 3. Unaltered pro-fibrotic genes in adipose of aP2-*Phd2*KO mice. WAT mRNA levels of pro-fibrotic genes involved in adipose "scarring" such as collagens 1 (*Col1*), 3 (*Col3*), 6 (*Col6*), matrix metalloproteinases 2 and 13 (*Mmp2, Mmp13*) and the collagen crosslinking protein lysyl oxydase (*Lox*) in **aP2-*Phd2*KO** mice (black bars, n=6) were similar to control littermate levels (white bars, n=5).



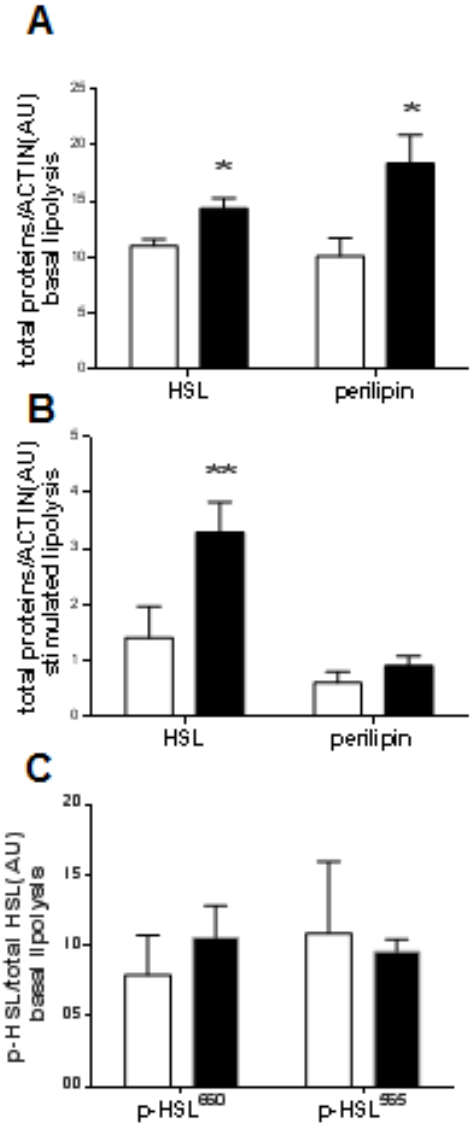
SUPPLEMENTARY DATA

Supplementary Figure 4. Opposing metabolic responses in aP2-*Hif1a*KO and aP2-*Hif2a*KO mice during High FatFeeding. aP2-*Hif1a*KO ***(A-C)*** and aP2-*Hif2a*KO ***(D-F)*** mice with their littermate controls were fed a High fat diet (HF, 58%kcal fat) for 12 weeks. ***(A)*** aP2-*Hif1a*KO (black squares-dashed line, n=6) gained less weight on a HF diet compared to control *Hif1a* mice (open circle-solid line, n=9). ***(B)*** aP2-*Hif1a*KO had similar glucose levels during oral glucose tolerance test (OGTT) at 6weeks (open square-dashed line) on HF diet to control mice and retained their glucose response after 12 weeks (black square-bold dashed line) on the diet, in contrast to control mice that showed impairment (open circle versus black circle, n=5/group). ***(C)*** Similar insulin levels during the OGTT (n=5/group). ***(D)*** aP2-*Hif2a*KO gained similar body weight to control *Hif2a* mice during HF. ***(E)*** aP2-*Hif2a*KO showed impaired response to OGTT at 6 and 12 weeks on HF diet and ***(F)*** aP2-*Hif2a*KO had higher basal fasting insulin during the OGTT compared to control littermates (n=6/group). * $p<0.05$, **$p<0.01$comparisons between genotypes and +$p<0.05$ comparisons of time (6-12 weeks) within genotype.



SUPPLEMENTARY DATA

Supplementary Figure 5. Adipose *Hif1a* deficiency induces NEFA release under hypoxic conditions. aP2-*Hif1a*KO adipocytes (black bars) cultured in normoxia (21%O_2) or hypoxia (1%O_2) and stimulated with CL316,243 show increased lipolytic response in hypoxia (n=4/group). Quantification of immunoblots of***)*** basal and CL316,243 stimulated HSL, phosphorylated HSL and perilipin levels ***(A-C)*** (n=3/group) in aP2-*Hif1a*KO adipocytes in hypoxia. Total HSL and perilipin protein levels are corrected for beta ACTIN (AU), and phosphorylated HSL corrected for total HSL (AU). * p<0.05, ***p<0.001 comparisons between genotypes.



SUPPLEMENTARY DATA

Supplementary Figure 6. Adipose *Hif2a* deficiency does not affect lipolysis. ***(A)*** NEFA release in medium of Ap2-*Hif2a* (black bars) adipocytes cultured in normoxia (21% O_2) or hypoxia (1% O_2) and stimulated with CL316,243 show similar lipolytic response to control *Hif2a* (white bars) adipocytes (n=4/group). ***(B)*** Representative immunoblots of basal total HSL levels and quantification graph (n=3/group) in Ap2-*Hif2a* adipocytes in normoxia and hypoxia. ***(C)*** Representative immunoblots of CL316,243 stimulated total HSL levels and quantification graph (n=3/group) in Ap2-*Hif2a* adipocytes in nomoxia and hypoxia. Protein levels are corrected for beta ACTIN levels.