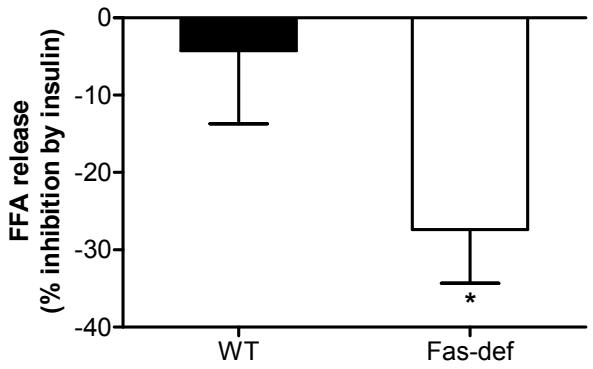
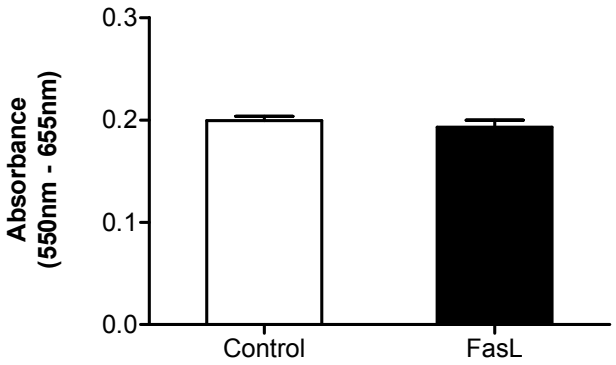
Supplemental Figure 1



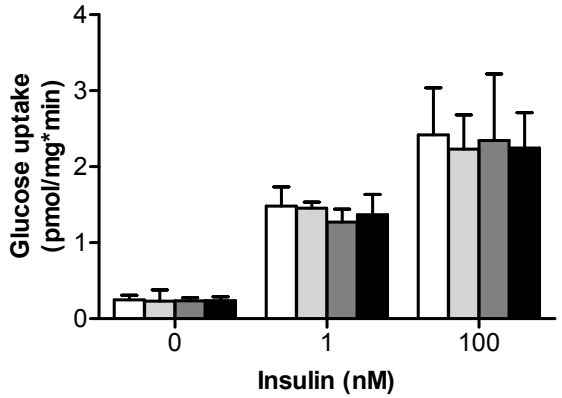
Insulin significantly reduces FFA release from adipocytes isolated from HFD-fed Fas-def mice
Effect of insulin on FFA release from isolated perigonadal adipocytes of HFD-fed WT and Fas-def mice was determined. Results represent the mean ± SEM of 4-5 experiments. *$p < 0.05$ (one sample *t* test).

Supplemental Figure 2



Fas-ligation for 12 hours does not affect viability of 3T3-L1 adipocytes
Mature 3T3-L1 adipocytes were incubated for 12 hours with 2ng/ml FasL. Thereafter, cells were incubated with MTT. Salt was extracted from the cells with DMSO. The amount of yellow MTT reduced to purple formazan was measured spectrophotometrically. Results are the mean ± SEM of 3 independent experiments.

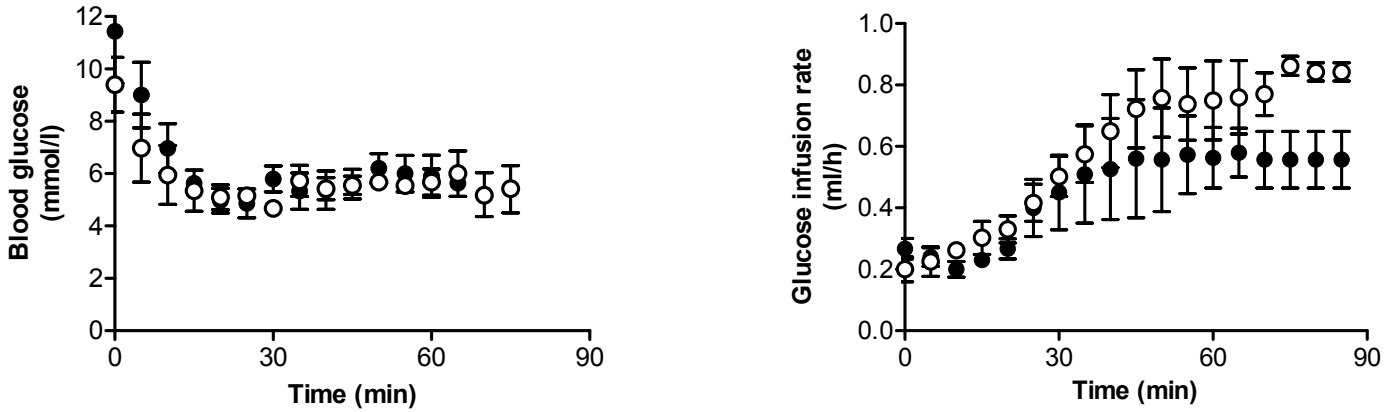
Supplemental Figure 3



Lower FasL concentrations (up to 1 ng/ml) did not reduce insulin-stimulated glucose uptake in 3T3-L1 adipocytes

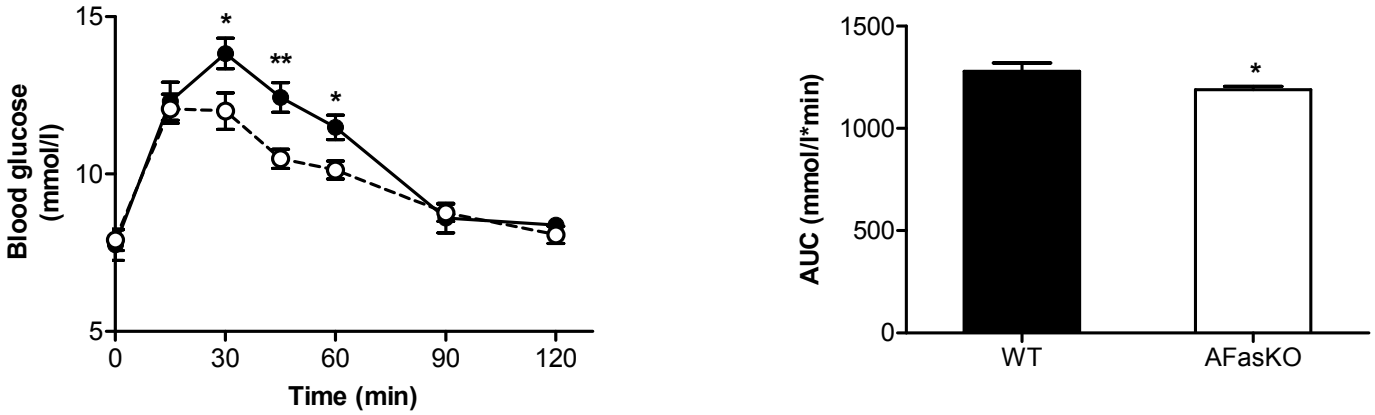
Mature 3T3-L1 adipocytes were incubated without (white bars) or in the presence of 0.05 (light grey bars), 0.2 (dark grey bars) or 1 (black bars) ng/ml FasL for 12 hours. 2-deoxy-^{3}H-D-glucose (^{3}H-2dG) glucose uptake was determined after treatment with or without insulin (1nM or 100 nM). Shown are absolute values of ^{3}H-2dG uptake in untreated or FasL-treated 3T3-L1 adipocytes. Results are the mean ± SEM of 3 independent experiments.

Supplemental Figure 4



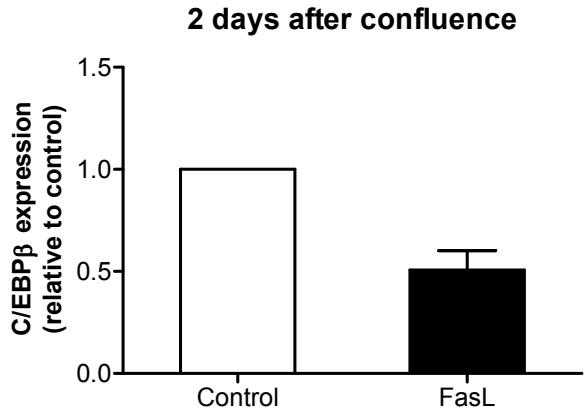
Blood glucose concentrations and glucose infusion rate during hyperinsulinemic-euglycemic clamp
Blood glucose levels were clamped upon insulin infusion between 5 and 6 mmol/l in both WT (●) and AFasKO (○) mice (left graph). In order to maintain euglycemia, glucose infusion rate was adjusted over time (right graph).

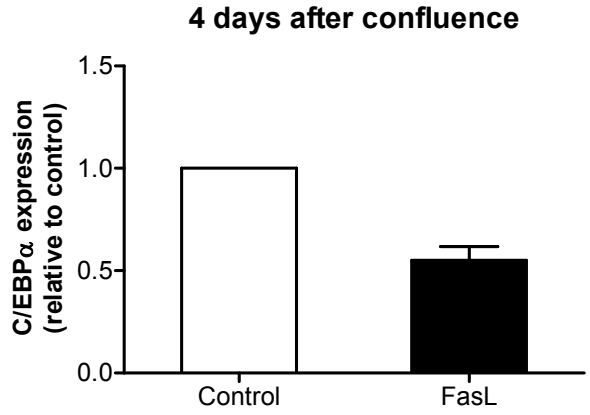
Supplemental Figure 5

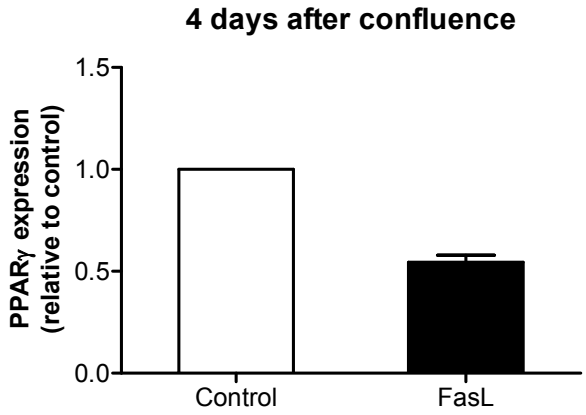


Lower gluconeogenic flux in HFD-fed AFasKO mice
Intraperitoneal pyruvate tolerance test in wild-type (●) and AFasKO (○) mice (left graph). Pyruvate (2g/kg BW) was injected intraperitoneally and plasma glucose levels were detected at indicated time points. Right graph depicts the corresponding analysis of the area under the curve. Results are the means ± SEM of 7 animals per group. *p < 0.05, **p<0.01 (Student's *t* test).

Supplemental Figure 6

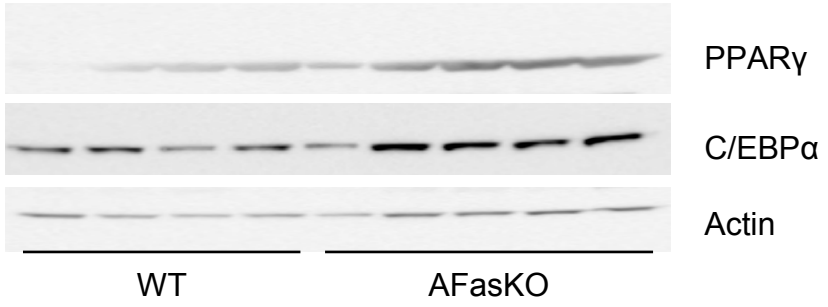


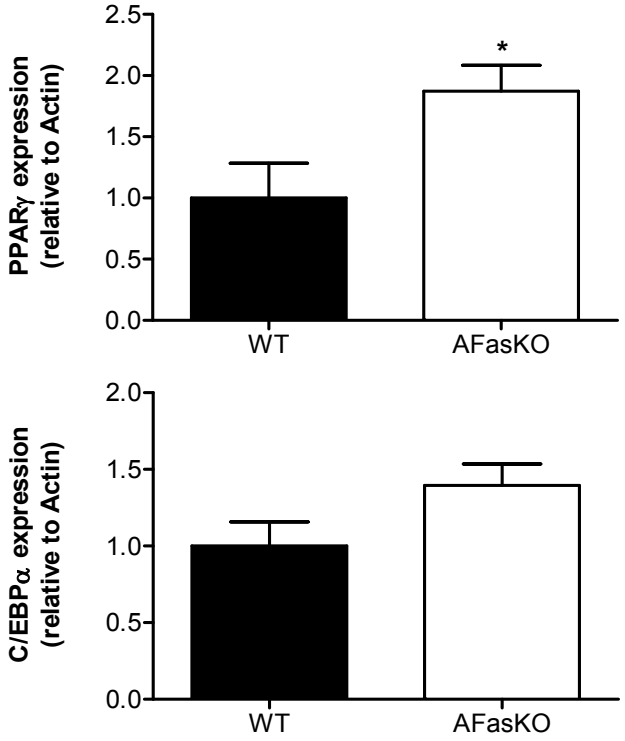




FasL treatment decreases expression of adipocyte differentiation markers
After reaching confluence, 3T3-L1 preadipocytes were incubated with or without 2ng/ml FasL. Differentiation was induced 48 hours later with isobutylmethylxanthine (IBMX), dexamethasone, insulin and rosiglitazone. Total cell lysates were resolved by LDS-PAGE and immunoblotted with anti-C/EBPβ, anti-C/EBPα or anti-PPARγ antibody. Results are the mean ± SEM of 2-3 independent experiments.

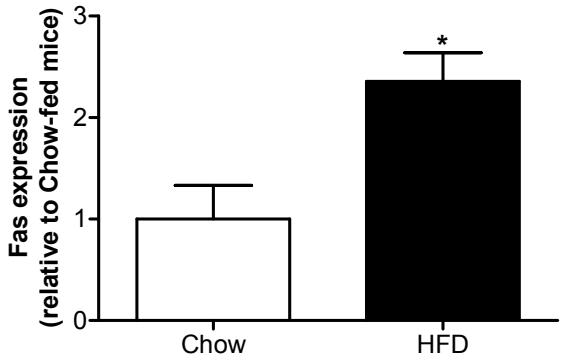
Supplemental Figure 7





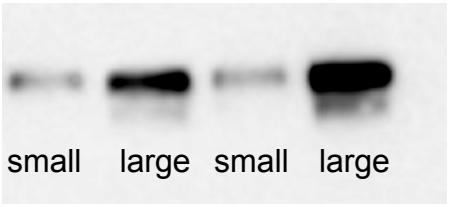
PPARγ and C/EBPα expression is increased in WAT of HFD-fed AFasKO mice
Total lysates were prepared from inguinal fat pads harvested from HFD-fed wild-type and AFasKO mice, resolved by LDS-PAGE and immunobloted with anti-C/EBPα, anti-PPARγ or anti-actin antibody. Results are the mean ± SEM of 4-5 mice per group. *$p < 0.05$ (Student's t test).

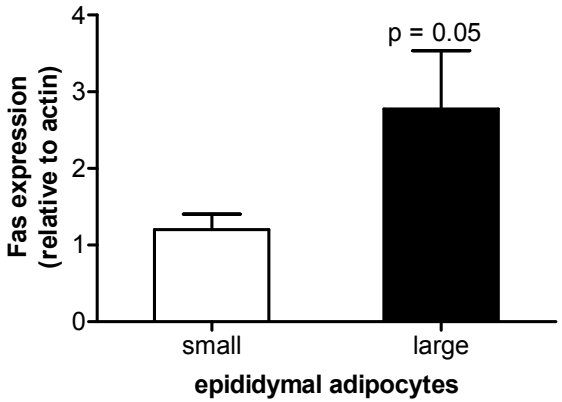
Supplemental Figure 8



Increased Fas-expression in adipocytes of wildtype mice after 4 days of HFD
Total cell lysates were prepared from isolated perigonadal adipocytes harvested from wild-type C57Bl6/J mice fed either chow-diet or HFD for 4 days. Lysates were resolved by LDS-PAGE and immunoblotted with anti-Fas antibody. Results are the mean ± SEM of 3-5 mice per group. *$p < 0.05$ (Student's *t* test).

Supplemental Figure 9

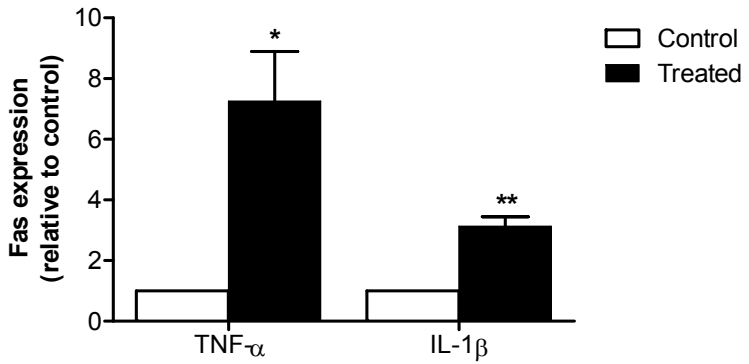




Fas expression is increased in large adipocytes
Wildtype C57Bl6/J mice were fed a HFD for 8 weeks. Adipocytes were harvested from perigonadal fat pads and separated according to their size as described elsewhere[1]. Total cell lysates were resolved by LDS-PAGE and immunoblotted with anti-Fas or anti-actin antibody. A representative immunoblot is shown. Results are the mean ± SEM of 4 independent experiments and are normalized to actin expression.

[1] Wueest, S., Rapold, R.A., Rytka, J.M., Schoenle, E.J., and Konrad, D. 2009. Basal lipolysis, not the degree of insulin resistance, differentiates large from small isolated adipocytes in high-fat fed mice. *Diabetologia* 52:541-546.

Supplemental Figure 10



Fas expression is induced by pro-inflammatory cytokines in 3T3-L1 adipocytes
Mature 3T3-L1 adipocytes were incubated with 5nM TNF-α or 20 ng/ml IL-1β for 12 hours. Total cell lysates were resolved by LDS-PAGE and immunoblotted with anti-Fas antibody. Results are the mean ± SEM of 4 independent experiments and are expressed relative to untreated cells. *$p < 0.05$, **$p < 0.01$ (One sample *t* test).

Supplemental Table 1 Basic clinical characteristics of patients

	Lean (n=5)	Obese (n=10)	Obese and diabetic (n=9)
Age (y)	41.8 ± 2.3	36.2 ± 2.9	47.6 ± 3.5
BMI (Kg/m^2)	23.7 ± 0.5	41.5 ± 1.3	42.6 ± 0.6
FPG (mg/dl)	89 ± 3	89 ± 3	187 ± 32
Fasting insulin (_U/ml)	8.9 ± 2.7	16.0 ± 2.6	14.8 ± 3.8
HbA1C (%)	5.3 ± 0.1	5.6 ± 0.1	7.8 ± 0.5
Triglycerides (mg/dl)	116 ± 3	143 ± 21	230 ± 46
Total cholesterol (mg/dl)	177 ± 5	199 ± 12	239 ± 16
AST (IU/L)	n. d.	21.8 ± 2.9	34.4 ± 11.2
ALT (IU/L)	n. d.	21.5 ± 4.6	41.6 ± 16.3

n. d.: not determined

Supplemental Table 2 mRNA expression in white adipose tissue of HFD-fed wild-type (WT) and AFasKO mice relative to WT

	WT	AFasKO
Adiponectin	1.0 ± 0.06	1.12 ± 0.10
PPAR_	1.0 ± 0.07	0.88 ± 0.09
Resistin	1.0 ± 0.07	0.79 ± 0.07 *
MCP-1	1.0 ± 0.10	0.69 ± 0.07 *
IL-6	1.0 ± 0.09	0.70 ± 0.08 *
IL-1_	1.0 ± 0.30	0.65 ± 0.07
KC	1.0 ± 0.11	0.90 ± 0.09
TNF-_	1.0 ± 0.08	0.89 ± 0.13
CD11b	1.0 ± 0.06	0.63 ± 0.11 **
IL-10	1.0 ± 0.18	3.24 ± 0.66 **
Arginase 1	1.0 ± 0.10	1.89 ± 0.45

Results are the means ± SEM of five to nine independent experiments. *p < 0.05, **p < 0.01 (Student's *t* test).