Disruption of glucose homeostasis by β–cell specific deletion of ABCA1 and ABCG1 is linked to increased adiposity

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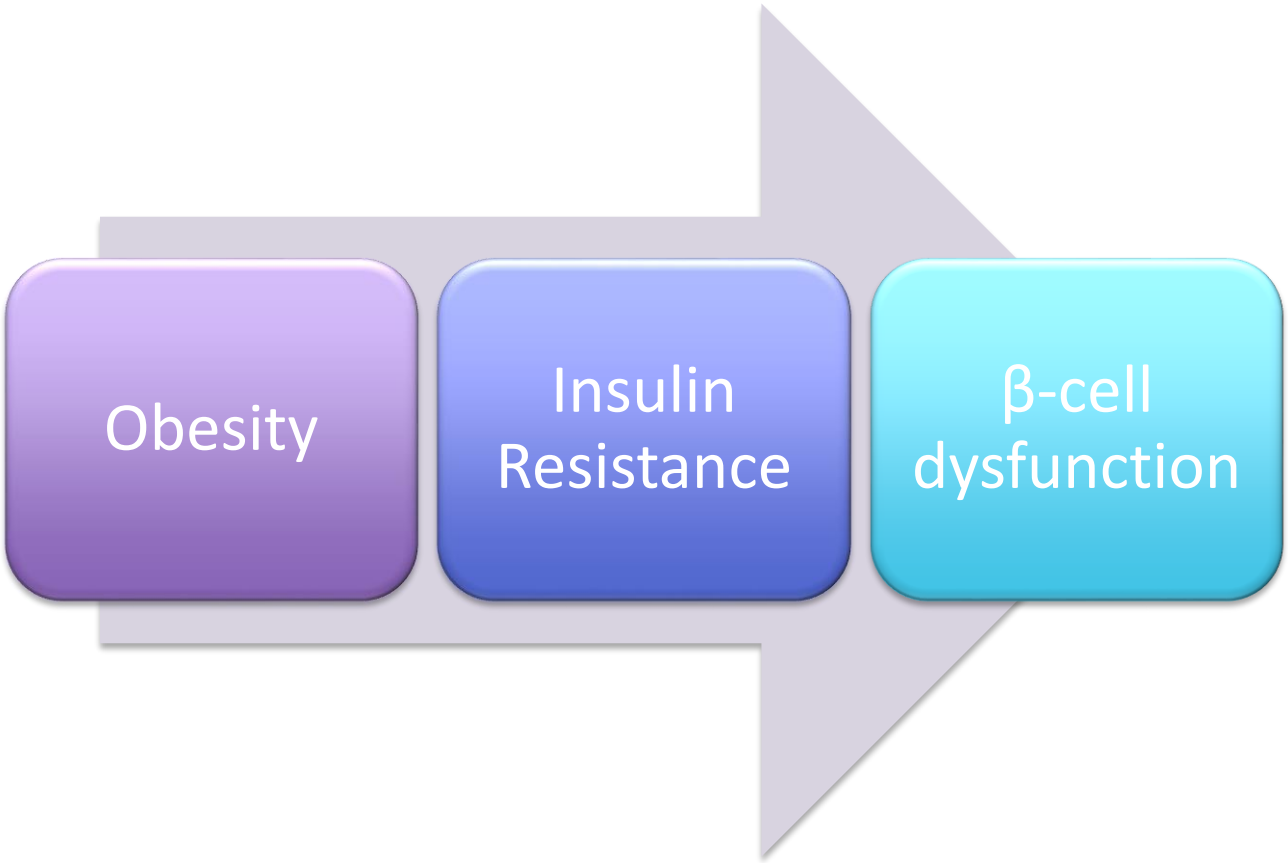
Background

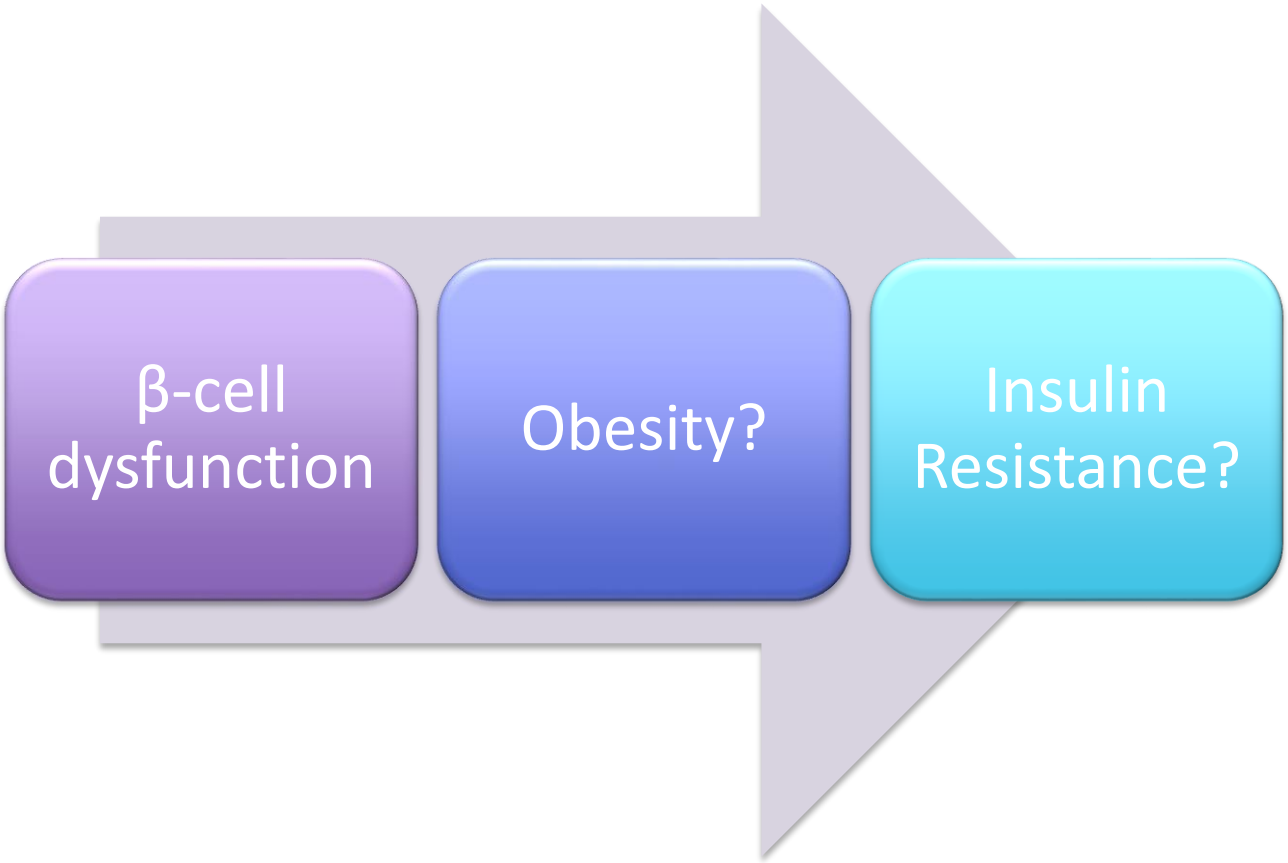
- Pancreatic lipid accumulation can decrease β-cell insulin secretion independent of insulin resistance

- β-cell dysfunction can precede insulin resistance in:
  - patients genetically predisposed to type 2 diabetes
  - obese adolescents
  - Japanese and Pima Indian populations
  - patients with ABCA1 loss of function mutations

Dogma of diabetes



Dogma of diabetes



Background

- Previous studies on β-cell specific ABCA1 KO mice on WT and ABCG1 global KO background:
  - Increased islet sterol accumulation
  - Increased basal blood glucose
  - Decreased glucose tolerance
  - Decreased insulin release from β-cells
  - Increased expression of inflammatory markers in β-cells
  - Macrophage infiltration in islets
  - Normal insulin sensitivity

Brunham et. al, *Nature Medicine* 2007
Kruit et. al, *Diabetes* 2012

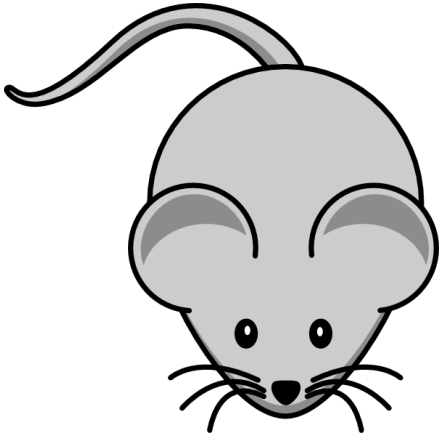
Background

- Global knockout of ABCG1 protects mice from obesity (Buchmann et. al, *Endocrinology* 2007)

Aim

What impact does specific deletion of ABCA1 AND ABCG1 have on β-cell function?

Methodology



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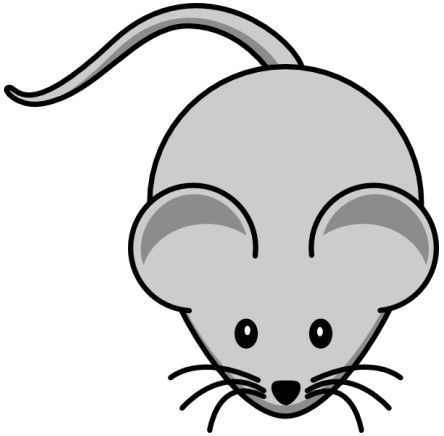
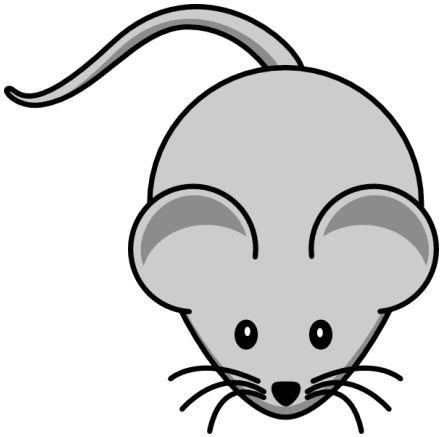


Ins2Cre

=

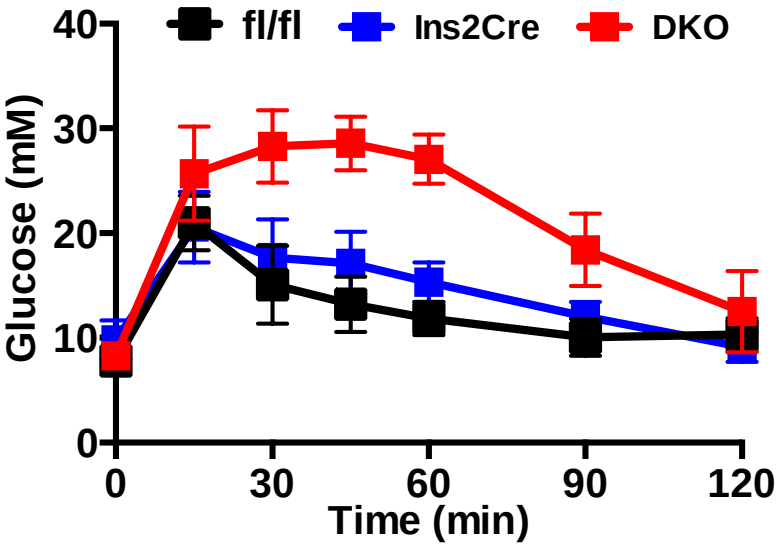
abca1fl/fl abcg1fl/fl
(fl/fl)

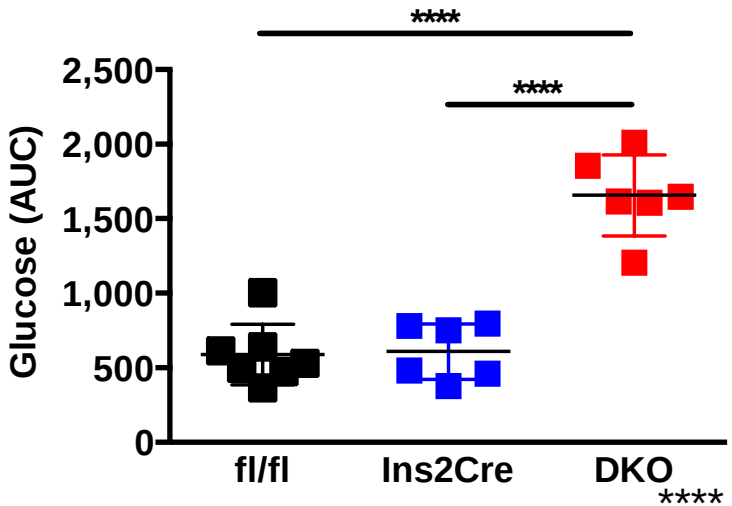


β-cell ABCA1 ABCG1 KO (DKO)

Glucose tolerance

- DKO mice have impaired glucose tolerance
- 16 week old mice fasted for 5 h, i.p. injection 2 g glucose/kg
- No significant difference between fl/fl and Ins2Cre control mice.

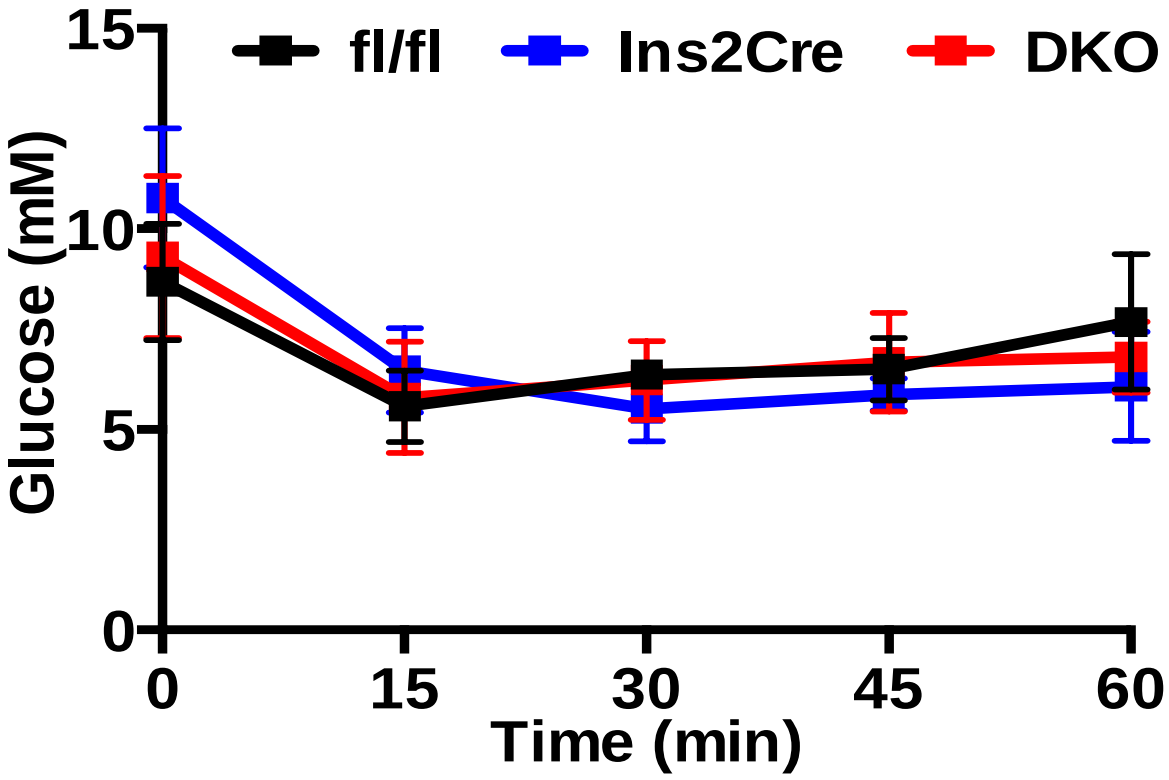




**** $p < 0.001$

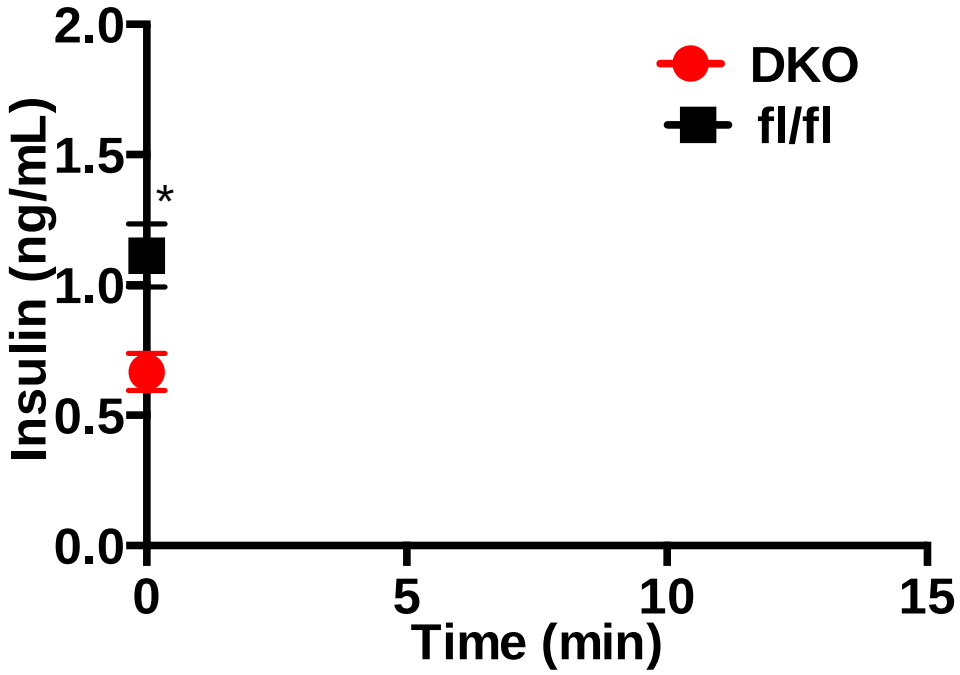
Insulin sensitivity

- DKO mice have normal insulin sensitivity
- 16 week old mice, random fed, i.p. injection 1 U insulin/kg



Insulin release

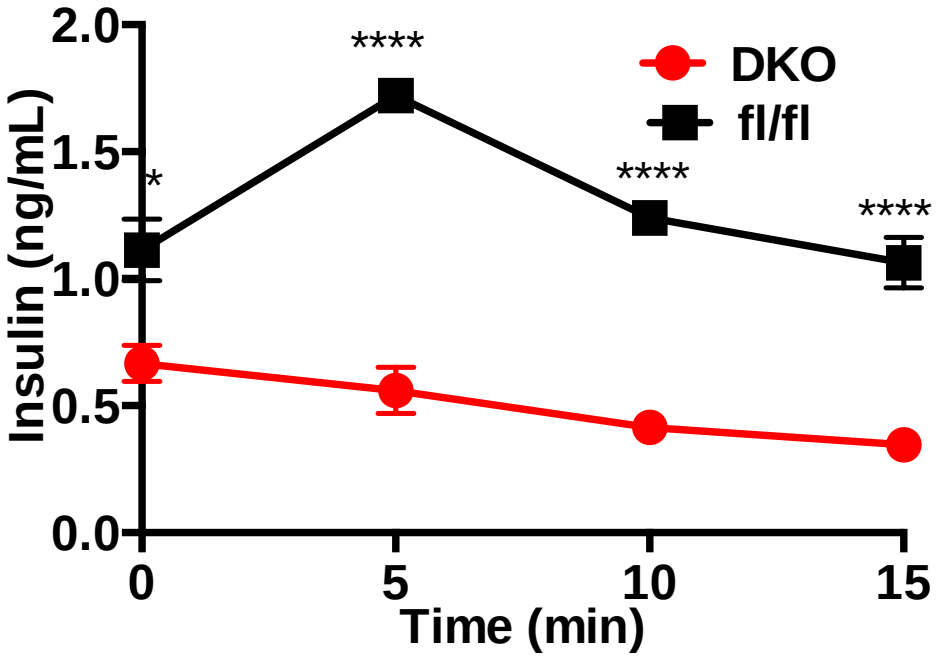
- DKO mice have decreased basal plasma insulin



* $p < 0.05$, **** $p < 0.001$

Insulin release

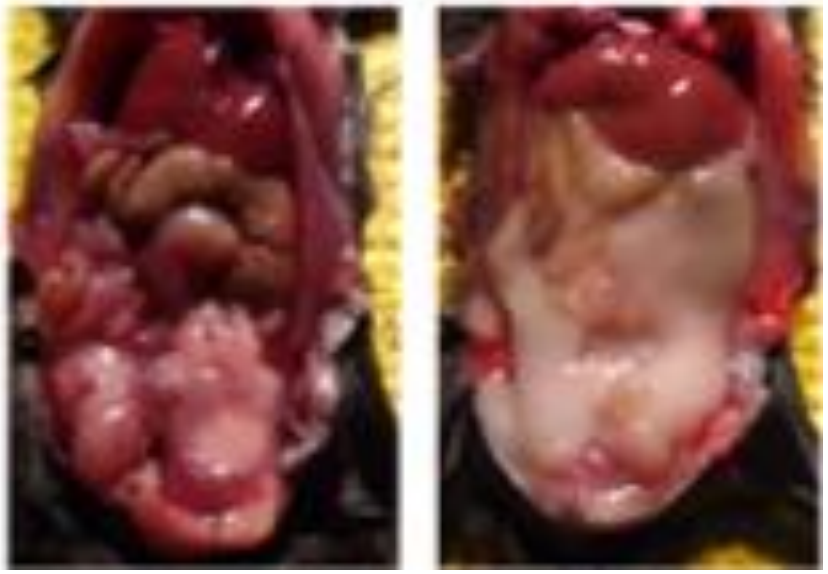
- DKO mice have decreased basal plasma insulin
- Impaired insulin release in response to glucose challenge
- 16 week old mice fasted for 5 h, i.p. injection 3 g glucose/kg



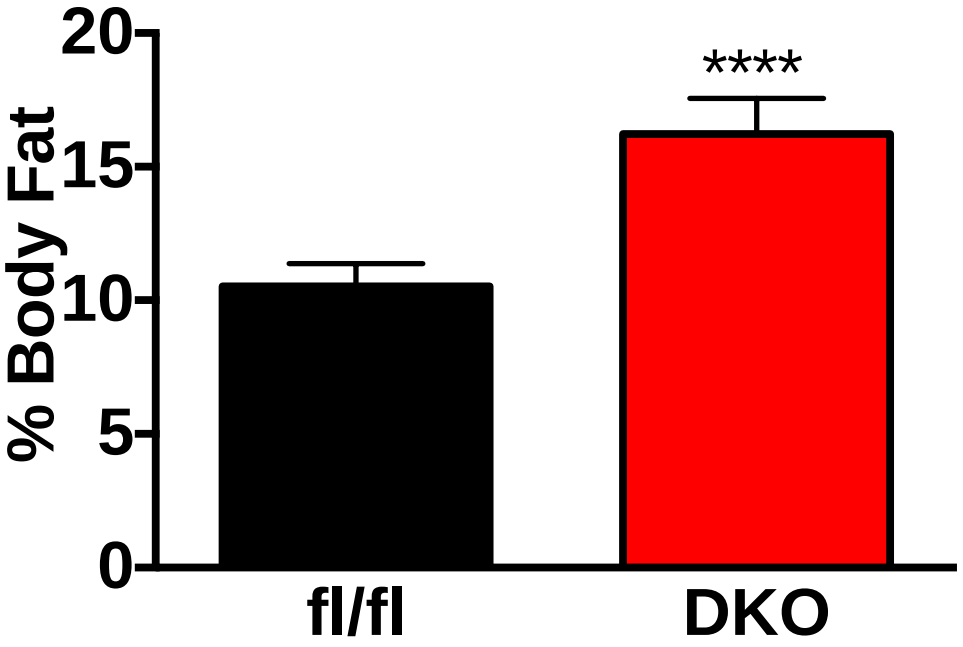
* $p < 0.05$, **** $p < 0.001$

Adiposity

- At 16 weeks, DKO mice have increased adiposity

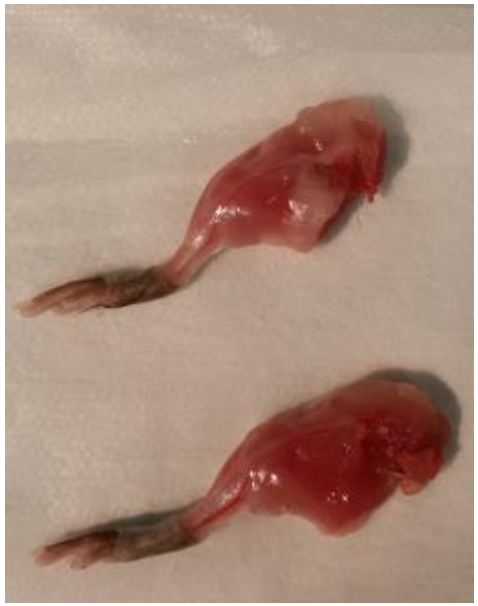


fl/fl DKO



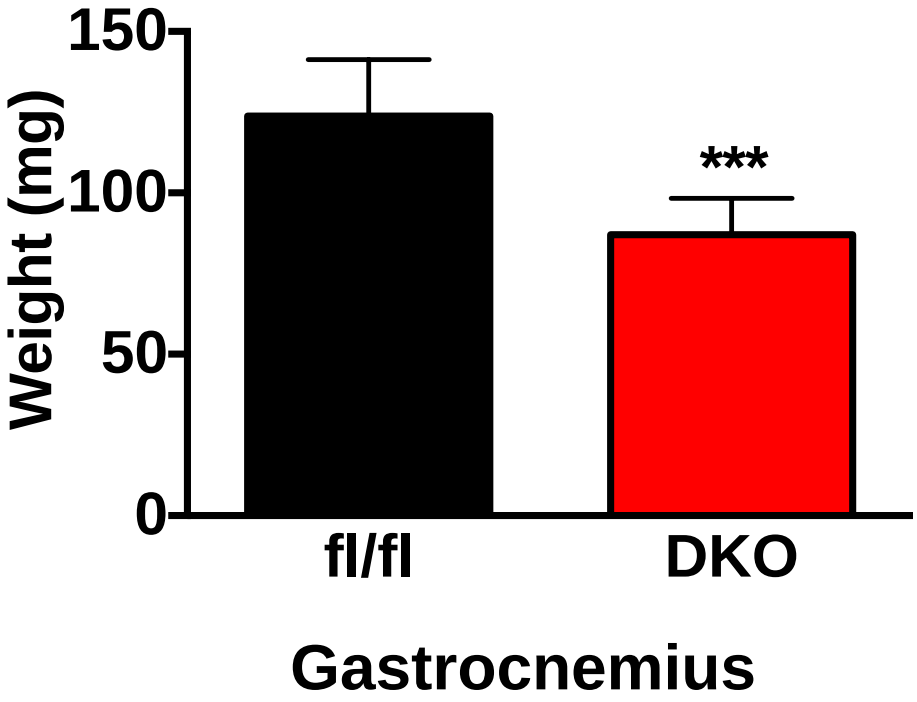
Skeletal muscle

- At 16 weeks, DKO mice have increased reduced muscle mass



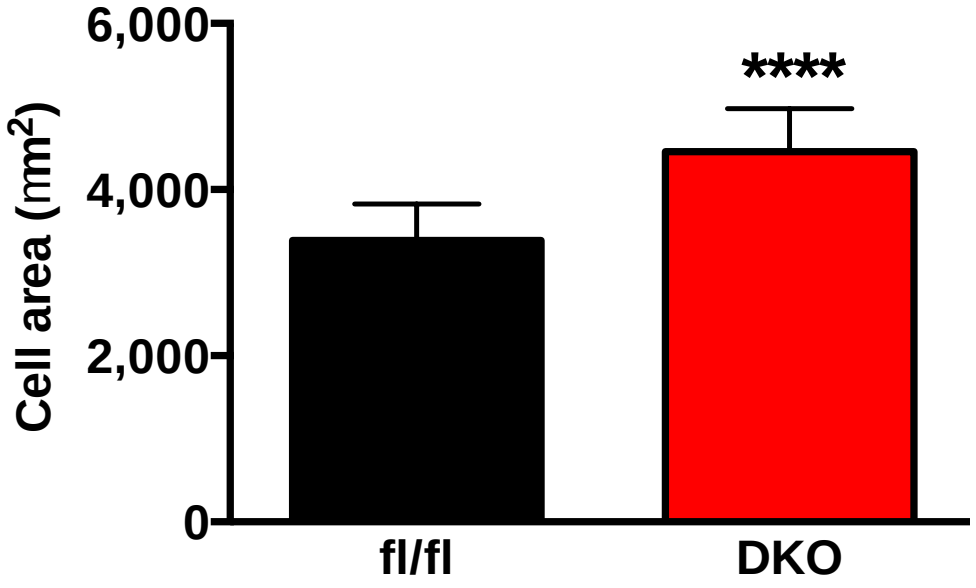
DKO

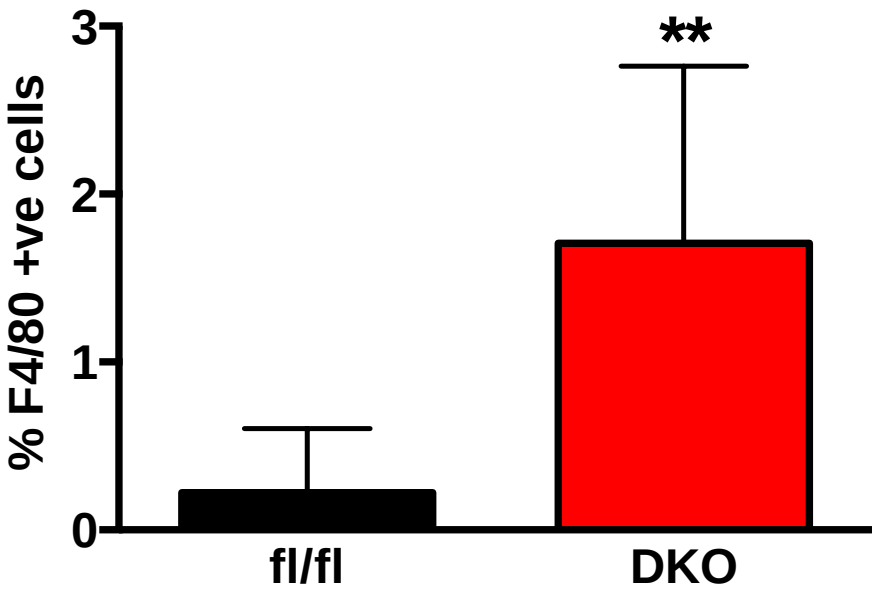
fl/fl



Adipose inflammation

- Adipocyte size increased in DKO mice
- White adipose tissue from DKO mice has increased macrophage infiltration

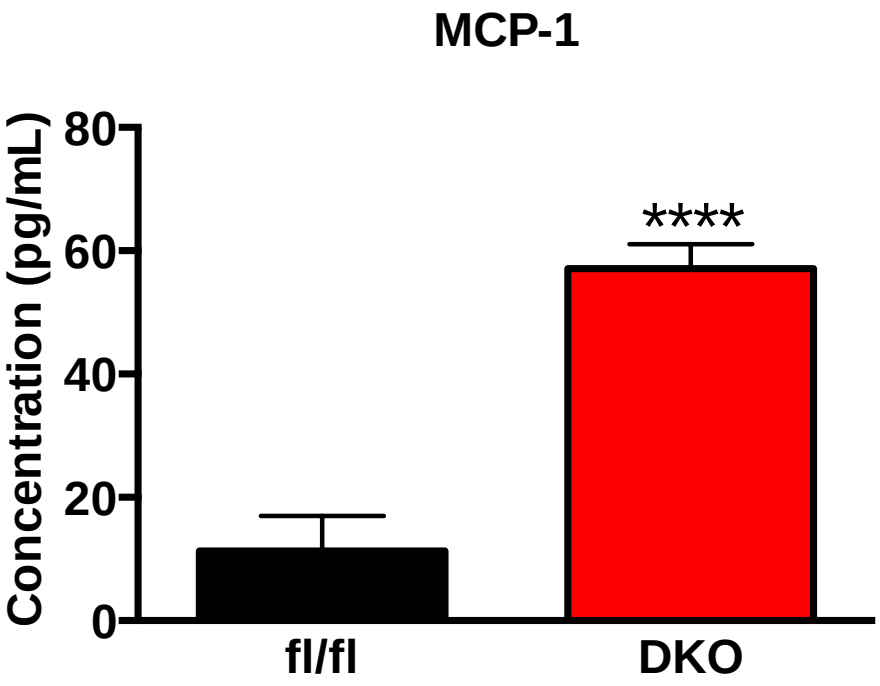


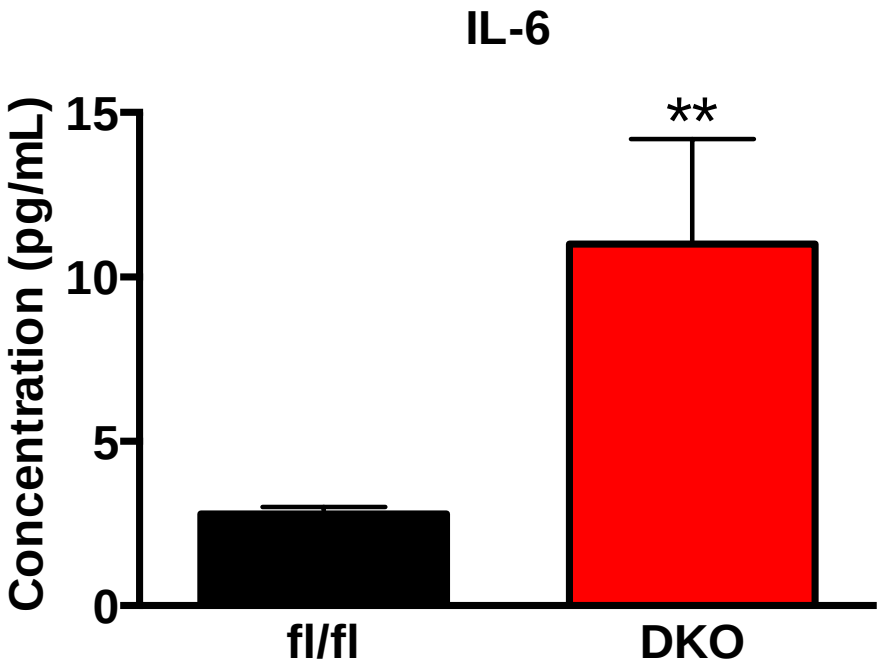


** $p < 0.01$, **** $p < 0.001$

Inflammation

DKO mice have increased plasma levels of inflammatory markers

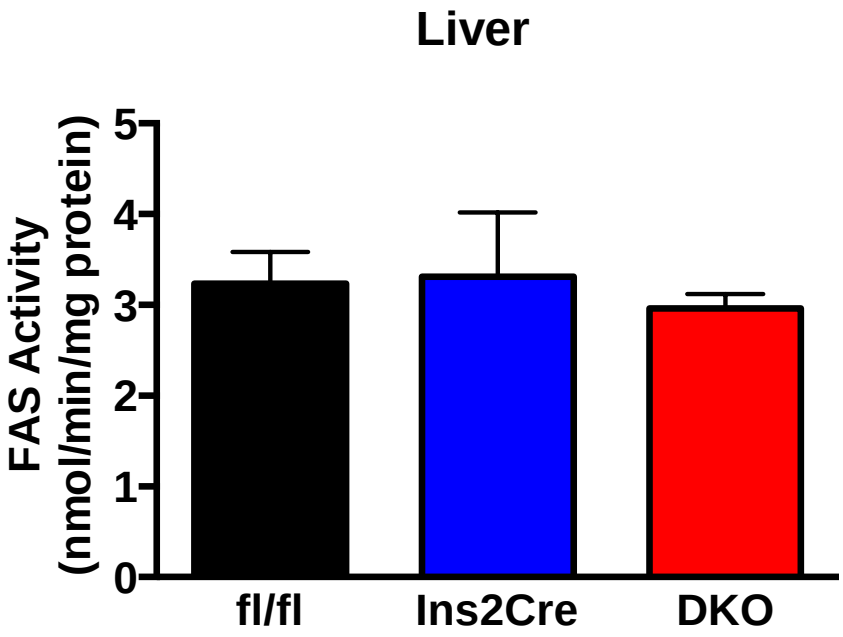


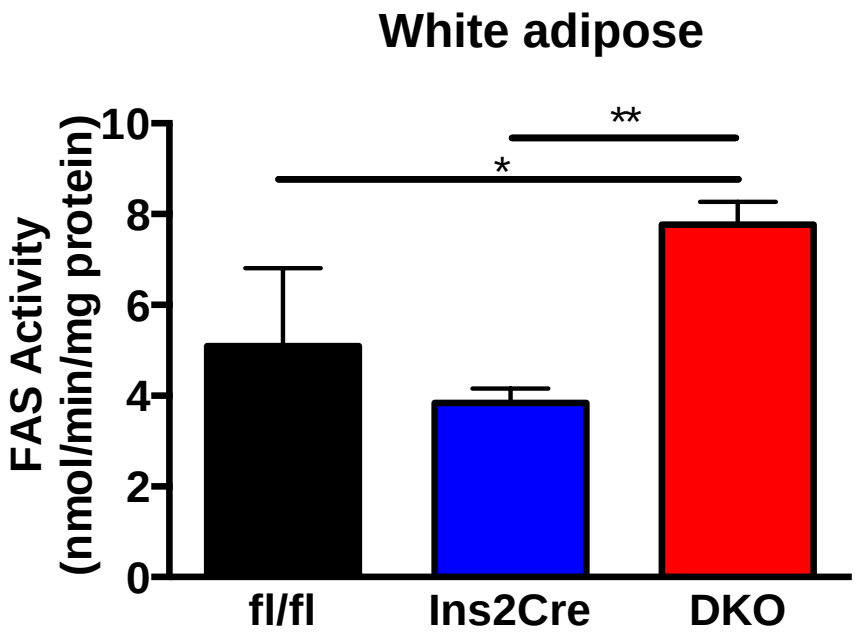


** $p < 0.01$, **** $p < 0.001$

Fatty Acid Synthase

Fatty Acid Synthase activity unchanged in liver, but increased in white adipose of DKO mice



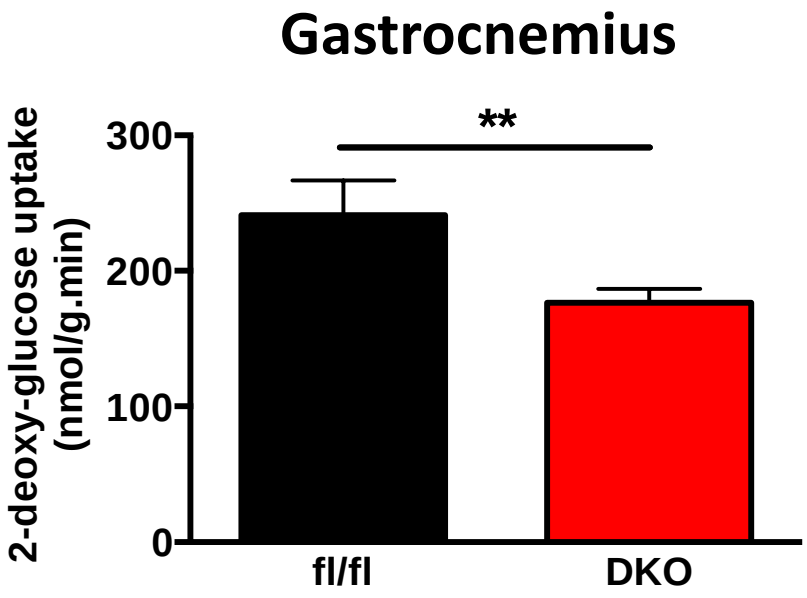


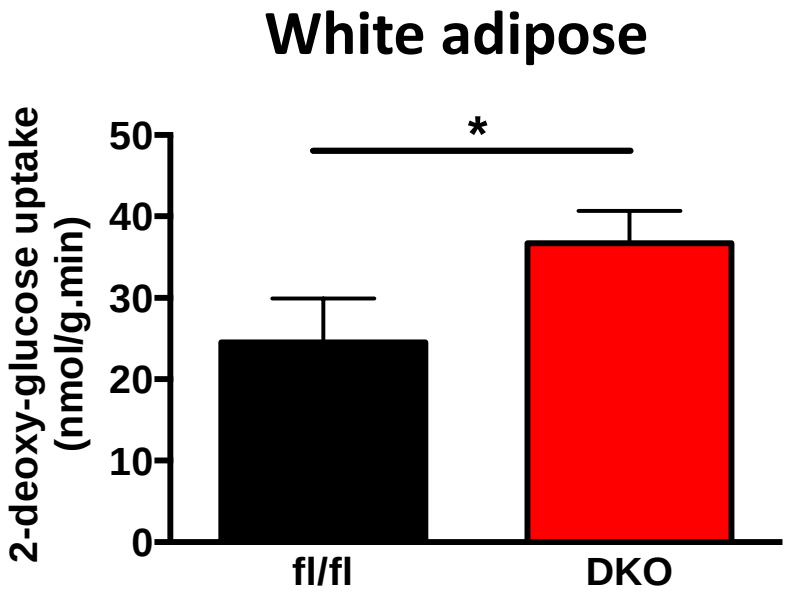
Acetyl -CoA + Malonyl-CoA $\xrightarrow[\text{NADPH}]{\textit{Fatty acid synthase}}$ Palmitic acid + NADP

* $p < 0.05$, ** $p < 0.01$

Glucose uptake

- Glucose uptake into skeletal muscle decreased in DKO mice.
- Uptake into white adipose tissue increased





Altered glucose metabolism

- Protein changes in skeletal muscle identified by ESI-MS and pathway analysis

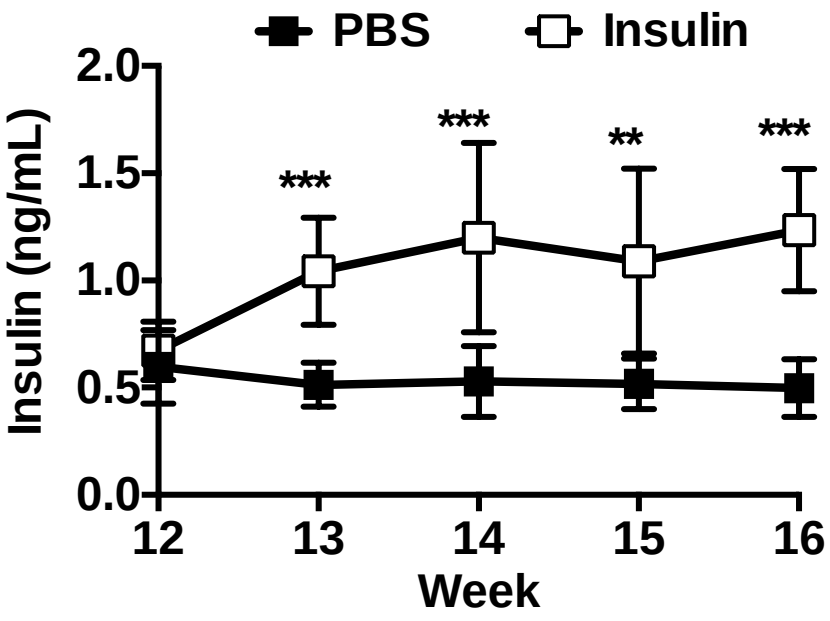
- Significant changes in proteins involved in:
  - Glycolysis
  - Gluconeogenesis
  - Amino acid metabolism
  - Glutaryl-CoA degradation

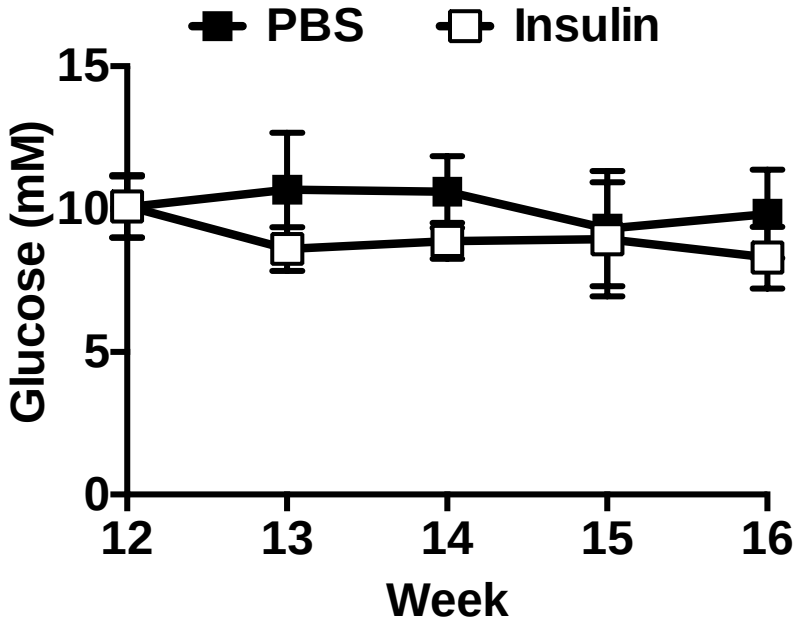
- Suggestive of decreased glucose metabolism and utilisation of amino acid metabolism for energy production

Are suboptimal insulin levels driving this increase in adipose mass, increased inflammation and redistribution of metabolic substrates from muscle to adipose?

Insulin supplementation

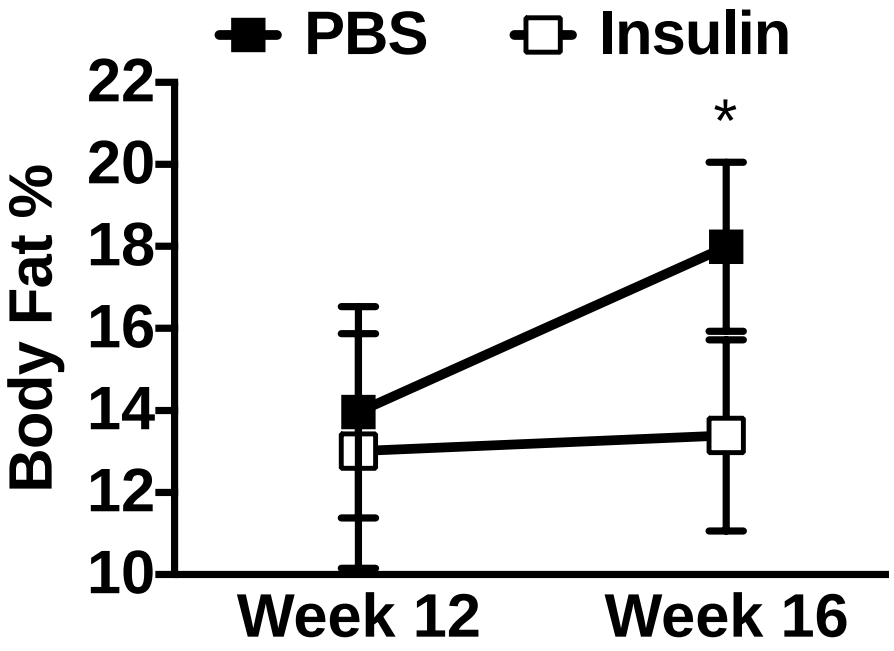
Insulin pumps raised plasma insulin and had a non-significant effect on fed plasma glucose

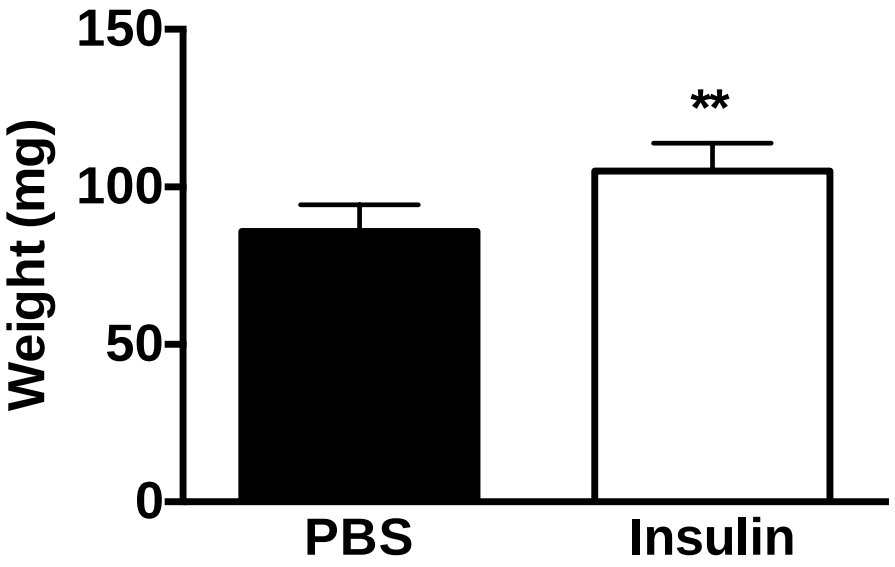




Insulin supplementation

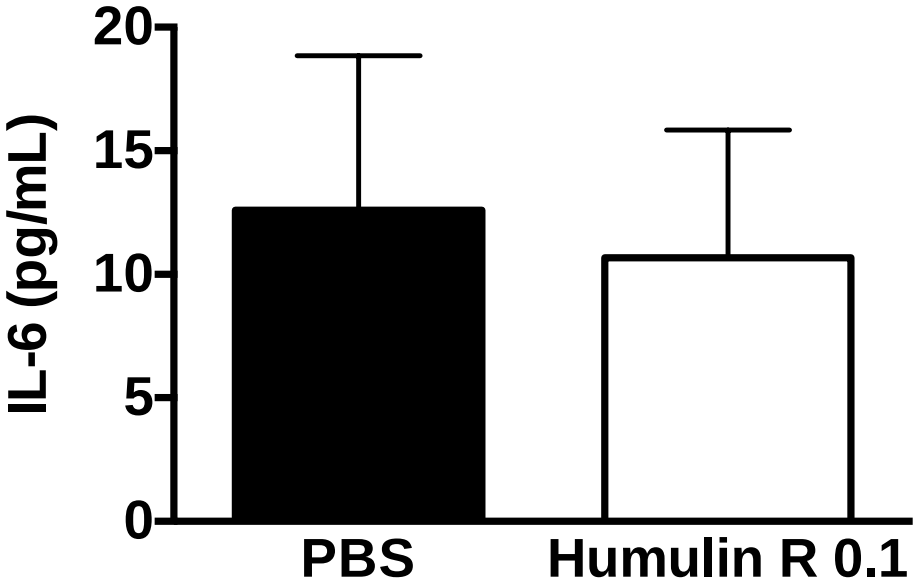
- Mice treated with insulin via osmotic pumps had significantly **less body fat** accumulation **more muscle** between 12 and 16 weeks relative to control

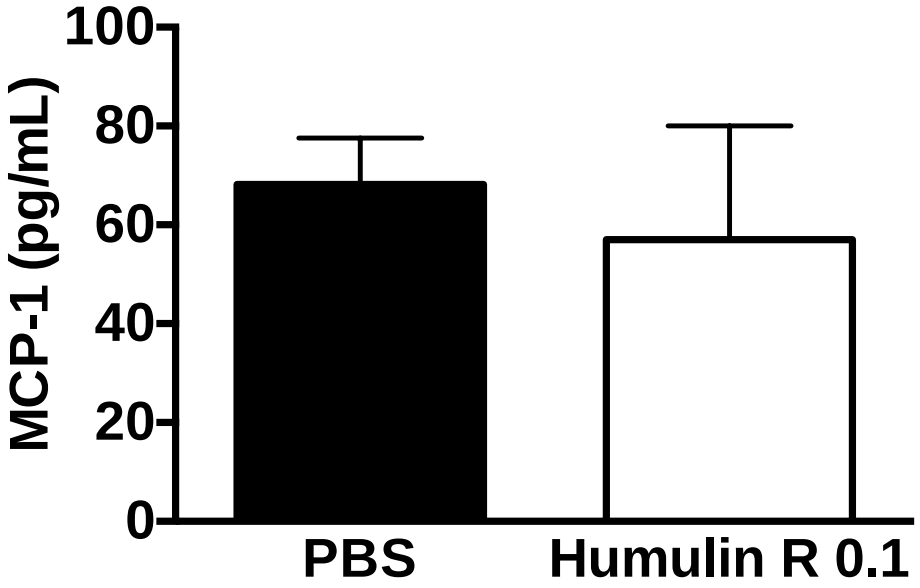




Osmotic Pumps

- Restoring insulin did not reverse inflammatory markers





Conclusions

- β-cell specific knockout of ABCA1 and ABCG1 results in:
  - Glucose intolerance
  - Impaired insulin release in response to glucose
  - Increased adiposity
  - Reduced muscle mass

Conclusions

- Increased adiposity due to redistribution of metabolic substrates to adipose
- Insulin supplementation ablates adipose expansion but appears not to decrease inflammation