

Nutrients, control of gene expression and metabolic homeostasis



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BARCELONA

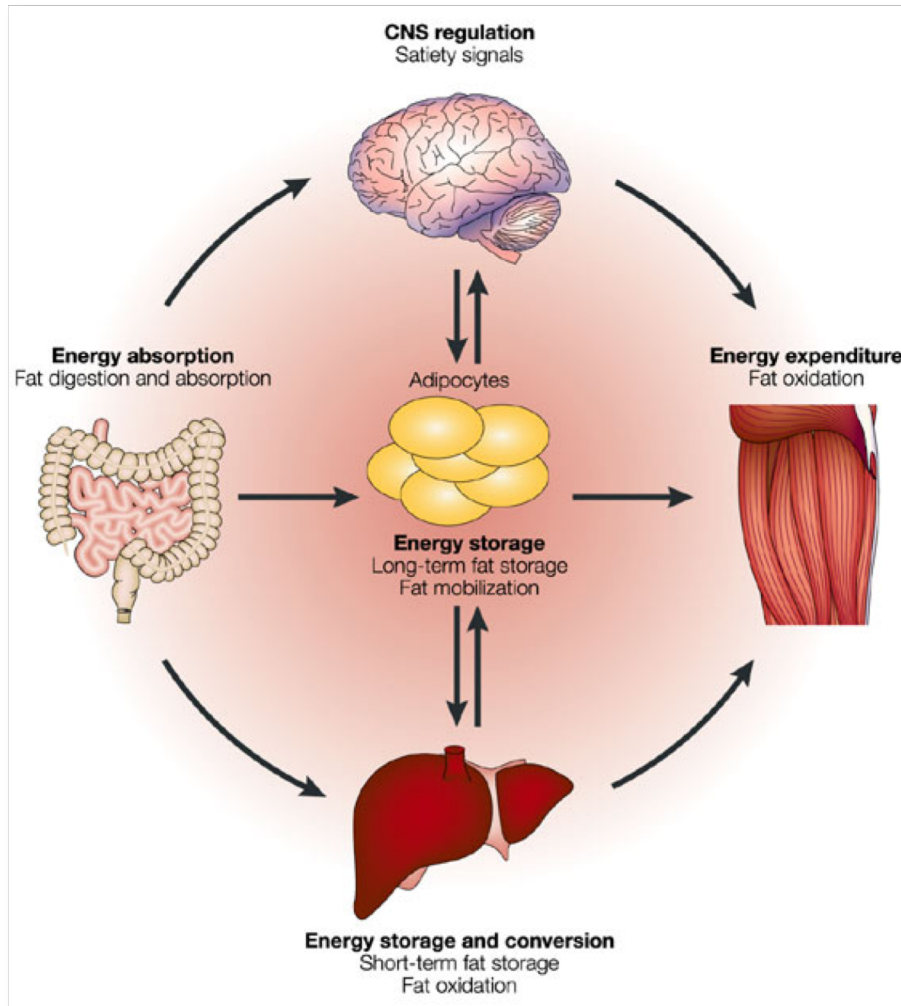


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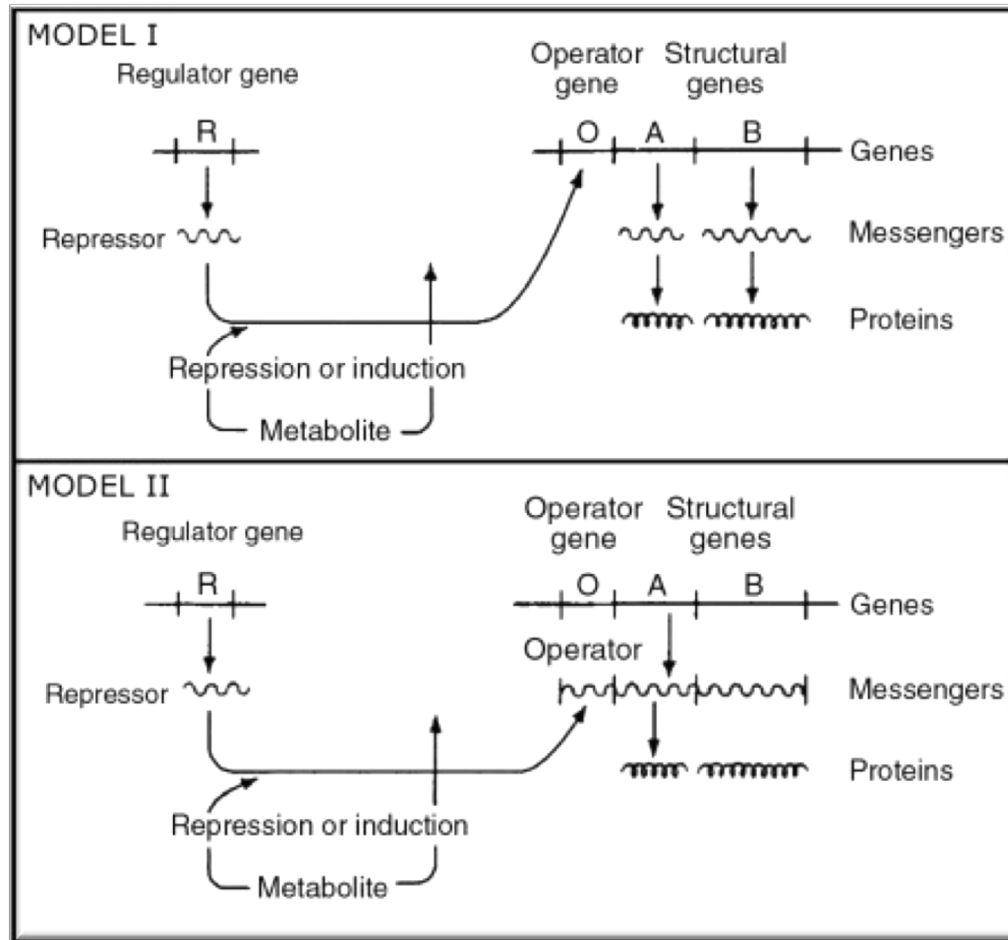
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Lipid metabolic enzymes: emerging drug targets for the treatment of obesity

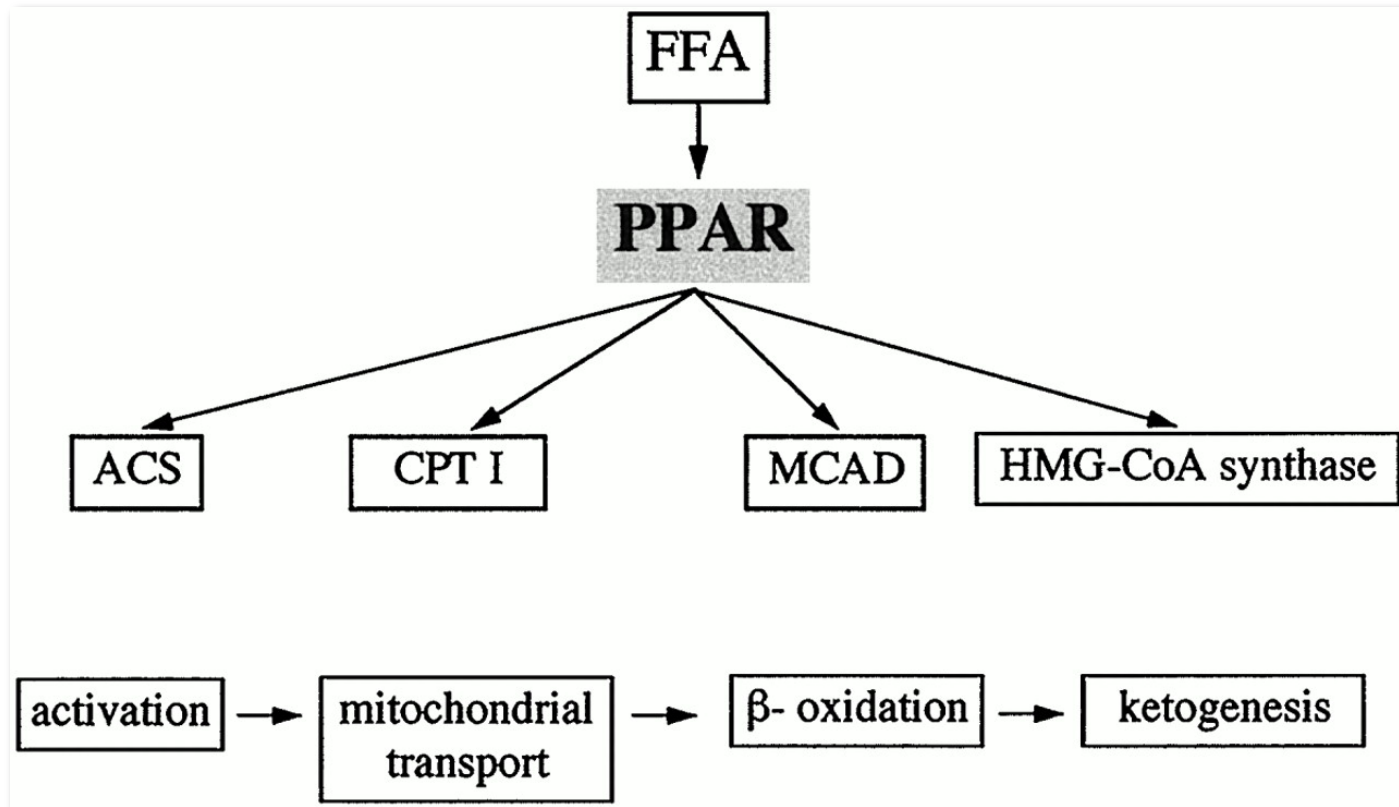


- Obesity
 - Type 2 diabetes
 - Insulin resistance
 - Dyslipidaemia
 - Hypertension
 - Coronary heart disease
 - Stroke
 - Gallbladder disease
 - Sleep apnoea
 - Osteoarthritis
 - Hyperuricaemia
 - Cancer

Metabolic control of gene expression. The beginning



PPAR-mediated fatty acid control of mitochondrial fatty acid metabolism

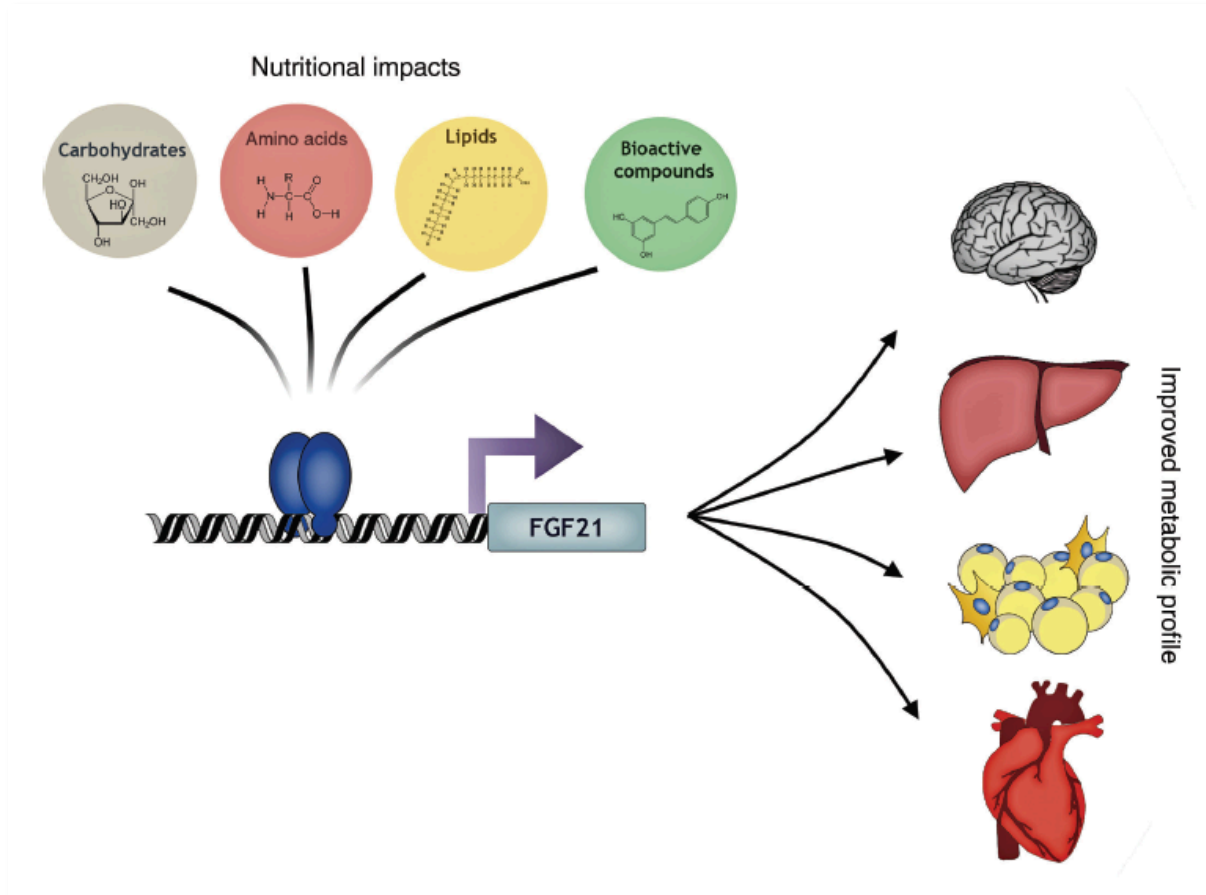


Mascaró C et al. J. Biol. Chem. 1998;273:8560-8563

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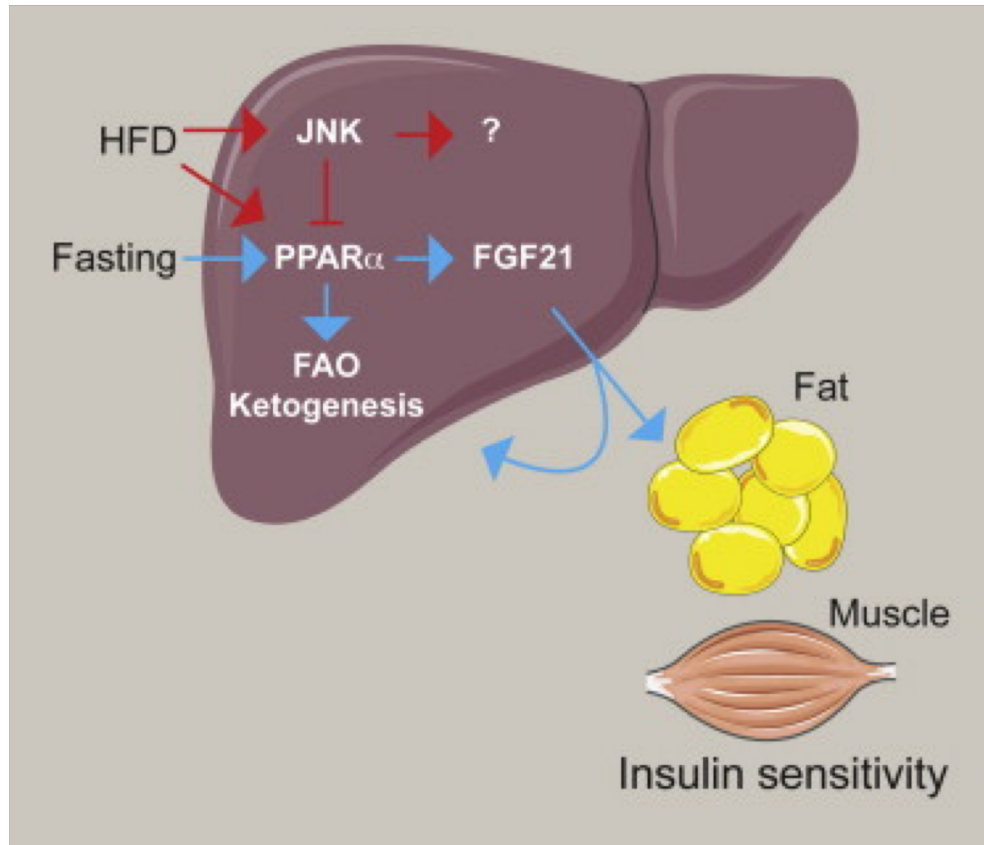
jbc

FGF21 expression is regulated by diet and its effects are widely distributed.

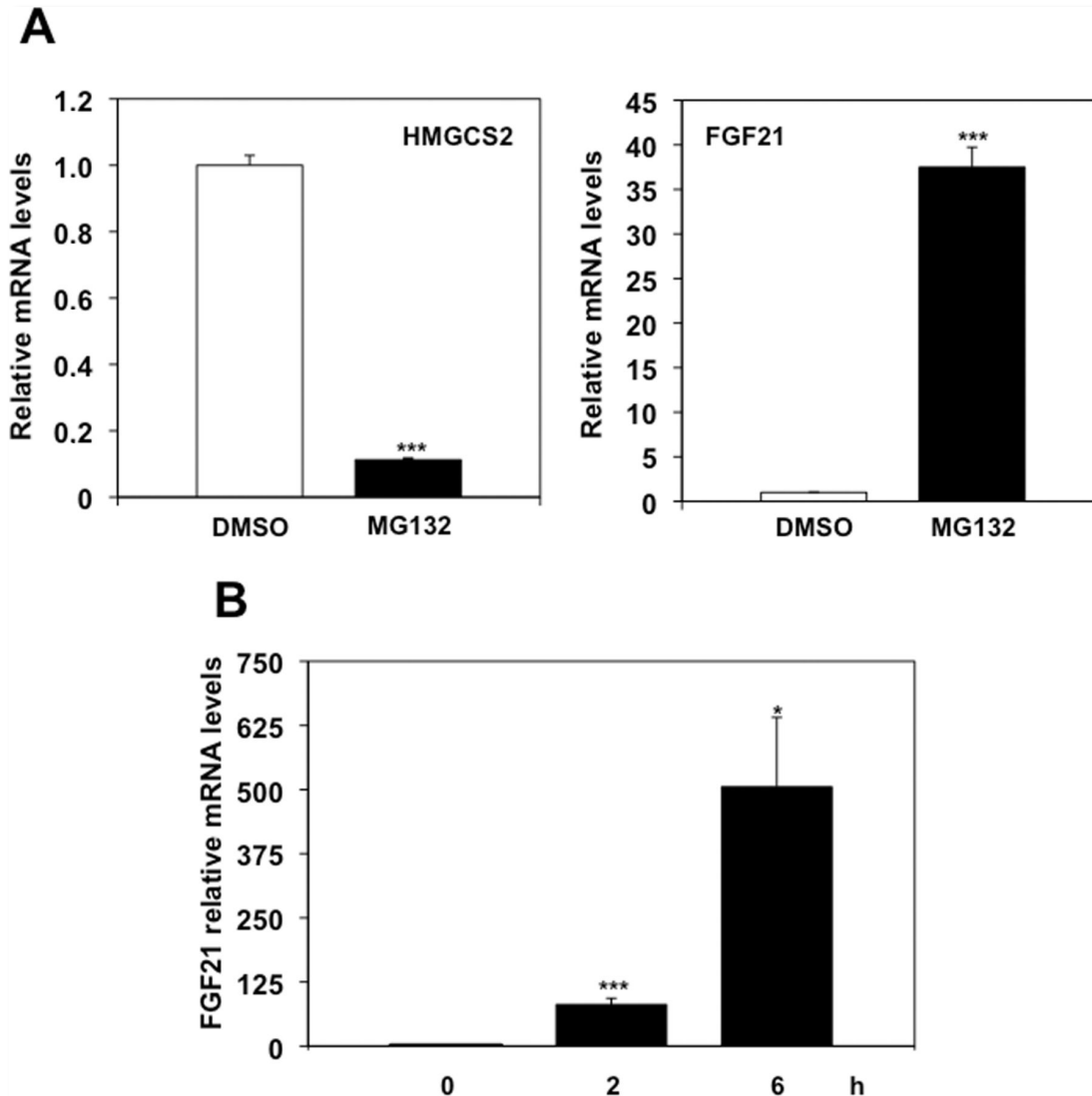


FGF21: A missing link in the biology of fasting

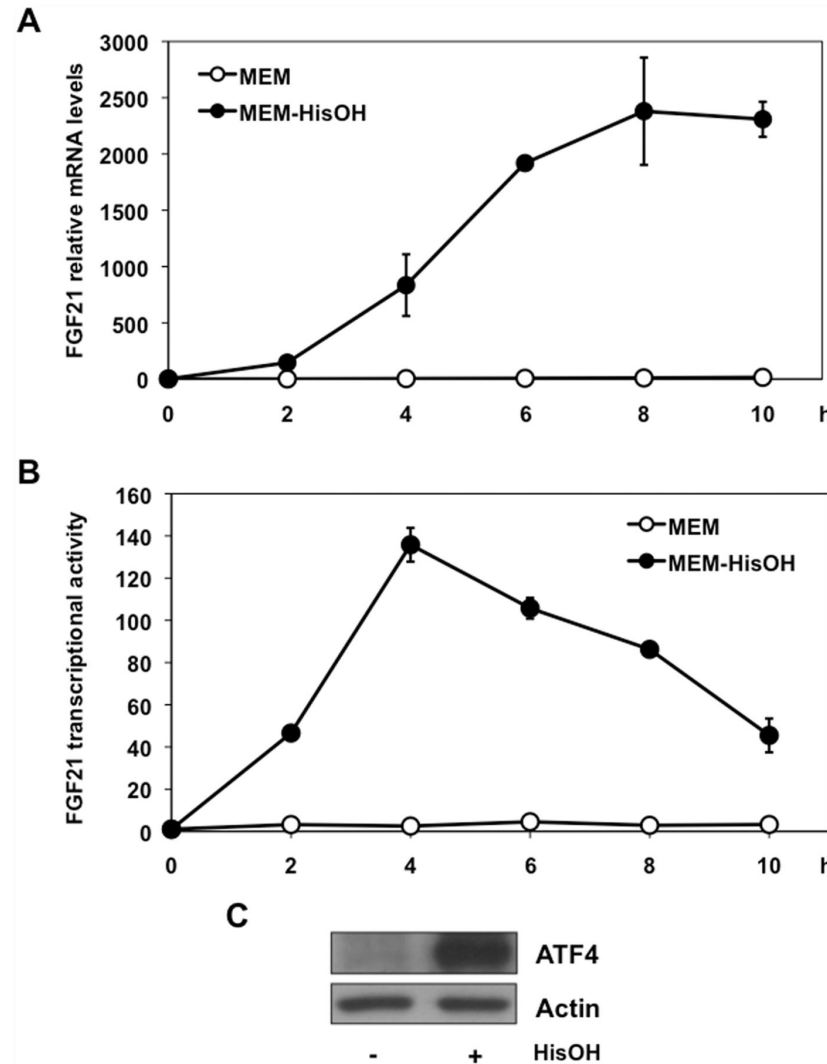
Fibroblast growth factor (FGF) 21 is a member of the FGF family, predominantly produced by the liver in response to the PPAR α transcription factor, inducing adipose tissue lipolysis, liver ketogenesis, and metabolic adaptation to the fasting state.



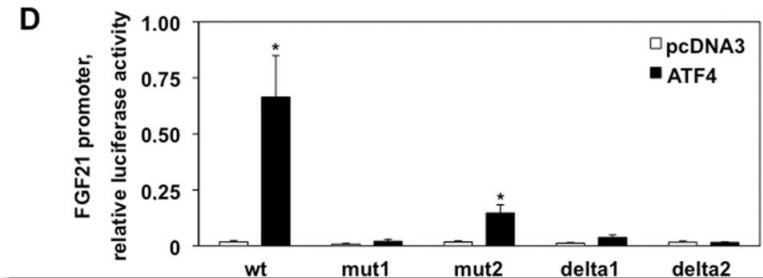
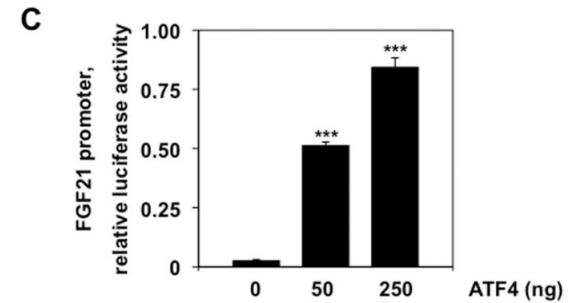
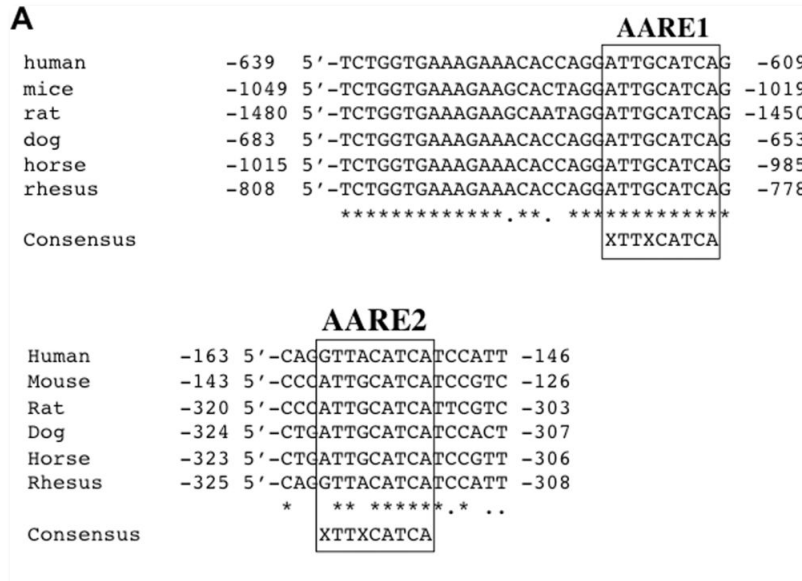
FGF21 expression is induced by the 26S proteasome inhibitor MG132



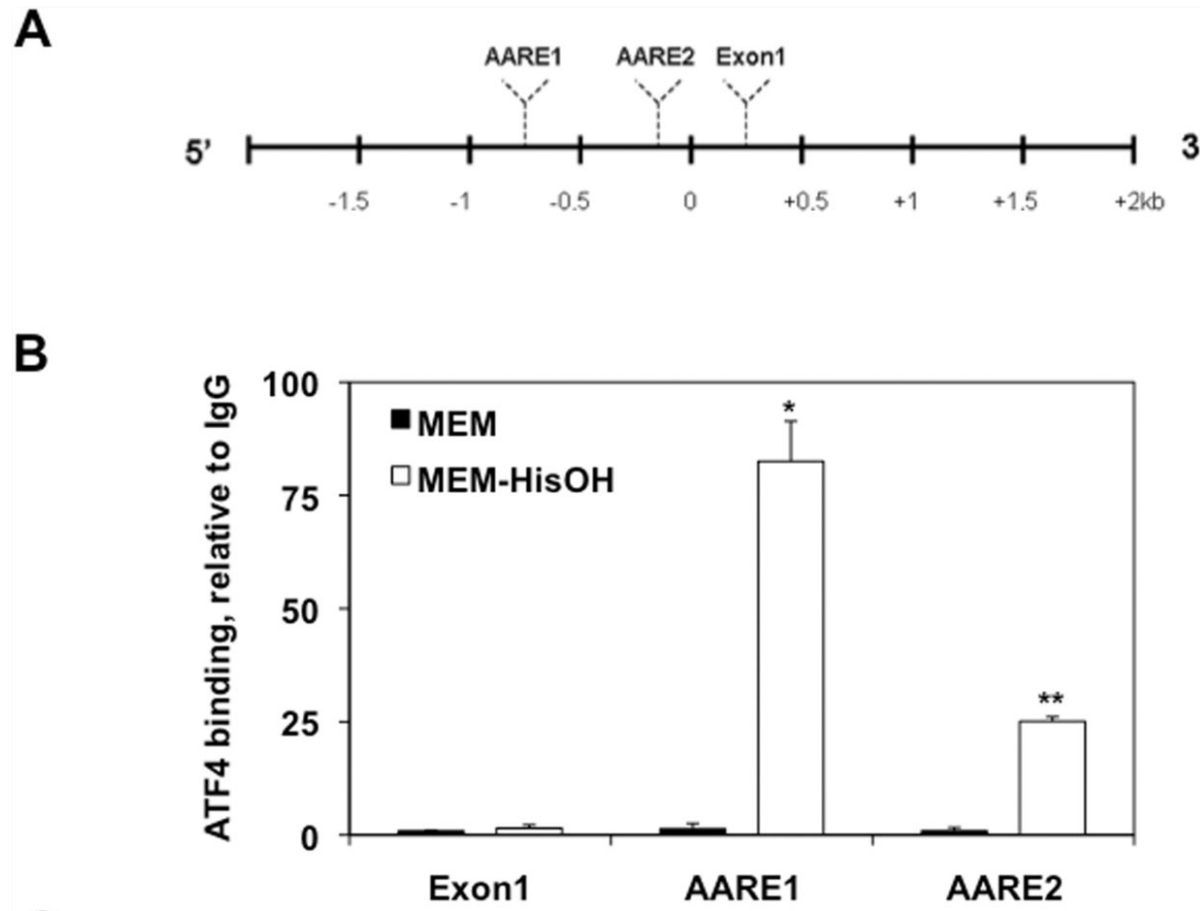
Amino acid starvation (HisOH) induces FGF21 transcription



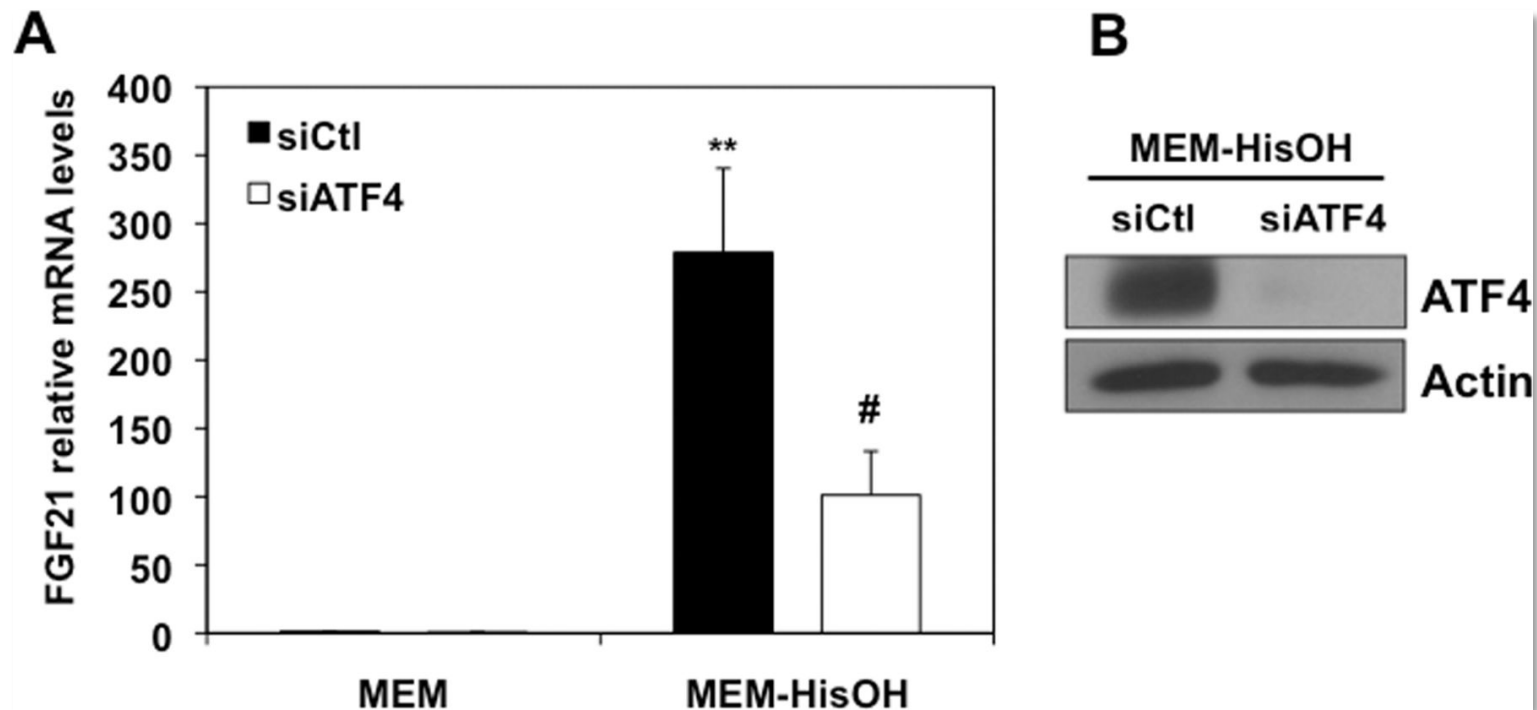
FGF21 is an ATF4 target gene



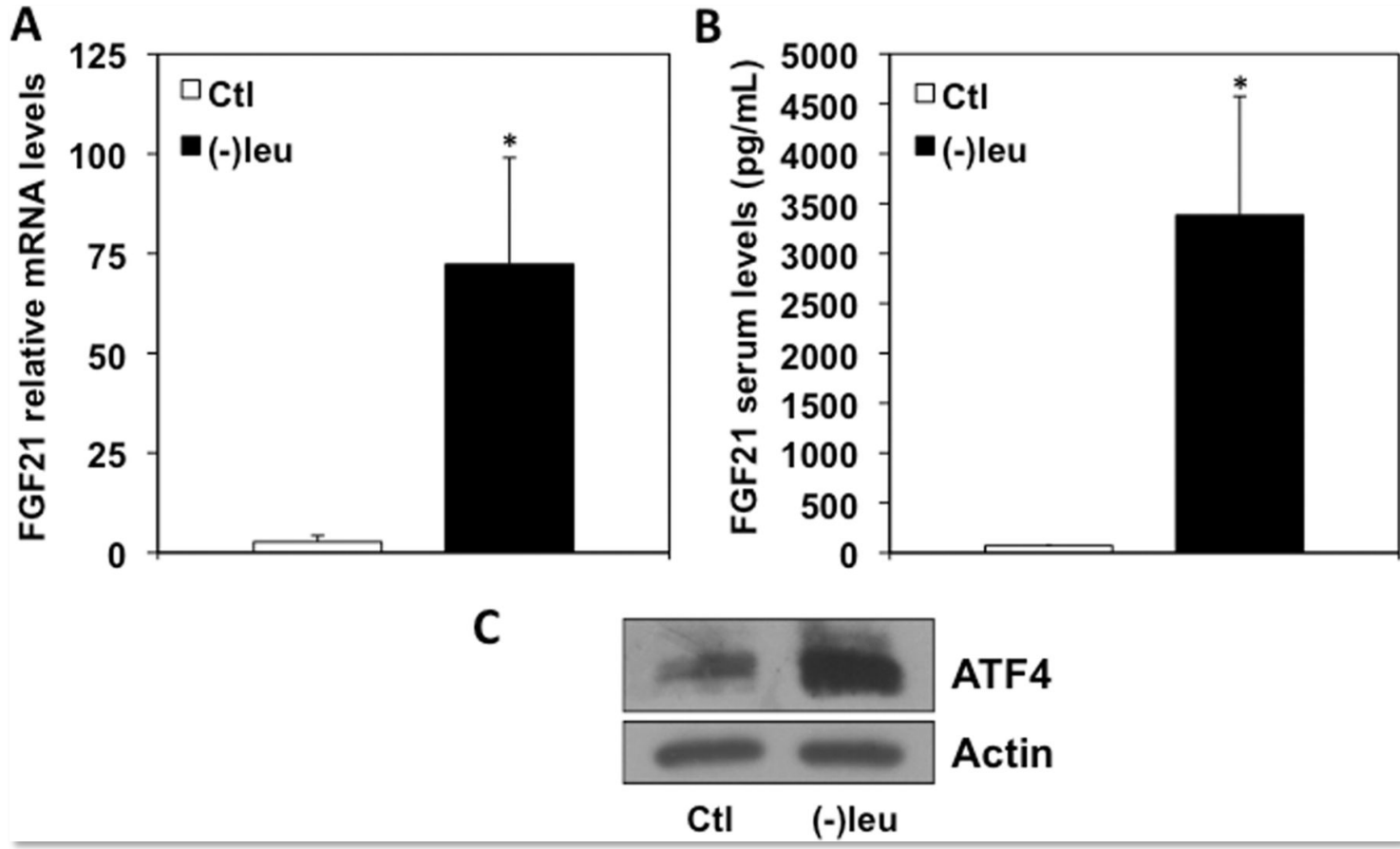
ATF4 binds to the FGF21 gene (ChIP analysis)



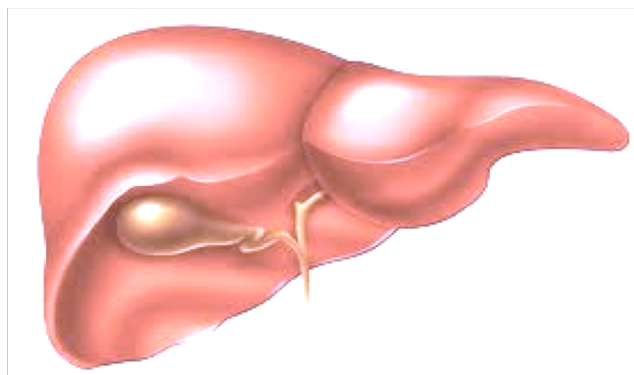
Effect of siRNA-mediated ATF knockdown on endogenous FGF21 expression



Leucine deprivation induces FGF21 serum levels and mRNA expression in liver



FGF21, the missing link between amino acid deprivation and lipid metabolism



FGF21 induces:

- gluconeogenesis
- fatty acid oxidation
- ketogenesis
- brown fat activation
- reduction in adipose tissue and body weight

FGF21: ADAPTATIVE STARVATION RESPONSE



LIVER:

-Inhibits Lipogenesis

-Induces mobilization of lipid

stores

-WAT: Increases FAO gene expression

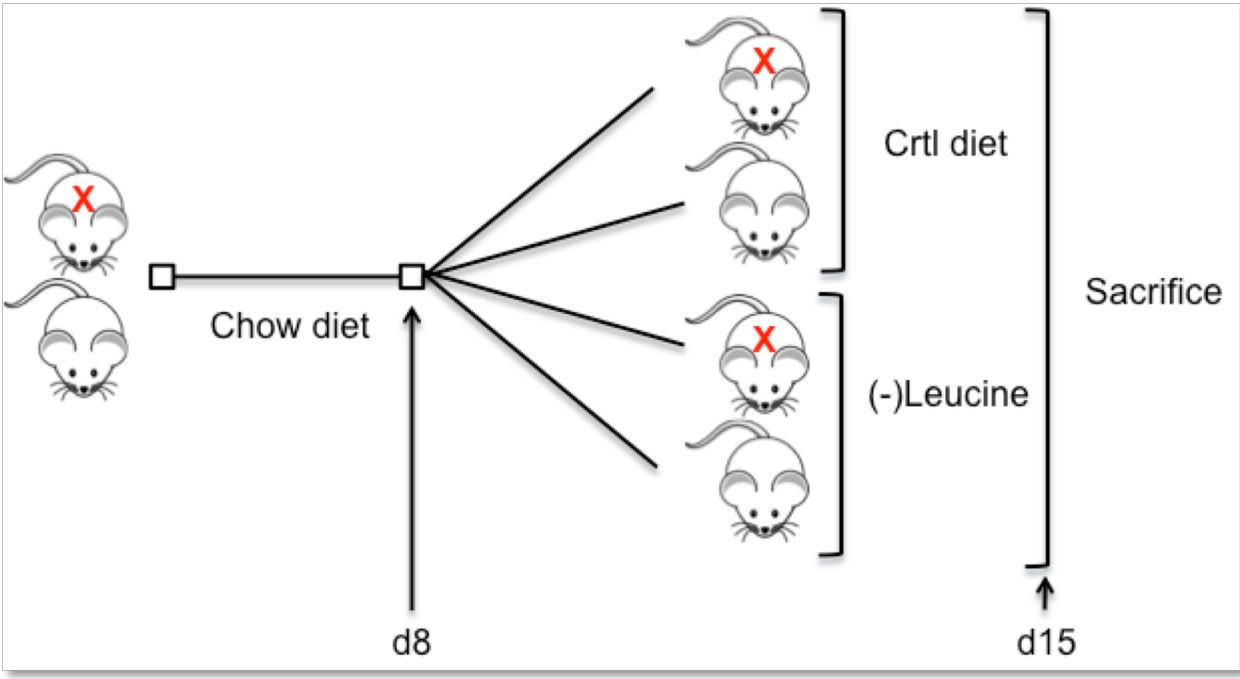
Decreases Lipogenesis

-BAT: Increases UCP1 expression

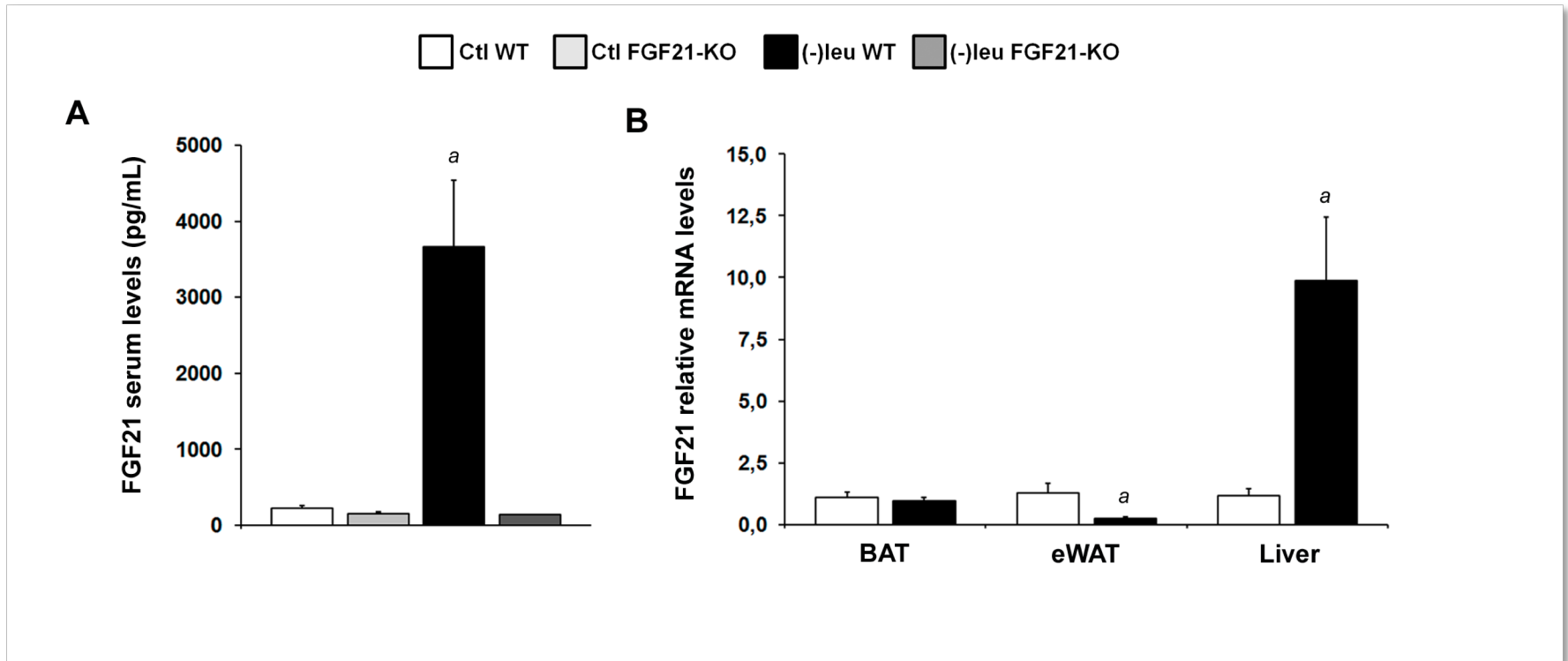
LEUCINE DEPRIVATION

Could be FGF21 the link between amino acid deprivation and lipid metabolism response observed in liver, WAT, and BAT?

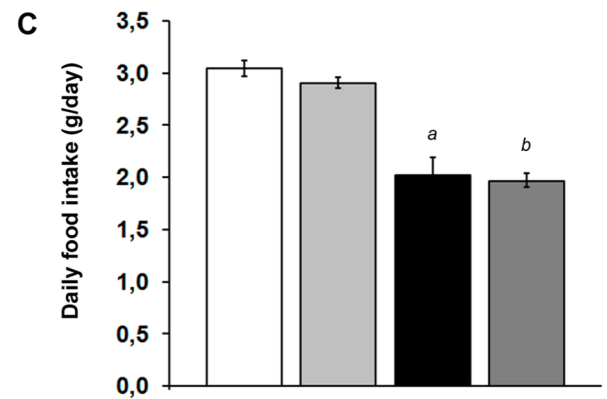
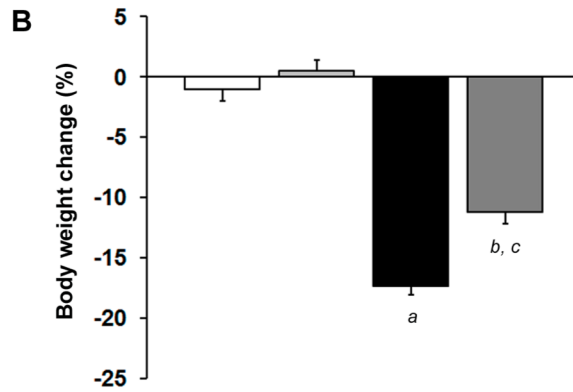
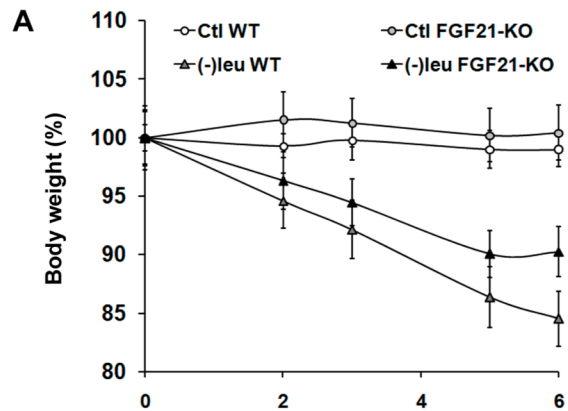
Leucine deprivation in FGF21 knockout mice



FGF21 is differently regulated by leucine deprivation in liver and adipose tissues

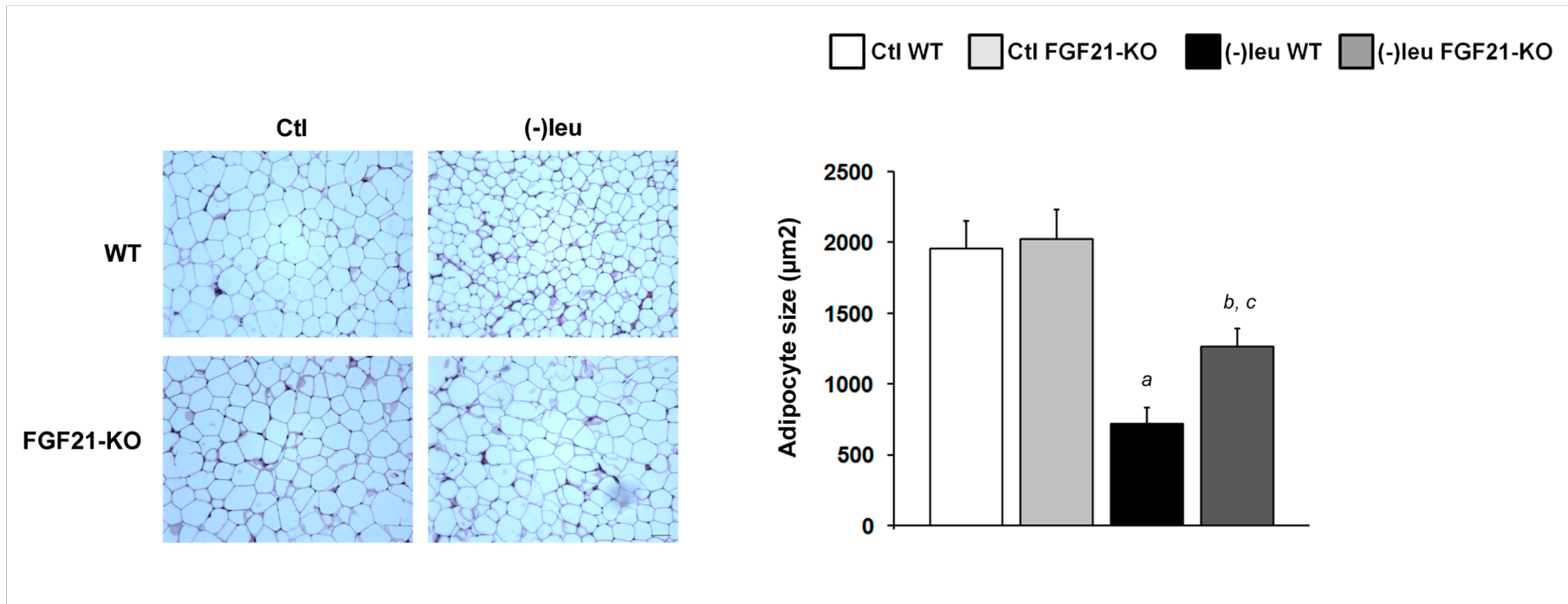


FGF21 is required for (-)leu diet effects on body weight without affecting food consumption.

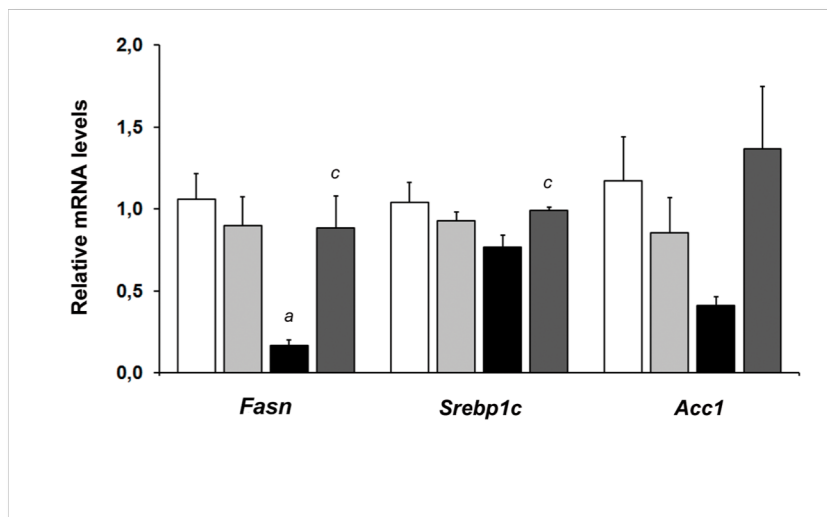
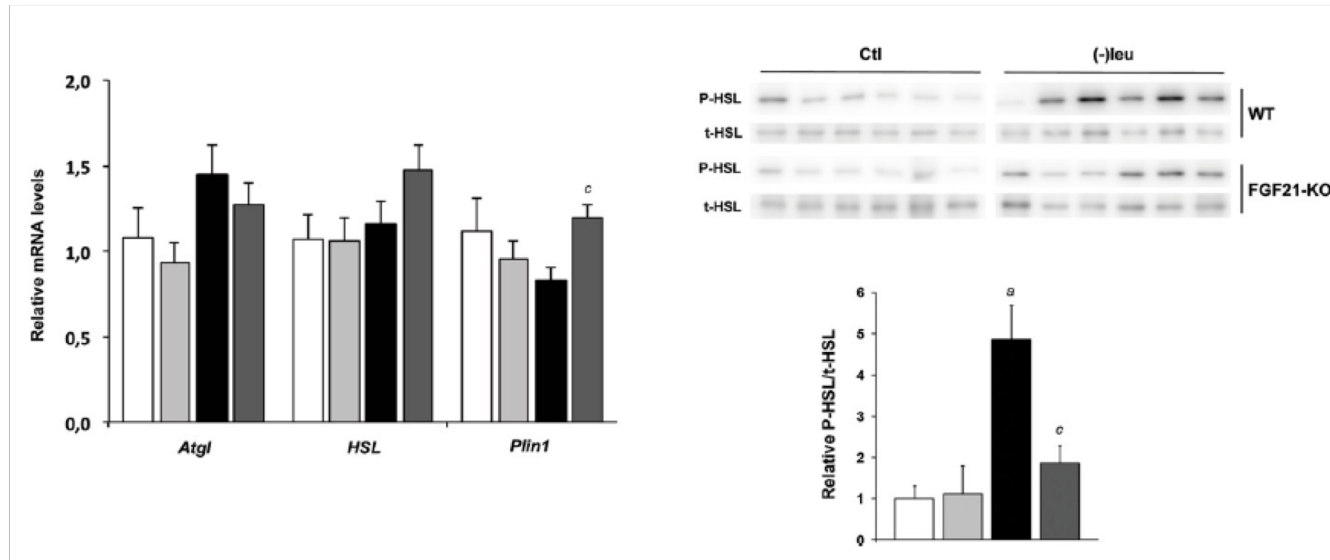


□ Ctl WT □ Ctl FGF21-KO ■ (-)leu WT ■ (-)leu FGF21-KO

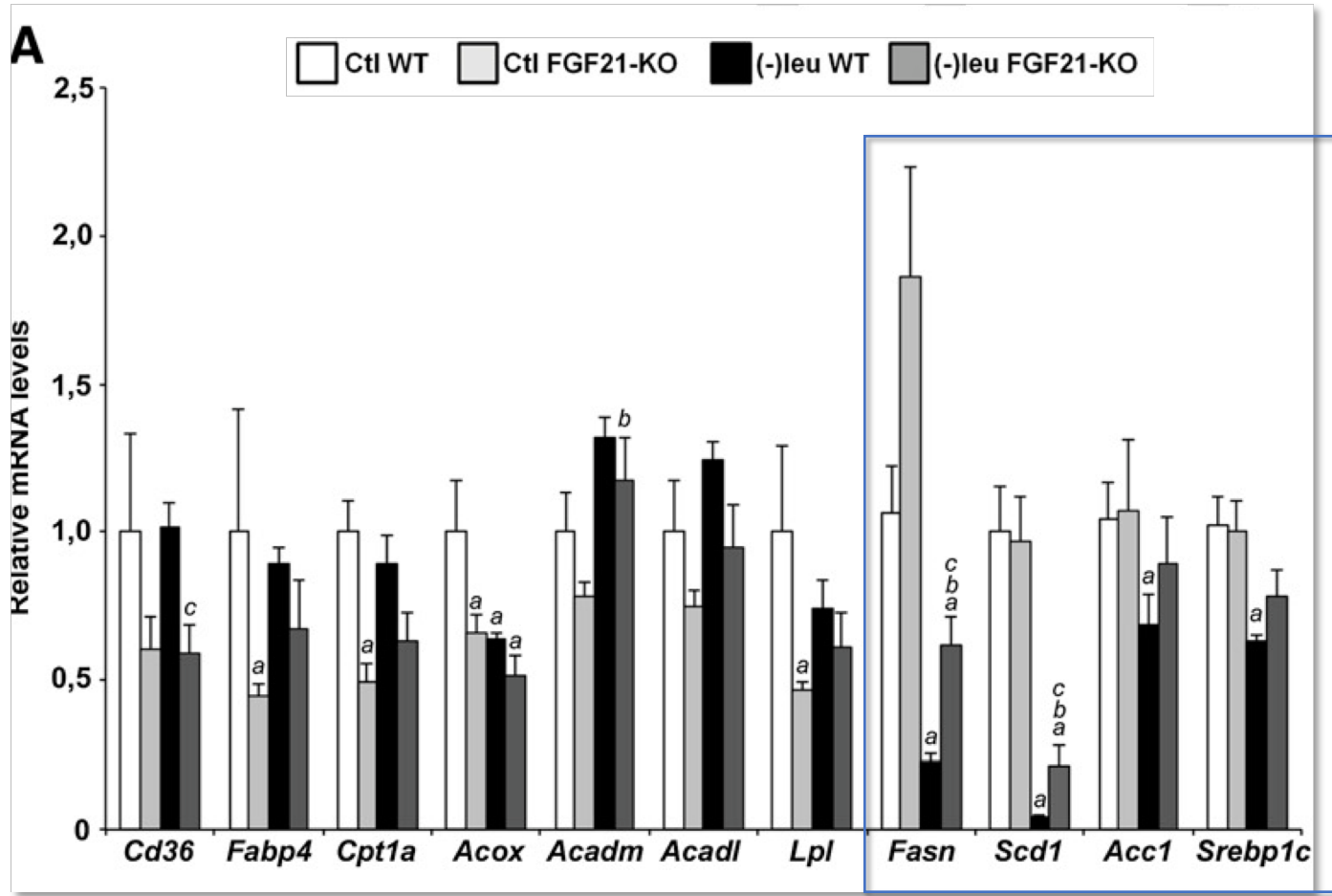
Leucine deprivation effects on white adipocytes size are FGF21 dependent



Leucine deprivation effects on lipid metabolism in WAT are FGF21 dependent

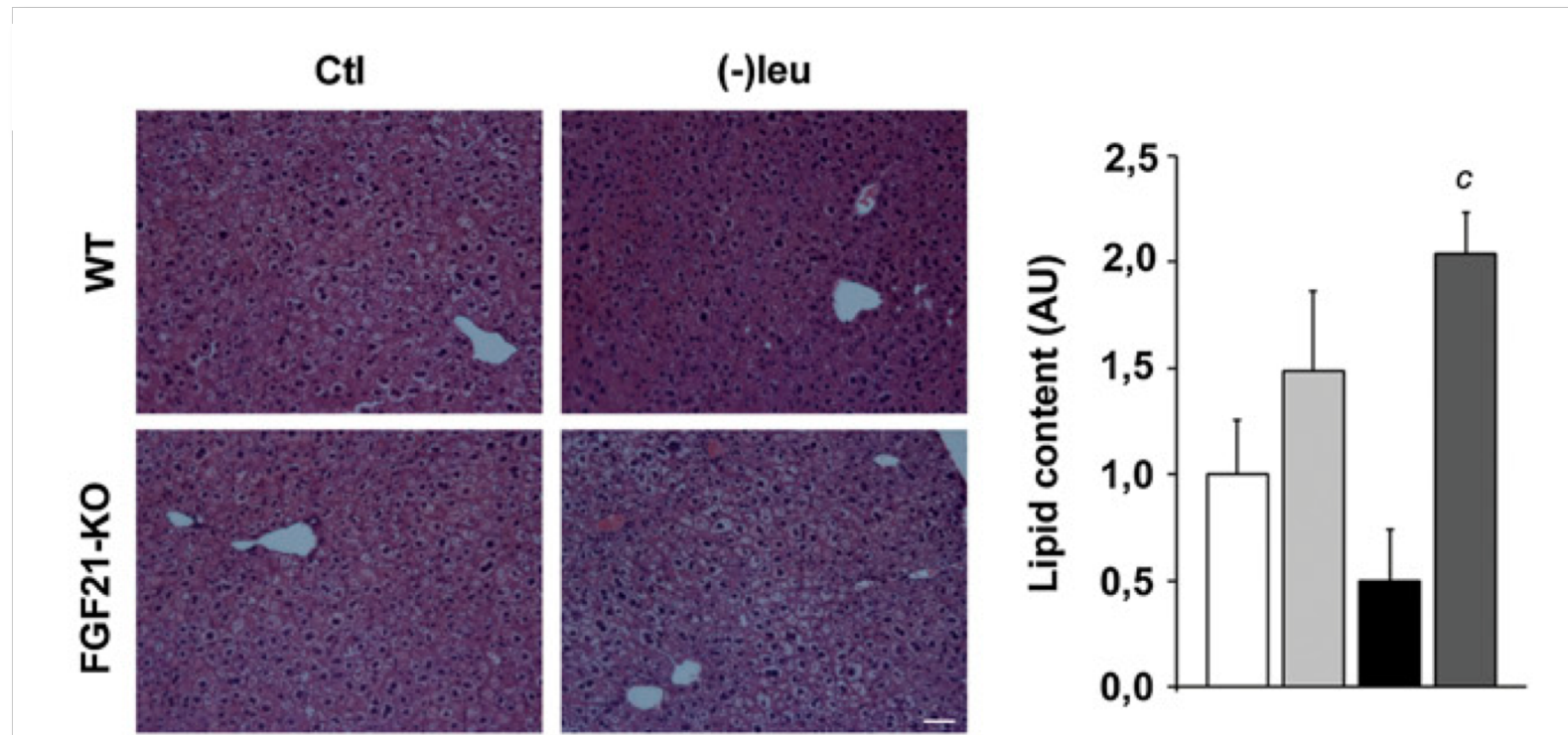


FGF21-KO liver has impaired lipid metabolism in response to leucine deprivation



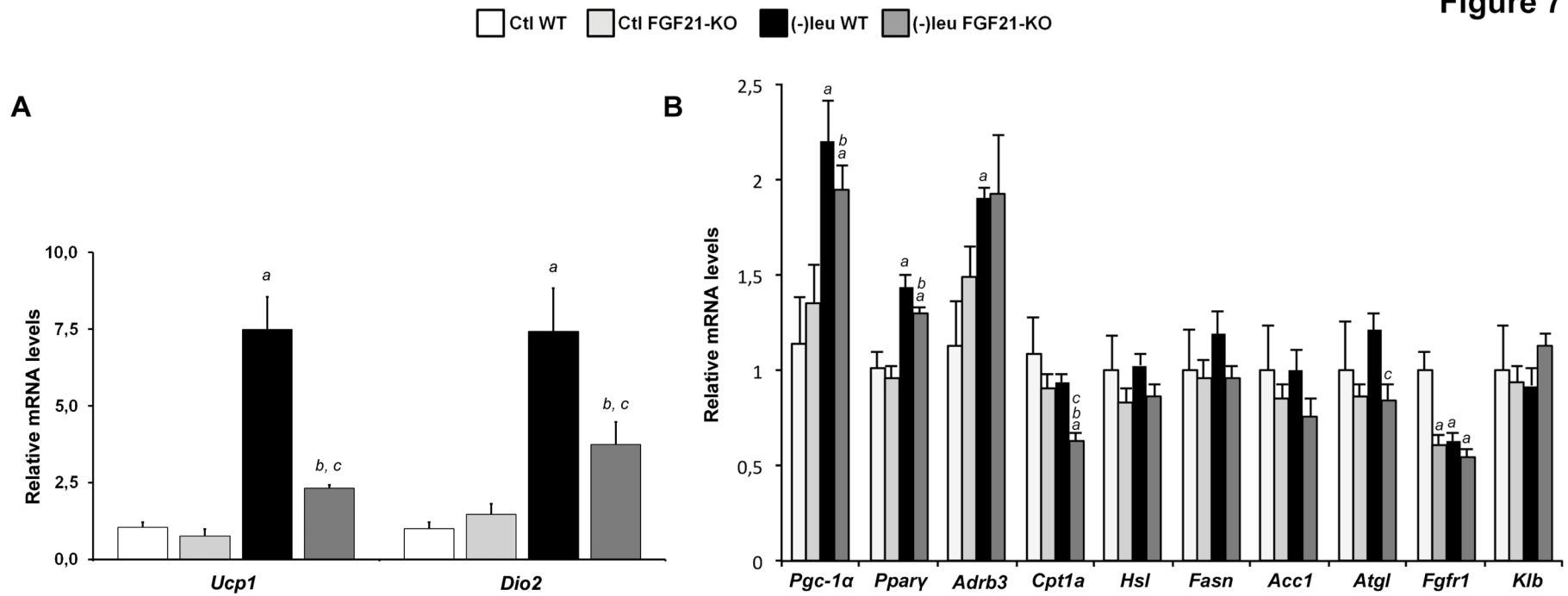
FGF21-KO liver has impaired lipid accumulation in response to leucine deprivation

□ Ctl WT □ Ctl FGF21-KO ■ (-)leu WT ■ (-)leu FGF21-KO

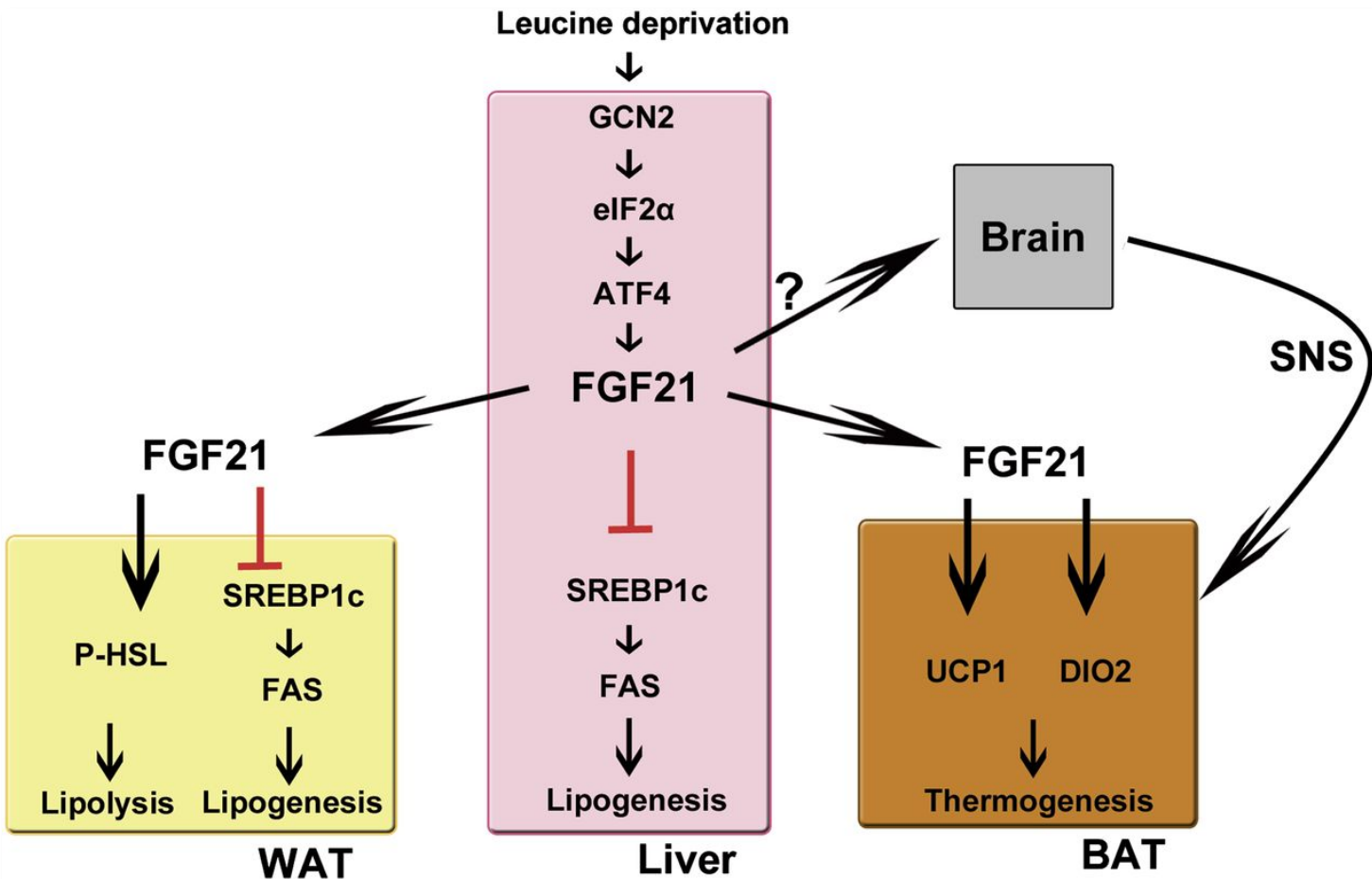


FGF21 is required for inducing BAT activation during amino acid deprivation

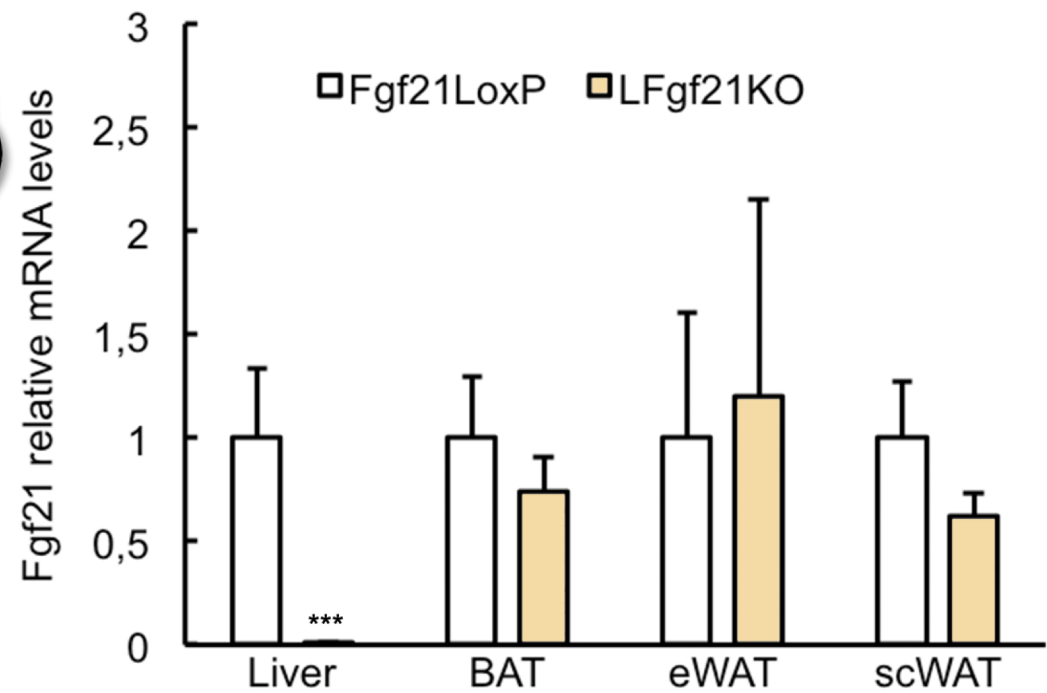
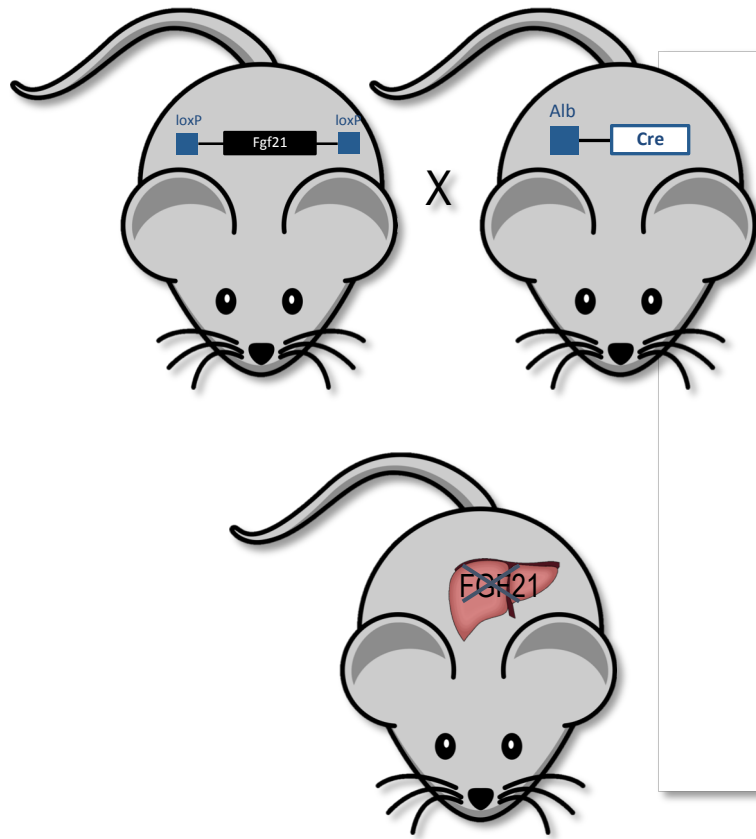
Figure 7



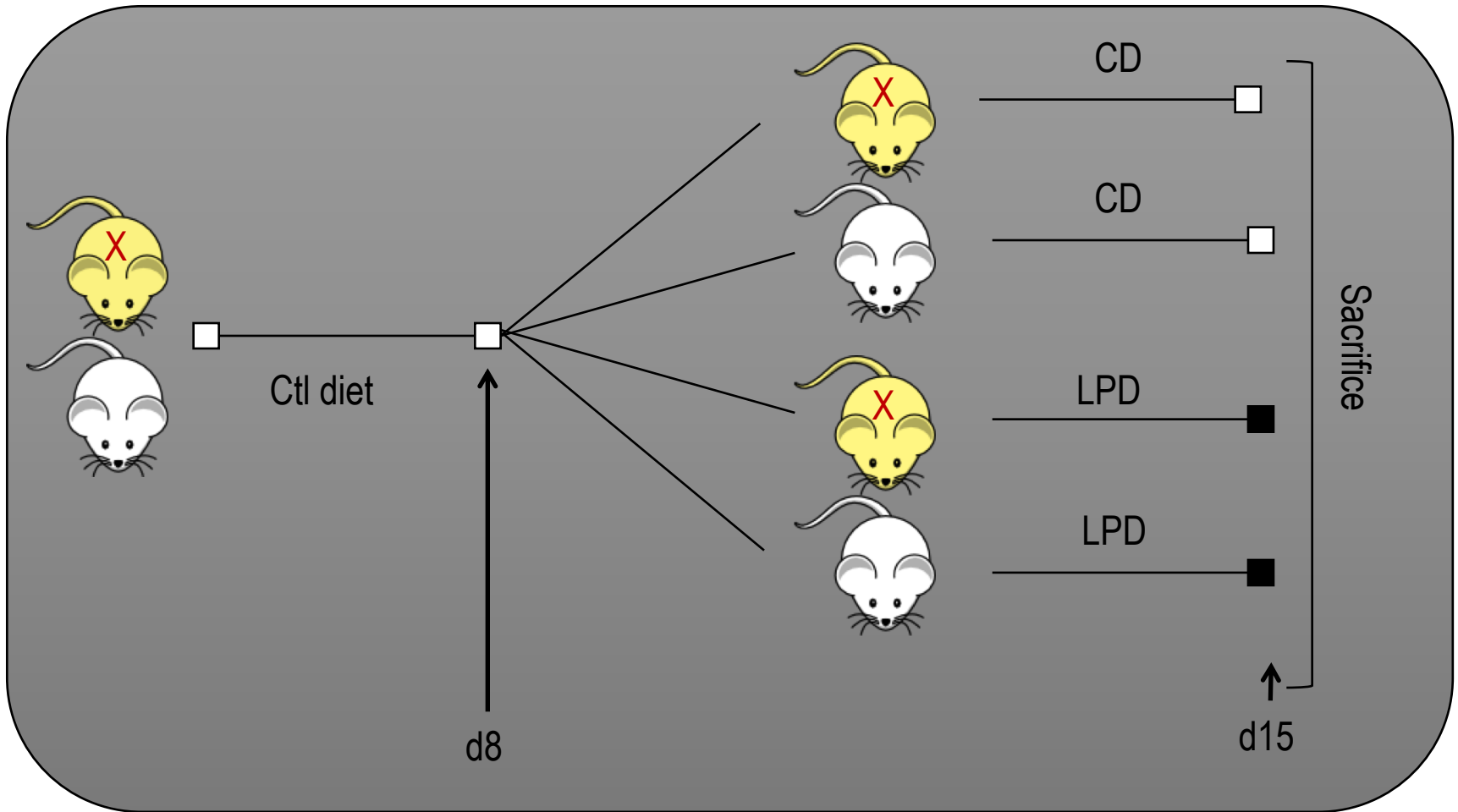
Working model of the FGF21 regulatory pathway under leucine deprivation



Generation and characterization of the Fgf21 liver-specific knockout mice



Experimental design



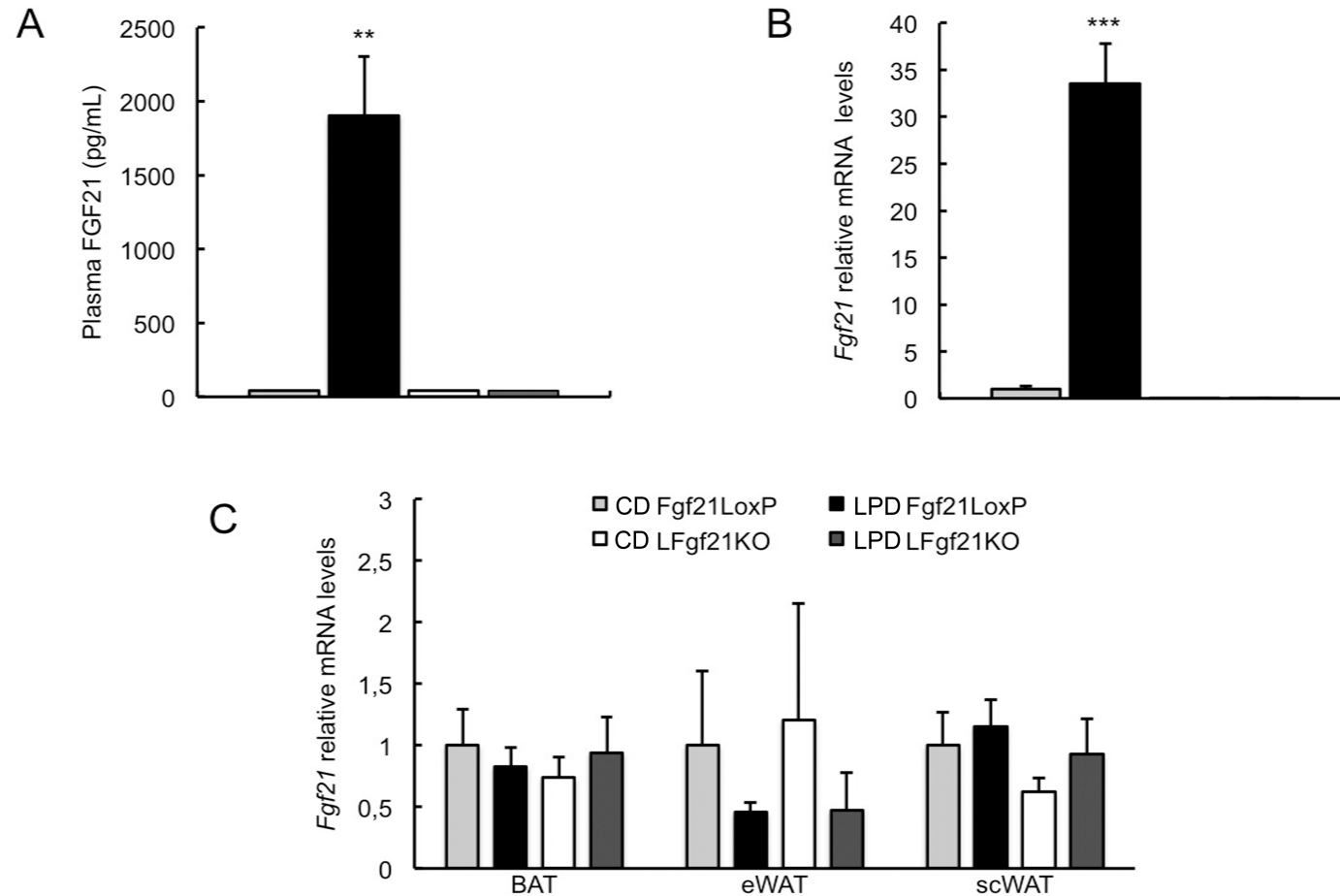
Fgf21 liver-specific knockout mice



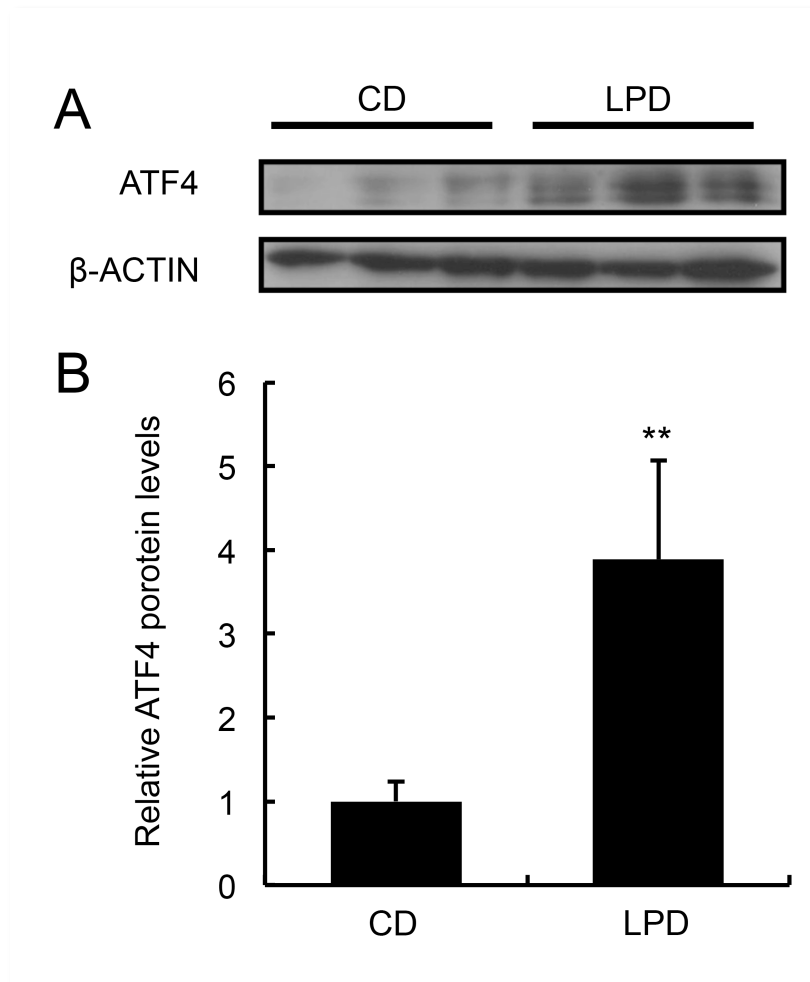
LoxP mice

LPD: Low protein diet (5%)
CD: Control diet (20%)

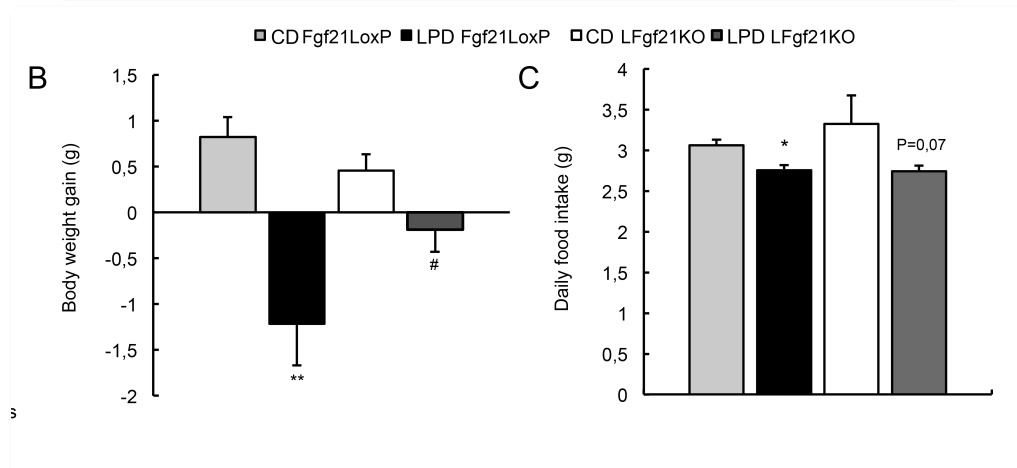
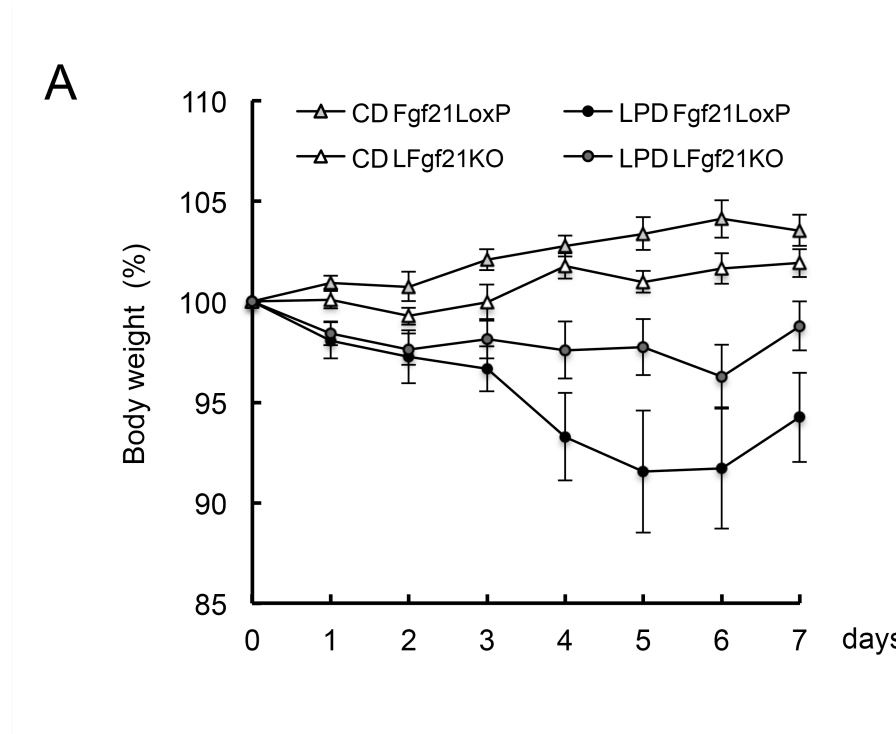
FGF21 is induced by a LPD in liver but not in BAT or WAT, and this induction correlates positively with plasma concentration



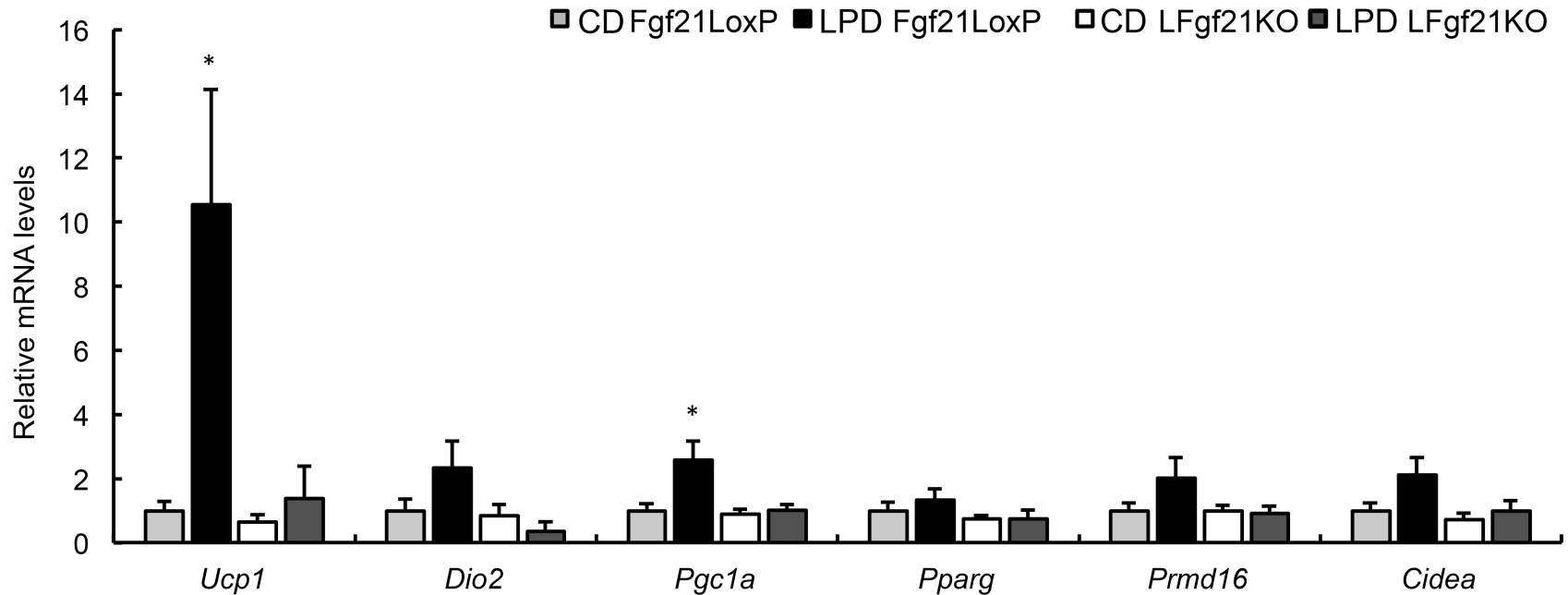
LPD increases ATF4 protein levels in liver



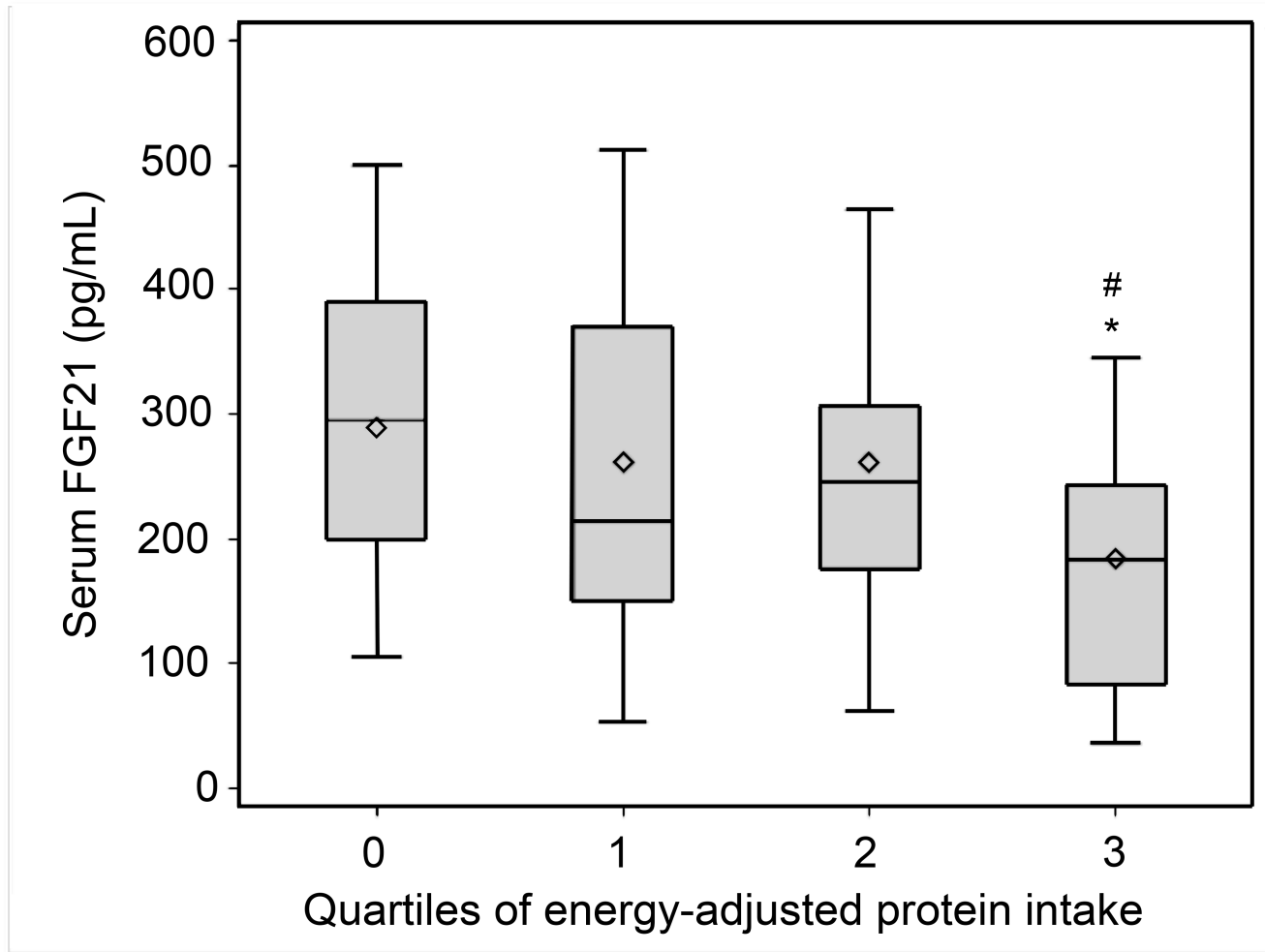
Fgf21 deficiency significantly attenuates weight loss under a LPD



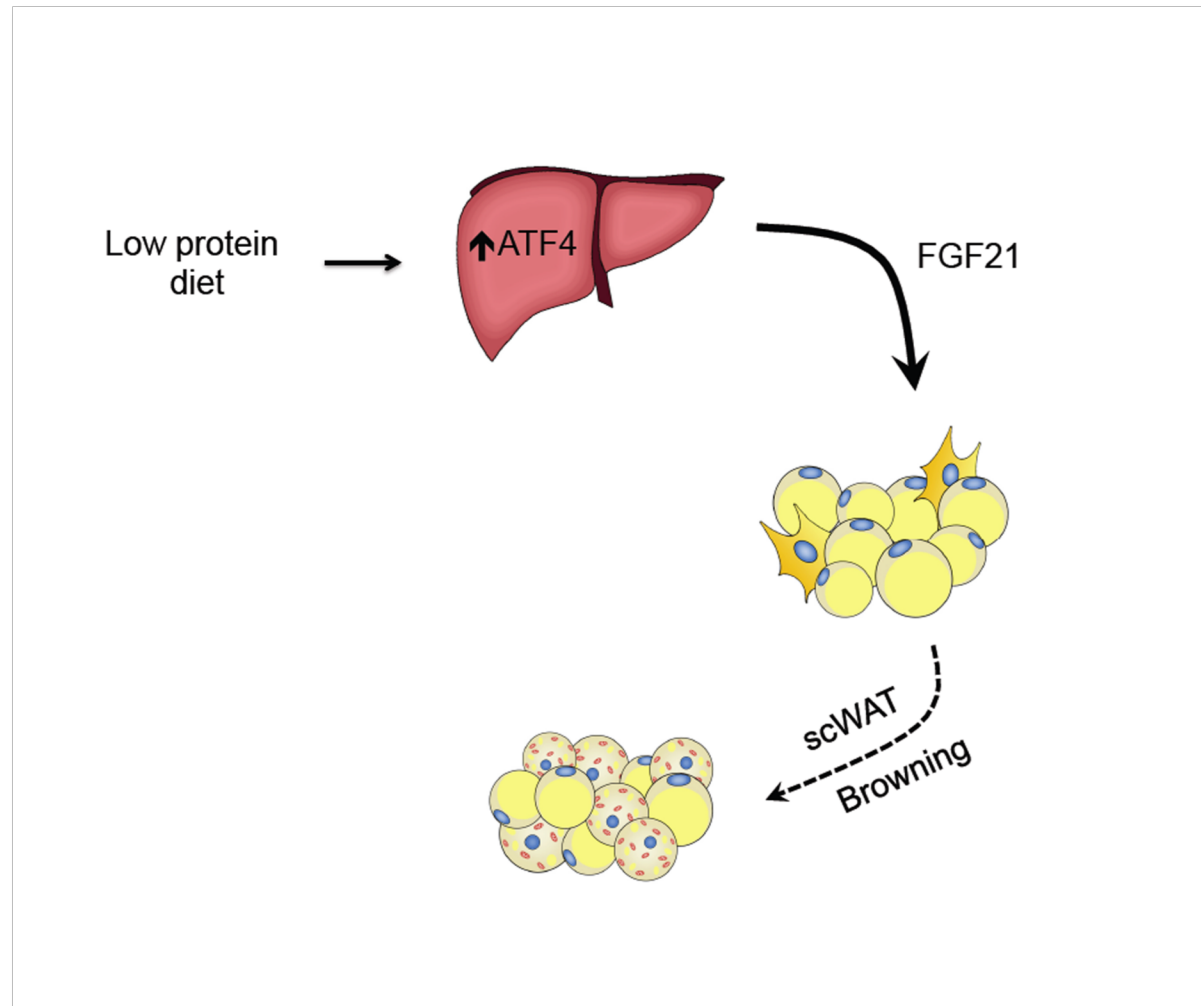
Hepatic FGF21 is required for inducing thermogenic gene expression in scWAT under a LPD.



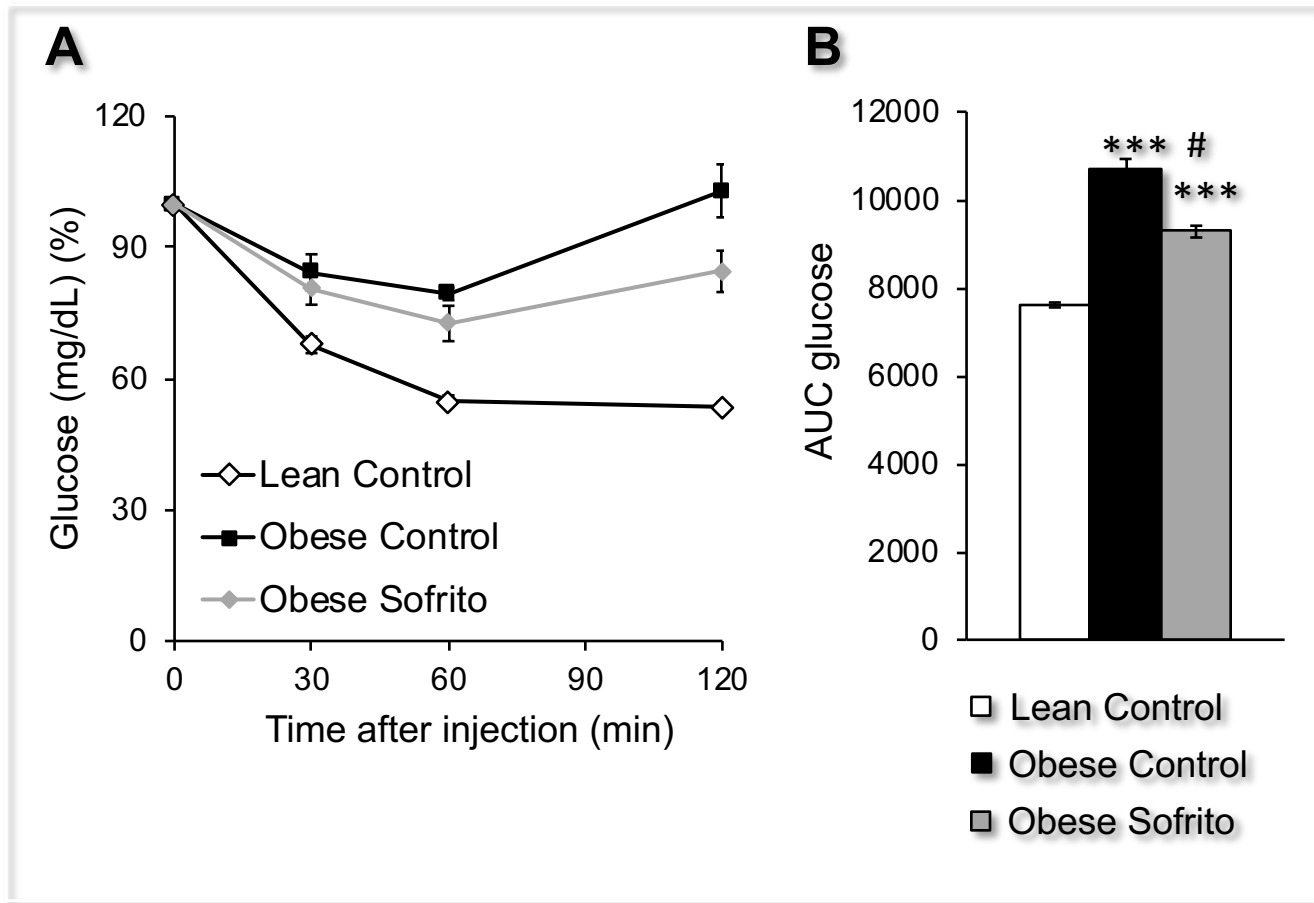
FGF21 plasma levels correlate negatively with protein intake in humans



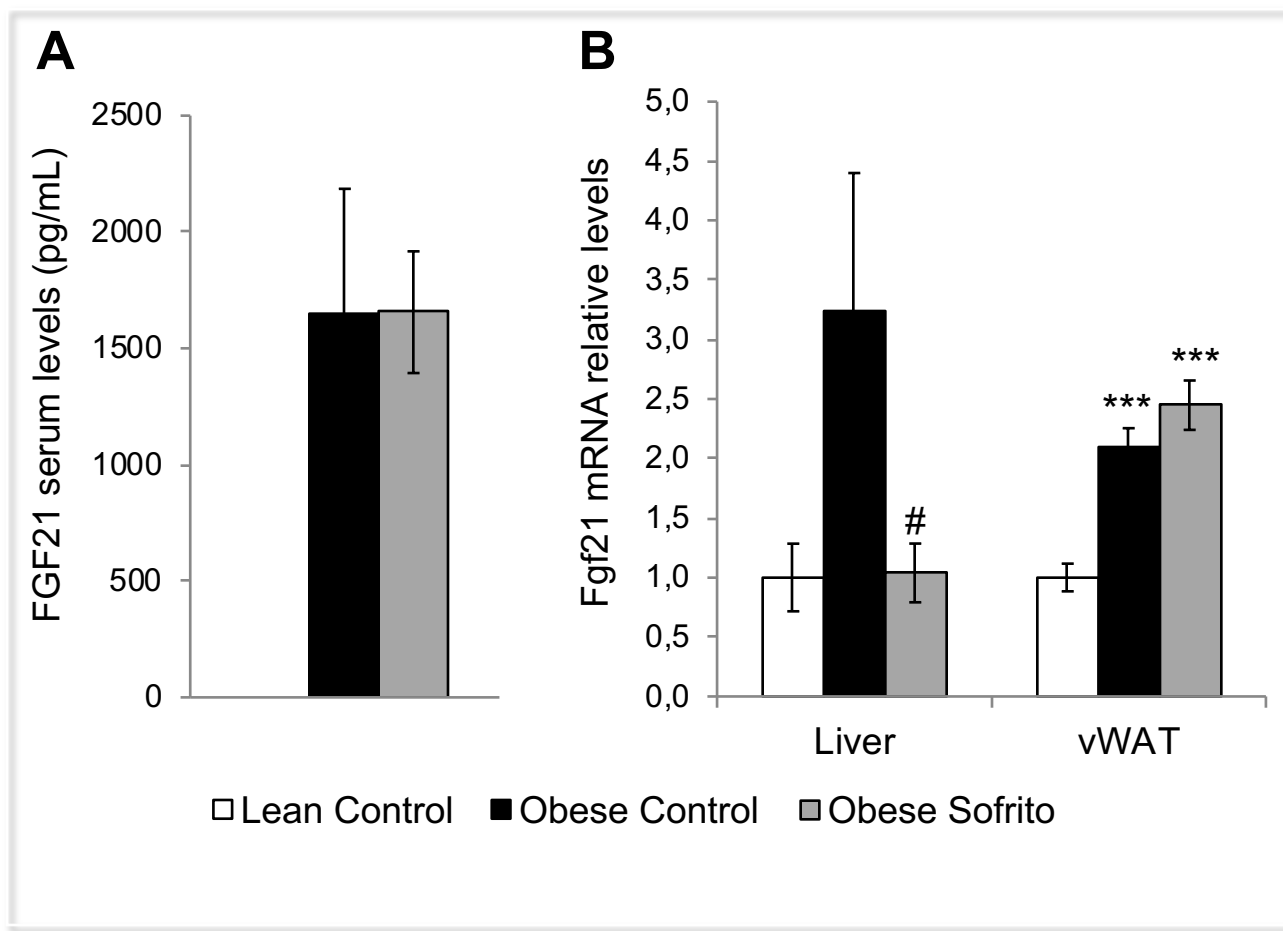
A low-protein diet induces body weight loss and browning of subcutaneous white adipose tissue through enhanced expression of hepatic FGF21



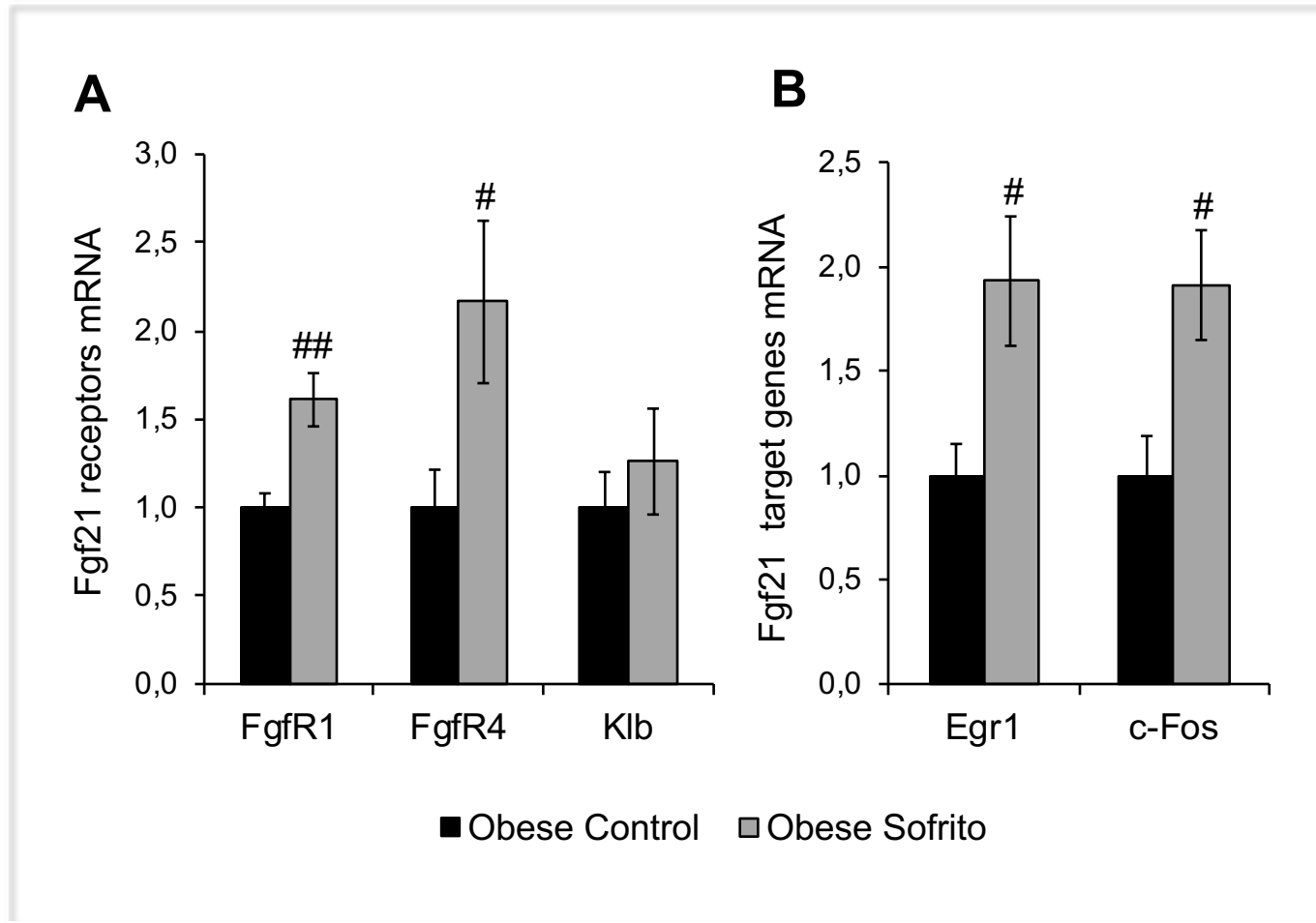
Insulin Resistance is Attenuated by Sofrito Supplemented-Diet in OZR



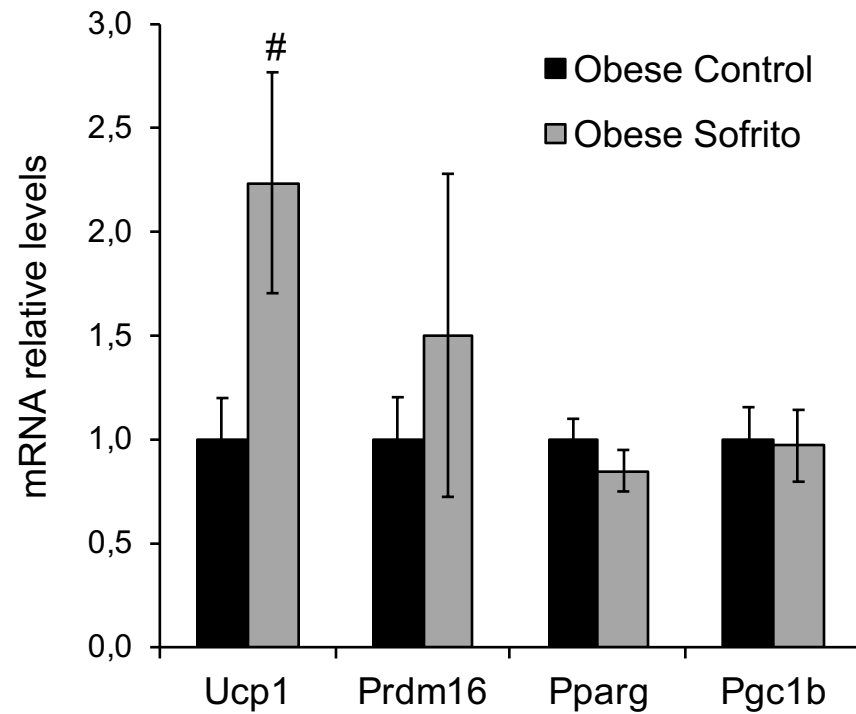
FGF21 Serum Levels are not Influenced by Sofrito



FGF21 Signaling is Improved in vWAT of OZR Fed with a Sofrito-Supplemented Diet



Sofrito Induces UCP1 Expression in the vWAT of OZR



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