

读书报告

报告人：秦超彬

2016年4月9日



日本語要約

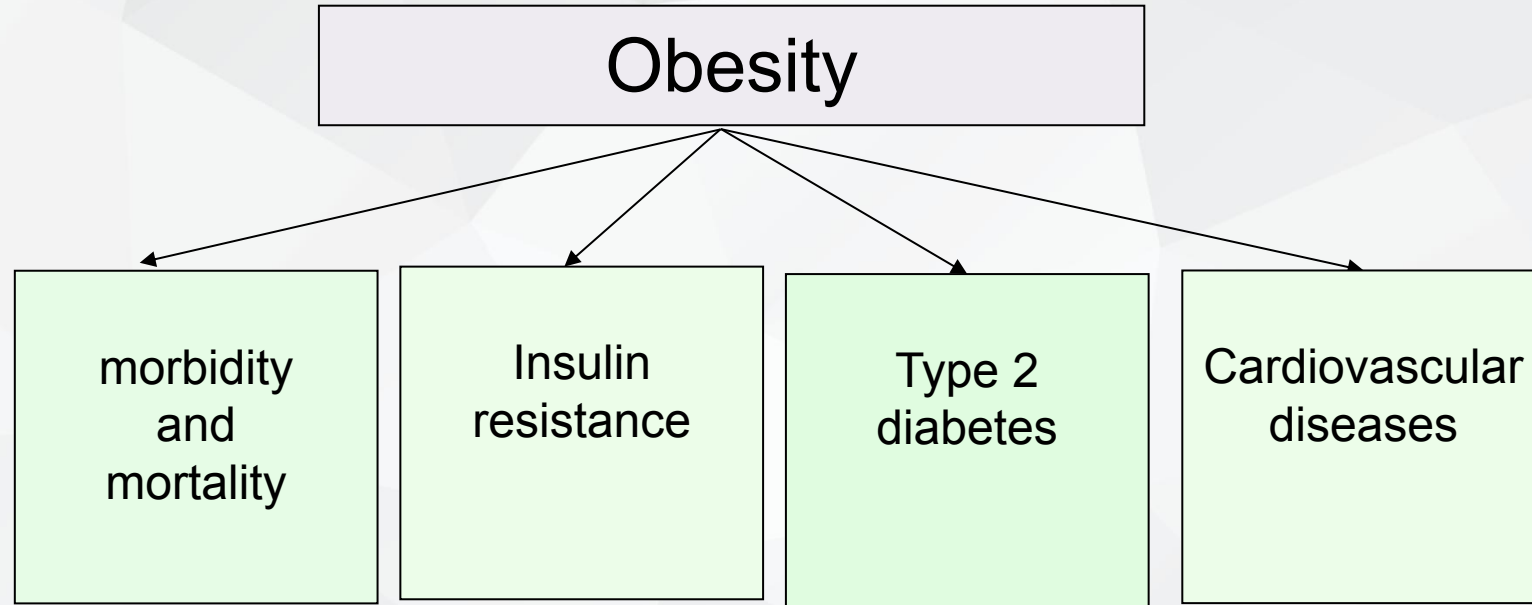
A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity

Miki Okada-Iwabu, Toshimasa Yamauchi, Masato Iwabu, Teruki Honma, Ken-ichi Hamagami, Koichi Matsuda, Mamiko Yamaguchi, Hiroaki Tanabe, Tomomi Kimura-Someya, Mikako Shirouzu, Hitomi Ogata, Kumpei Tokuyama, Kohjiro Ueki, Tetsuo Nagano, Akiko Tanaka, Shigeyuki Yokoyama & Takashi Kadowaki

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Insulin resistance and type 2 diabetes: satisfactory treatment modalities remain limited.

Introduction

Adiponectin is an antidiabetic and antiatherogenic adipokine.

Decreased in obesity, insulin resistance and type 2 diabetes

Replenishment of adiponectin:
ameliorate insulin resistance, glucose intolerance

Insulin sensitizing effect:
increase fatty acid oxidation

AMPK: AMP activated protein kinase
PPAR α : peroxisome proliferator activated receptor
 α

Introduction

AdipoR1 and AdipoR2 serve as the major receptors for adiponectin, with AdipoR1 activating the AMPK pathways and AdipoR2 activating the PPAR α pathways.

Letters to Nature

Nature **423**, 762-769 (12 June 2003) | doi:10.1038/nature01705; Received 31 December 2002; Accepted 1 May 2003

Cloning of adiponectin receptors that mediate antidiabetic metabolic effects

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Skeletal muscle

Predominantly AdipoR1

Activates AMPK and PPAR γ coactivator PGC-1 α as well as Ca²⁺ signalling pathways.

Activated by exercise

Exercise:

- Beneficial effects on obesity related diseases such as type 2 diabetes
- Contribute to healthy longevity

Liver

AdipoR1 and AdipoR2

Regulation of glucose and lipid metabolism.

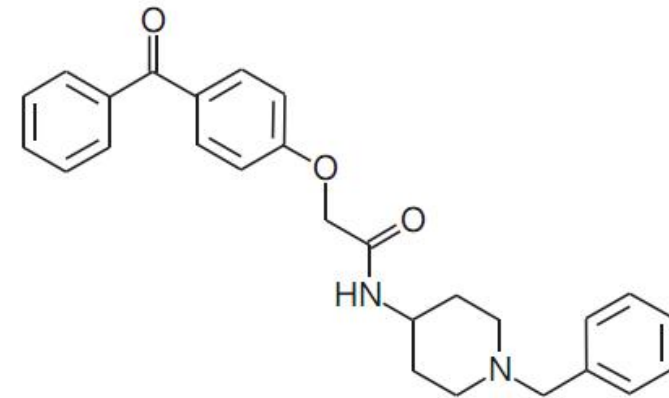
Introduction

Here we report the discovery of an orally active synthetic small molecule that binds to and activates both AdipoR1 and AdipoR2, ameliorates insulin resistance and type 2 diabetes, and prolongs the shortened life span of *db/db* mice.

2.1 Identification of small molecule agonists of AdipoR

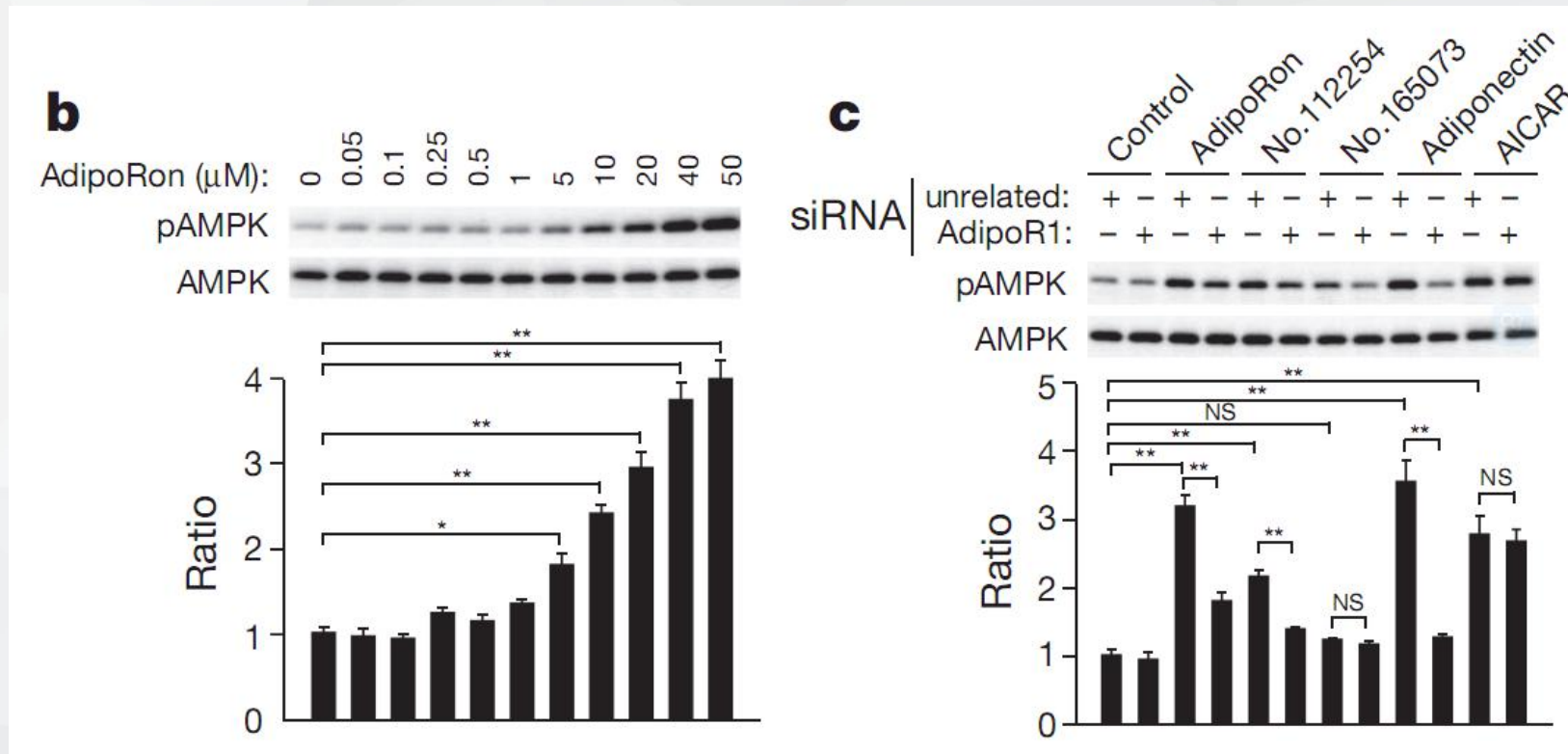
Screened a number of small molecules in the chemical library at Open Innovation Center for Drug Discovery, The University of Tokyo (东京大学药物发现开放创新中心化学库).

- Activate AMPK
- The dependency of stimulated AMPK on AdipoR in C2C12 myotubes.

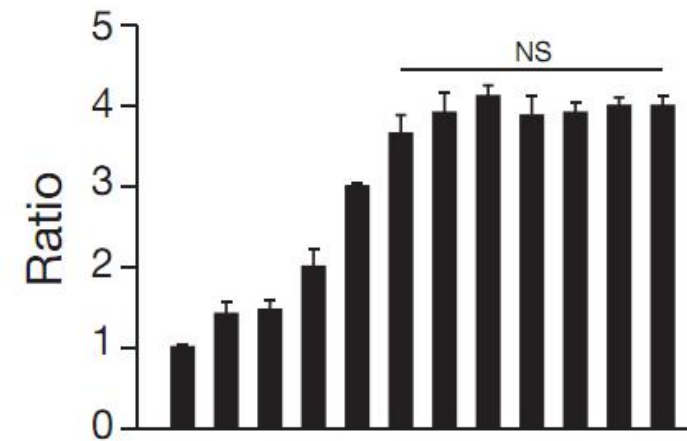
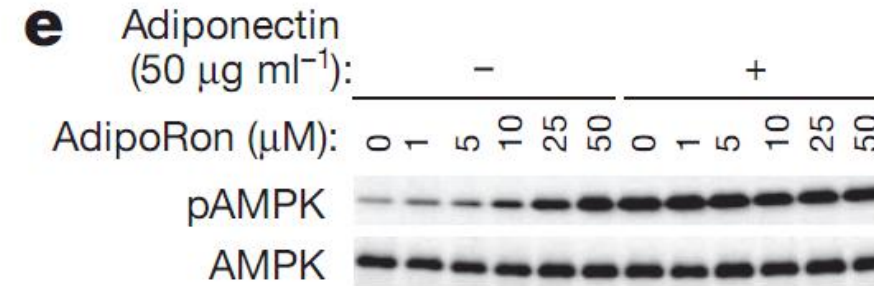
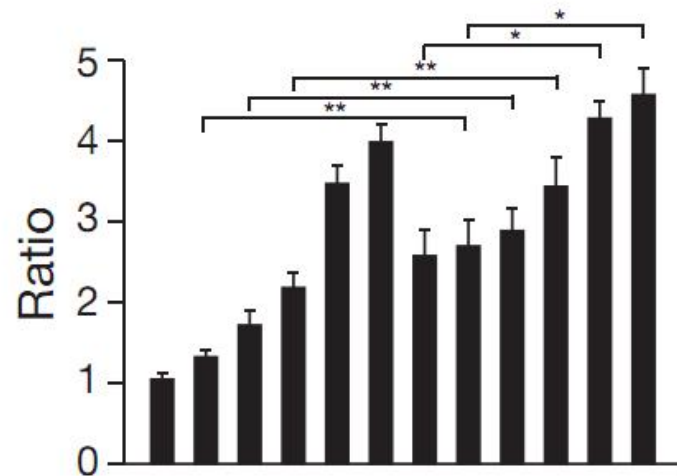
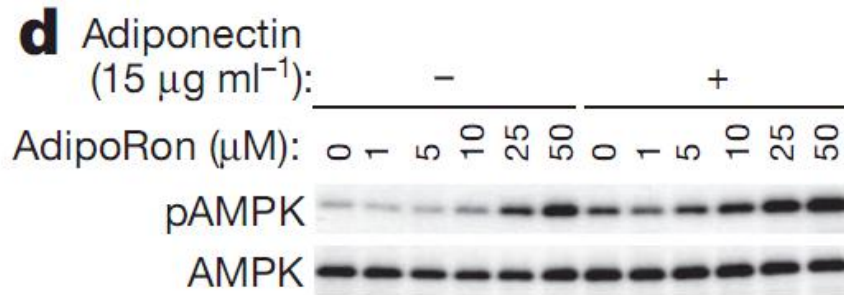
a

AdipoRon

2.1 Identification of small molecule agonists of AdipoR

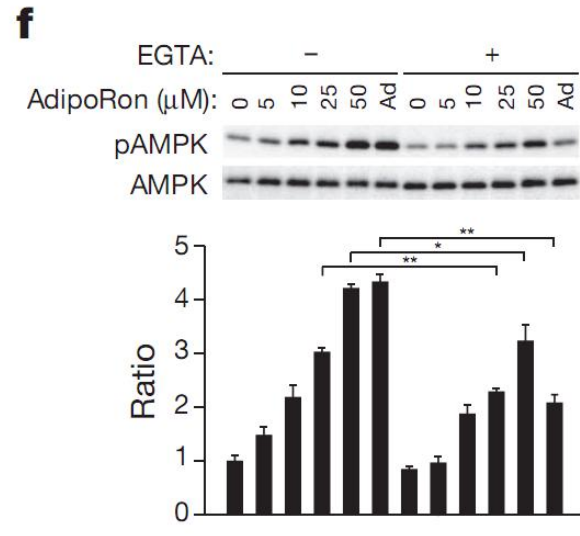


C2C12 myotubes: AdipoRon increase the phosphorylation of AMPK α ; Suppression of AdipoR1 by specific siRNA greatly reduced the increase in AMPK phosphorylation induced by AdipoRon, indicating that AdipoRon increased AMPK phosphorylation via AdipoR1.

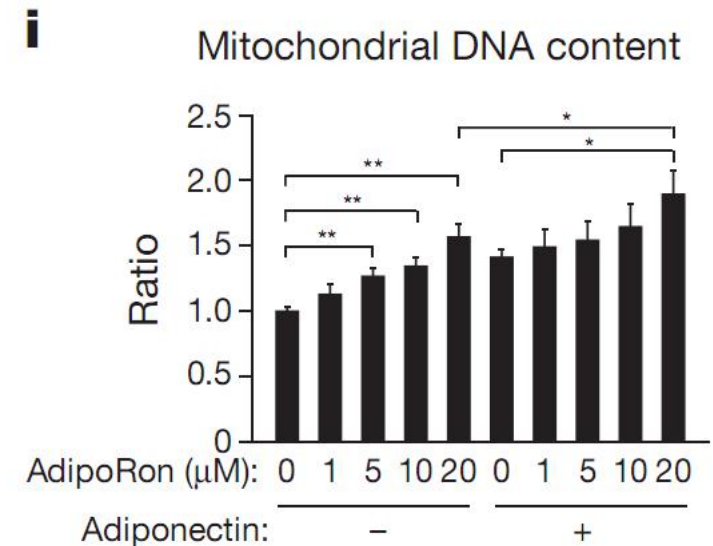
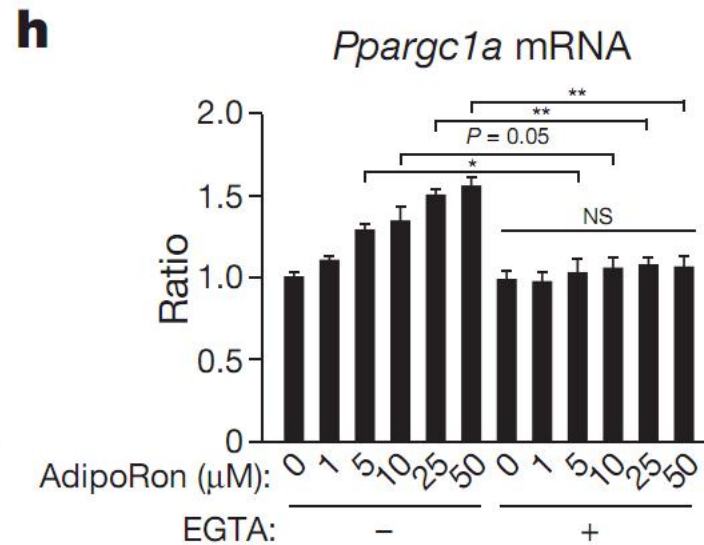
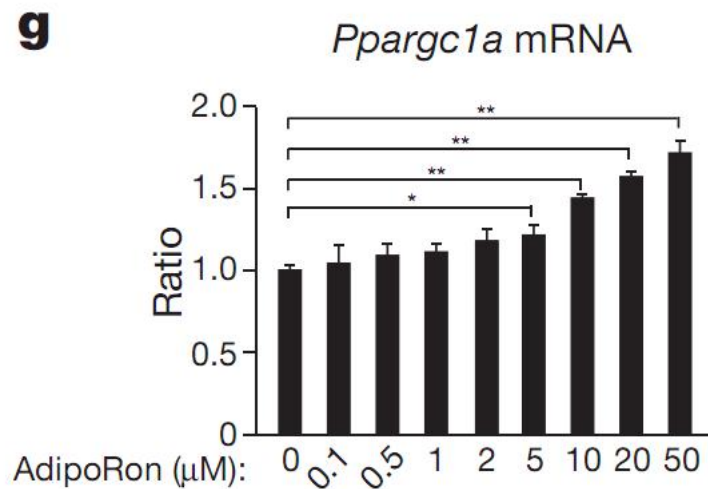


AdipoRon replenished AMPK phosphorylation stimulated by adiponectin.

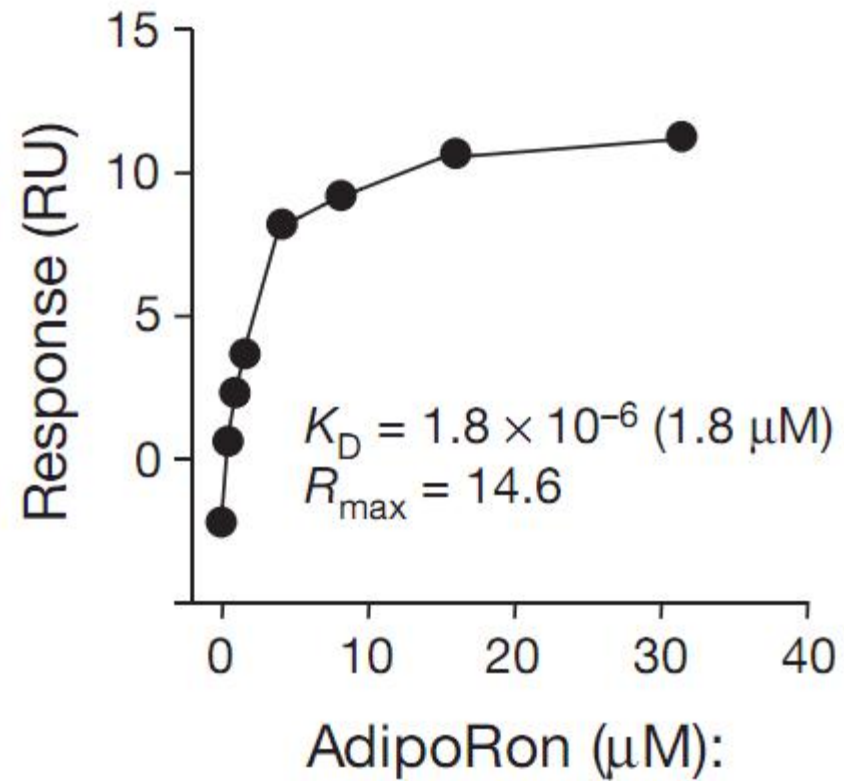
2.1 Identification of small molecule agonists of AdipoR



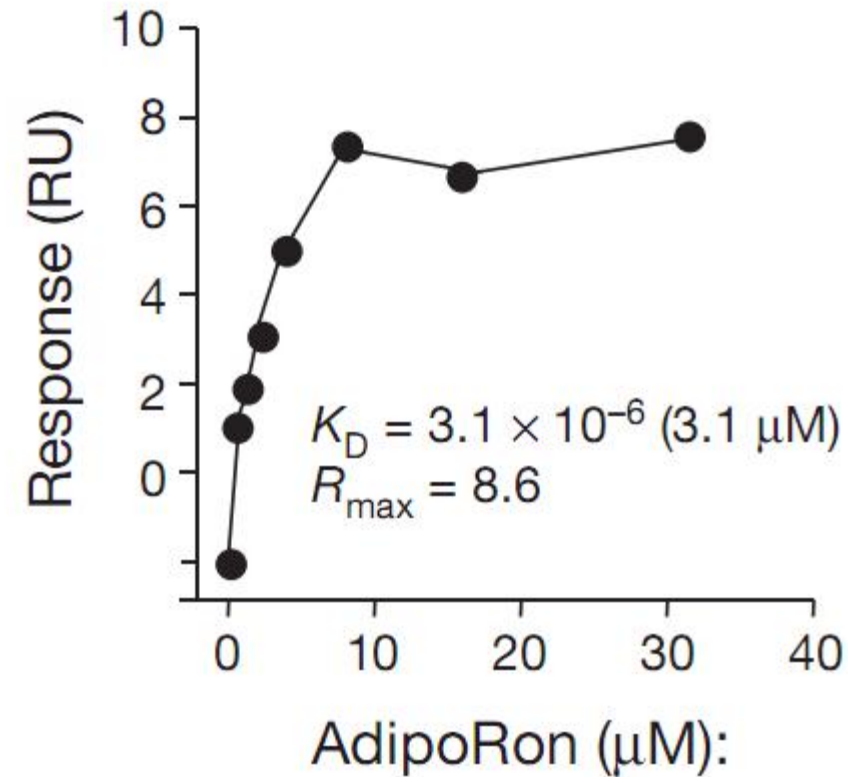
AdipoRon increased PGC-1 α expression which is dependent on Ca²⁺ signalling.



j AdipoR1–AdipoRon binding

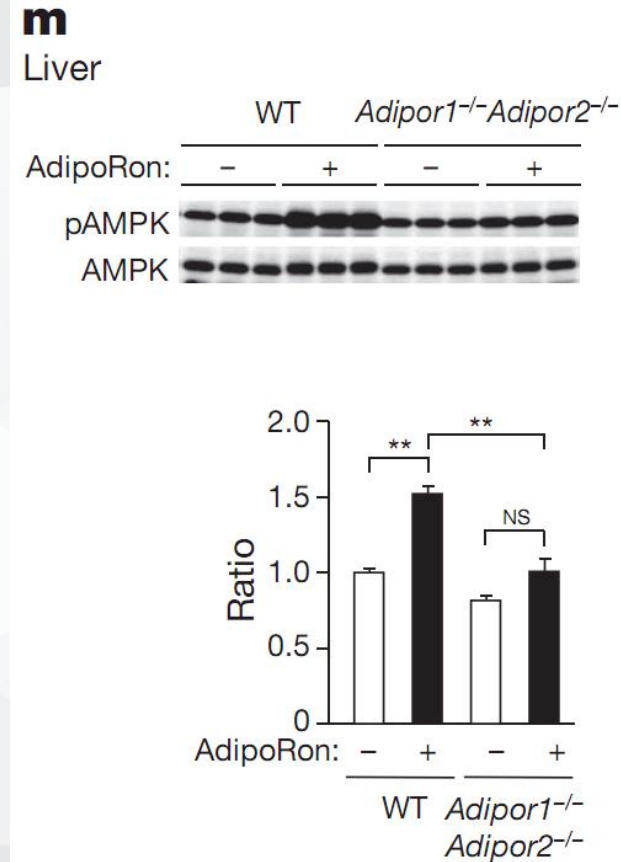
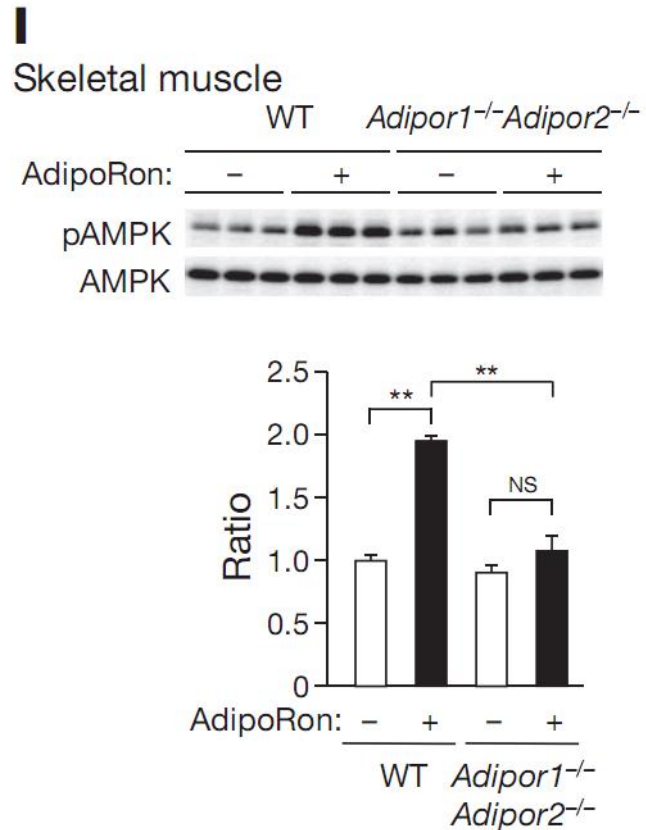


k AdipoR2–AdipoRon binding



AdipoRon bound to both AdipoR1 and AdipoR2

2.1 Identification of small molecule agonists of AdipoR



Intravenous injection of AdipoRon (50mg/kg bodyweight)

AdipoRon could activate AMPK in skeletal muscle and liver via AdipoR1 and AdipoR2

Summary for part 2.1

AdipoRon 促进AMPK磷酸化，敲除AdipoR1后次效应消失

AdipoRon能够起到补充脂联素的作用，激活AMPK

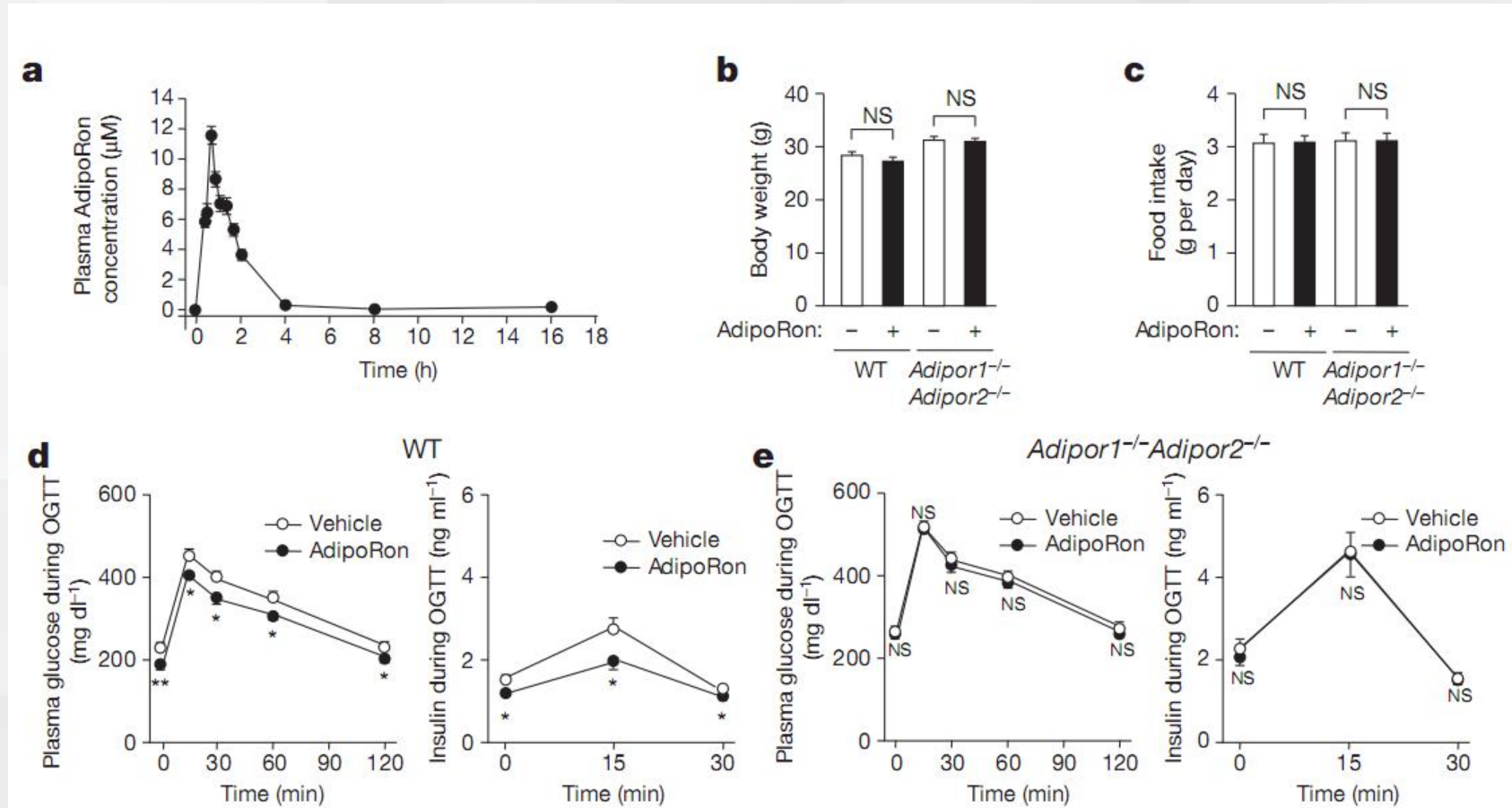
与脂联素相同，AdipoRon依赖于Ca²⁺促进PGC-1 α 表达

Binding assay by surface plasmon resonance

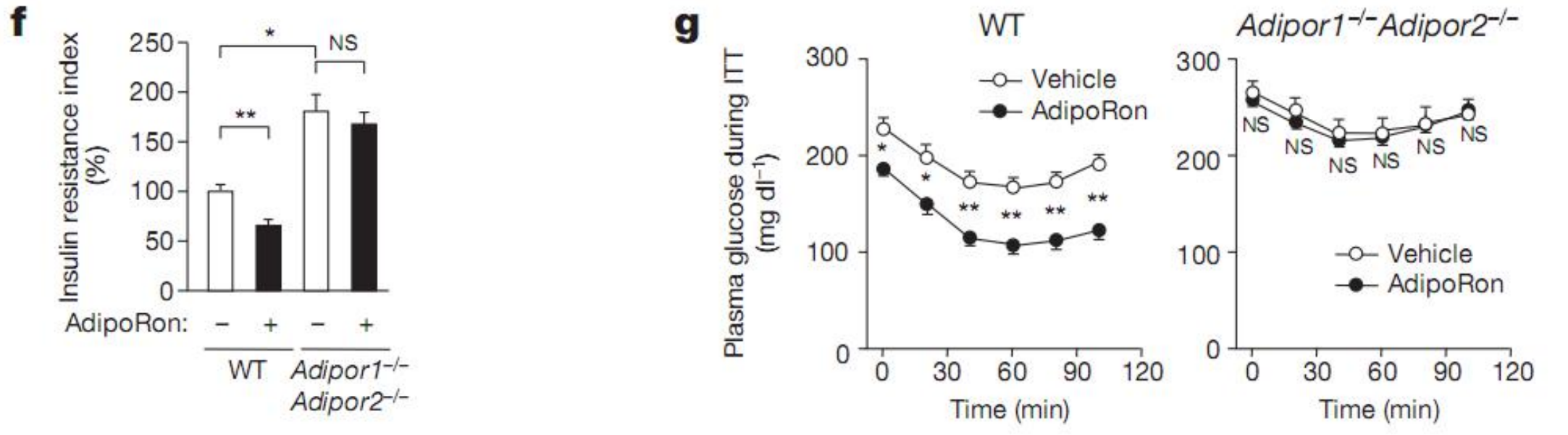
AdipoR敲除前后，静脉注射AdipoRon，肝脏和骨骼肌AMPK磷酸化

Identification of small molecule agonists of AdipoR

2.2 AdipoRon ameliorates diabetes via AdipoR

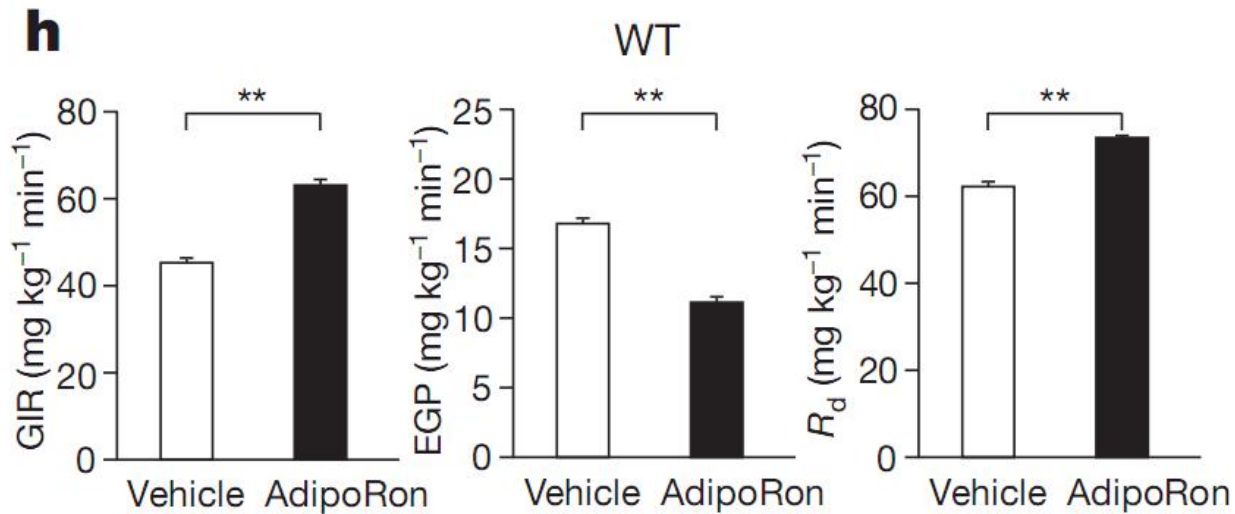


Orally administered AdipoRon (50mg/kg body weight) for 10d.
Had no effect on bodyweight and foodintake in mice on a high-fat diet, but reduced fasting plasma glucose and insulin levels.



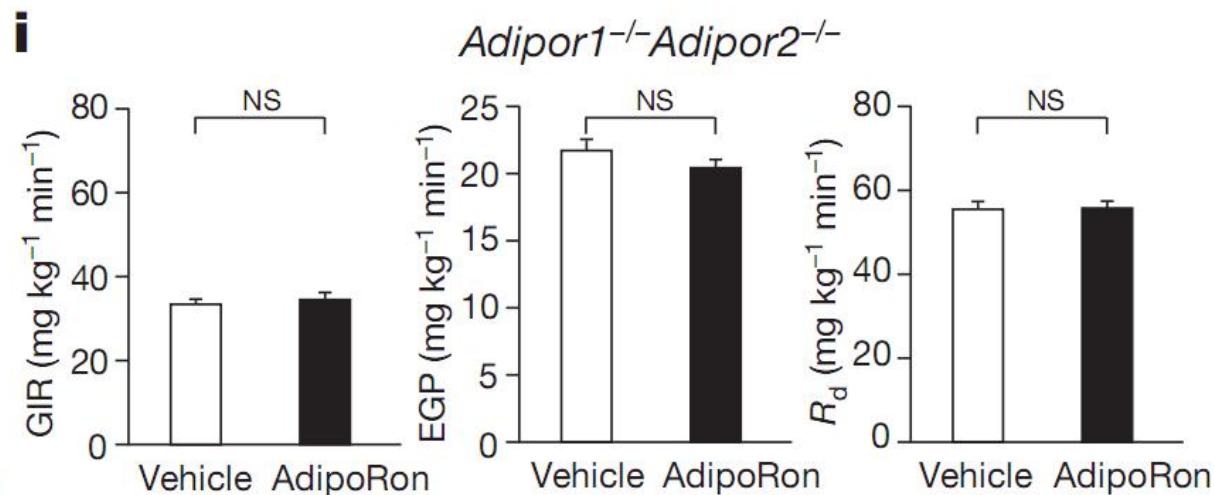
Insulin resistance index and glucose-lowering effect of exogenous insulin

2.2 AdipoRon ameliorates diabetes via AdipoR

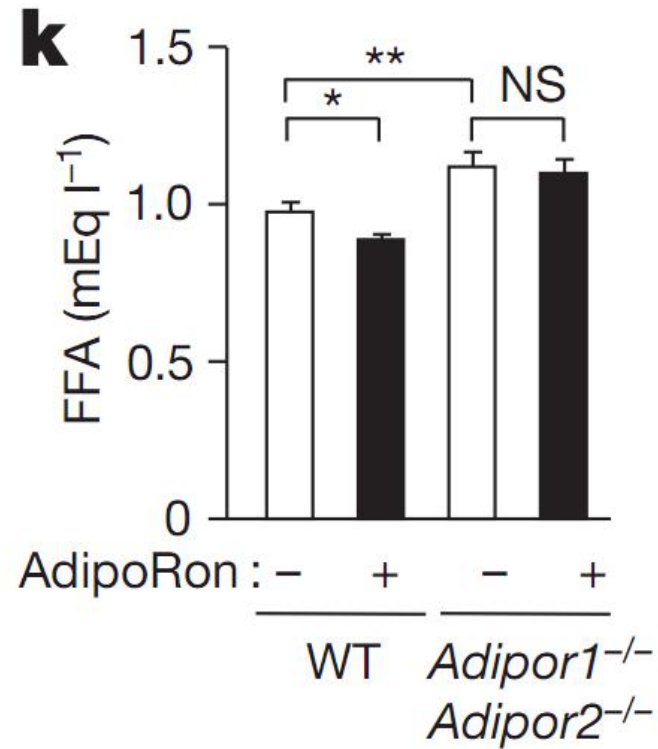
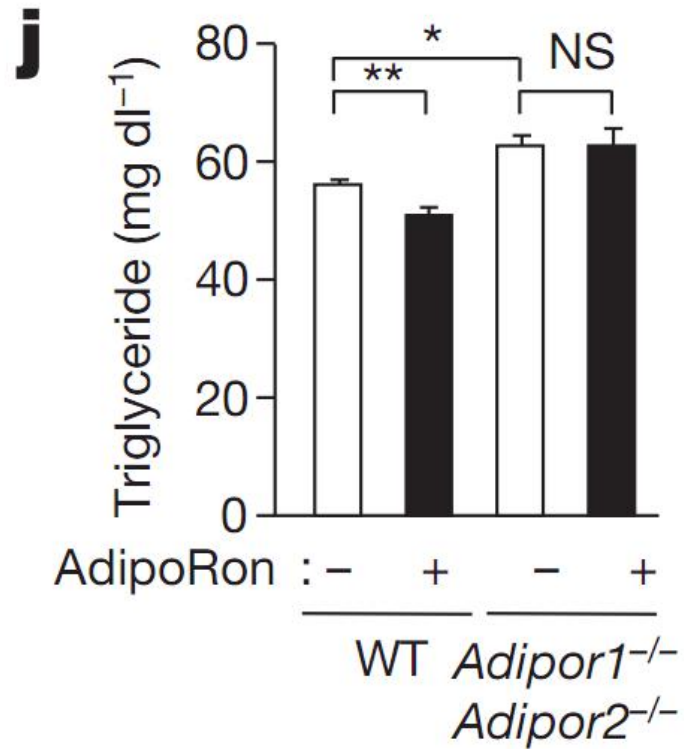


Hyperinsulinaemic euglycaemic clamps in mice on a high-fat diet after 10 days of treatment.

The glucose infusion rate increased, the endogenous glucose production was suppressed, and the glucose disposal rate was increased.



None of these parameters was improved on AdipoRon treatment in *Adipor1^{-/-}Adipor2^{-/-}* double knockout mice.



Treatment with AdipoRon for 10d reduced plasma concentrations of TG and FFA in wild-type mice fed a high-fat diet, these effects were not observed in *Adipor1*^{-/-} *Adipor2*^{-/-} double knockout mice.

Summary for part 2.2

口服AdipoRon后，药物动力学

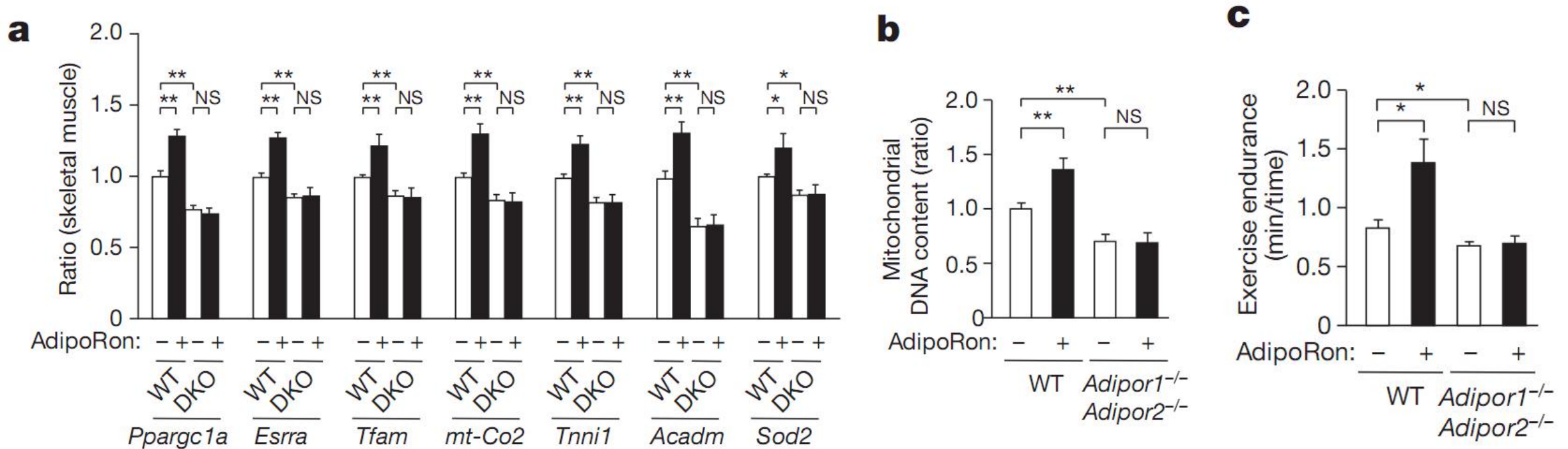
AdipoR敲除前后，口服AdipoRon对高脂饲喂肥胖小鼠体重、摄食、血糖、胰岛素抵抗指数、胰岛素降血糖效应的影响。

高胰岛素-正常血糖钳夹实验：AdipoR敲除前后，口服AdipoRon对葡萄糖灌注率，内源性葡萄糖的产生，葡萄糖代谢速率的影响。

口服AdipoRon对脂代谢的影响：AdipoR敲除前后，血清TG和FFA

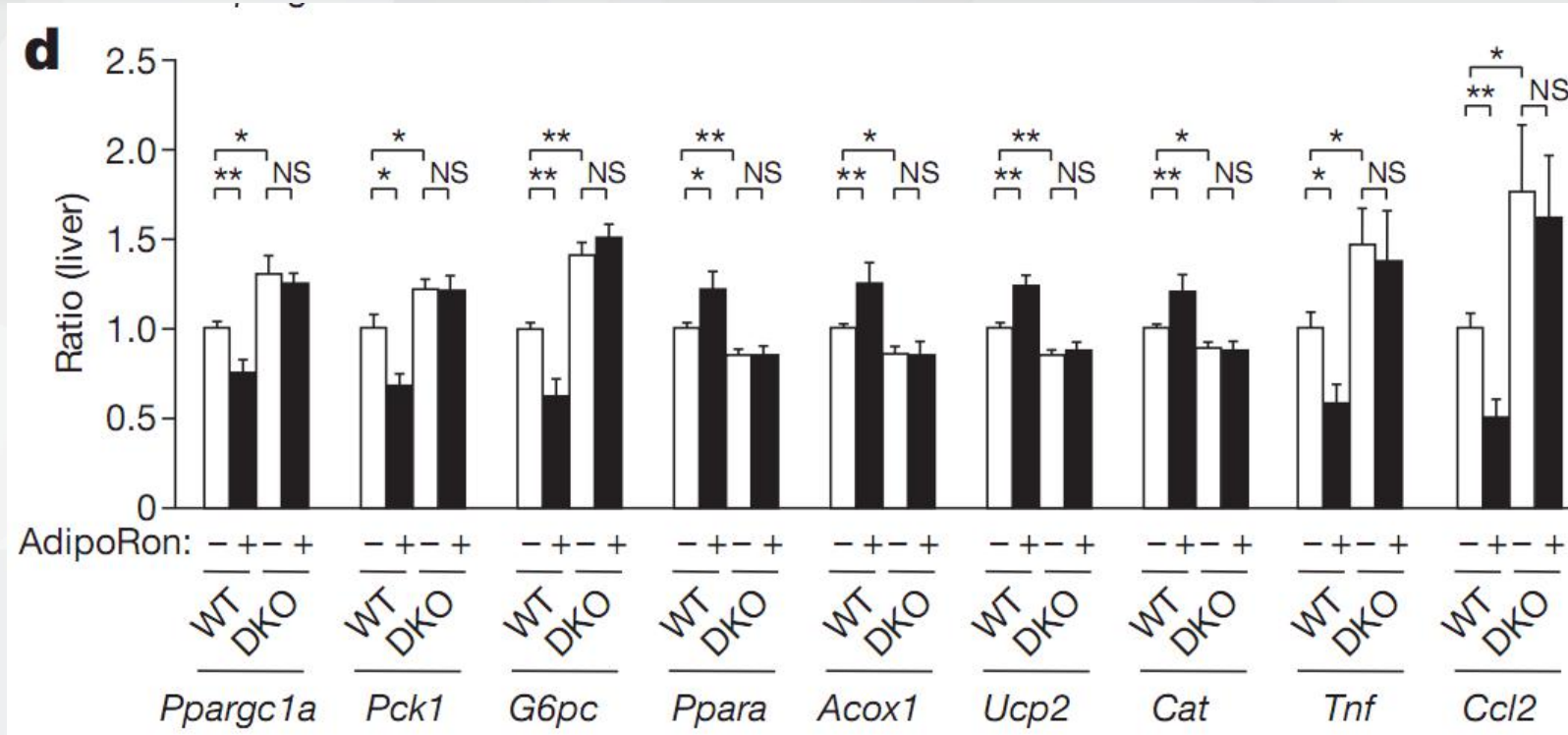
AdipoRon ameliorates diabetes via AdipoR

2.3 Skeletal muscle : AdipoRon activates AdipoR1–AMPK–PGC-1 α pathways



In skeletal muscle, AdipoRon increased the expression of genes involved in mitochondrial biogenesis (*Ppargc1a*, *Esrra*), mitochondrial DNA replication/translation (*Tfam*), oxidative phosphorylation (*mt-Co2*), and increased mitochondrial DNA content, increased exercise endurance. These effects were completely obliterated in *AdipoR1*^{-/-}*AdipoR2*^{-/-} double knockout mice.

2.4 Liver: AdipoRon also activates AdipoR2–PPAR α pathways



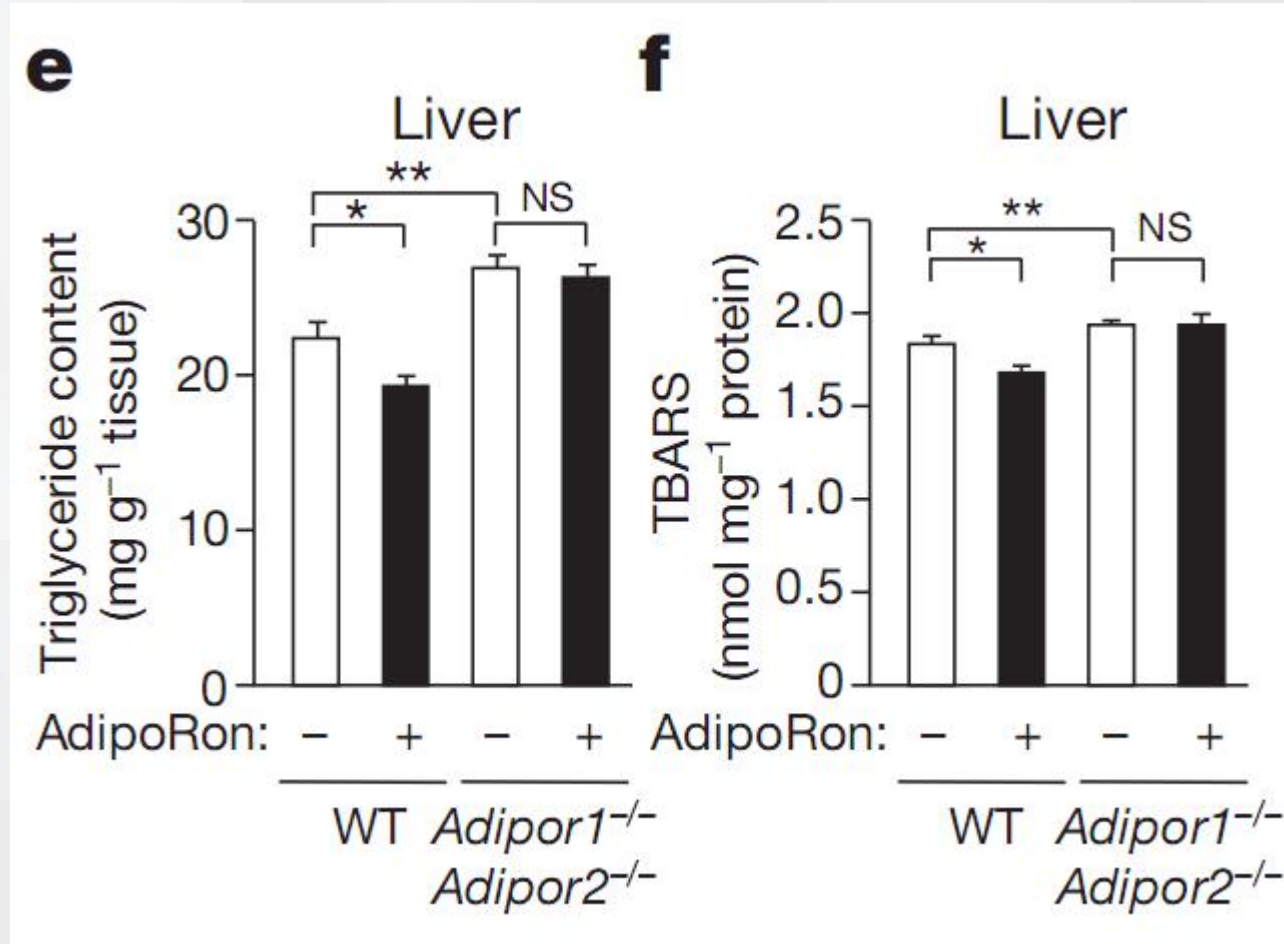
AdipoRon significantly decreased the expression of *Ppargc1a*, *Pck1* and *G6pc* in the liver.

--- Activation of AdipoR1–AMPK pathway

AdipoRon increased the expression levels of the gene encoding PPAR α itself (*Ppara*) and its target genes.

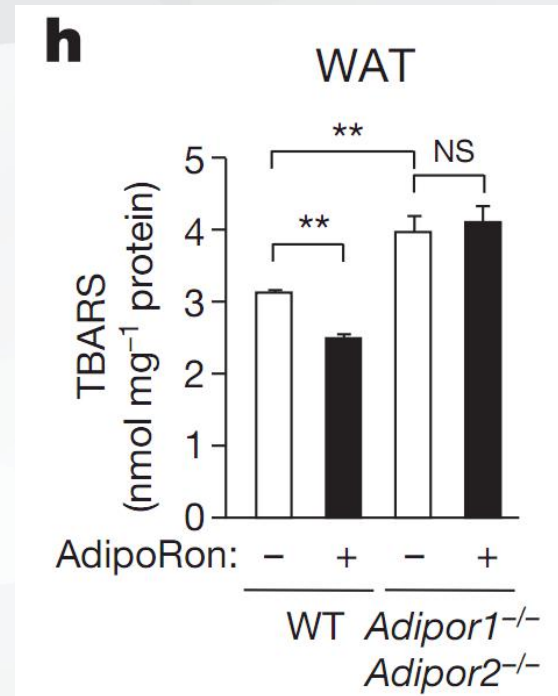
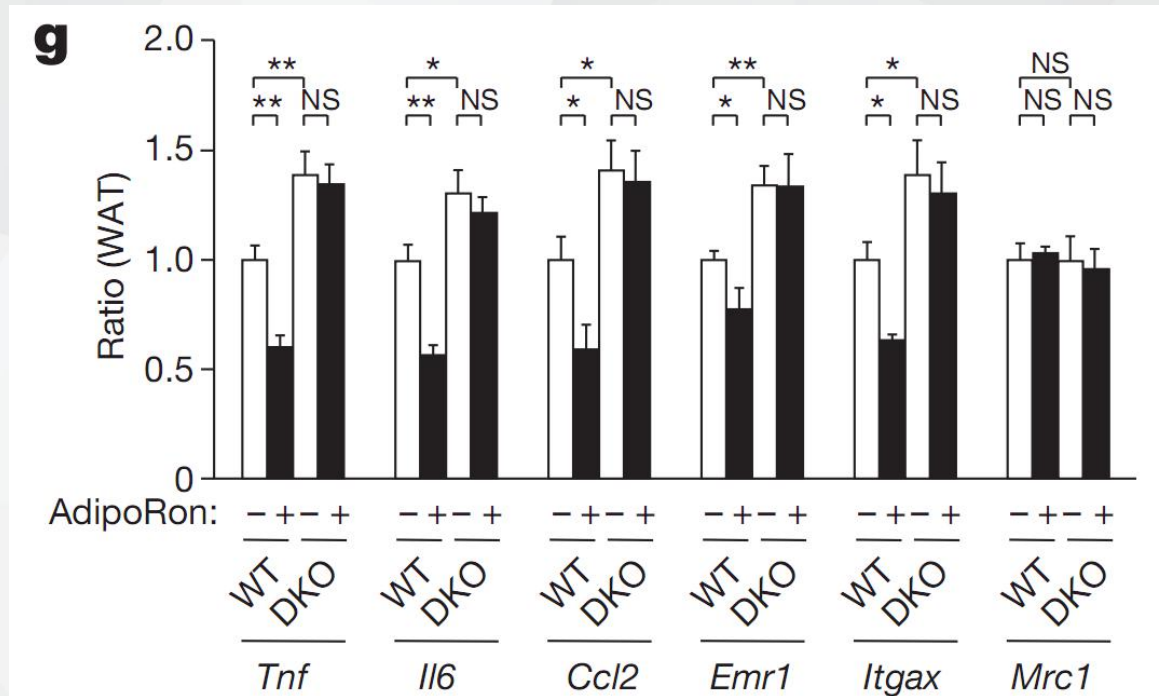
Activation of AdipoR2–PPAR α pathway

2.4 Liver: AdipoRon also activates AdipoR2-PPAR α pathways



AdipoRon significantly reduced triglyceride content and oxidative stress

2.5 WAT : AdipoRon decreases inflammation

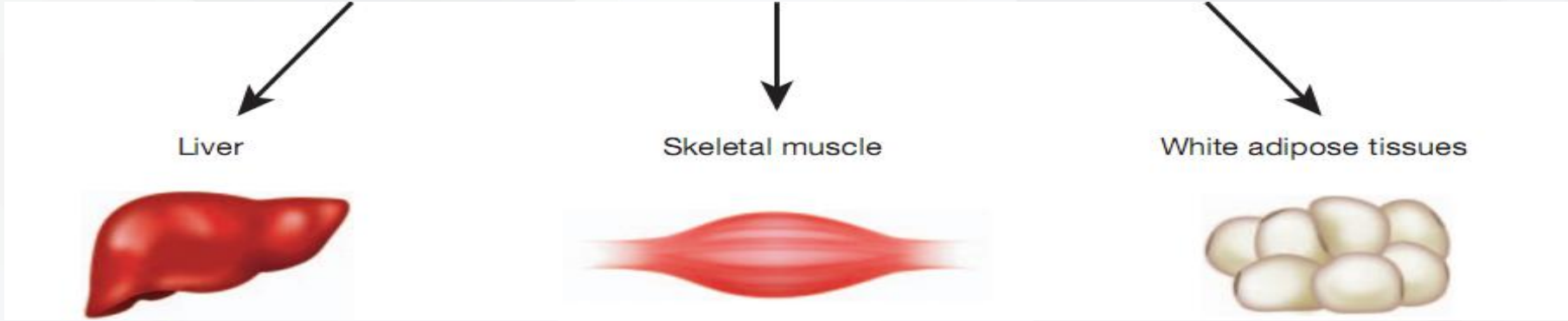


AdipoRon reduced the expression levels of genes encoding proinflammatory cytokines in the white adipose tissue.

AdipoRon reduced TBARS and reduced levels of macrophage markers such as F4/80(Emr1), and markers for classically activated M1 macrophages such as CD11c (Itgax), but not the markers for the alternatively activated M2 macrophages such as CD206(Mrc1)

Summary for part 2.3-2.5

AdipoRon

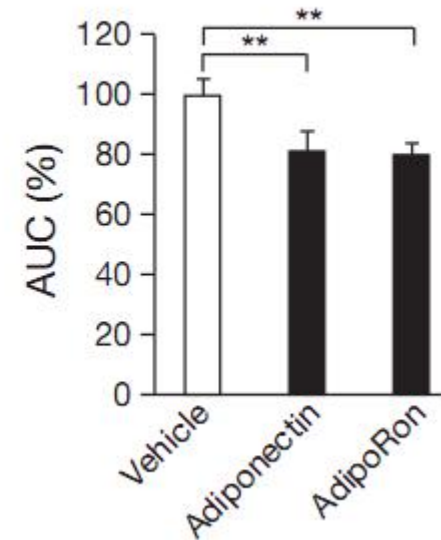
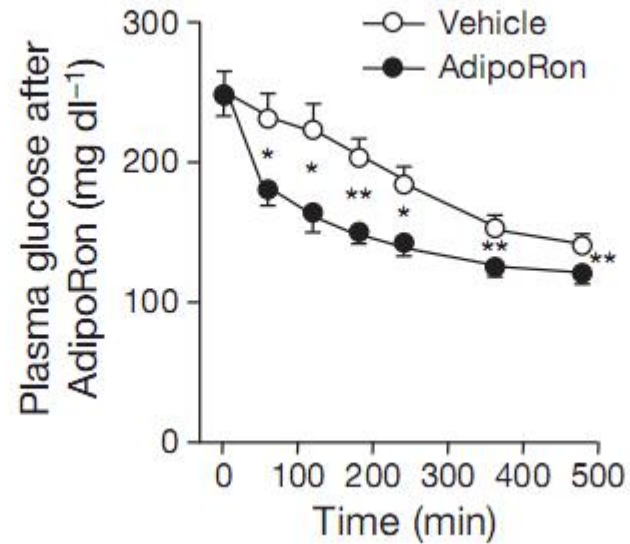
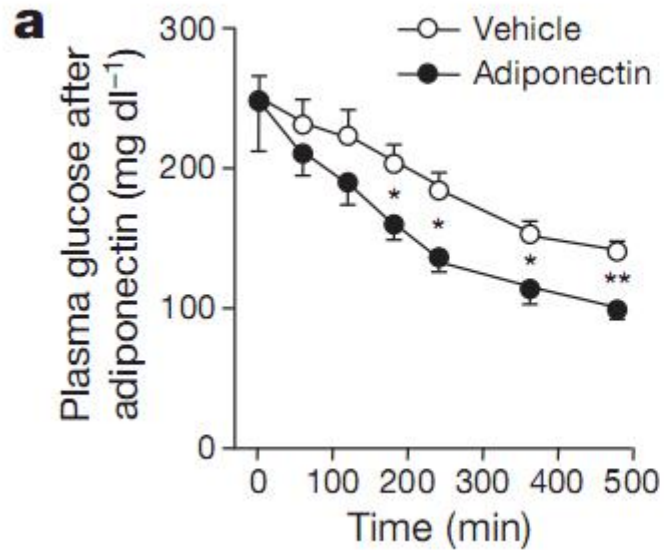


Activates
AdipoR1–AMPK–PGC-1 α
pathways;
Activates AdipoR2–PPAR α
pathways

Activates
AdipoR1–AMPK–PGC-
1 α pathways

Decreases
Pro-inflammatory cytokines
M1 macrophage accumulation
Oxidative stress

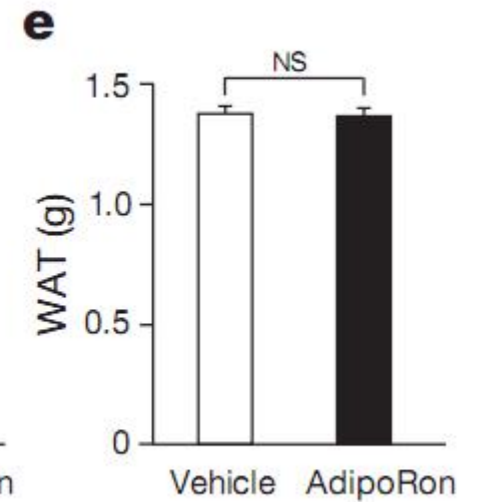
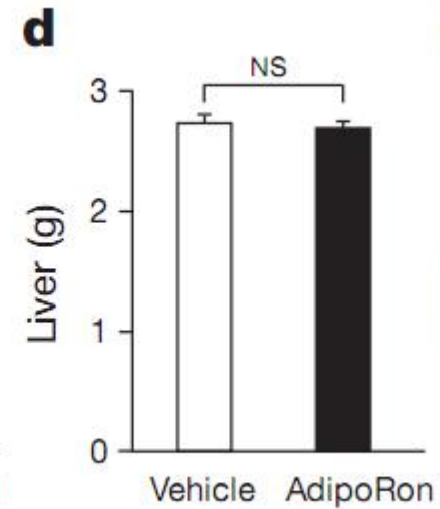
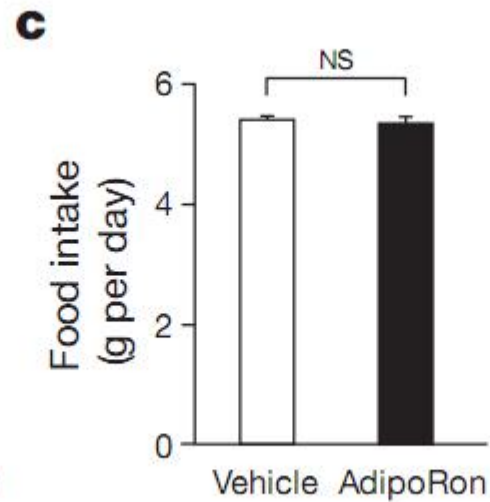
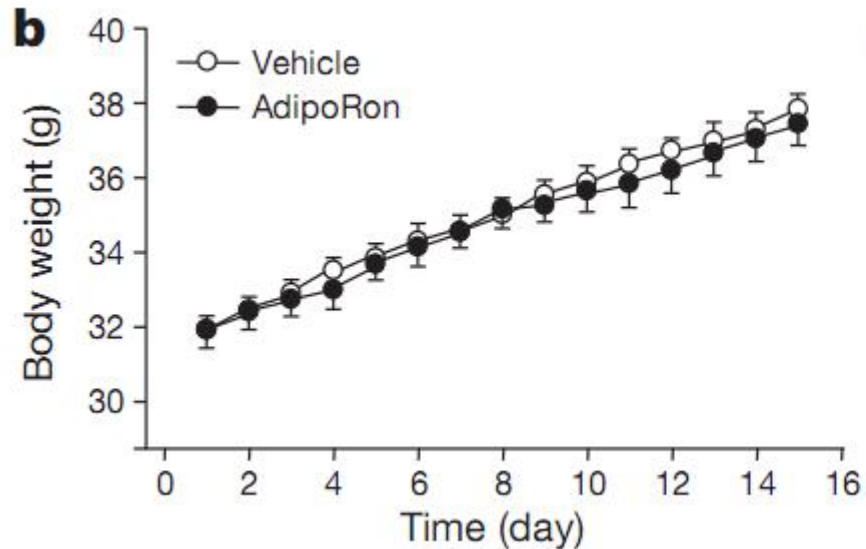
2.6 AdipoRon ameliorates diabetes in *db/db* mice



db/db mice:

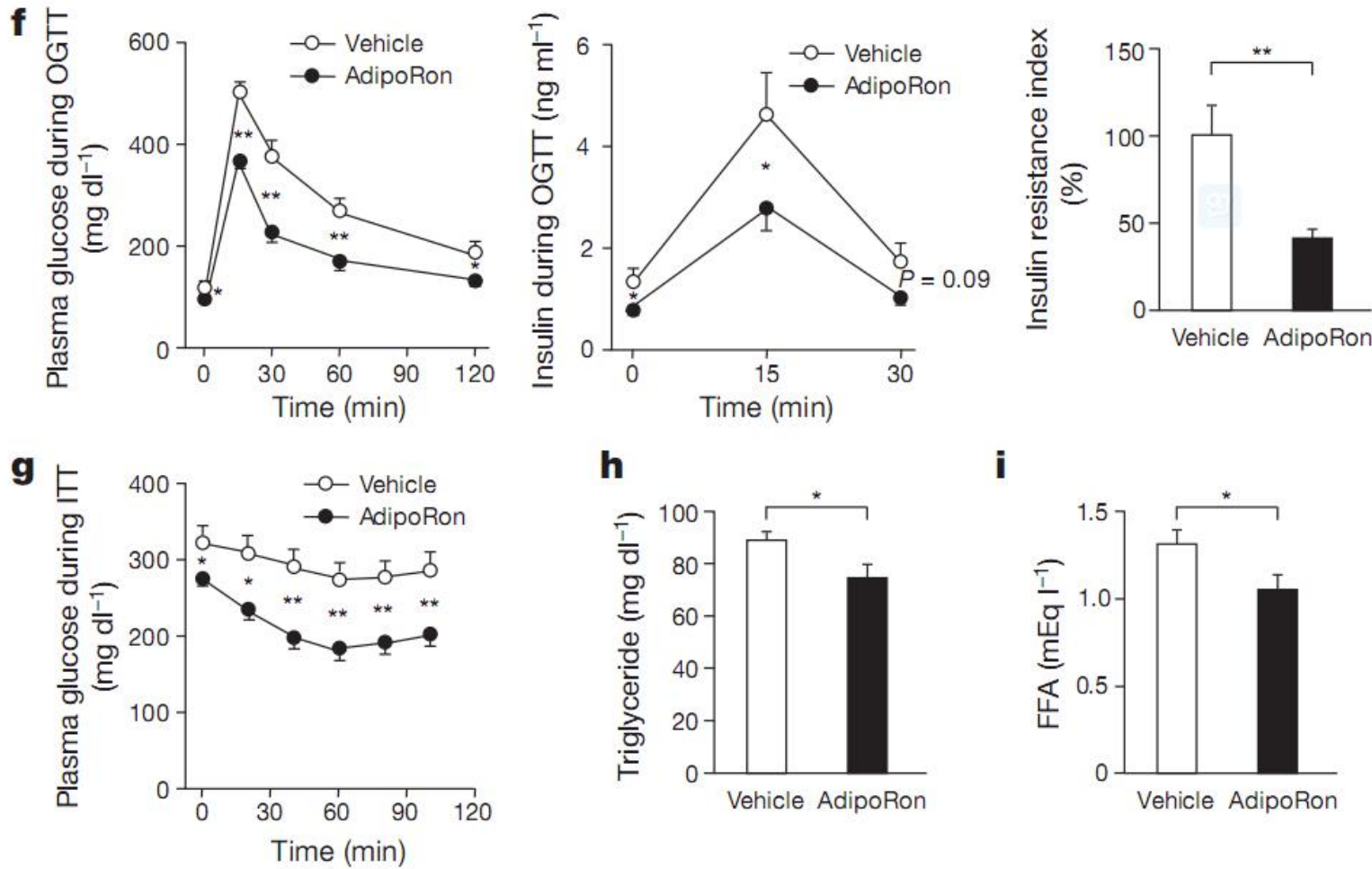
Intraperitoneal injection of adiponectin, and orally administered AdipoRon reduced plasma glucose

2.6 AdipoRon ameliorates diabetes in *db/db* mice



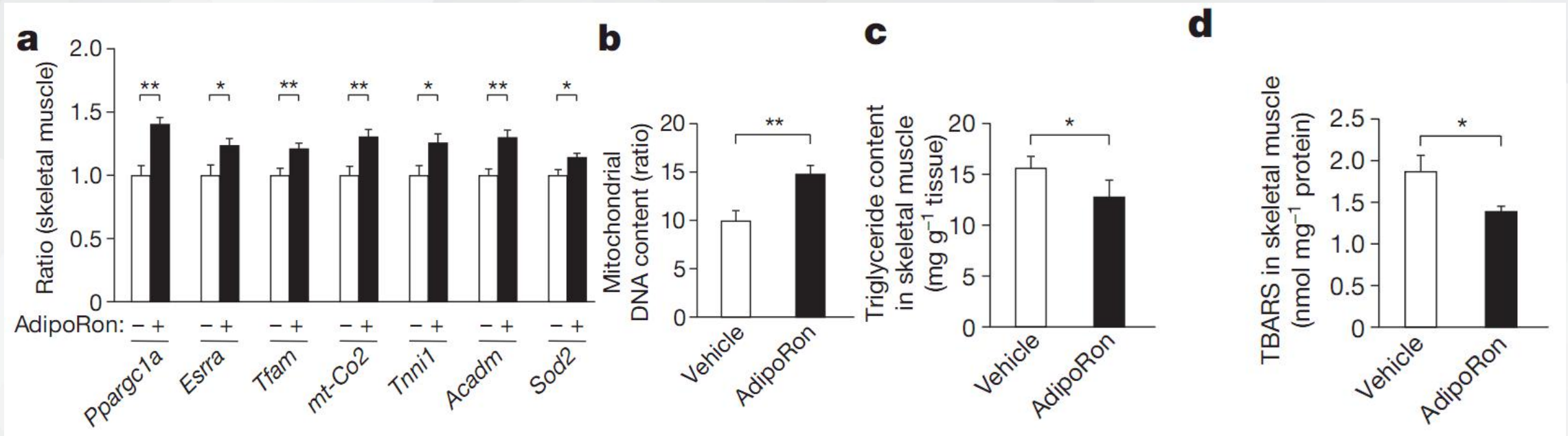
Orally administered AdipoRon for 2 weeks had no effects on bodyweight, foodintake, liver weight and WAT weight.

2.6 AdipoRon ameliorates diabetes in *db/db* mice



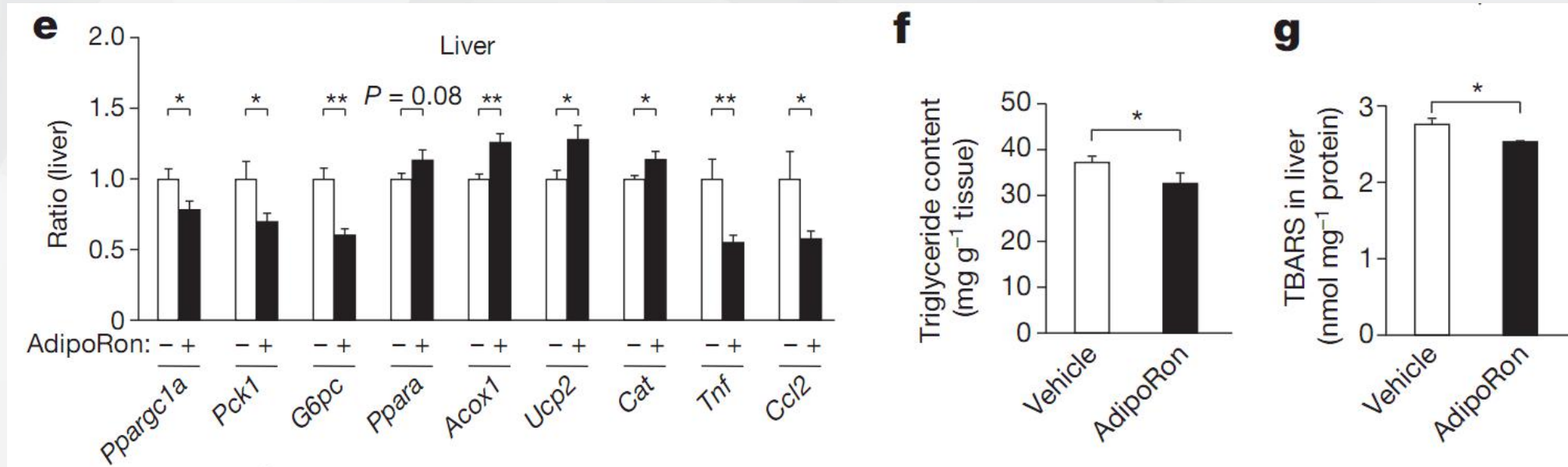
Orally administered AdipoRon for 2 weeks significantly ameliorated glucose intolerance, insulin resistance and dyslipidaemia in *db/db* mice fed a normal chow diet.

2.6 AdipoRon ameliorates diabetes in *db/db* mice



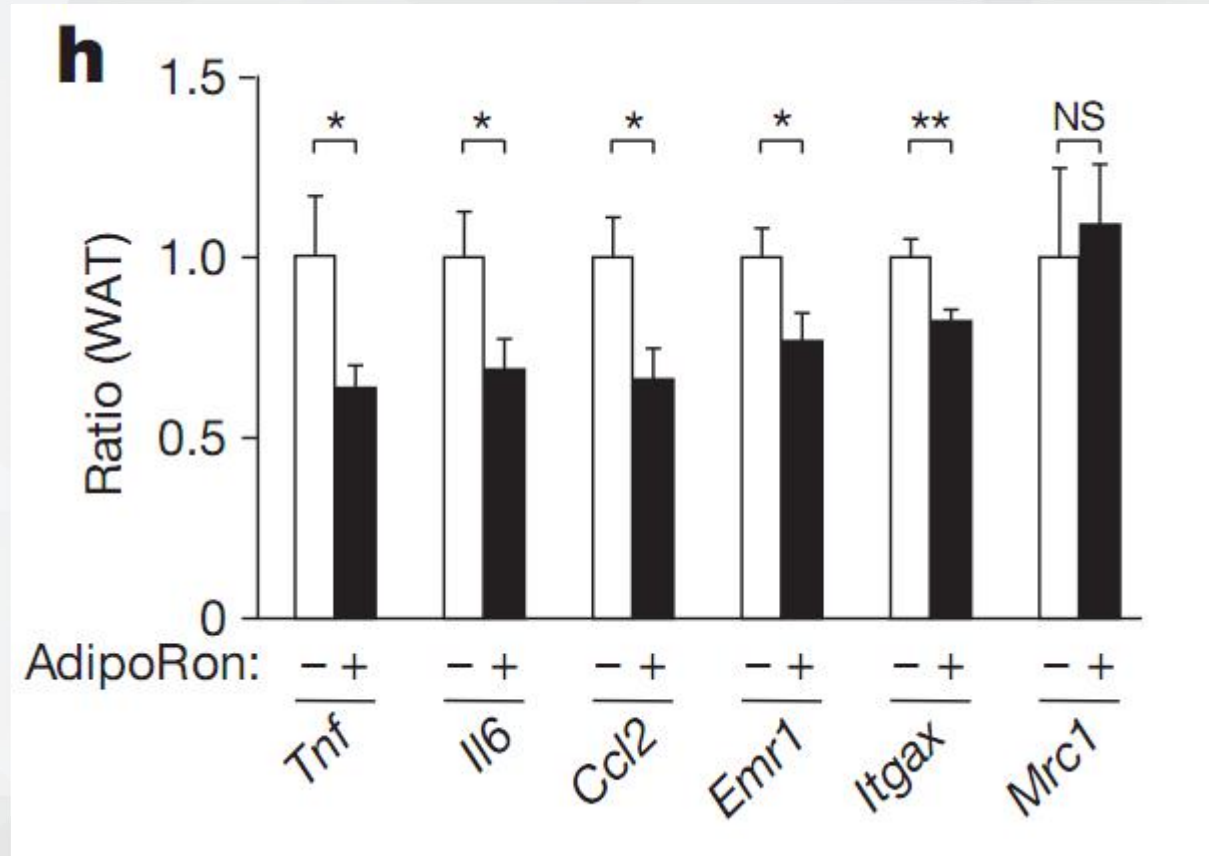
In the skeletal muscle of *db/db* mice fed a normal chow diet, AdipoRon significantly increased the expression levels of genes involved in mitochondrial biogenesis functions and DNA content, and also *Acadm* and *Sod2* which were associated with decreased triglyceride content and TBARS, respectively.

2.6 AdipoRon ameliorates diabetes in *db/db* mice



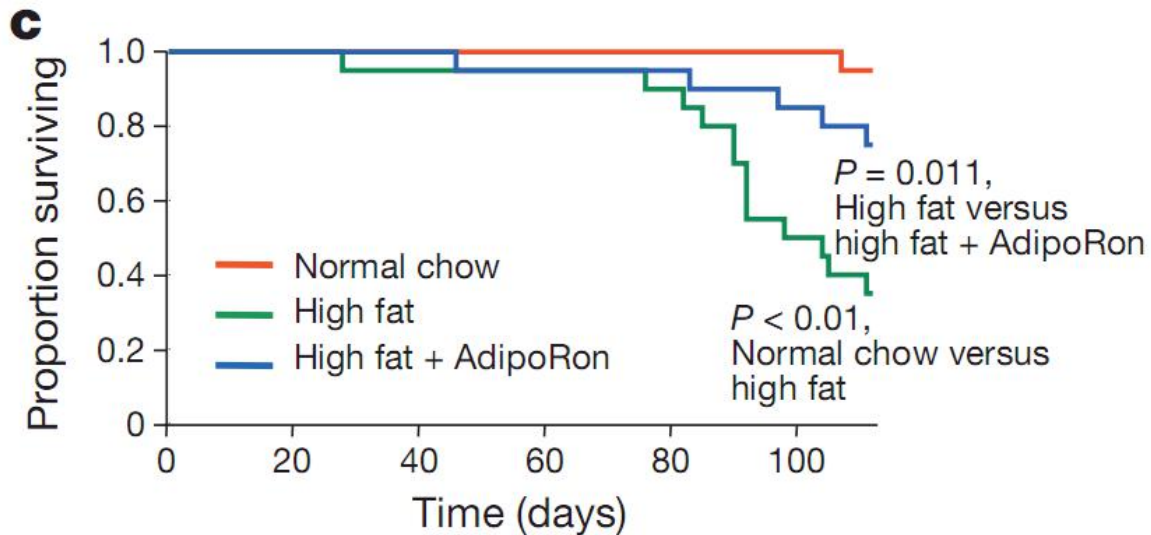
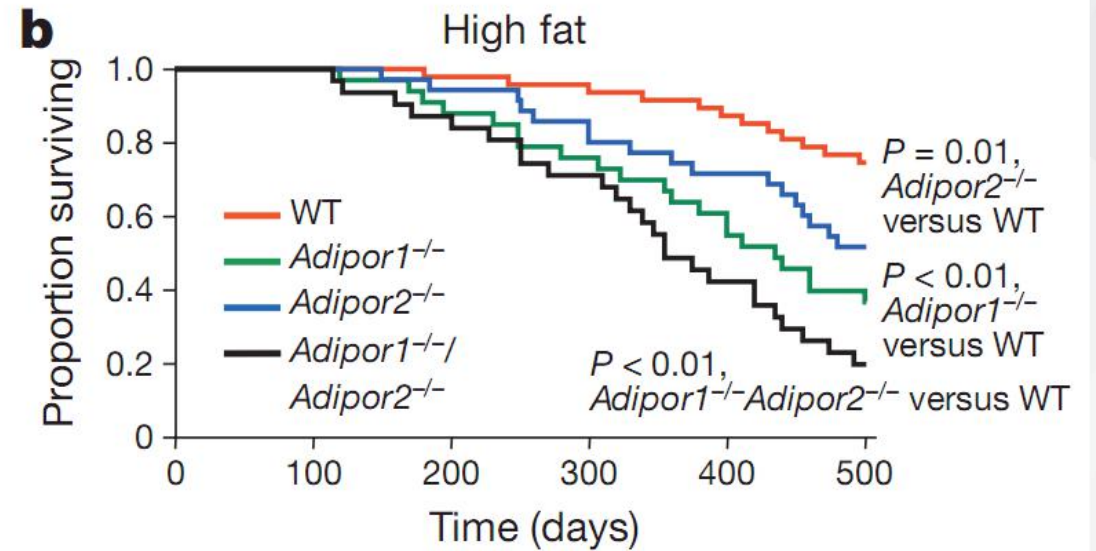
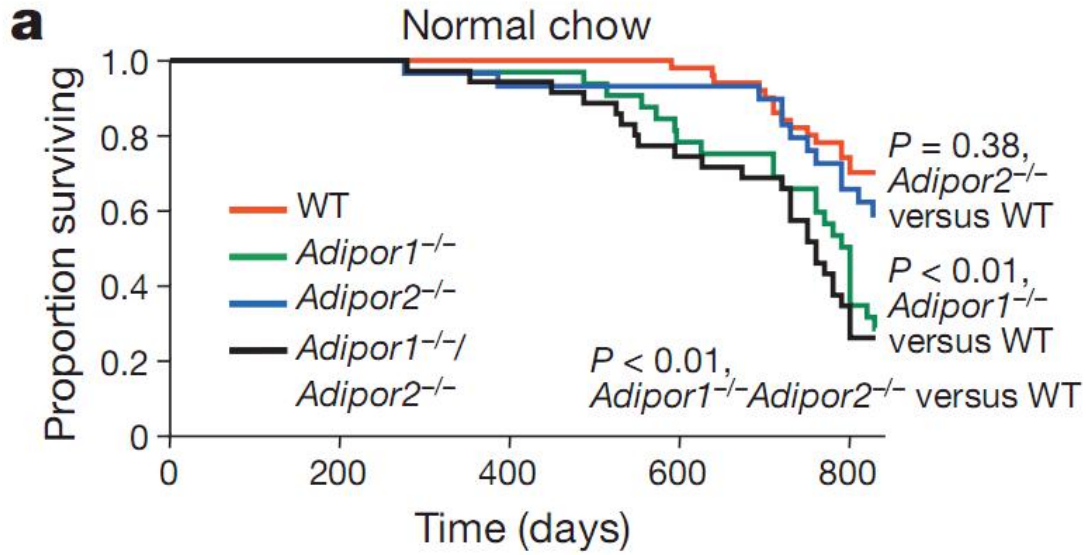
In the liver, AdipoRon significantly decreased the expression of Ppargc1a, Pck1 and G6pc, increased the expression of PPAR α and its target genes. Therefore, AdipoRon significantly reduced triglyceride content, oxidative stress and reduced the expression levels of genes encoding pro-inflammatory cytokines.

2.6 AdipoRon ameliorates diabetes in *db/db* mice

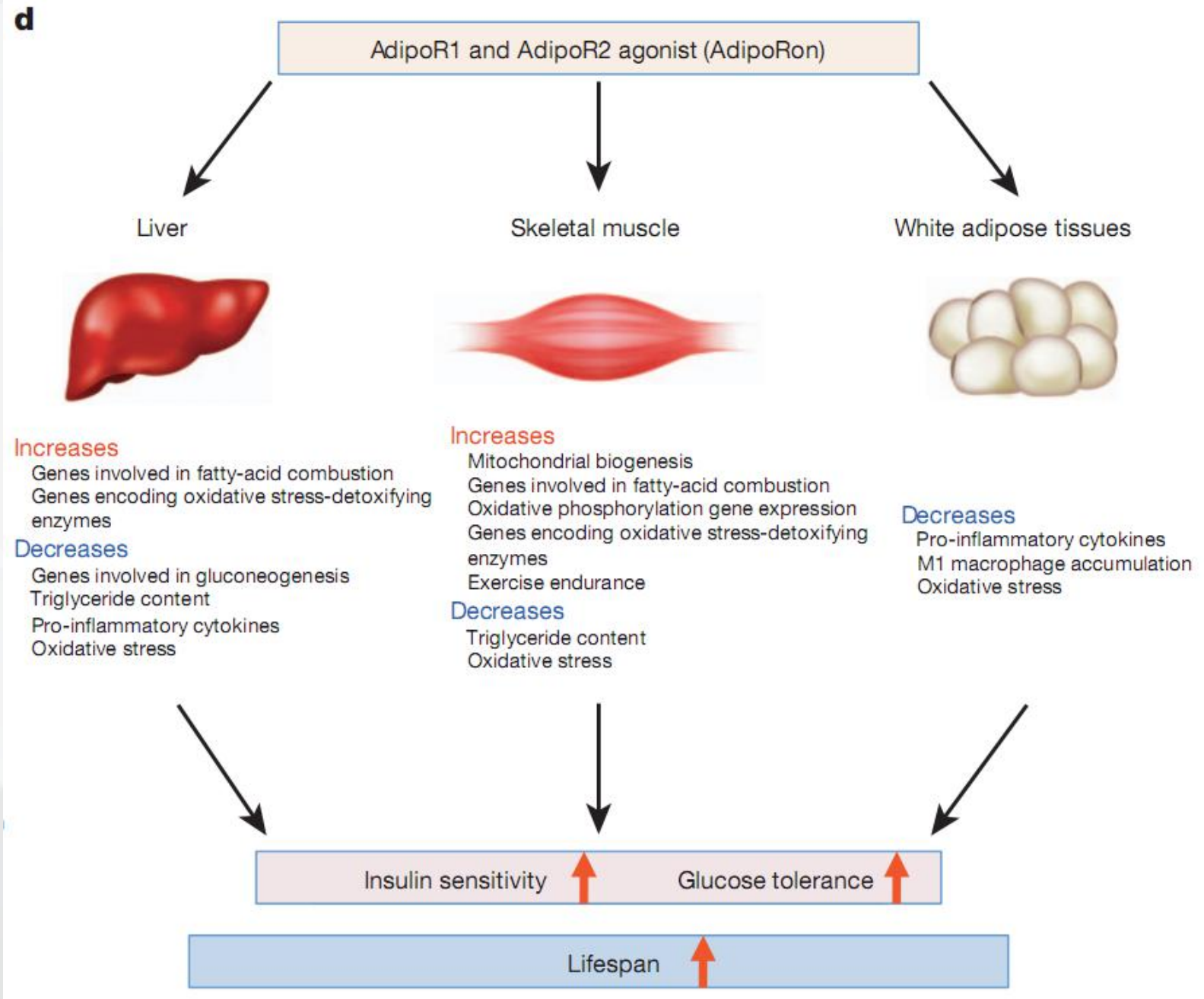


In the WAT, AdipoRon reduced the expression levels of genes encoding pro-inflammatory cytokines and macrophage markers, especially the levels of markers for classically activated M1 macrophages, but not the levels of markers for the alternatively activated M2 macrophages.

2.7 AdipoRon prolonged the shortened lifespan



Summary



启发



1

直接应用

2

筛选受体激活剂

3

配体分子改良

Otvos et al. *BMC Biotechnology* 2011, **11**:90
<http://www.biomedcentral.com/1472-6750/11/90>



RESEARCH ARTICLE

Open Access

Design and development of a peptide-based adiponectin receptor agonist for cancer treatment

Laszlo Otvos Jr¹, Eva Haspinger^{2,3}, Francesca La Russa^{2,3}, Federica Maspero^{2,3}, Patrizia Graziano^{2,3}, Ilona Kovalszky⁴, Sandor Lovas⁵, Kaushik Nama¹, Ralf Hoffmann⁶, Daniel Knappe⁶, Marco Cassone¹, John Wade⁷ and Eva Surmacz^{2*}



General and Comparative Endocrinology

Volume 113, Issue 1, January 1999, Pages 155–164



42314||

Regular Article

Preparation of Recombinant Gilthead Seabream (*Sparus aurata*) Growth Hormone and Its Use for Stimulation of Larvae Growth by Oral Administration ☆

I Ben-Atia^a, M Fine^{b, c}, A Tandler^a, B Funkenstein^b, S Maurice^c, B Cavari^b, A Gertler^{c, 1}