

Seminaris de Recerca de la Facultat de Farmàcia  
8 de Maig de 2012

# Noves estratègies de modulació del metabolisme lipídic per al tractament de l'obesitat

**Dolors Serra**

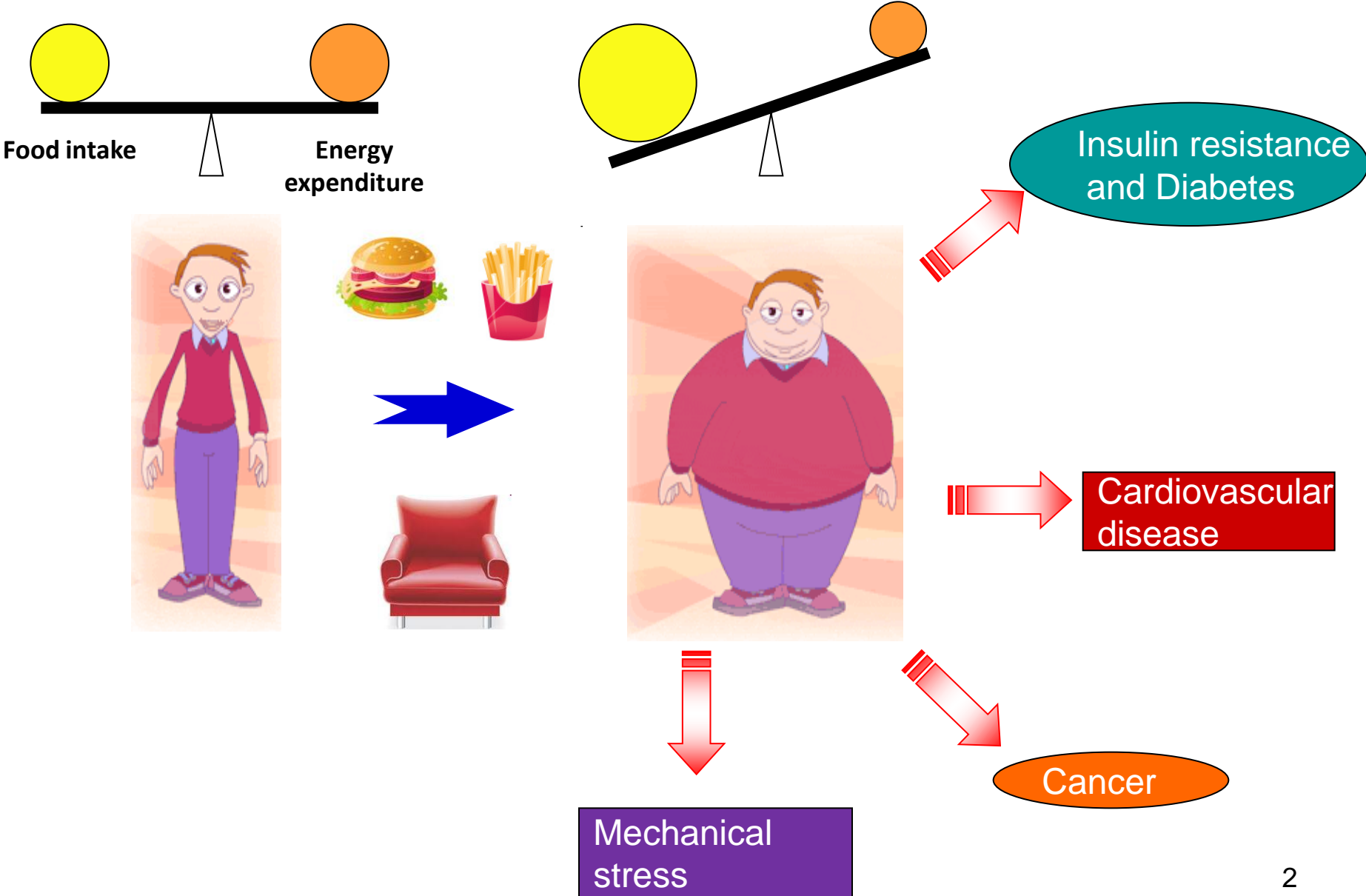
Departament de Bioquímica i Biologia Molecular



UNIVERSITAT DE BARCELONA



# Obesity



# Prevalence and trends

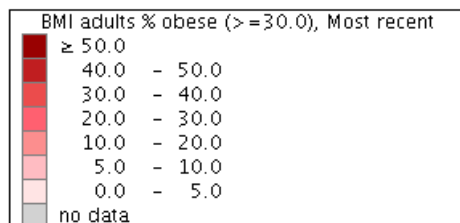
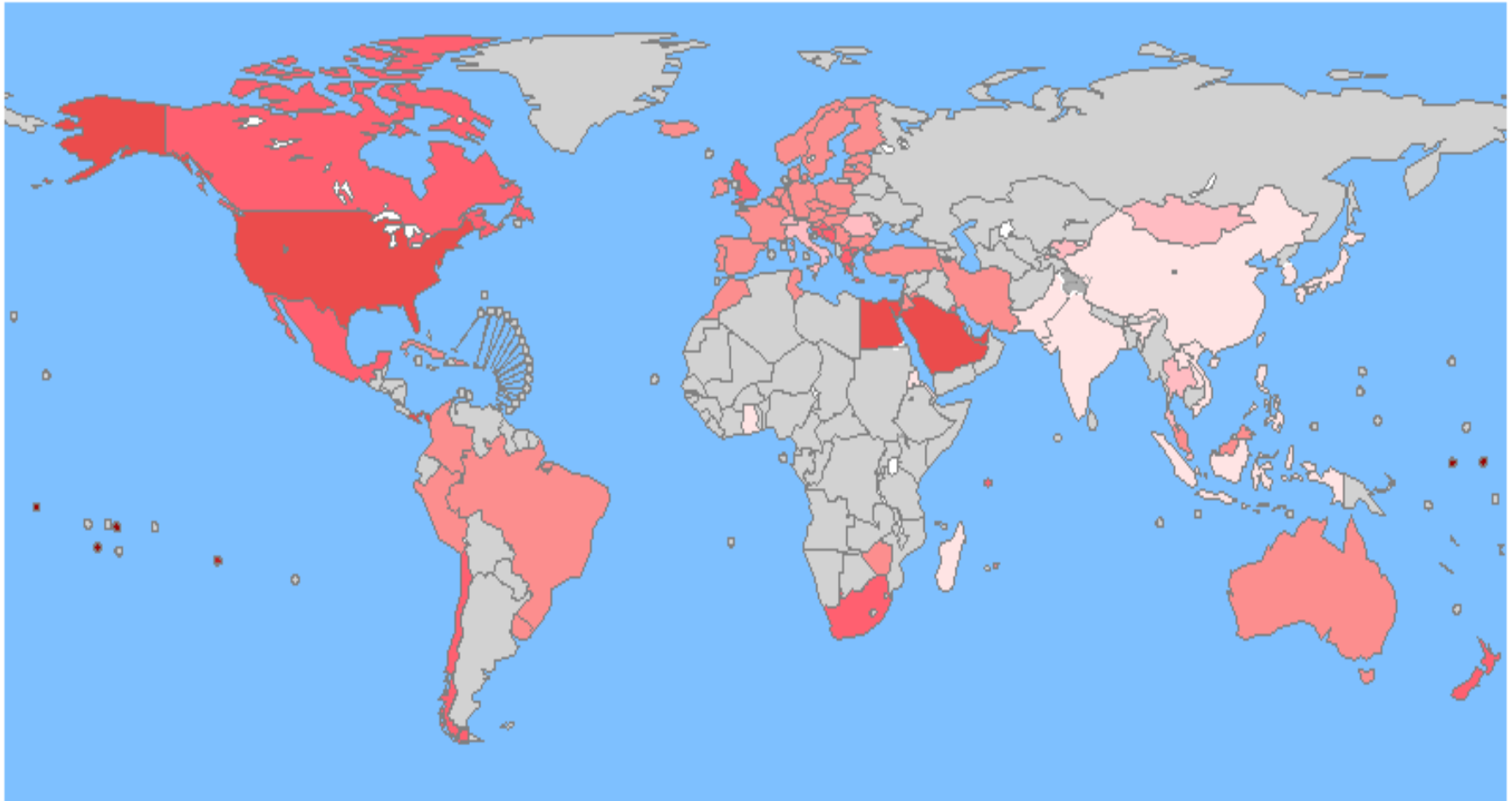
- Currently, **1.600 million adults** worldwide are overweight and **312 million** of them are clinically obese



- Obesity is also a serious health concern for children  
**17%** obese children (US)



# Obesity in the World 2012



BMI: kg/m<sup>2</sup>

BMI>25 overweight

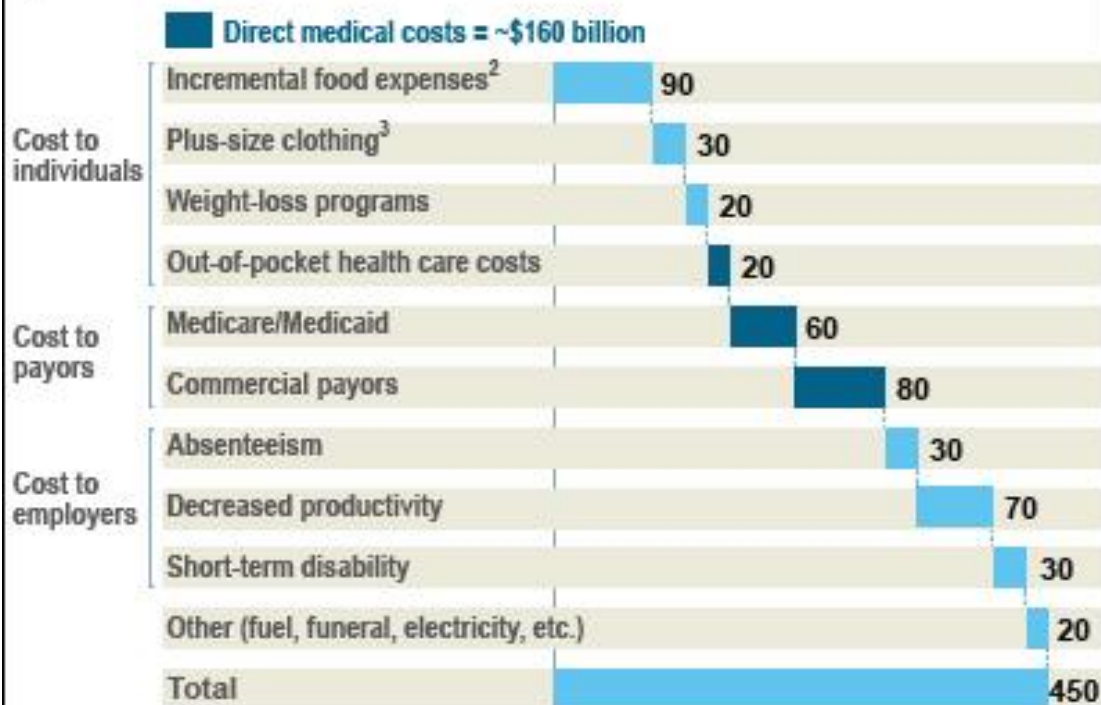
BMI>30 obese

# Economic impact-2010

## Why governments must lead the fight against obesity

Total U.S. obesity costs are nearly three times direct medical costs.

Estimated increased spending associated with obesity in the United States<sup>1</sup>  
\$ billion



<sup>1</sup> Rounded estimates.

<sup>2</sup> Based on estimated cost of incremental calorie intake to maintain obese weight.

<sup>3</sup> Based on incremental costs of plus-size clothing.

# Obesity Interventions

- Obesity is a multi-level problem and requires a multi-level approach to integrate treatment and prevention:
  - Individual and Family
  - School and Community
  - Government

# Policies focused on changing behaviours

## Healthy diet



## Increasing physical activity



# Policies focused on changing behaviours

Your health. Your choice.



38 seconds  
to the top

38 steps  
to better health



## EXPERT OPINION

1. Introduction

## Anti-obesity drugs: a review about their effects and their safety

Giuseppe Derosa<sup>†</sup> & Pamela Maffioli

**Introduction:** Amphetamines, rimonabant and sibutramine licenses as anti-obesity drugs have been withdrawn because of their adverse effects. In fact, orlistat is the only available long-term treatment for obesity.

# A PGC1- $\alpha$ -dependent myokine that drives brown-fat-like development of white fat and thermogenesis

Pontus Boström<sup>1</sup>, Jun Wu<sup>1</sup>, Mark P. Jedrychowski<sup>2</sup>, Anisha Korde<sup>1</sup>, Li Ye<sup>1</sup>, James C. Lo<sup>1</sup>, Kyle A. Rasbach<sup>1</sup>, Elisabeth Almer Boström<sup>3</sup>, Jang Hyun Choi<sup>1</sup>, Jonathan Z. Long<sup>1</sup>, Shingo Kajimura<sup>4</sup>, Maria Cristina Zingaretti<sup>5</sup>, Birgitte F. Vind<sup>6</sup>, Hua Tu<sup>7</sup>, Saverio Cinti<sup>5</sup>, Kurt Højlund<sup>6</sup>, Steven P. Gygi<sup>2</sup> & Bruce M. Spiegelman<sup>1</sup>

### EL PAIS

**Irisina**, hormona quemagrasas

**Irisina**, hormona contra la obesidad

Recientes investigaciones sacaron a la luz un nuevo descubrimiento, una **hormona quemagrasas** llamada **Irisina**. Esta hormona es sumamente importante para el tratamiento **contra la obesidad**. Al parecer cuando realizas actividad física, se ponen en marcha una serie de procesos metabólicos que favorecen la síntesis de la hormona Irisina, que tendría efectos directos sobre el tejido graso.

LA VANGUARDIA.com/salud

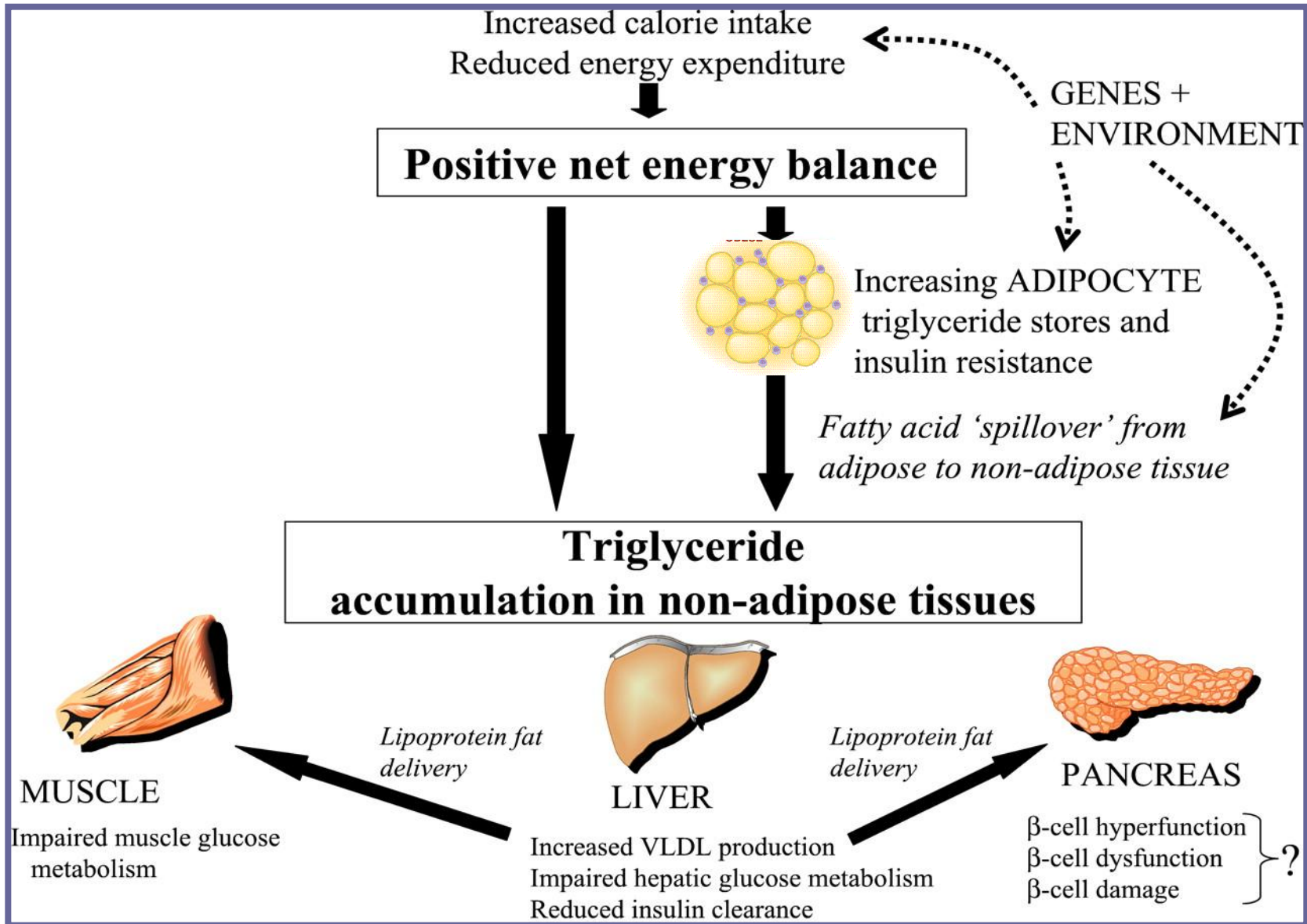
**Irisina**, la hormona de la actividad física

Científicos de Harvard descubren una sustancia clave en los efectos saludables del deporte y buscan un fármaco que imite su actividad | [Empleada como fármaco, podría mejorar el tratamiento de la diabetes y la obesidad](#)

**Salud** | 13/01/2012 - 02:44h

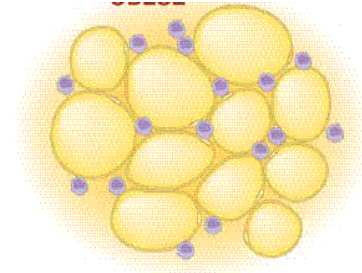
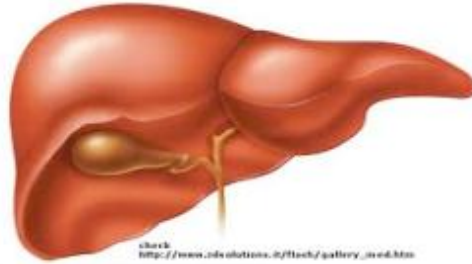
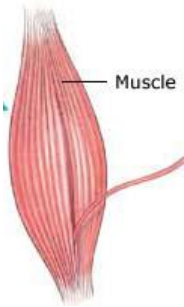
[Ana Macpherson](#) Barcelona , [Josep Corbella](#) Barcelona

# Pathophysiology of Obesity

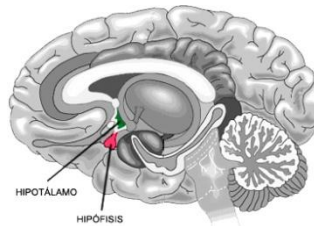


# Estratègies contra l'obesitat

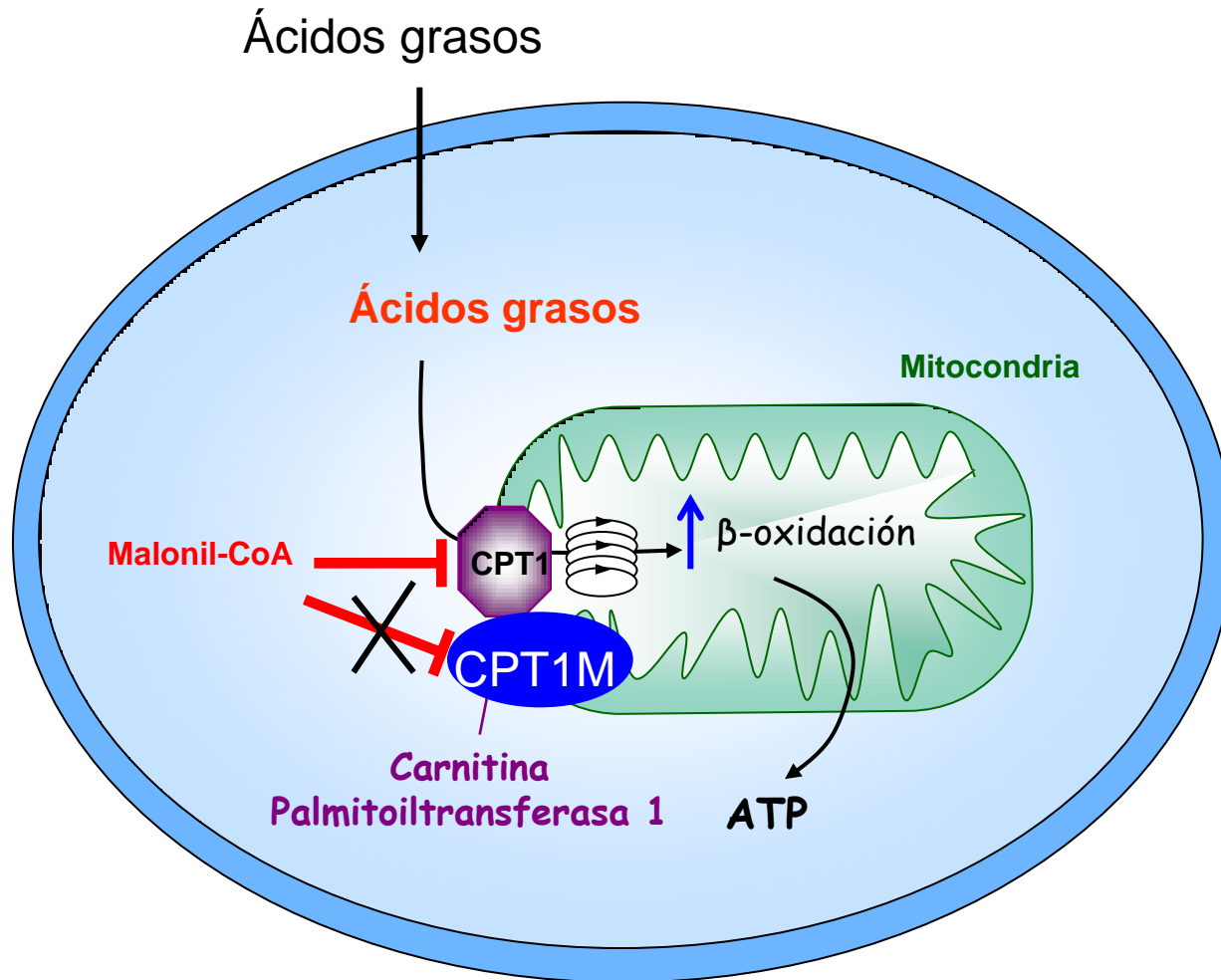
- Augment de l'oxidació d'àcids grassos en diferents teixits



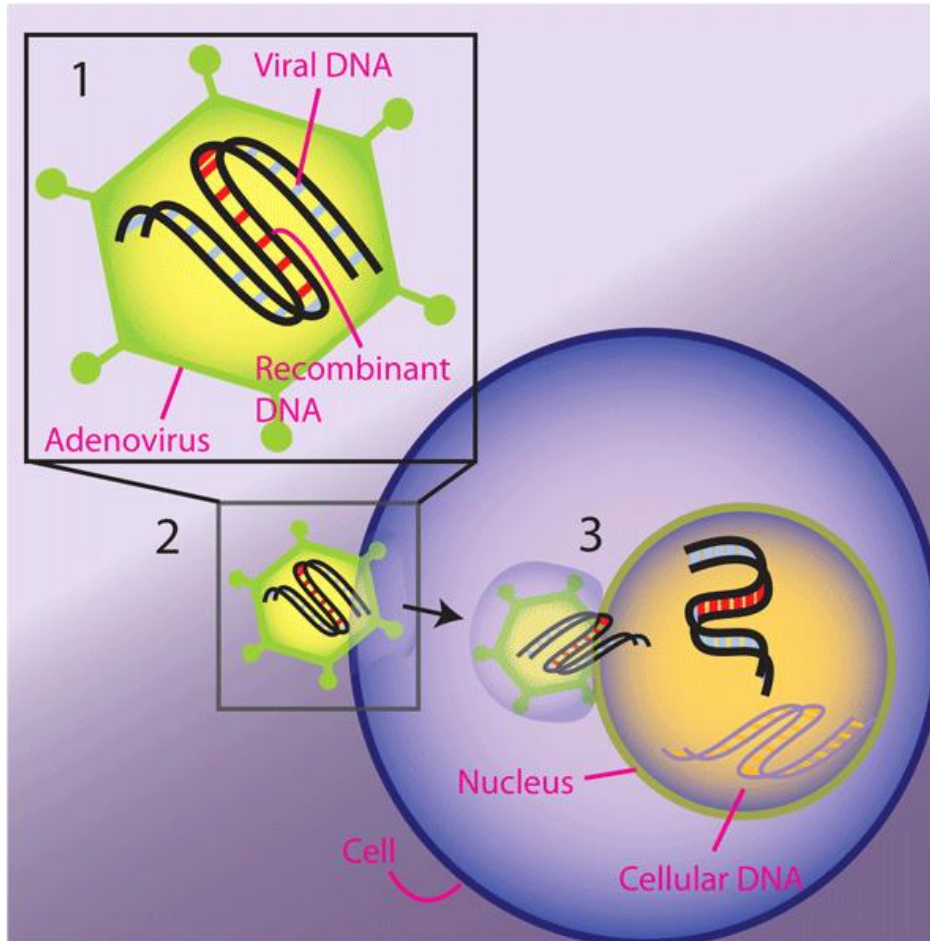
- Control de la ingesta a nivel del SNC



# Oxidación de los ácidos grasos



# Viral vectors



## Adenovirus

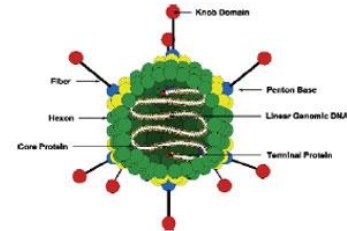
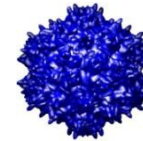


Figure 1:  
Adenovirus Morphology

Ad-LacZ  
Ad-CPT1  
Ad-CPT1M

## Virus Adenoasociados



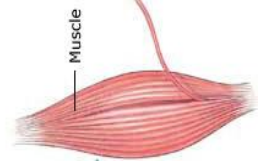
AAV1-GFP  
AAV1-CPT1A  
AAV1-CPT1AM



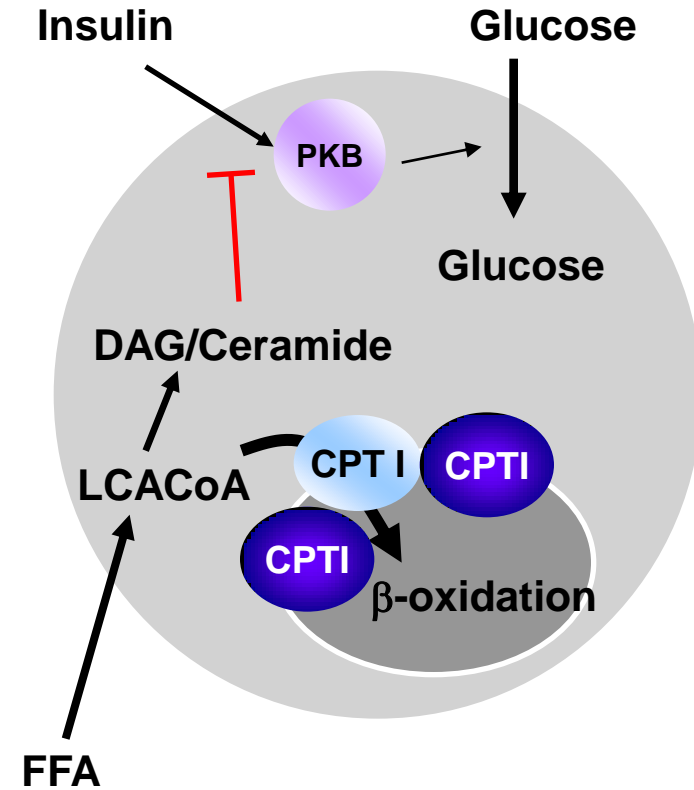
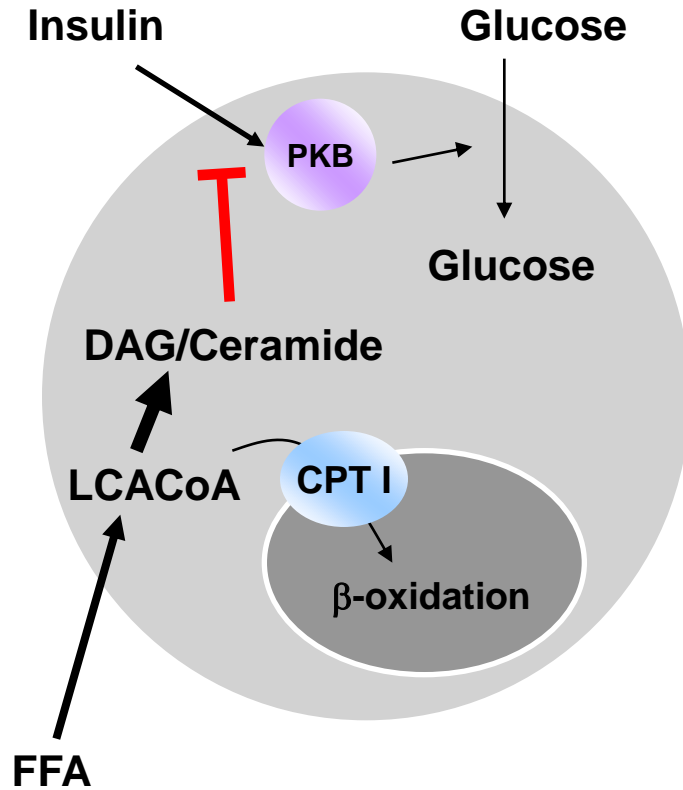
**Amsterdam Molecular Therapeutics**  
**Netherlands**

- 1) Expresión a largo plazo
- 2) No respuesta inmune

# Reversión de la resistencia a la insulina inducida por palmitato



Células musculares L6E9



# Sobreexpresión de la CPT1A en células musculares L6E9

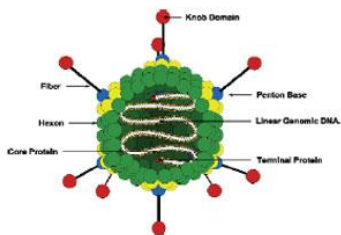
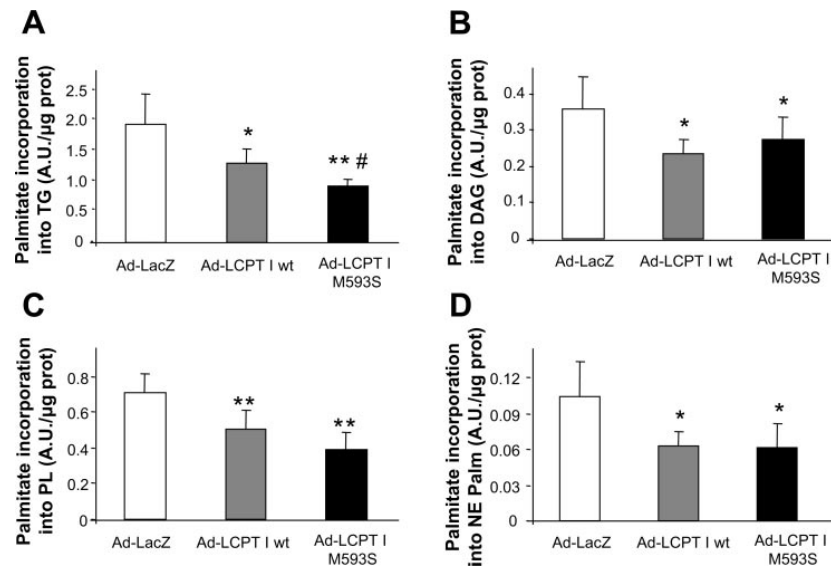
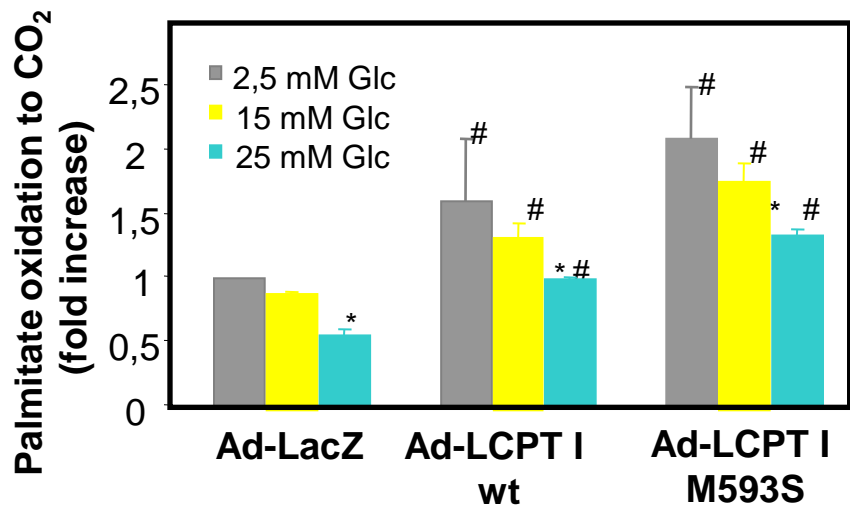
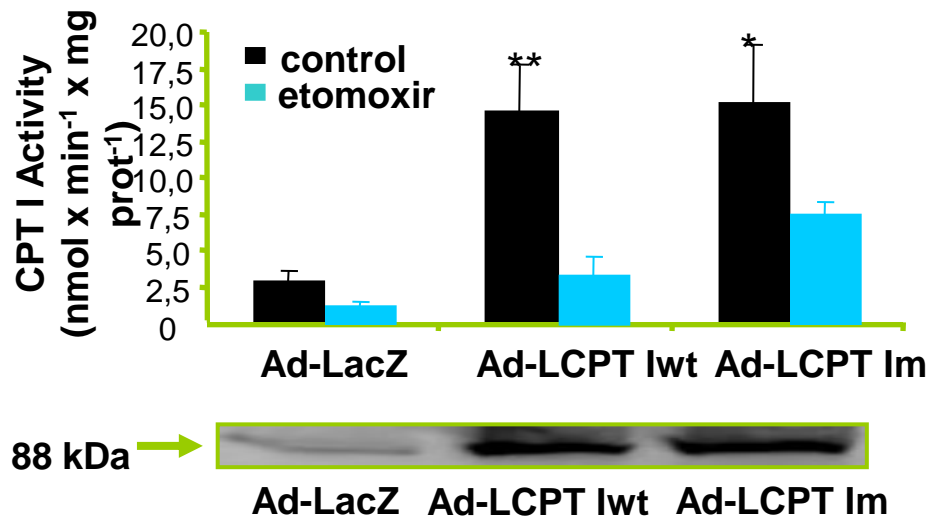


Figure 1: Adenovirus Morphology

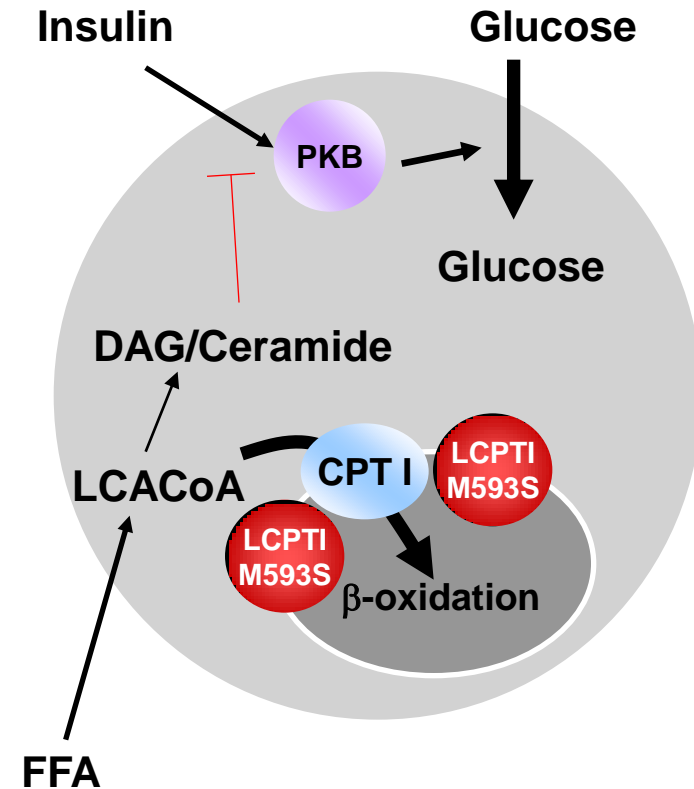
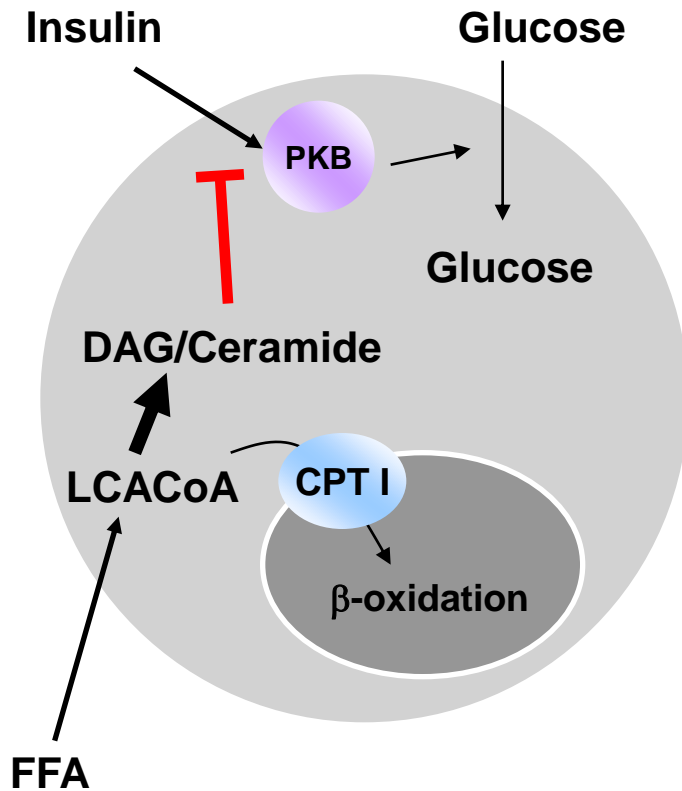
Ad-LacZ  
Ad-CPT1  
Ad-CPT1M



Sebastián D. et al. *AJP*. 2007

Sebastián D. et al. *J Lipid Res*. 2009

# La sobreexpresión de CPT1 en células musculares mejora la resistencia a la insulina inducida por palmitato



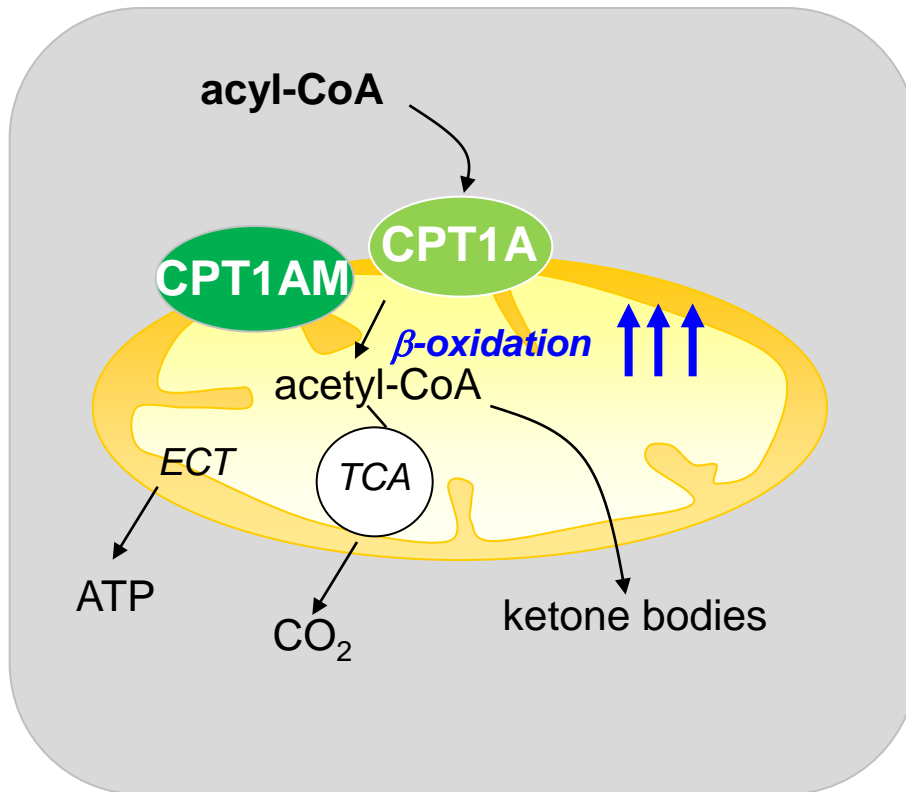
Sebastián D. et al. *AJP*. 2007

Sebastián D. et al. *J Lipid Res.* 2009

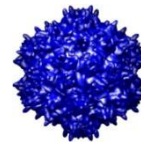
# Our strategy in the liver



## Hepatocyte



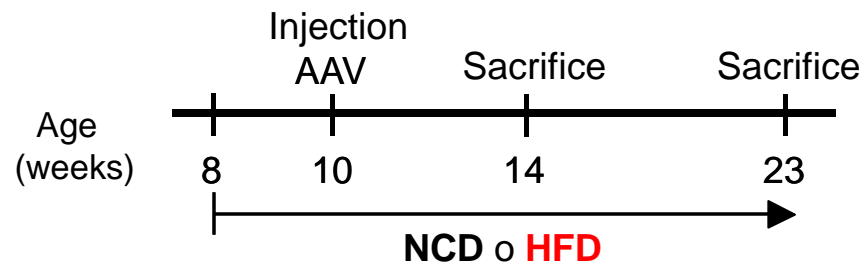
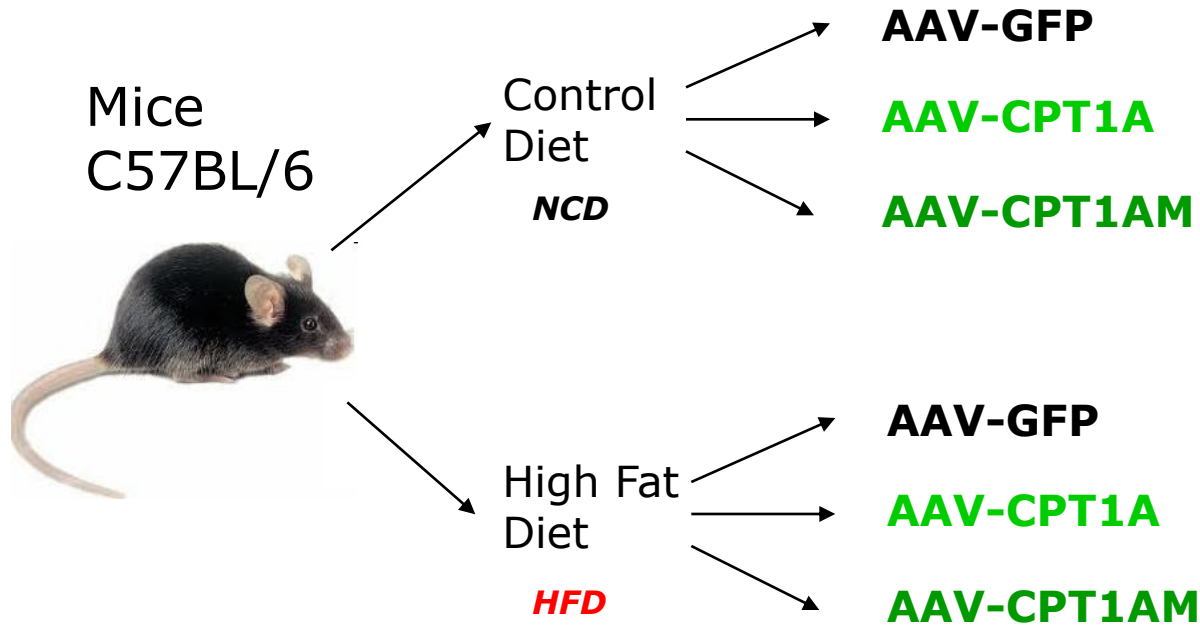
1. Overexpression of a **CPT1AM** isoform insensitive to malonyl-CoA.
2. Long term overexpression using as a vector **adenoassociate virus (AAVs)**.



AAV1-GFP  
AAV1-CPT1A  
AAV1-CPT1AM

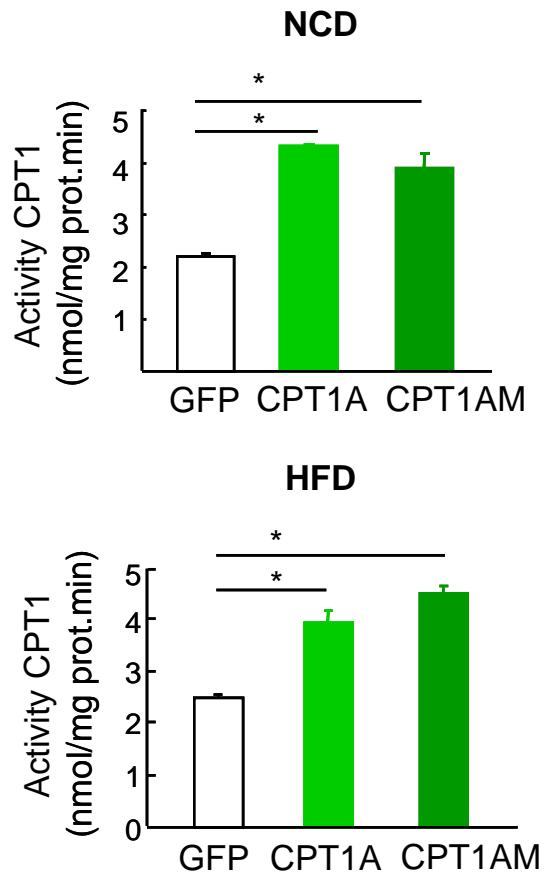
Two animal models: Obesity induced by HFD  
Genetic obesity

# Effect of CPT1AM overexpression on HFD Mice

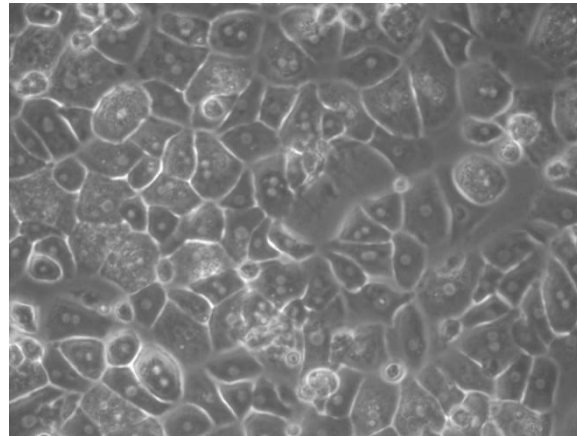




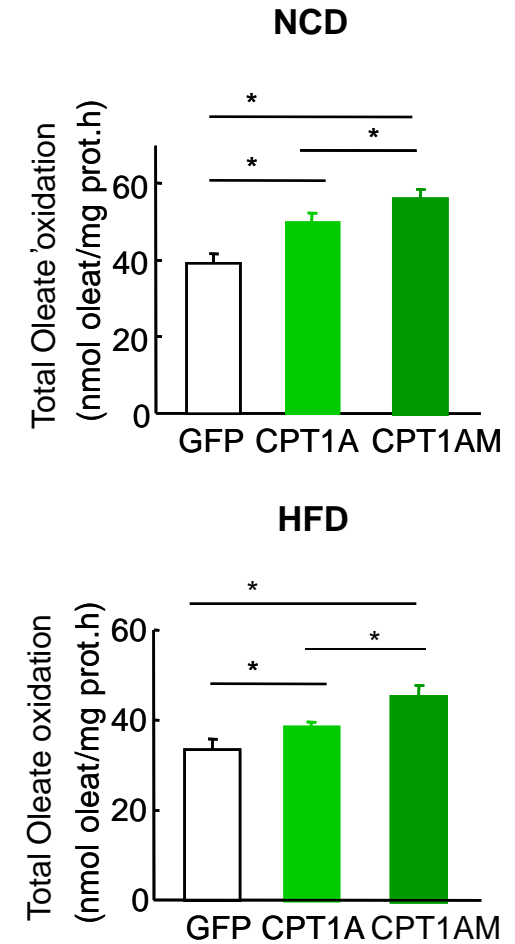
## CPT1 Activity



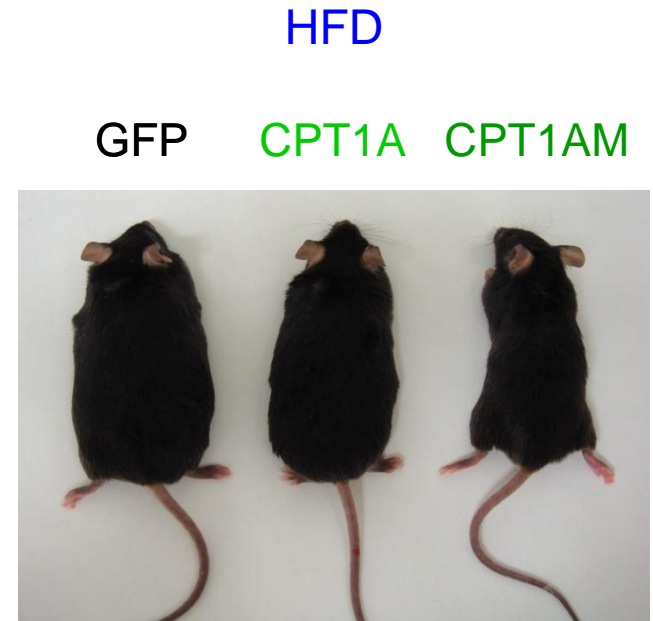
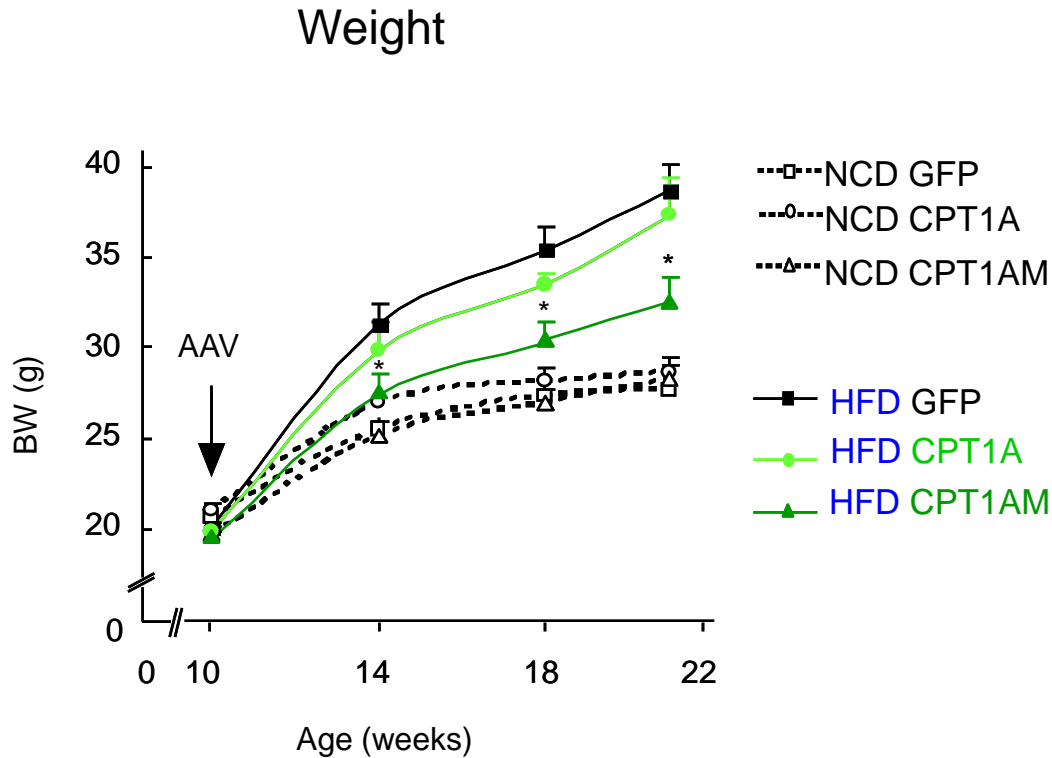
## Hepatocyte primary culture



## Oleic acid oxidation



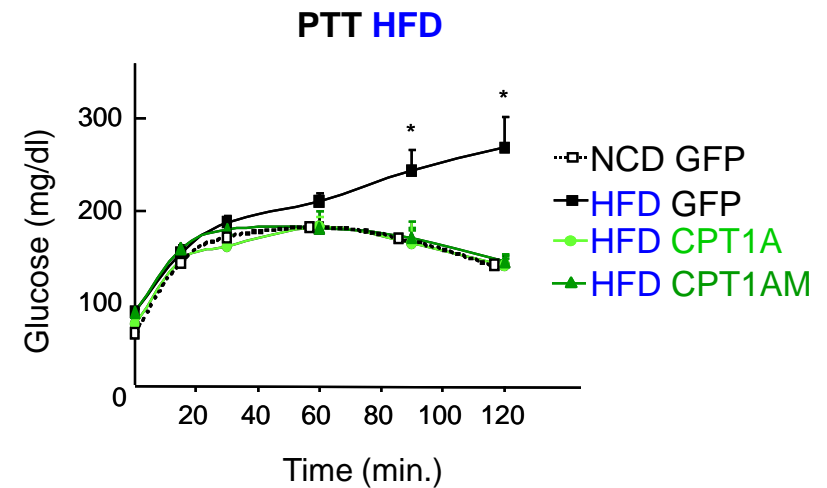
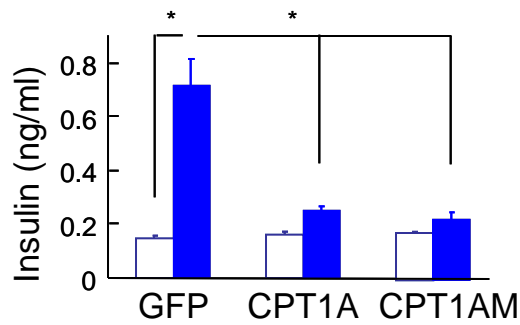
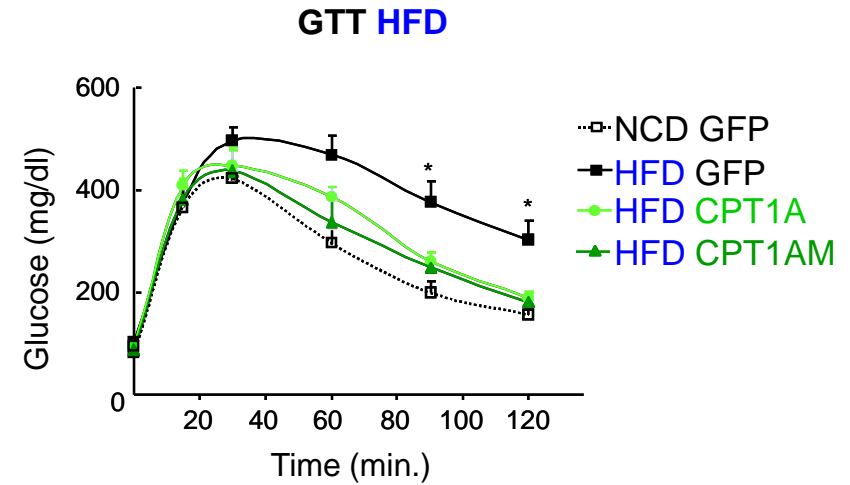
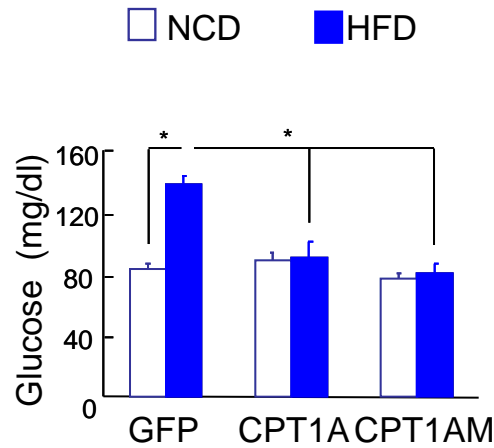
# Analysis of the phenotype



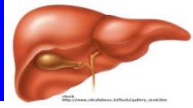
# Restored glucose and insulin levels



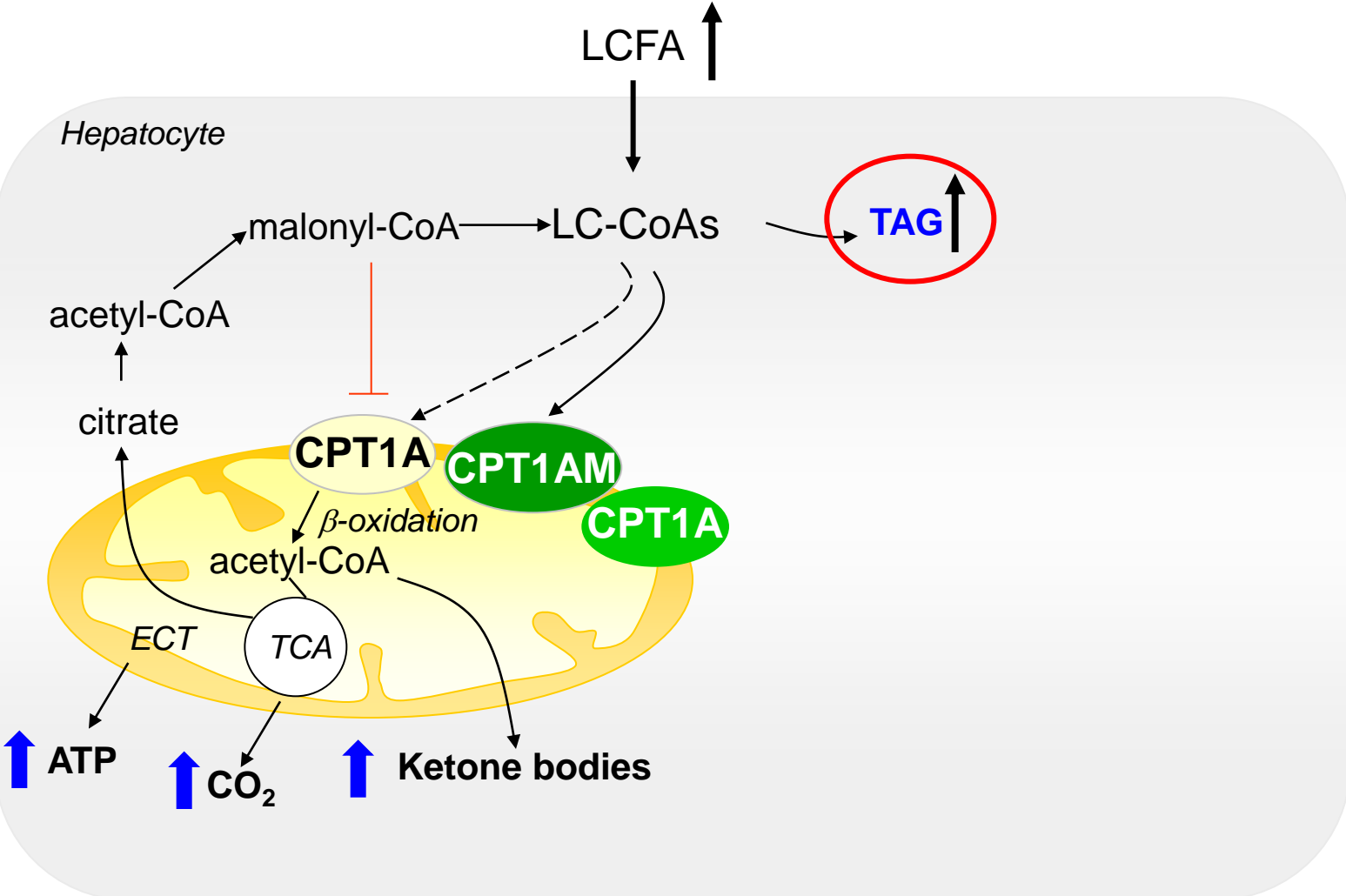
11 weeks



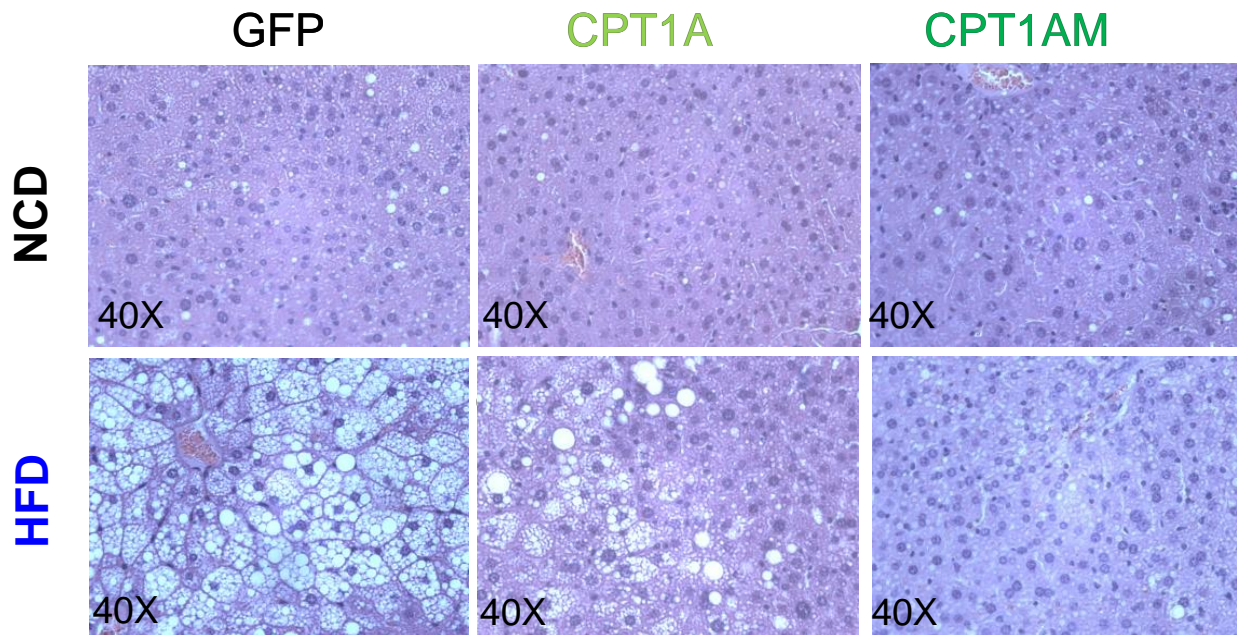
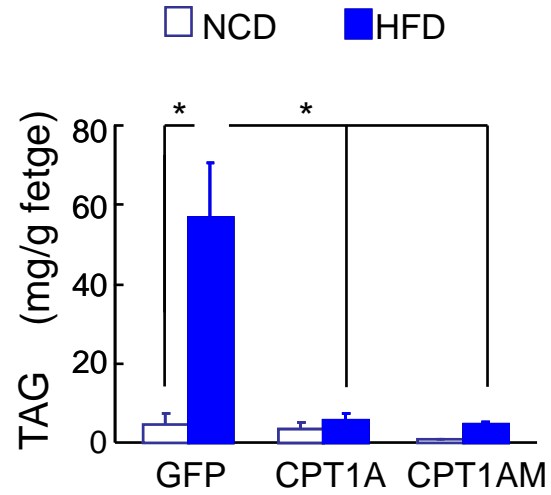
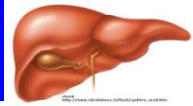
# Lipid metabolism



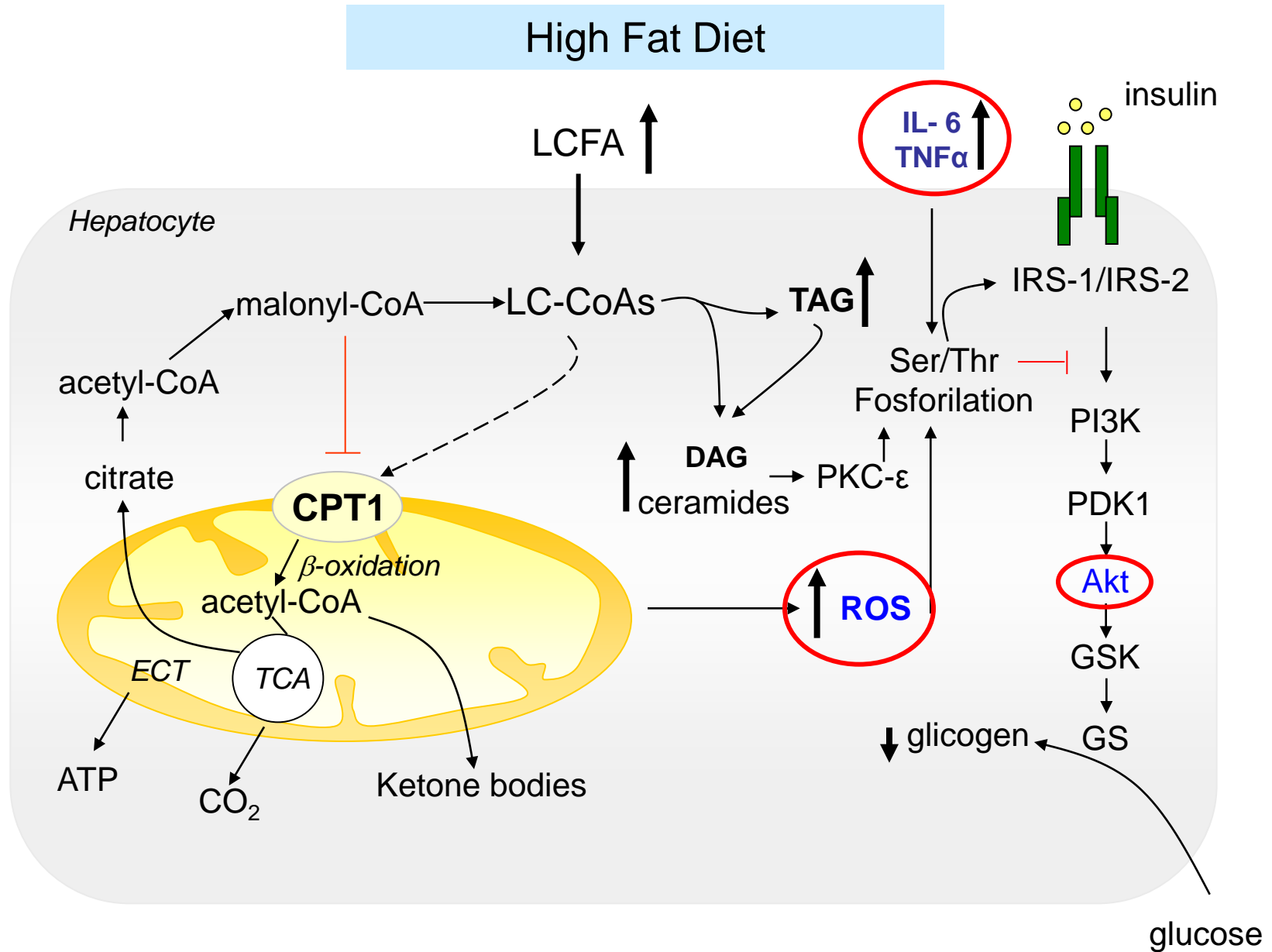
High Fat Diet



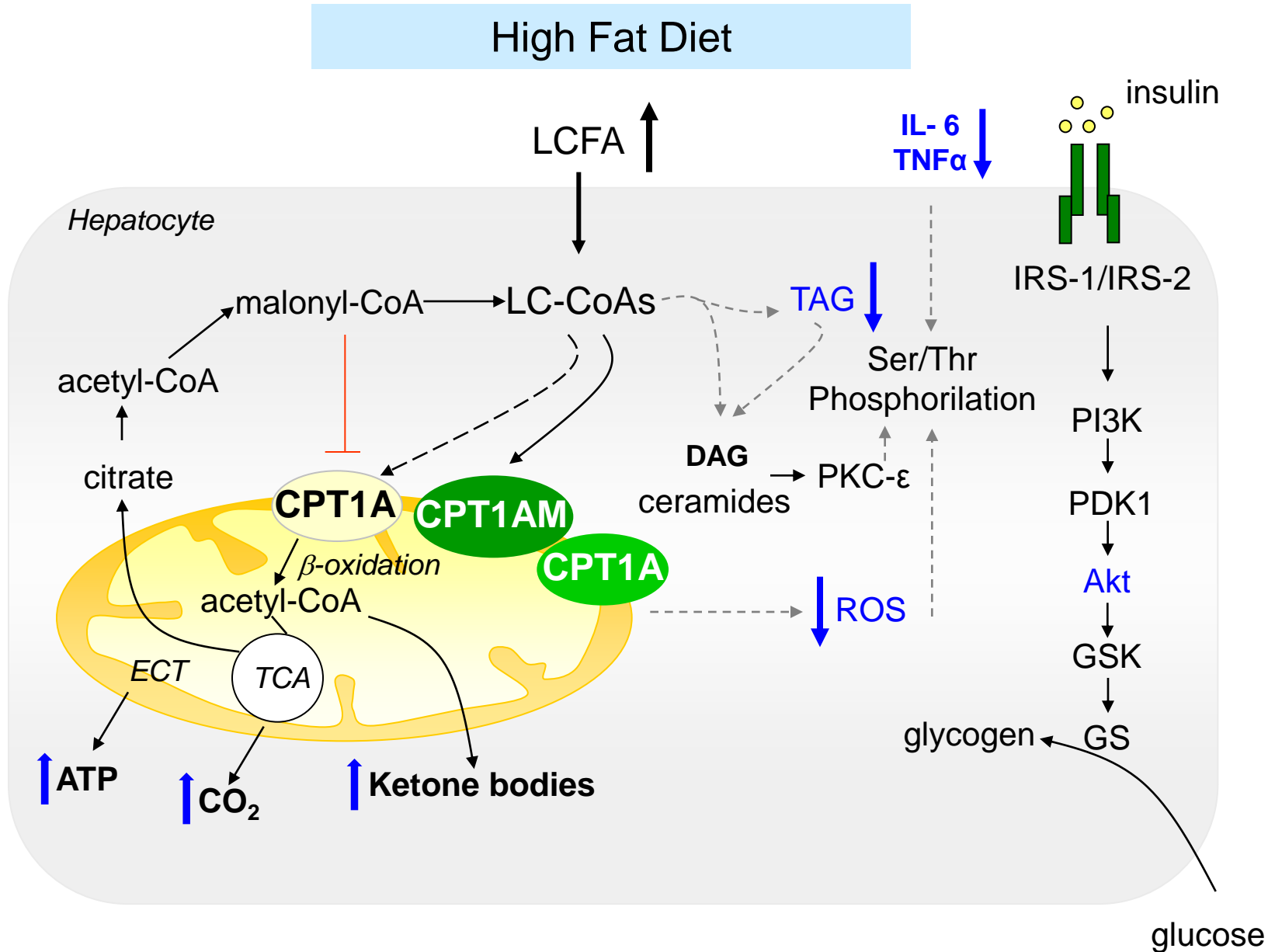
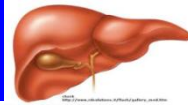
# Decreased steatosis



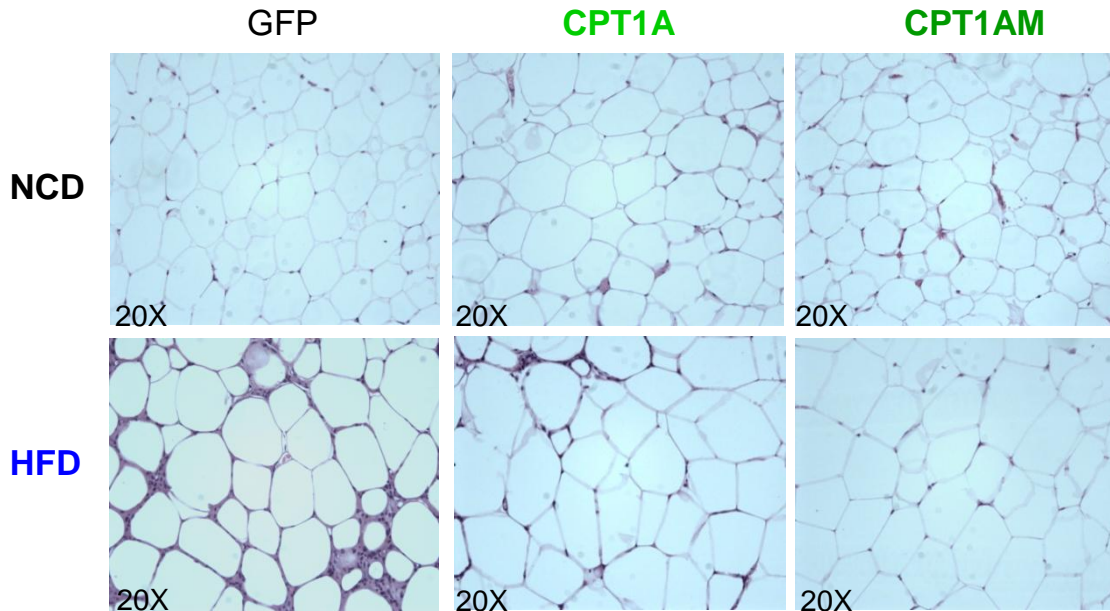
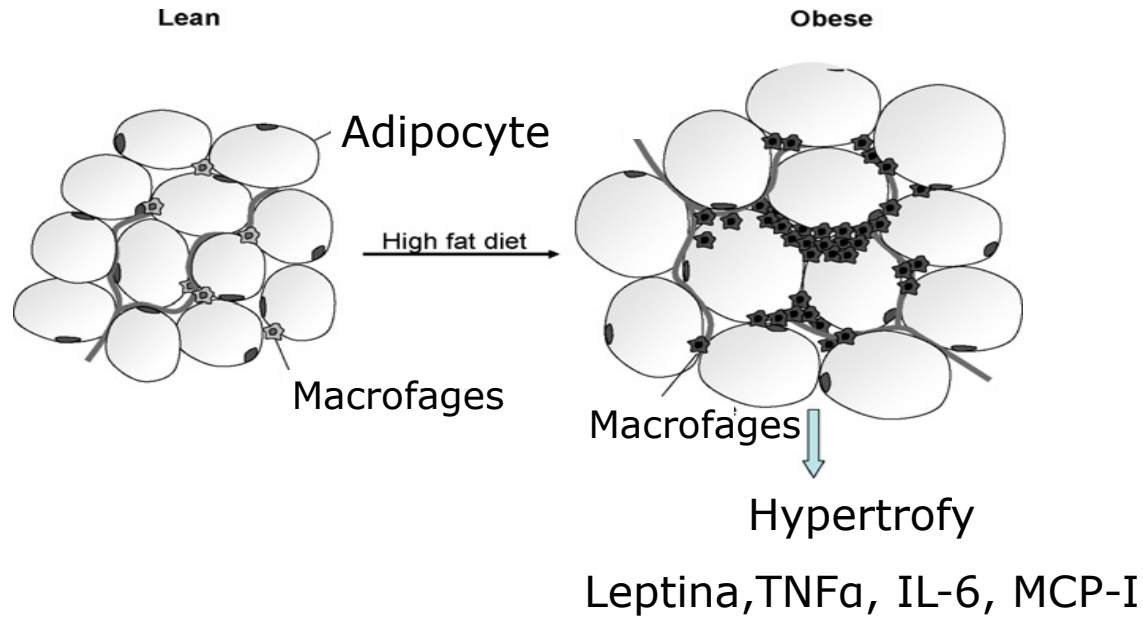
# Inflammation and oxidative stress



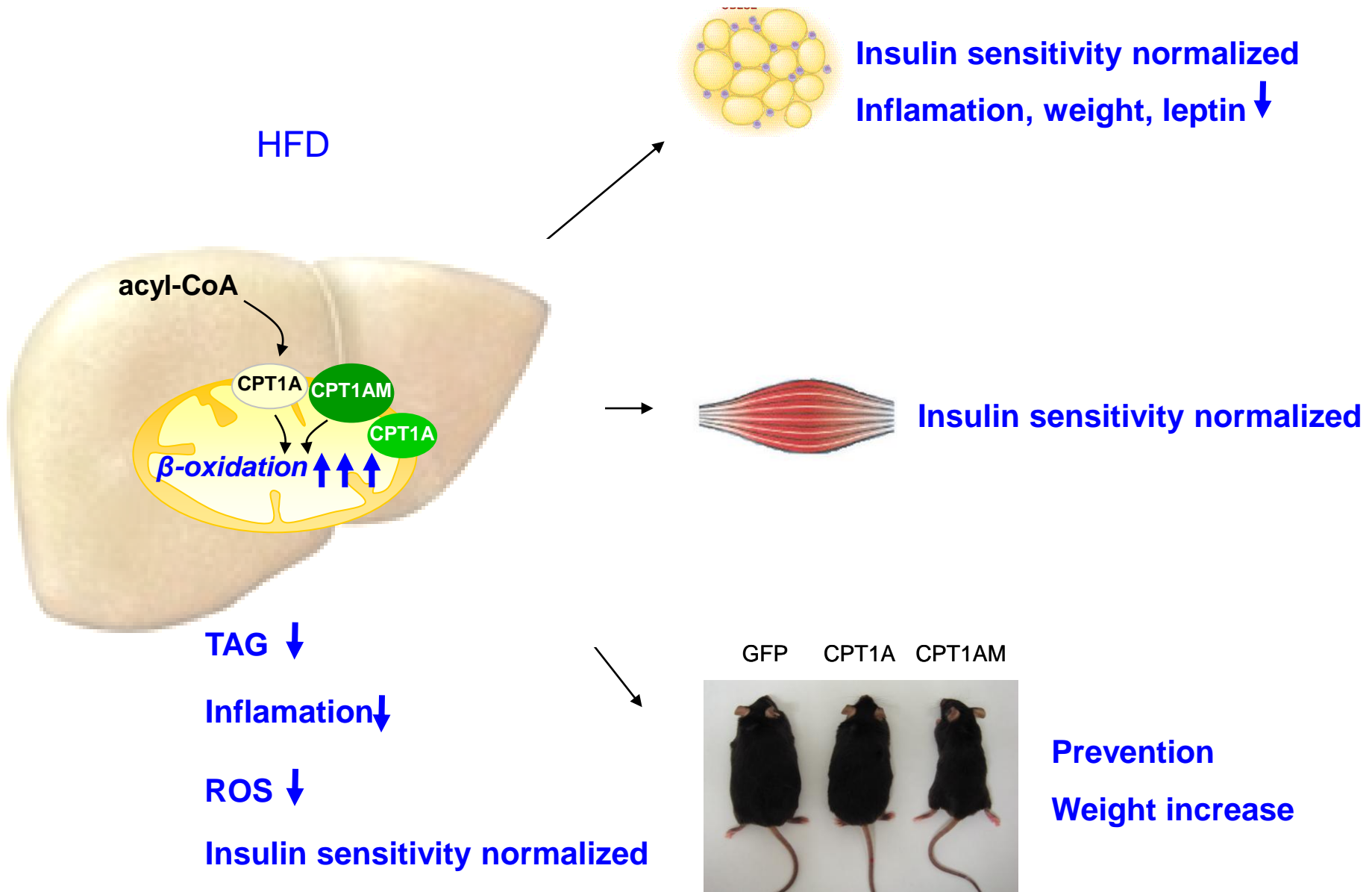
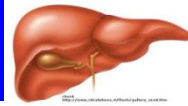
# Effect of CPT1A or CPT1AM expression



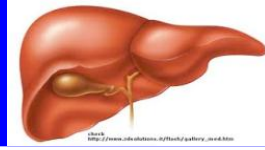
# Effect on Adipose tissue



# Conclusion



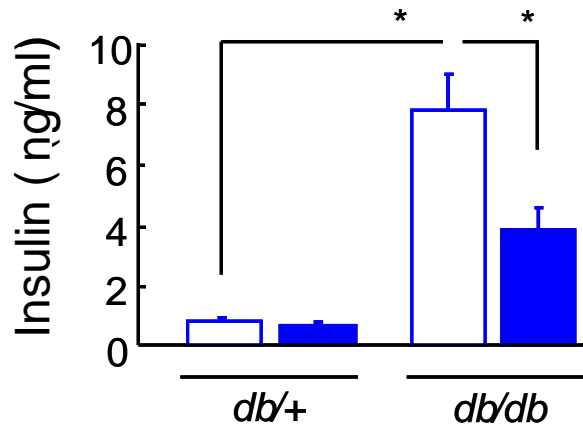
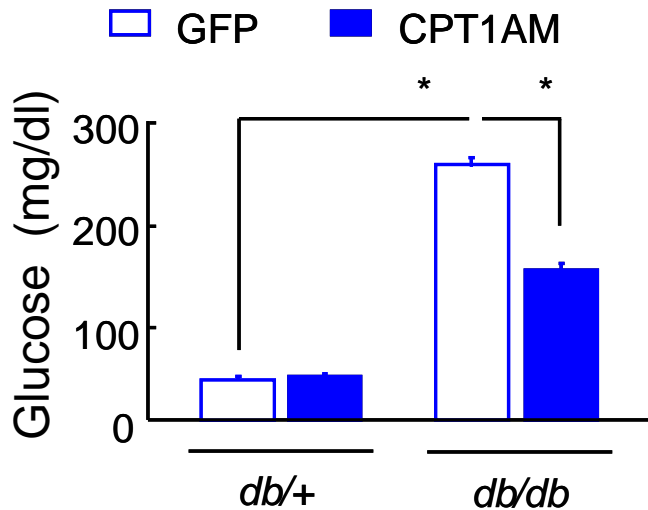
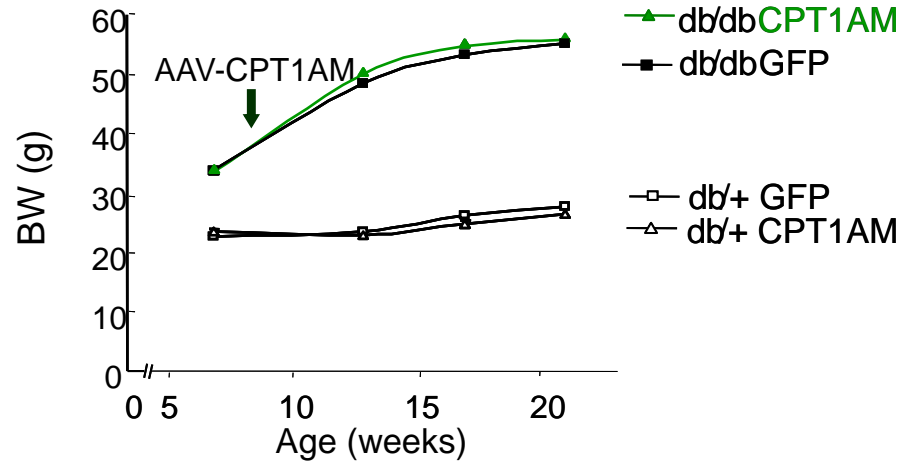
# Effect of CPT1AM overexpression on genetically obese *db/db* mice



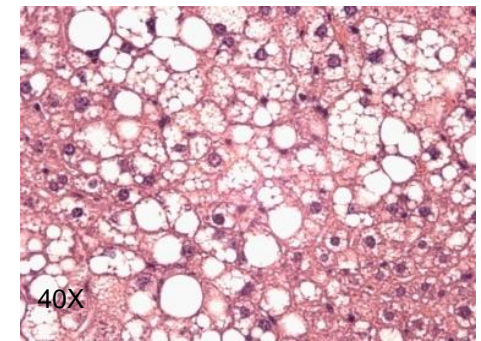
*db/+ db/db*

AAV-GFP

AAV-CPT1AM

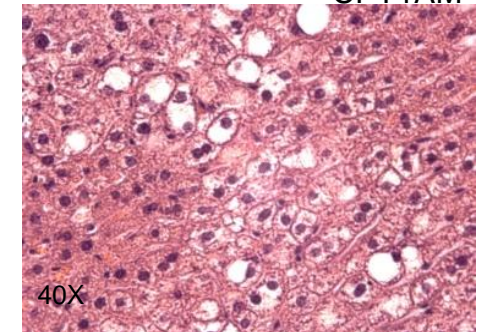


LIVER *db/db*



40X

CPT1AM



40X

## 2-Control de la ingesta



Chris Madden

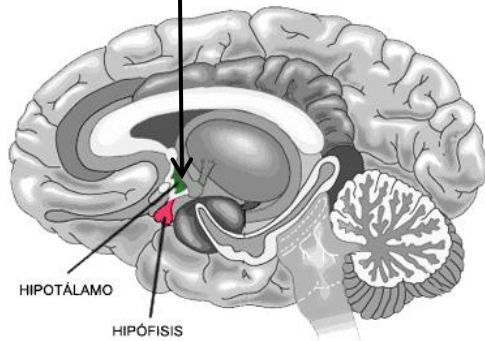
## 2-Papel de la CPT1 en el control de la ingesta

**Metabolitos**

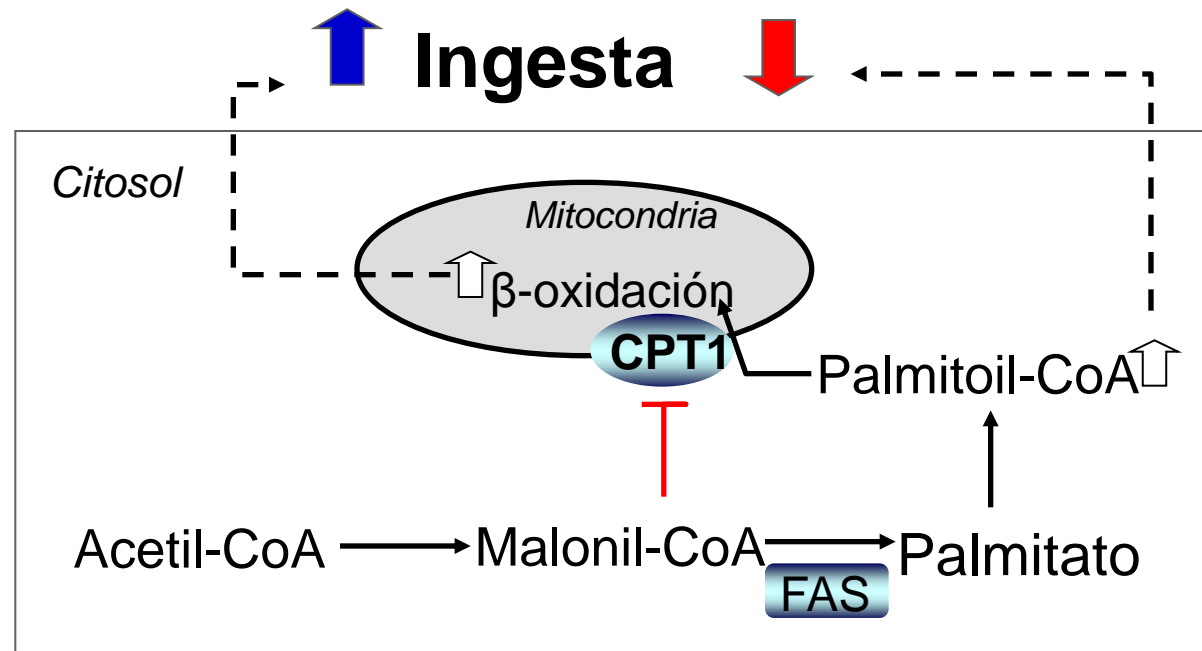
(glucosa, ácidos grasos)

**Hormonas**

(insulina, leptina)

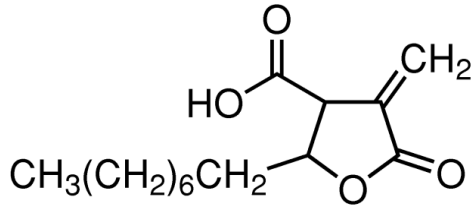


**CONTROL DE LA INGESTA**

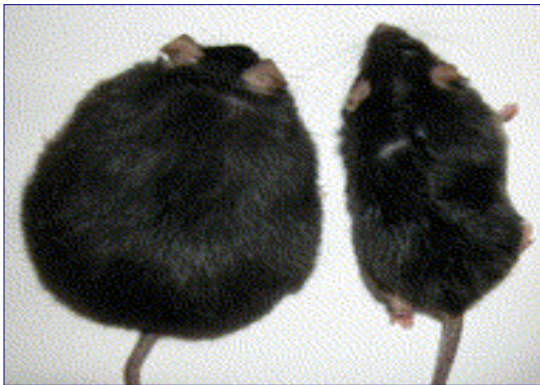
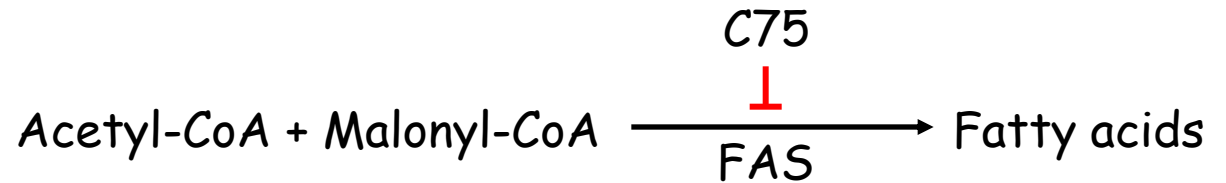


Aproximación farmacológica

# C75 es un inhibidor de la ingesta



C75: inhibitor of fatty acid synthase (FAS)



control

C75

Reduced food intake and dramatic weight loss

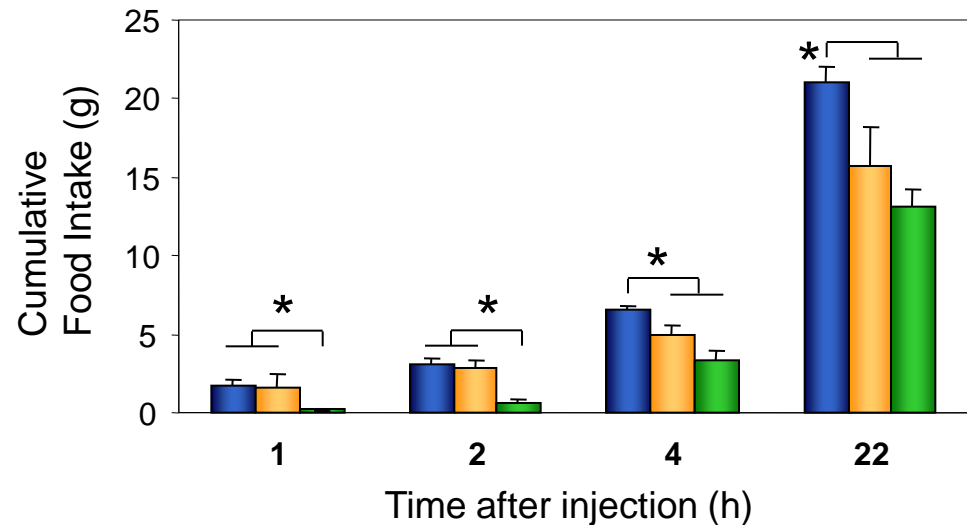
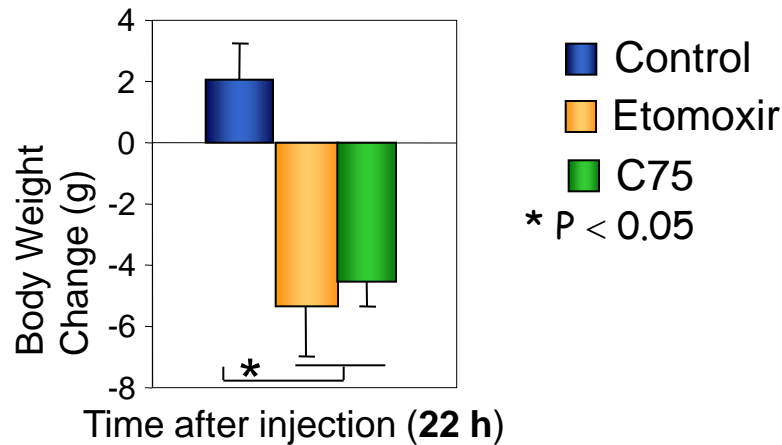
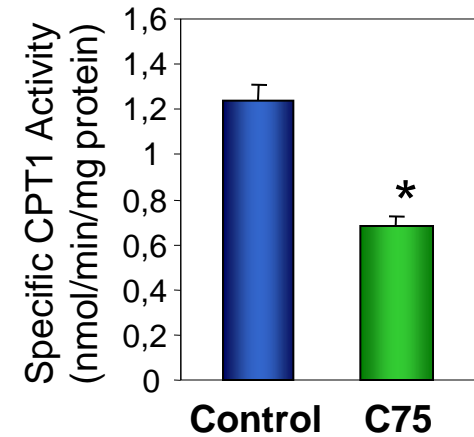
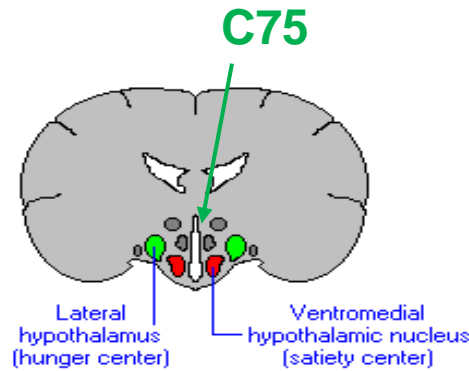
ob/ob mice (leptin deficient)

Diet-induced obese (DIO) mice

Lean mice

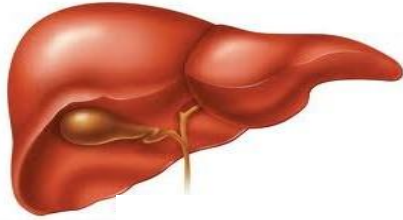
# Efecto del C75 en la actividad CPT1 y en la ingesta

estereotaxis



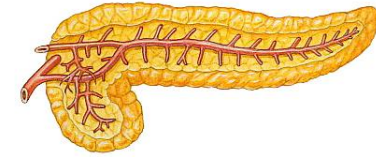


Hígado



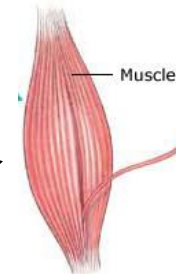
Orellana-Gavaldà et al. *Hepatology* (2011)

Páncreas



Herrero L. et al. *Diabetes* (2005)

**CPT1**

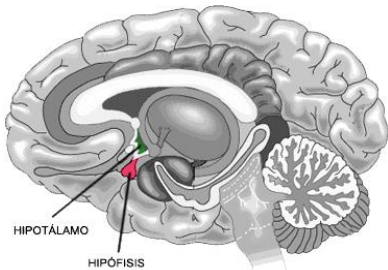


Músculo

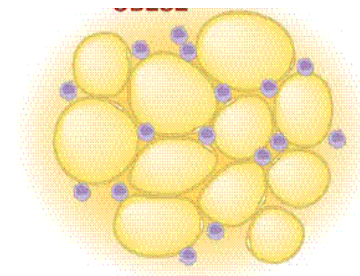
Sebastián D. et al. *Am. J. Physiol. Endocrinol. Metab.* 2007

Sebastián D. et al. *J Lipid Res.* 2009

Hipotálamo



Tejido adiposo



Bentebibel A. et al. *Biochemistry* (2006)

Mera P. et al. *Biochemical Pharmacology* (2009)

Gao S. et al. *Am J Physiol Regul Integr Comp Physiol* (2011)

Gao S. et al. *Proc Natl Acad Sci U S A.* (2011)

Carraco P. et al. *J. Biol Chem* (2012)



## Colaboradores:

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Holanda

Jordi Garcia y Xavier Ariza  
Universidad de Barcelona

Núria Casals  
Universidad Internacional de Catalunya

Su Gao y Gary Lopaschuck  
University of Alberta. Edmonton. Canada

