Jornades Doctorals en Farmacologia de la UAB i UB

Efectos de la cafeína sobre el estrés de retículo y la autofagia en un modelo de esteatosis hepática

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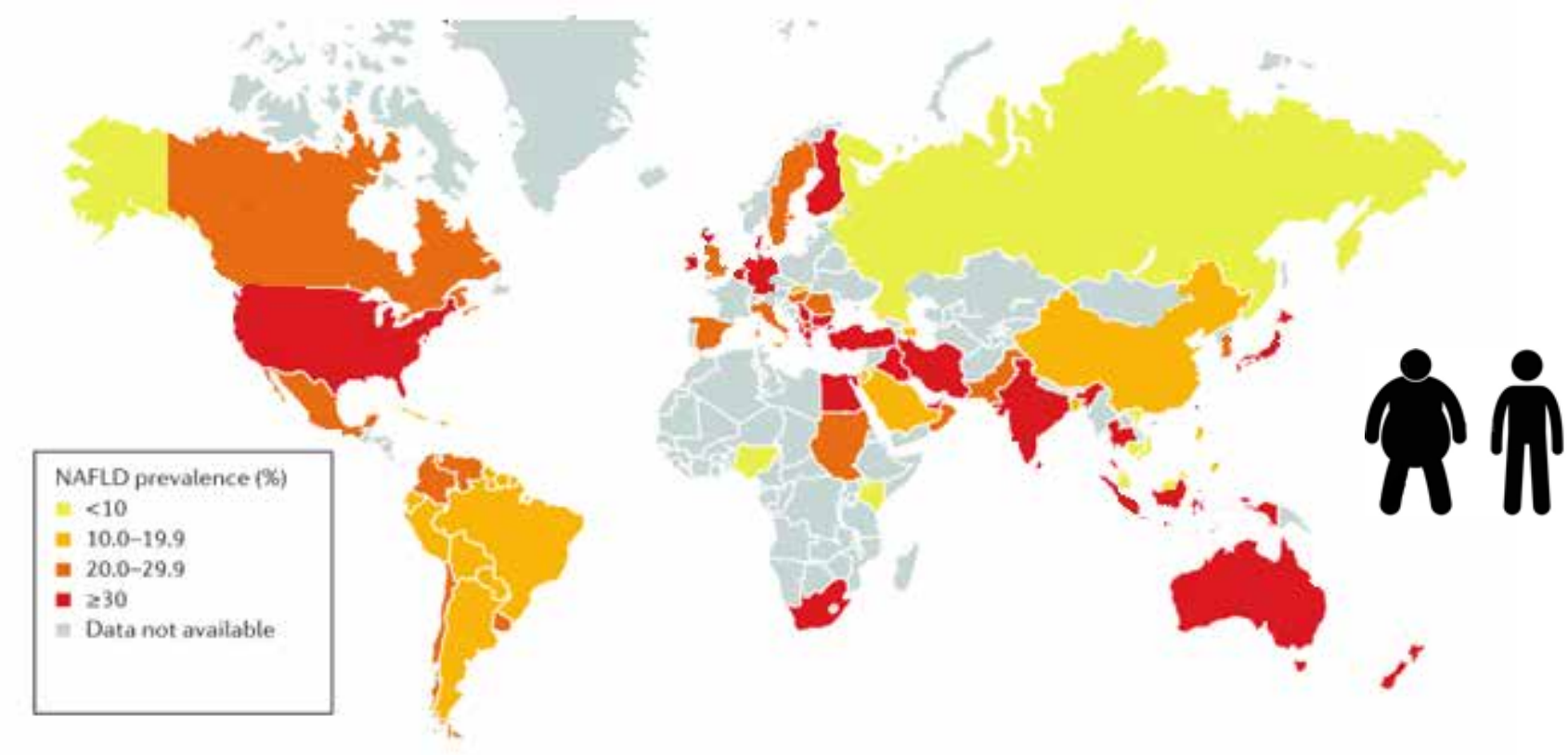
PhD student

Supervisores: Marta Alegret y Juan Carlos Laguna

Introducción

Prevalencia mundial estimada de NAFLD



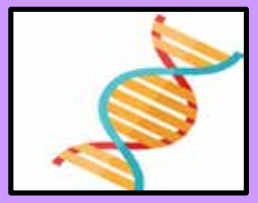
Modificado de Younossi, et al. *Nature*. 2017

Introducción

Enfermedad del Hígado graso no-alcoholico

Factores ambientales

Genéticos



Hígado sano

Esteatosis Hepática

Esteatohepatitis Hepatocarcinoma

Friedman *et al., Nature*, 2018

Introducción

Enfermedad del Hígado graso no-alcoholico

Friedman *et al., Nature*, 2018

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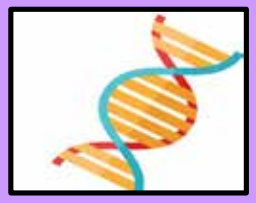
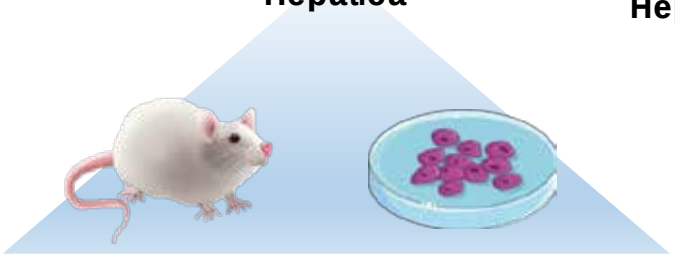


Hígado sano

?

Esteatosis Hepática

Esteatohepatitis Hepatocarcinoma



Cafeína

- Autofagia
- Estrés de retículo

Friedman *et al.*, *Nature*, 2018

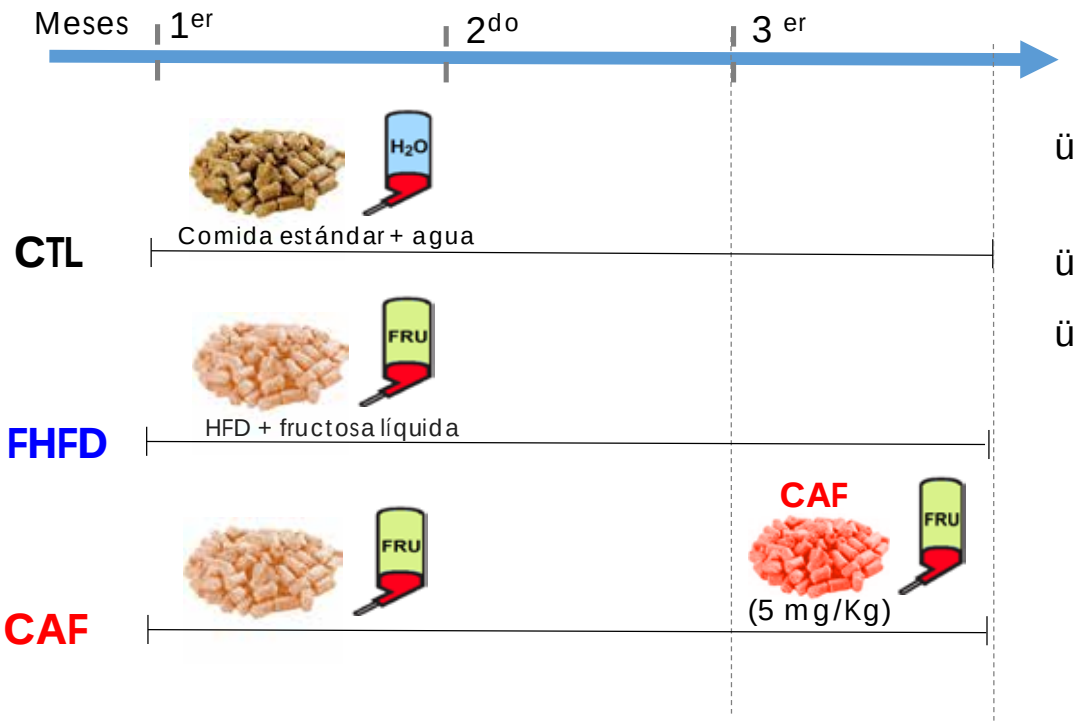
Sinha *et al.*, *Hepatology*, 2014

Metodología

Diseño experimental *in vivo*

N=12

Ratas hembras Sprague Dawley 2 meses



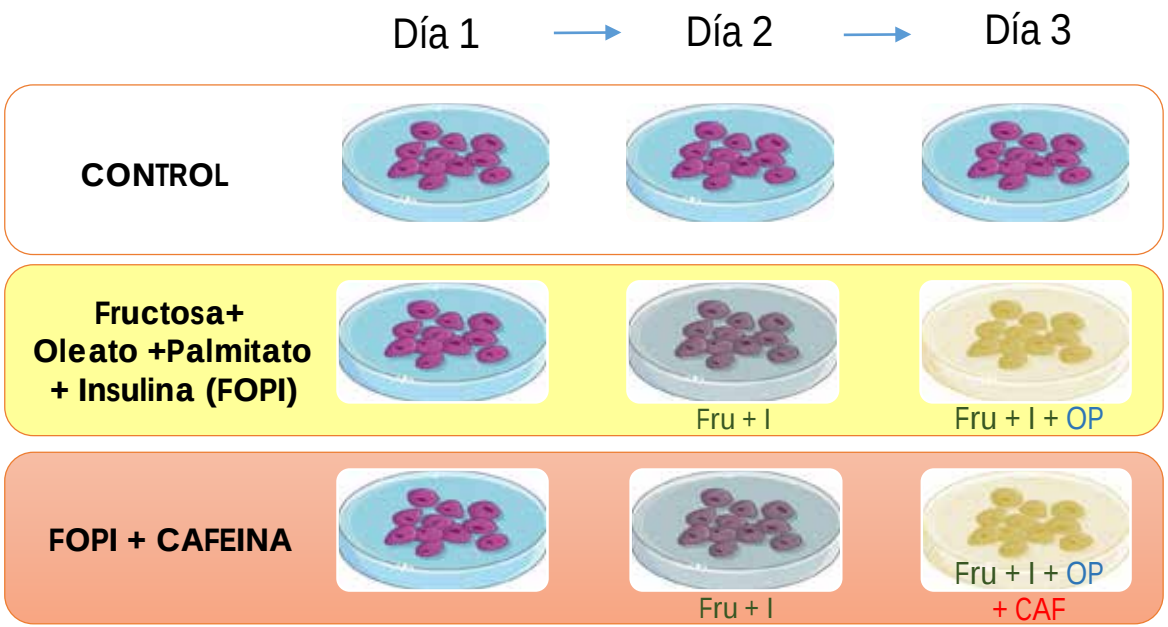
Análisis:

- ü Caracterización metabólica
- ü Estrés de Retículo
- ü Autofagia

Metodología

Diseño experimental *in vitro*

Células *Huh7D12; n=3*

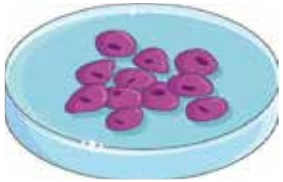


Análisis:

- ü ORO staining
- ü Triglicéridos secretados
- ü PCR –RT
- ü Western Blot

Resultados

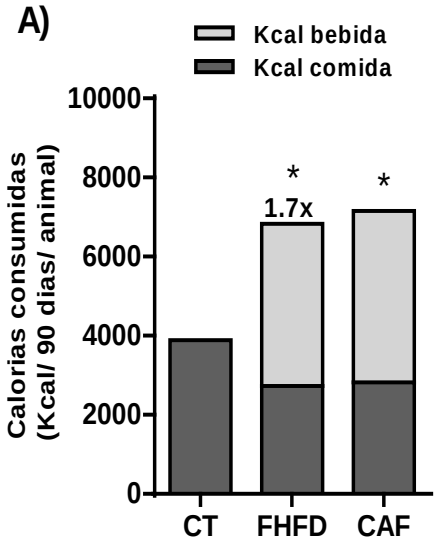
Caracterización metabólica

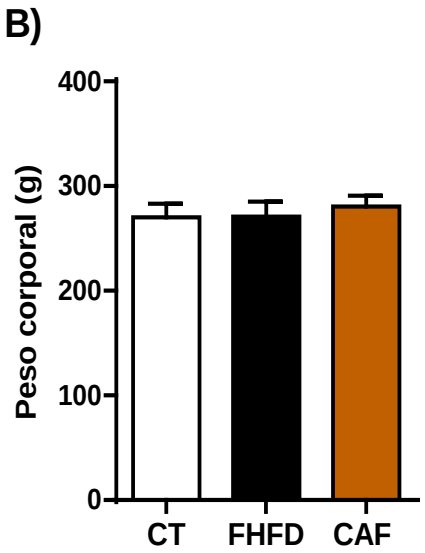


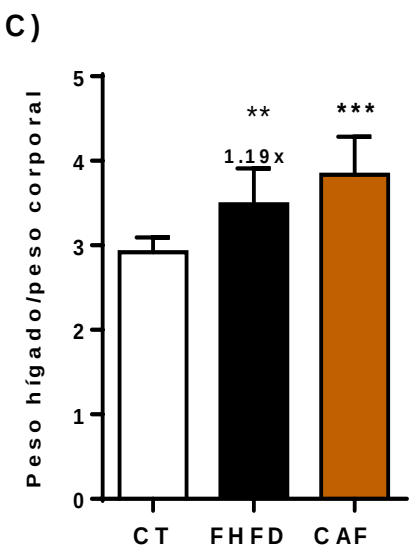
Resultados

in vivo

FHFD aumenta ingesta calórica produciendo un aumento de peso del hígado pero sin cambios en el peso corporal







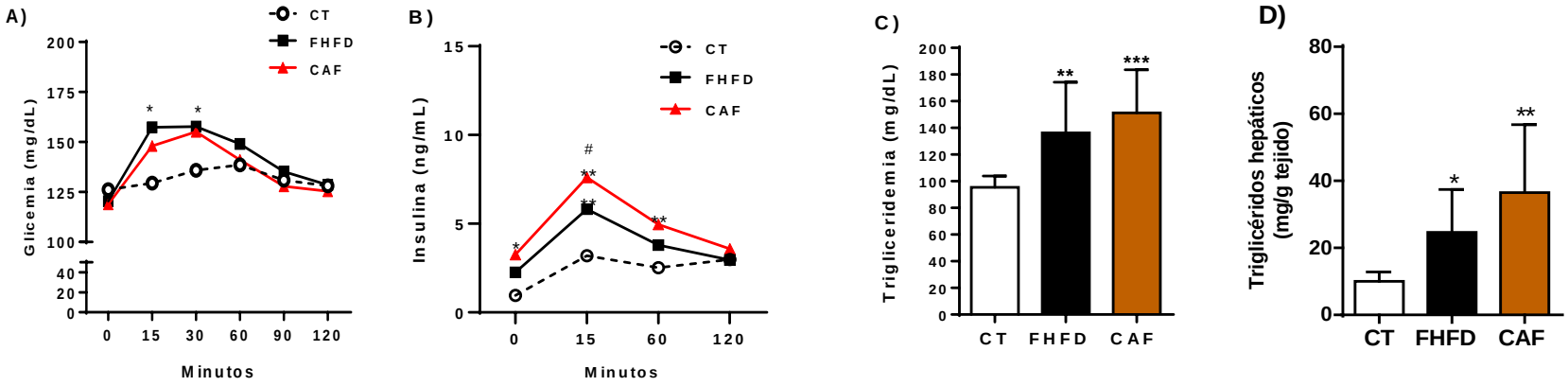
CT: Control
FHFD: Fructosa + HFD
CAF: Cafeína

(A) Y (B) ANOVA una vía; * Vs CT; $p<0,05$

Resultados

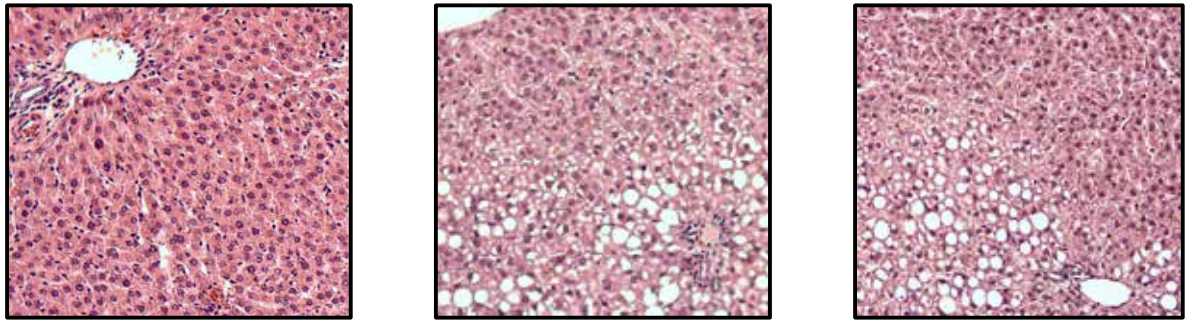
in vivo

FHFD produce alteraciones metabolismo de glucosa y triglicéridos



(A) Y (B) ANOVA one way; n=12 * Vs CT; p<0,05

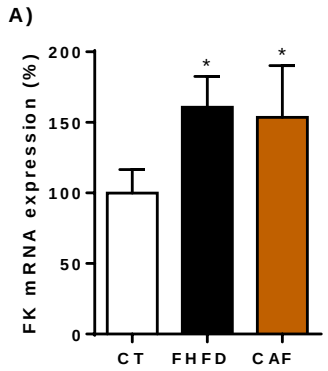
Cortes histológicos

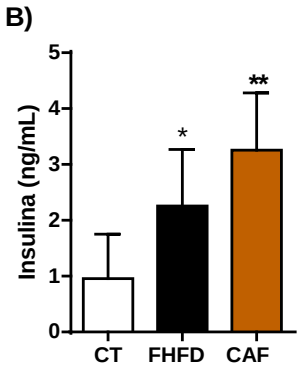


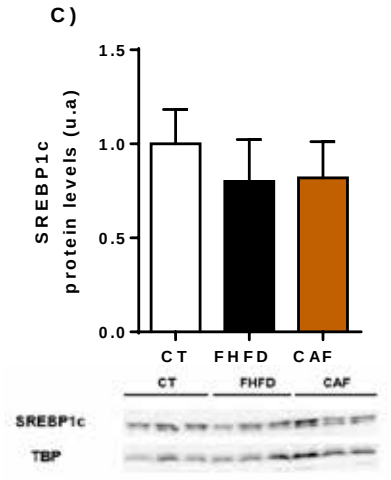
Control FHFD CAF

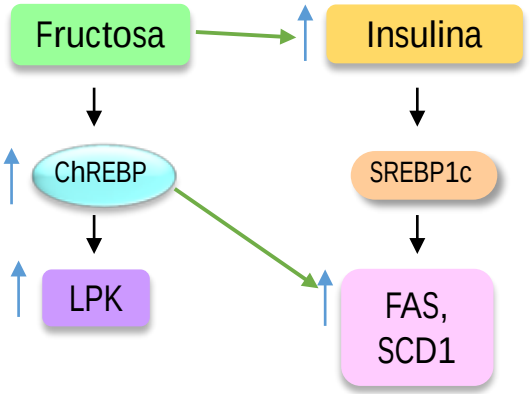
Resultados

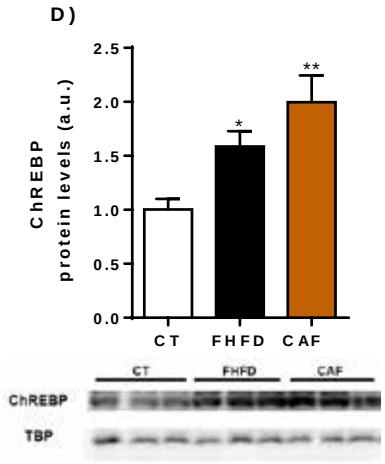
Fructosa activa la vía ChREBP, induciendo la síntesis de ácidos grasos en el hígado

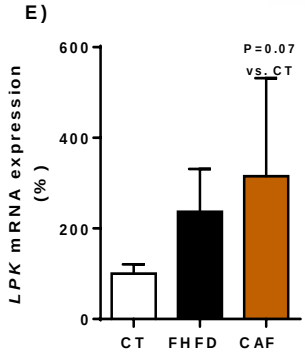


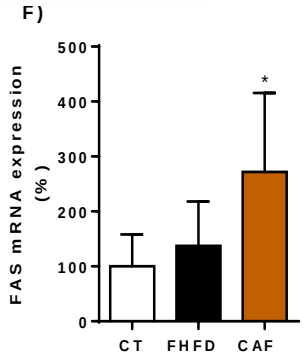


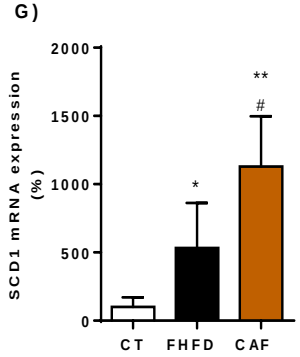








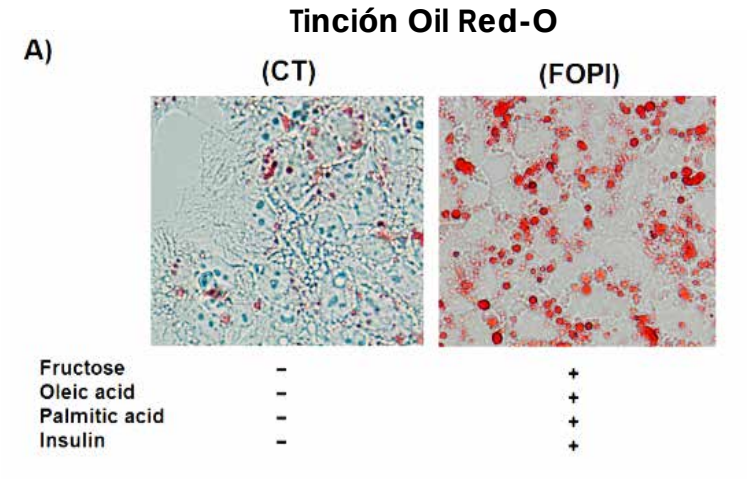




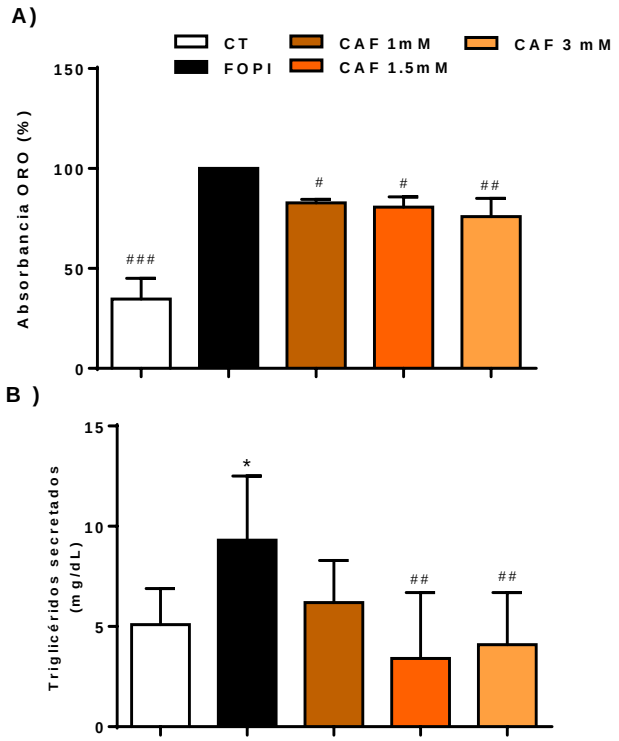
Resultados

in vitro

Cafeína previene la acumulación de lípidos en Huh7D12



CT: Control
FOPI: Fructosa, ácidos palmítico y oleico e insulina

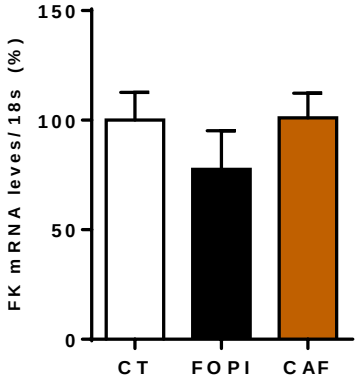


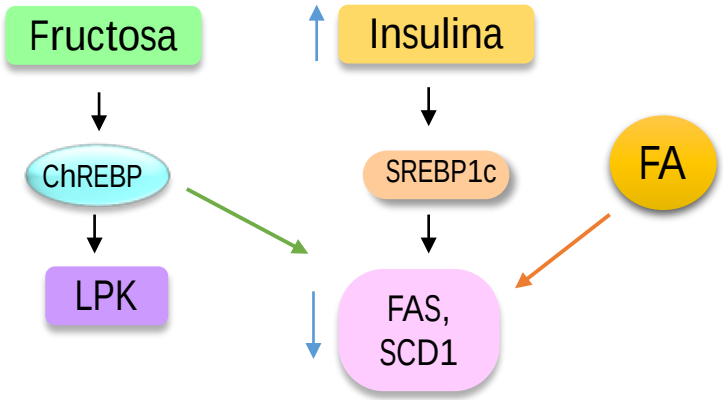
(A) y (B) ANOVA una vía
* Vs cT; # vs FOPI; n=3/triplicados

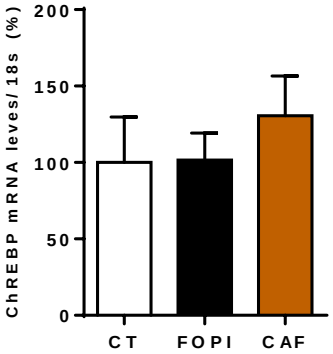
Resultados

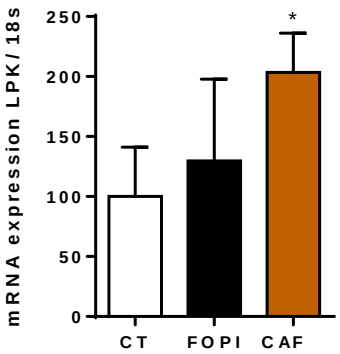
in vitro

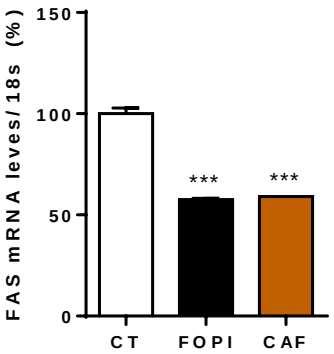
FOPI disminuye la síntesis de ácidos grasos

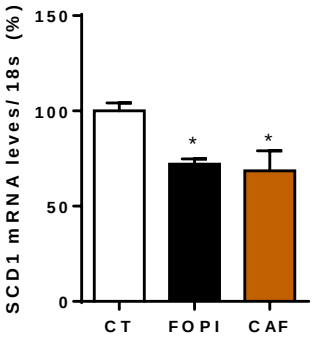








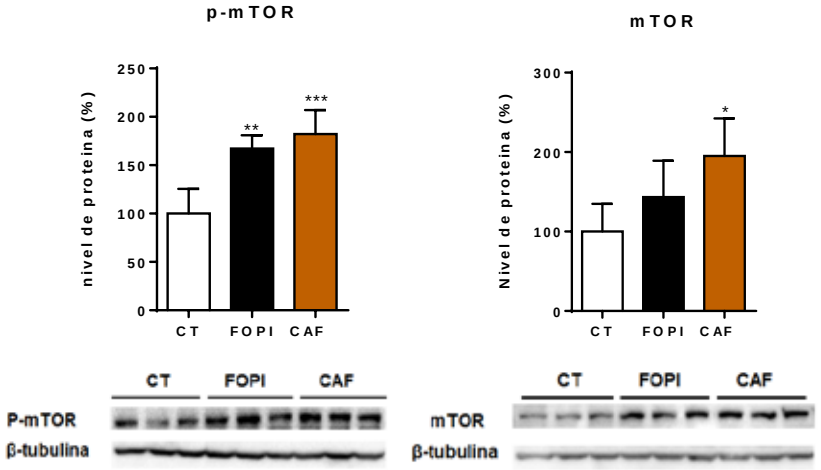




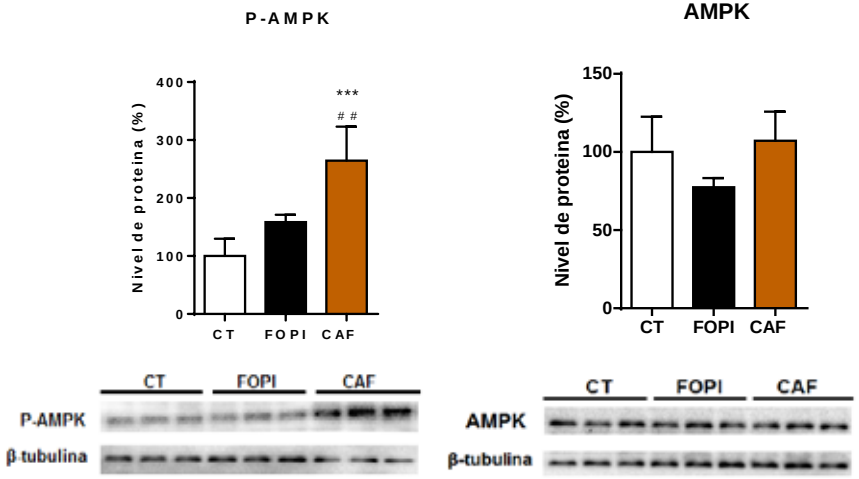
Resultados

in vitro

Cafeína induce activación de AMPK



ANOVA una vía, * Vs cT, n=3/triplicados

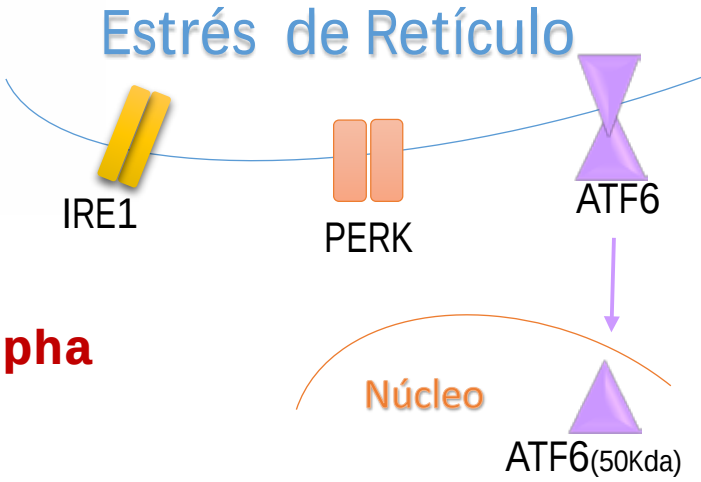


ANOVA una vía, * Vs cT; # vs FOPI; n=3/triplicados

Resultados

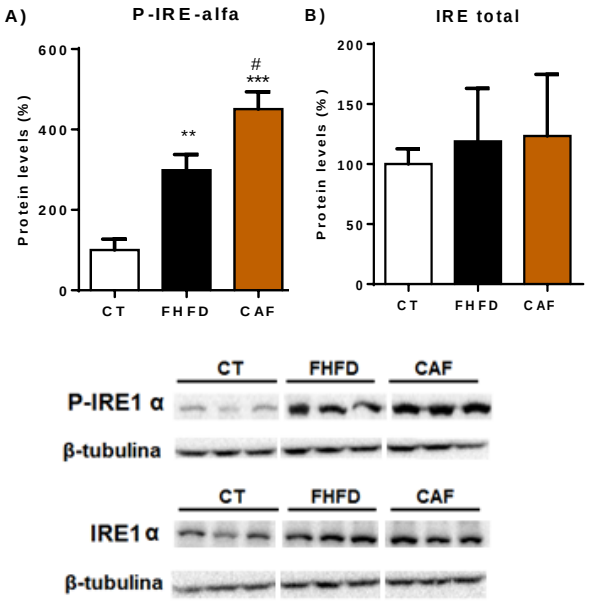
Efecto de la cafeína sobre el estrés de retículo en el modelo de esteatosis hepática

Resultados

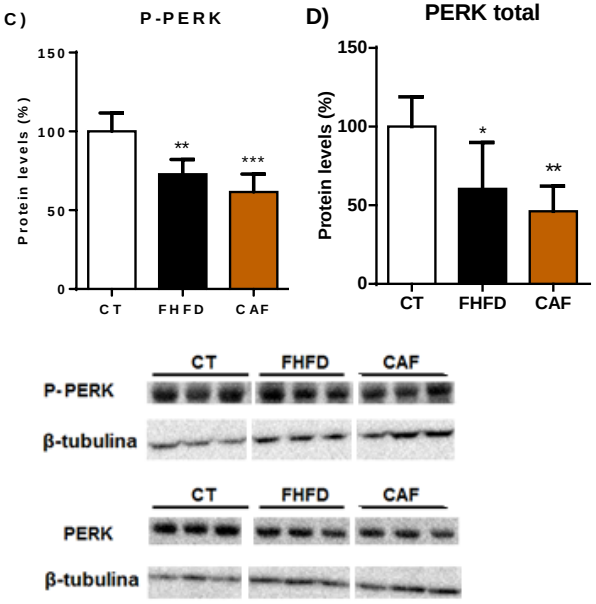


FHFD incrementa la fosforilación de IRE1alpha

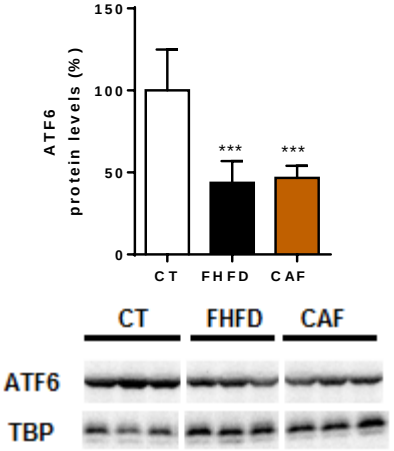
Activación IRE 1



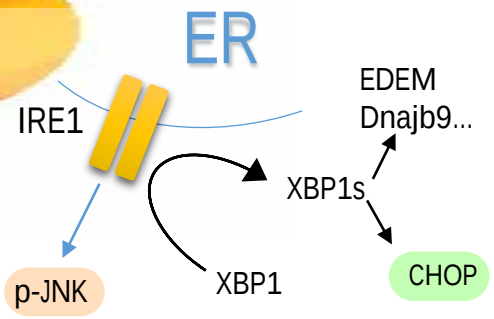
PERK



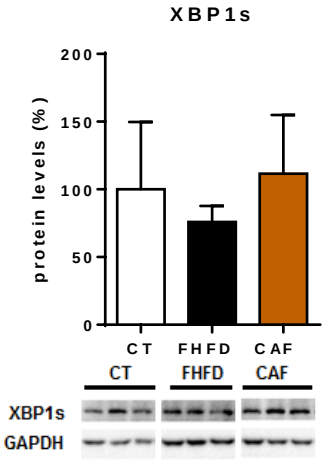
ATF6aplha (EN)

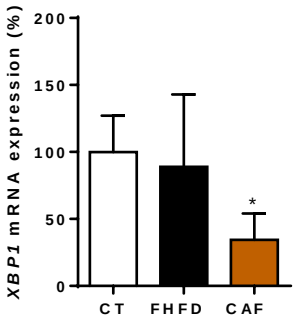


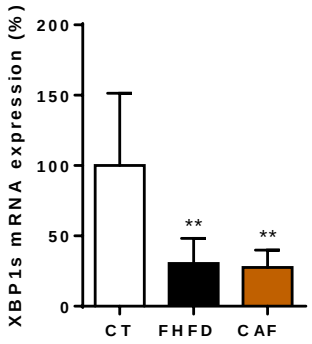
Resultados

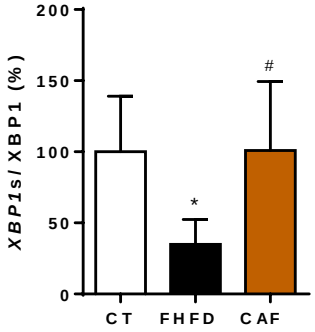


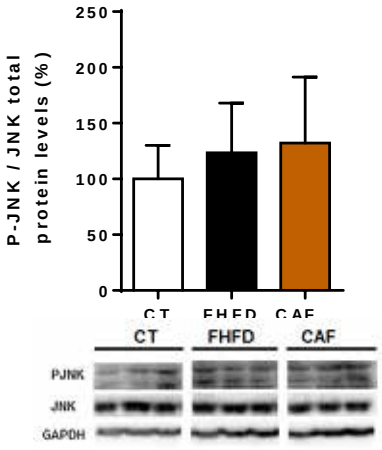
Vía IRE1α–XBP1

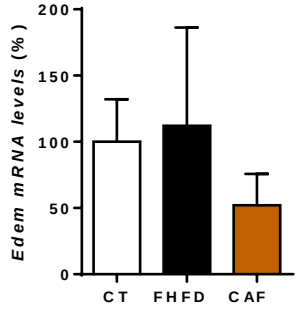


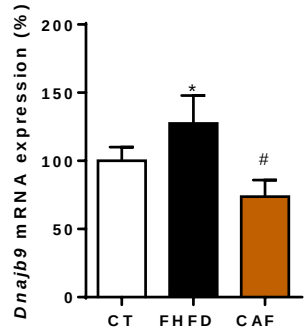


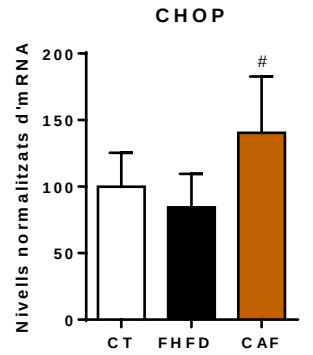








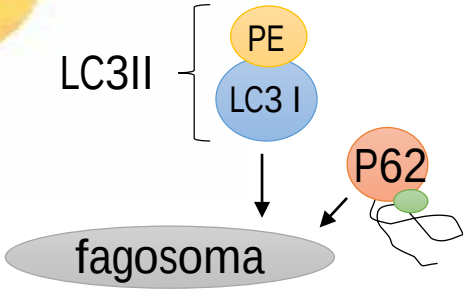




Resultados

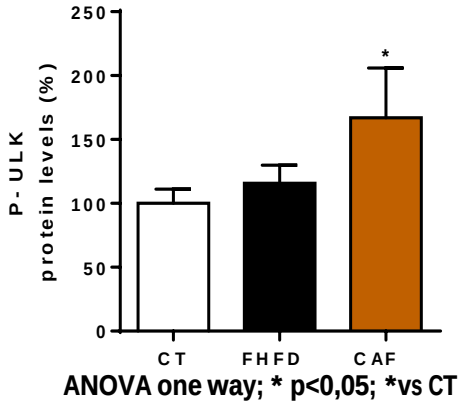
Efecto de la cafeína sobre autofagia en el modelo de esteatosis hepática

Resultados

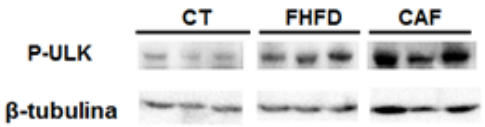


Cafeína altera marcadores de autofagia

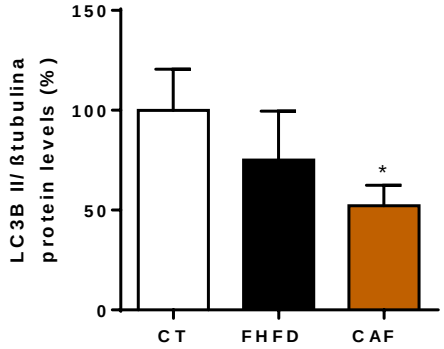
P-ULK



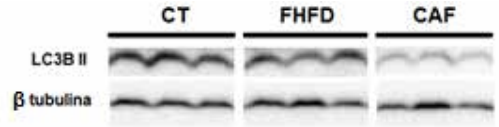
ANOVA one way; * p<0,05; *vs CT



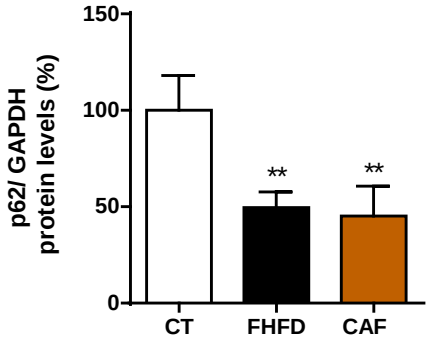
LC3B II



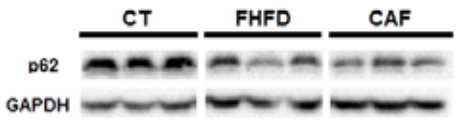
ANOVA one way; * p<0,05; *vs CT



P62



ANOVA one way; p<0.01; **vs CT



Discusión-conclusión

Caracterización metabólica

Esteatosis, TGL ↑
Cafeina =
ChREBP, LPK ↑
FK, FAS, SCD1↑

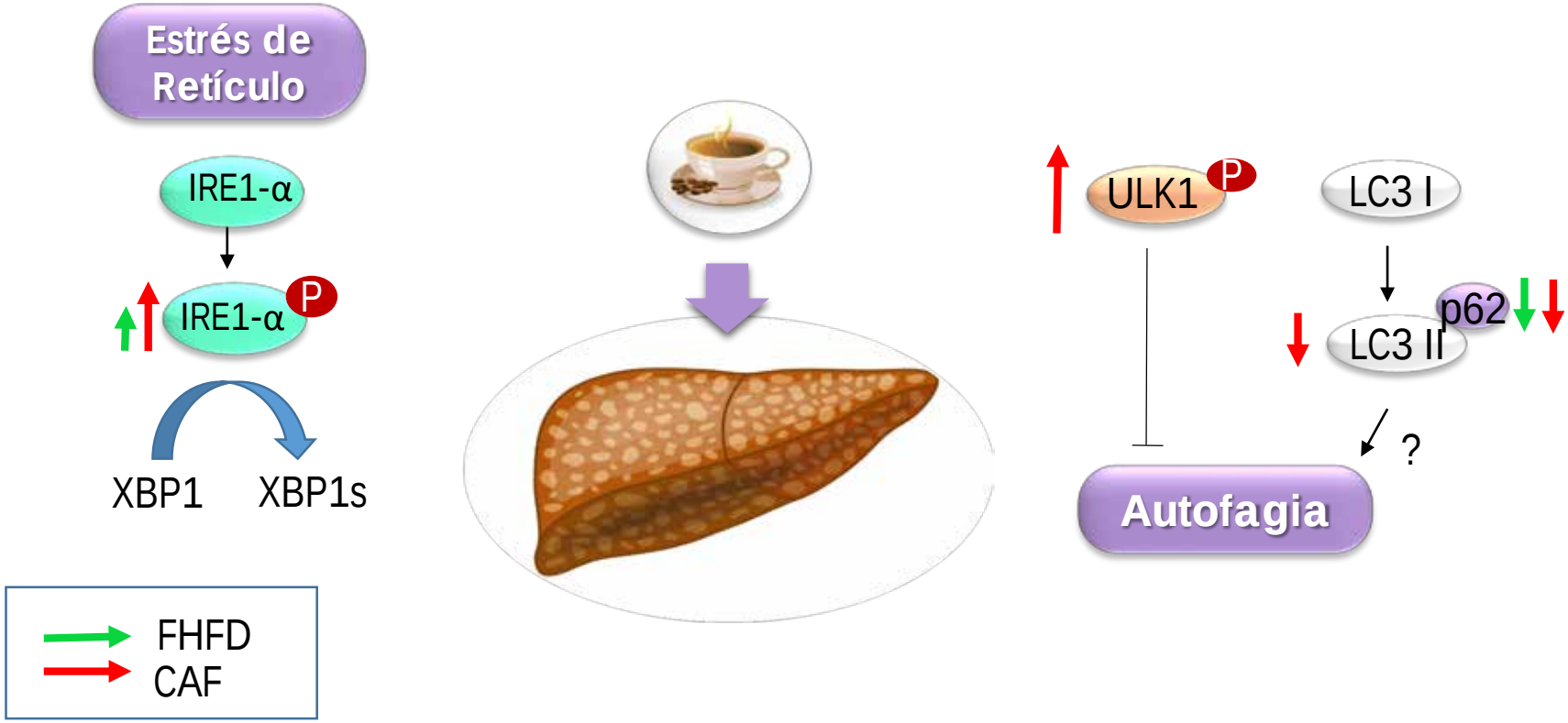
in vivo

in vitro

Esteatosis, TGL ↑
Cafeina ↓
P-AMPK ↑
ChREBP, LPK =
FK =, FAS, SCD1↓

Discusión-conclusión

Efectos sobre el estrés de retículo y la autofagia



Muchas gracias
por su atención