

Dipeptidyl peptidase III and oxidative stress *in vivo*

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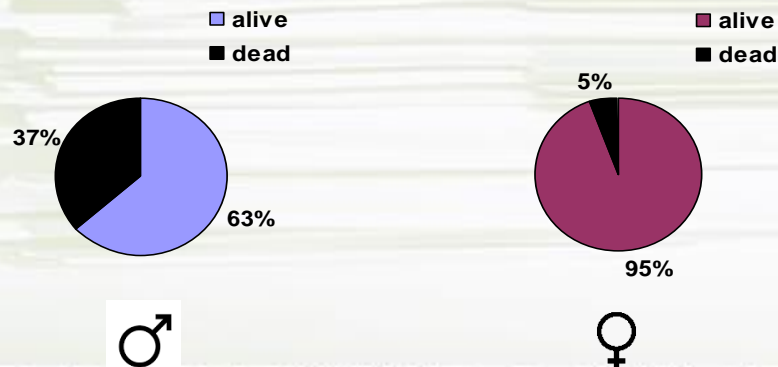
DPP III Minisymposium, Zagreb, 2016.

- resistance to oxidative damage is sex-related
- women live longer than men (4,4 years average)
- most age-related diseases are delayed in women compared to men
- Prevalence of hepatocellular carcinoma in CBA/H mice (18 months old):

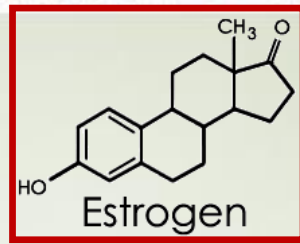


60% ♂ vs. 0% ♀ *Sobočanec et al. Biogerontology. (2008);5:235*

- Survival in acute oxidative stress conditions in CBA/H mice (4 months old):



Šarić et al. ABP. (2014);61:1



Sirt1

*Nisoli et al.,
Science (2005): 310:
5746*

eNOS

cGMP

NAD⁺/NADPH

PGC-1 α

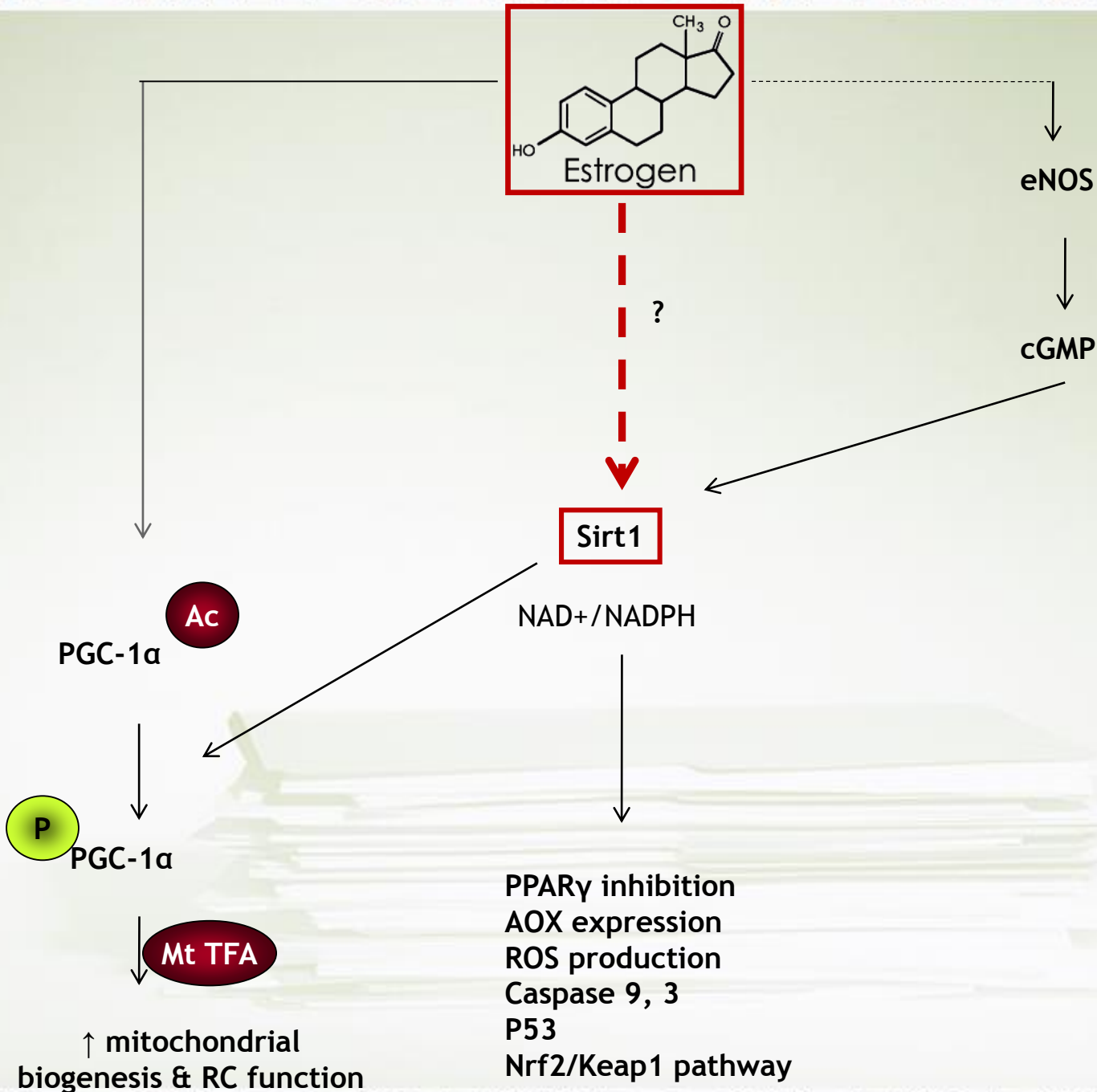
Ac

PGC-1 α

Mt TFA

↑ mitochondrial
biogenesis & RC function

PPAR γ inhibition
AOX expression
ROS production
Caspase 9, 3
P53
Nrf2/Keap1 pathway



17-beta estradiol (E₂)



Ovariectomy (females)

E₂ pellet implantation
(males and females)



GROUPS

Males

- normoxia control
- normoxia control + E₂

- hyperoxia
- hyperoxia+ E₂



Females

- normoxia sham
- normoxia ovx
- normoxia ovx + E₂

- hyperoxia sham
- hyperoxia ovx
- hyperoxia ovx + E₂

DPP III (dipeptidyl peptidase III)

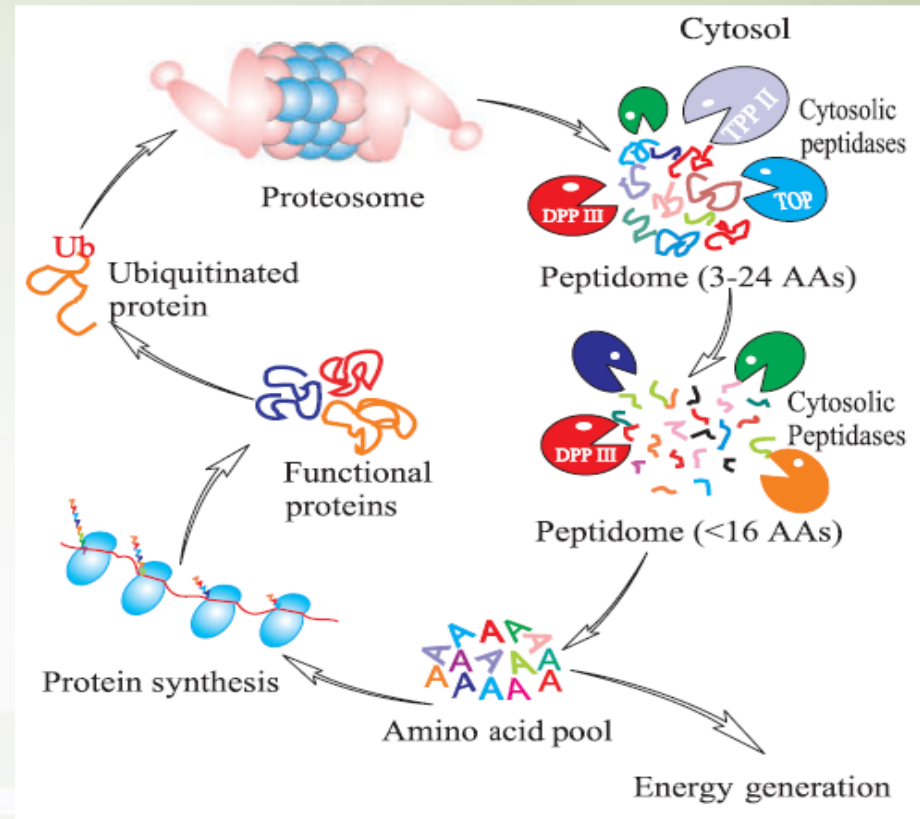
Representative of M49 family of zinc-metallopeptidases

The ubiquitous cytosolic peptidase

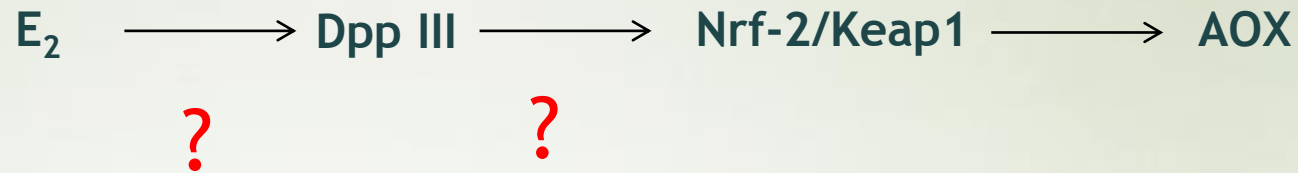
hDPP III - 82.5-84 kDa

Important role in cytosolic protein turnover

Altered expression in ovarian carcinoma, oxidative stress, inflammation, pain
(*Šimaga et al. (1998) Eur J Cancer 34;3:399-405*)



Physiological role of Dpp III *in vivo*?



-it is **not known** if and how E_2 influences Dpp III

-it is **not known** if and how E_2 influences AOX via alteration of Dpp III and Nrf2/Keap1 pathway

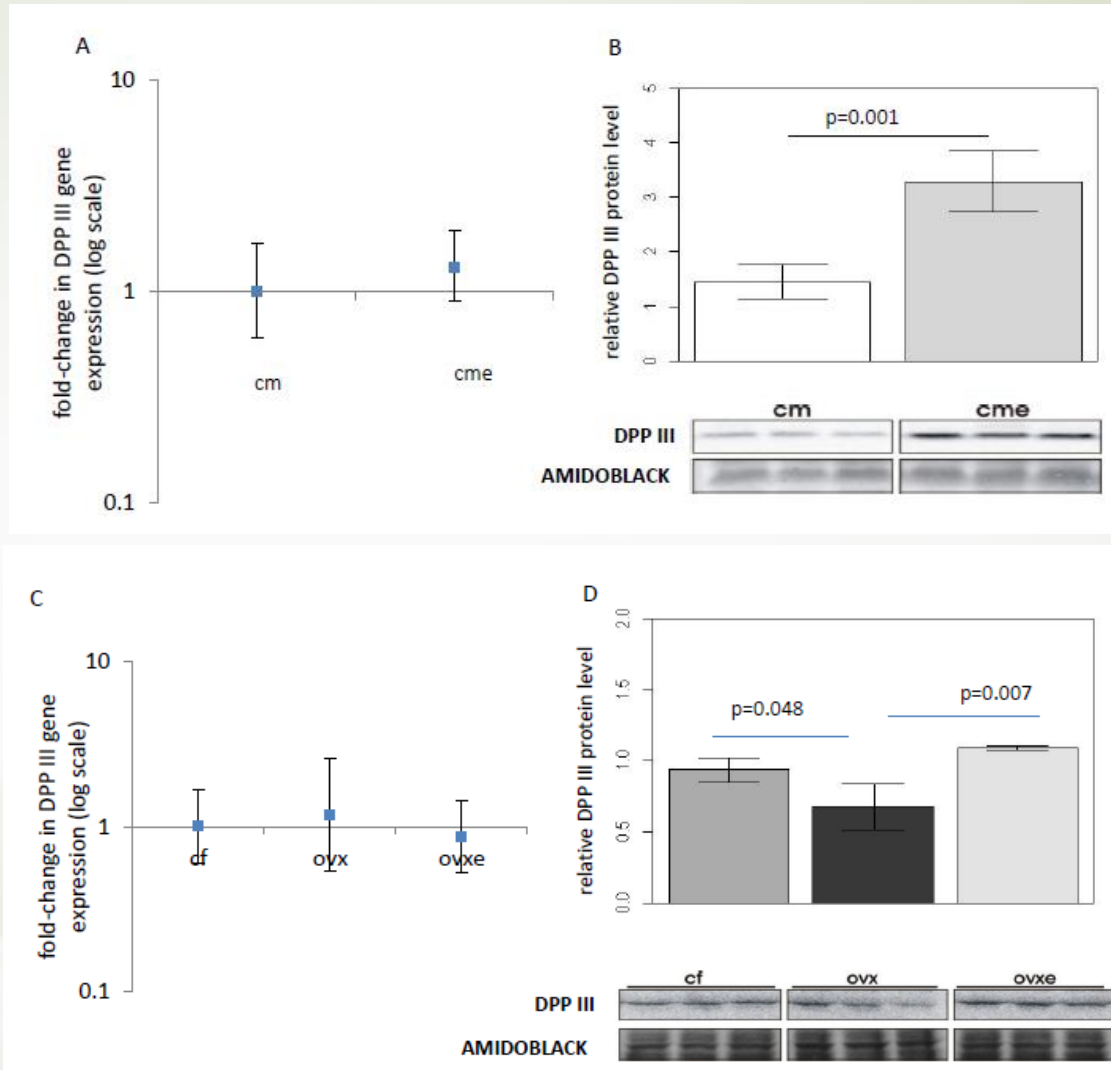


OBJECTIVES:

- to examine the effect of E₂ on the expression of DPP III and heme oxygenase 1 (HO-1) under physiologic conditions

FINDINGS:

Dpp III (NEW)

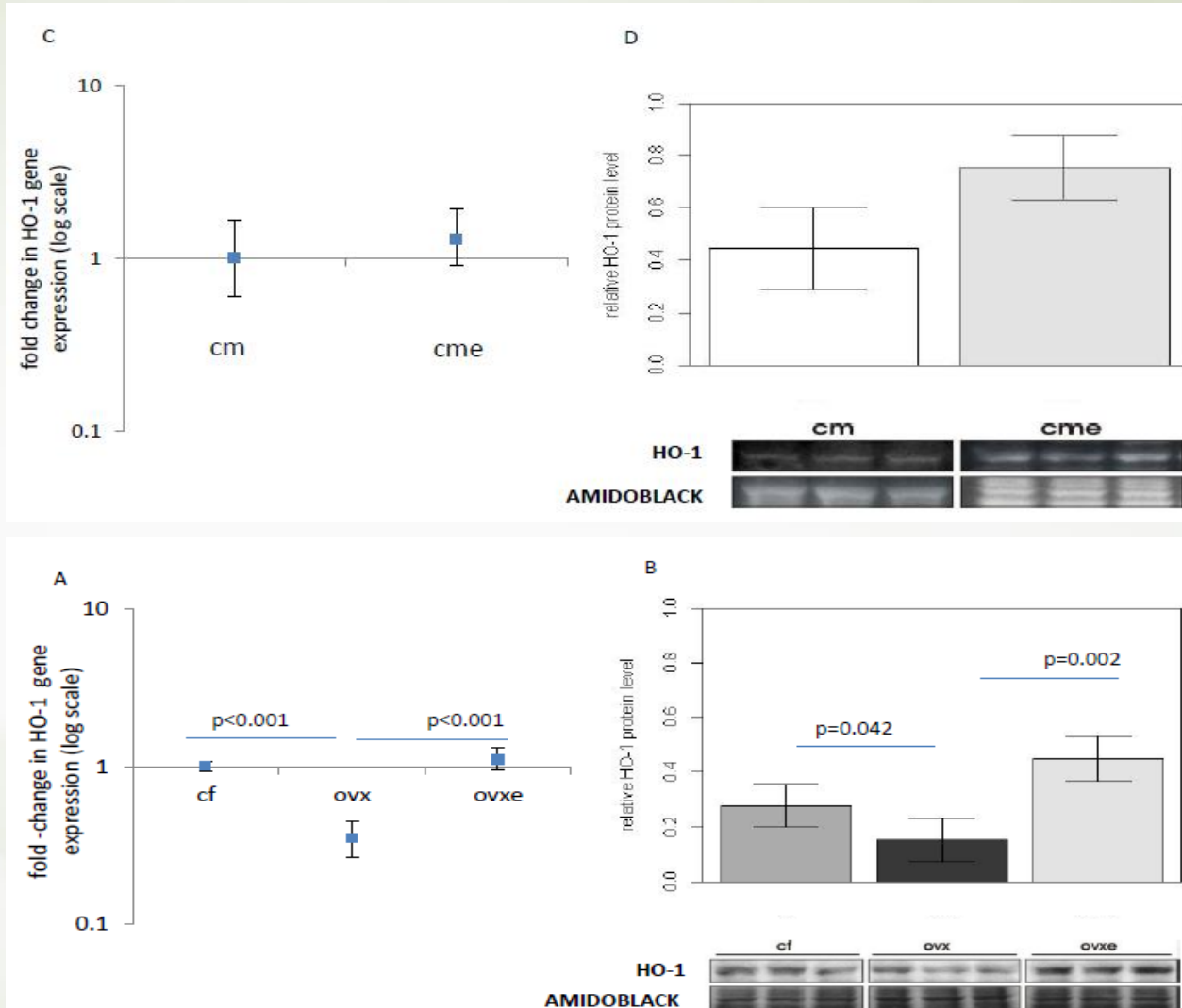


OBJECTIVES:

- to examine the effect of E₂ on the expression of DPP III and heme oxygenase 1 (HO-1) under physiologic conditions

FINDINGS:

Ho-1

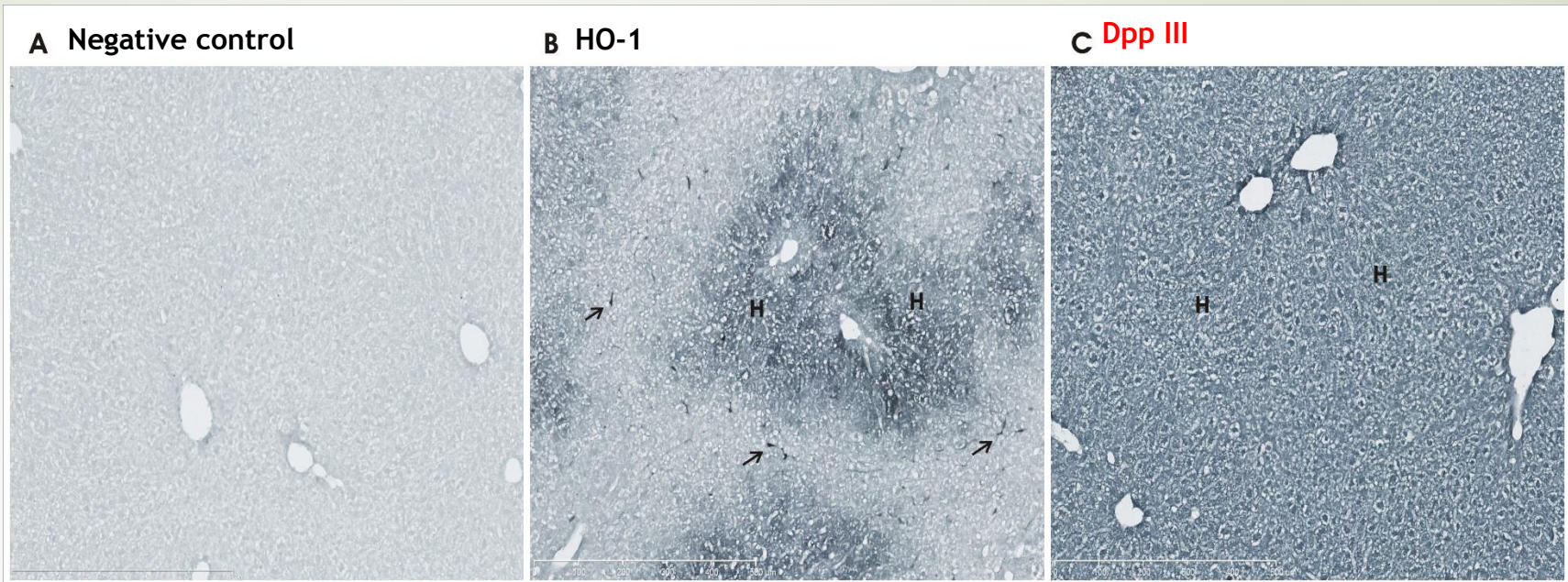


OBJECTIVES:

- to examine the effect of E_2 on the expression of DPP III and heme oxygenase 1 (HO-1) under physiologic conditions

FINDINGS:

(NEW)



localized in the pericentral areas of hepatic lobules (Kupffer cells, hepatocytes)

uniform distribution within hepatic tissue.

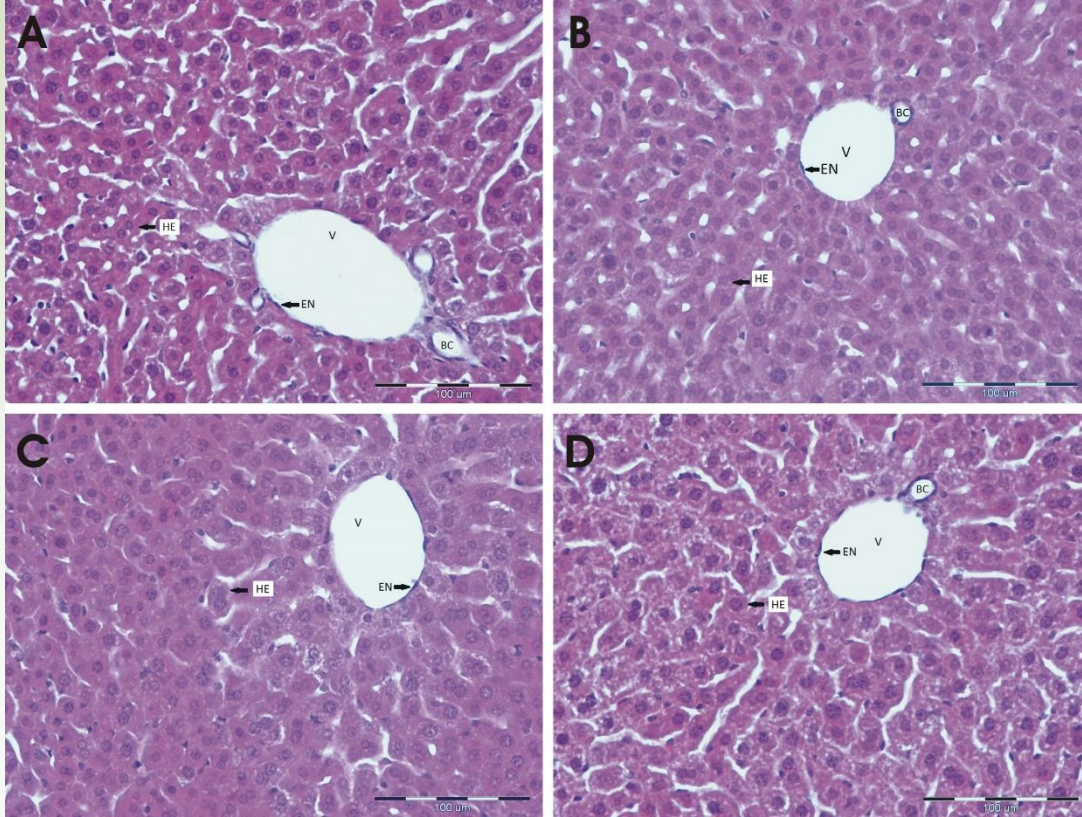
The effect of 17 β -estradiol on the expression of dipeptidyl peptidase III and heme oxygenase 1 in liver of CBA/H mice

Ž. Mačak Šafranko · S. Sobočanec · A. Šarić ·
N. Jajčanin-Jozić · Ž. Krsnik · G. Aralica · T. Balog ·
M. Abramić

NEXT OBJECTIVES :

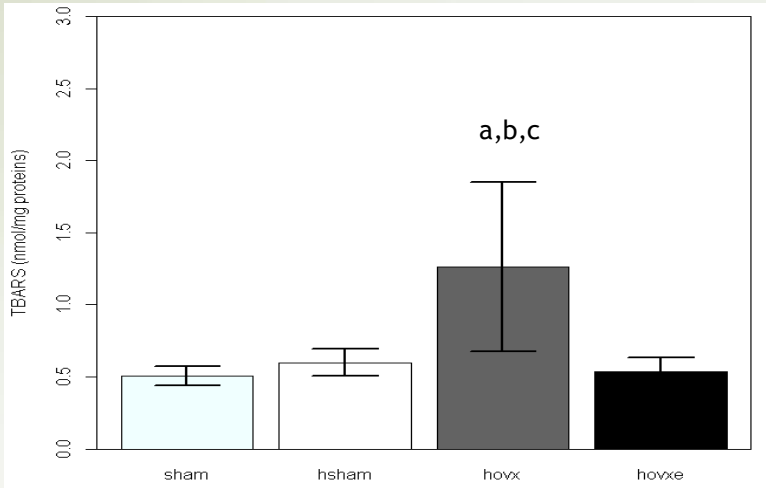
- To examine the effect of acute oxidative stress on the Dpp III expression and concomitant alteration of AOX enzymes via Nrf2/Keap1 pathway
- To examine the effect of E₂ on hyperoxia-induced changes in Dpp III – Nrf2/Keap1 – AOX axis
- To examine if either oxidative stress or administration of E2 caused hepatic injury by histopathological procedure
- To investigate presence/absence of the association between Dpp III and GSH levels (GSH may reverse oxidation of sensitive DppIII cysteines and reactivate DppIII)
- To localize Dpp III inside cell upon oxidative stress insult

Histopathological findings in liver of female CBA/H mice



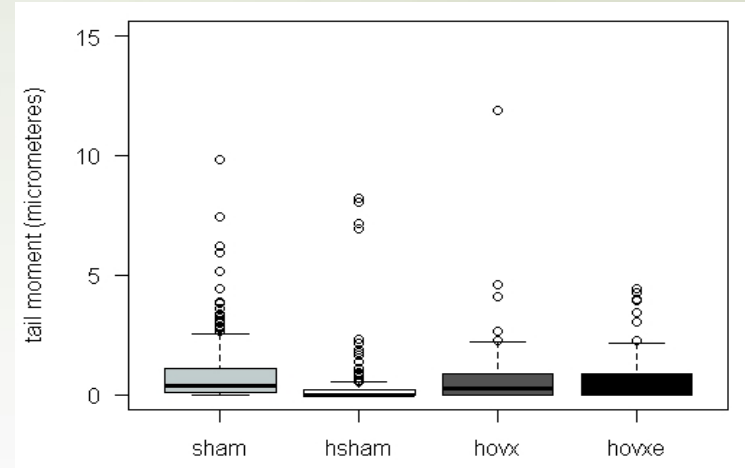
Sham (A)
Hsham (B)
Hovx (C)
Hovxe (D)

LPO

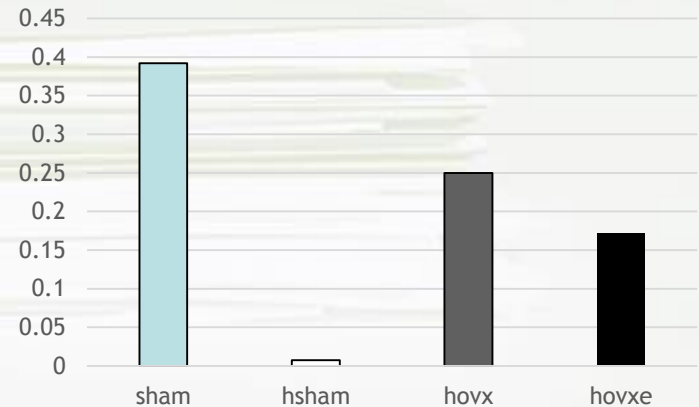


a, $p=0.003$ sham vs. hovx; b, $p=0.004$ hsham vs. hovx; c, $p=0.002$ hovxe vs. hovx

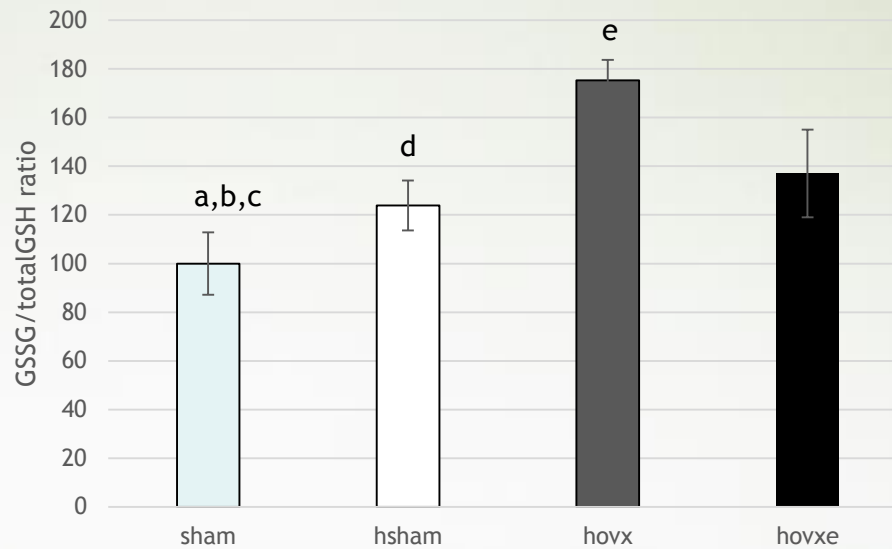
DNA damage



	sham	hsham	hovx	hovxe
sham	1	$p<0.001$	$p<0.01$	$p<0.01$
hsham	$p<0.001$	1	$p<0.001$	$p<0.001$
hovx	$p<0.01$	$p<0.001$	1	n.s.
hovxe	$p<0.01$	$p<0.001$	n.s.	1



GSSG/total GSH ratio



^ap<0.05, sham vs. hsham;

^bp<0.001, sham vs. hovx;

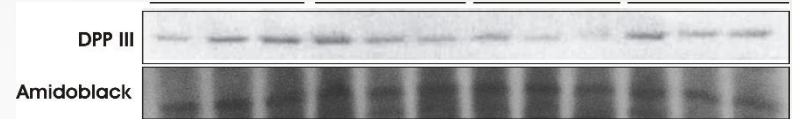
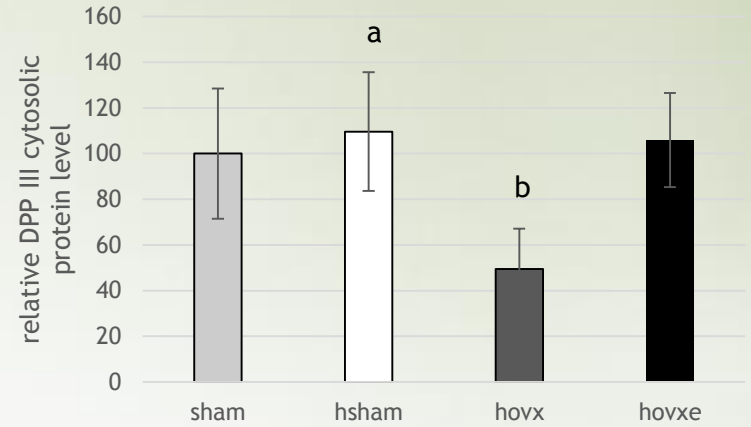
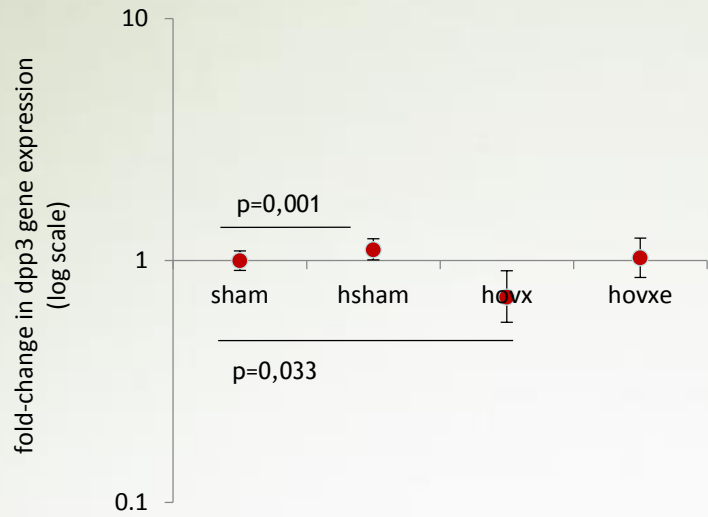
^cp<0.01, sham vs. hovxe;

^dp<0.001, hsham vs. hovx;

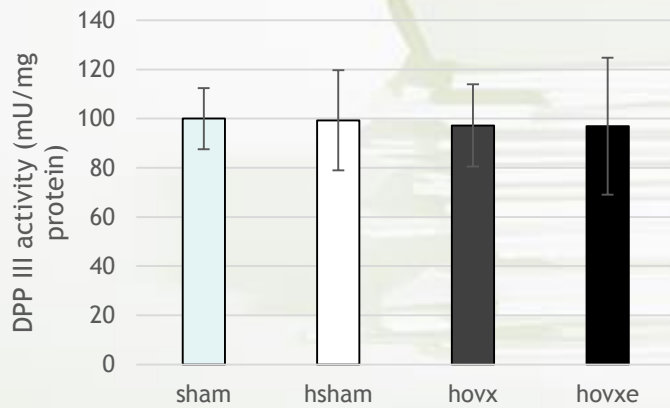
^ep<0.001 hovx vs. hovxe.

n=6 per group

Gene and protein expression Dpp III



Dpp III activity

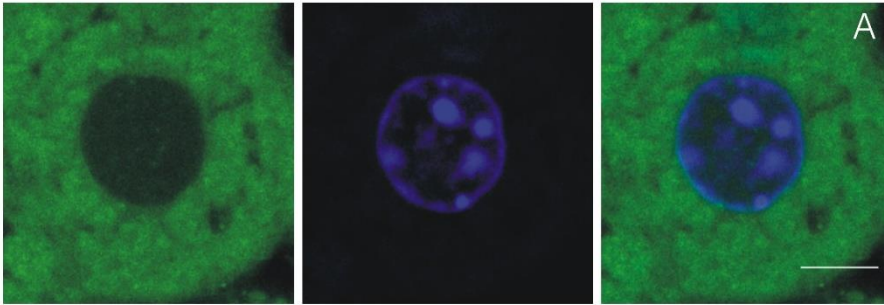


DppIII-FITC

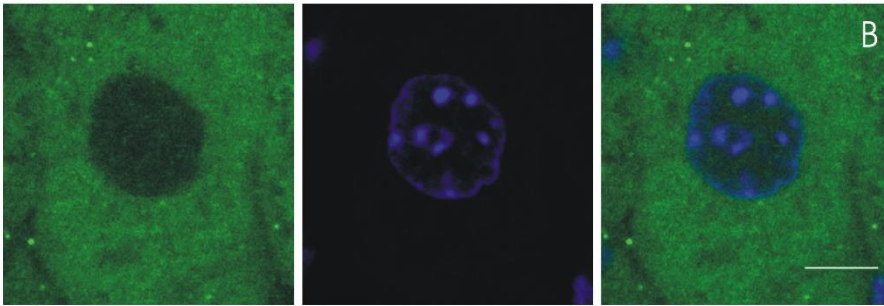
DAPI

Overlay

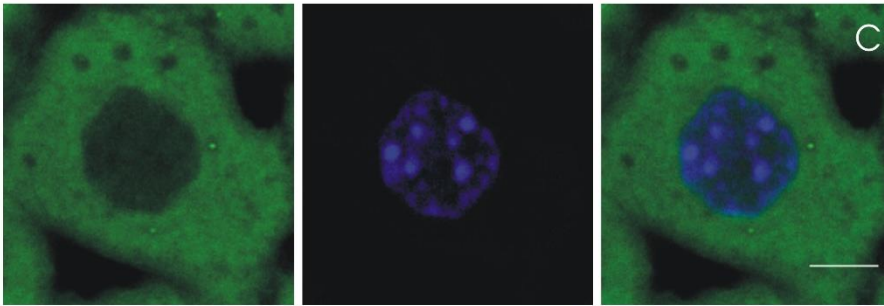
sham



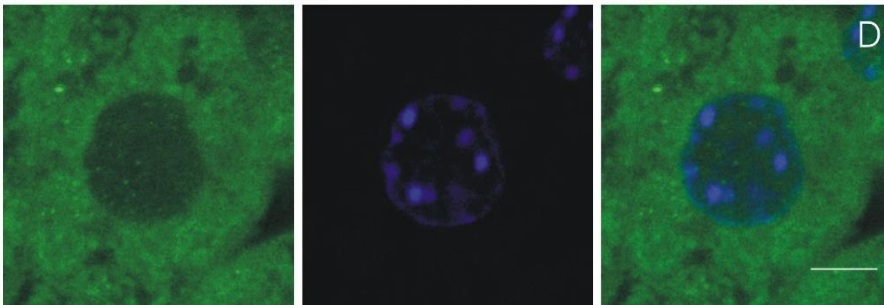
hsham



hovx



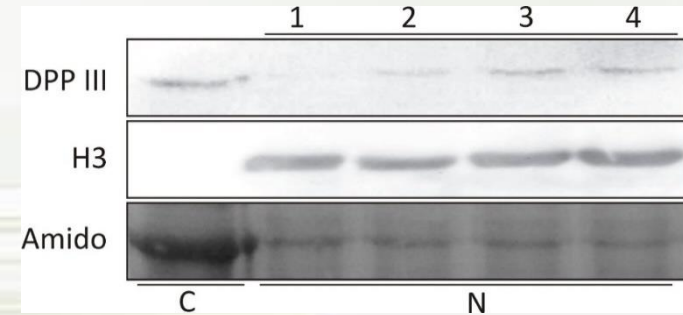
hovxe



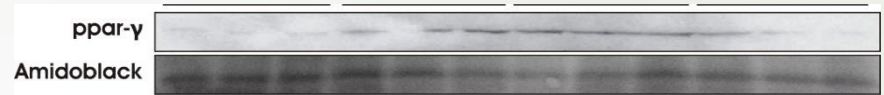
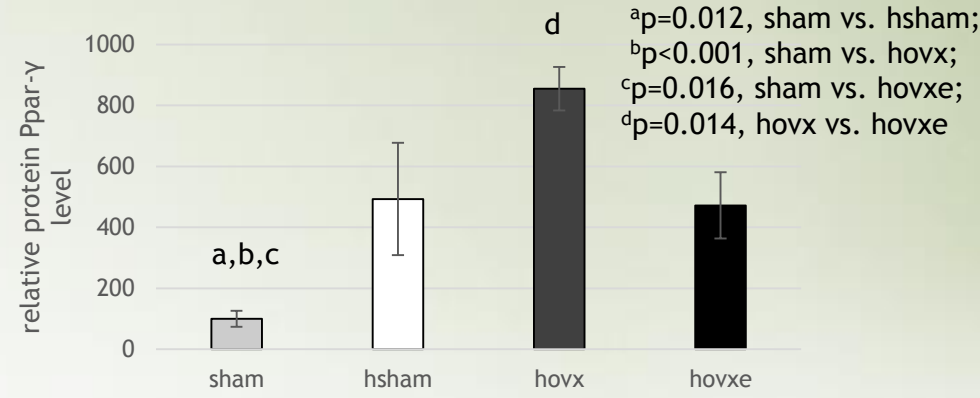
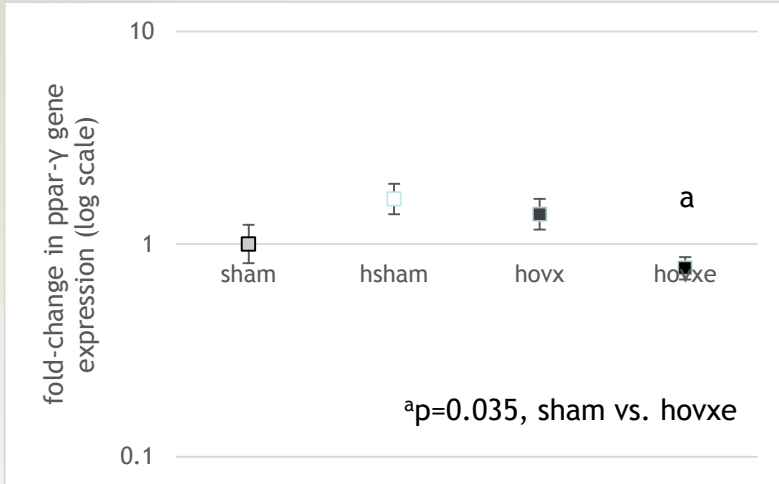
Dpp III localization



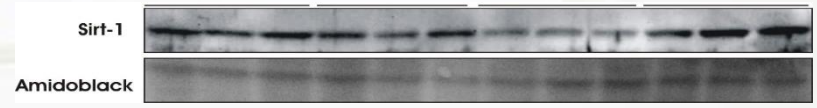
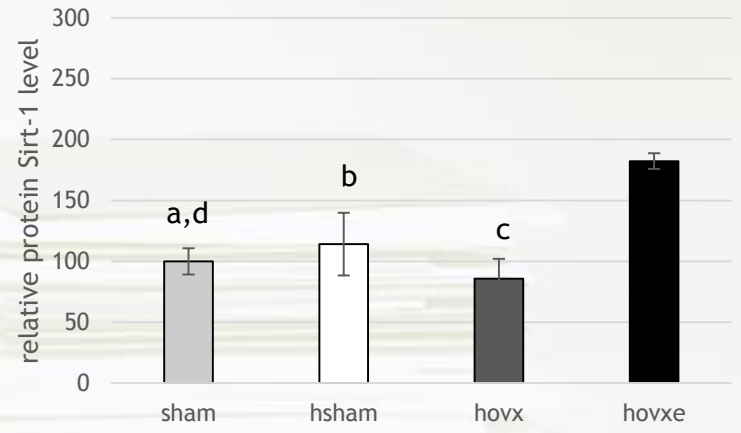
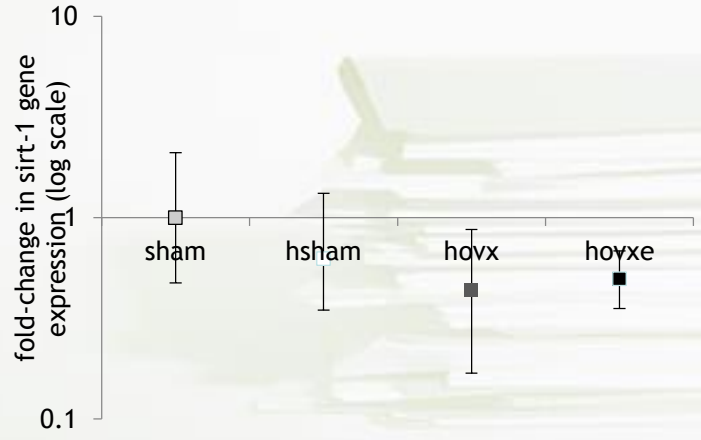
*p=0.042 hovxe vs sham

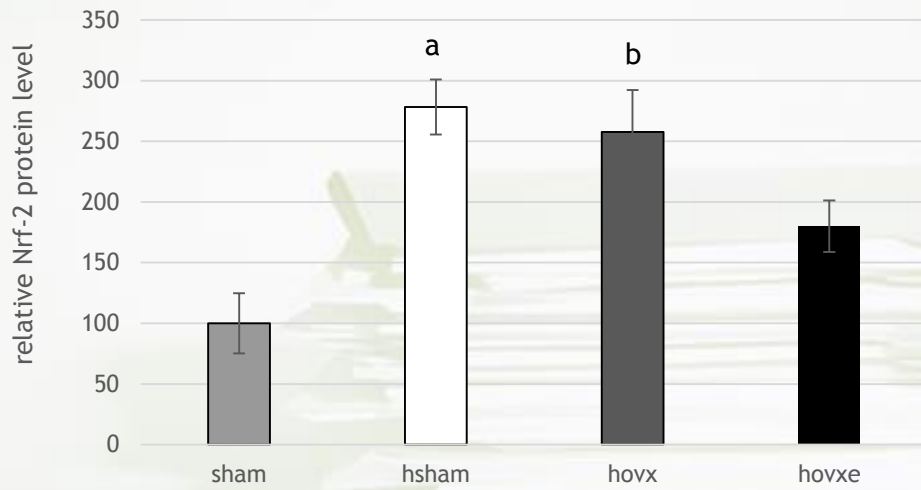
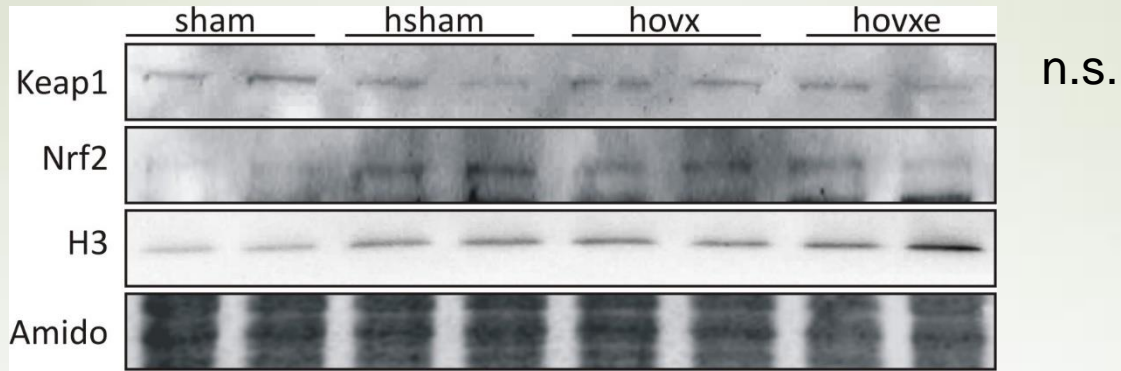


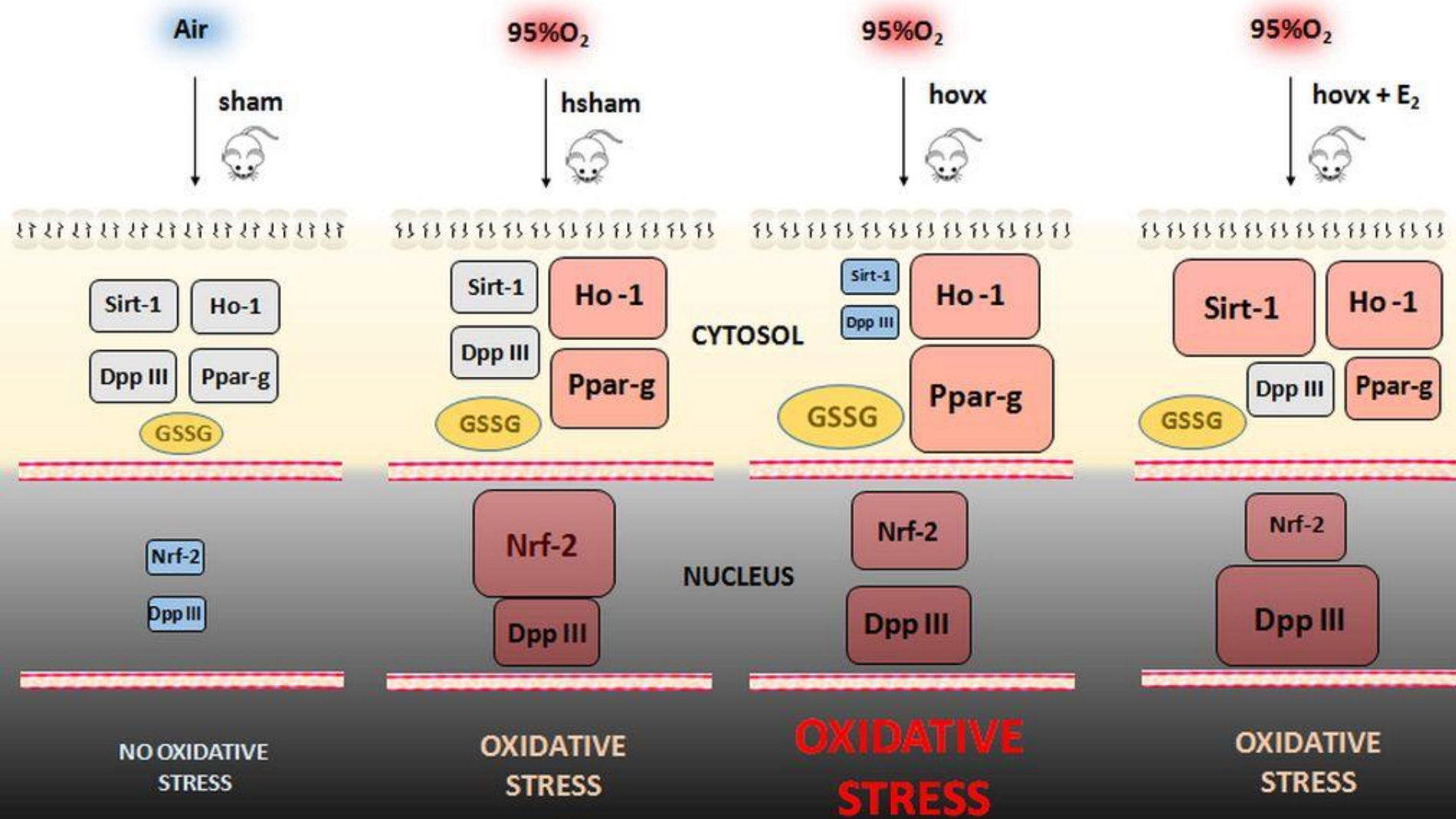
Ppar-gamma



Sirt-1









Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox



Research Paper

Prominent role of exopeptidase DPP III in estrogen-mediated protection against hyperoxia *in vivo*



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Interactome analysis → Interacting partners of dpp3



ATP5C1 (subunit of mitochondrial ATP synthase) - catalyses ATP synthesis

k.o. Dpp3 mice - kindly provided by prof.dr. R. Zimmermann, University of Graz, Institute for Molecular Biosciences

AIM:

To determine if DPP III, as a possible mediator of hormetic response, influences mitochondrial function and homeostasis, by regulation of ATP production.

International cooperation Croatia - Austria 2017

ICGEB Research Grants 2016

Participants in the study

ZMM - IRB

LAMBDA

- Ana Šarić
- Željka Mačak Šafranko
- Iva Pešun Međimurec
- Marijana Popovic Hadzija
- Sandra Sobočanec
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