Le stress oxydant, toujours délétère ?

ou

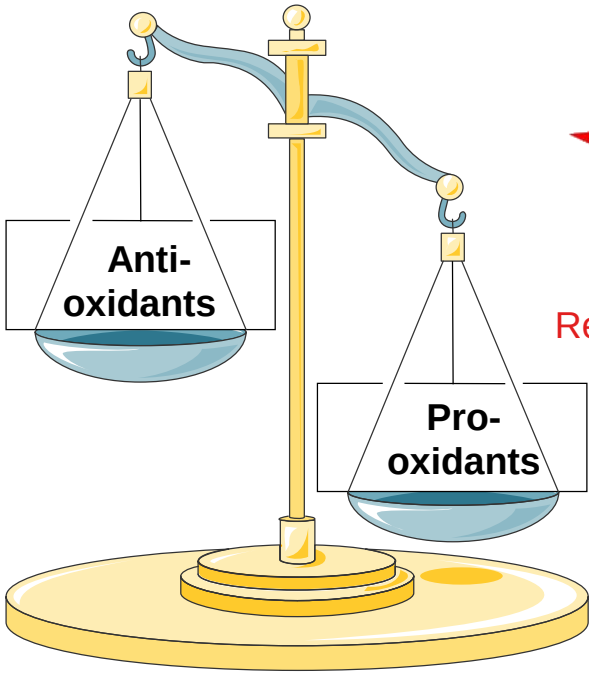
Comme disait Paracelse (médecin et philosophe suisse du XVIème s.):

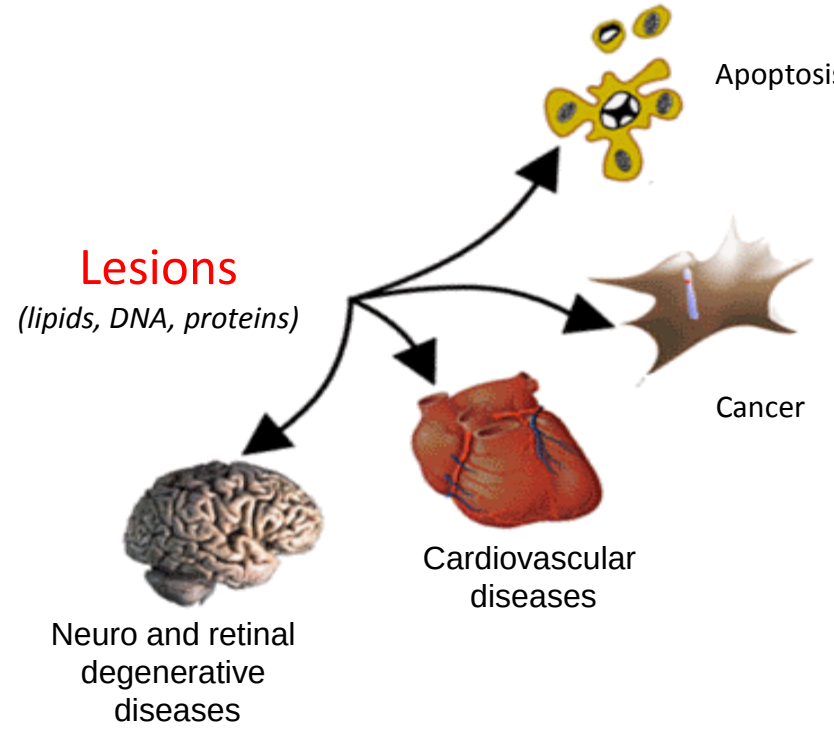
Toute chose est un toxique et rien n'existe sans toxicité, seul le dosage fait qu'une chose n'est pas un poison.

Jean-Yves Le Guennec

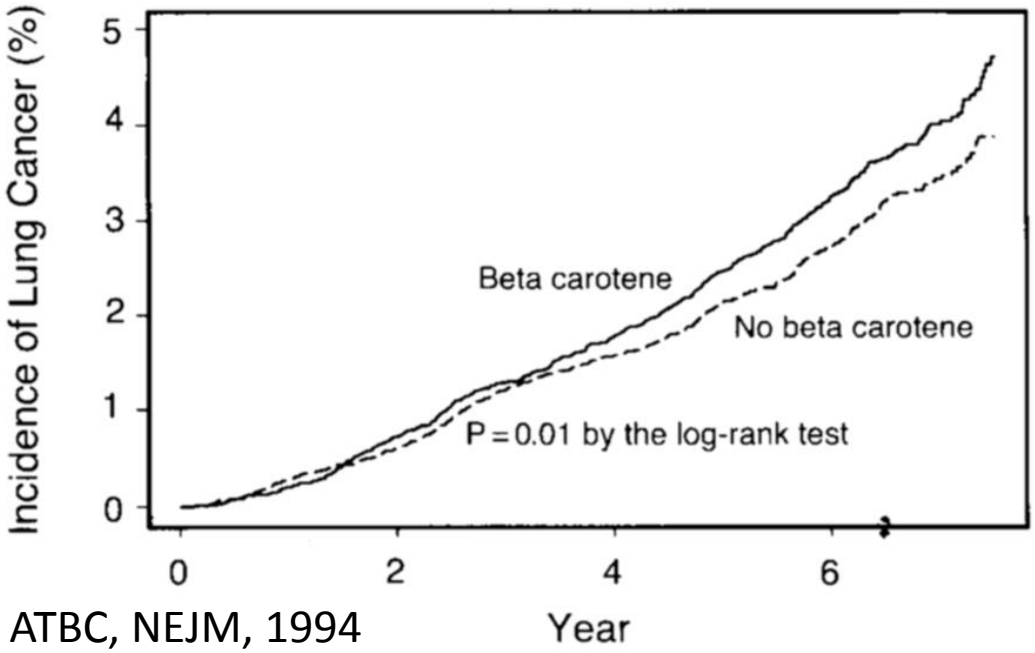
Inserm U1046 - CNRS UMR 9214 - UM
Physiologie et Médecine Experimentale du Cœur et des Muscles
MONTPELLIER

Le stress oxydant: c'est pas bon …

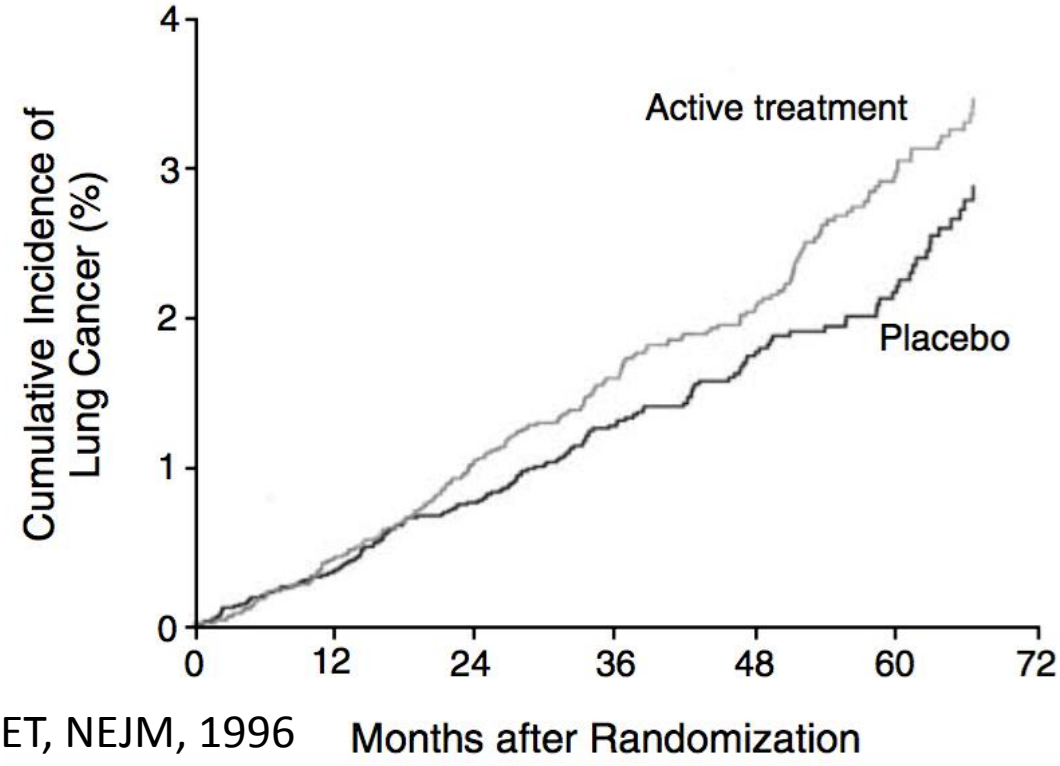




Le stress oxydant: mais ça peut être utile …



ATBC, NEJM, 1994

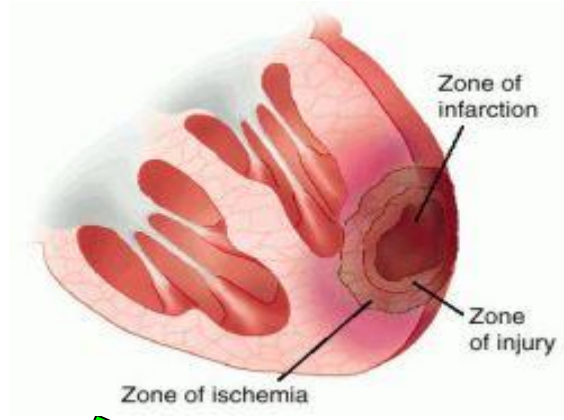


CARET, NEJM, 1996

Et si les ROS étaient nécessaires à homéostasie physiologique ?

Comment les AGPI ω3 PUFAs exercent leur cardioprotection ?

Infarctus du myocarde: quelles conséquences ?

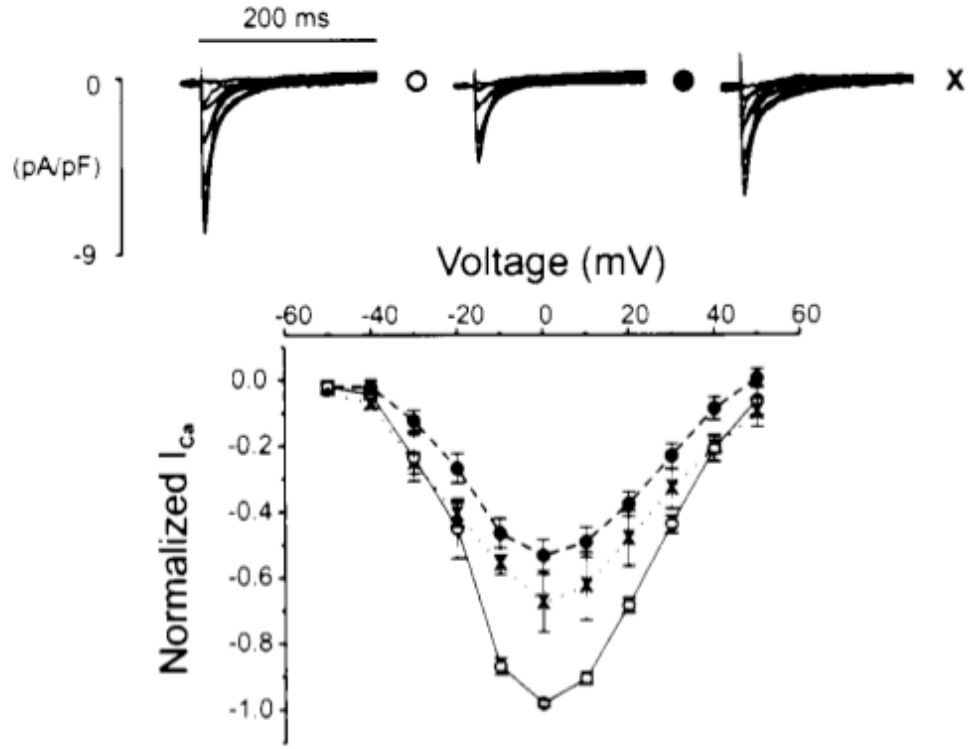


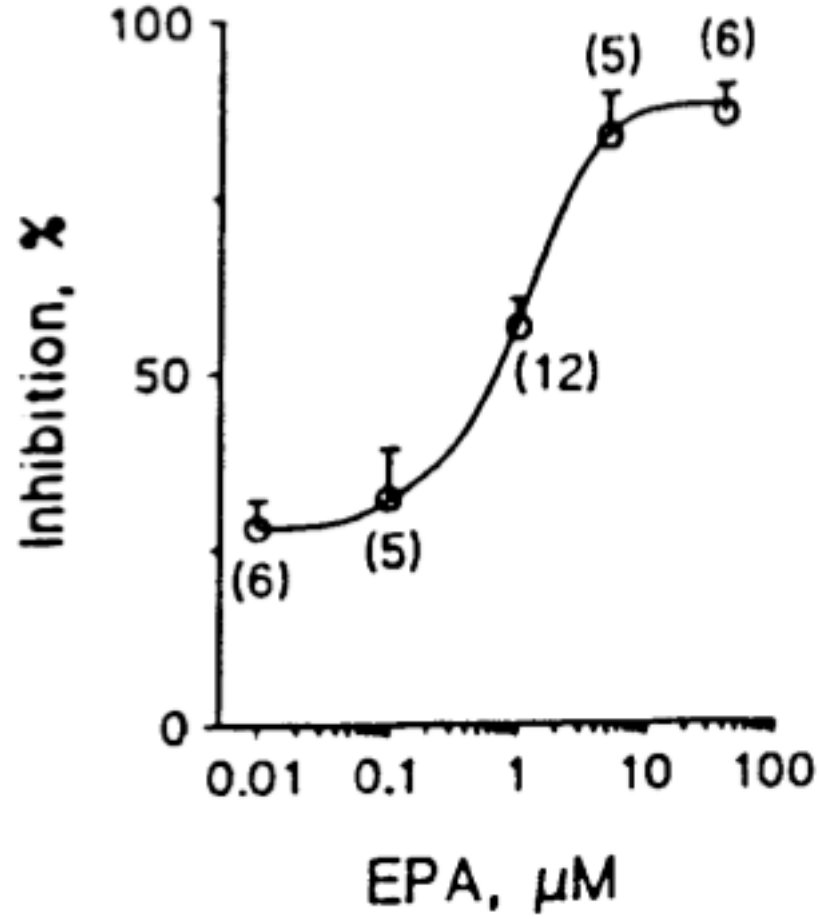
Insuffisance cardiaque

AGPI ω3

AGPI ω3 et courants ioniques

Exemple de I_{CaL}





Xiao *et al.*, PNAS, 1997

British Journal of Pharmacology (2003) 139, 816–822

www.nature.com/bjp

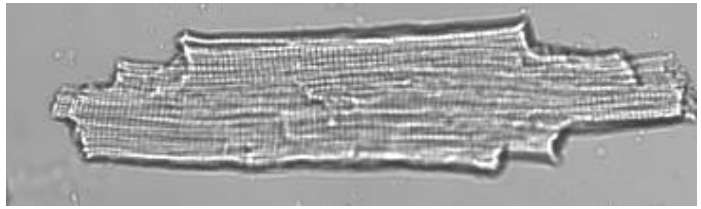
Peroxidation of docosahexaenoic acid is responsible for its effects on I_{TO} and I_{SS} in rat ventricular myocytes

[1,2]S. Judé, [1]S. Bedut, [1]S. Roger, [1]M. Pinault, [2]P. Champeroux, [3]E. White & *,[1]J-Y. Le Guennec

[1]Nutrition Croissance et Cancer, Emi 0211 Inserm, Faculté de Médecine, 2 Bd Tonnellé, 37032 Tours Cedex, France; [2]Centre de Recherches Biologiques, Chemin de Montifault, 18800 Baugy, France and [3]School of Biomedical Sciences, University of Leeds, Leeds LS2 9JT

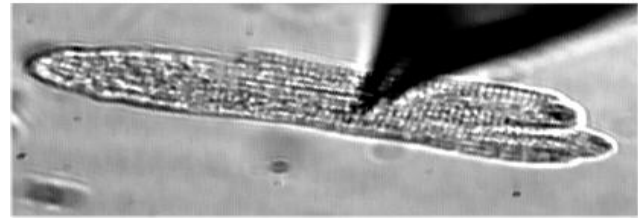
Rats Wistar

Isolement enzymatique

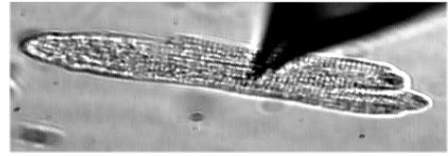


Cardiomyocyte ventriculaire

Investigation électrophysiologique

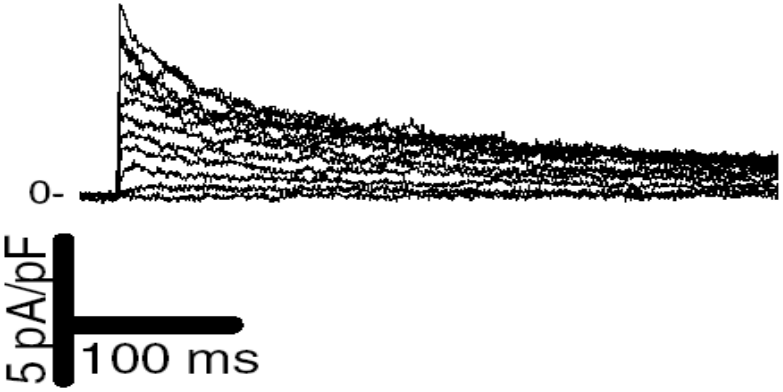


Cellule « patchée »

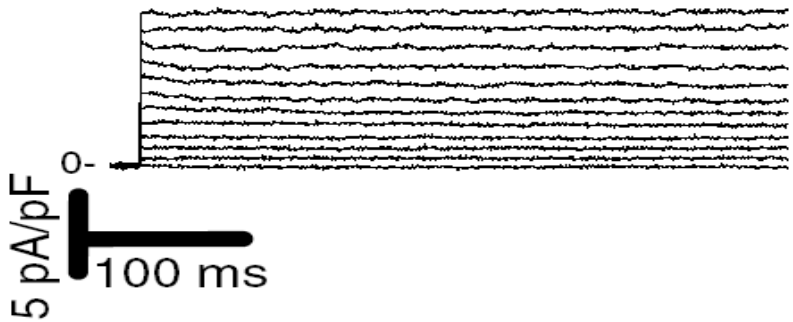


Témoin

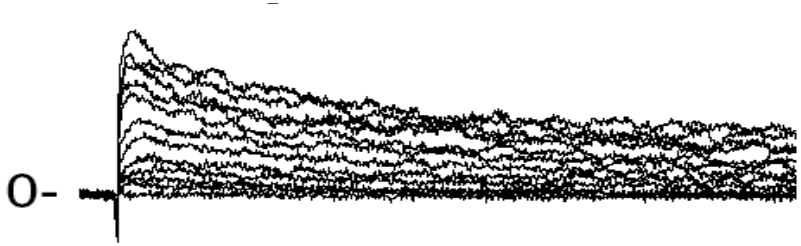
I_{TO}

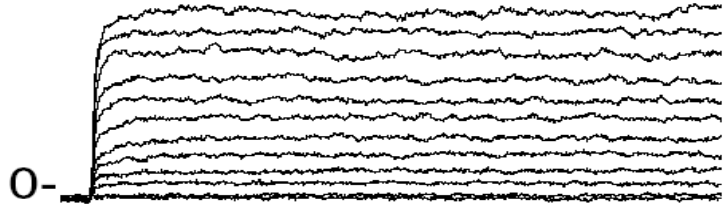


I_{SS}



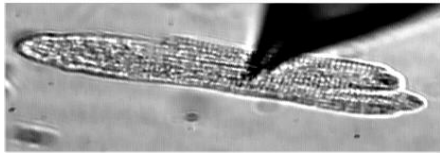
10 µM DHA
1 µM α-tocopherol

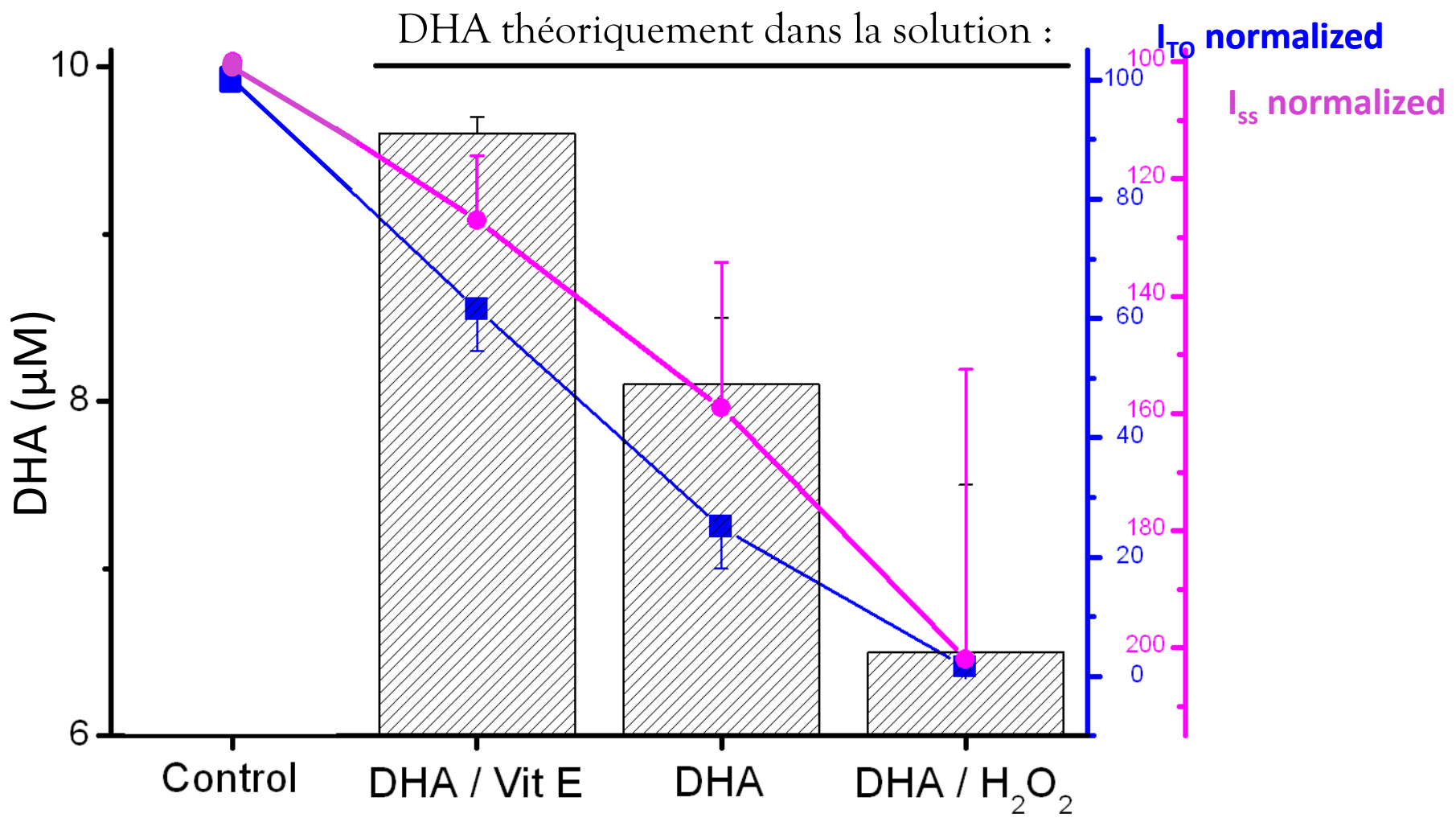




Judé *et al.*, 2003, *BJP*, **139**: 816

Relation DHA-Effect





Judé *et al.*, 2003, *BJP*, **139**: 816

British Journal of Pharmacology (2003) 139, 816–822

www.nature.com/bjp

Peroxidation of docosahexaenoic acid is responsible for its effects on I_{TO} and I_{SS} in rat ventricular myocytes

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Discussion

Our main finding is that the well-known effects of DHA on I_{TO} and I_{SS} are mainly due to a peroxidized product of the PUFA.

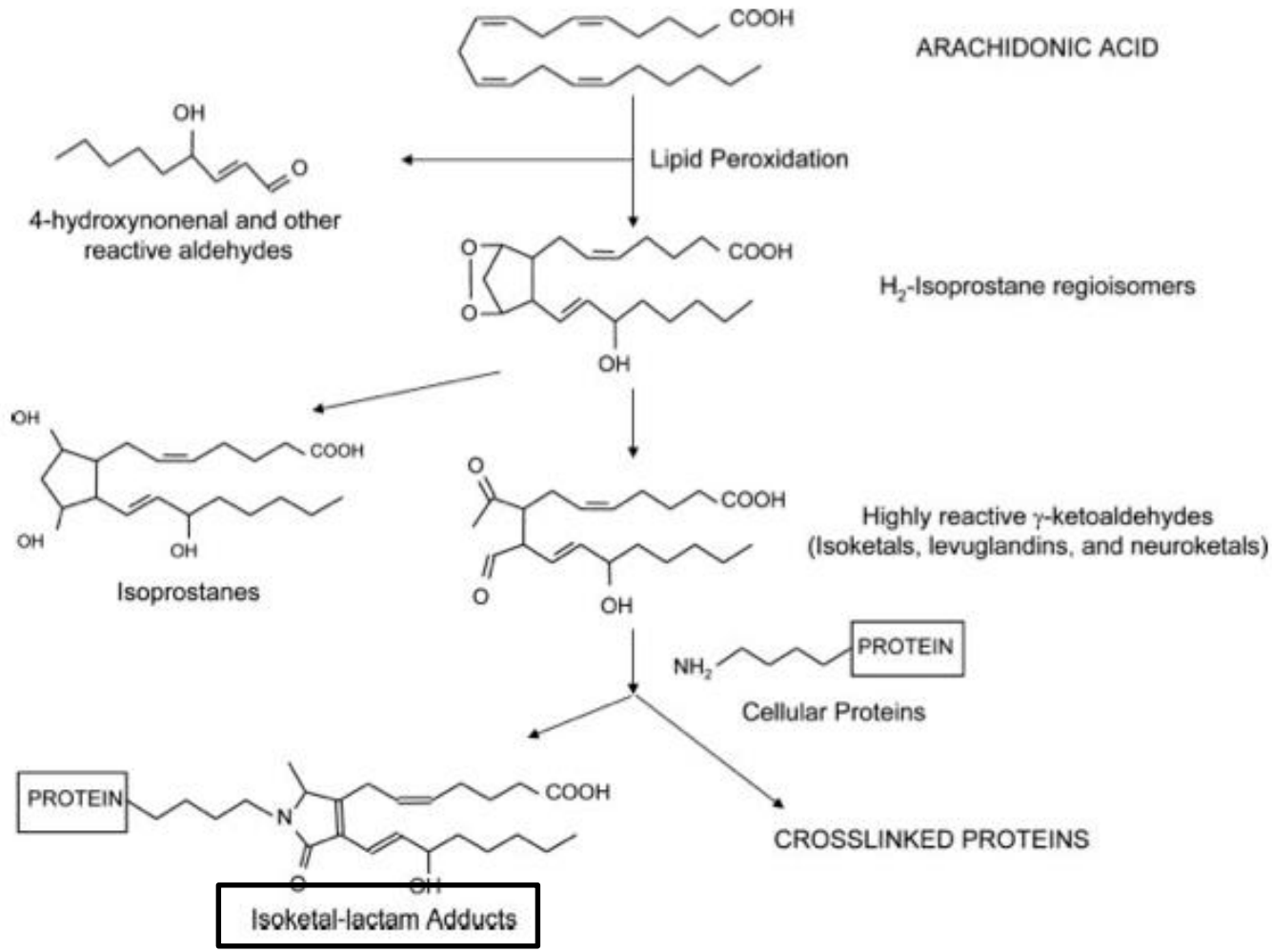
It is known that DHA peroxidation products such as F_4-isoprostane are very different from the precursor, DHA, and thus might have different pharmacological properties

Le dogme actuel: les péroxides d'ω3 ou d'ω6 sont délétères

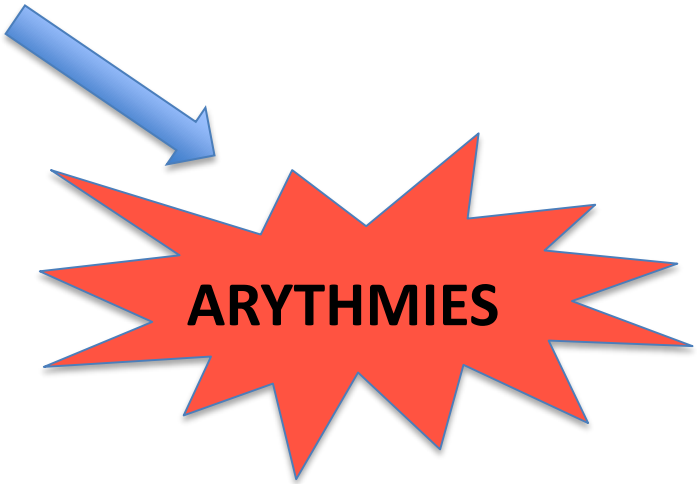
Oxidative Mediated Lipid Peroxidation Recapitulates Proarrhythmic Effects on Cardiac Sodium Channels

Koji Fukuda, Sean S. Davies, Tadashi Nakajima, Boon-Hooi Ong, Sabina Kupershmidt, Joshua Fessel, Venkataraman Amarnath, Mark E. Anderson, Penelope A. Boyden, Prakash C. Viswanathan, L. Jackson Roberts II and Jeffrey R. Balser

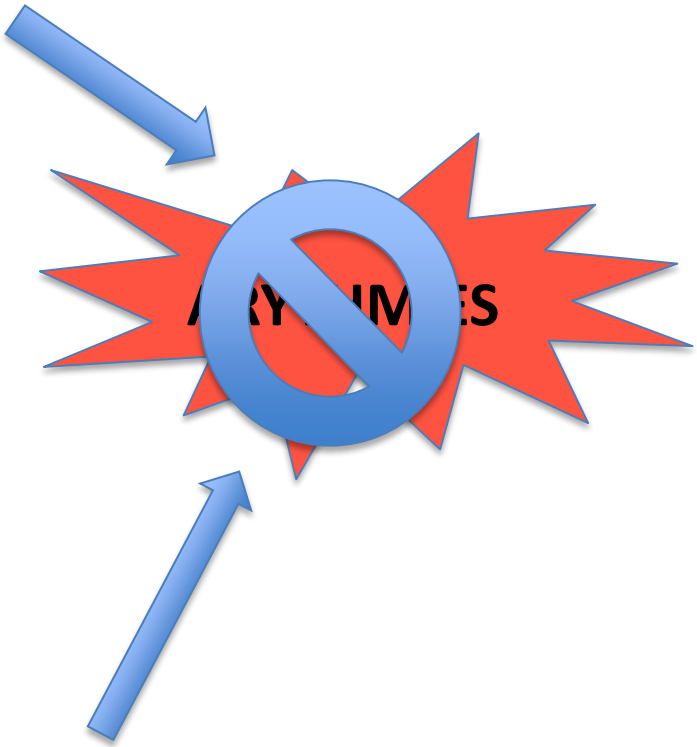
Circulation, 2005



Infarctus du myocarde → Stress oxydant → Peroxydes lipidiques



Infarctus du myocarde → Stress oxydant → Peroxydes lipidiques



Notre hypothèse

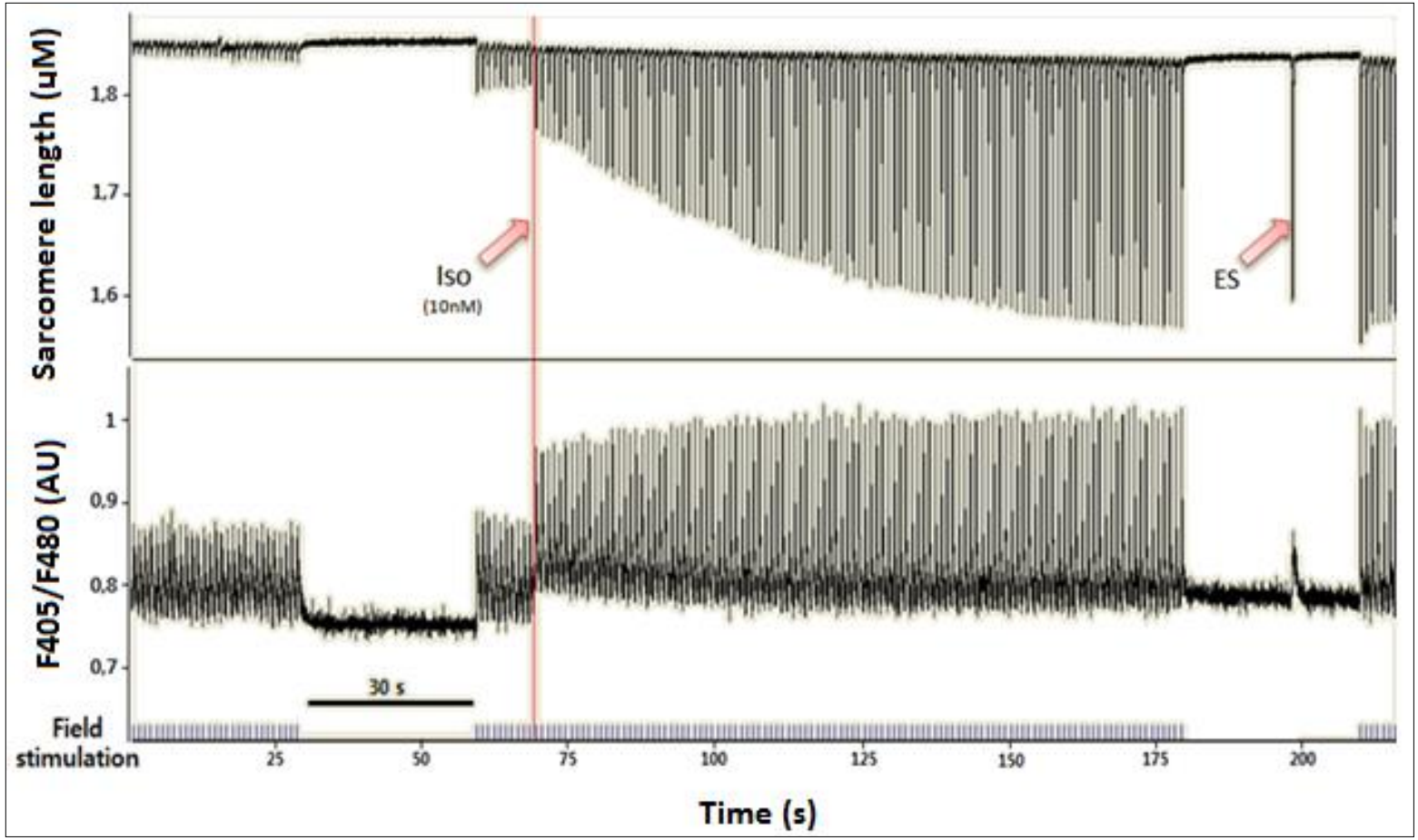
Infarctus du myocarde → Stress oxydant

Métabolites oxydés du DHA

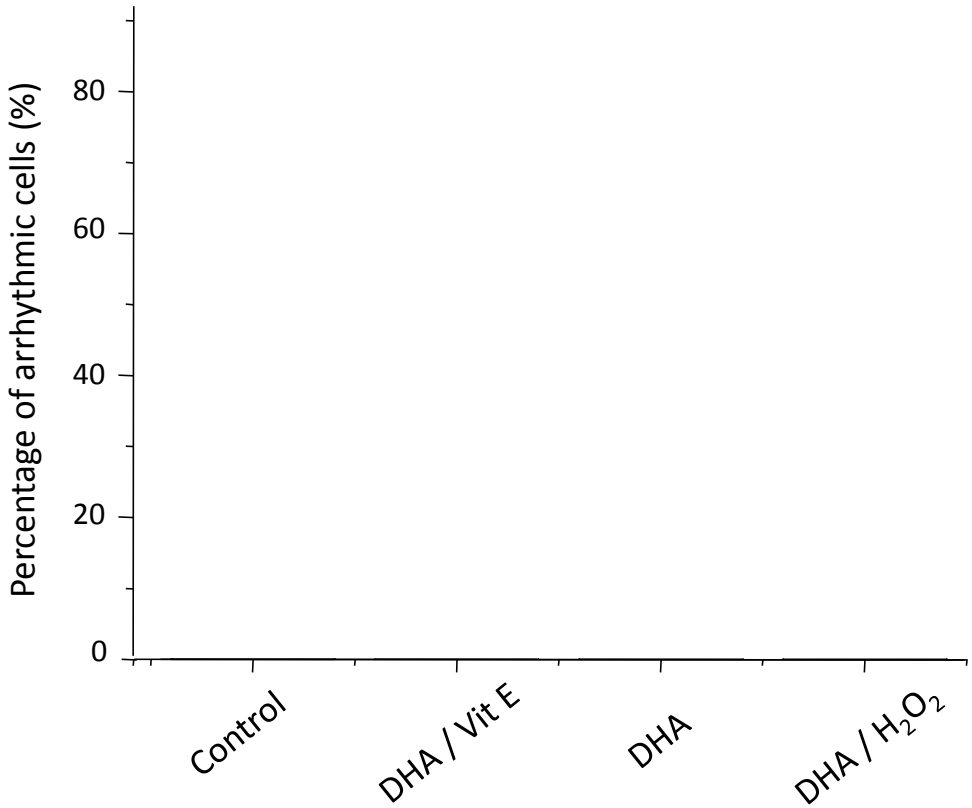
Acide Docosahexaenoïque (DHA)

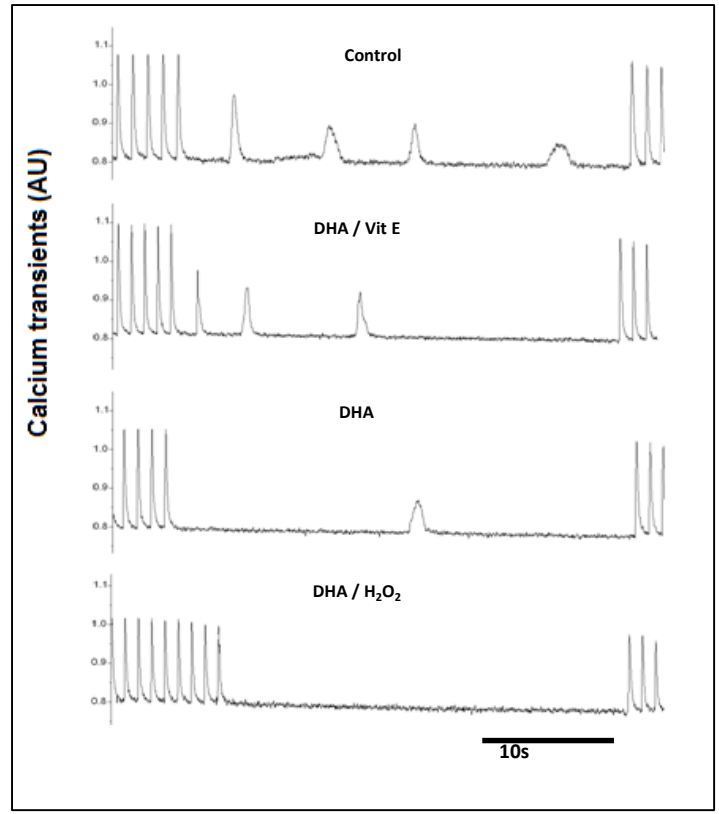
METHODES

Cardiomyocytes ventriculaires de souris



Influence de la balance oxydative





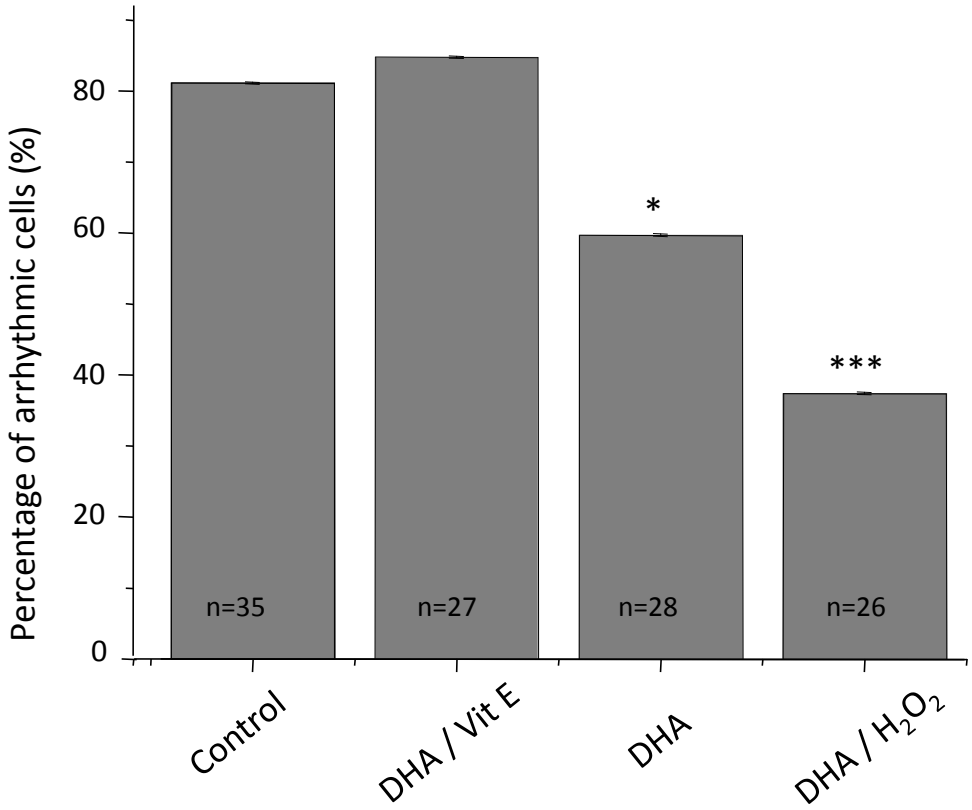
Control : Physiological saline solution (PSS)

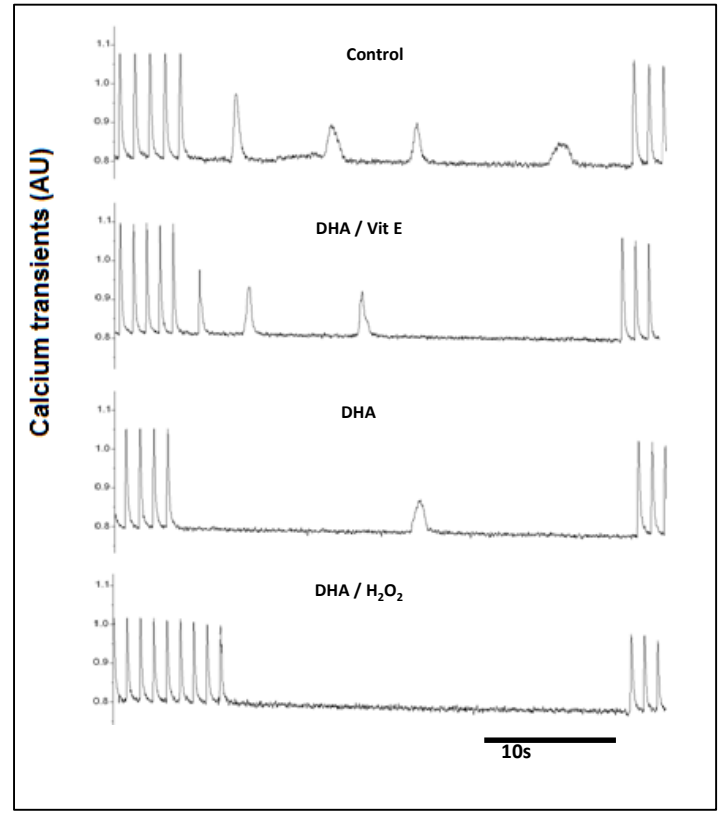
DHA : PSS + 10µM DHA

DHA / Vit E : PSS + 10µM DHA + 1µM α-tocopherol

DHA / H_2O_2 : PSS + 10µM DHA + 1µM H_2O_2

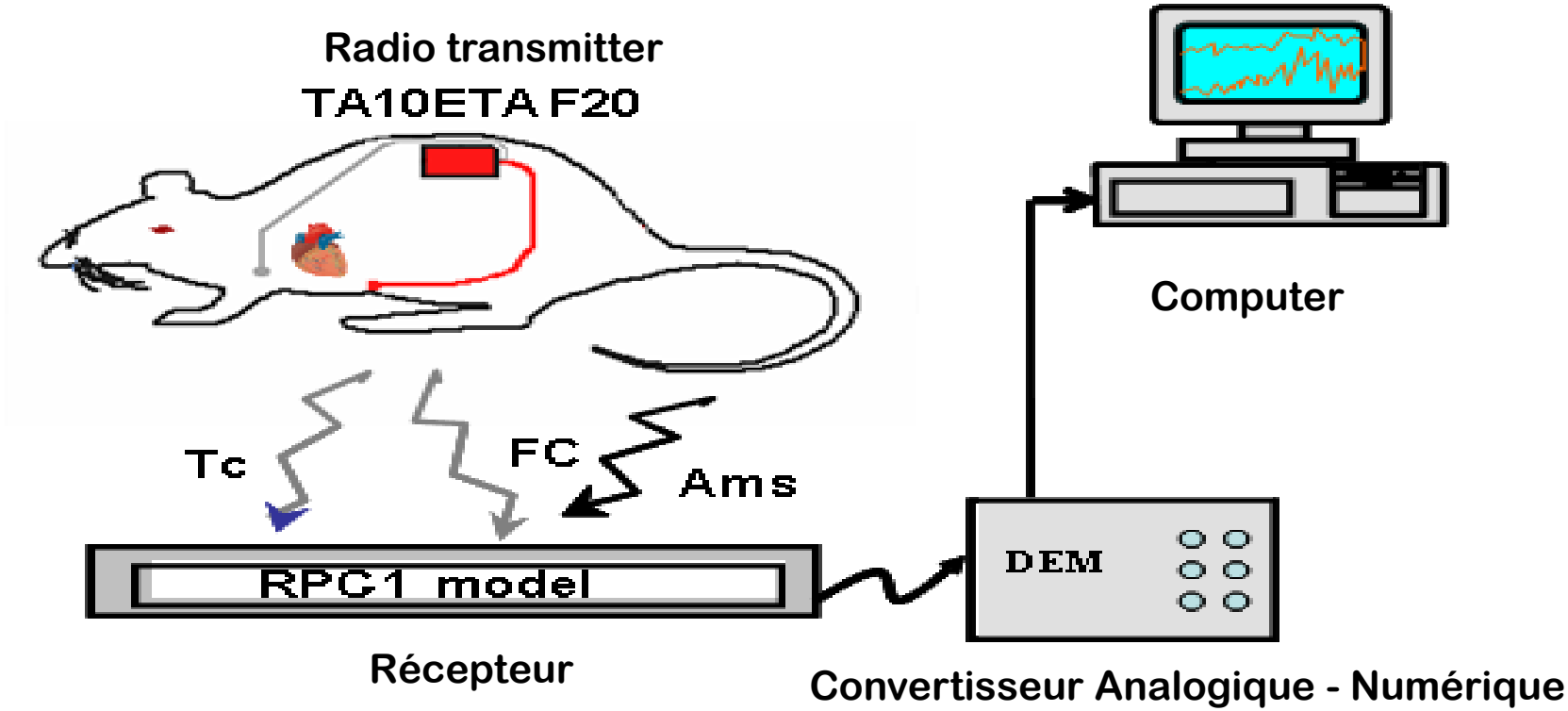
Sur cellules isolées :





Quid chez l'animal ?

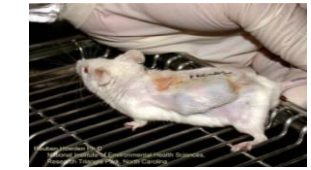
Télémétrie ECG

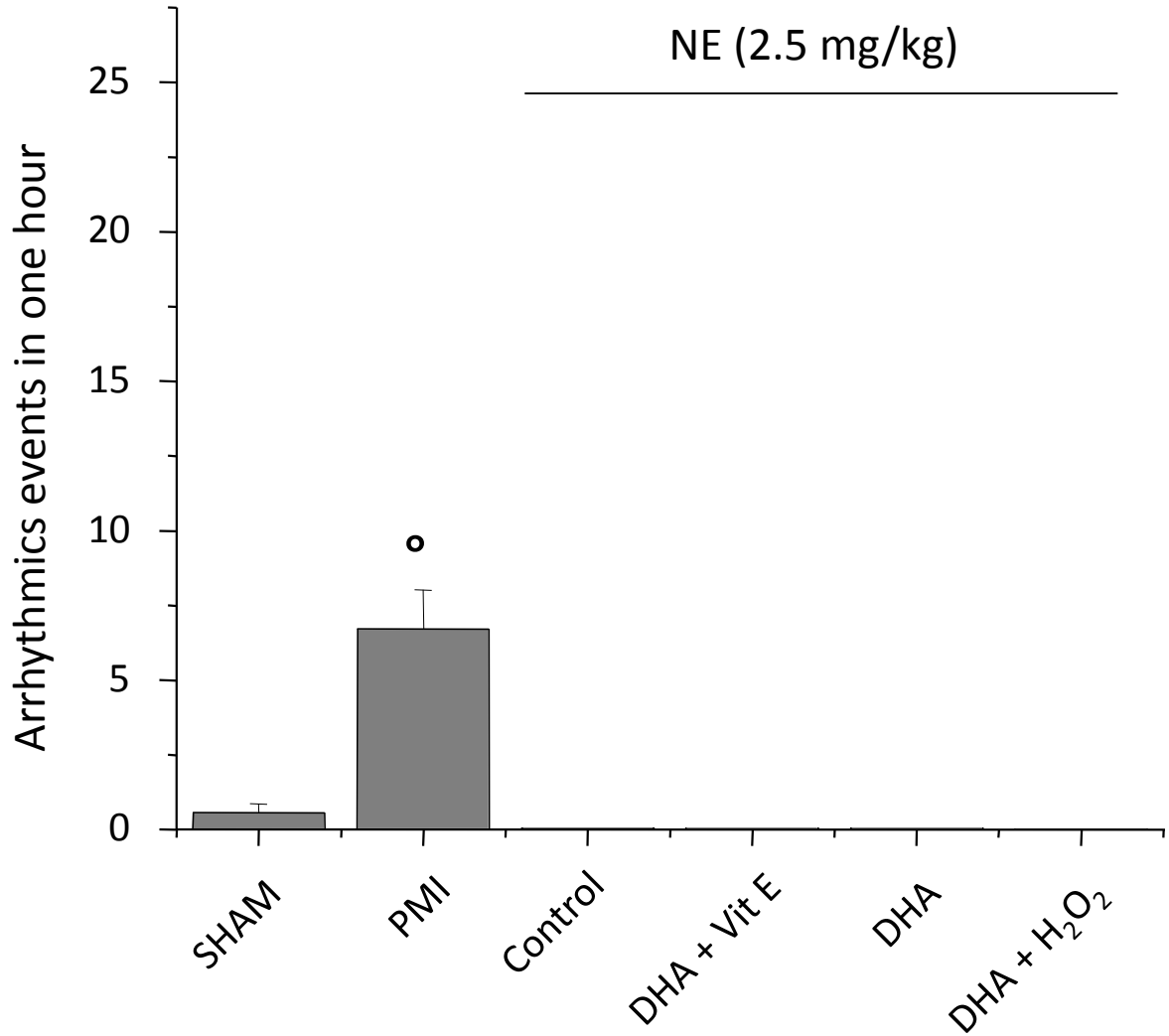


Avantages

Enregistrement continu de l'ECG pendant plusieurs heures chez des animaux éveillés

Chaque animal est son propre témoin





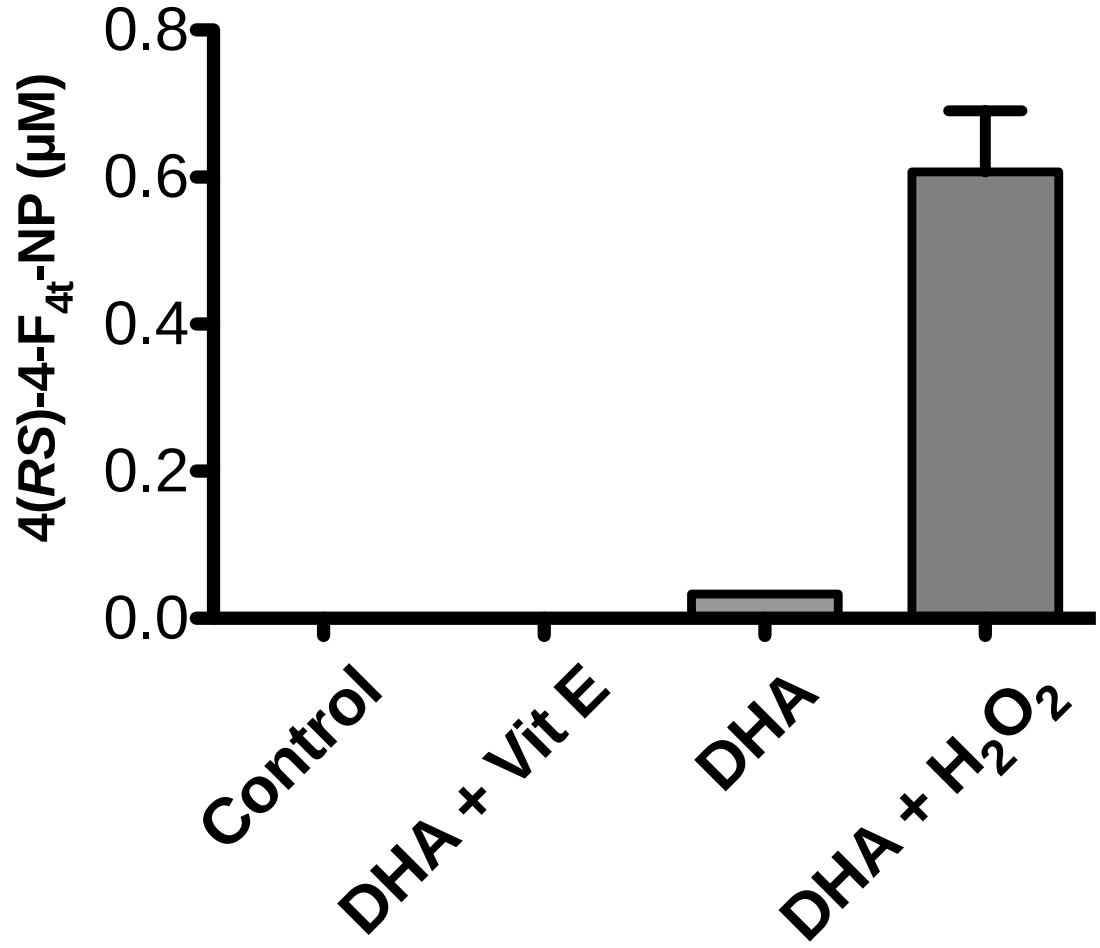
*** : p<0.001

*** : p<0.01

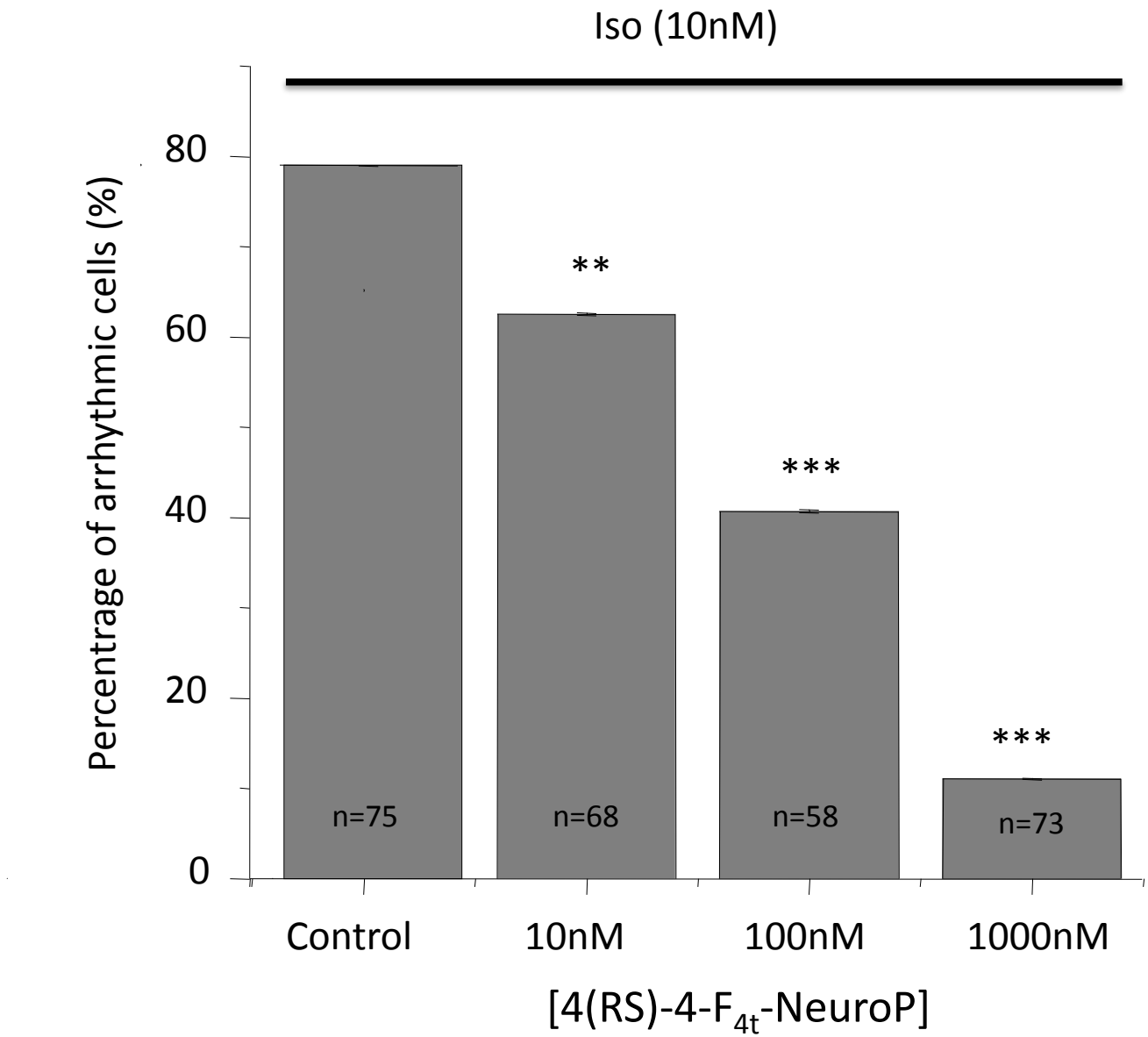
° : p<0.05 (PMI vs Sham)

Dosage des neuroprostanes

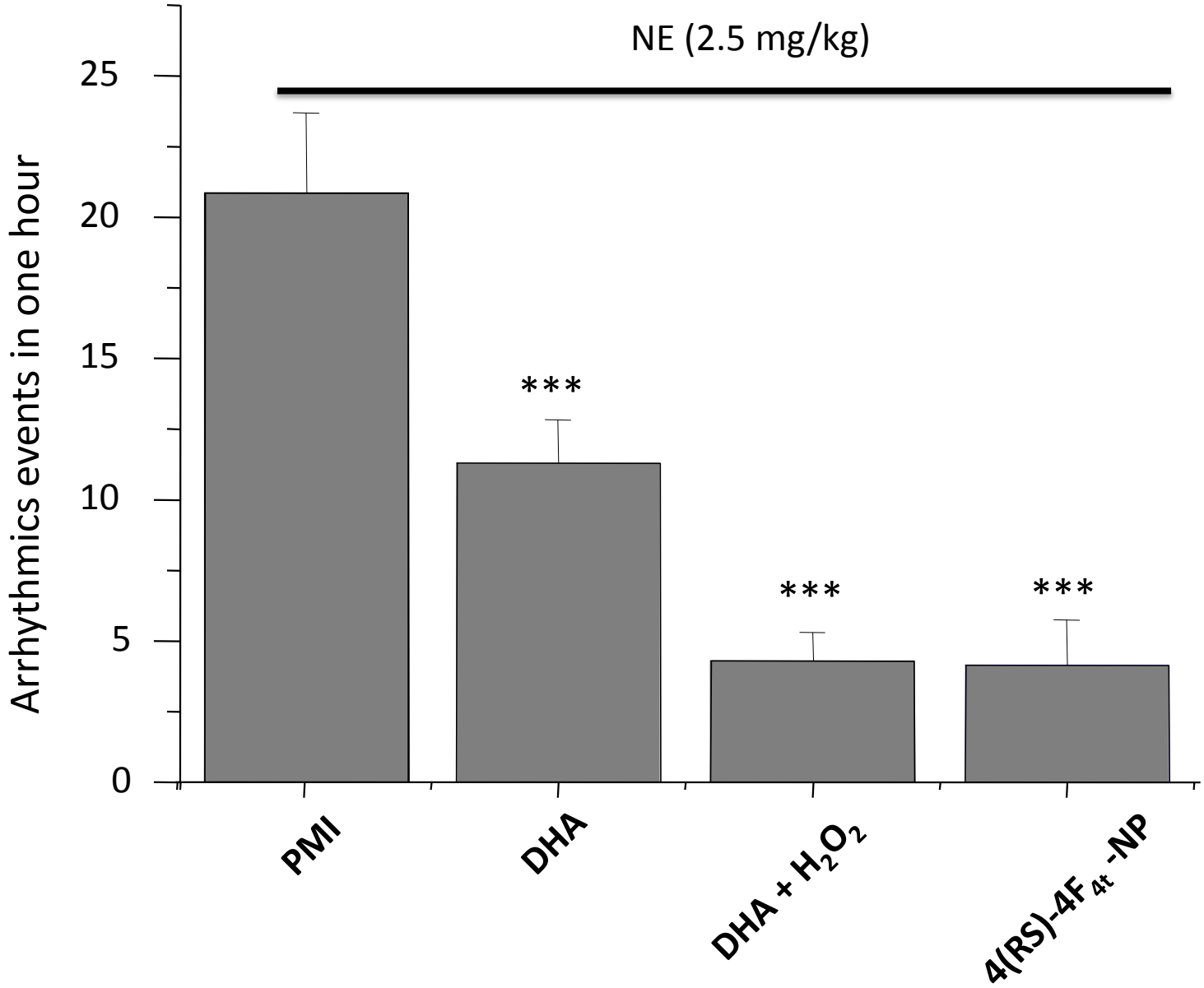
Une neuroprostane augmente corrélativement avec le déséquilibre de la balance oxydative : la 4(RS)-4-F_{4t}-NeuroP



Propriétés anti-arythmiques de la 4(RS)-4-F_{4t}-NeuroPs sur cellules isolées

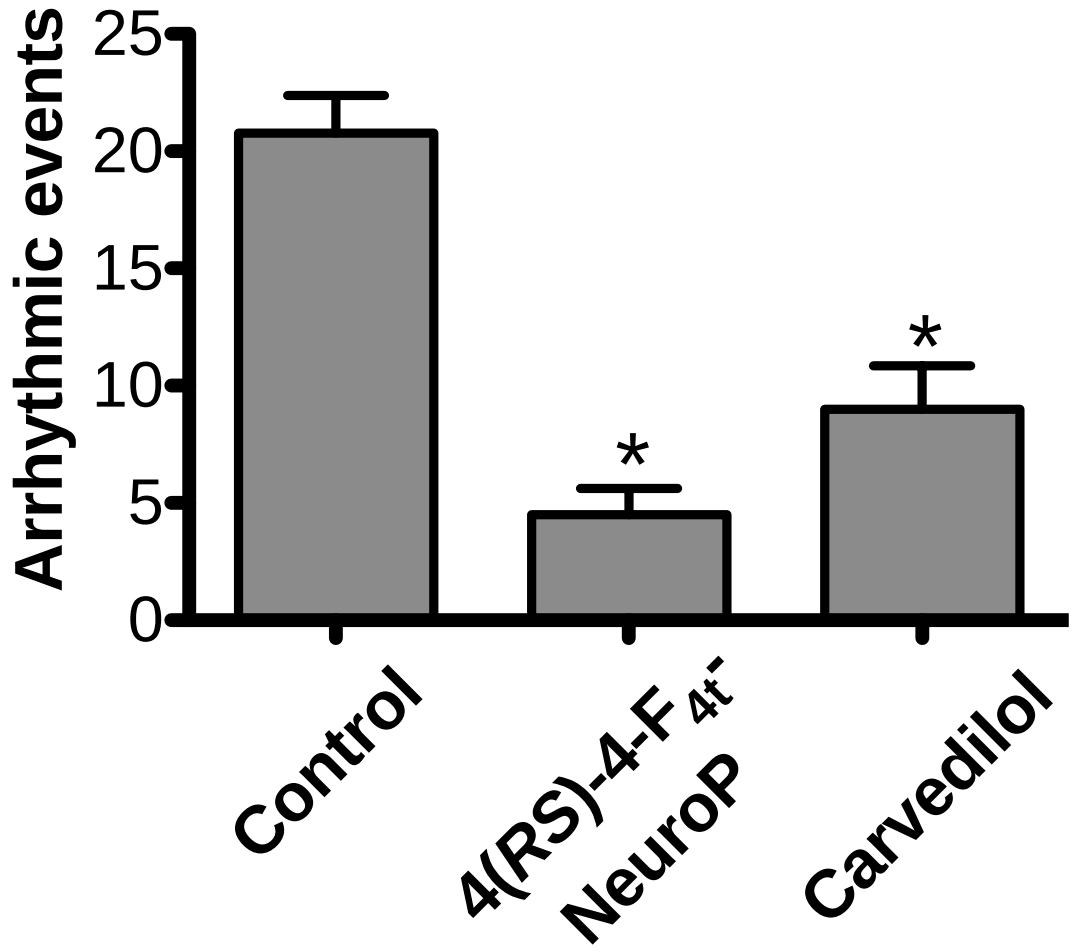


Propriétés anti-arythmiques de la 4(RS)-4-F_{4t}-NeuroPs chez l'animal éveillé

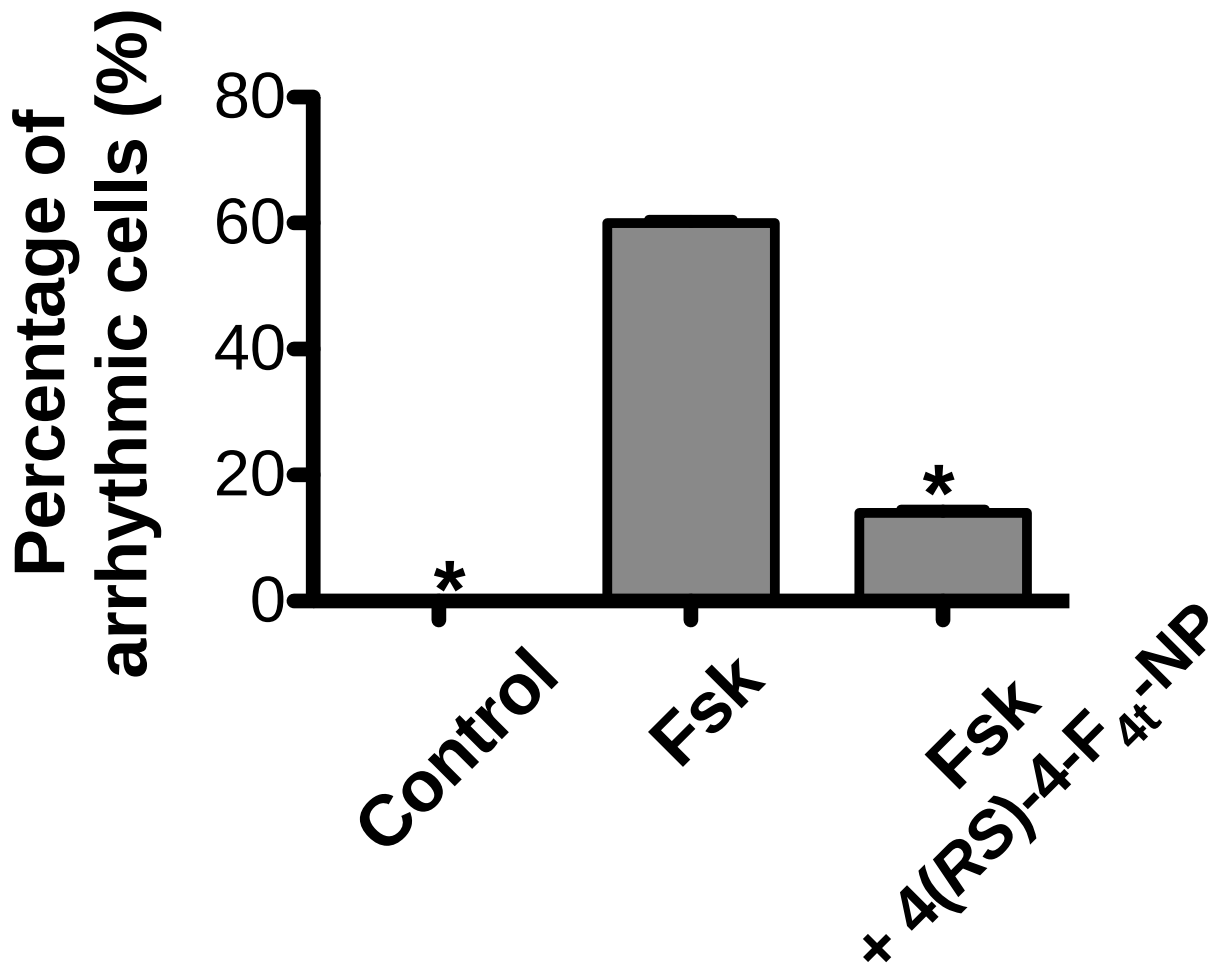


*** : P<0.001

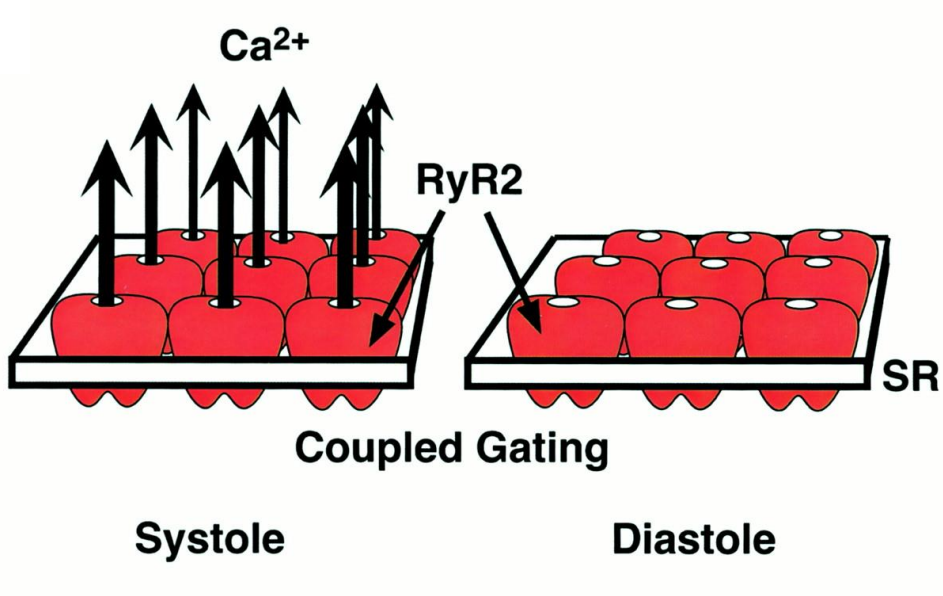
Comparaison avec un anti-arythmique de référence: le carvédilol



Mécanismes d'action : β-bloquant ?

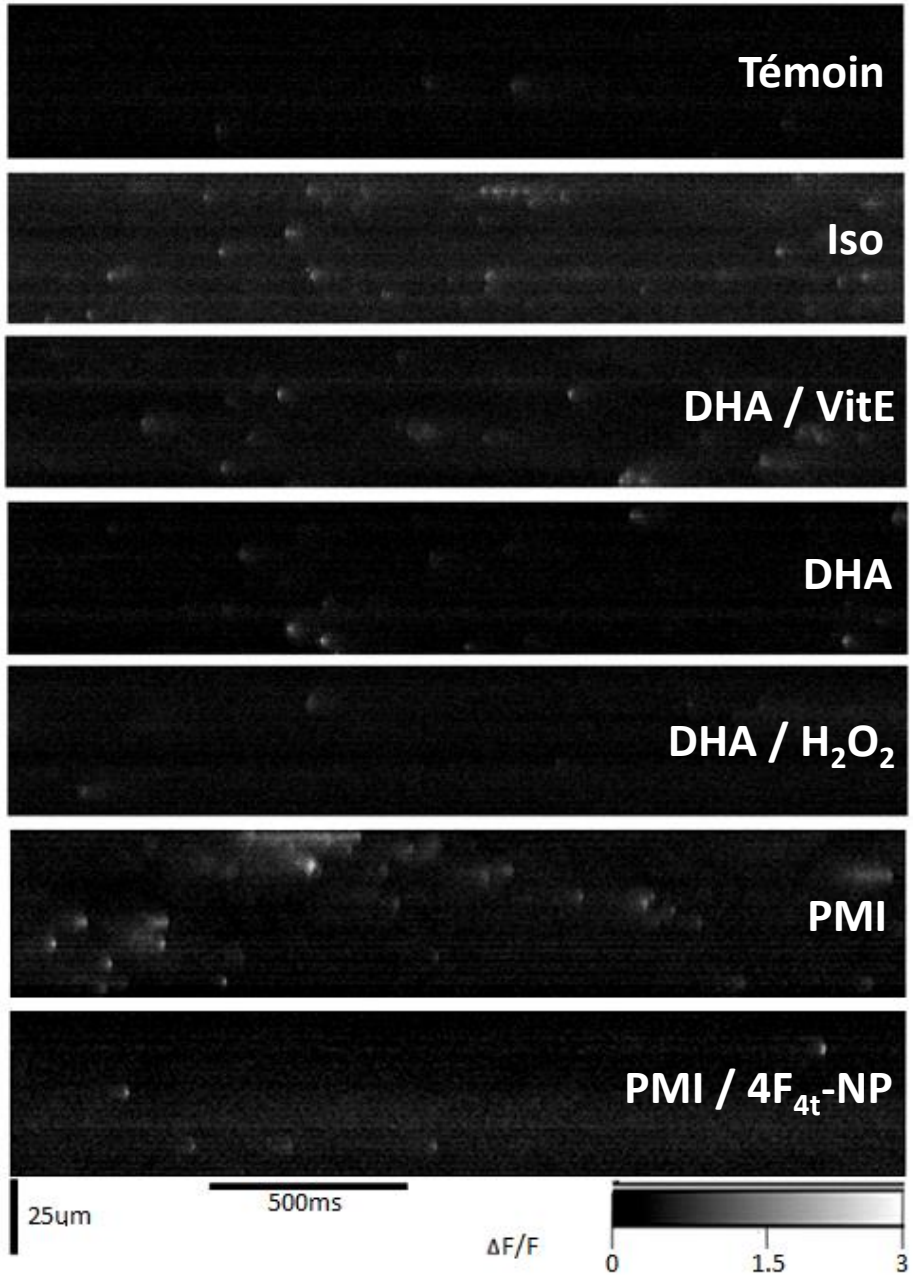


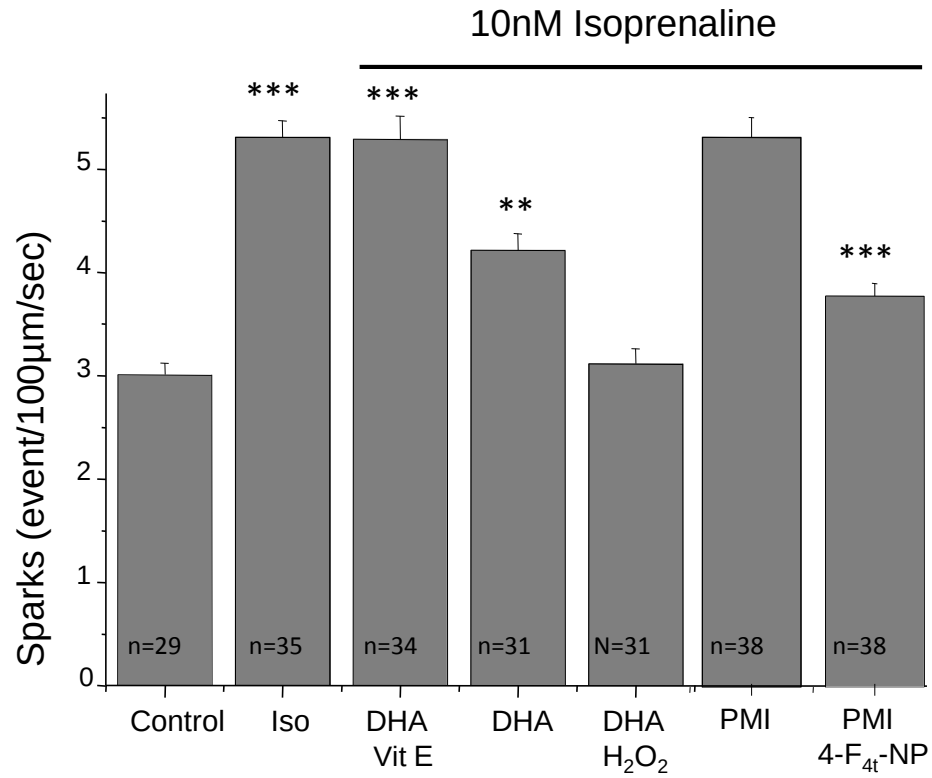
Représentation schématique du gating du RyR2



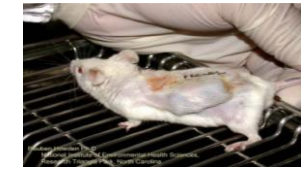
Situation normale

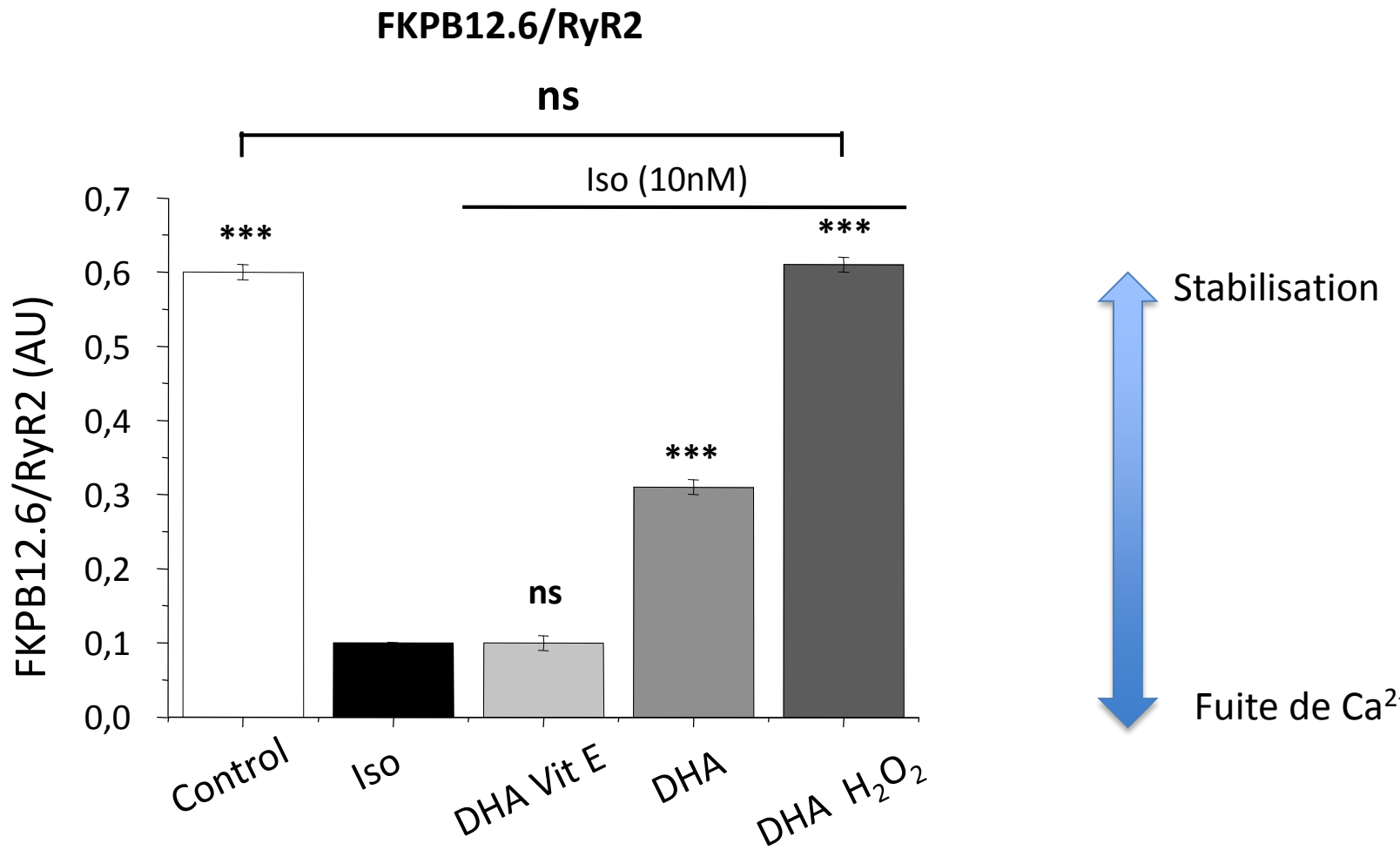
Microscopie confocale et sparks calciques





Biochimie : CO-IP





CONCLUSIONS

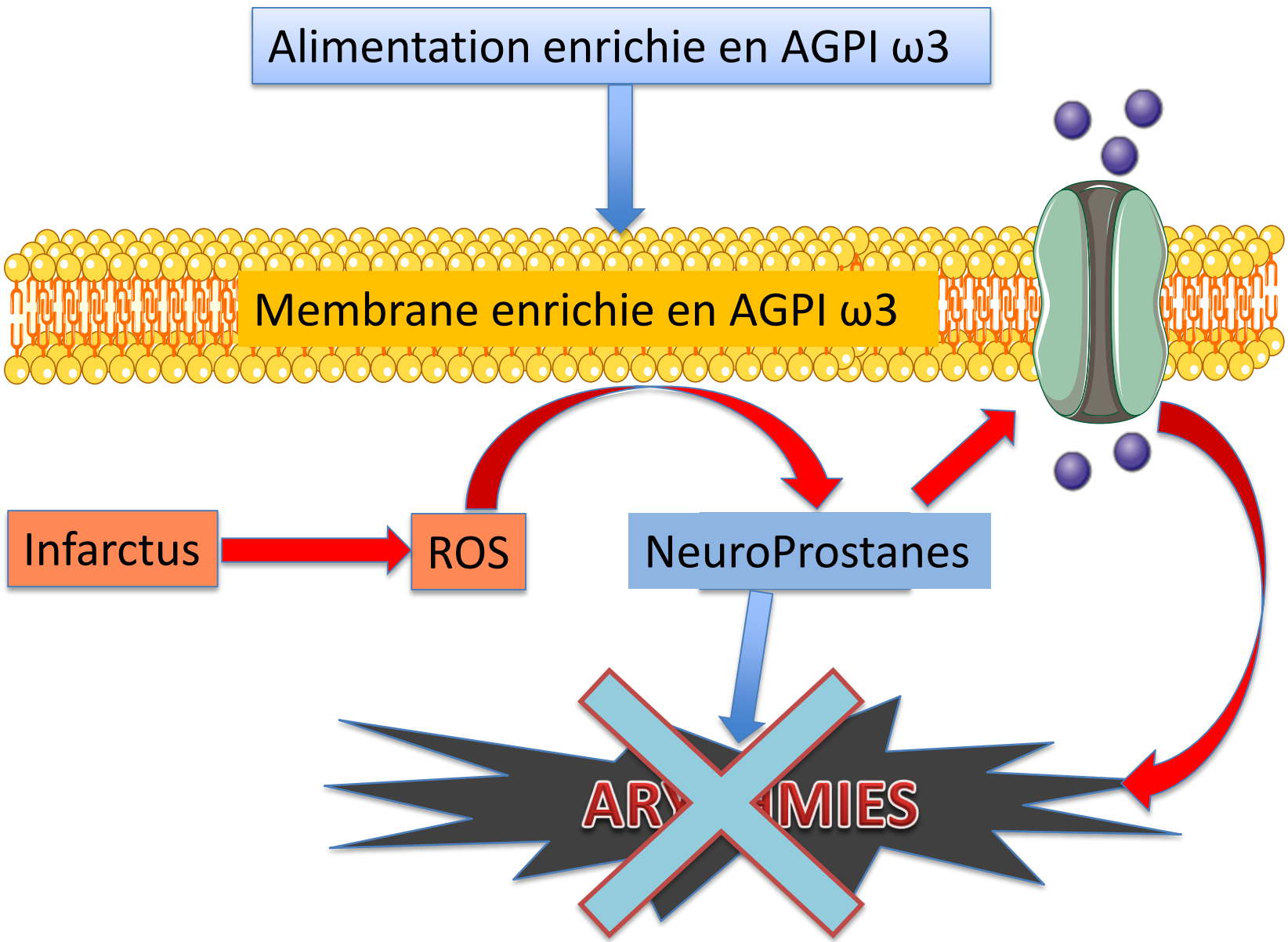
- Le DHA *per se* n'est pas anti-arythmique

- Le DHA doit être oxydé pour être anti-arythmique

- La 4(RS)-4-F_{4t}-NeuroP est un de ces métabolites oxydés

- La 4(RS)-4-F_{4t}-NeuroP stabilise le complexe RyR2/FKBP12.6 ce qui concoure à ses propriétés anti-arythmiques:

CONCLUSIONS



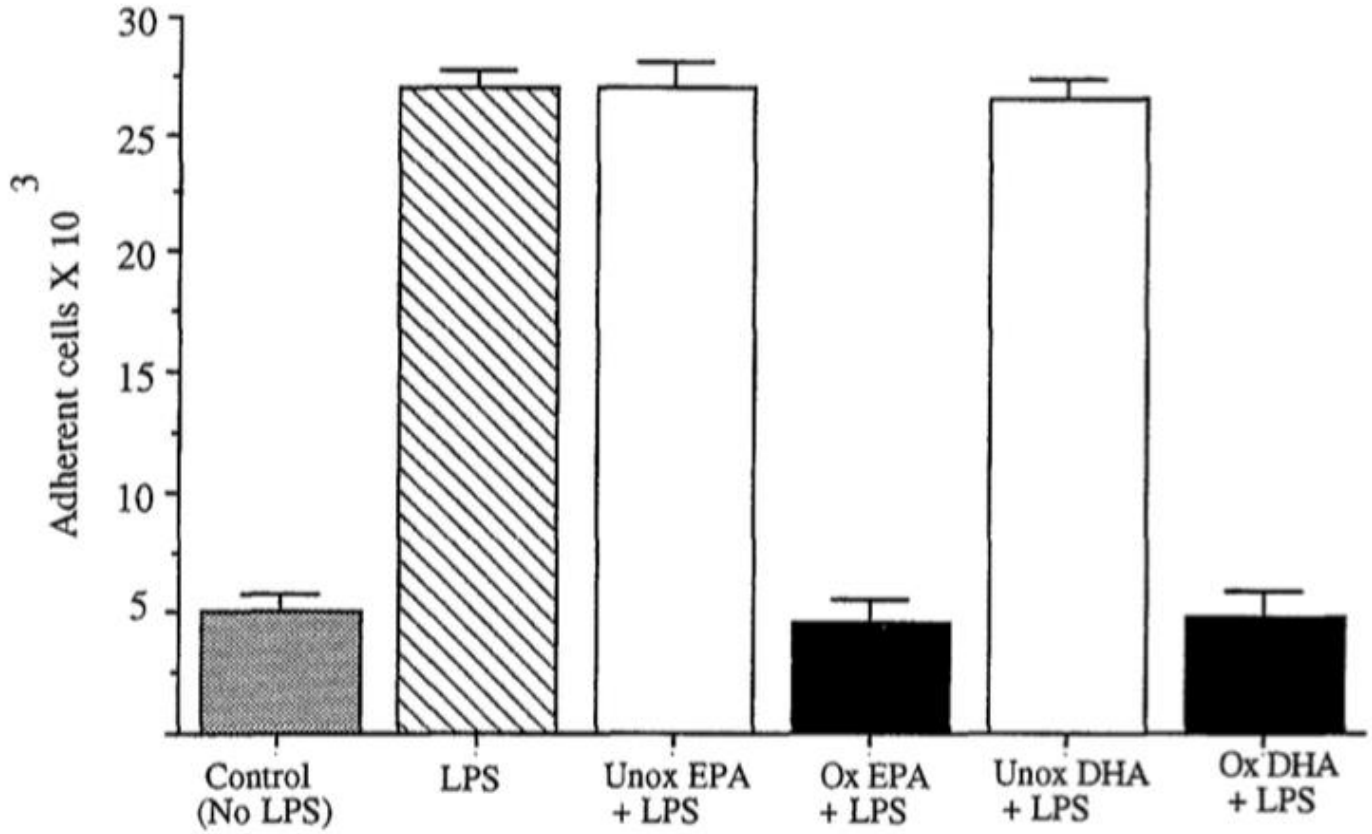
EXISTE T-IL D'AUTRES EXEMPLES DE PHÉNOMÈNES PHYSIOLOGIQUES NÉCESSITANT L'OXYDATION DES AGPI W3 ?

PROPRIÉTÉS ANTI-INFLAMMATOIRES DES AGPI W3

Inhibition of phagocyte-endothelium interactions by oxidized fatty acids: A natural anti-inflammatory mechanism?

SANJEEV SETHI, ALLISON Y. EASTMAN, and JOHN W. EATON

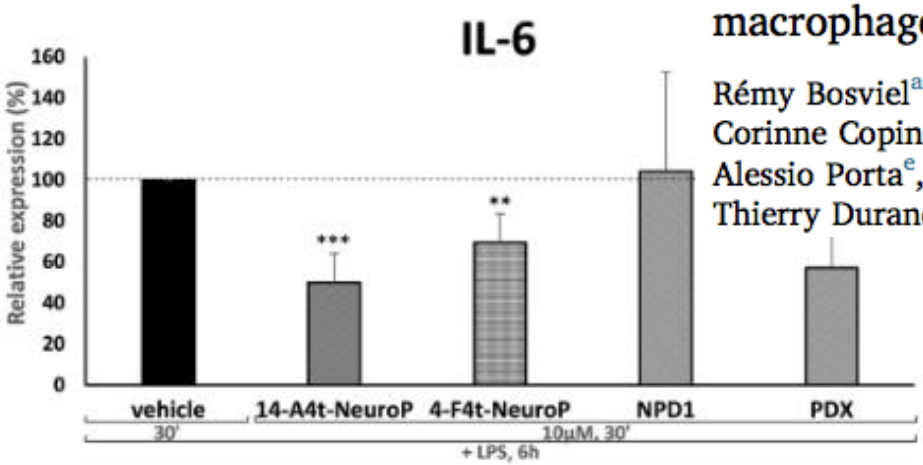
ALBANY, NEW YORK

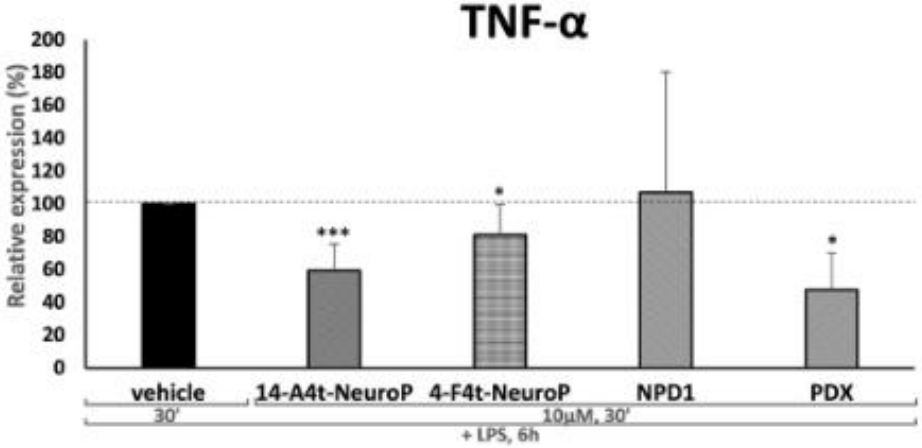


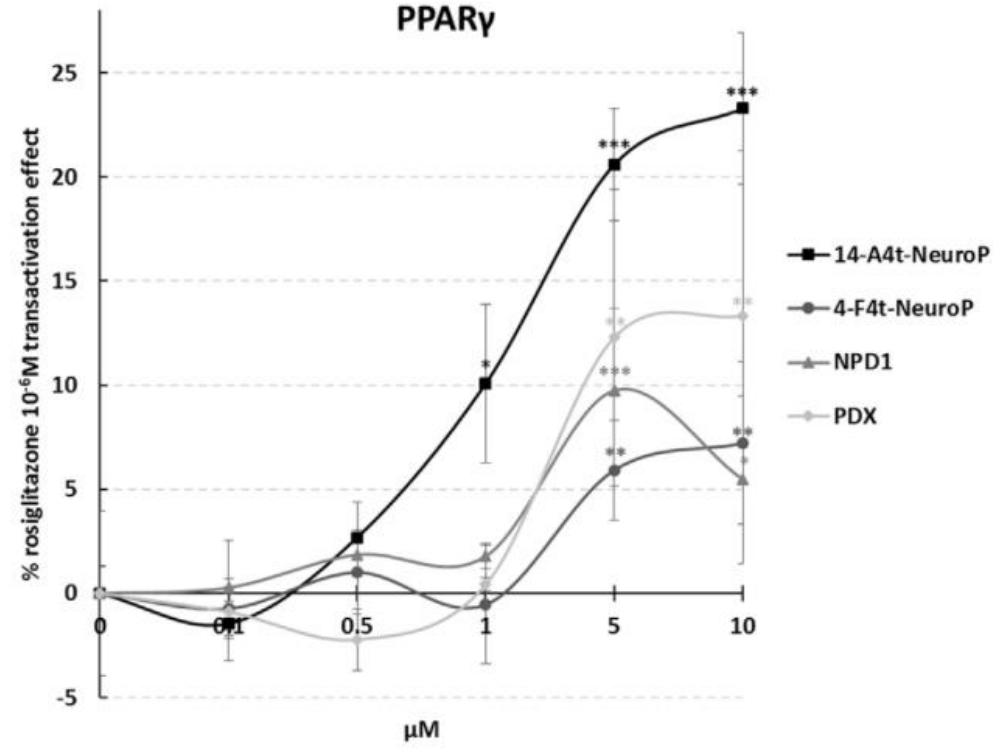
J Lab Clin Med, 1996

DHA-derived oxylipins, neuroprostanes and protectins, differentially and dose-dependently modulate the inflammatory response in human macrophages: Putative mechanisms through PPAR activation

Rémy Bosviel[a,b], Laurie Joumard-Cubizolles[a,b], Giulia Chinetti-Gbaguidi[c,d], Dominique Bayle[a,b], Corinne Copin[c], Nathalie Hennuyer[c], Isabelle Duplan[c], Bart Staels[c], Giuseppe Zanoni[e], Alessio Porta[e], Laurence Balas[f], Jean-Marie Galano[f], Camille Oger[f], Andrzej Mazur[a,b], Thierry Durand[f], Cécile Gladine[a,b,*]







MÉCANISME D'ACTION ?

FRBM, 2017

LE VIEILLISSEMENT EST DU AU SO: UN DOGME REVISITÉ

Lifespan Control by Redox-Dependent Recruitment of Chaperones to Misfolded Proteins

Sarah Hanzén,[1,4] Katarina Vielfort,[1,4] Junsheng Yang,[1] Friederike Roger,[1] Veronica Andersson,[1] Sara Zamarbide-Forés,[1] Rebecca Andersson,[1,4] Lisa Malm,[1] Gael Palais,[2] Benoît Biteau,[2,3] Beidong Liu,[1] Michel B. Toledano,[2] Mikael Molin,[1,*] and Thomas Nyström[4,*] Cell 2016

The data reveal a conceptually new role for H_2O_2 signaling in proteostasis and lifespan control and shed new light on the selective benefits endowed to eukaryotic peroxiredoxins by their reversible hyperoxidation.

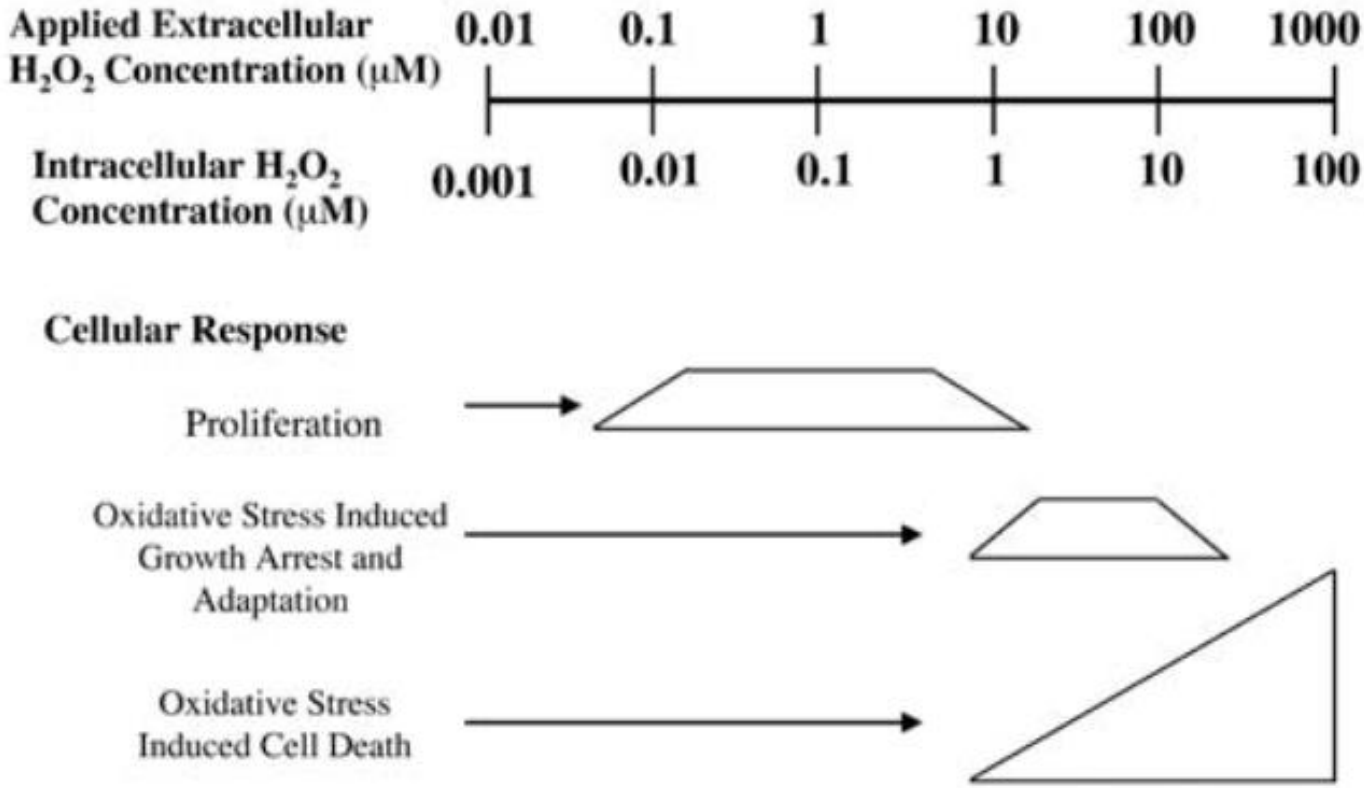
AUTRES EFFETS PHYSIOLOGIQUE DU STRESS OXYDANT

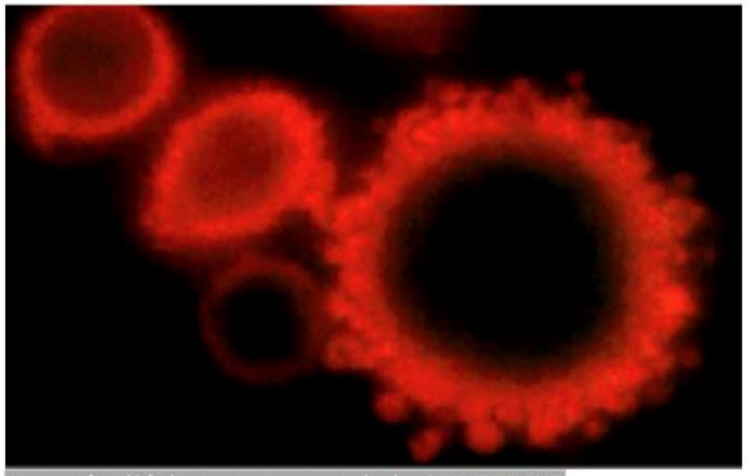
- Signalisation béta-adrénergique dans le cœur …
- Fermeture du ductus arteriosus à la naissance …
- …

UN CONCEPT QUI A RENCONTRÉ PEU D'ÉCHO:

Hydrogen Peroxide: A Signaling Messenger

Yang & Stone, Antioxidants & Redox signaling, 2006



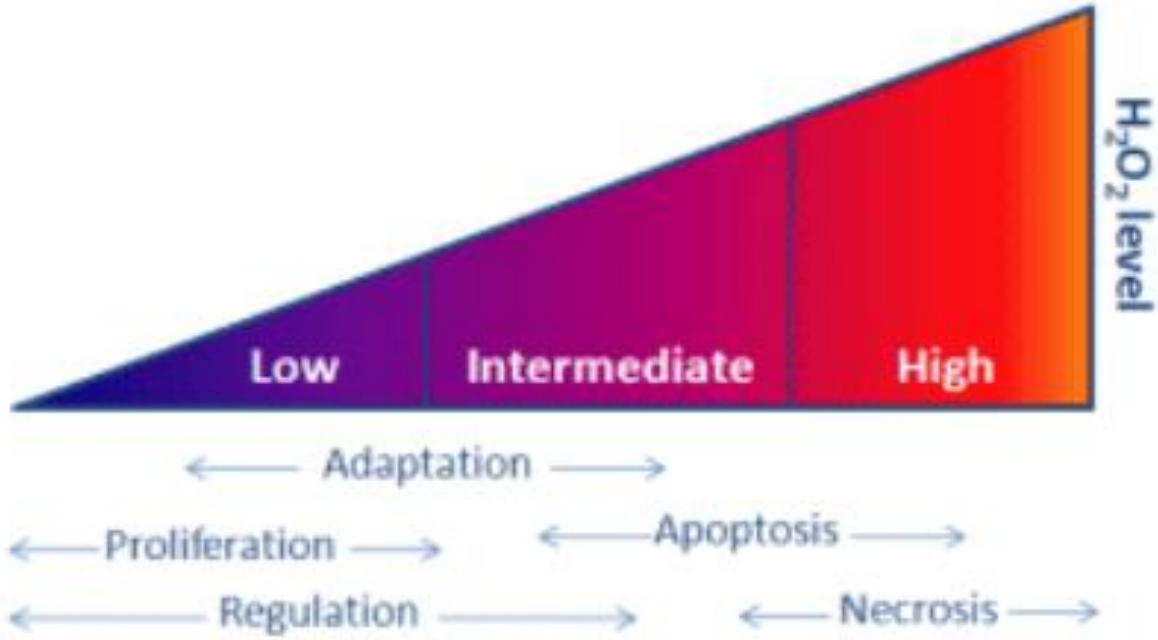


Journée d'échanges – axe 4 de la SFR TERSYS

Stress oxydant
et désordres biologiques :
Mythe ou réalité ?

Toute chose est un toxique et rien n'existe sans toxicité, seul le dosage fait qu'une chose n'est pas un poison.

Quid de no ROS ?



http://redox.fc.ul.pt/research.html

EQUIPE PROJET A L'ORIGINE DE CE TRAVAIL

Jérôme ROY (doctorant)

Olivia MERCIER-TOUZET (post-doc)

Jérôme THIREAU (CR CNRS)

Marie DEMION (maître de conférences UM

Edith PINOT (Post-doc)

Camille OGER (maître de conférences UM)

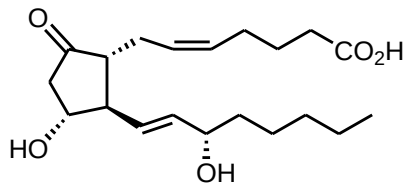
Jean-Marie GALANO (CR CNRS)

Thierry DURAND (DR CNRS)

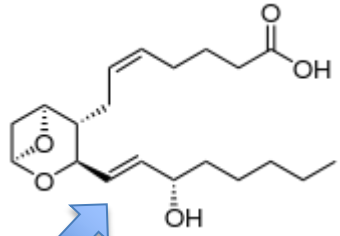

FONDATION
RECHERCHE
MÉDICALE
MERCI DE VOTRE ATTENTION ...

Oxydation de l'acide arachidonique (C20:4w-6)

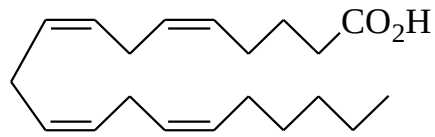
Prostaglandines (PGs)



Tromboxane A_2



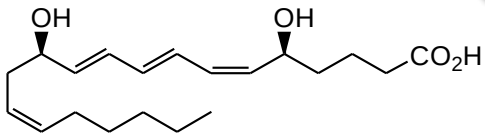
COX-1 COX-2



AA

LOX

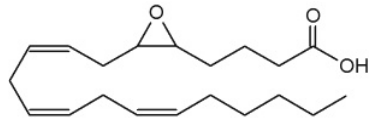
Leukotrienes (LTs)



CO

Cytochrome P_{450}

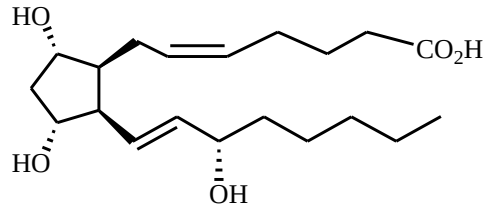
EpoxyEicosaTrienoic acids (EETs)



Voies Enzymatiques

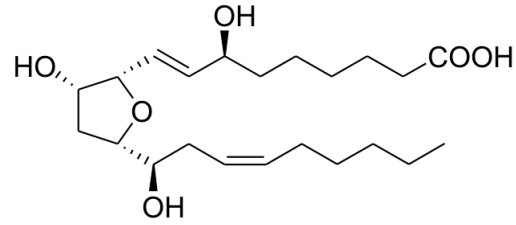
ROS

IsoProstanes (IsoPs)



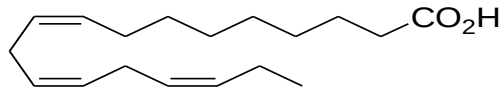
ROS

IsoFuranes (IsoFs)

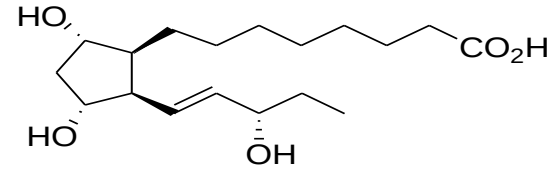


Voies Radicalaires non-enzymatiques

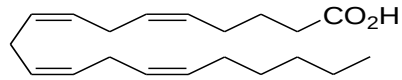
Isoprostanes – classement par précurseurs



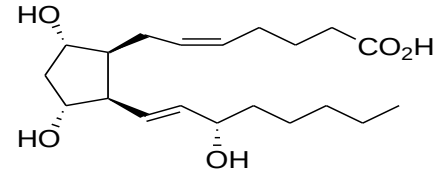
Acide α-linolénique (ALA)



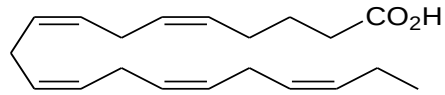
F1-Phytoprostanes



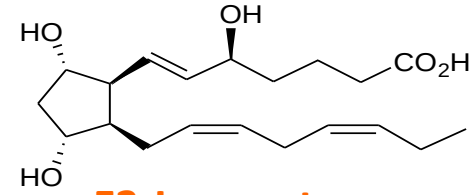
Acide arachidonique (AA)



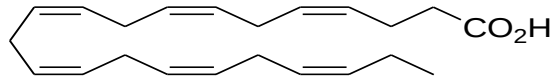
F2-Isoprostanes



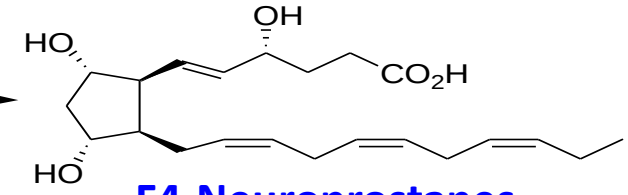
Acide Eicosapentaenoique (EPA)



F3-Isoprostanes

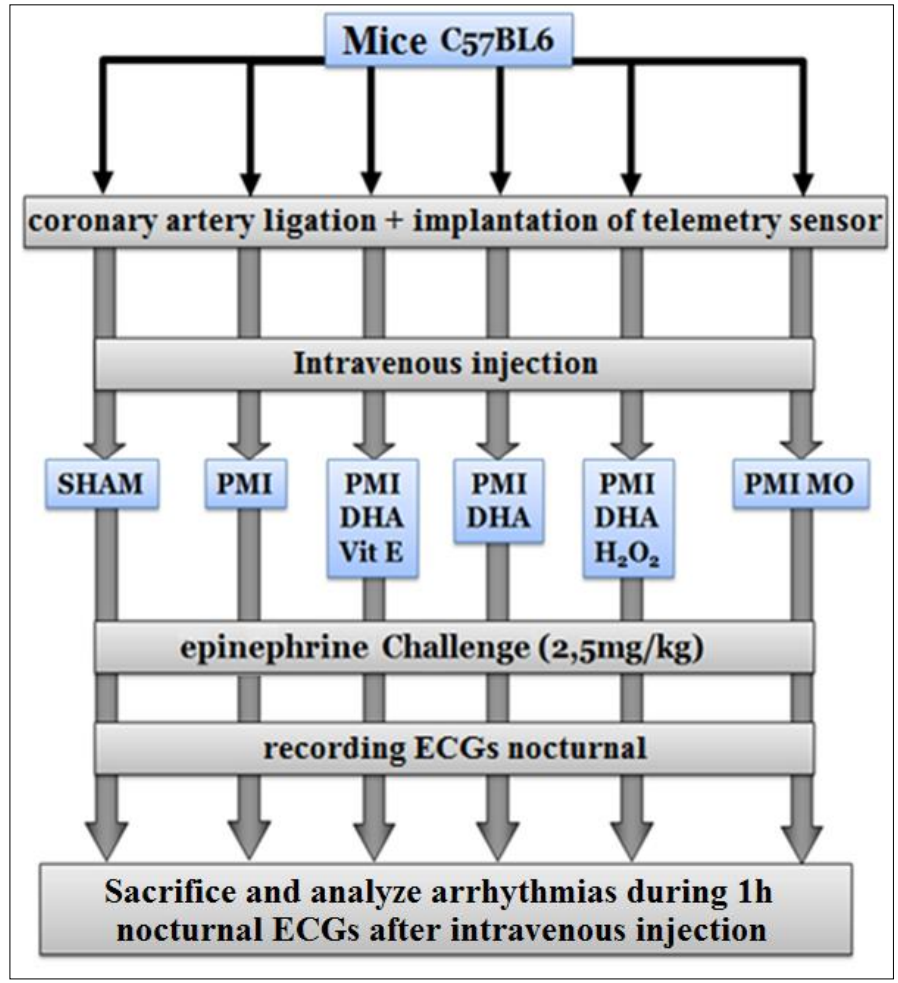


Acide Docosahexaenoique (DHA)

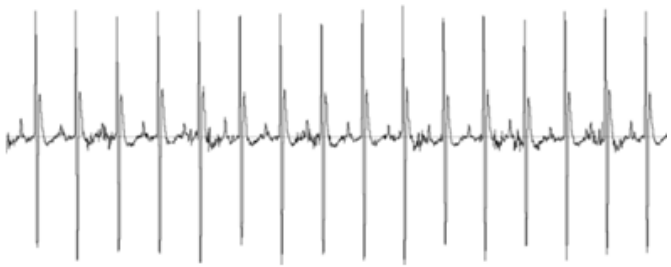


F4-Neuroprostanes

Protocoles *In Vivo*



SHAM



PMI