JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

Physiologisches Institut

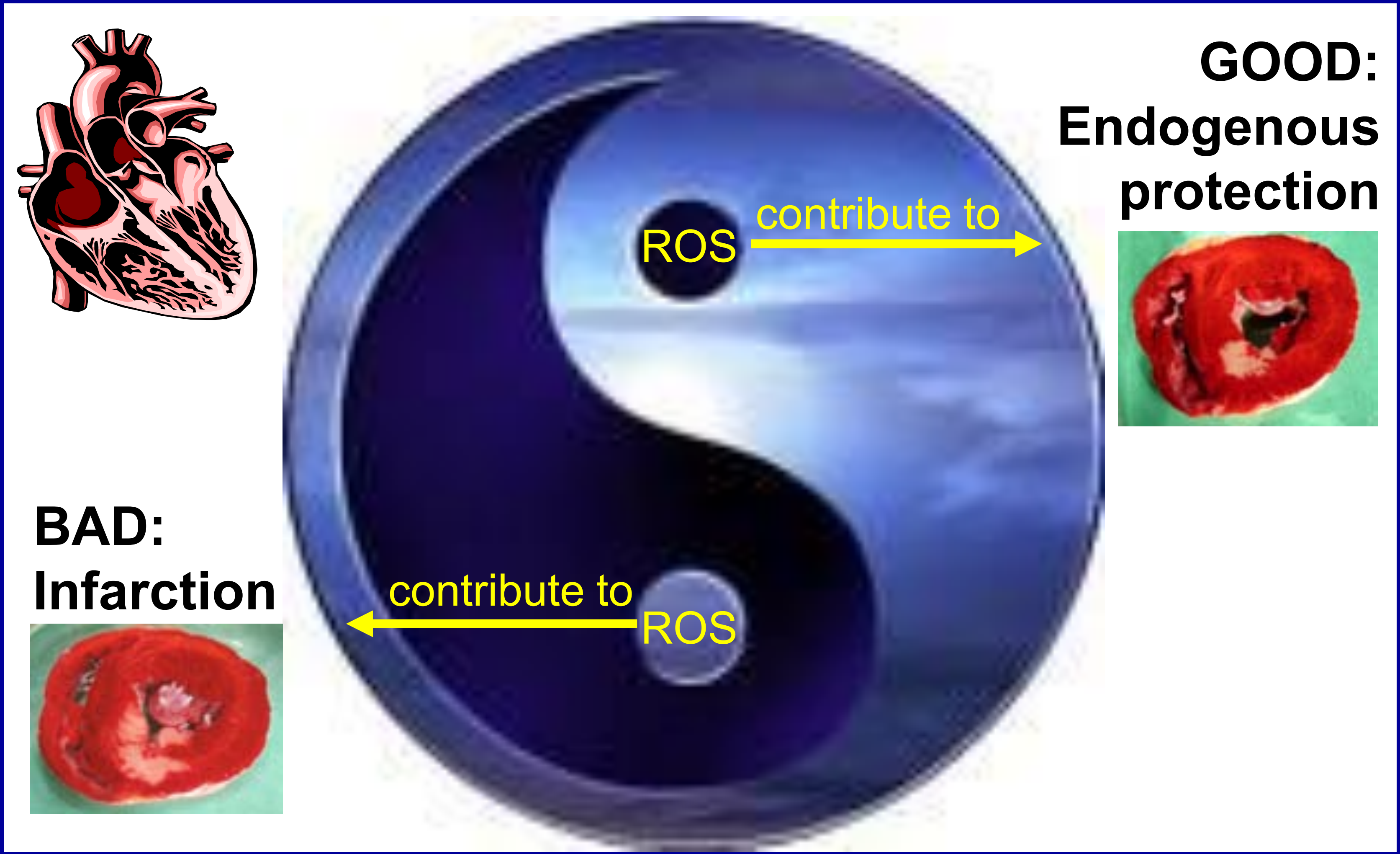
PROMISE IRTG GIESSEN BARCELONA

UGCVR UNIVERSITY OF GIESSEN CARDIOVASCULAR RESEARCH CENTER

Oxidant stress: Consequences for ischemia/reperfusion

PD Dr. Kerstin Boengler

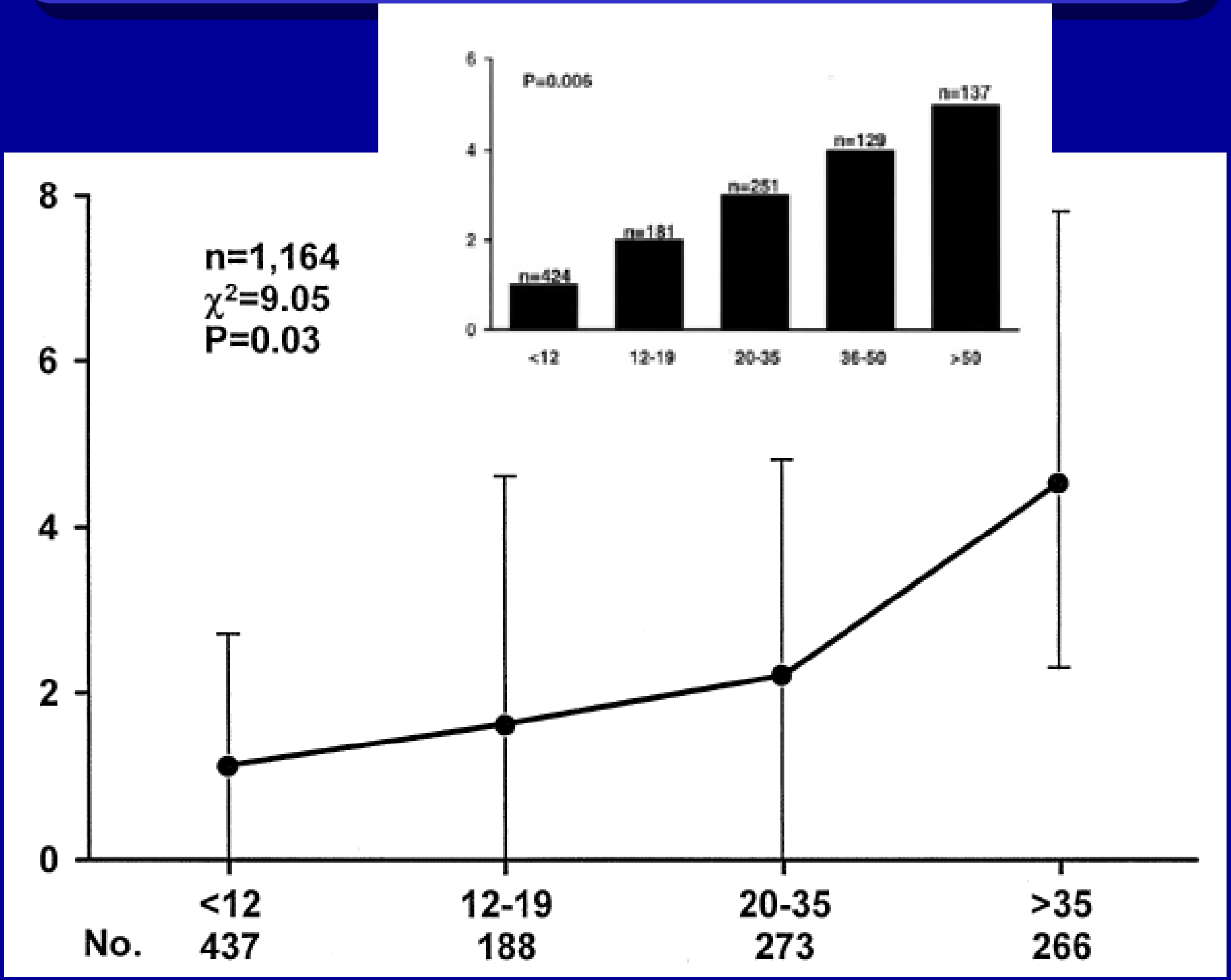
Reactive oxygen species (ROS) in ischemia/reperfusion injury (IRI)



Patient

Myocardial infarction and prognosis

6 Month mortality (%)

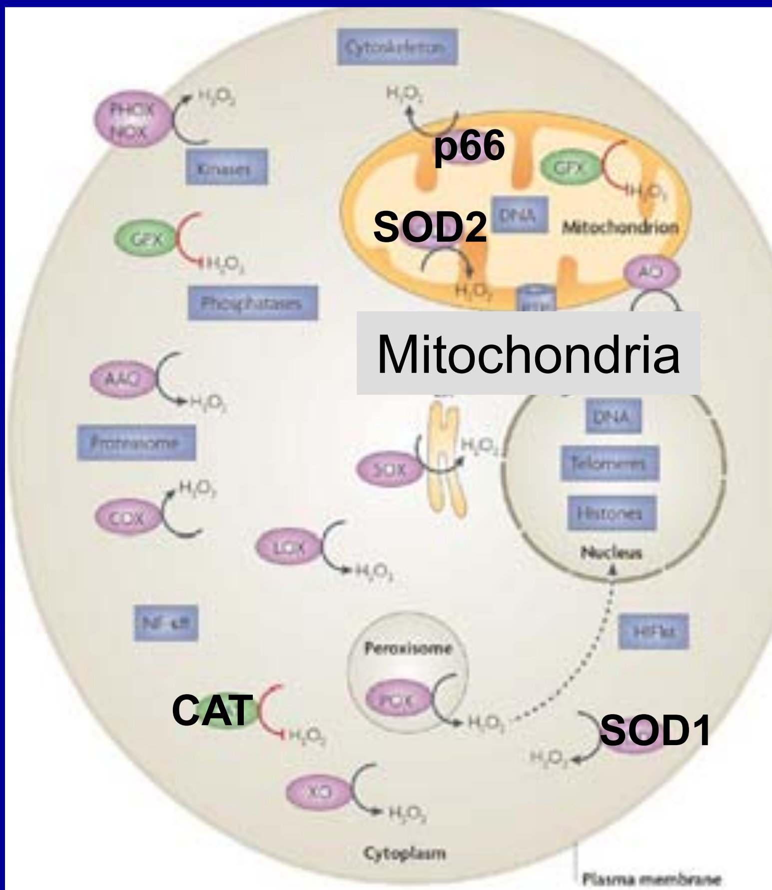


Infarct size (% area at risk)

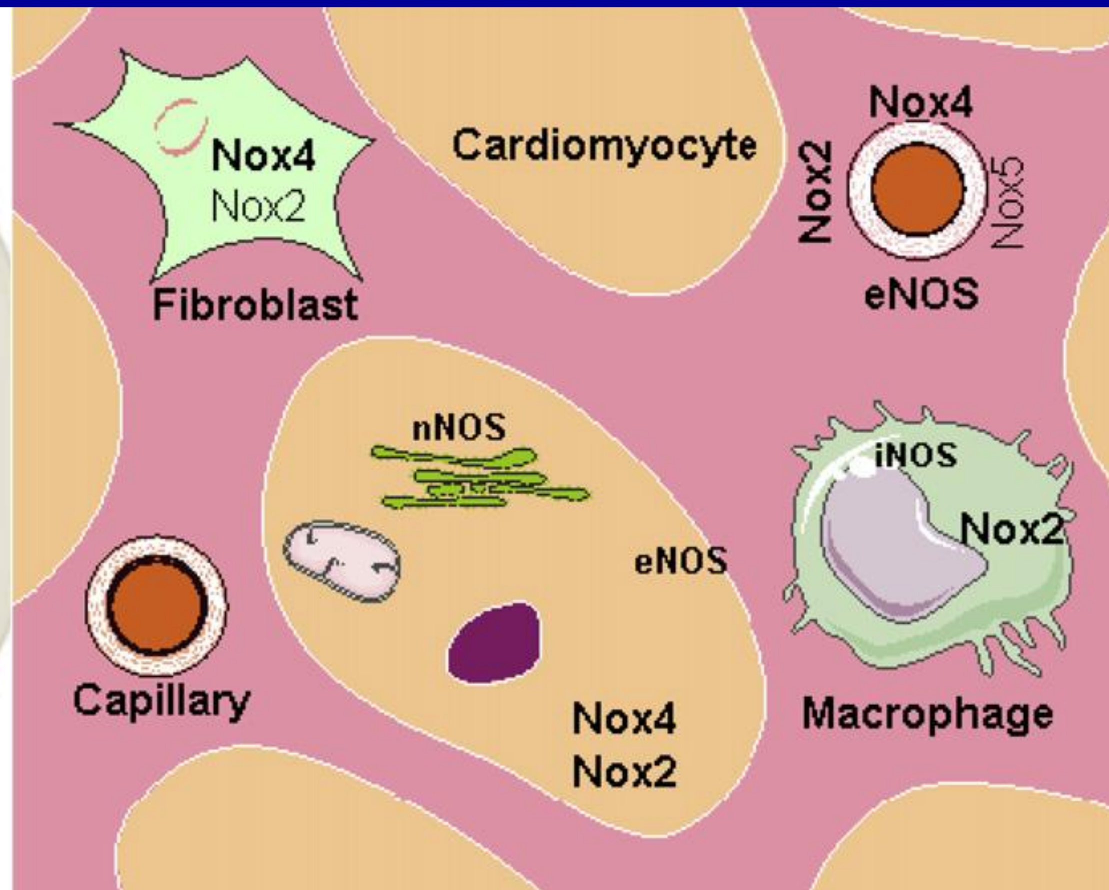
Burns et al., J Am Coll Cardiol 39:30–36, 2002

Potential sources of ROS

Cardiomyocytes



Other cell types

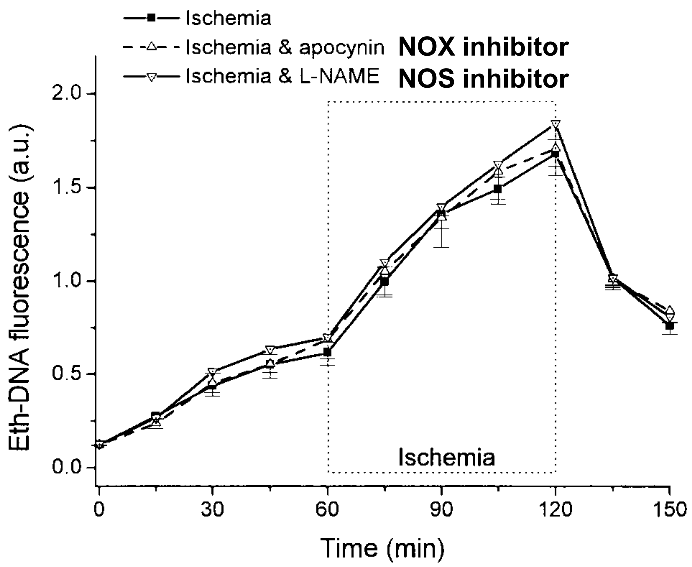


Giorgio et al., Nat Rev Mol Cell Biol, 8:722-728, 2007; Akki et al., J Mol Cell Cardiol 47: 15–22, 2009

Rat cardiomyocytes

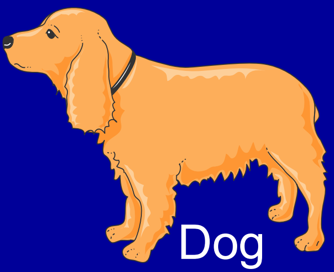
Formation of ROS during ischemia

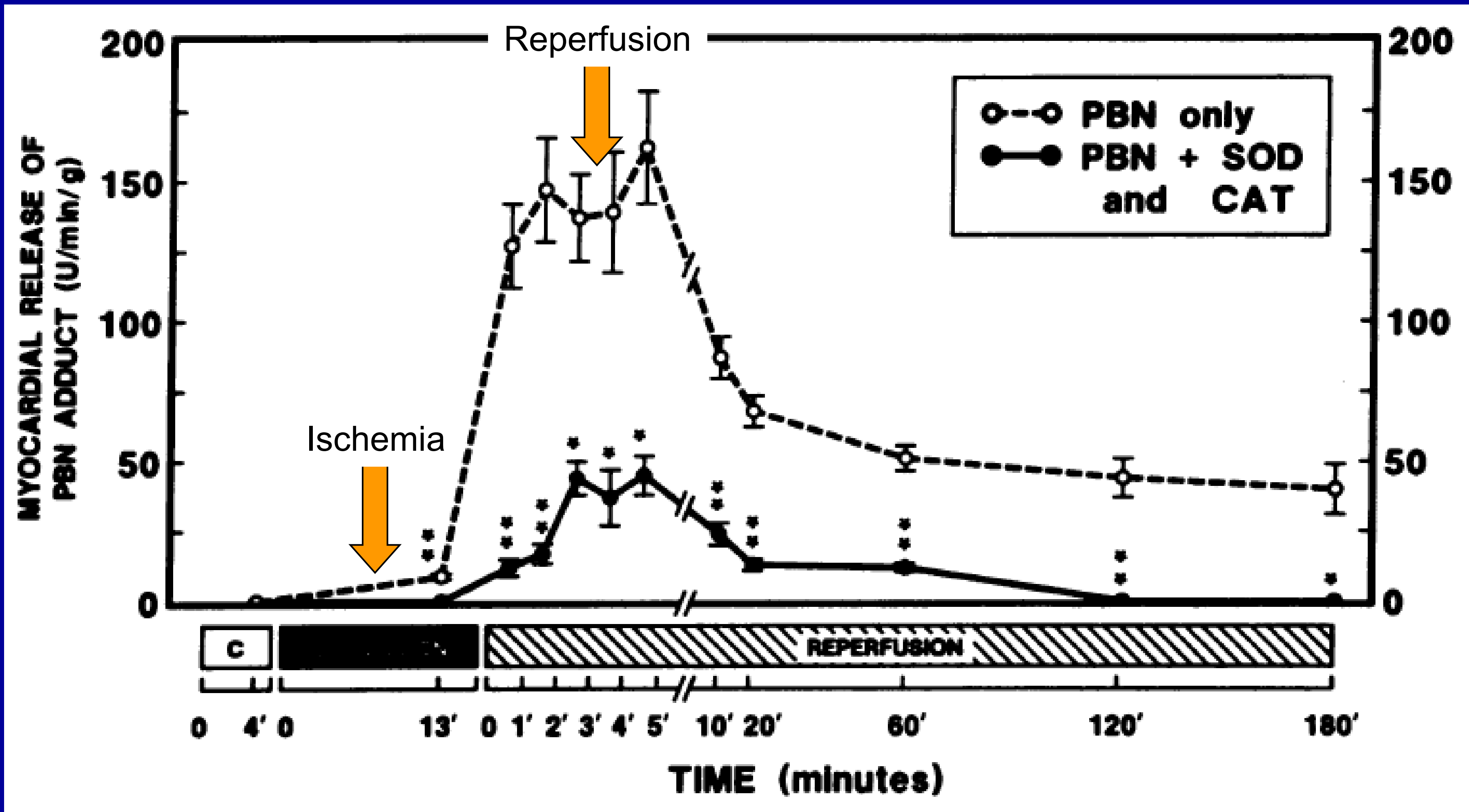
ROS formation during (low-flow) ischemia appears to be primarily caused by mitochondria!



Becker et al., Am J Physiol 277 Heart Circ Physiol 46: H2240–H2246, 1999

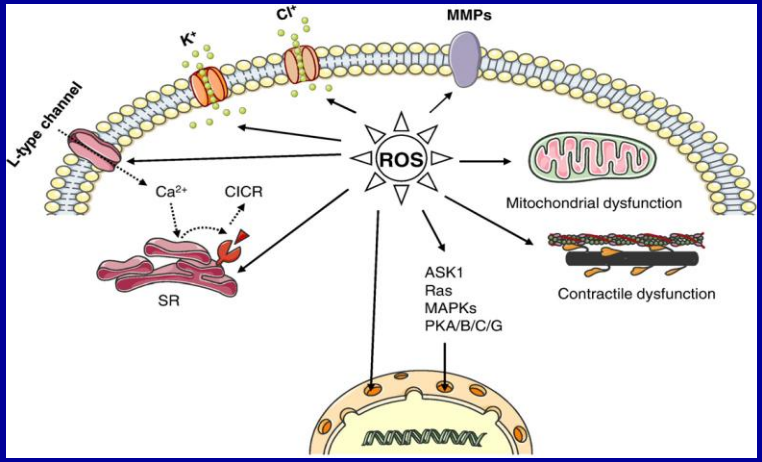
Formation of ROS during ischemia/reperfusion





Bolli et al., Proc Natl Acad Sci USA 86: 4695-4699, 1989

ROS during IRI



contribute to cellular damage

contribute to cellular protection

Function

Morphology

Function

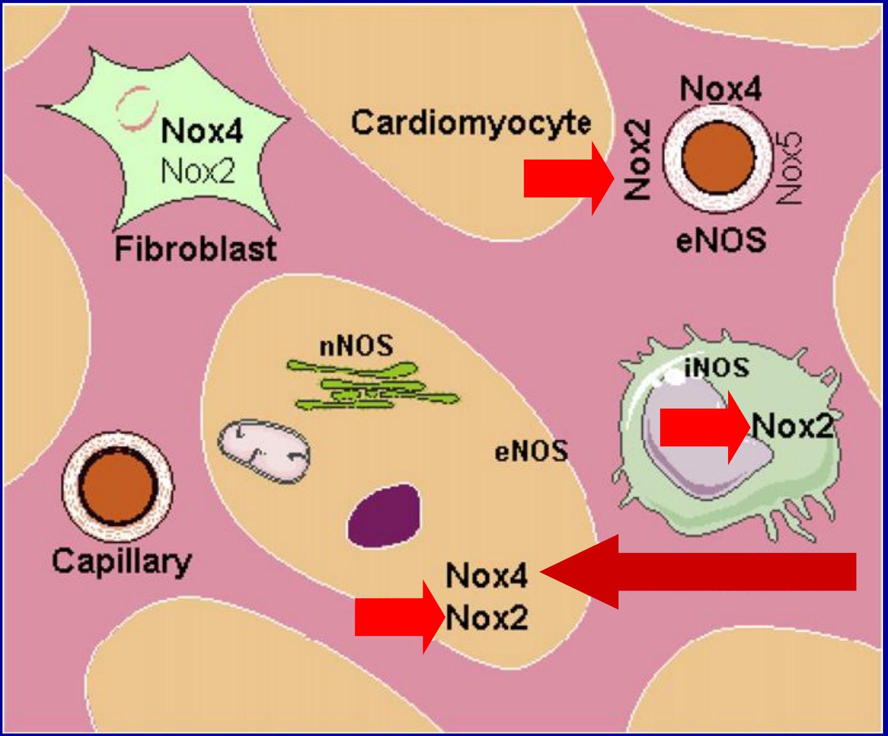
Morphology

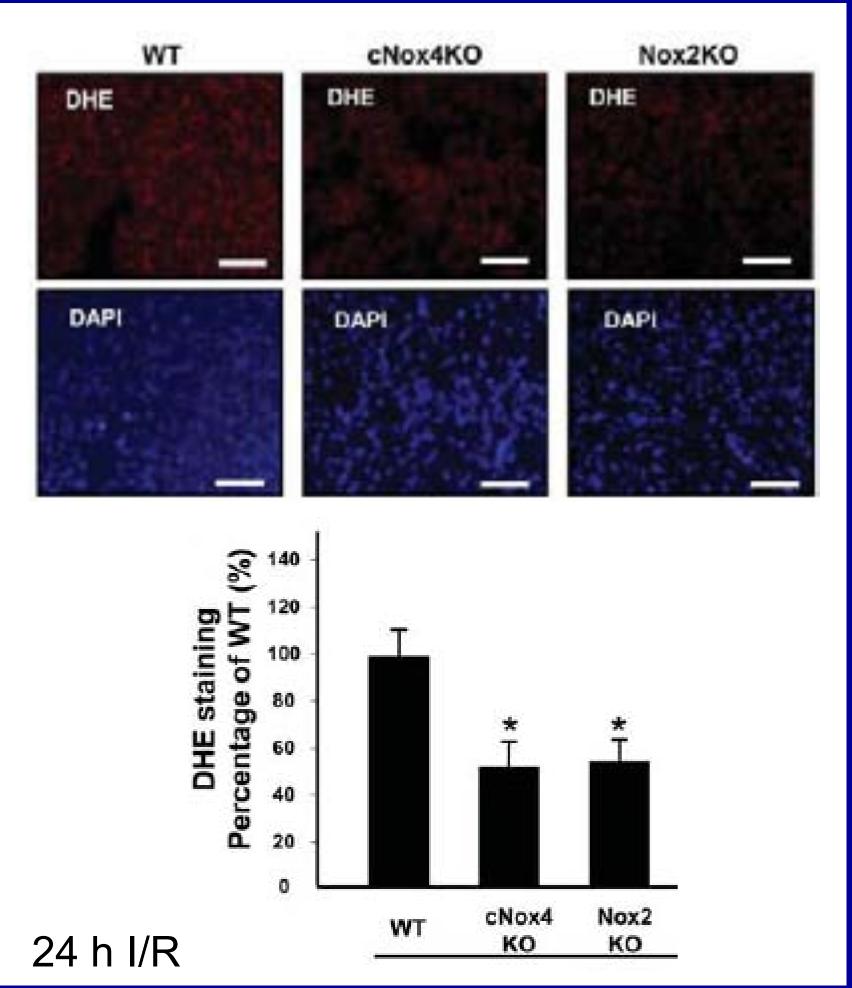
(Postischemic Reperfusion, Heart Failure)

(Ischemia/Reperfusion Injury)

Mice

NOX2, NOX4 and irreversible IRI

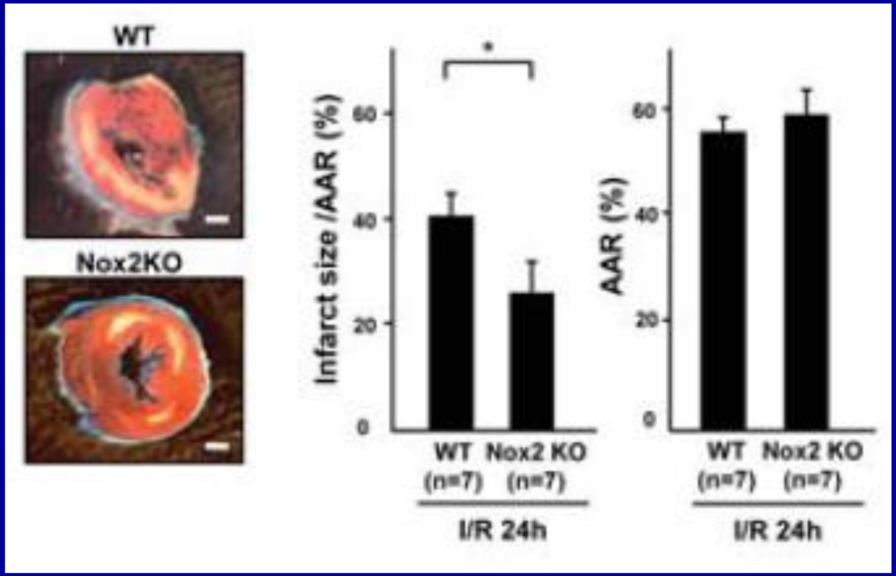




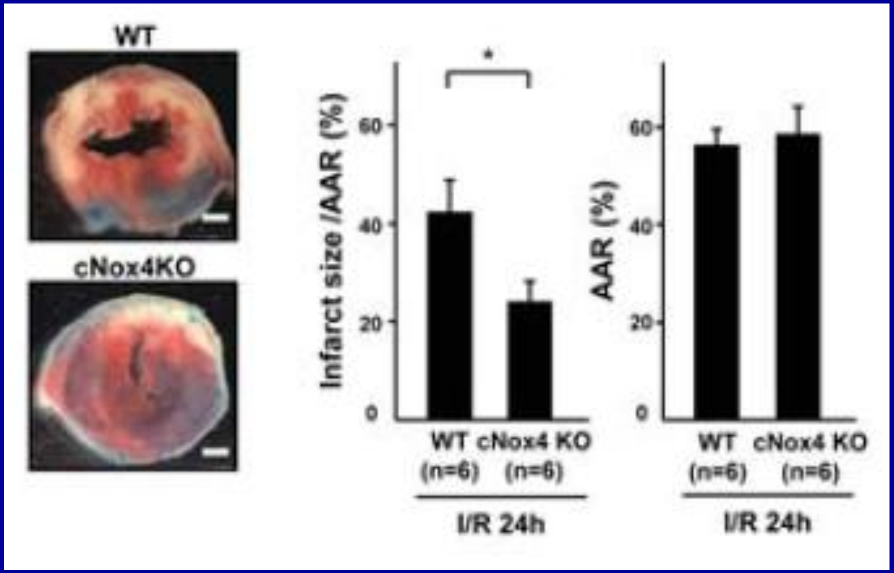
Matsushima, Circ Res 2013

NOX2, NOX4 and irreversible IRI

systemic NOX2 KO mice



cardiac NOX4 KO mice

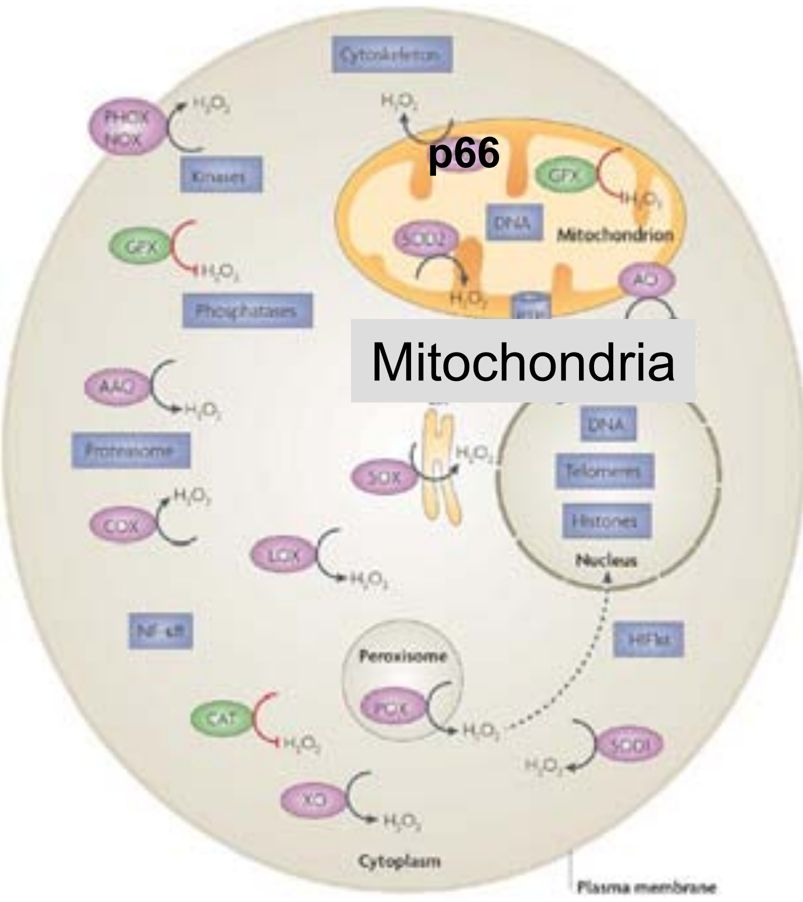


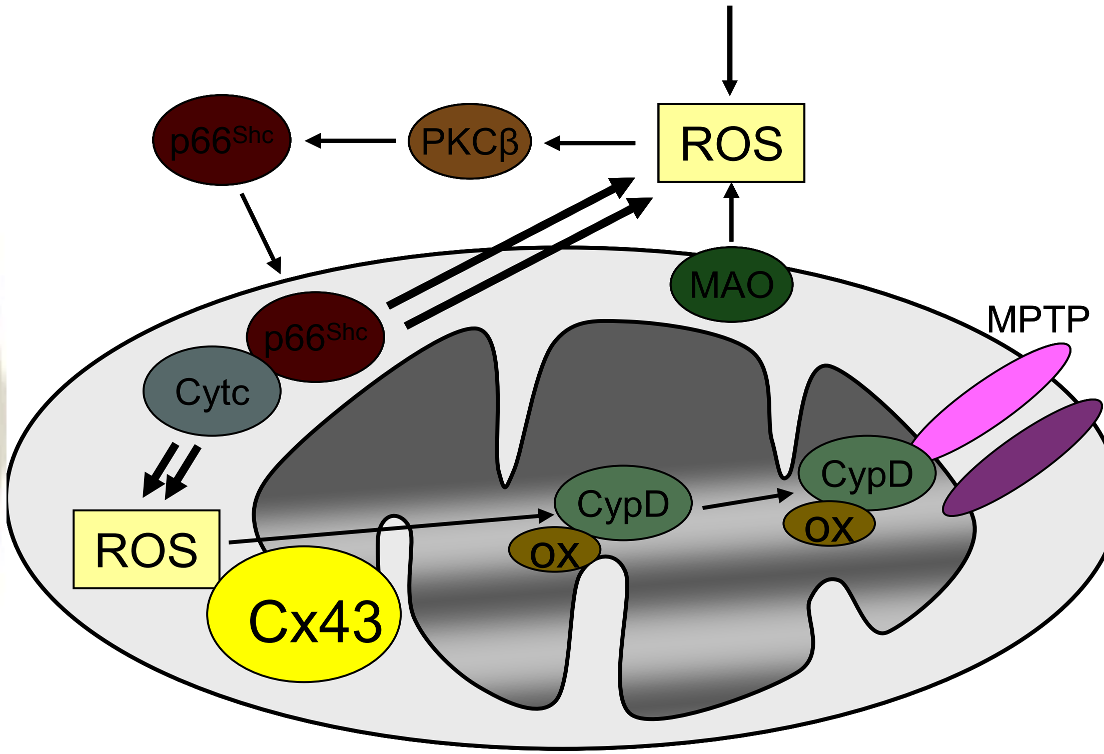
Matsushima, Circ Res 2013

Mice

Mitochondria-derived ROS

Cardiomyocytes

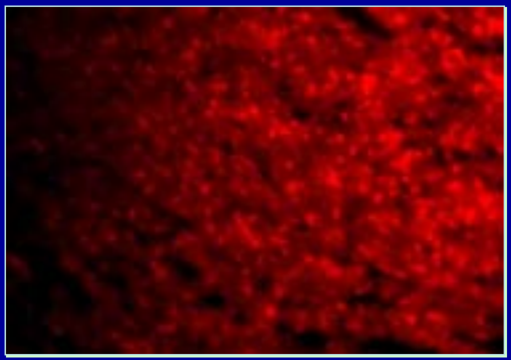




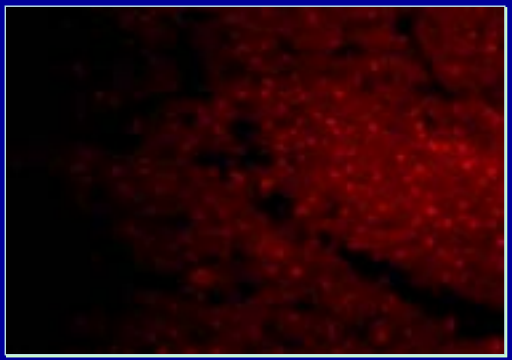
Giorgio et al., Nat Rev Mol Cell Biol, 8:722-728, 2007

Rat

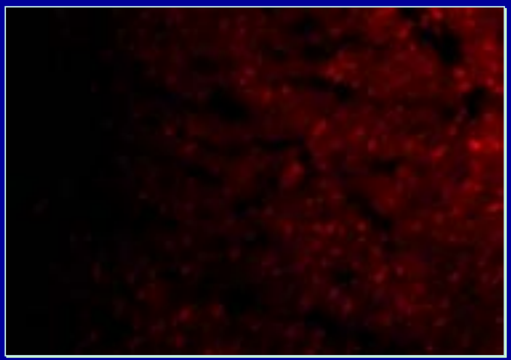
Mitochondria-derived ROS



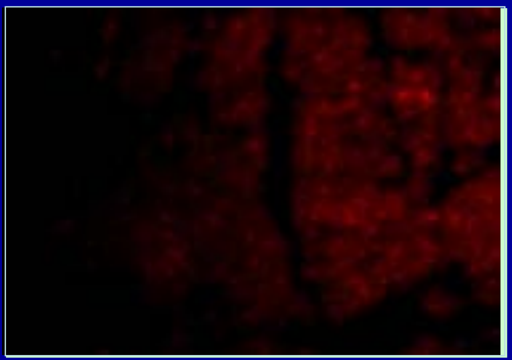
Ischemia/Reperfusion



Clorgyline 25 μM

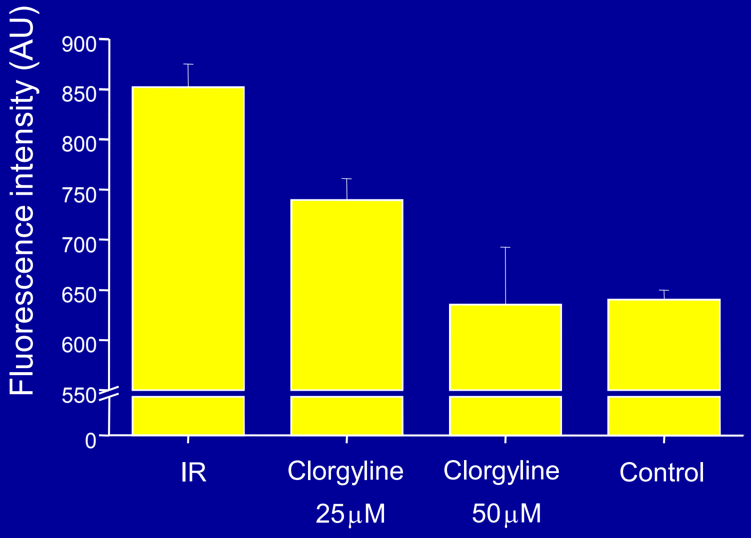


Clorgyline 50 μM



Normoxia

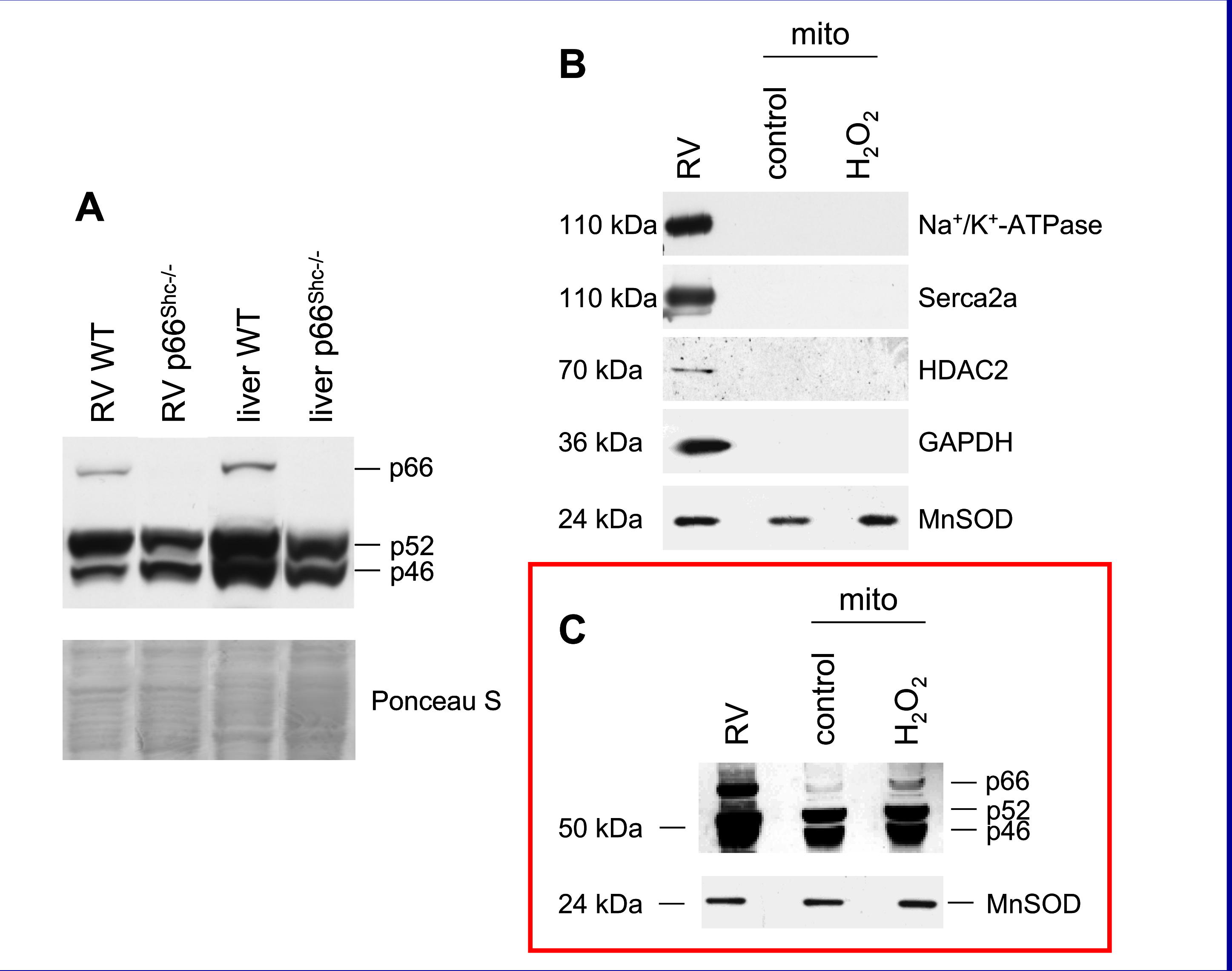
ROS formation by MAO during ischemia/reperfusion



Fabio di Lisa

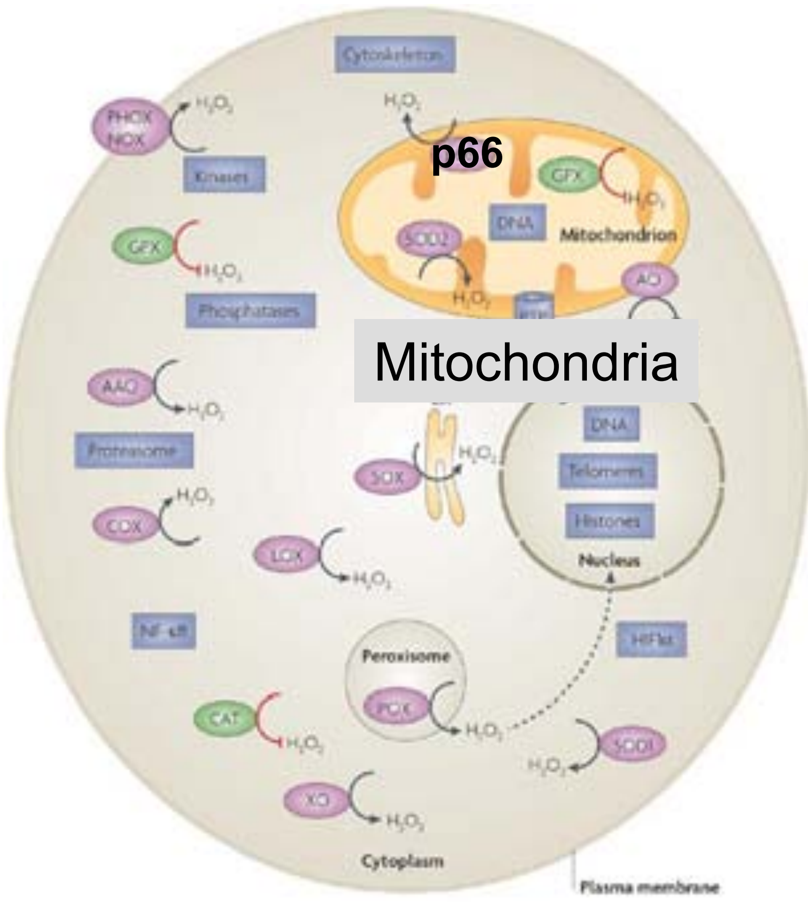
Mice

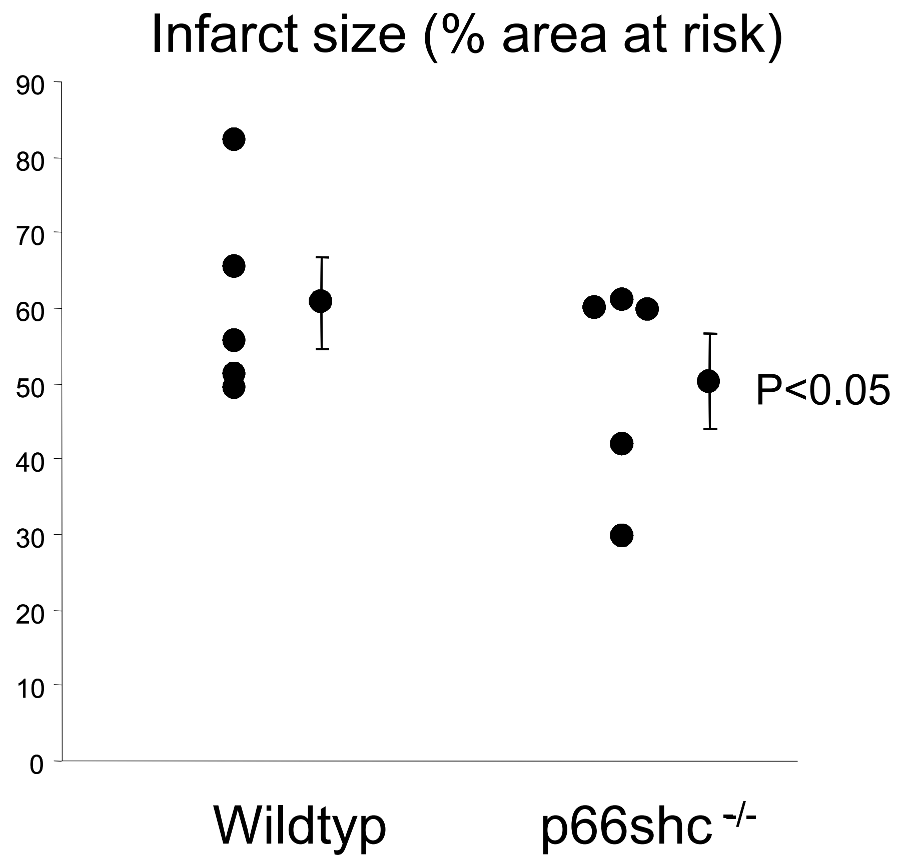
Stress-induced p66^{Shc} translocation



Mice

$p66^{shc}$ and irreversible IRI

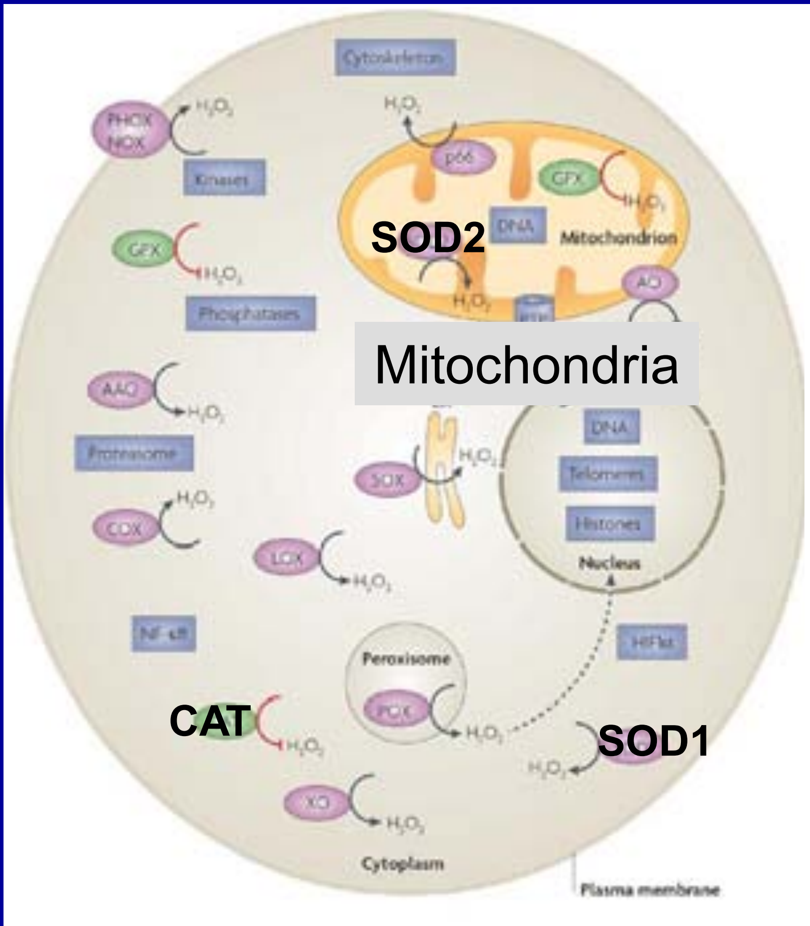




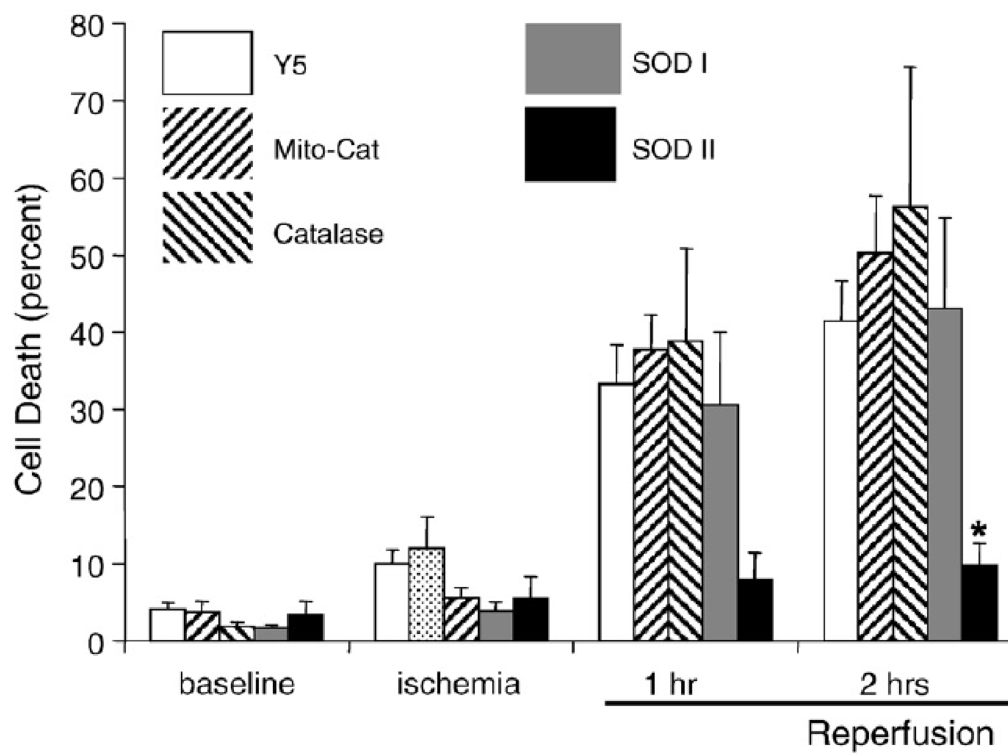
Mice

Catalase (CAT), superoxide dismutase (SOD) and irreversible IRI

Cardiomyocytes



Cardiomyocytes



Giorgio et al., Nat Rev Mol Cell Biol, 8:722-728, 2007

Loor et al., Biochem Biophys Acta 2011

GSH during ischemia/reperfusion

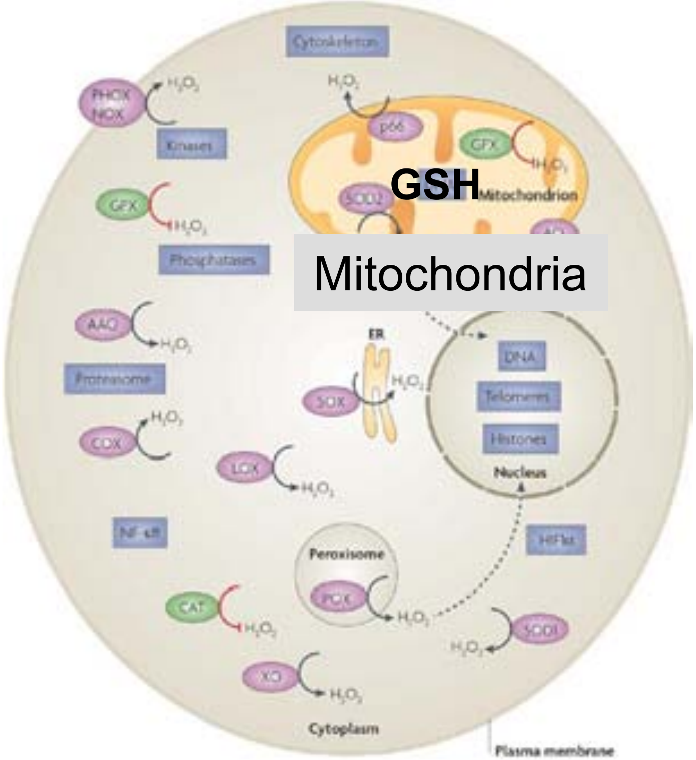
Mice

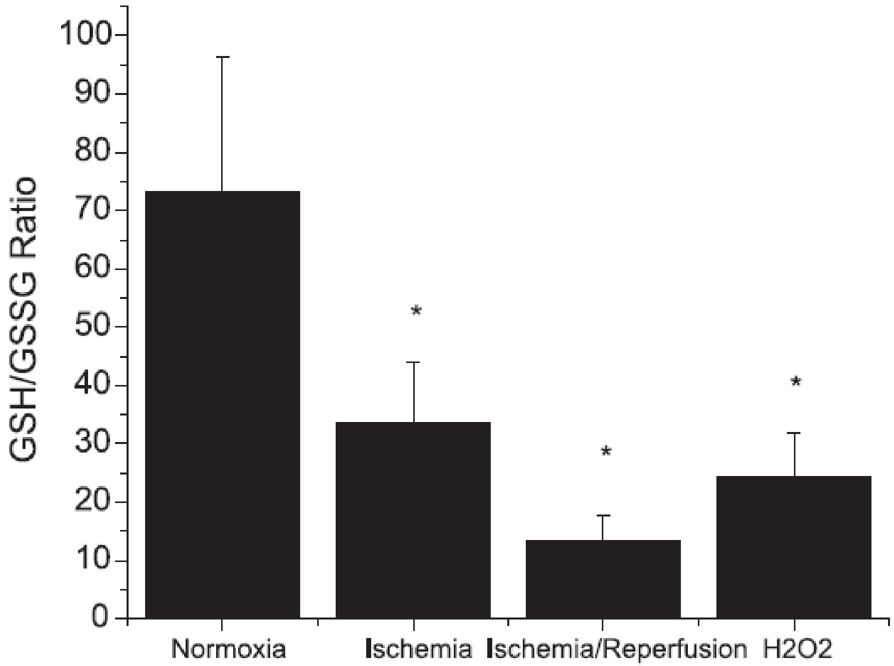
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 282, NO. 26, pp. 19133–19143, June 29, 2007

Oxidant Stress during Simulated Ischemia Primes Cardiomyocytes for Cell Death during Reperfusion*

Received for publication, March 5, 2007, and in revised form, April 16, 2007 Published, JBC Papers in Press, May 7, 2007, DOI 10.1074/jbc.M701917200

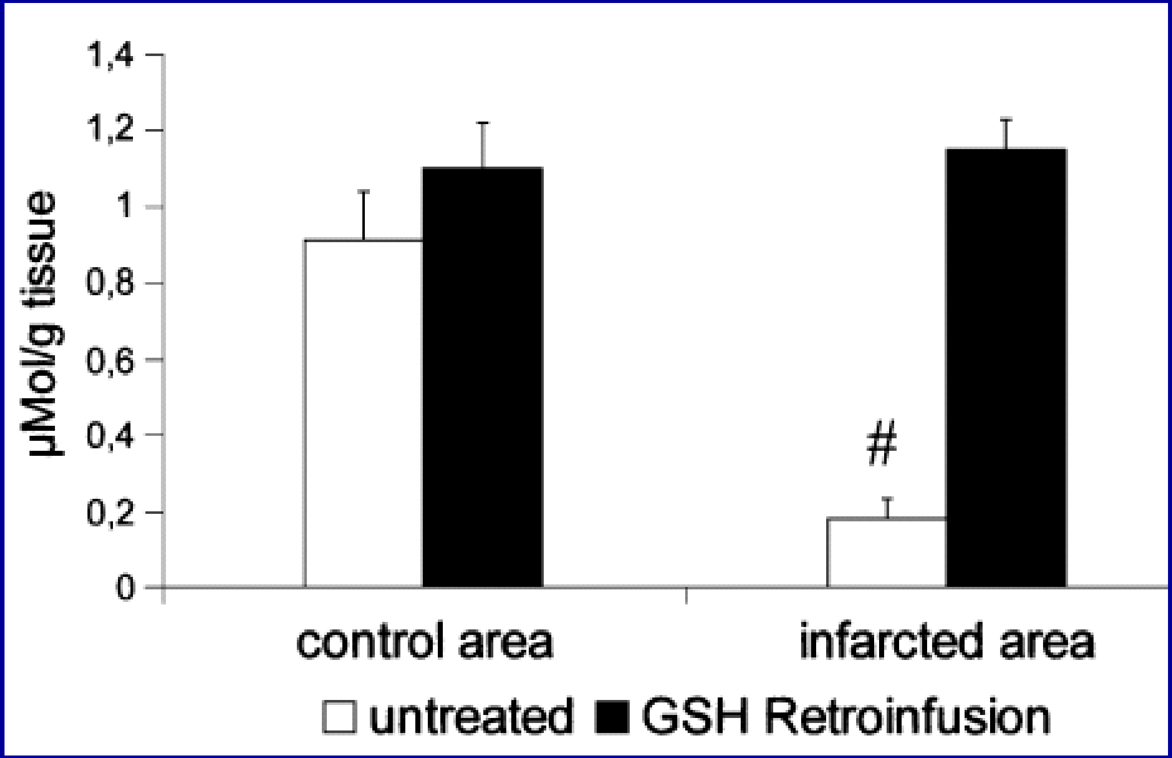
Emmanuel Robin[‡1], Robert D. Guzy[§], Gabriel Loor[¶], Hirotaro Iwase[‡], Gregory B. Waypa[§], Jeremy D. Marks[‖],

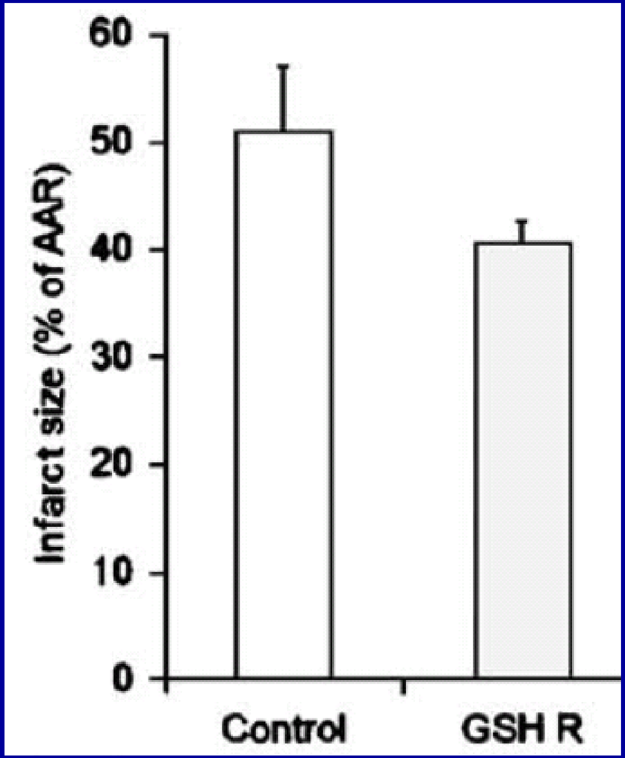




Pig

GSH and irreversible IRI



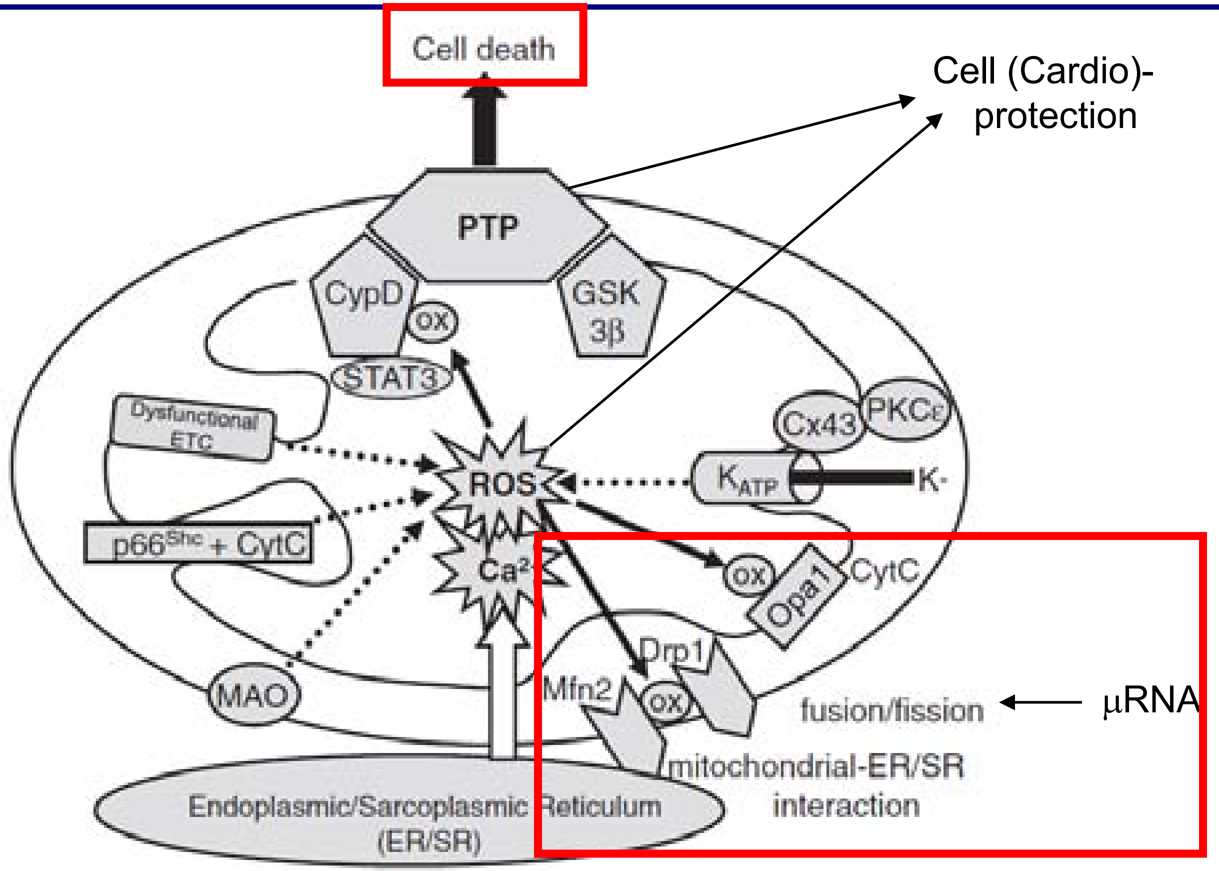


Kupatt et al., Cardiovasc Res 61: 530-537, 2004

ROS and mitochondrial morphology

Nuclear-encoded mitochondrial proteins and their role in cardioprotection☆

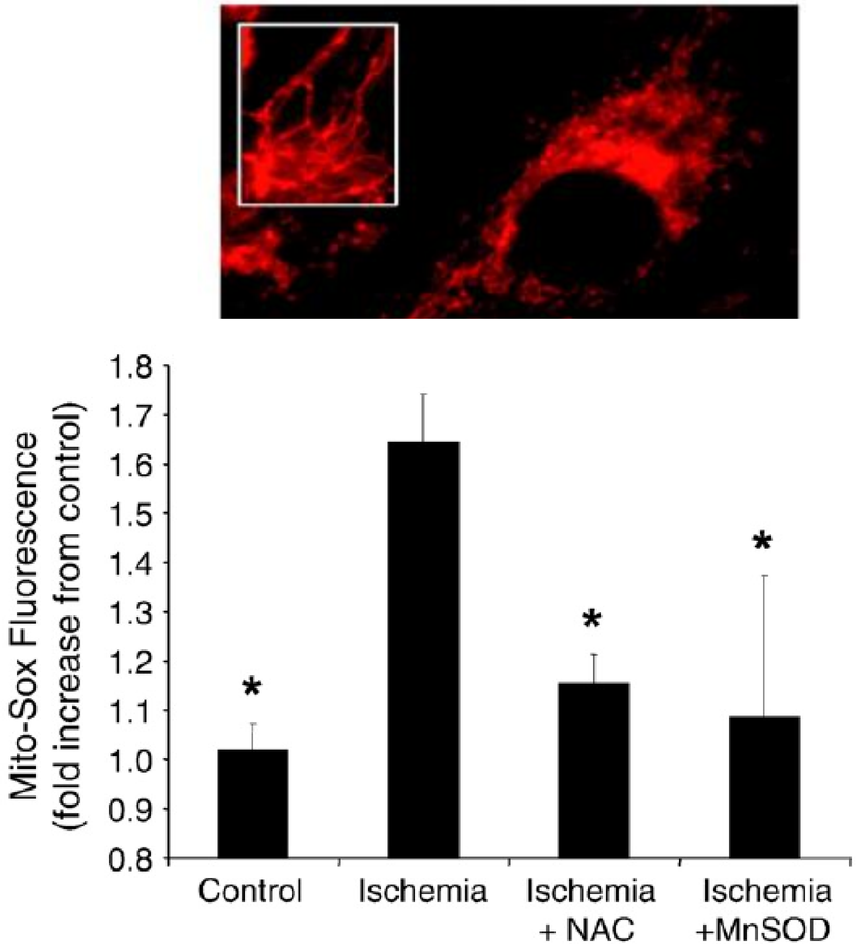
Kerstin Boengler [a,*], Gerd Heusch [a], Rainer Schulz [b]

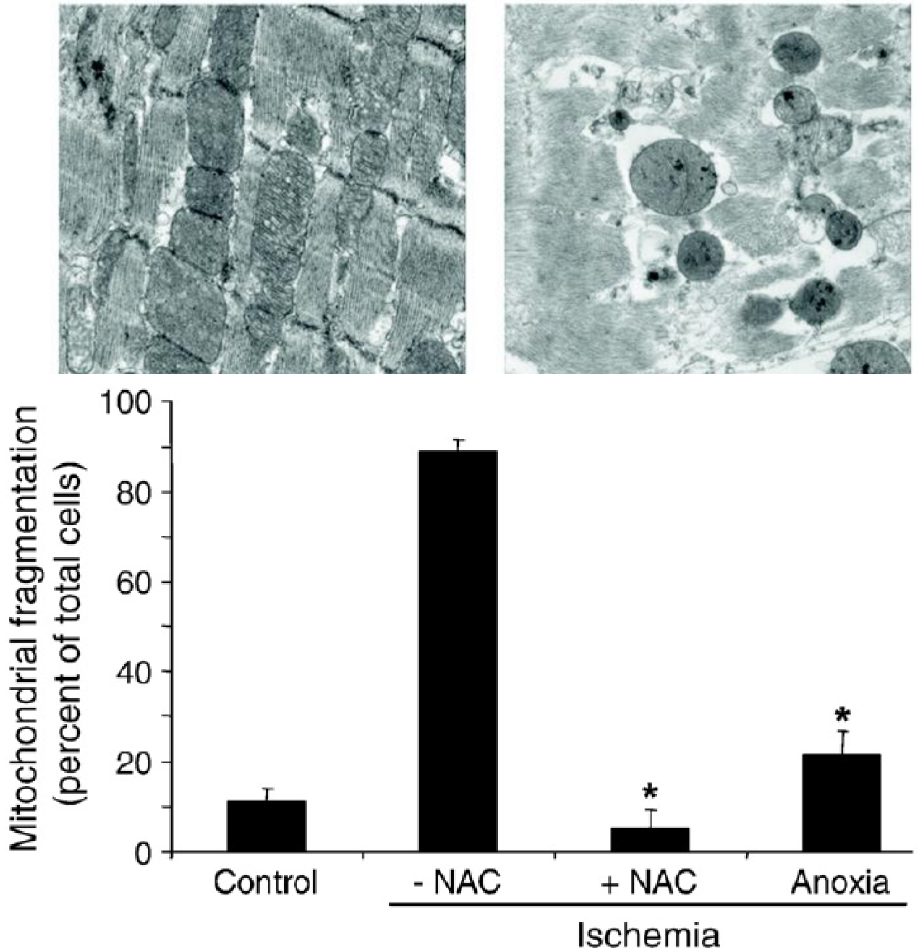


BBA 2011

Mice

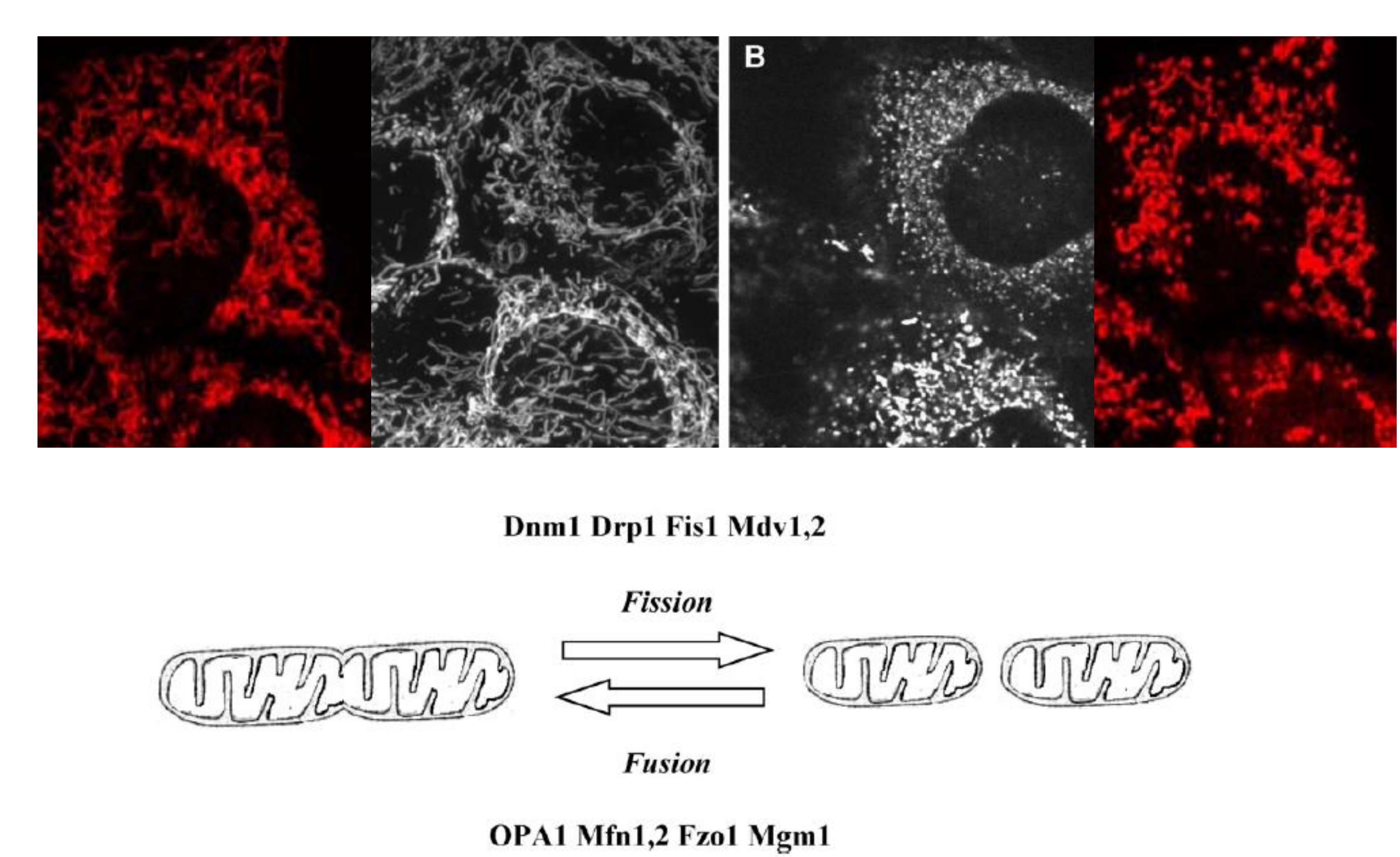
ROS and mitochondrial morphology





Loor et al., Biochem Biophys Acta 2011

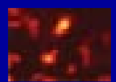
ROS and mitochondrial morphology

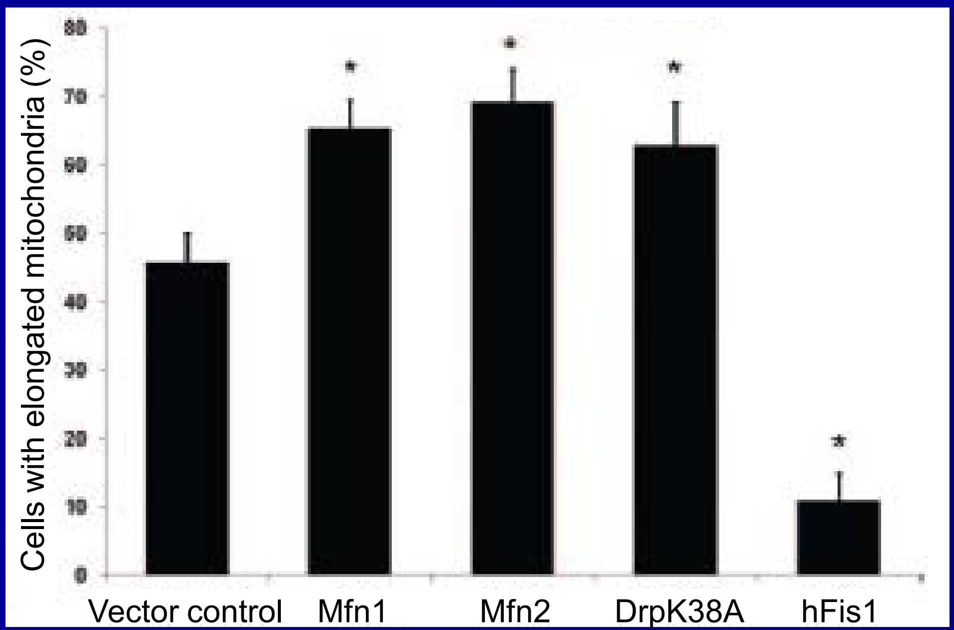


Kuznetsova et al, Int J Biochem & Cell Biol 41: 1928–1939, 2009

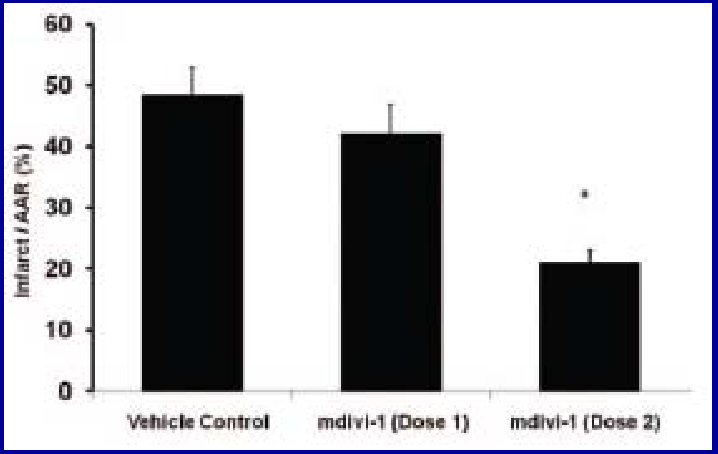
Mice

Mitochondrial fission and IRI



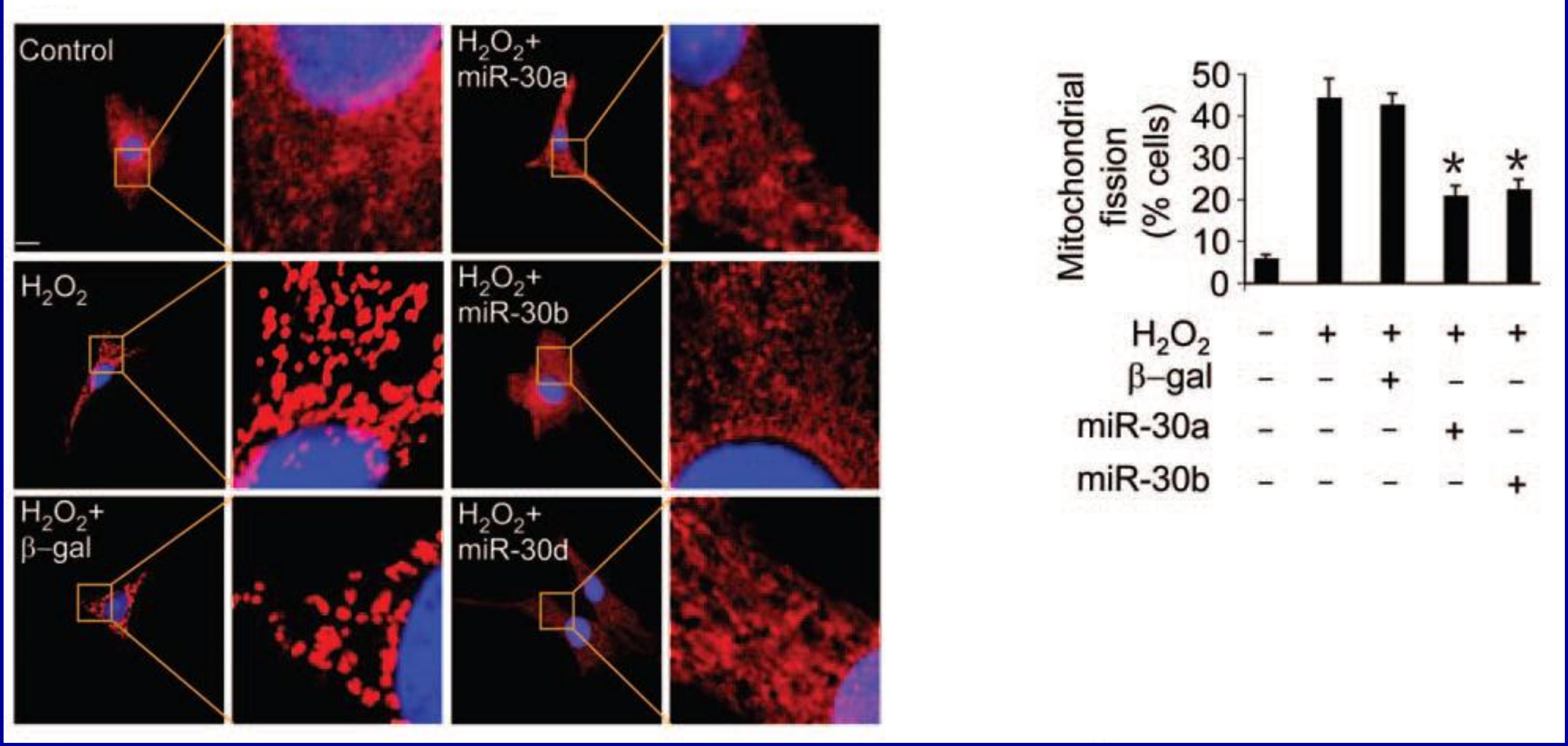


Mdivi: mitochondrial division inhibitor



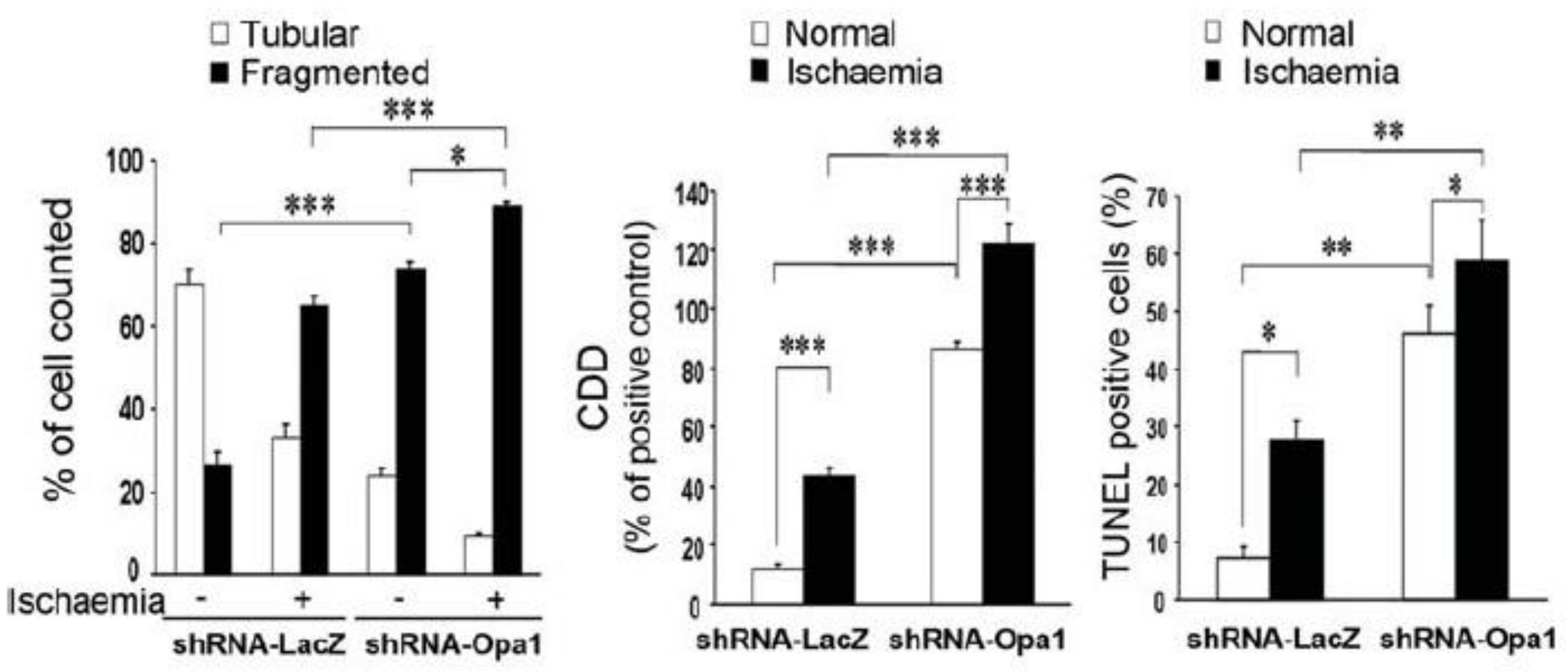
Ong et al., Circulation 2010

ROS and mitochondrial morphology



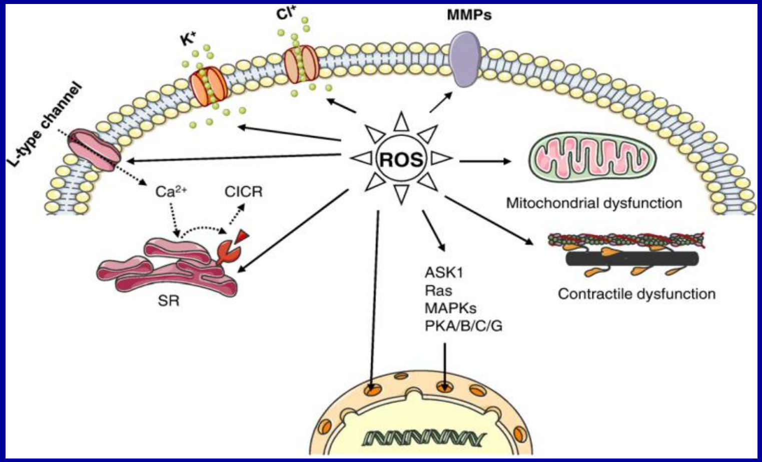
Li et al., PLoS Genetics 6: e1000795, 2010

OPA1, mitochondrial morphology and IRI



Chen et al., Cardiovasc Res 84: 91-99, 2009

ROS during IRI and protection from it



contribute to cellular damage

Function

Morphology

(Postischemic Reperfusion, Heart Failure)

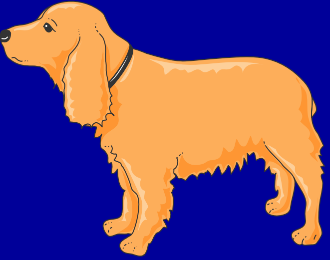
contribute to cellular protection

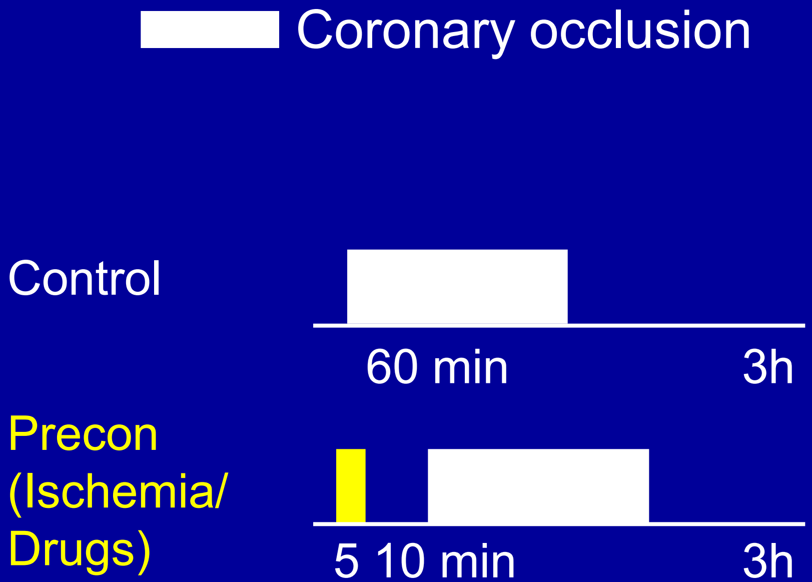
Function

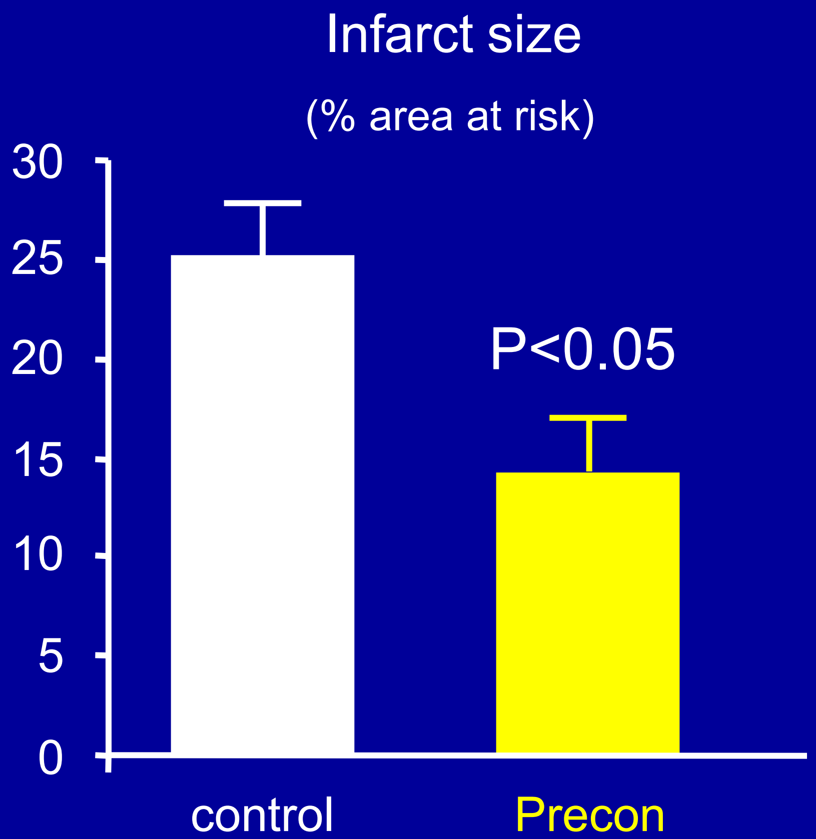
Morphology

(Ischemia/Reperfusion Injury)

Ischemic preconditioning

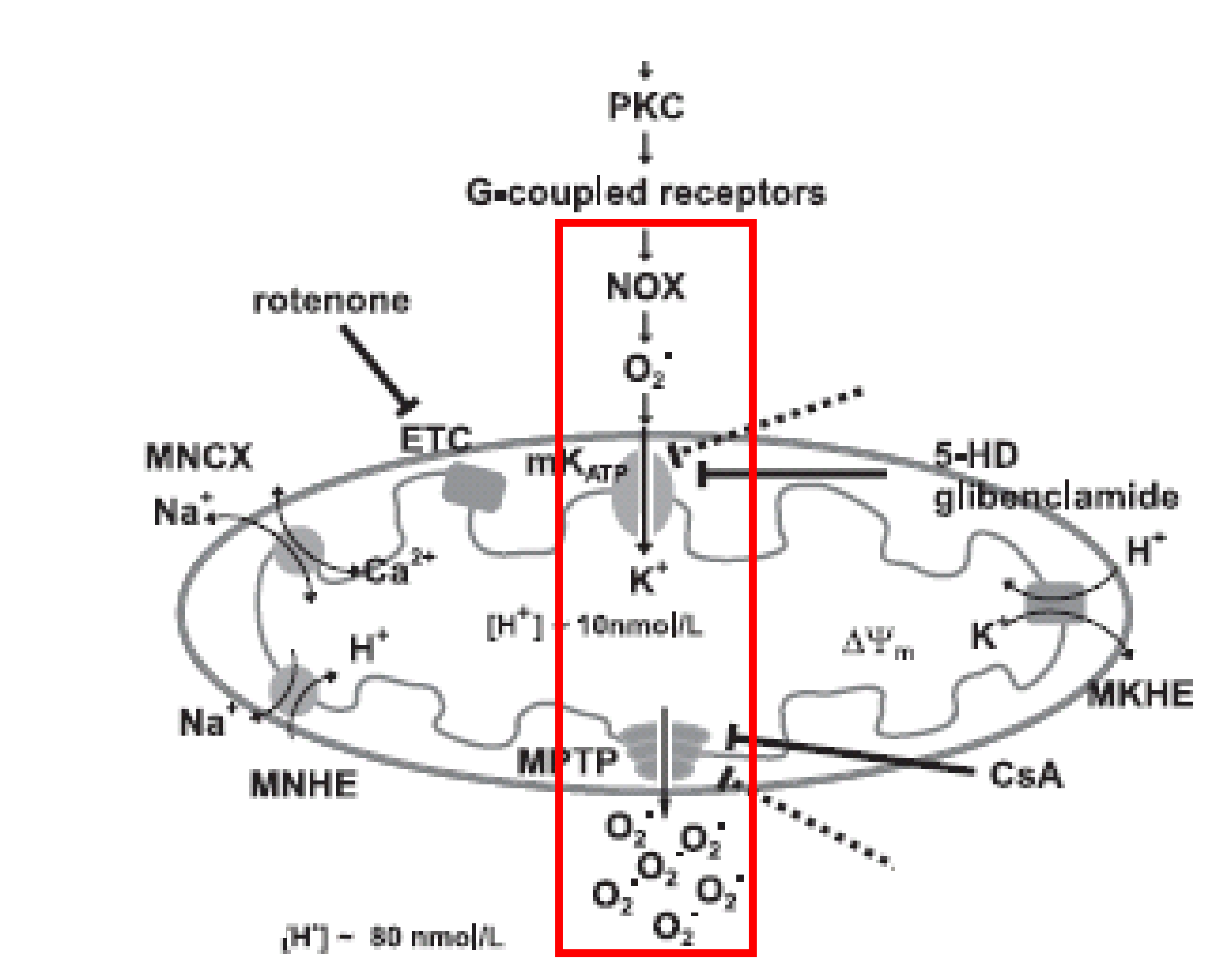






Zhao et al., Am J Physiol 285: H579-H588, 2004

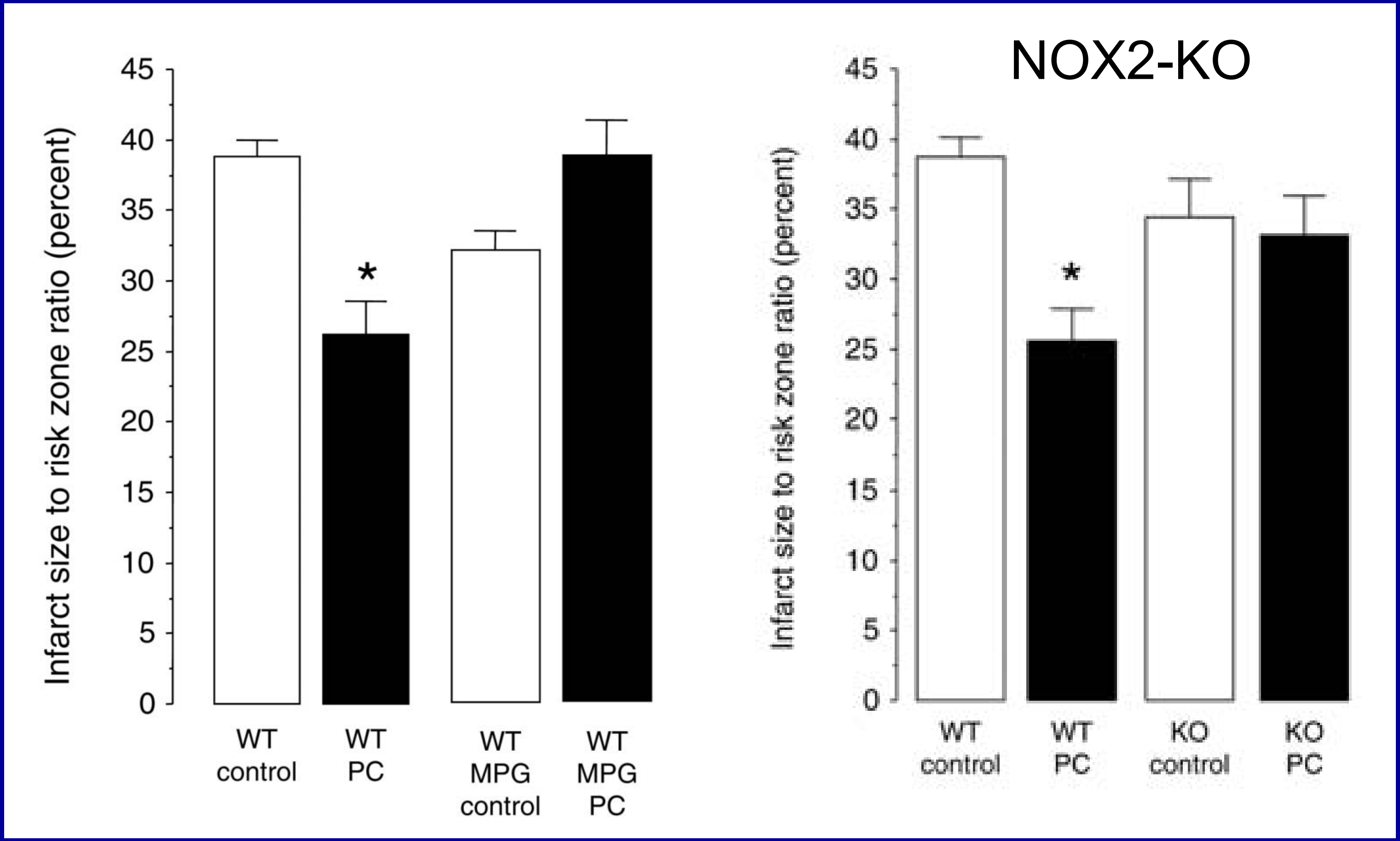
ROS and ischemic preconditioning



Garciarena et al., J Appl Physiol 105: 1706-1713, 2008

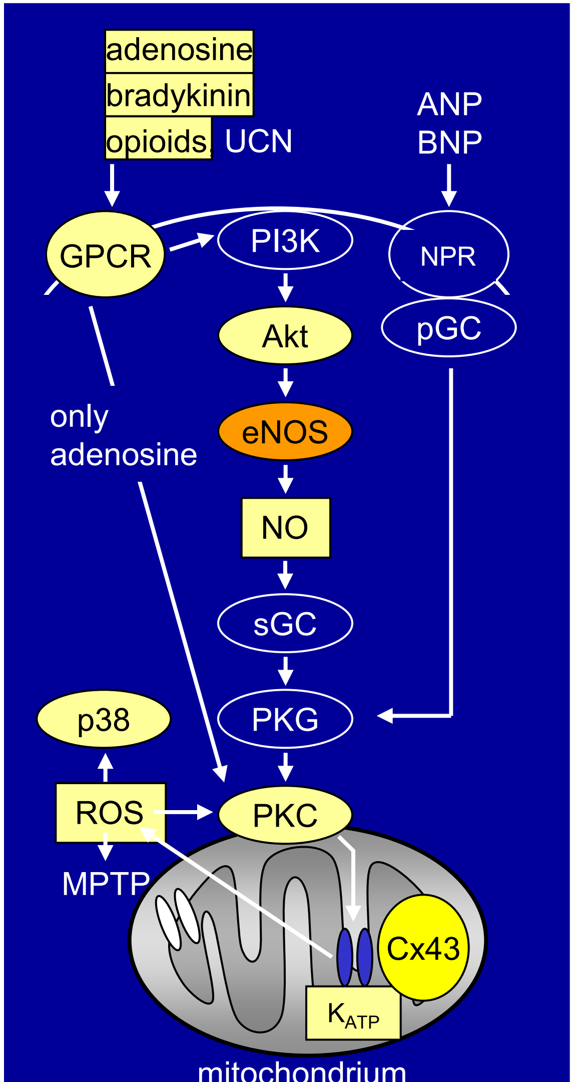
NOX2, ROS and ischemic preconditioning

Mice

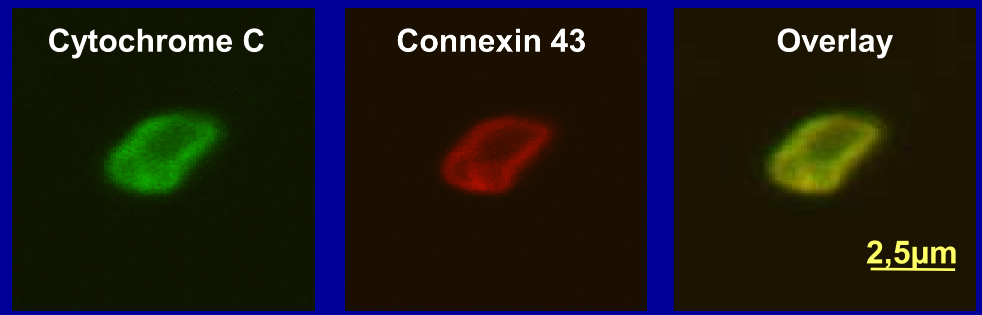


Bell et al., FASEB J 2005

Preconditioning: Signal transduction



Mitochondria from human LV tissue



Heinzel et al., Circ Res 97:583-586, 2005

Boengler et al., Cardiovasc Res 67: 234-244, 2005

Rodriguez-Sinovas et al., Circ Res 99:93-101, 2006

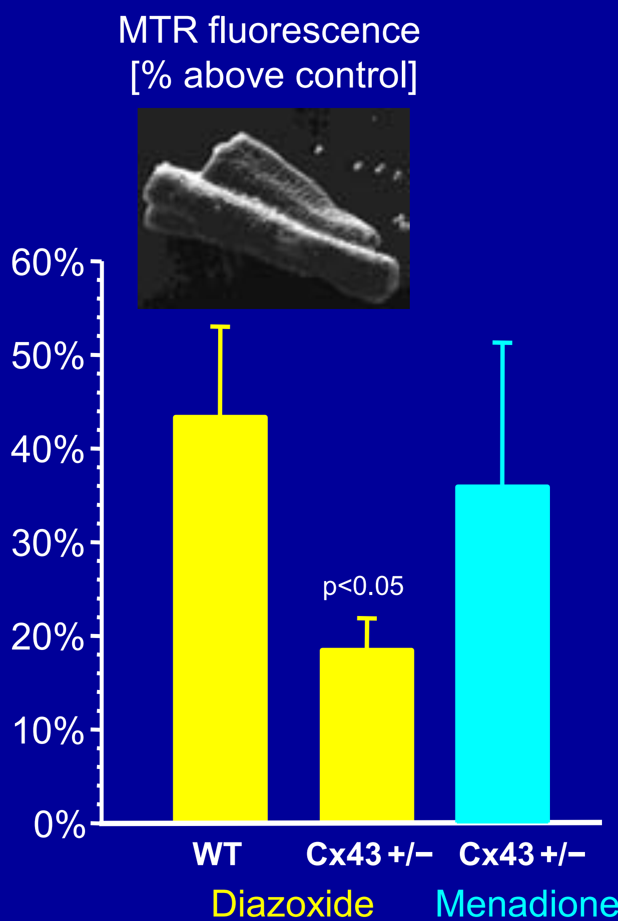
Boengler et al., Basic Res Cardiol 104: 141-147, 2009

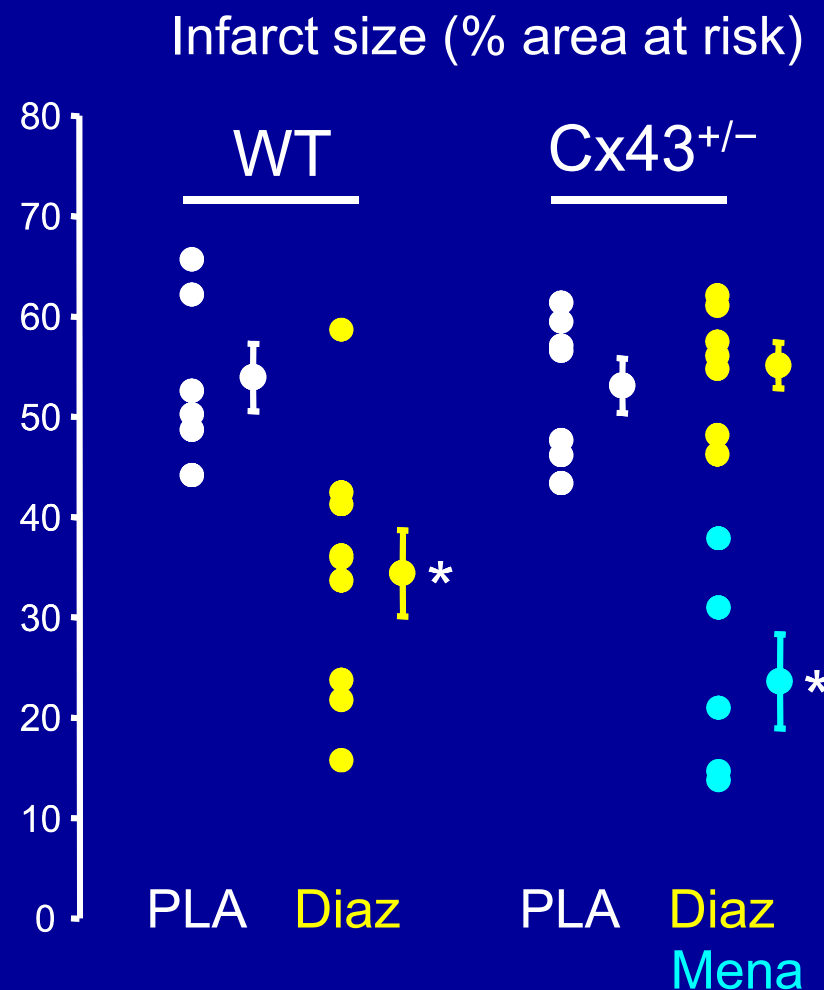
Görbe et al., Am J Physiol Heart Circ Physiol. 2011 Mar 11

Heusch, Boengler, Schulz, Circulation 118: 1915-1919, 2008; Boengler, Schulz, Heusch, Cardiovasc Res 2009

Connexin 43 (Cx43), ROS and ischemic preconditioning

Knockout mice





Heinzel et al., Circ Res 97:583-586, 2005

Mitochondria and stem cell differentiation

STEM CELLS®

TISSUE-SPECIFIC STEM CELLS

Mitochondria Determine the Differentiation Potential of Cardiac Mesoangioblasts

Nuria San Martin[1], Ana M. Cervera[1], Claudia Cordova[1], Diego Covarello[2], Kenneth J. McCreath[1] and Beatriz G. Galvez[1].

www.nature.com/clinicalpractice/cardio

Mitochondrial oxidative metabolism is required for the cardiac differentiation of stem cells

Susan Chung, Petras P Dzeja, Randolph S Faustino, Carmen Perez-Terzic, Atta Behfar and Andre Terzic*

STEM CELLS®

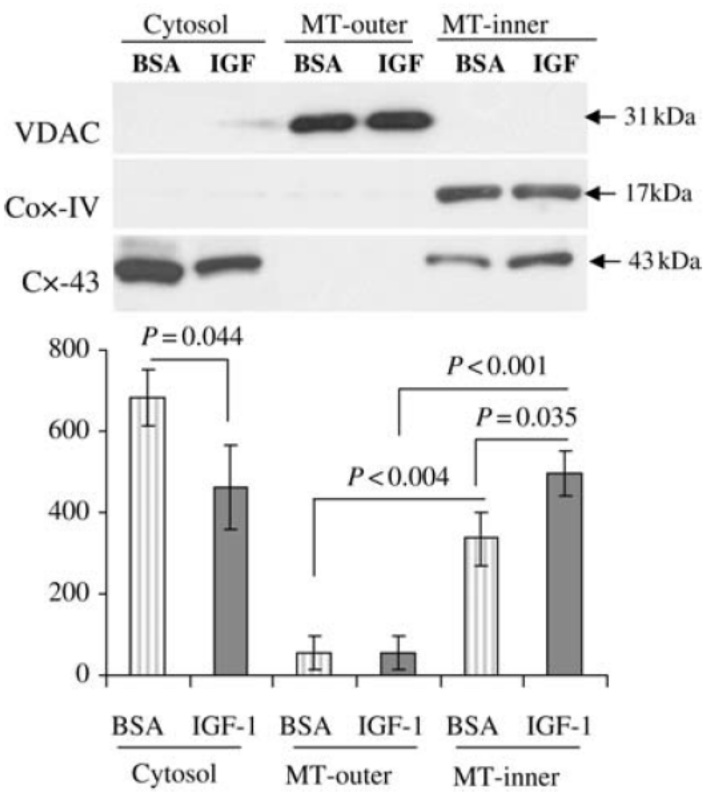
EMBRYONIC STEM CELLS/INDUCED PLURIPOTENT STEM CELLS

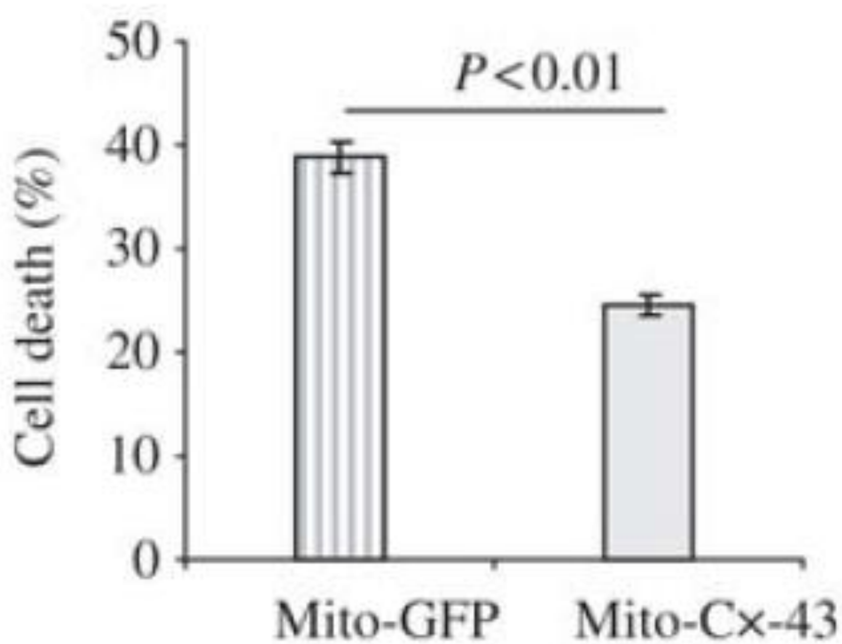
Mitochondrial Reactive Oxygen Species Mediate Cardiomyocyte Formation from Embryonic Stem Cells in High Glucose

FRANCISCO LUNA CRESPO, VERONICA R. SOBRADO, LAURA GOMEZ, ANA M. CERVERA, KENNETH J. MCCREATH

Mitochondrial Cx43 and stem stell protection

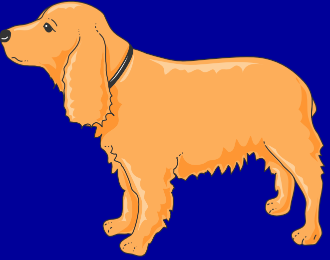
Mitochondria-specific transgenic overexpression of connexin-43 simulates preconditioning-induced cytoprotection of stem cells



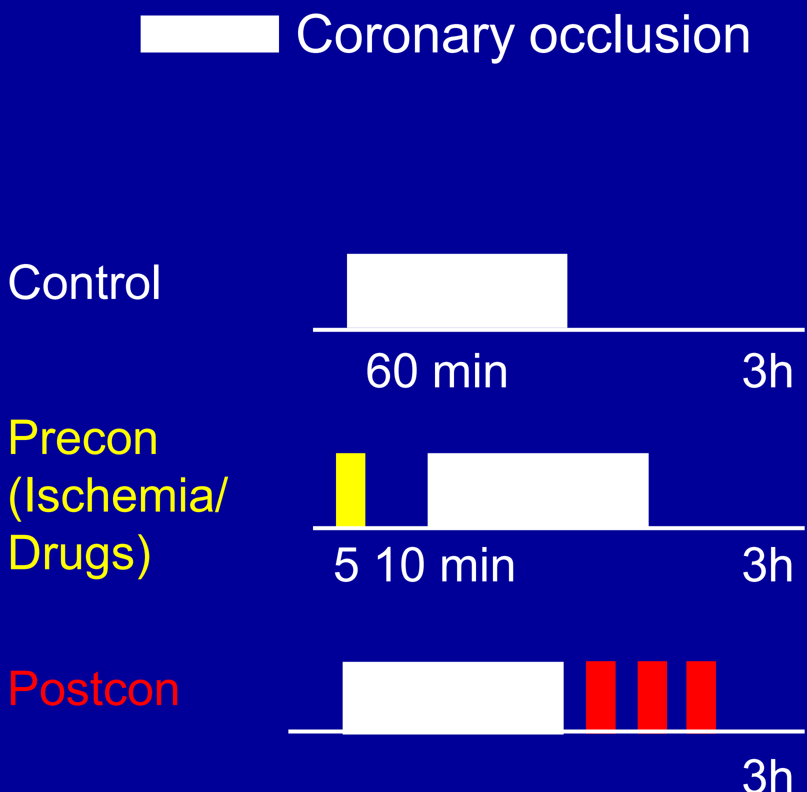


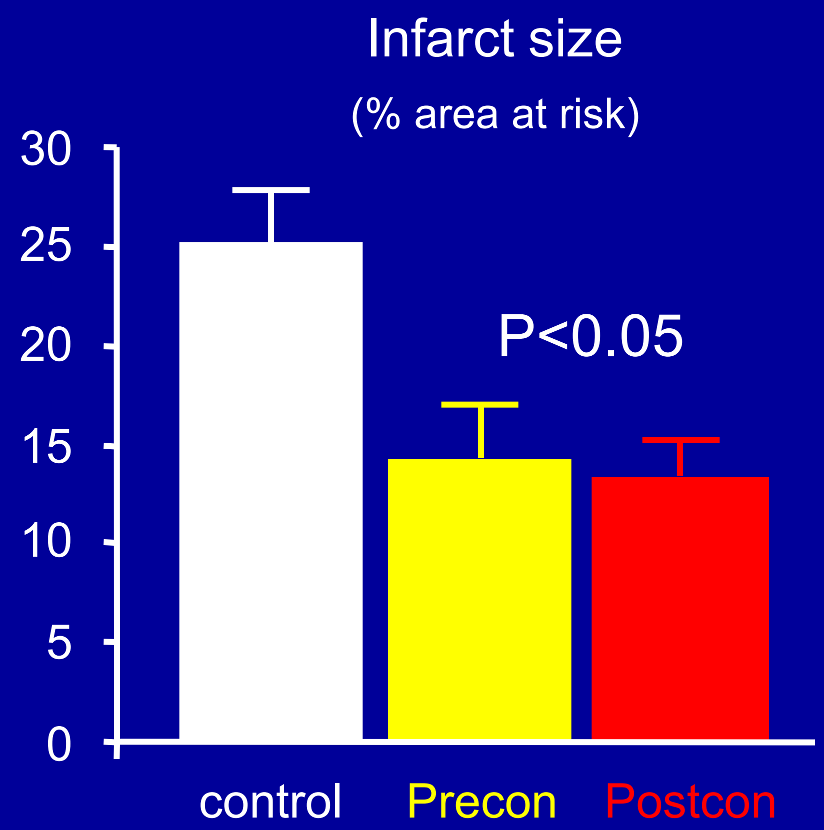
Lu et al., Cardiovasc Res 88: 277-286, 2010

Ischemic pre- and post-conditioning



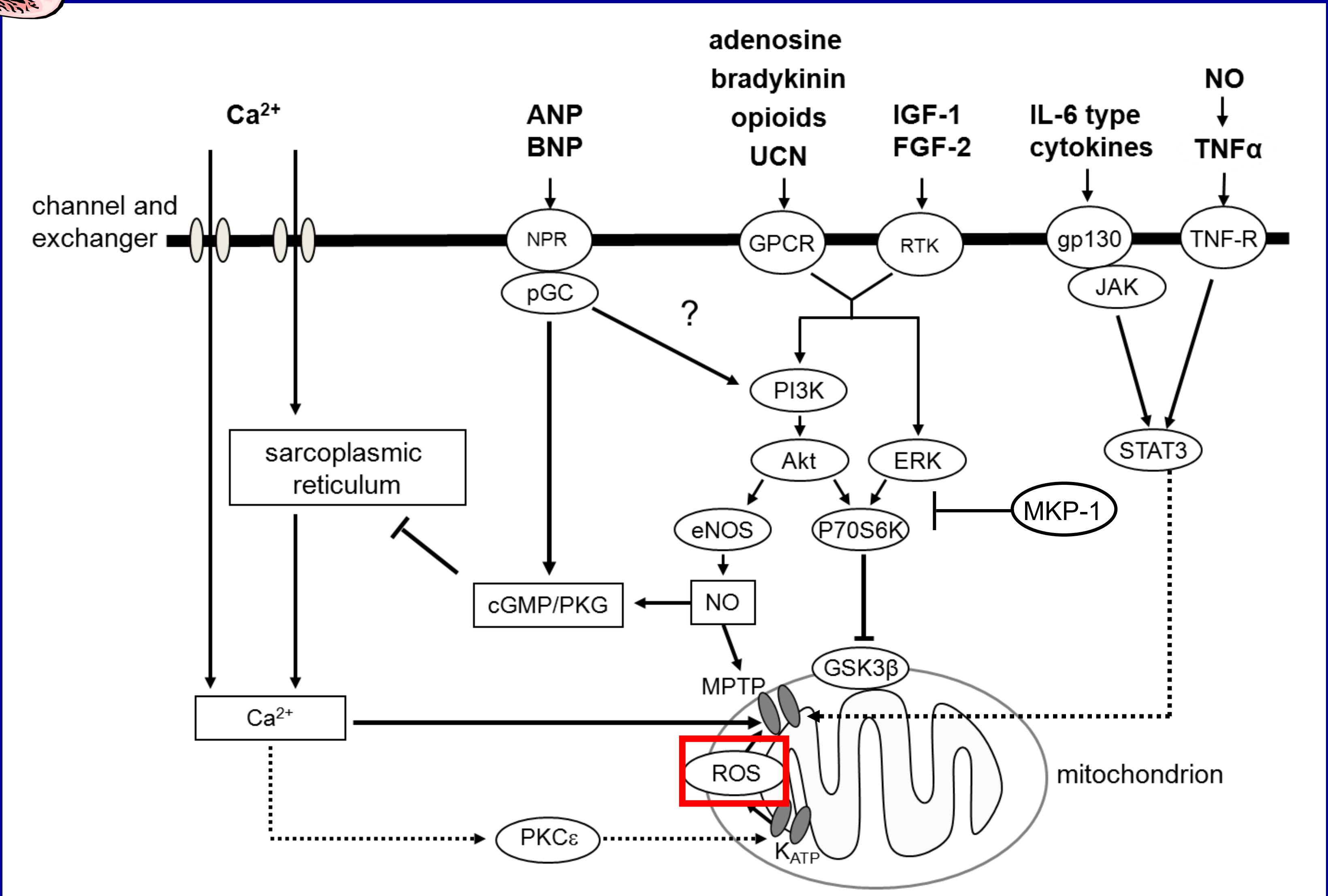
Dog





Zhao et al., Am J Physiol 285: H579-H588, 2004

Ischemic Postconditioning: Signal transduction

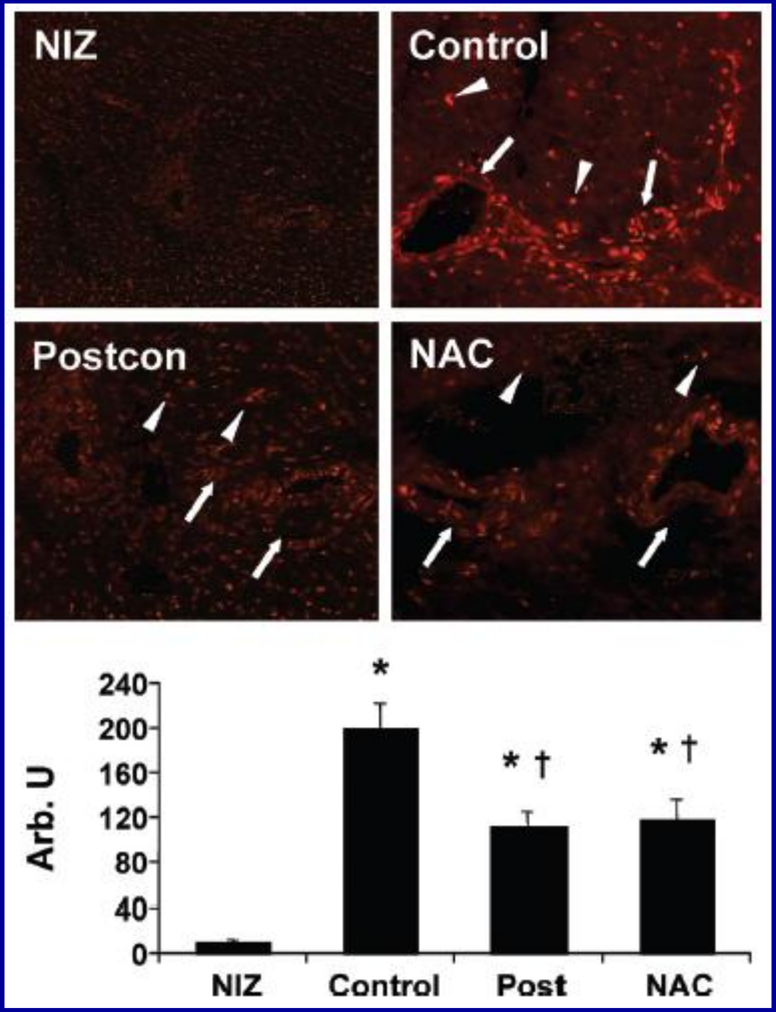


Ovize et al, Cardiovasc Res 87: 406-423, 2010

ROS scavenging and ischemic postconditioning

Rat

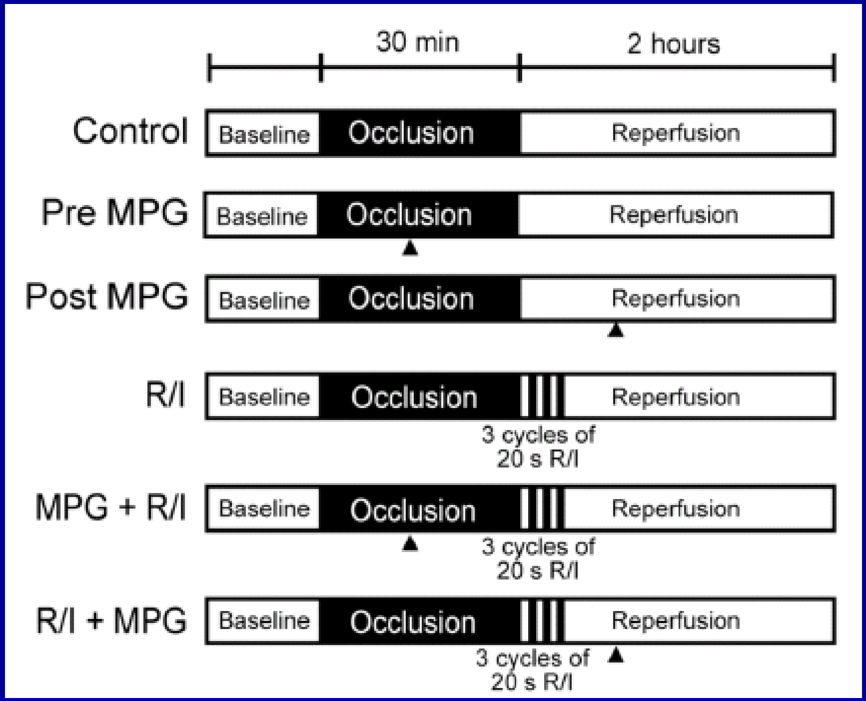
Detection of superoxide anions

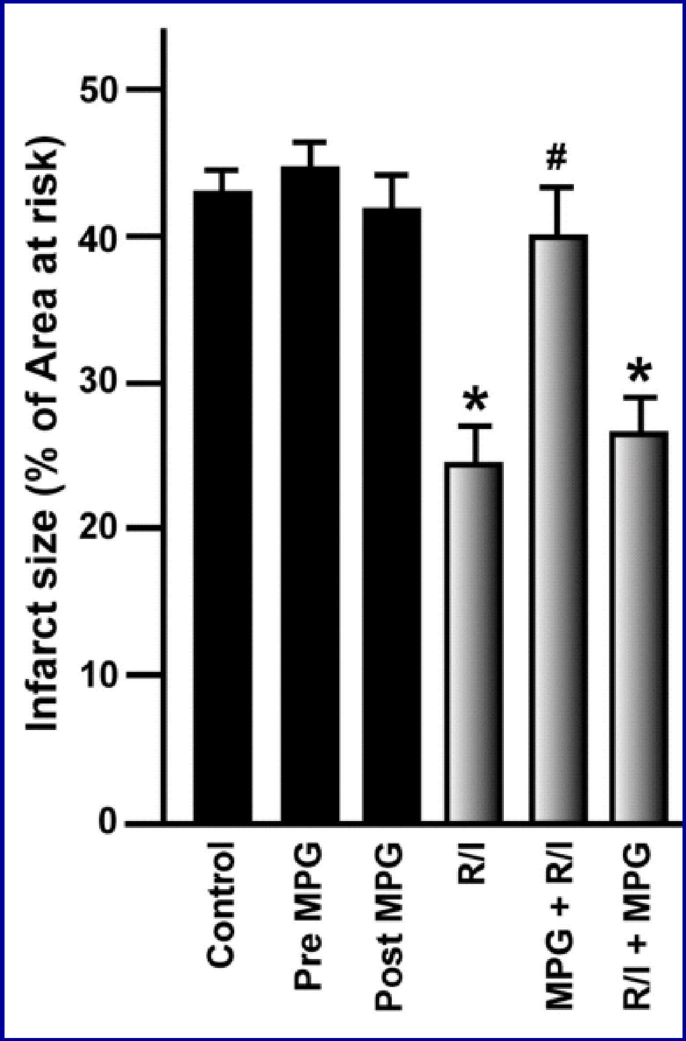


Kin et al., Shock 2008

ROS scavenging and ischemic postconditioning

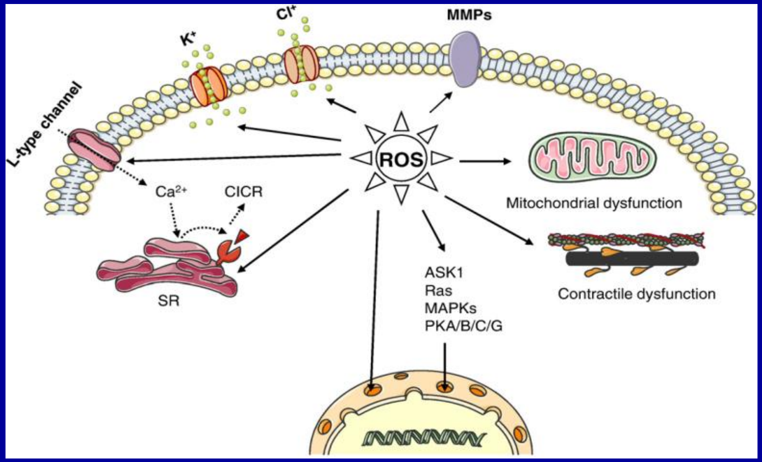
Mice





Tsutsumi et al., Life Sci 81: 1223-1227, 2007

ROS during IRI and protection from it



contribute to cellular damage

Function

Morphology

(Postischemic Reperfusion, Heart Failure)

contribute to cellular protection

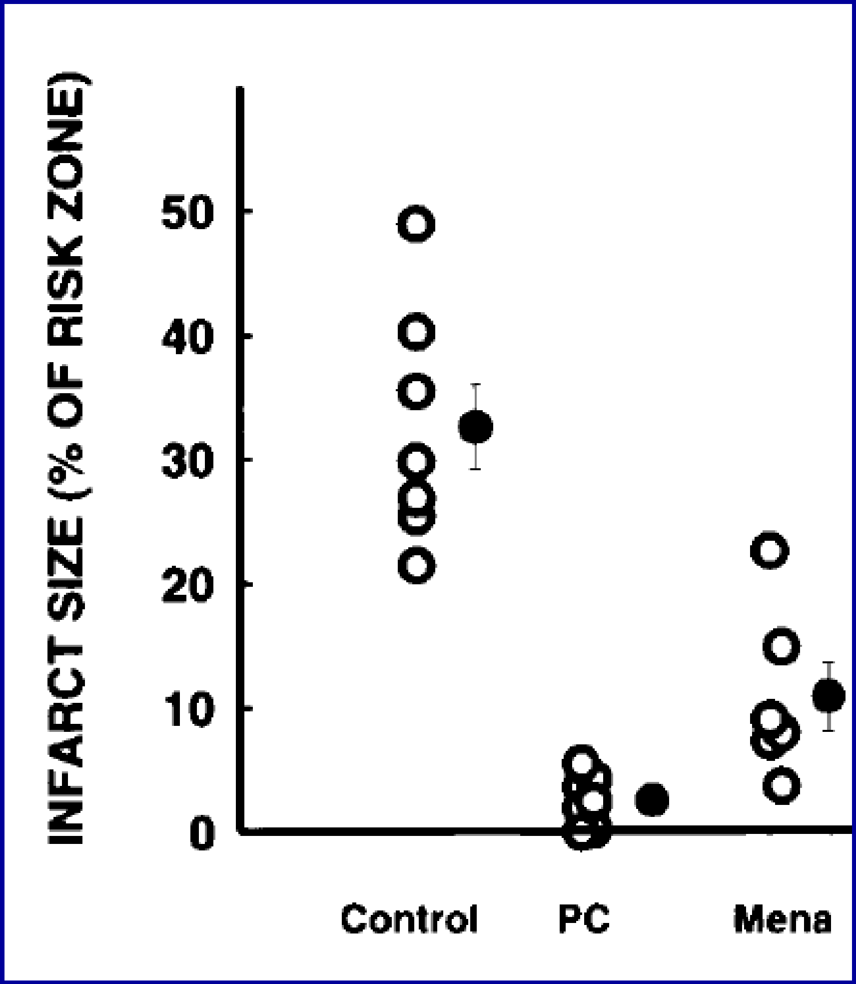
Function

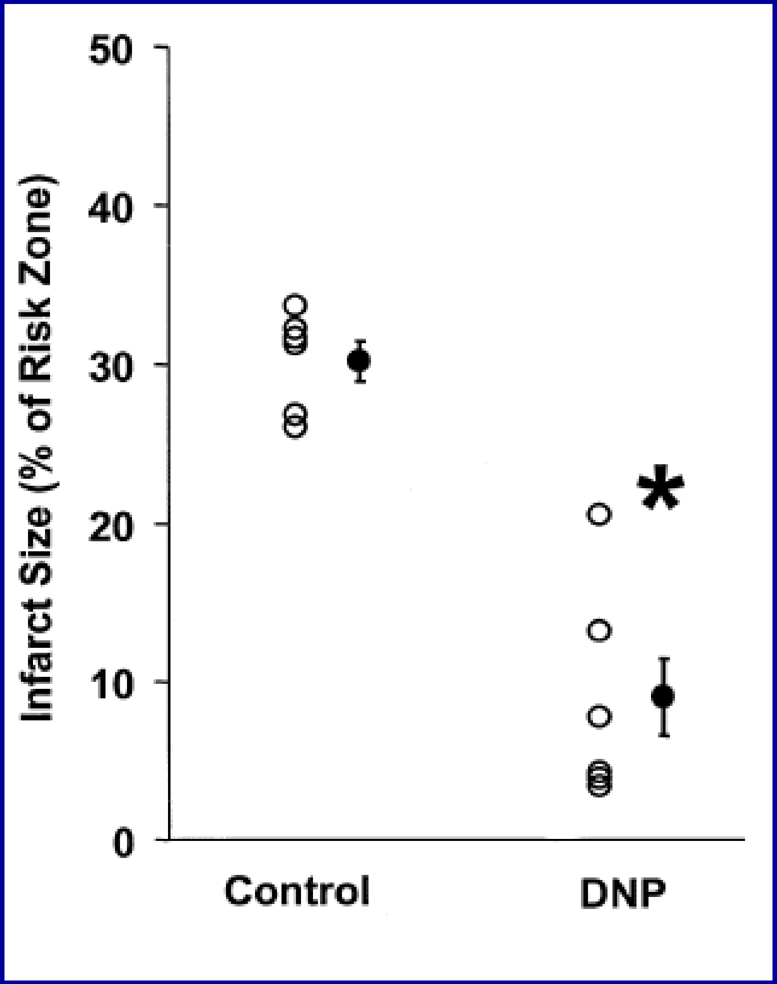
Morphology

(Ischemia/Reperfusion Injury)

Mitochondrial uncoupling, ROS and IRI

Rat heart in vitro

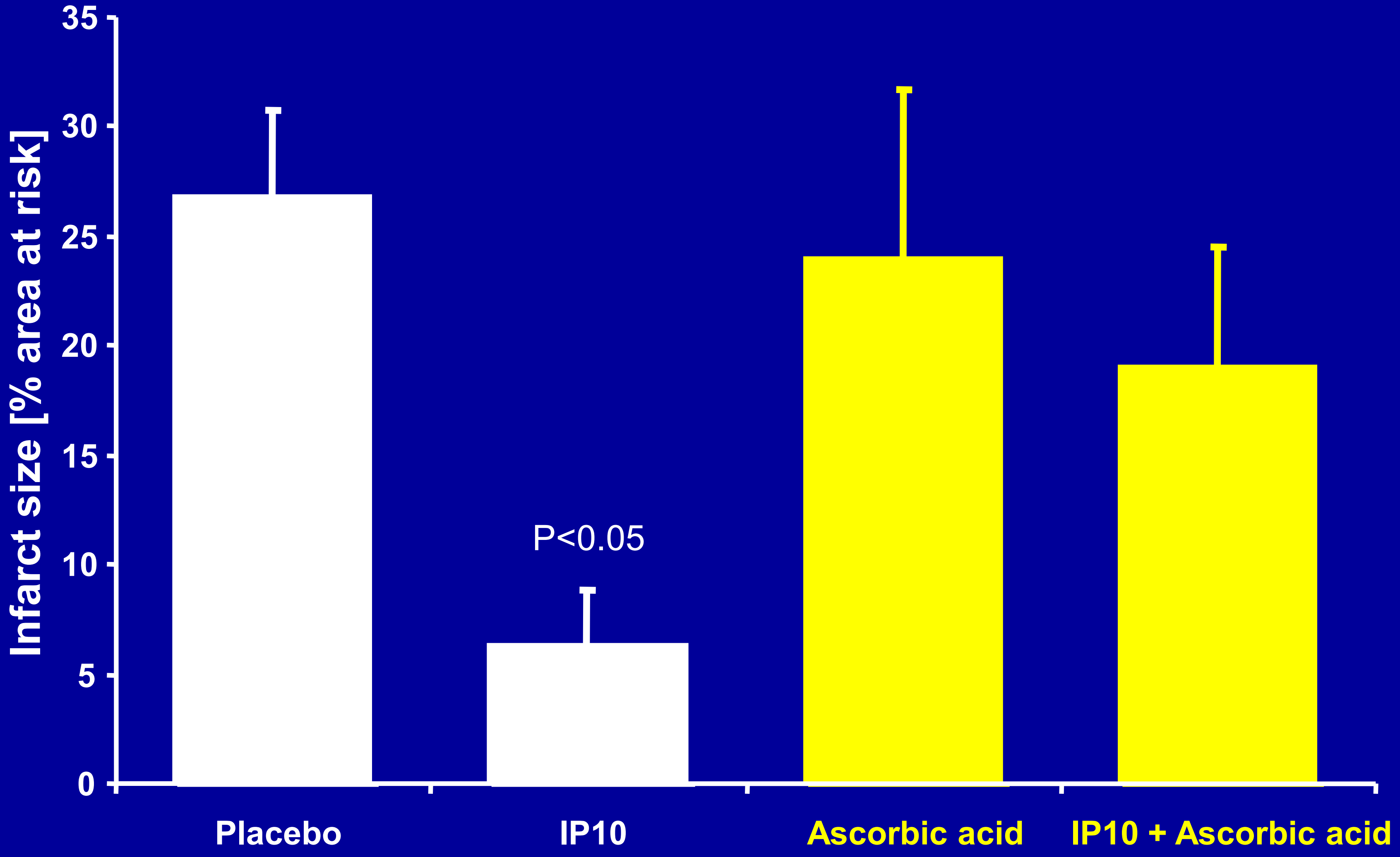




Yue et al., Am J Physiol 281: H590-H595, 2001

Minners et al., Cardiovasc Res 47: 68-73, 2000

ROS scavenging and ischemic preconditioning



Aldolase reductase and irreversible IRI

Am J Physiol Heart Circ Physiol 296: H333–H341, 2009.
First published December 5, 2008; doi:10.1152/ajpheart.01012.2008.

Aldose reductase mediates myocardial ischemia-reperfusion injury in part by opening mitochondrial permeability transition pore

Radha Ananthakrishnan, Michiyo Kaneko, Yuying C. Hwang, Nosirudeen Quadri, Teodoro Gomez, Qing Li, Casper Caspersen, and Ravichandran Ramasamy