Inflammation and oxidative stress after stroke

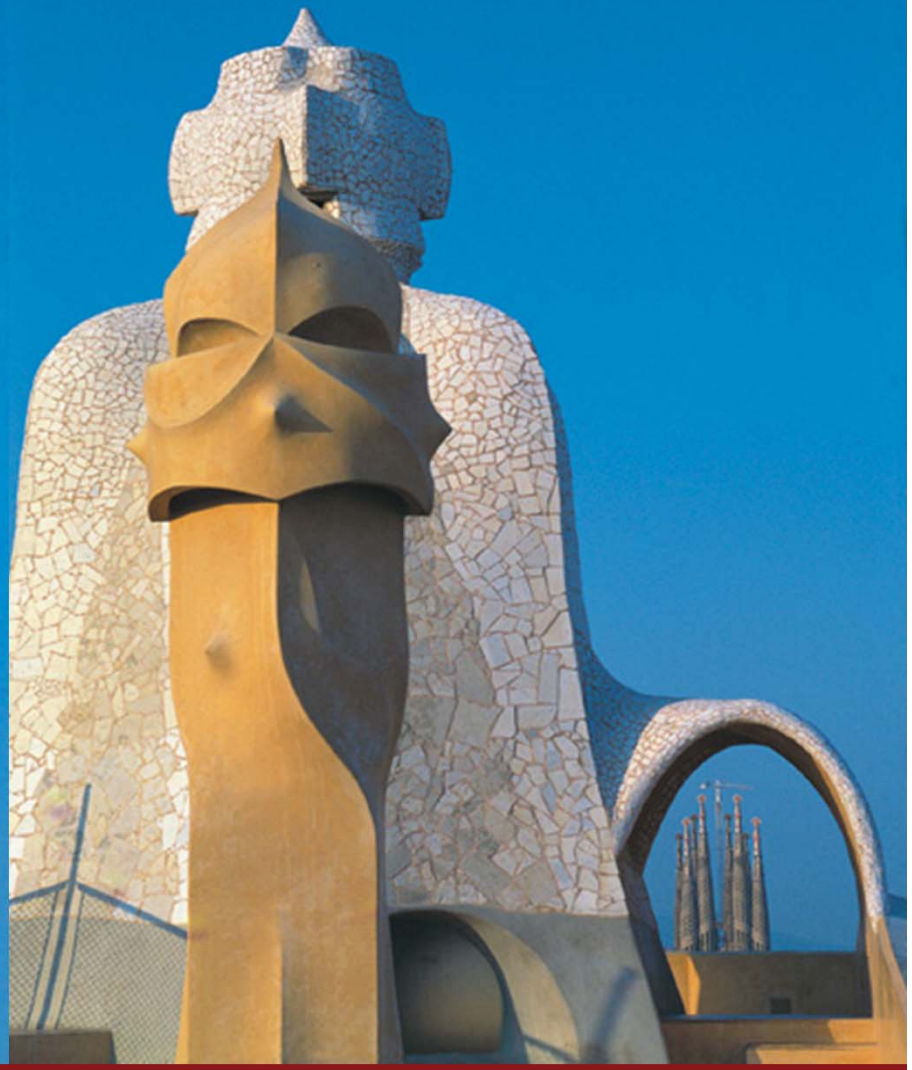
Anna M. Planas

Cerebrovascular Research Team
IIBB-CSIC, Hospital Clínic
IDIBAPS, Barcelona

CSIC

IDIBAPS
Institut D'Investigacions Biomèdiques August Pi i Sunyer

EUROPEAN STROKE NETWORK



Oxidative stress after brain ischemia

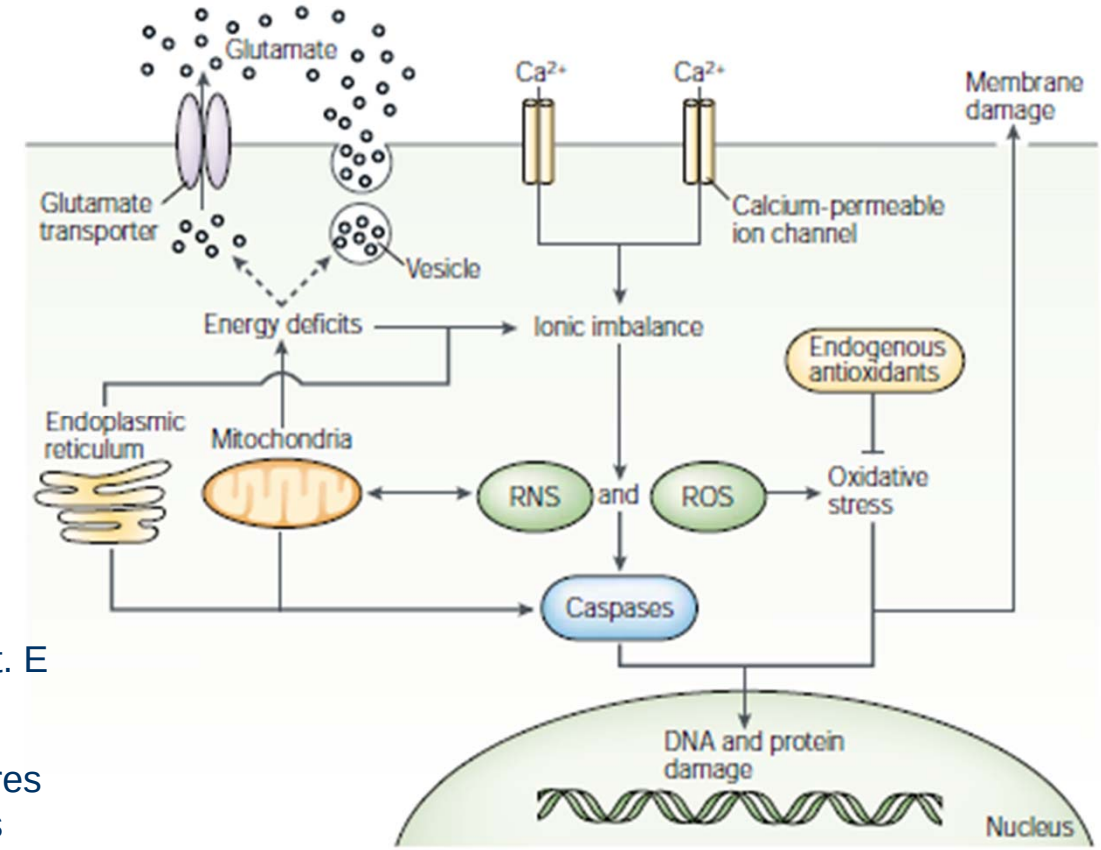
Sources:
-Mitochondrial electron transport chain
-NADH/NADPH oxidase
-Xanthine-xanthine oxidase system
-Cyclooxigenases
-Inflammation

ROS:
-superoxide anion
-hydrogen peroxide
-hydroxyl radical
-hypochlorous acid

RNS:
-nitric oxide
- peroxinitrite

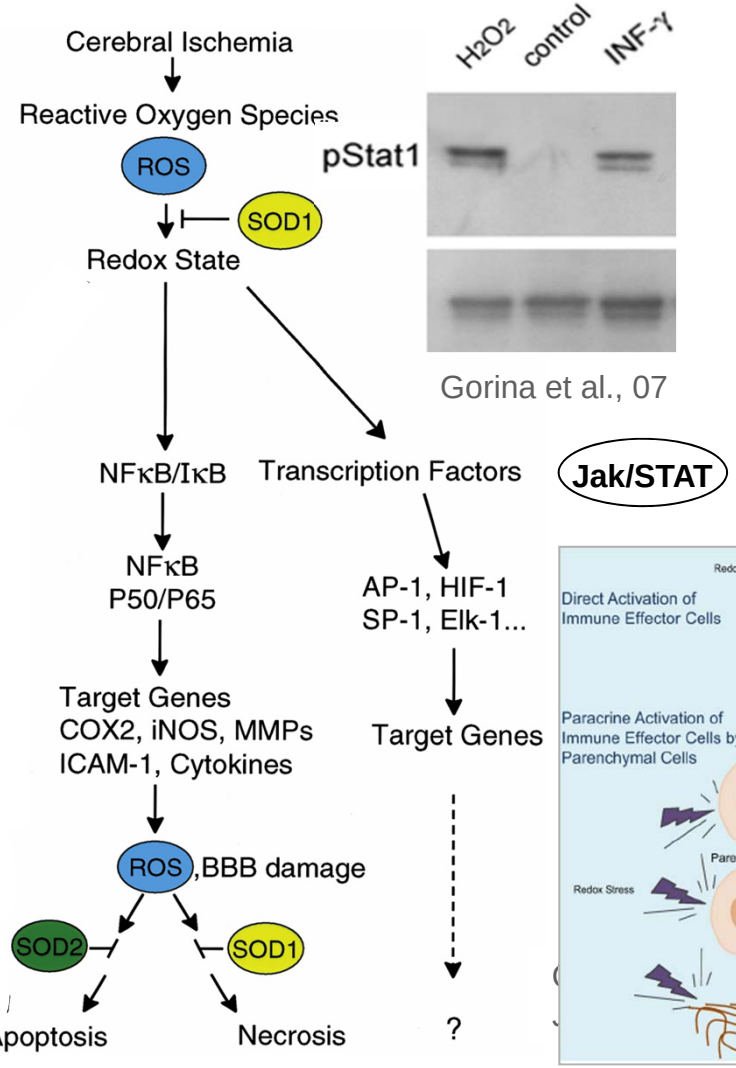
Antioxidant reserve:
-superoxide dismutase (SOD)
-catalase
-glutathione peroxidase (GSHPx)
- antioxidants: glutathione (GSH), vit.C, vit. E

Effects:
-depletion of endogenous antioxidant stores
-dysfunction of mitochondrial ion channels
-protein nitration
-lipid peroxidation
-DNA damage
-MMP activation



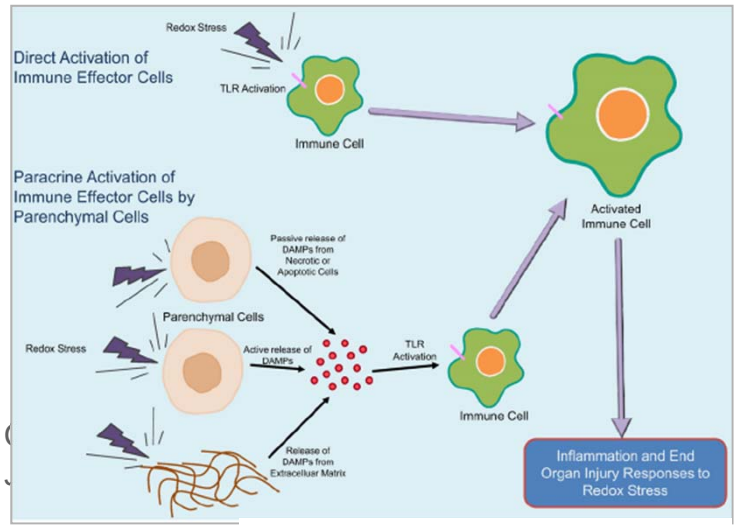
Lo et al. (2003) *Nat Rev Neurosci* 4:399-415

Oxidative stress triggers inflammation



Gorina et al., 07

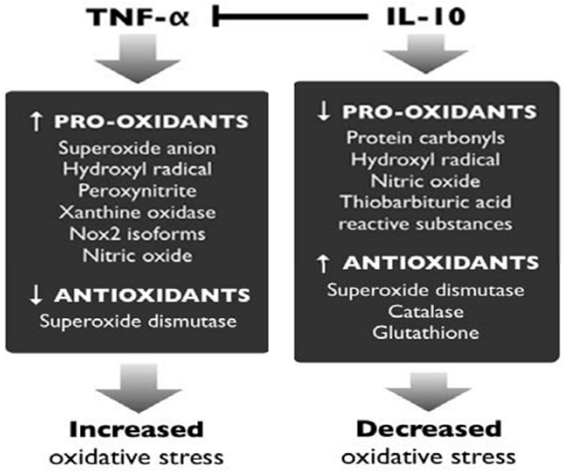
Jak/STAT



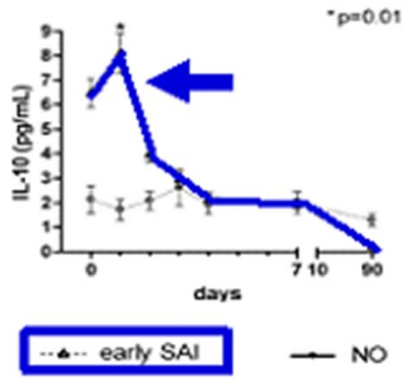
Gill et al., 2010 *Free Radic Biol Med.*

Inflammation triggers oxidative stress

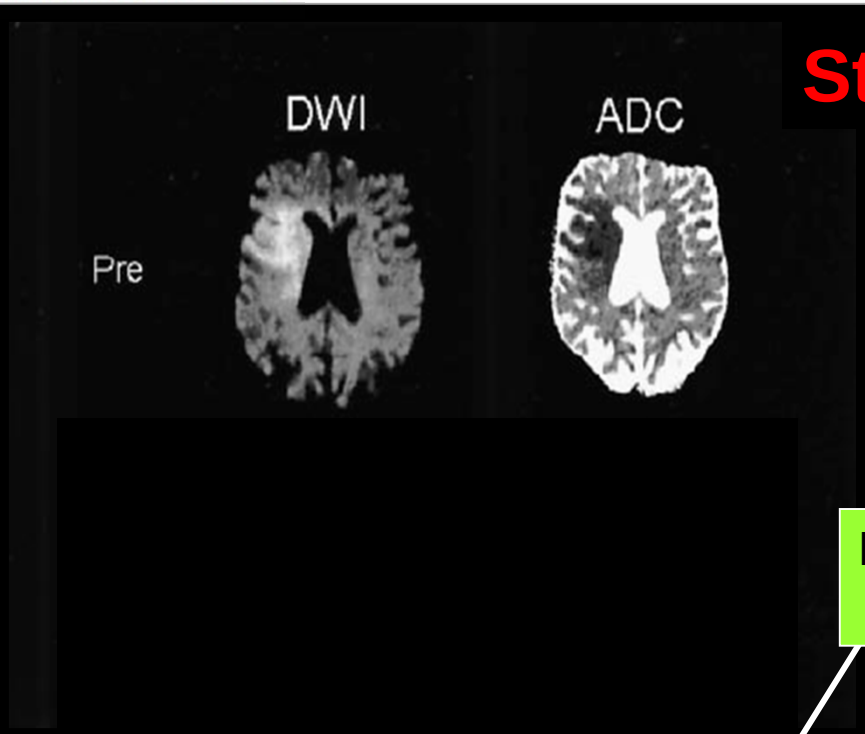
Khaper et al., 2010 *Antioxid Redox Signal.*



Stroke-associated infection

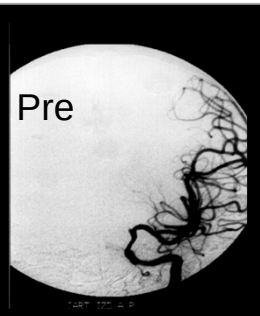


Chamorro et al., 2007. *Stroke*



Stroke

<3h
4.5h



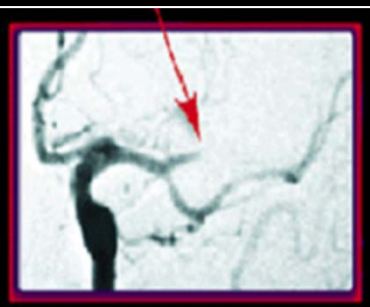
tPA possible (5-10%)

Recanalization

No recanalization

Recanalization within the first 2h

Late Recanalization

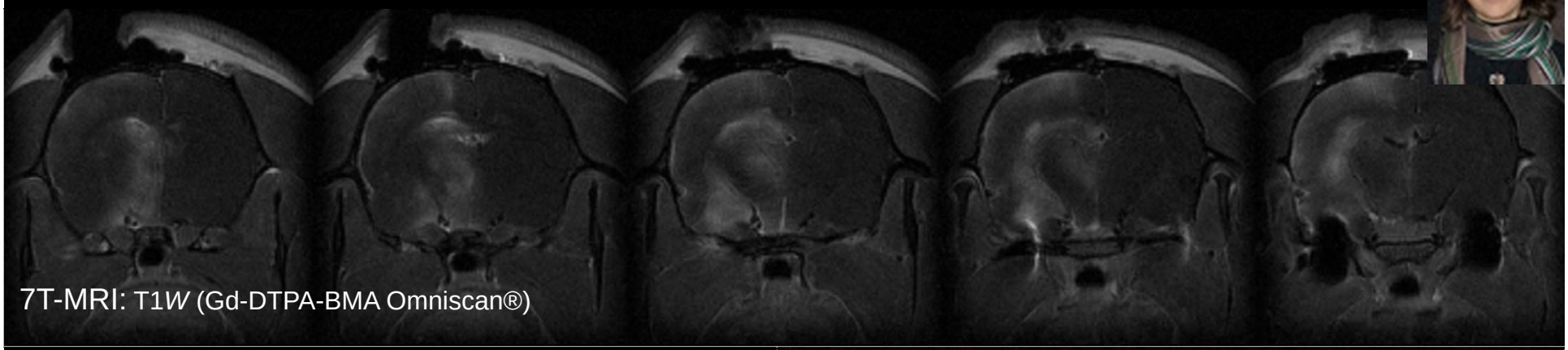


Reperfusion injury???

Hemorrhagic transformation
Oxidative stress
BBB breakdown

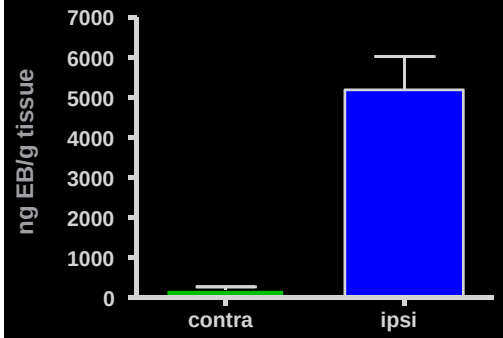
Re-occlusion and neurologic impairment (30%)

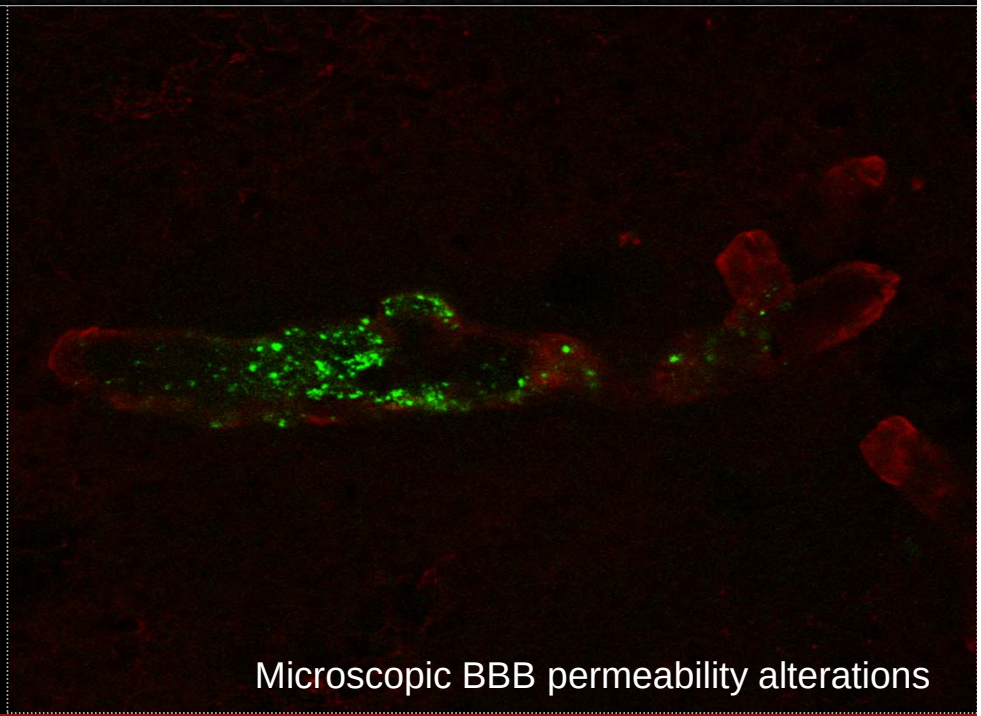
Alterations in blood-brain barrier permeability



7T-MRI: T1*W* (Gd-DTPA-BMA Omniscan®)

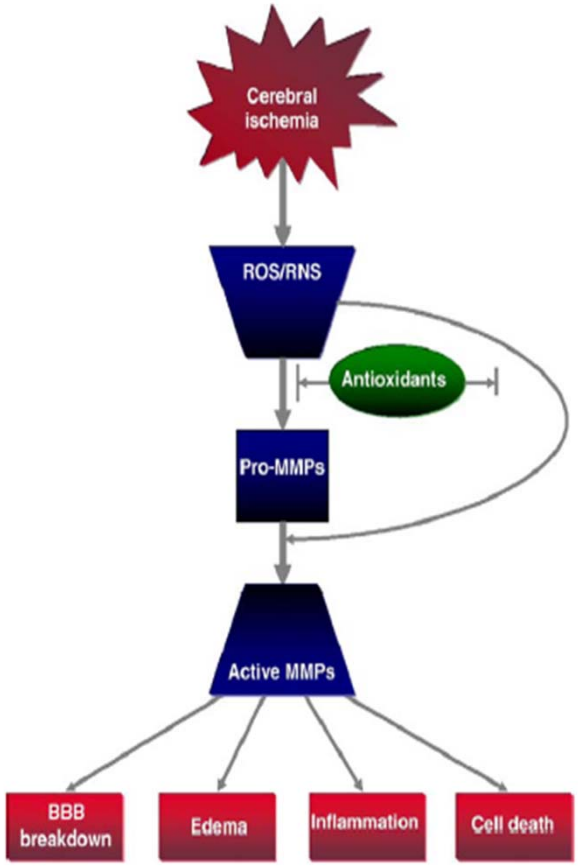
Evans Blue extravassation



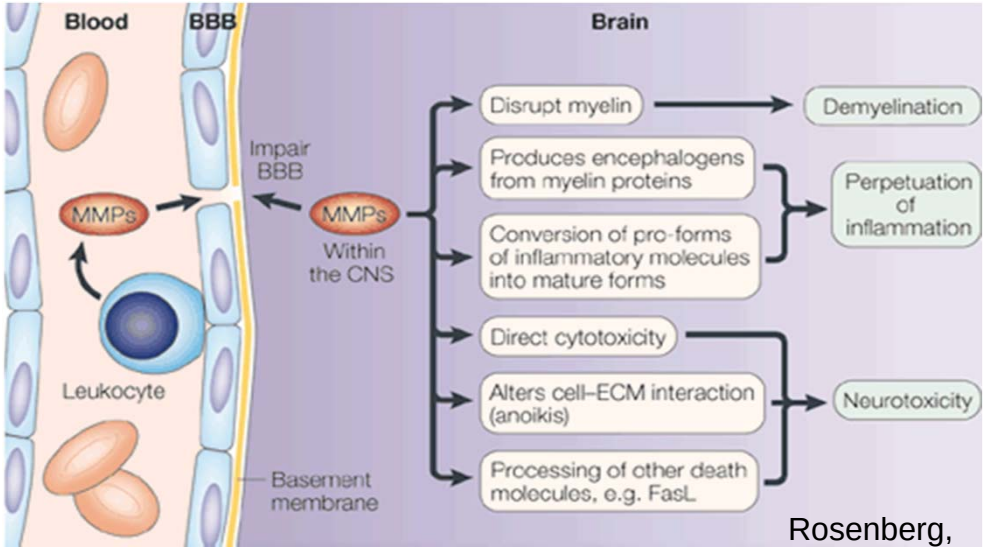


Microscopic BBB permeability alterations

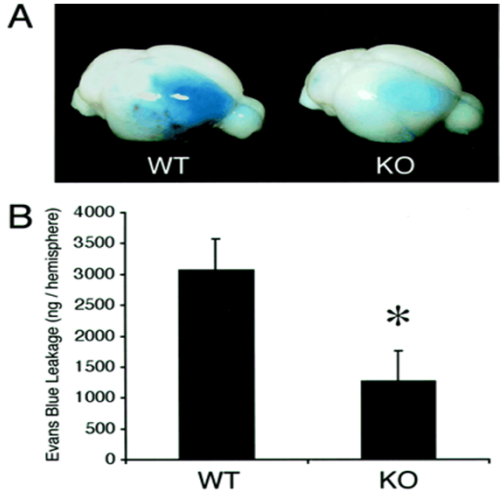
Matrix Metaloproteinases (MMP) and changes at the blood brain barrier (BBB)



Liu & Rosenberg, 2005
Free Radic Biol Med 39:71-80



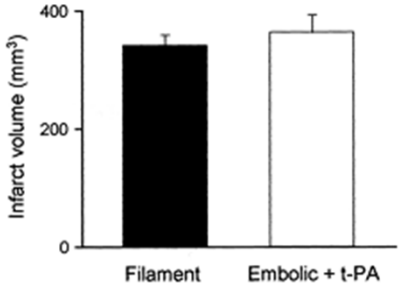
Rosenberg, 2002

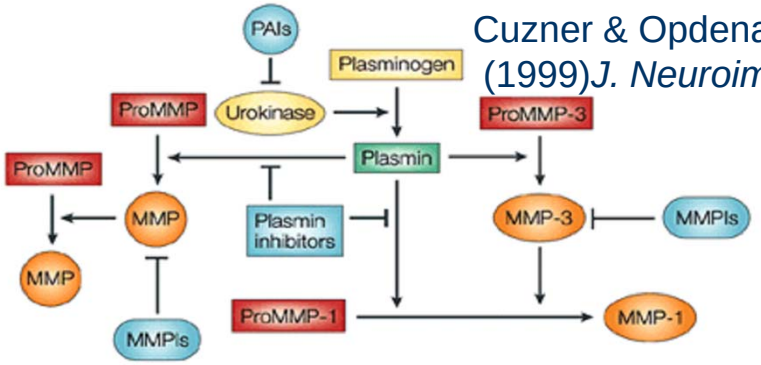


Asahi et al., (2001)
J Neuroscience

tPA increases MMP-9 activity and BBB breakdown

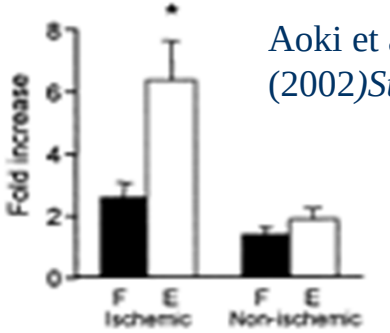
Infarct volume





Cuzner & Opdenakker (1999)*J. Neuroimmunol*.

MMP-9 4h after reperf.

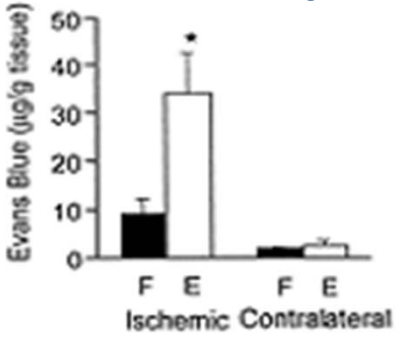


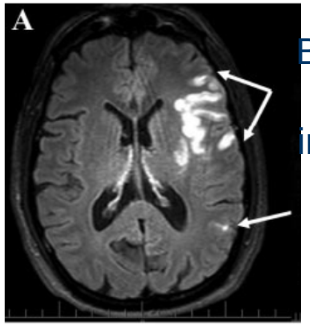
Aoki et al. (2002)*Stroke*

MMP-9 levels are predictors of hemorrhagic transformation after tPA

Montaner et al. *Circulation*, 2003; Castellanos et al. *Stroke* 2003

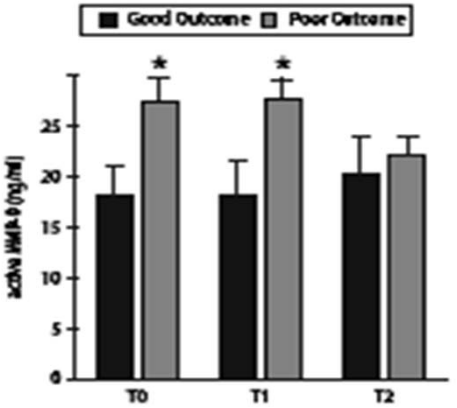
BBB leakage





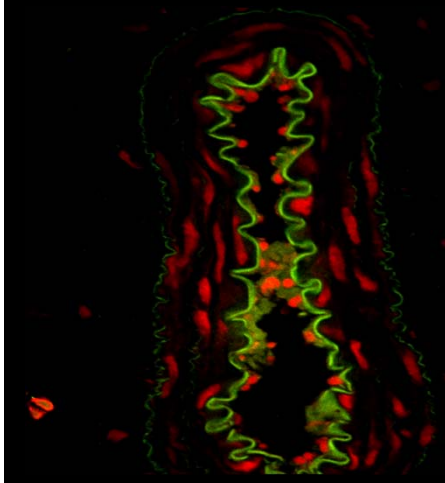
BBB disruption is associated with increased MMP-9

Barr et al., *Stroke* 2010

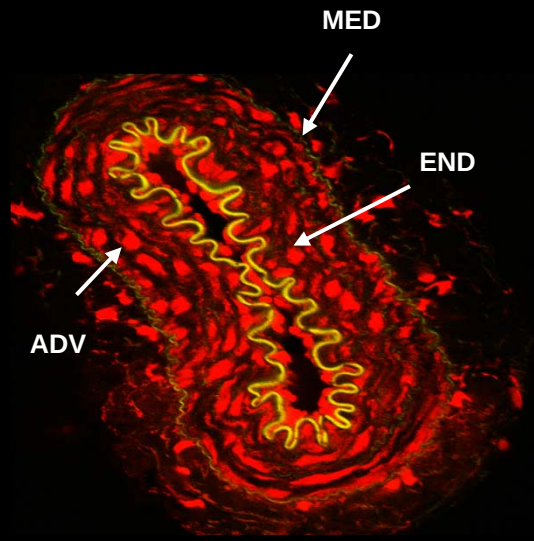


Amaro et al, *J Neurol* 09

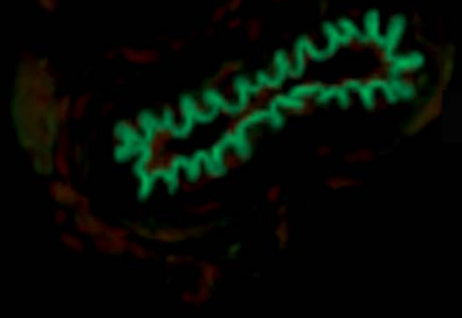
Oxidative stress in rat middle cerebral artery 24h post-ischemia



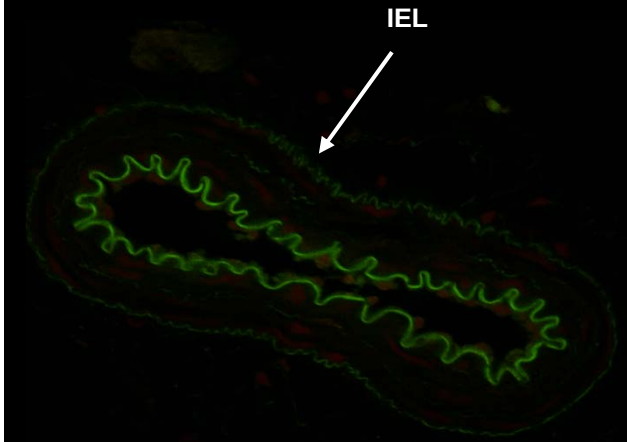
Sham



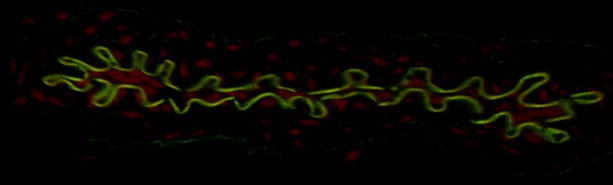
Ischemic



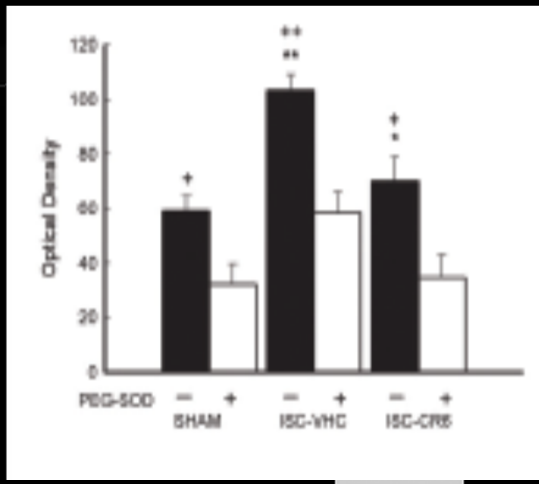
Ischemic +CR6



Sham+PEG-SOD

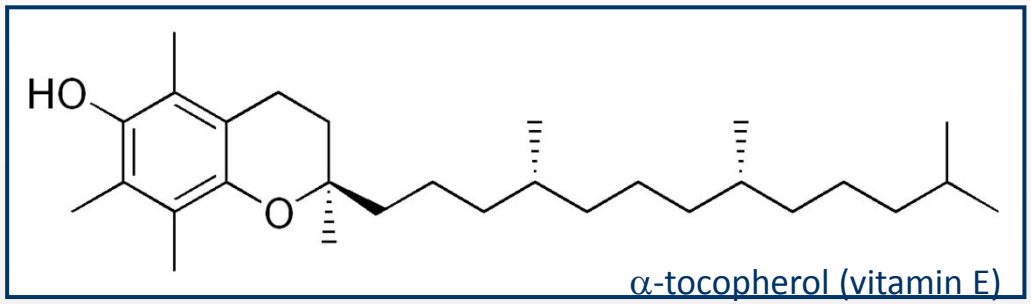


Ischemic+PEG-SOD

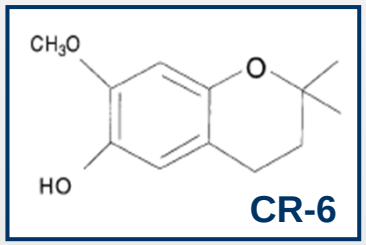


Jimenez-Altayó et al., *JPET* 2009

CR-6 is synthetic derivative of vitamin E with the antioxidant features of the latter and additional nitrogen scavenger properties

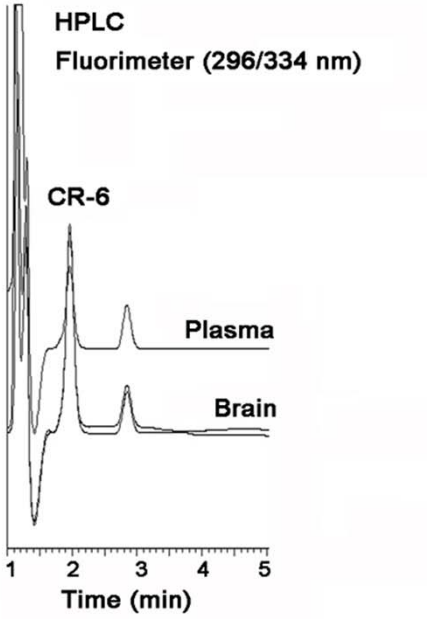


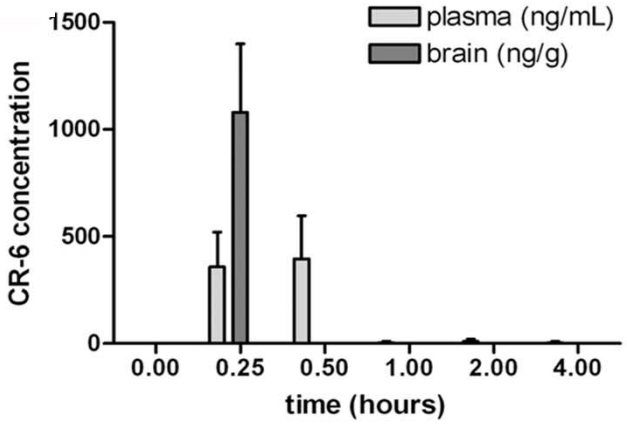
α-tocopherol (vitamin E)



CR-6

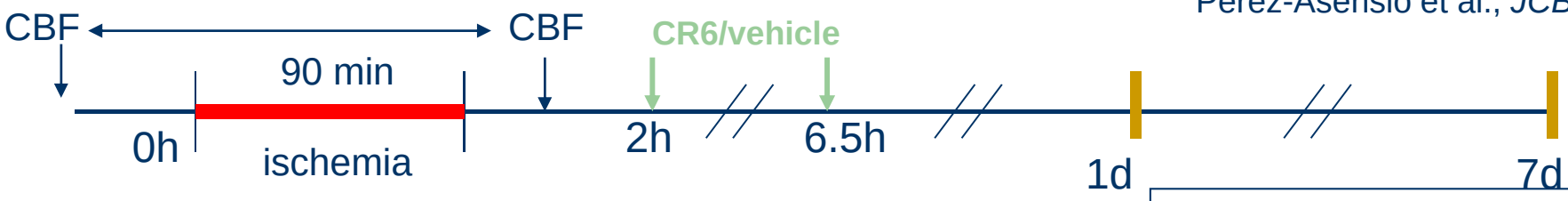
CR-6 is a lipophilic molecule that gets into the brain after oral administration to rats

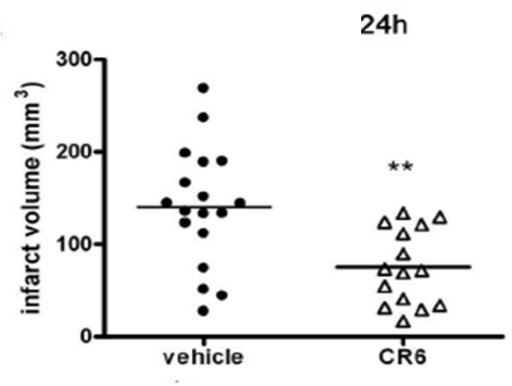


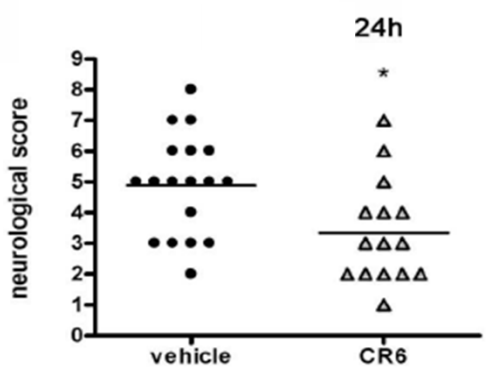


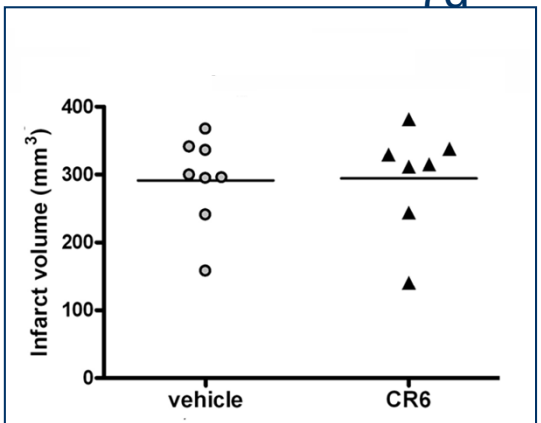
Oral administration of CR-6 at 2h and 6.5h after the onset of ischemia

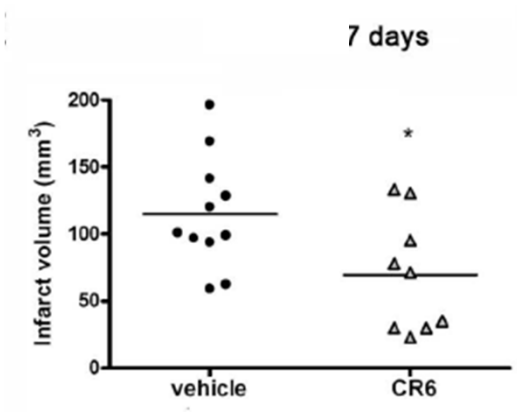
Pérez-Asensio et al., *JCBF* 2010

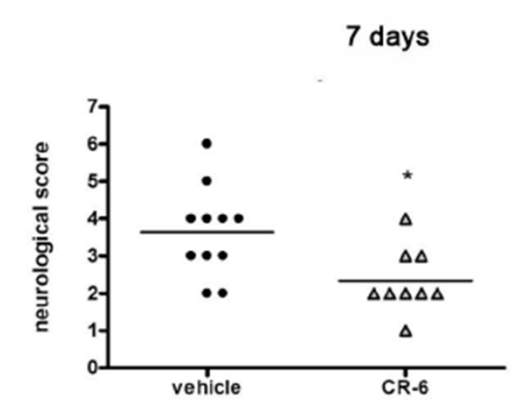


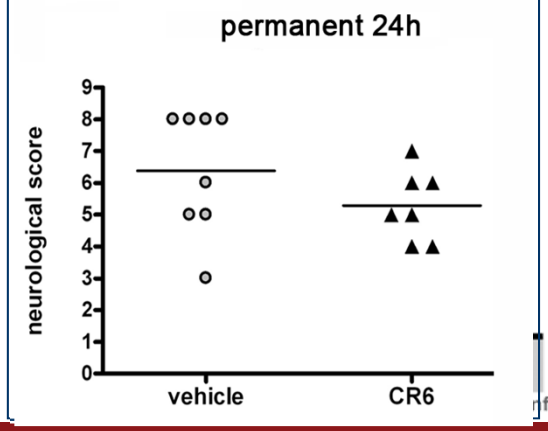


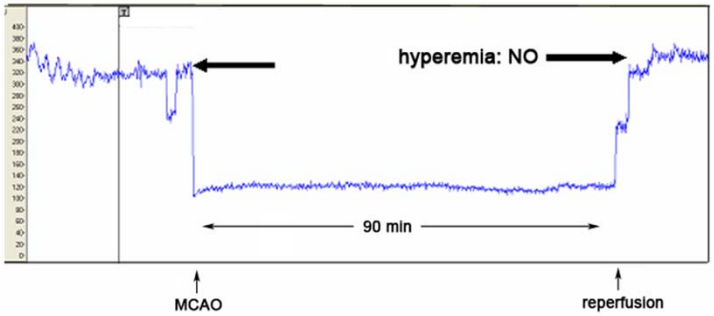


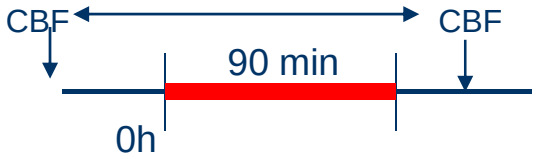


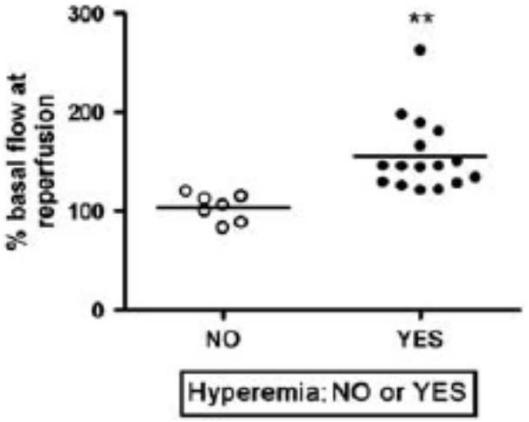






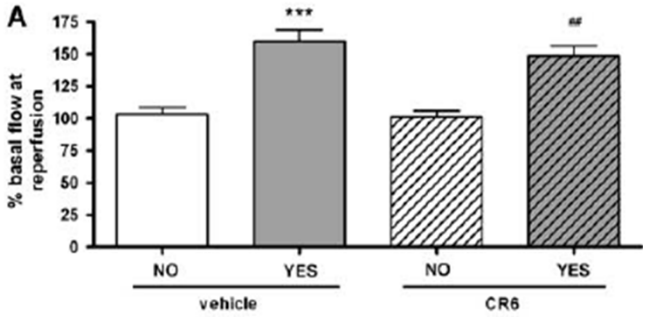


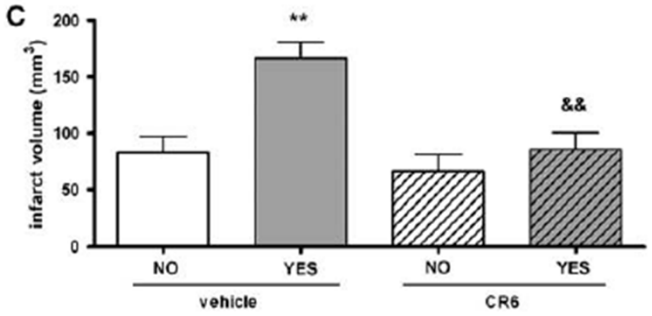


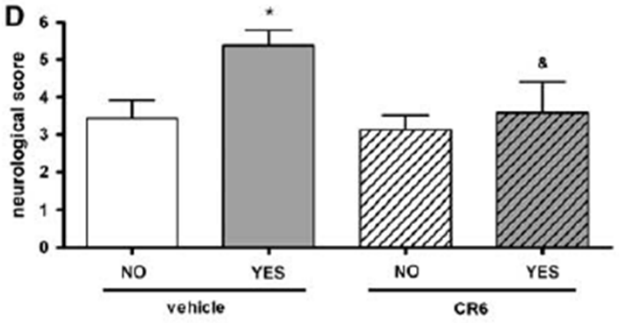


Pérez-Asensio et al., *JCBF* 2010

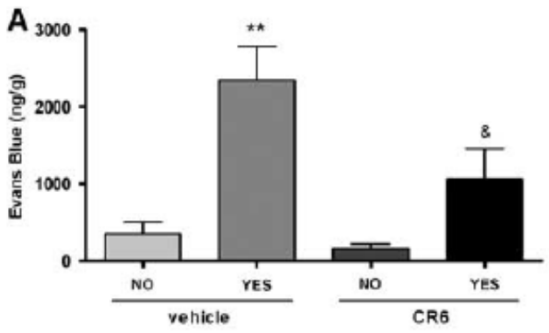
CR-6 is beneficial in rats developing hyperemia

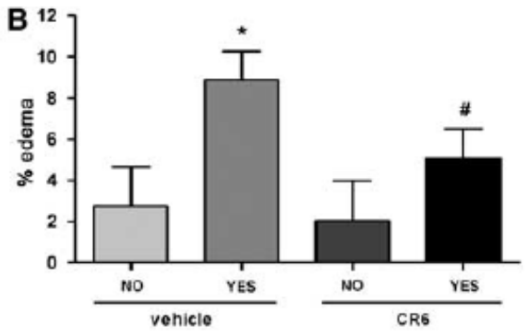


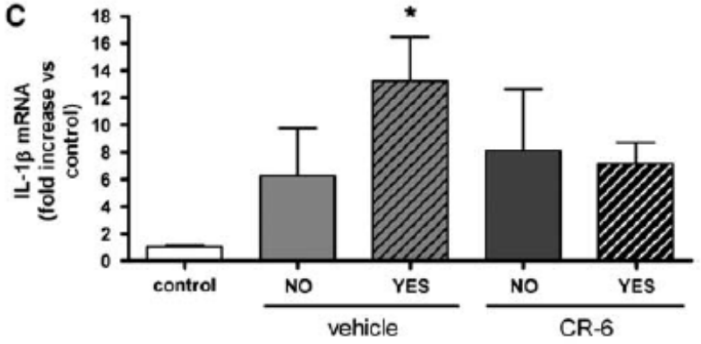




Pérez-Asensio et al., *JCBF* 2010



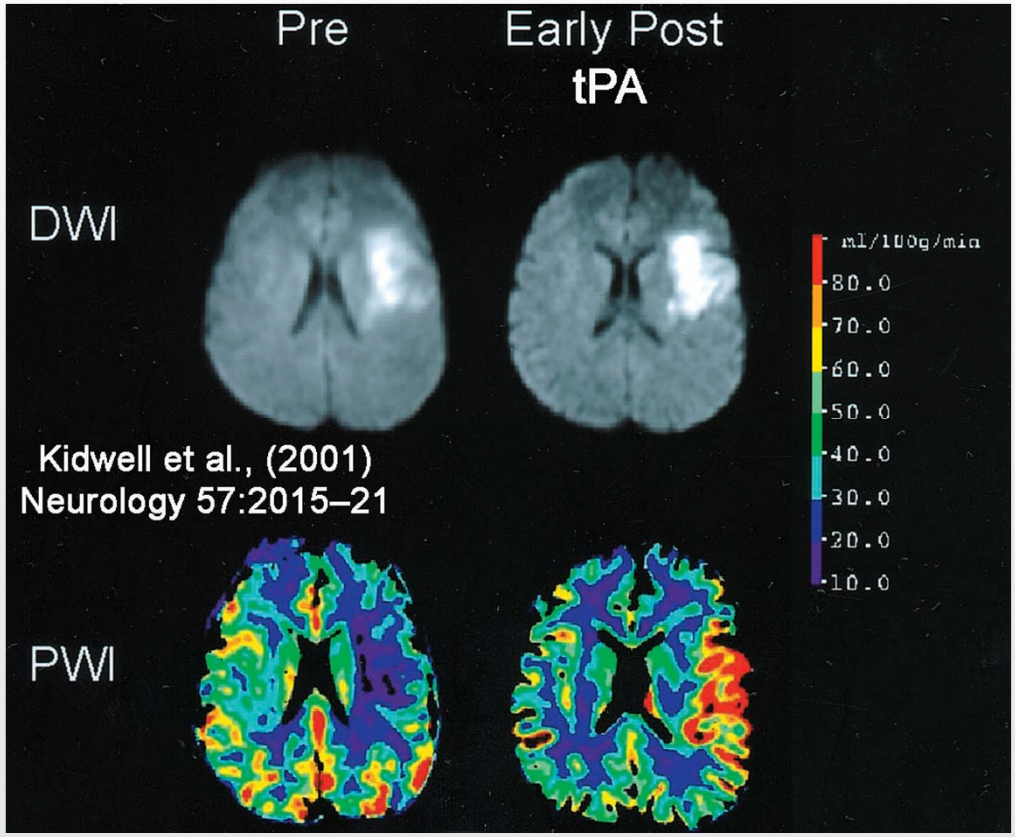




Hyperemia may be a marker of reperfusion injury in rats

Does hyperemia occur after thrombolysis in humans stroke?

Is hyperemia a sign of reperfusion injury in humans?



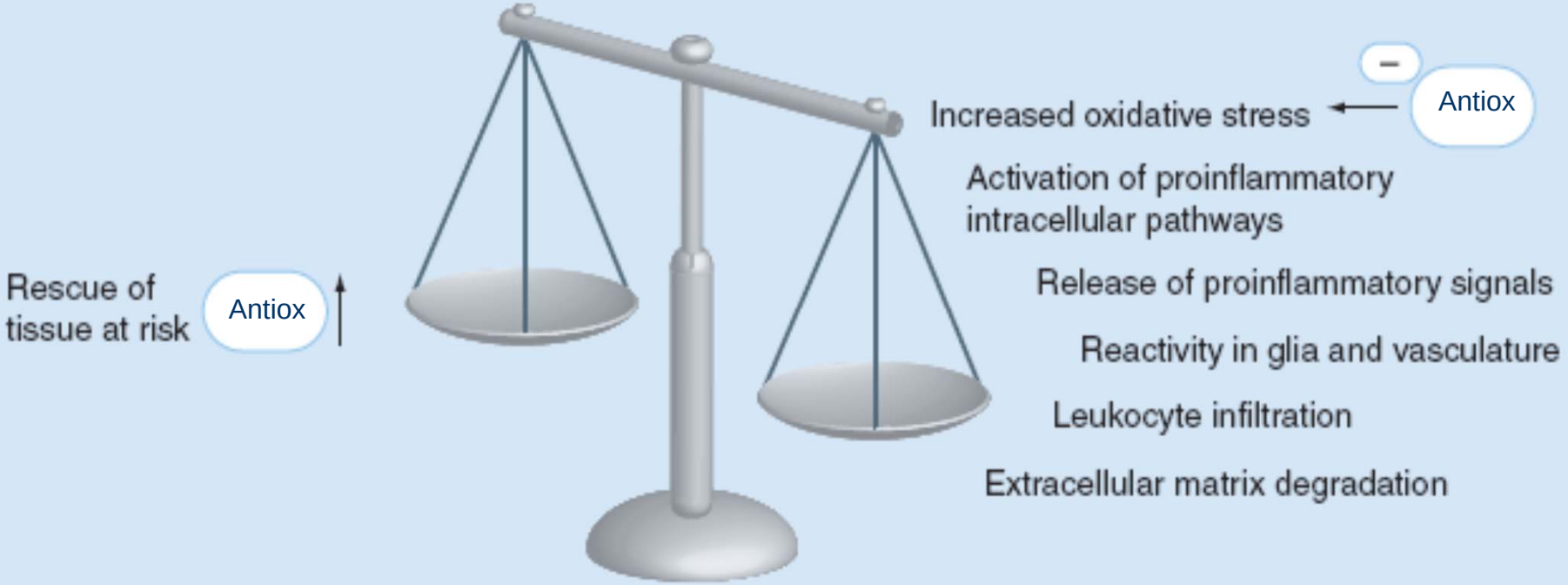
Postischemic hyperperfusion, visualized with perfusion MRI in humans following recanalization by intra-arterial thrombolytic therapy, occurred in about 40% of patients within hours

CAN WE IMPROVE THE BENEFITS OF REPERFUSION?

Does reperfusion injury occur in human ischemic stroke after thrombolysis?

- Can patients at risk of developing reperfusion injury be identified early after stroke?
  MRI assessement of hyperperfusion at reperfusion????

- Can these patients be the target of specific therapeutic intervention?
  Certain antioxidant agents?????



The Clinical and Experimental Stroke Team
IIBB-CSIC and Hospital Clínic, IDIBAPS, Barcelona, SPAIN