Inflammation and oxidative stress after stroke

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Oxidative stress after brain ischemia

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

**ROS:**
- Superoxide anion
- Hydrogen peroxide
- Hydroxyl radical
- Hypochlorous acid

**RNS:**
- Nitric oxide
- Peroxynitrite

**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

Inflammation triggers oxidative stress

Cerebral Ischemia → Reactive Oxygen Species (ROS) → Redox State → NFκB/IκB

NFκB/P50/P65 → Transcription Factors

Target Genes: COX2, iNOS, MMPs, ICAM-1, Cytokines → ROS, BBB damage → Apoptosis, Necrosis

pStat1

H2O2 control INF-γ

Gorina et al., 07

Khaper et al., 2010 Antioxid Redox Signal.

Increased oxidative stress

Decreased oxidative stress

TNF-α → IL-10

↑ PRO-OXIDANTS
- Superoxide anion
- Hydroxyl radical
- Peroxynitrite
- Xanthine oxidase
- NOx2 isoforms
- Nitric oxide

↓ ANTIOXIDANTS
- Superoxide dismutase
- Catalase
- Glutathione

↑ ANTIOXIDANTS

Stroke-associated infection

Gill et al., 2010 Free Radic Biol Med.
Recanalization within the first 2h

Recanalization

No recanalization

Reocclusion and neurologic impairment (30%)

Hemorrhagic transformation
Oxidative stress
BBB breakdown

Reperfusion injury???

<3h
4.5h

tPA possible (5-10%)

Stroke
Alterations in blood-brain barrier permeability

7T-MRI: T1W (Gd-DTPA-BMA Omniscan®)

Evans Blue extravasation

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

Asahi et al., (2001)
*J Neuroscience*
tPA increases MMP-9 activity and BBB breakdown


MMP-9 levels are predictors of hemorrhagic transformation after tPA

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 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
Reactive hyperemia at reperfusion is a marker of reperfusion injury in rats.

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 assessment of hyperperfusion at reperfusion????

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