THE ROLE OF IMMUNITY IN CEREBROVASCULAR DISORDERS

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Inflammation, cytokines and stroke

Inflammatory mediators in cerebral ischemia

Initiation	Progression	Repair	Tolerance
Endothelial and perivascular cell activation	Inflammation, apoptosis, necrosis	Inflammation and suppression of inflammation	Suppression of inflammation apoptosis, necrosis

How stroke-risk factors may operate to increase stroke likelihood

STROKE RISK FACTORS

endothelium
- chemotaxis
- adhesion molecule expression

monocytes
- cytokine release
- integrin expression

STEP 1: Increased adhesion & transendothelial migration of monocytes

↓

endothelium
- anticoagulant factors ↓
- procoagulant factors ↑

monocytes
- prothrombotic factors

STEP 2: Risk for stroke ⇑

↓

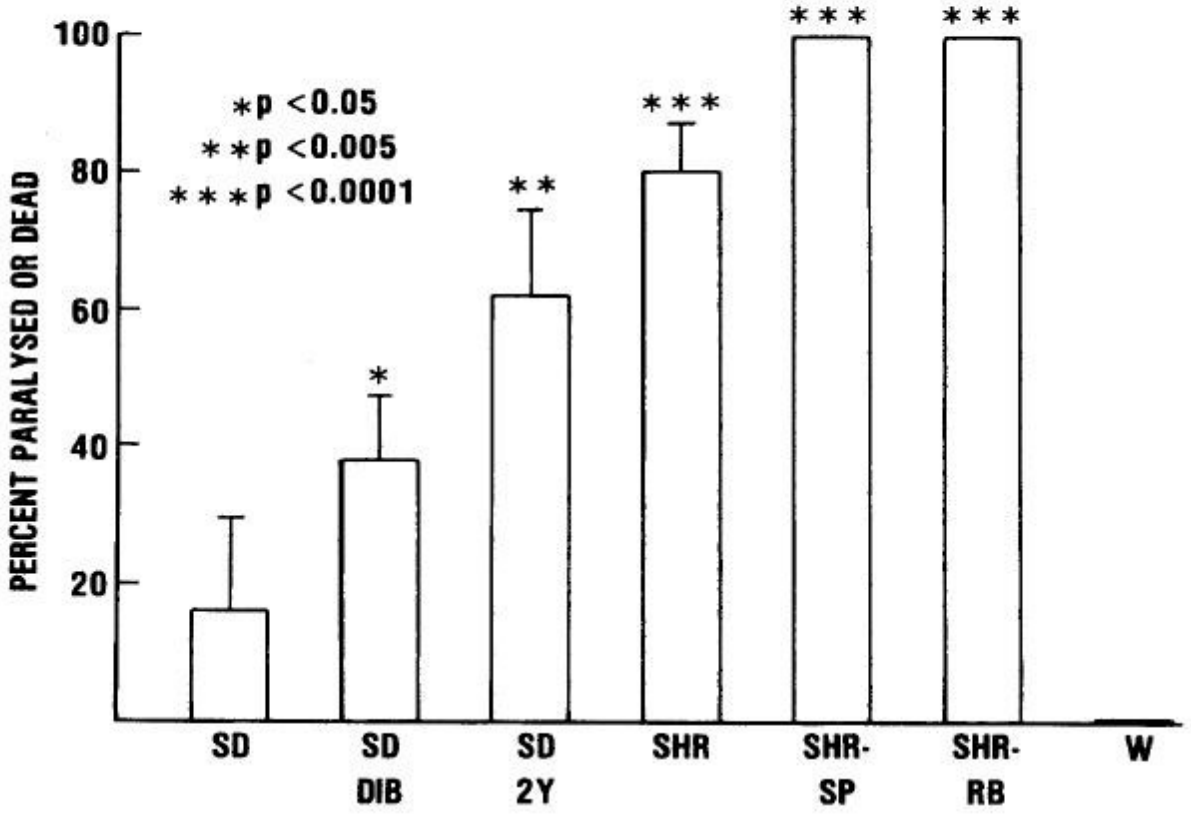
- natural oscillation of coagulation potential
- inflammation , infection , trauma , stress

STEP 3: Coagulation / Complement activation

➔ ➔ ➔ **THROMBOSIS / HEMORRHAGE**

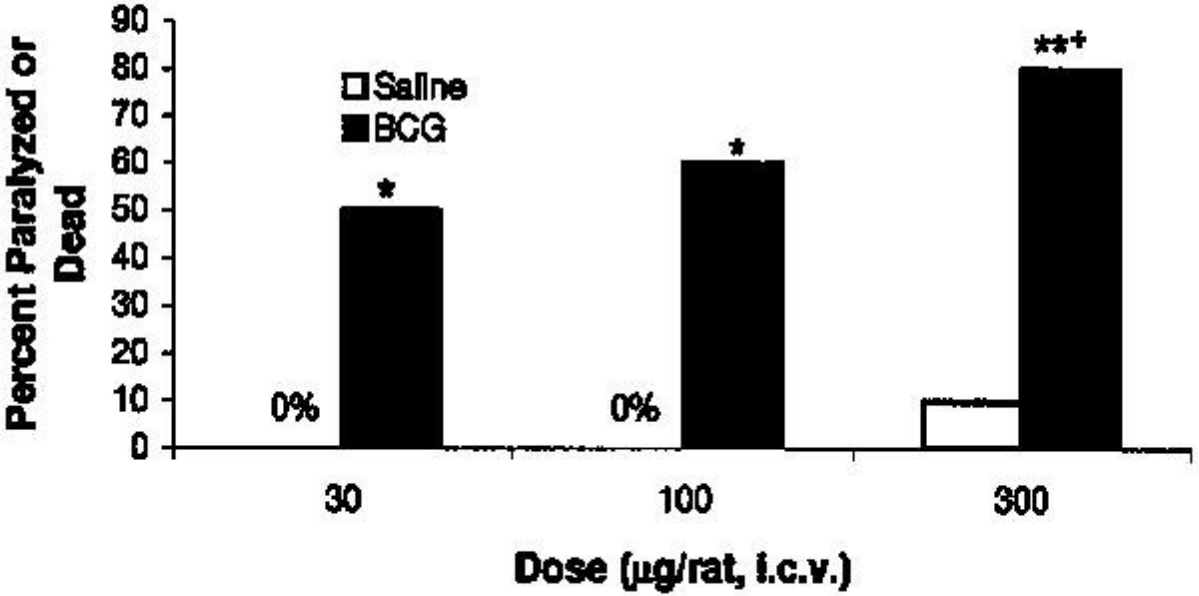
Monocyte Activation and Stroke-Risk

Stroke-risk factors augment LPS-induced brain injury



Monocyte activation increases stroke-risk

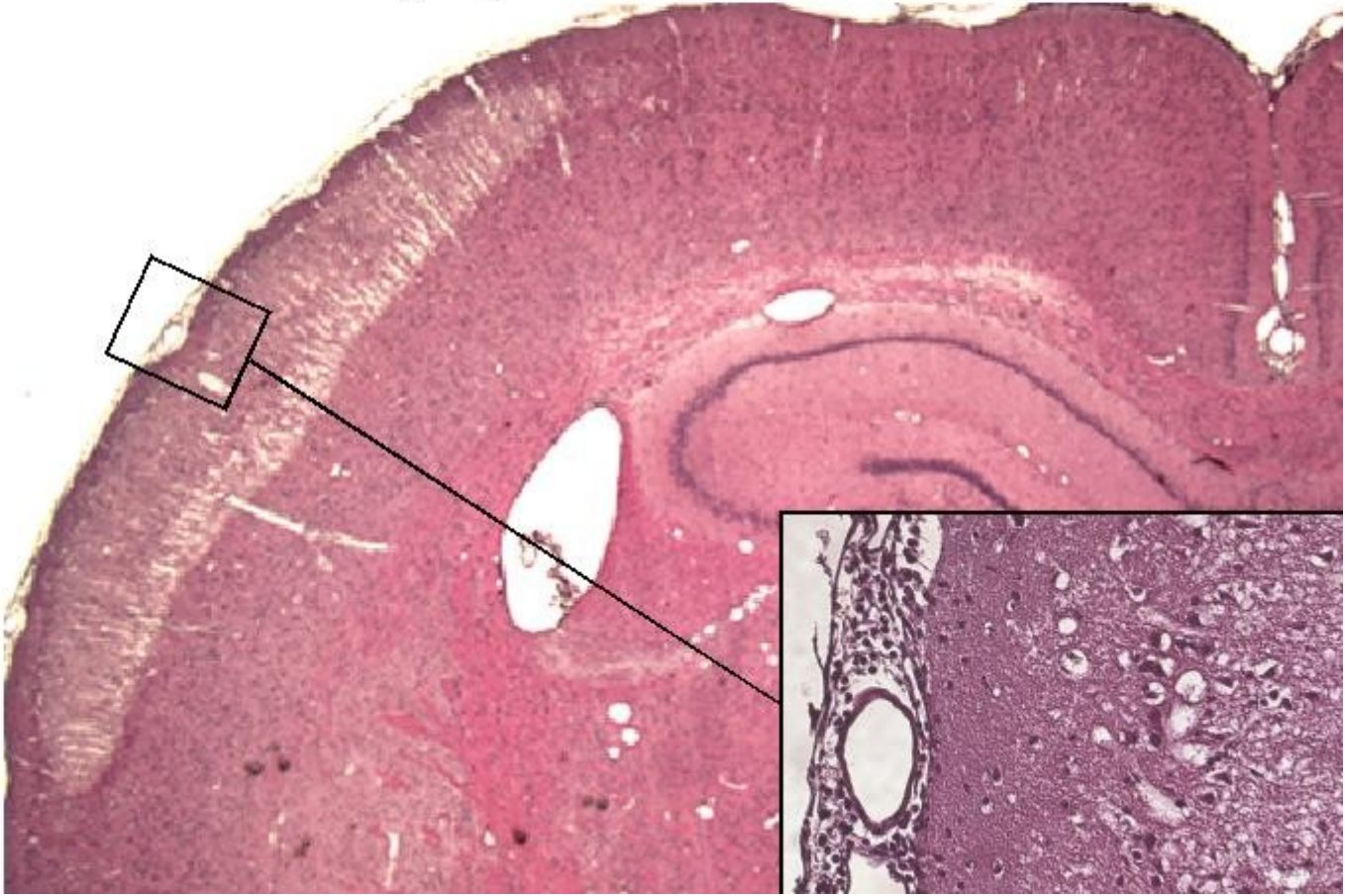
LPS-induced paralysis or death is augmented by BCG-priming



Sirén et al., 2001

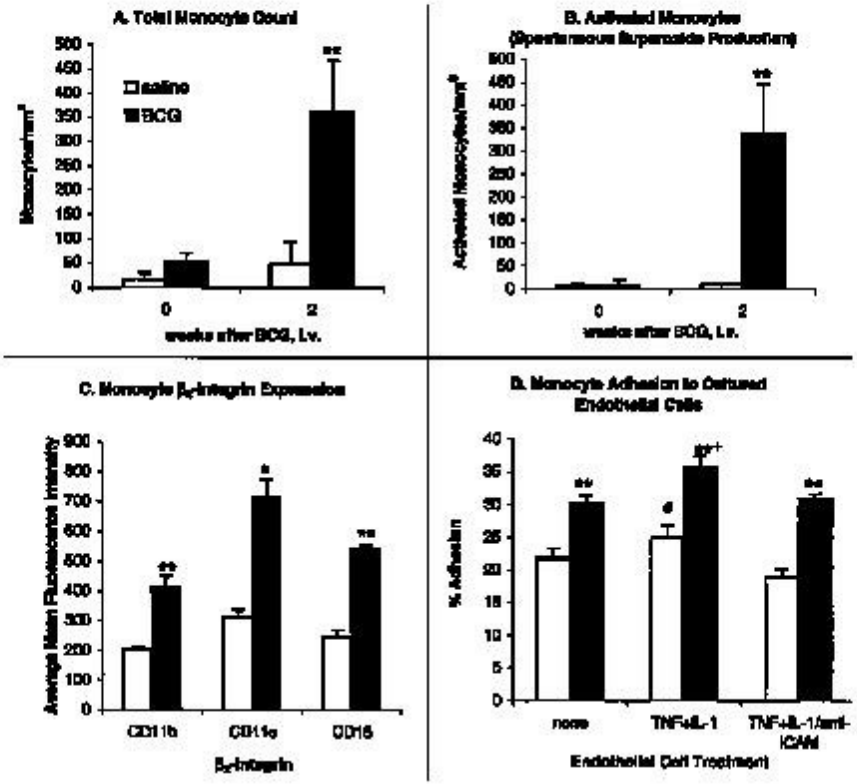
Monocyte activation increases stroke-risk

Ischemic brain damage upon LPS-treatment in BCG-primed rats



Monocyte activation increases stroke-risk

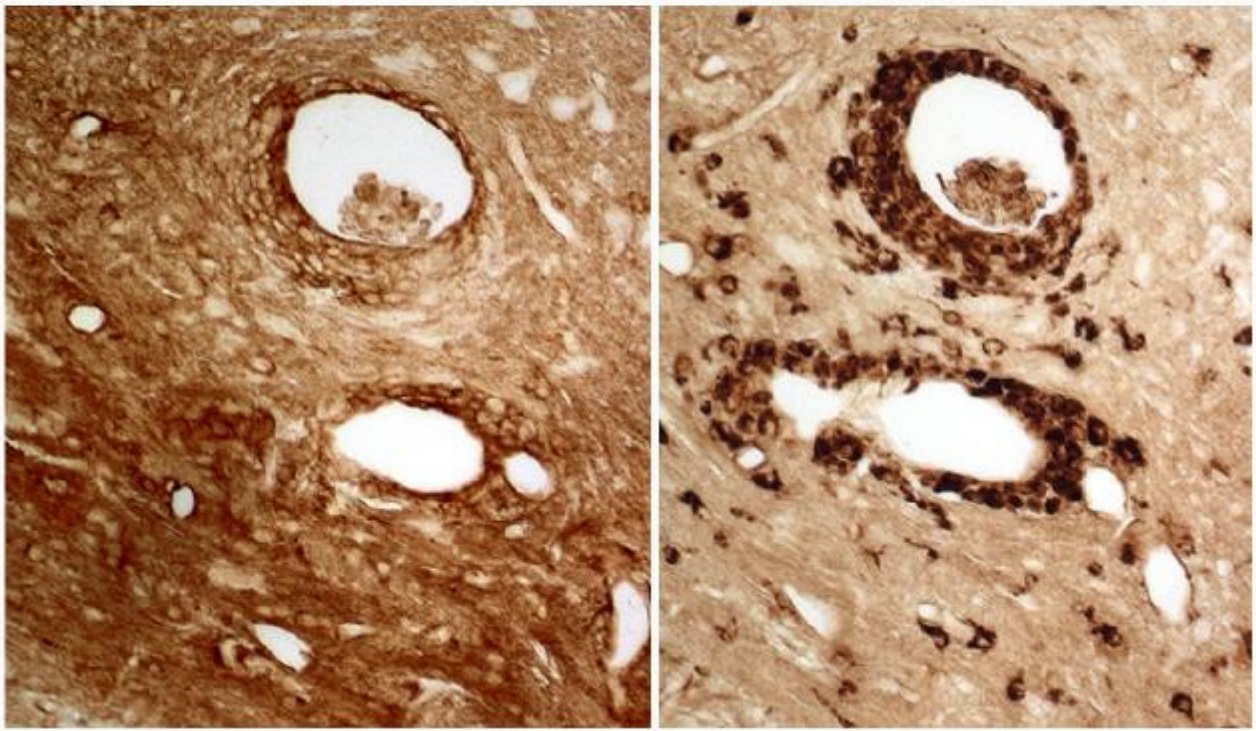
Monocyte activation in BCG-primed vs saline-treated rats



Sirén et al., 2001

Monocyte activation increases stroke-risk

Stimulation of monocyte migration into the brain by BCG-priming

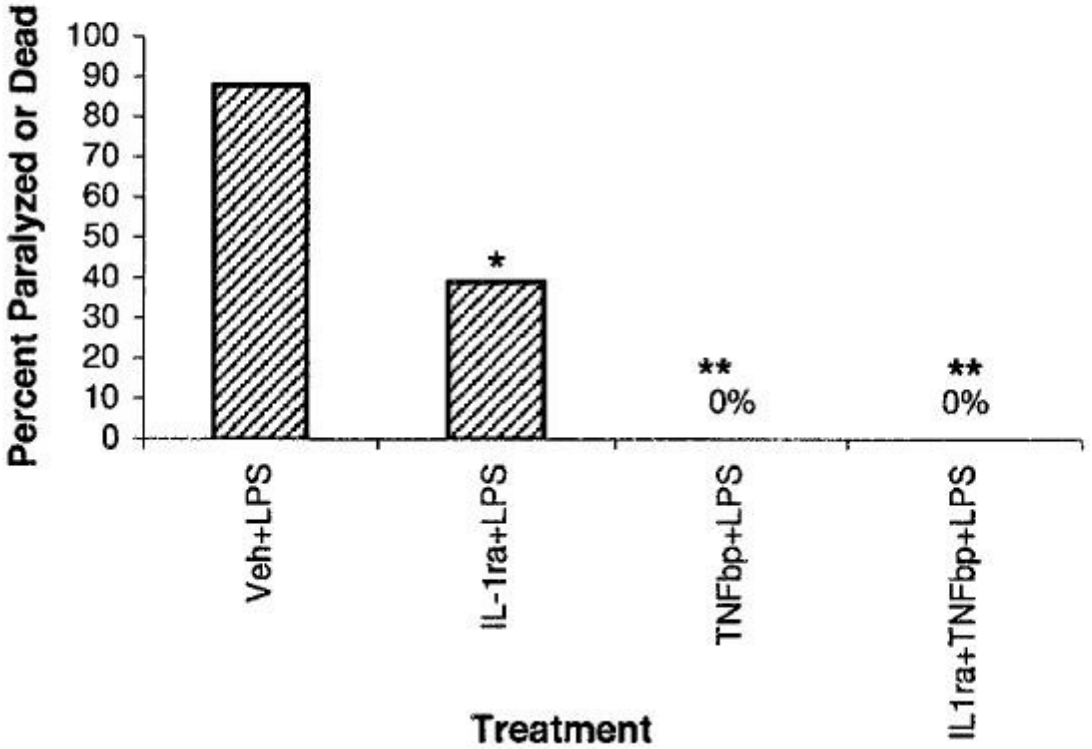


ICAM-1 (endothelium/astrocytes)

Monocyte /Macrophages (ED1)

Monocyte activation increases stroke-risk

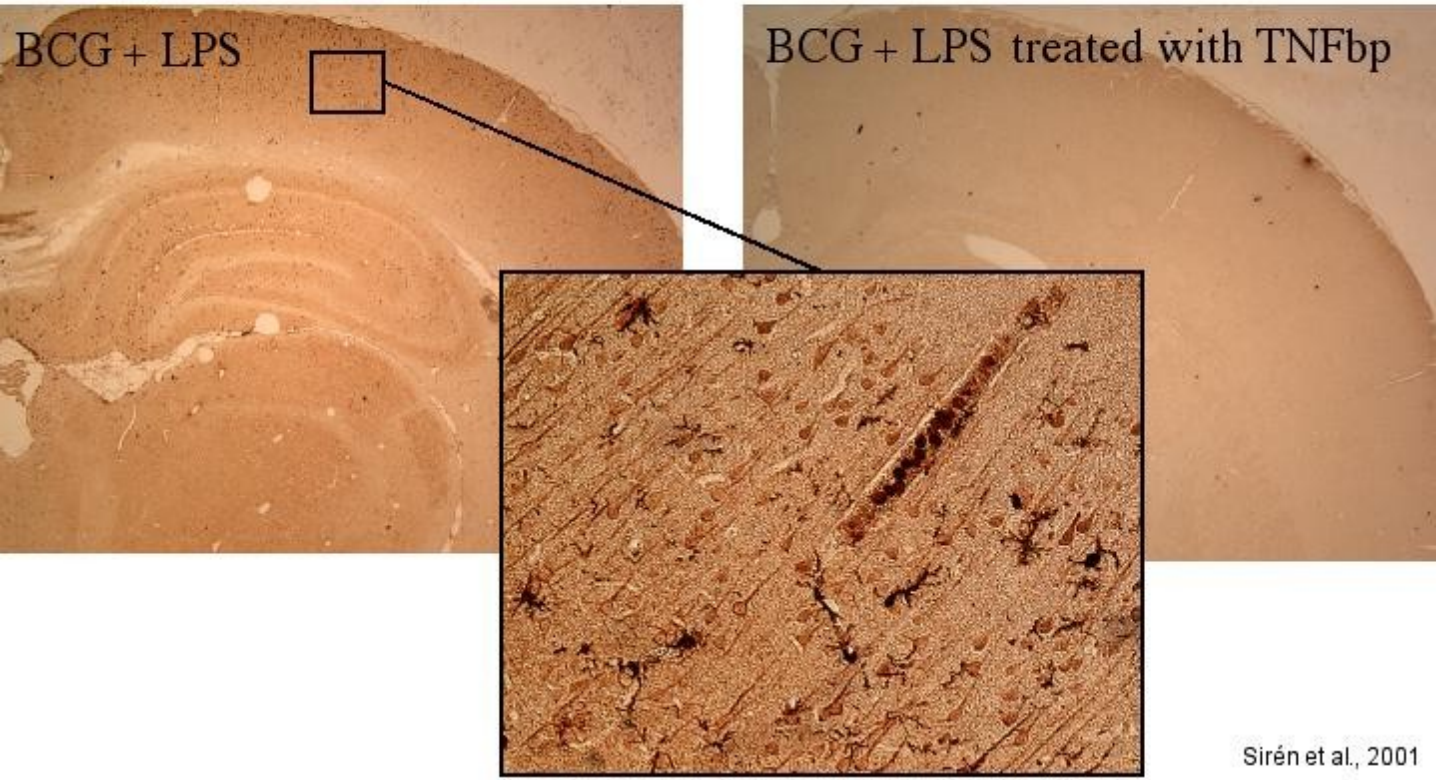
Effect of anti-cytokine treatments on
LPS-induced paralysis or death



Sirén et al., 2001

Monocyte activation increases stroke-risk

IL-1β expression in microglia and invading cells



Sirén et al., 2001

Monocyte activation increases stroke-risk

Effect of anti -cytokine treatments on IL-1β expression

Table 1. Quantitation of IL-1β immunoreactivity in the cortex and hippocampus.

	Number of IL-1β Immunoreactive Cells/1 mm²			
Group	**Cortex**	**Hippocampus**	**N**	**Cell Type Expressing IL-1β**
Saline i.v. + saline i.c.v.	58 ± 23	36 ± 10	3	Neurons
Saline i.v. + LPS i.c.v.	107 ± 30	5 ± 1	3	Microglia, monocytes > neurons
BCG i.v. + LPS i.c.v.	124 ± 19^{x}	112 ± 28^{*x}	4	Microglia, monocytes > neurons
BCG i.v. + IL1ra + LPS i.c.v.	42 ± 39	32 ± 29	4	Microglia, monocytes > neurons
BCG i.v. +TNFbp + LPS i.c.v.	7 ± 5	2 ± 1	5	Microglia, monocytes > neurons

Asterisks denote statistical significance in glial IL-1β-expression between BCG + LPS and the saline + LPS group ($^{*}p < 0.05$), crosses depict statistical significance between BCG + LPS– and TNF-bp-treated BCG + LPS group ($^{x}p < 0.01$). A single bolus of saline (10 μl) or LPS (100 μg/rat) was administered i.c.v. 2 weeks after the i.v. treatment with BCG or saline. The anticytokine treatments, both at a dose of 100 μg/10 μl, were administered i.c.v. 30 min before and 30 min after the injection of LPS (100 μg/rat, i.c.v.).

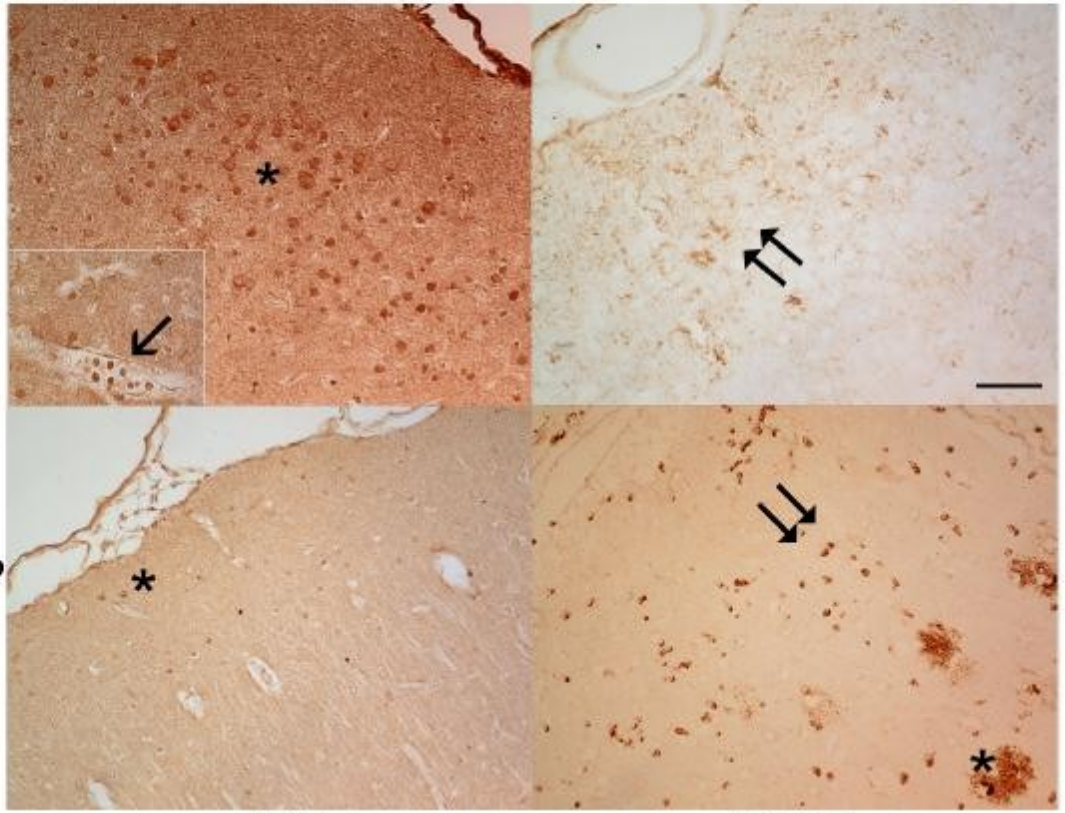
Sirén et al., 2001

Monocyte activation increases stroke-risk

TNF-α and TNF-R1 expression in neurons and invading cells

BCG + LPS

BCG + LPS
treated with TNFbp



TNF-α TNF-R1

Sirén et al., 2001

Inflammation after stroke

Inflammatory mediators in cerebral ischemia

Initiation	**Progression**	Repair	Tolerance
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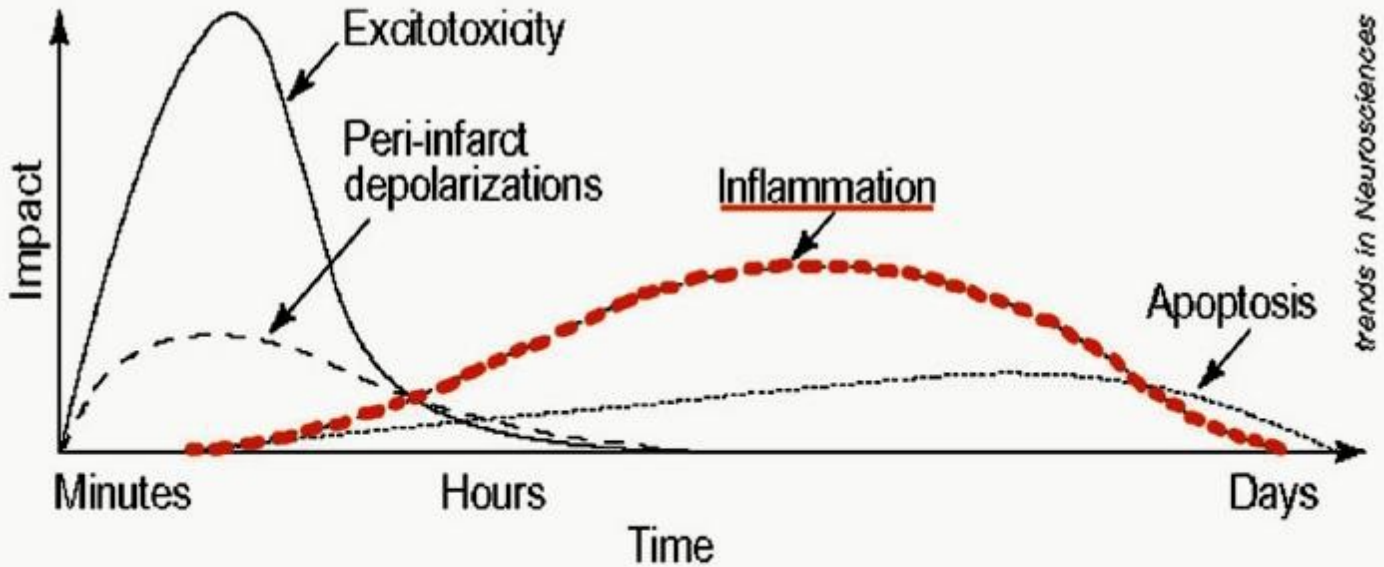
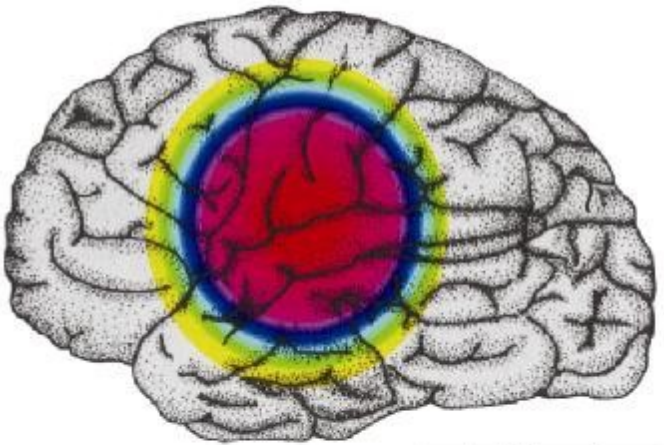
Inflammation after stroke



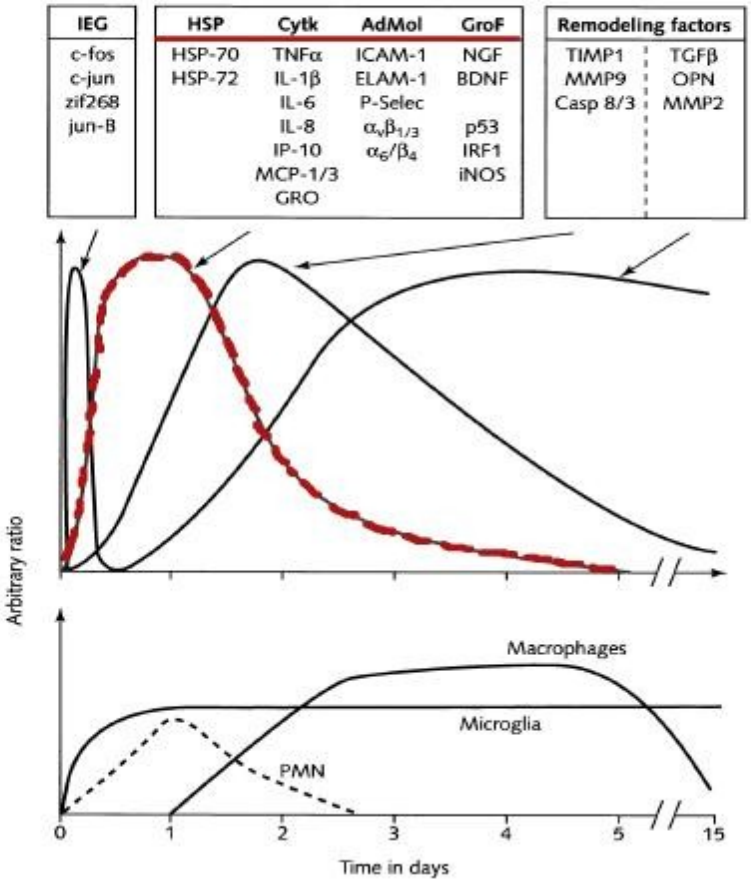
Inflammation after stroke

Morphology		Biochemistry
Infarction	CORE	Ionic failure Anoxic depolarization Glucose use ↓
	PENUMBRA	Glutamate release Glucose use ↑
Inflammation and apoptosis		Protein synthesis ↓ Acidosis Oxygen extraction ↑
		Selective gene expression



trends in Neurosciences

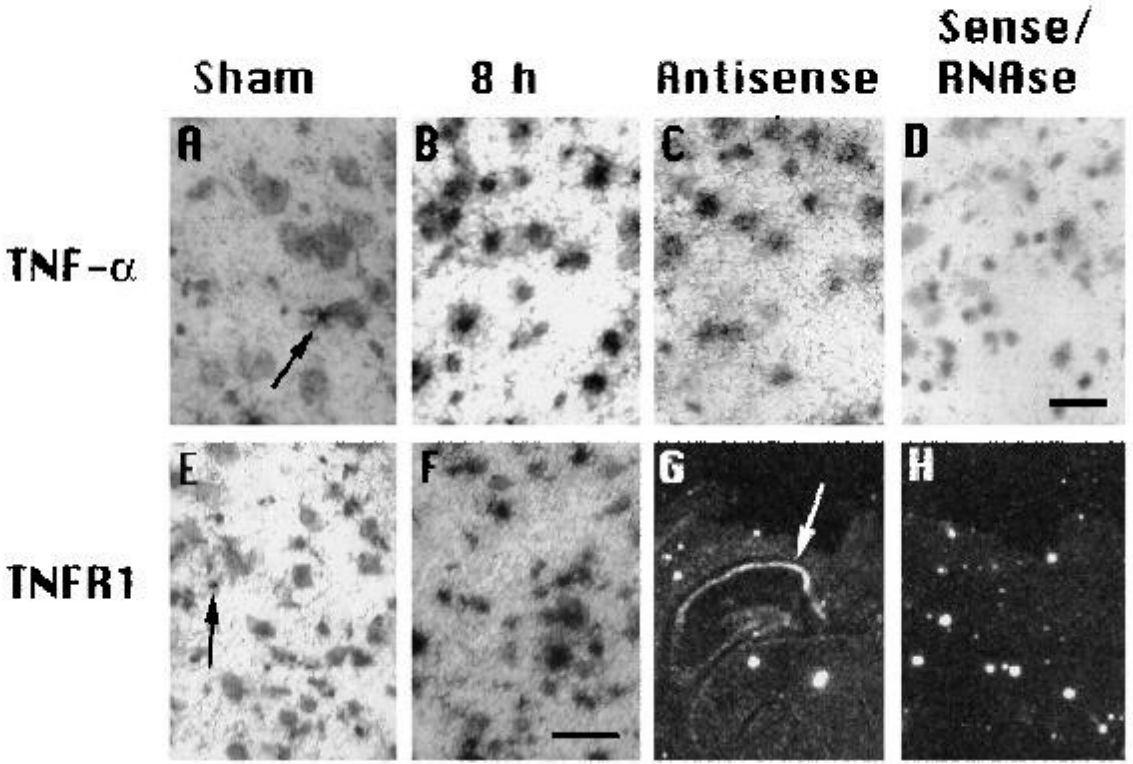
Inflammation after stroke



Feuerstein & Wang, 2001

Inflammation after stroke

TNF and TNF-R1 expression after global cerebral ischemia



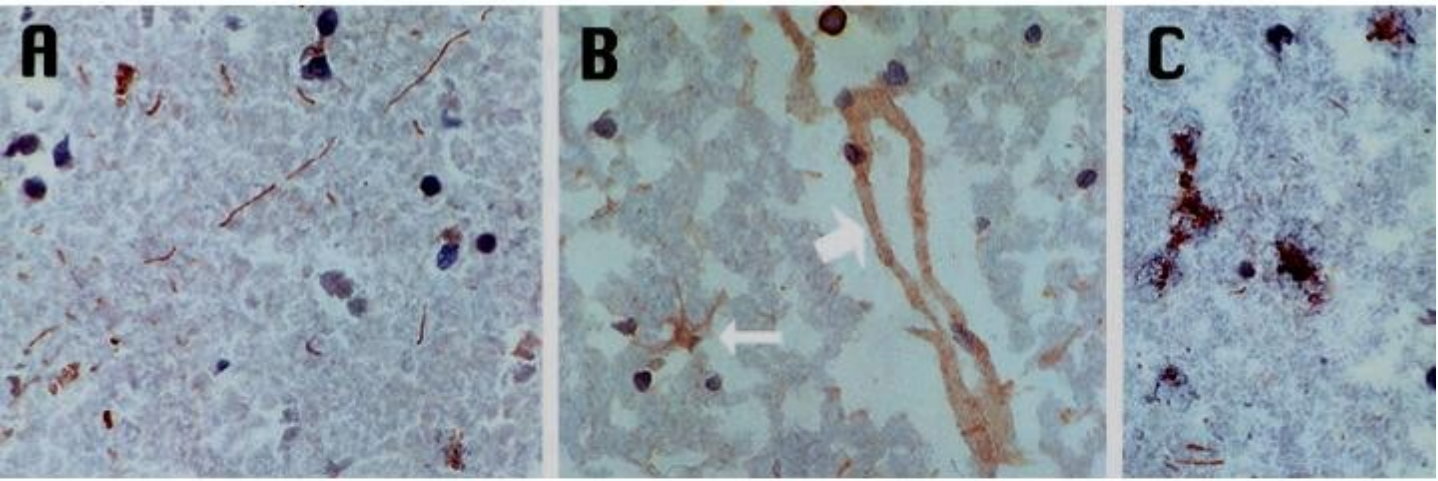
Sairanenet al., 2001

Inflammation after stroke

TNF expression in human stroke

(Sairanen et al., Stroke 2001)

- expression in neuronal, glial, phagocytic cells as early as 1 day after stroke



Inflammation after stroke

Inflammatory mediators mediate neuronal damage after stroke

Evidence from preclinical stroke models

- direct neurotoxic effects
- increased risk of thrombosis
- secondary injury (penumbra): edema, microvascular occlusion, increased local metabolic demand, cytotoxic effects
- anticytokine treatments reduce infarct volume

Inflammation after stroke

Inflammatory mediators in cerebral ischemia

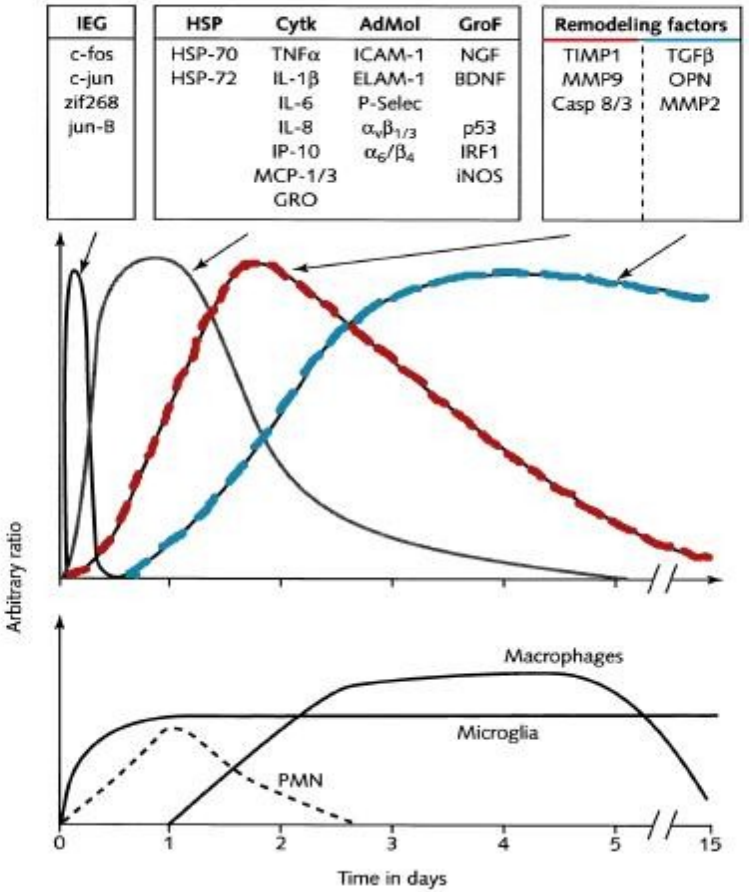
Initiation	Progression	**Repair**	**Tolerance**
Endothelial and perivascular cell activation	Inflammation, apoptosis, necrosis	**Inflammation and suppression of inflammation**	**Suppression of inflammation apoptosis, necrosis**

Inflammation after stroke

Inflammation in tissue repair and remodelling

- inflammation = protect & repair
- release of neuroprotective & growth promoting factors from activated immune cells and astrocytes
- neuroprotective effects of activated immune cells (macrophages, T-cells)

Inflammation after stroke



Feuerstein & Wang, 2001

Inflammation after stroke

Ischemic tolerance

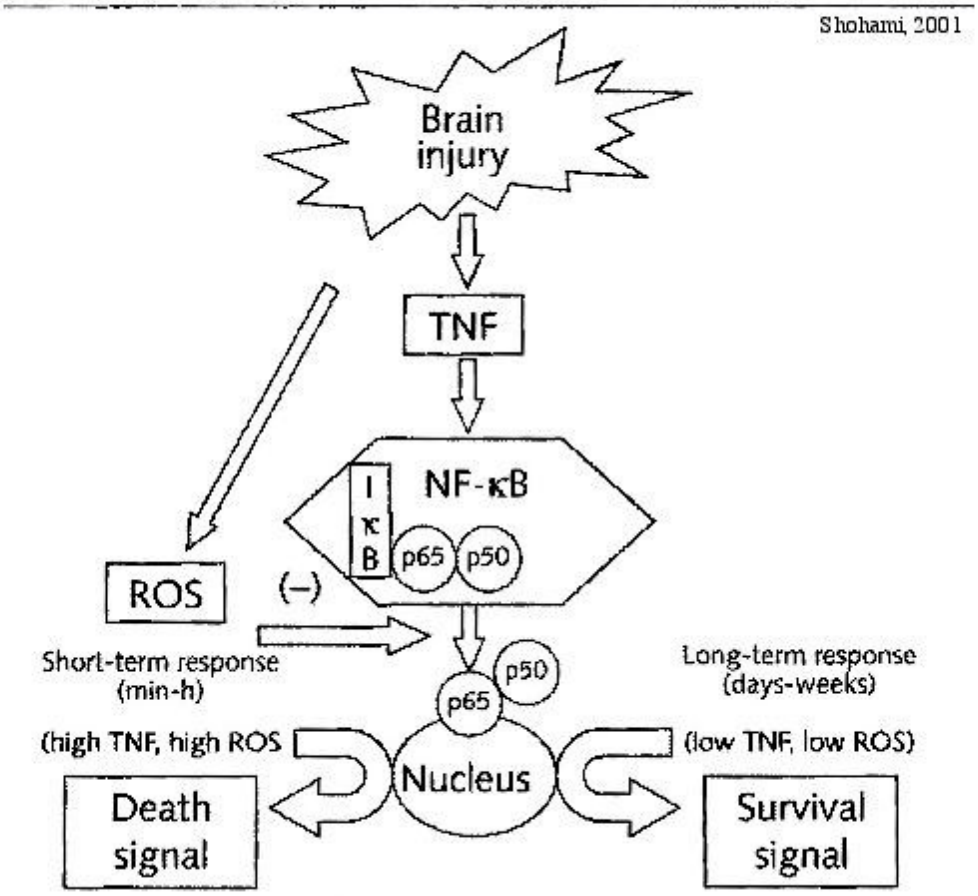
- sublethal stressors (ischemia, hypoxia, hyperthermia, oxidative stress)

cytokine signalling

suppression of inflammation
apoptosis, necrosis

tolerance to subsequent ischemia

Inflammation after stroke



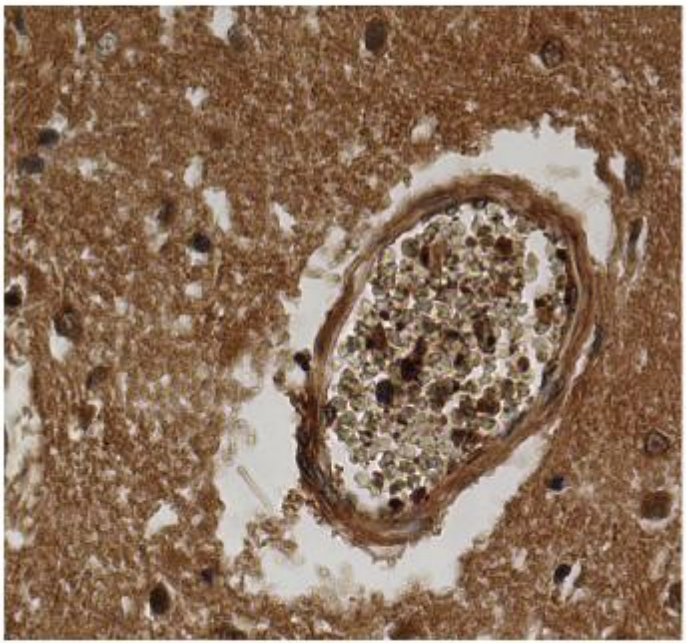
Inflammation after stroke

Erythropoietin (EPO)

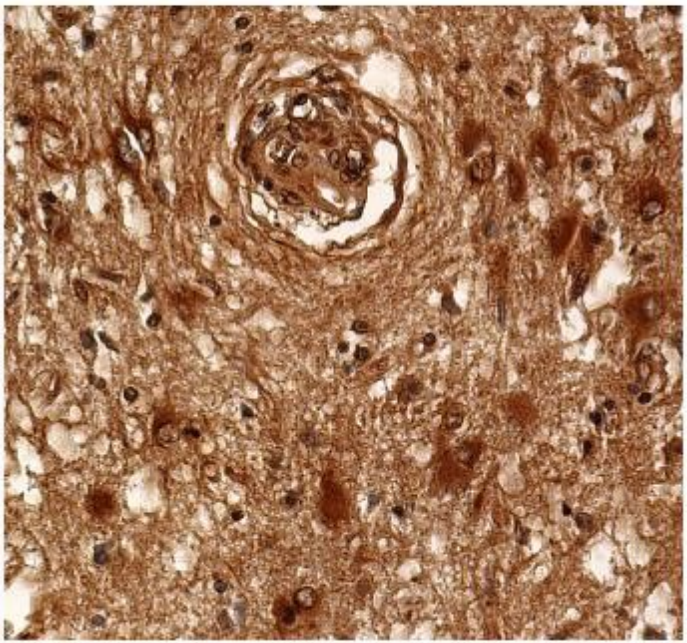
- hematopoietic growth factor
- hypoxia-induced expression in *brain*
- multiple mechanisms of neuroprotection (anti-apoptosis, angiogenesis, neurotrophic, antioxidant, glutamate inhibitory effect and anti-inflammatory actions)

Inflammation after stroke

EPO in old ischemic infarcts :
A role in ischemic tolerance ?



EPO in invading cells

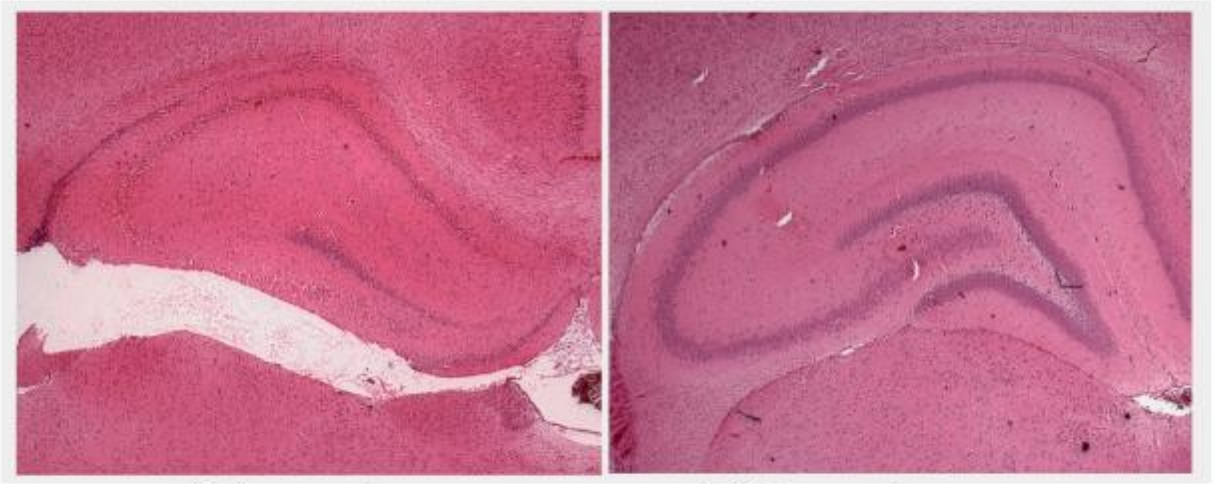


EPO in astrocytes

Sirén et al., ActaNeuropath, 2001

Inflammation after stroke

EPO protects against brain damage in a rat model of hypoxia-ischemia



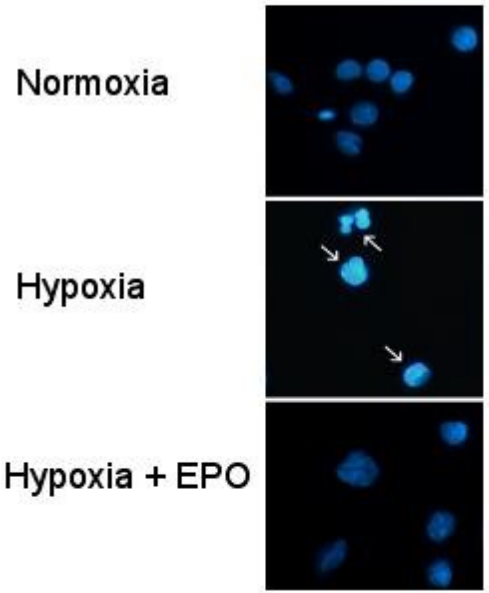
vehicle treated

EPO treated

Inflammation after stroke

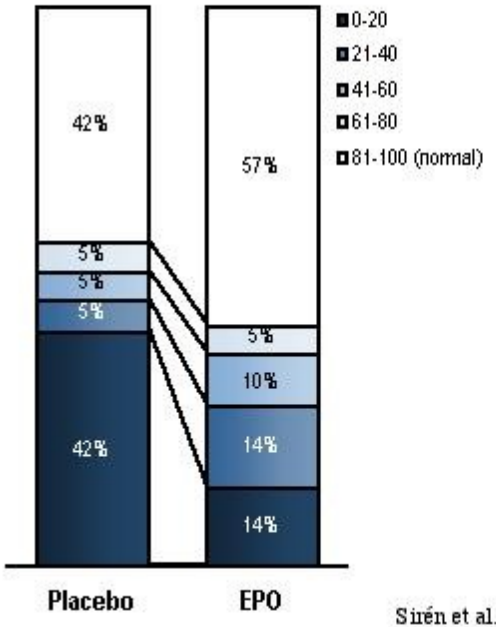
Neuroprotective effect of EPO: From cell to man

Neurons



Functional Outcome

Barthel Index



Sirén et al., PNAS, 2001
Ehrenreich et al., Mol. Med., 2002

Inflammation after stroke

Inflammation - Friend or Foe?

depends on spatial, temporal & contextual factors