Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration

MEDIZINISCHE UNIVERSITÄT WIEN

Stroke research at a crossroad: asking the brain for directions

Iadecola C. et al.
Nat Neurosci 14:1363 (Oct 2011)

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Overview

- Introduction
- The Janus face of ischemic injury: balancing life and death
- Preconditioning
- Exercise and brain protection
- Endogenous cytoprotection preserving tissue homeostasis
- Stroke therapeutics – what can we learn from the brain?
- Conclusions

Background

- Stroke as leading cause of brain injury
- **800,000 people per year** in the U.S. alone

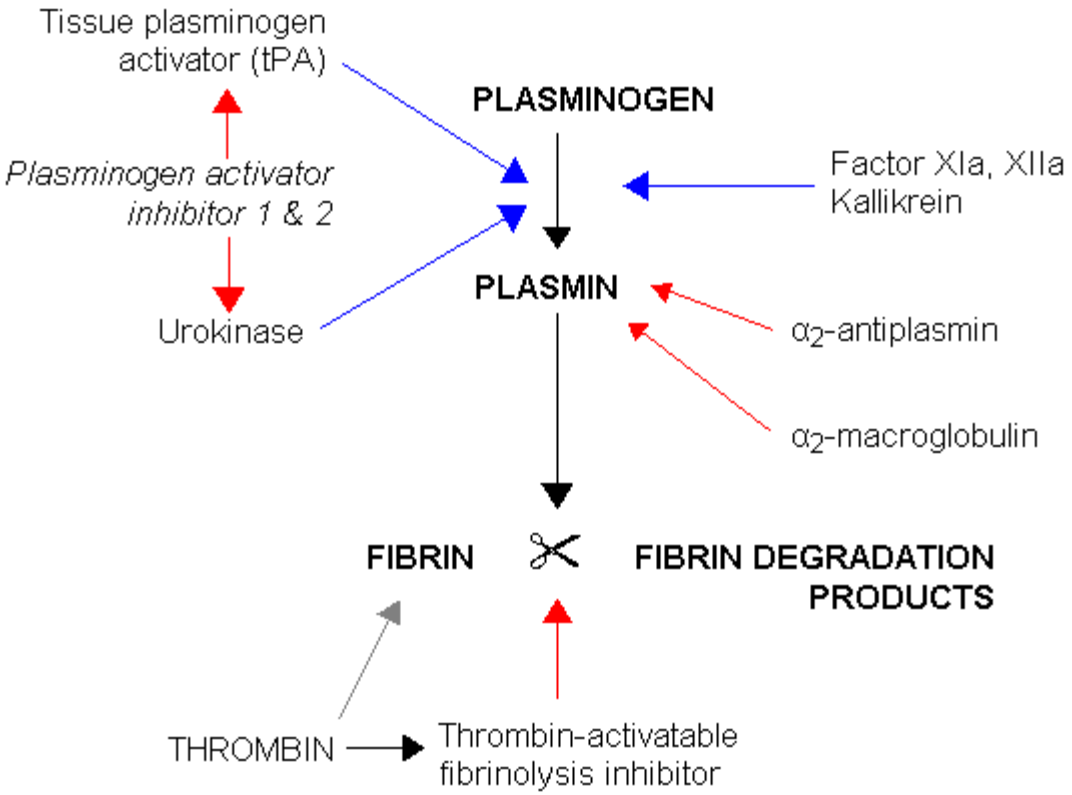
- **Progress** has been made:
  - Measures of prevention reduced incidence and mortality
  - Introduction of specialized ICUs improved functional outcome of stroke victims

tPA

- Tissue plasminogen activator
- Introduced in 1996
- Currently the **only treatment** available
- Narrow therapeutic window (<4,5h)
- Less than **5% of patients** are treated with tPA

- Most stroke victims receive only supportive care

Fibrinolysis



Pathogenic mechanisms

- Most therapeutic approaches developed in the laboratory have focused on protecting neurons from the **main pathogenic mechanisms** causing ischemic injury:
  - Excitotoxicity
  - Oxidative stress
  - Inflammation
  - Apoptosis
- However, these experimental treatments have often failed in large clinical trials

The ischemic core

- *Interruption of blood flow…*

  glucose and **oxygen** ↓

  → no generating of **ATP**

- *Ischemic core:* most severe energy deficit

  lowest residual flow

  → rapid cell death

Penumbra and tissue damage

- Ischemic penumbra = less severe ischemia
- **Waves of depolarisation**
  - → neurotransmitter release
  - → toxic concentration of **extracellular glutamate**
  - → activation of glutamate receptors = **excitotoxicity**
  - → accumulation of intracellular **Ca++**
    - → activation of lytic enzymes
    - → mitochondrial dysfunction/oxidative stress
    - → programmed cell death

Counteractions (1)

- Increase of **arterial pressure** through sympathetic activation and hormonal release
- Promoting **collateral circulation**
- Local release of **potent vasodilators**:
  Adenosine, vasoactive ions (K+, H+), NO
- Hypoxia preventing **HIF1** from being degraded

  → which may promote oxygen and glucose delivery

Counteractions (2)

- *Reducing energy demands:*

  suppression of neuronal activity and protein synthesis
- *Limiting excitotoxicity:*

  NMDA receptors become desensitized

  Inhibitory neurotransmitters suppress synaptic activity
- *„Antioxidant response“:*

  Nrf2 (nuclear factor-erythoid 2-related factor 2)

  IAP, **Bcl2** and **HSPs** are upregulated

  Akt (prosurvival kinase) dampens proapoptotic signaling

Counteractions (3)

- *Anti-inflammation and neuroprotection:*

IL-10, **TGF-β**: *) limiting leukocyte invasion

*) suppressing innate and adaptive immune responses

*) protecting surviving neurons

Counteractions (4)

- The inhibition of these counteractive measures increases ischemic damage…

  … those seemingly protective measures can, however, also be damaging:

  *) *high blood pressure* can lead to brain hemorrhages and exacerbate cerebral edema

  *) *post-stroke immunosuppression* is associated with potentially fatal systemic infections

Protective pathways (1)

- In the late stages of the ischemic cascade, repair processes in the damaged brain can be promoted:

  EPO, **IGF-1**: produced by microglia, macrophages, neurons, astrocytes and vascular cells

  Glutamatergic synaptic activity induces **BDNF**-expression (brain derived neurotrophic factor) through activation of **CREB**

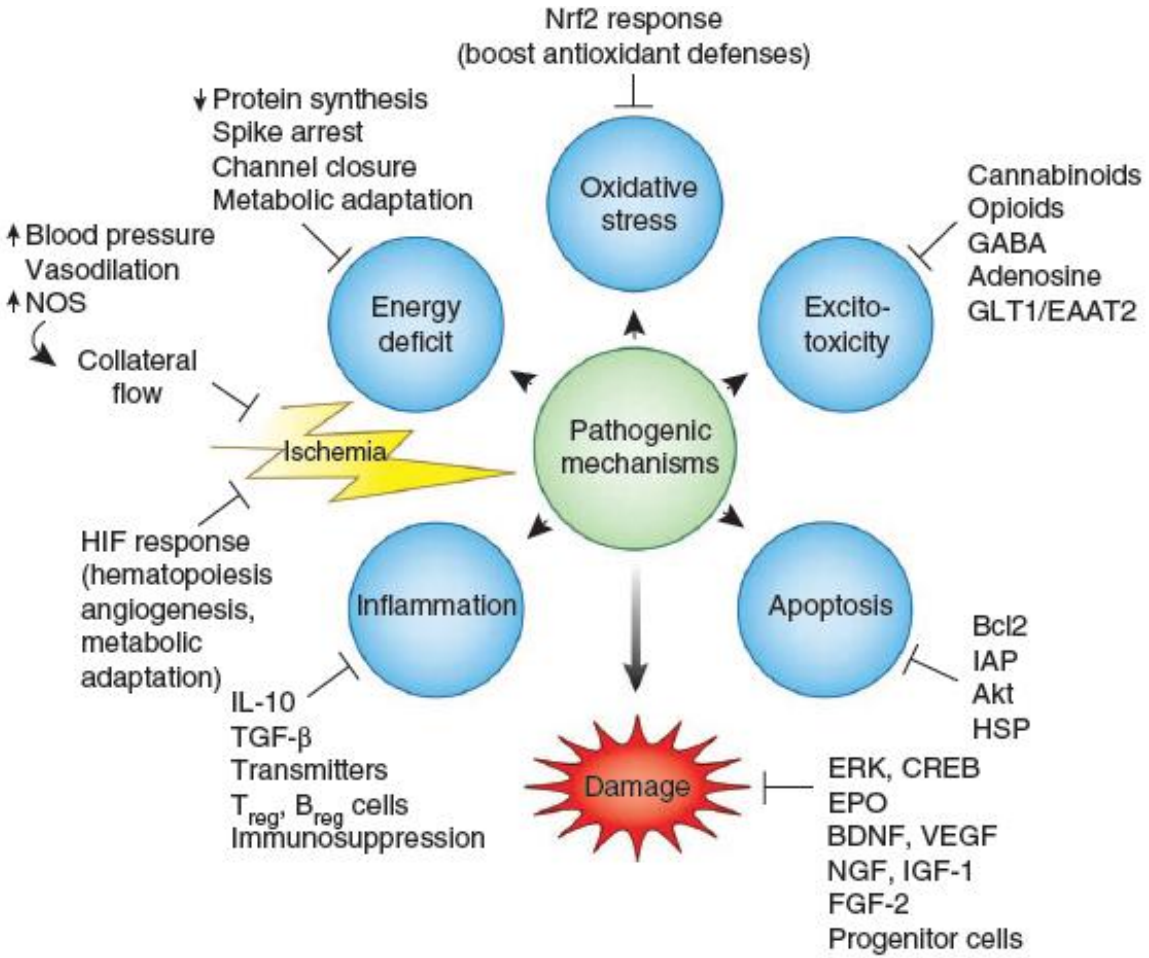
- Neuronal precursors invade the damaged area

Protective pathways (2)

- … these processes act to reconstitute tissue homeostasis

„These findings collectively suggest that ischemic injury, while activating destructive pathways that lead to cell death, also triggers local and systemic protective mechanisms aimed at counteracting the development of the injury.“

Protective pathways activated by cerebral ischemia



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Preconditioning (1)

- A mild cerebral ischemic insult – not producing extensive damage – **protects** the brain from subsequent damaging ischemia
- **Ischemic tolerance** can also be induced by:
  - hypoxia
  - inflammatory mediators
  - anesthetics
  - seizures

Preconditioning (2)

- These tolerance inducing stimuli can protect the brain even when applied…

  … during the ischemic event **(periconditioning)**

  … after the ischemic event **(postconditioning)**
- **Remote preconditioning** is the induction of ischemic tolerance from one organ to another

- Possibility of using ischemic tolerance as

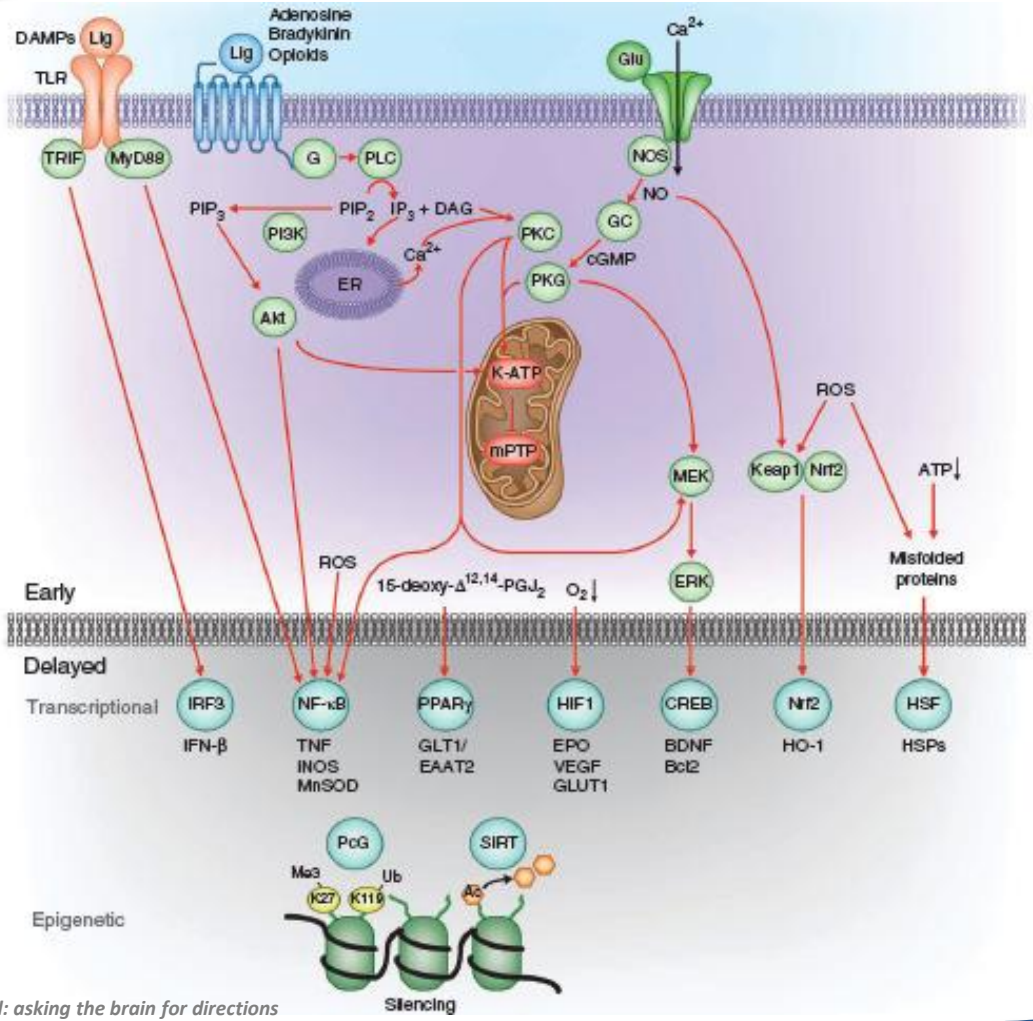
  a preventive strategy

  treatment for acute stroke

The effects of preconditioning

- Protection of **oxidative phosphorylation**
- Preservation of the **membrane potential**
- Activation of **hypoxia-responsive genes**
- Induction of **antiapoptotic genes**
- Upregulation of **growth factors**
- Inhibition of intravascular platelet-leukocyte aggregates
- Suppression of **inflammation** by dampening
  - the post-ischemic expression of adhesion molecules
  - leukocyte infiltration
  - microglial activation

Ischemic tolerance



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Exercise and brain protection

- 2 or 3 weeks of exercise reduces ischemic injury in rodents
- Moderate exercise reduces stroke risks and improves recovery after stroke in humans
- Exercise…
  - … upregulates **VEGF** and **eNOS**
  - … enhances post-ischemic cerebral perfusion
  - … increases **BDNF**, **FGF-2**, **IGF-1**
  - → factors involved in recovery and the increased resistance to brain injury

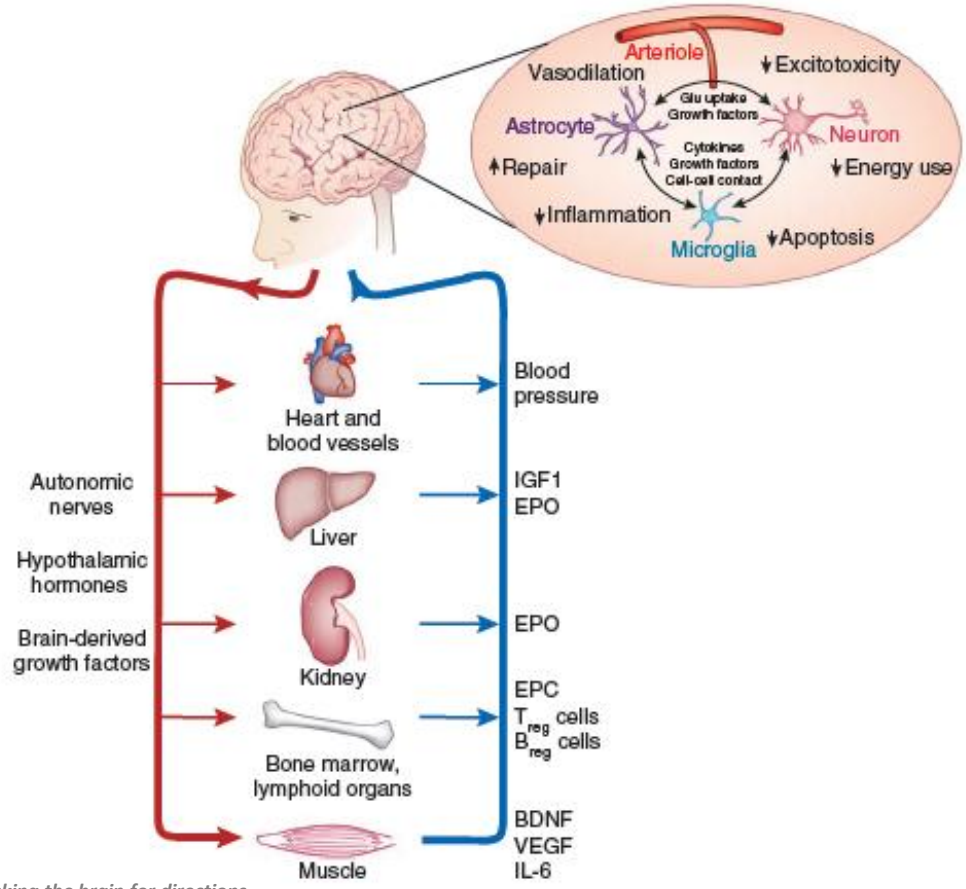
Exercise and brain protection

- A key feature is the *participation of systemic organs:*

  *) the full expression of cardiovascular, neurohumoral and metabolic effects of exercise needs **feedback** from contracting muscles

  *) some growth factors (such as IGF-1) are **produced in the periphery and the brain alike**

Mechanisms of endogenous neuroprotection



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Stroke therapeutics – *what can we learn from the brain?*

- Reperfusion therapy as the mainstay
- However:

  … anticoagulants proved ineffective as treatment for acute ischemic stroke

  … only a few patients qualify for tPA

- Targeting only one individual pathogenic component of the ischemic cascade proved insufficient

Stroke therapeutics – *what can we learn from the brain?*

- Brain tissue homeostasis relies on multifaceted central and peripheral protective programs!

- Acute stroke treatment should

  … include a **similarly coordinated** approach

  and

  … engage **several** neuroprotective pathways

Successful (?) clinical trials

- **Minocycline**

  antiapoptotic, anti-inflammatory, antiexcitotic

  showed promise when combined with tPA
- **EPO, G-CSF, GM-CSF**

  broadly neuroprotective and involved in preconditioning
- **Hypothermia**

  improves neurological outcome in patients with cardiac arrest and in children with hypoxic-ischemic brain injury

Successful (?) clinical trials

- **Remote preconditioning**

  *) r.c. by limb ischemia has already shown promise in cardiac ischemia

  *) it is currently being investigated concerning its therapeutic benefits in patiens with subarachnoid hemorrhage

Conclusions

- The brain has rich central and peripheral defense mechanisms
- Reproducing these coordinated neuroprotective programs could provide new treatment options

My conclusions

- Understanding the pathophysiology of stroke opens up a new perspective on finding new therapeutic approaches
- Researching the effects of APOSEC on proteins that play a role in the brain‘s neuroprotective pathways might provide interesting results
- For the future, we should consider combining APOSEC with other therapeutic agents, such as Minocycline or EPO

„Learning how to mimic or engage endogenous neuroprotectice mechanisms may provide new directions in stroke research and open new avenues in the treatment of this devastating disease.“

Thank you for your attention!