CEREBRAL BLOOD FLOW AND METABOLISM

Part 10.
Face
Ask the person to smile. Does one side of the face droop?

Arms
Ask the person to raise both arms. Does one arm drift downward?

Speech
Ask the person to repeat a simple sentence. Are the words slurred? Can the patient repeat the sentence correctly?

Time
Get the affected person to a hospital right away to receive the most effective treatment.

TIME = BRAIN
Acute treatment of Stroke

- Accurate diagnosis of stroke
- Definition of stroke type
- Acute general medical care
- Re-perfusion
- Neuroprotection
If patient is candidate, then will proceed with thrombolytic therapy (t-PA).

Dosing: 0.9 mg/kg; maximum dose less than or equal to 90mg.

- 10% of the total dose is administered as an IV bolus over 1 minute.
- Remaining 90% is infused over 60 minutes
- Follow up: admit to ICU or Stroke Unit, monitor Vital signs, Maintain SBP greater than 185 mmHg; No anticoagulant therapy for 24 hours.
Goal

- Provide thrombolytic within 60 mins of the patient reaching the ECC.
- Within the 3 hours of beginning signs and symptoms (or within 6 hours for basilar or vertebral arteries)

* Must be informed on time of start of symptoms in order to treat with thrombolytic.
Acute Stroke Thrombolysis

Risk of death dependency and good functional outcome in randomised trials of rt-PA given within 3 hours of acute stroke

Cochrane September 1999
Pathogenesis of Hypoxic-Ischemic Cerebral Injury

Interruption of Placental Blood Flow

Acute
Intermittent

Hypoxia-Ischemia

Resuscitation

In-utero
Postnatal

Reperfusion Injury
Benefit of rt-PA for Acute Stroke

mRS 0-1 at day 90

Adjusted odds ratio with 95% confidence interval by stroke onset to treatment time (OTT)

< 3 h  SITS-MOST

3-4 h  uncertain

> 4.5 h  except selected patients

Brott TG. International Stroke Conference 2002; abstract.
Mechanical clot removal in acute stroke
MERCI trial

Phase 1 Trial

- Cerebral embolectomy successful recanalisation in 69 / 141 (48%)
- In combination with rtPA in 17 cases
- Procedural complications 7.1%
- Could extend the time window to 8 hours
Effects of Hypoxia-Ischemia on Carbohydrate and Energy Metabolism-Anaerobic Glycolysis

- ↓ Brain Glycogen
- ↑ Lactate production
- ↓ Phosphocreatine
- ↓ Brain Glucose
- ↓ ATP
- Tissue acidosis
Ischemia

Anaerobic Glycolysis

↓ PCr  
↓ ATP  
↑ Lactate

[K⁺] out  [Ca++] in  [Na⁺] out
Deleterious Effects of Calcium in Hypoxia-Ischemia

- Activates phospholipases → membrane injury
- Activates proteases → cytoskeleton degraded
- Activates nucleases → DNA breakdown
- Uncouples oxidative phosphorylation → ↓ ATP
- ↑ neurotransmitter release i.e. glutamate
- Activates NOS → generates nitric oxide
Additional Mediators of Cell Death During and Following Hypoxia-Ischemia (HI)

**Free radicals**
- Highly reactive compounds can react with certain cellular constituents, e.g., membrane lipids, generating more radicals and thus a chain reaction with irreversible biochemical injury.

**Glutamate**
- Excitatory amino acid acts on NMDA receptors to facilitate intracellular Ca\(^{++}\) entry and delayed cell death.
- Glutamate accumulates during HI in part because of \(\downarrow\) reuptake that requires ATP.
FREE RADICALS

HYPOXIA-ISCHEMIA

ANAEROBIC GLYCOGOLYSIS

ADENOSINE

HYPOXANTHINE

XANTHINE

OXIDASE

XANTHINE

O₂

GLUTAMATE

NMDA RECEPTOR

INTRACELLULAR Ca+

ACTIVATES LIPASES

FREE FATTY ACIDS

O₂

NITRIC OXIDE

LACTATE

FREE RADICALS
Ischemic preconditioning paradigms

U. Dirnagl

Experimental Neurology, Charité, Humboldt University, Berlin
Induced tolerance = Preconditioning
‘Preconditioning paradigms’

1. Elegant experimental paradigm which can guide investigators to targets for acute therapy against the consequences of brain ischemia: A window into endogenous neuroprotection!

2. Clinical paradigm to protect the brain when cerebral ischemia can be anticipated (?)
- History of IP
- In vivo IP paradigms
- In vitro IP paradigms
- 'Special' IP paradigms: cross tolerance & remote IP
- Clinical paradigms
‘Similia similibus curentur’ (Hippocrates)
‘The dose makes the poison’ (Paracelsus);
‘Adaptation to perturbations is the basis for homeostasis’ (Cannon)
‘The general adaptation syndrome’ (Selye)
‘Poisons are stimulants in small doses’ (Amdt-Schultz)
‘If it doesn't kill you, it will make you stronger’ (German beerhall)

‘Induced tolerance’ & ‘Preconditioning’ (Janoff 1964)
THE DEVELOPMENT OF RESISTANCE BY RATS AND GUINEA PIGS TO AMOUNTS OF TRAUMA USUALLY FATAL

R. L. NOBLE

From the Research Institute of Endocrinology, McGill University, Montreal

Received for publication September 2, 1942

and caused only a minimal degree of hemorrhage, it was especially suited for a study of the effects of repeated trauma. In the initial experiments it was found that rats subjected to small amounts of trauma rapidly acquired a resistance so that they could withstand a degree of trauma otherwise fatal. A detailed study of this phenomenon forms the basis for this communication.

Am J Physiol (1943) 138:346-351

Prolonged anoxic survival due to anoxia pre-exposure: brain ATP, lactate, and pyruvate

NANCY ANN DAHL and WILLIAM M. BALFOUR

Department of Comparative Biochemistry and Physiology, University of Kansas, Lawrence, Kansas

Dahl, Nancy Ann, and William M. Balfour. Prolonged anoxic survival due to anoxia pre-exposure: brain ATP, lactate, and pyruvate. Am. J. Physiol. 207(2): 452-456. 1964.—Rats subjected to a brief anoxia can survive 90 sec in a second anoxia, compared to a 60-sec survival time of control animals. Slower

Am J Physiol (1964) 207:452-456

Adaptation of Adult Brain Tissue to Anoxia and Hypoxia in Vitro

AVITAL SCHURR, KENNETH H. REID, MICHAEL T. TSENG, CATHERINE WEST and BENJAMIN M. RIGOR

Departments of 1Anesthesiology, 2Physiology and 3Anatomy, Laboratory of Cellular Neuroscience, Anesthesia and Critical Care Research Unit (ACCRU), University of Louisville, School of Medicine, Louisville, KY 40292 (U.S.A.)

The rat hippocampal slice preparation was used in the present study to demonstrate the ability of adult brain tissue to adapt to anoxic and hypoxic conditions. Adaptation was induced by pre-exposure of hippocampal slices to a short (5 min) anoxic episode. The evoked electrical activity of pre-exposed slices recovered from a subsequent, longer anoxic insult, while that of controls (without pre-exposure), receiving the same insult, did not. The adaptation process is time-dependent; an interval of 0.5 h between the pre-exposure and the subsequent anoxic insult allowed slices to resist anoxic periods of 13 ± 2 min while after an interval of 2 h an anoxic period of 16 ± 2 min could be tolerated. Evoked electrical activity persisted in adapted slices during exposure to hypoxia while their non-adapted controls exhibited synaptic silence under hypoxic conditions.

Brain Res (1986) 374:244-248
'Ischemic tolerance' phenomenon found in the brain

Kazuo Kitagawa¹, Masayasu Matsumoto¹, Masafumi Tagaya¹, Ryuji Hata¹, Hirokazu Ueda¹, Michio Niinobe³, Nobuo Handa¹, Ryuzo Fukunaga¹, Kazufumi Kimura², Katsuhiko Mikoshiba³ and Takenobu Kamada¹

¹First Department of Internal Medicine and ²Biomedical Research Center, School of Medicine and ³Division of Regulation of Macromolecular Function, Institute for Protein Research, Osaka University, Osaka (Japan)

(Accepted 13 March 1990)

Key words: Gerbil; Cerebral ischemia; Ischemic tolerance; Hippocampus; Delayed neuronal death; Microtubule associated protein 2

Brain Res (1990) 528:21-24
Induction of tolerance against focal cerebral ischemia in vivo

'preconditioning' 30 min – 7 d focal cerebral ischemia 24 h – 7 d histology

Induction of tolerance against hypoxia/aglycemia in vitro

'preconditioning' 30 min – 3 d 90 min OGD 24 h – 3d LDH assay, cell counting
IP induced by

- Hyperbaric oxygenation
- Free radicals
- Metabolic inhibition (3-NPA, Ouabain)
- Volatile anesthetics (Isoflurane, Halothane)
- Hypoxia
- Iron-chelation (Desferoxamine)
- Erythropoietin

References:

Hypoxia induces stroke tolerance in the mouse

**A**

<table>
<thead>
<tr>
<th>Hypoxia (min)</th>
<th>30</th>
<th>60</th>
<th>180</th>
<th>300</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct volume (mm³)</td>
<td>[Graph]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th>Interval (hours)</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct volume (mm³)</td>
<td>[Graph]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**C**

<table>
<thead>
<tr>
<th>MCAO (min)</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>120</th>
<th>perm.</th>
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*Prass et al. Stroke (in press)*
Hypoxia induced tissue response

Volatile anesthetics induce tolerance against focal cerebral ischemia in the rodent

Kapinya, et al.

Volatile anesthetics induce tolerance against ‘ischemic’ neuronal injury in vitro

Transfer of hypoxic astrocyte conditioned medium to cortical neurons

180 min OGD

Neurons

transfer of medium

24 h

Astrocytes

120 min OGD

LDH assay
cell counting
Induction of tolerance in cortical neurons by astrocytic OGD preconditioned medium

'Cross' tolerance
Postischemic cascade of damage

- Energy failure
- Glutamate
- Reactive oxygen species
- Inflammation
- Apoptosis

Time scale: Min, Hours, Days, Weeks
'Cross' tolerance:
Heat shock protects against global cerebral ischemia

Article abstract—We heated Wistar rats (n = 10) to 41.5 ± 0.2 °C for 15 minutes, 24 hours before the induction of forebrain cerebral ischemia. We subjected 23 rats to forebrain ischemia without prior heating. Ischemic cell damage in the medial, lateral, and overall CA 1/2 hippocampus, inferior frontal cortex, and dorsal-lateral striatum was significantly (p < 0.05) less severe in heated animals than in nonheated animals.

NEUROLOGY 1989;39:1396-1398

M. Chopp, PhD; H. Chen, MD; K-L. Ho, MD; M.O. Dereski, PhD; E. Brown, MS; F.W. Hetzel, PhD; and K.M.A. Welch, MD

Transient hyperthermia protects against subsequent forebrain ischemic cell damage in the rat

Virtually all cells and organisms develop resistance (thermotolerance) to subsequent hyperthermia following an initial heat treatment. The acquisition of thermotolerance correlates with the preferential syn-thermal shock the rats were subjected to forebrain ischemia.7 Surgical procedures for all rats were initiated at the same time during the day to negate diurnal rhythm effects. Following induction of anesthesia with 3.5% halothane, the animals were intu-
'Remote' preconditioning
Remote preconditioning: Brain → Heart

Transient ischemic attacks (TIA) protect against stroke in humans

Erythropoietin Therapy for Acute Stroke Is Both Safe and Beneficial

Hannelore Ehrenreich, Martin Hasselblatt, Christoph Dembowski, Lukas Cepek, Piotr Lewczuk, Michael Stiefel, Hans-Heino Rustenbeck, Norbert Breiter, Sonja Jacob, Friederike Knerlich, Matthias Bohn, Wolfgang Poser, Eckart Rüther, Michael Kochen, Olaf Gefeller, Christoph Gleiter, Thomas C. Wessel, Marc De Ryck, Loretta Itri, Hilmar Prange, Anthony Cerami, Michael Brines, and Anna-Leena Sirén

Barthel Index

- Placebo: 42%, 57%
- EPO: 5%, 14%, 42%

Rankin Scale

- Placebo: 21%, 5%, 16%, 37%, 14%
- EPO: 14%, 33%, 21%, 5%, 14%
Table 1: Types and initial incidence of neurological complications after cardiac surgery (reproduced and modified with permission from Shaw and colleagues)\textsuperscript{135}

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
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<td>Fatal brain injury</td>
<td>0.3%</td>
</tr>
<tr>
<td>Non-fatal diffuse encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Depressed conscious level</td>
<td>3%</td>
</tr>
<tr>
<td>Behavioural changes</td>
<td>1%</td>
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<td>Intellectual/cognitive dysfunction</td>
<td>30–79%</td>
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<td>0.3%</td>
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<td>Ophthalmological</td>
<td></td>
</tr>
<tr>
<td>Visual field defects</td>
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<tr>
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<td>7%</td>
</tr>
<tr>
<td>Other peripheral neuropathy</td>
<td>6%</td>
</tr>
</tbody>
</table>
## Table 2: Perioperative (30-day) outcome events in patients who underwent endarterectomy

<table>
<thead>
<tr>
<th>Outcome event</th>
<th>Trial; % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NASCET, symptomatic</td>
</tr>
<tr>
<td></td>
<td>ACE, symptomatic</td>
</tr>
<tr>
<td></td>
<td>NASCET + ACE,</td>
</tr>
<tr>
<td></td>
<td>symptomatic</td>
</tr>
<tr>
<td></td>
<td>ACE, asymptomatic</td>
</tr>
<tr>
<td><strong>Any stroke or death</strong></td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Disabling stroke or death</strong></td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Any stroke or death or MI</strong></td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Nonfatal MI</strong></td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Fatal MI</strong></td>
<td>0.1</td>
</tr>
</tbody>
</table>

Note: NASCET = North American Symptomatic Carotid Endarterectomy Trial, ACE = ASA and Carotid Endarterectomy Trial, MI = myocardial infarction.
‘Preconditioning’ for preventive neuroprotection: study paradigm

Baseline assessment

Preconditioning

Outcome assessment

Anticipated ischemic event
Conclusions

- Practically any stimulus capable of causing injury, when applied close to the threshold of damage, but below it, can protect the brain against subsequent ischemia.

- IP/IT is an archetypical, nonspecific stress response, which opens a window into endogenous neuroprotection. It exists in humans.

- IP/IT can guide investigators to targets for acute therapy against the consequences of brain ischemia.

- Preventive neuroprotection by IP/IT may prove useful in patients at high risk for ischemic brain injury.
Konstantin Prass (HBO, Hypoxia, DFX; EPO)
Andreas Meisel, Karsten Ruscher (HIF, EPO)
Markus Weih (in vitro precond. TIA precond.)

The Department of Experimental Neurology is funded by the Hermann and Lilly Schilling Foundation
Desferrioxamine induziert Toleranz gegen Sauerstoff-Glukose Entzug (OGD) in kortikalen Neuronen in vitro

![Graph A](image1)

**J Cereb Blood Flow Metab. 2002; 22(5):520-5.**
Desferrioxamine induziert Toleranz gegen exp. Schlaganfall

Desferrioxamine induces tolerance against OGD in vitro

**A**

![Normalized LDH ratio (%)](chart)

<table>
<thead>
<tr>
<th>Co</th>
<th>OGD</th>
<th>1</th>
<th>3</th>
<th>12</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>*</td>
<td>**</td>
<td>*</td>
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**B**

![Normalized LDH ratio (%)](chart)

<table>
<thead>
<tr>
<th>Co</th>
<th>OGD</th>
<th>15</th>
<th>50</th>
<th>100</th>
<th>150</th>
<th>300</th>
<th>600</th>
</tr>
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<td></td>
<td></td>
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**C**

![Normalized LDH ratio (%)](chart)

<table>
<thead>
<tr>
<th>Co</th>
<th>OGD</th>
<th>OGD + DFX</th>
<th>OGD + CHX + DFX</th>
<th>OGD + CHX</th>
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Hypoxia induces HIF-1 & tolerance against OGD in primary cortical neurons

**Graph:**
- Y-axis: Normalized HIF-1 DNA Binding Activity
- X-axis: Control BSS, 30min OGD
- **Control BSS:** 1.00
- **30min OGD:** 2.60

**Bar Graph:**
- X-axis: control, HP, hypoxia, HP/hypoxia
- Y-axis: normalized LDH release (%)
- **Control:** 0%
- **HP:** 0%
- **Hypoxia:** 100%
- **HP/hypoxia:** 75%

Anoxia tolerance and hibernation

Evolution’s solution to substrate deprivation!
## Table 1: Types and initial incidence of neurological complications after cardiac surgery (reproduced and modified with permission from Shaw and colleagues)\(^\text{135}\)

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Central nervous system complications of cardiac surgery: Risk factors

<table>
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<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>((\text{Age} - 25) \times 1.43)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>18</td>
</tr>
<tr>
<td>Prior CABS</td>
<td>15</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>18</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>15</td>
</tr>
</tbody>
</table>

![Graph showing the relationship between stroke risk index (score) and CNS injury risk (%)]
Central nervous system complications of cardiac surgery

effect of age

Br J Anaesth 2000 Mar;84(3):378-93
The three modules of cerebral ischemic preconditioning

<table>
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<tr>
<th>Sensors</th>
<th>Transducers</th>
<th>Effectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADO; A1R</td>
<td>$K_{ATP}$; NO; PKC$\alpha$/$\delta$</td>
<td>$K_{ATP}$</td>
</tr>
</tbody>
</table>

Rapid

- **Triggers**
  - Hypoxia
  - Ischemia
  - Inflamm.
  - Epilepsy

- **Sensors**
  - ADO; A1R
  - OFR, HIF
  - NMDAR;
  - EAAT1-2;

- **Effectors**
  - Protection
  - HSP; BCI-proteins; OFR - scavengers; BDNF; VEGF; downregulation of NOS; GABA$_A$ receptor upregulation; enhanced GABA release; IL1-receptor antagonist; GluR2 downregulation

Delayed

- **Triggers**
  - Hypoxia
  - Ischemia
  - Inflamm.
  - Epilepsy

- **Sensors**
  - ADO; A1R;
  - OFR, HIF;
  - NMDAR;
  - EAAT1-2;
  - heme-containing sensor

- **Effectors**
  - Protection
  - HSP; BCI-proteins; OFR - scavengers; BDNF; VEGF; downregulation of NOS; GABA$_A$ receptor upregulation; enhanced GABA release; IL1-receptor antagonist; GluR2 downregulation

Neuroprotection of the Brain During Cardiopulmonary Bypass
A Randomized Trial of Remacemide During Coronary Artery Bypass in 171 Patients

J.E. Arrowsmith, MRCP(UK), FRCA; M.J.G. Harrison, DM, FRCP; S.P. Newman, DPhil, Dip Psych; J. Stygall, BSc, MSc; N. Timberlake, BA, BSc; W.B. Pugsley, FRCS(Ed)

Background and Purpose—Neuropsychological impairment may follow coronary artery bypass surgery as a result of peroperative cerebral microembolism. The hypothesis that remacemide, an NMDA receptor antagonist, would provide protection against such ischemic damage has been tested in a randomized trial.

Methods—One hundred seventy-one patients undergoing coronary artery bypass surgery by a single cardiothoracic surgical team were randomized to receive remacemide (up to 150 mg every 6 hours) or placebo from 4 days before to 5 days after their bypass procedure. Peroperative monitoring included an estimate of the number of microembolic events detected by transcranial Doppler ultrasonography of the middle cerebral artery. A battery of 9 neuropsychological tests was administered before and 8 weeks after surgery.

Results—The proportion of patients showing a decline in performance of 1 SD or more in 2 or more tests was reduced in the treated group (9% versus 12%), but this was not statistically significant. On the other hand, overall postoperative change (reflecting learning ability in addition to reduced deficits) was more favorable in the remacemide group, which demonstrated significantly greater improvement in a global z score \(P=0.028\) and changes in 3 individual tests \(P<0.05\). The 2 patient groups were well matched, including for the burden of microembolic events.

Conclusions—This is the first study to show statistically significant drug-based neuroprotection during cardiac surgery. In addition to offering improvement in cerebral outcome for such at-risk patients, it supports the hypothesis that drugs acting on the excitotoxic mechanism of ischemic cerebral damage can be effective in humans. (Stroke. 1998;29:2357-2362.)

Key Words: bypass surgery ■ neuroprotective agents ■ neuropsychological tests ■ ultrasonography, Doppler
Stroke study paradigm

- Stroke
- Treatment
- Outcome assessment
- time
‘Preconditioning’ neuroprotection study paradigm

Baseline assessment

Treatment

Anticipated ischemic event

Outcome assessment

time
Induced tolerance = Preconditioning
Postischemic cascade of endogenous protection

- **Excitotoxicity**
  - Phosphorylation/Nitrosylation of receptors, channels, etc.

- **‘Inflammation’**
  - Induction of antiinflammatory proteins, antioxidative enzymes, etc.
- **Apoptosis**
  - Induction of antiapoptotic proteins, inactivation of apoptotic proteins

Timeline:
- Minutes
- Hours
- Days
- Weeks
Tissue destruction

Endogenous protection
Remote preconditioning: Limb → Heart

control (naive tissue)

MCAO

preconditioned (protective mechanisms already induced)

MCAO