Underlying mechanisms: How hypothermia can protect the brain

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## Unspecific Effects of Hypothermia

<table>
<thead>
<tr>
<th>Level</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt; 32°C</td>
</tr>
<tr>
<td>Moderate</td>
<td>28 - 32°C</td>
</tr>
<tr>
<td>Severe</td>
<td>20 - 28°C</td>
</tr>
<tr>
<td>Profound</td>
<td>&lt; 20°C</td>
</tr>
</tbody>
</table>

*Hammer MD und Krieger D, CCJM 69:770-785, 2002*
Clinical problems with mild hypothermia as therapeutic approach

- Cardiac arrest
- Traumatic brain injury
- Stroke
- Encephalopathy
- Organ transplantation
- Cardiac surgery / acute myocardial infarction

Oxygen deprivation
Neonatal encephalopathy
Cardiac arrest
Cardiac surgery
Acute myocardial infarction
Traumatic brain injury
Oxygen deprivation
Neonatal encephalopathy

Ischaemia

Simplified Scheme of the Mechanisms After Ischaemia

Hossmann KA, 2003
1. General speed of reactions

Simplified Scheme of the Mechanisms After Ischaemia
Mechanisms of Mild Hypothermia

1. General speed of reactions ↓

- Consumption of glucose / oxygen ↓
  (5 - 7 % per °C temperature decrease) \(^{(1)}\)

- Levels of lactate / pyruvate ↓
  (if energetic phosphates are still available) \(^{(2)}\)

Mechanisms of Mild Hypothermia

... but it is far more than that

Ischaemic neurons [n]

Temperature [°C]

Simplified Scheme of the Mechanisms After Ischaemia

2. Inhibition of apoptosis
Mechanisms of Mild Hypothermia

2. Inhibition of apoptosis

- Inhibition of caspase activation \(^{(1)}\)
- Mitochondrial dysfunction \(^{(2)}\)
- Anti-apoptotic proteins (Bcl2) \(^{(3)}\) + pro-apoptotic (Bax) proteins \(^{(3)}\)

Mechanisms of Mild Hypothermia

2. Inhibition of apoptosis

*Padosch SA and Böttiger BW, Curr Opin Anaesthesiol 16:439-445, 2003*
3. Reduction of free radicals

Simplified Scheme of the Mechanisms After Ischaemia
Mechanisms of Mild Hypothermia

3a. Reduction of free radicals

- Microdialysis:
  free oxygen radicals \( \downarrow^{(1,2)} \)

Mechanisms of Mild Hypothermia

3b. Membrane stabilisation (vascular)

- Hypothermia: Release and activation of VEGF and consecutively NO↓ in I/R (1)

1. Fischer S et al., Brain Res Mol Brain Res 74:135-144, 1999
4. Excitatory neurotransmitters
Mechanisms of Mild Hypothermia

4. Excitatory neurotransmitters

- Release of glutamate
- Extracellular concentration of excitatory neurotransmitters
- Release of Zn$^{++}$
- Intracellular Ca$^{++}$

5. Changes in gene expression
Mechanisms of Mild Hypothermia

5. Changes in gene expression

- BDNF and its receptor TrkB \( \uparrow \)\(^{(1)}\) despite inhibition of protein synthesis
- Maintained expression of AMPA-GluR-S2 with Ca\(^{++-}\) / Zn\(^{++-}\)-influx \( \downarrow \)\(^{(2)}\)
- Matrix-metalloproteinase-9 \( \downarrow \)\(^{(3)}\)
  (Degradation of basal lamina + blood-brain barrier)

2. Colbourne F et al., PNAS 100:2906-2910, 2003
6. Coagulopathy

Simplified Scheme of the Mechanisms After Ischaemia
7. Immunosuppression

Simplified Scheme of the Mechanisms After Ischaemia
Simplified Scheme of the Mechanisms After Ischaemia

7. Immunosuppression

• Overall inflammatory response not markedly influenced $^{(1)}$

• Leukocytes and TNFalpha in CSF $\downarrow$
  (in experimental meningitis) $^{(2)}$

1. Tokutomi T et al., Neurocrit Care 1:171-182, 2004
Mechanisms of Mild Hypothermia

8. ... in severe brain trauma

- Oedema formation \(\downarrow^{(1)}\)
- Increase in intracranial pressure \(\downarrow^{(1)}\)
- Inflammatory response \(\downarrow^{(2)}\)

... mild hypothermia is doing nearly everything ...
Mechanisms of Mild Hypothermia

The future

„Hibernation“

Body temperature during a typical hibernation cycle

van Breukelen F et al. 2001

Proteinsynthesis (14C-Leucin incorporation) in the brain of an active (A) and a hibernating ground squirrel (B)

Frerichs KU et al. 1998
Induction of prolonged mild hypothermia by infusion of neurotensin in rats

Popp E, Schneider A, Böttiger BW, in press 2006