Changing belief
‘toward anesthetic neuroprotection’

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Yonsei University Health System
Seoul, Korea
Topics relating to anesthetic protections given in the past annual meetings of Korean Society of Neuroanesthesia since 1995

1996. The effect of dexmedetomidine on the change of excitatory amino acids after transient global ischemia in the rabbit


1999. 마취중 뇌보호.

2001. 뇌신경마취 영역에서의 apoptosis.

2002. 두부손상환자의 마취관리: 뇌신경마취가 임상결과에 영향을 미칠수 있는가?


2004. Effects of hypothermia and anesthetics on conditioned learning after transient global cerebral ischemia in rabbit.


Simplified pathophysiological mechanisms in focal ischemic brain

Activation of proteases, lipases, endonucleases
Dynamic changes in focal cerebral ischemia

**Temporal changes**

- Excitotoxicity
- Inflammation and apoptosis
  - IL-1
  - COX-2
  - MMPs
  - Caspases

**Spacial changes**

- Impairment of function ('penumbra')
- Structural lesion

- Minutes
- Hours
- Days and weeks
Anesthetics might reduce CMR... then, offer some protection??

How dpress CMR? Questel & Wheatley, 1932

Interfere O2 transport or utilization → alter neuronal function and produce the anesthetic state
Anesthetics (barbiturates) protects hypoxic brain

- Barbiturates prolonged survival time even in exposure to hypoxia
  
  
  Wilhjelm BJ and Arnfred I. Acta Pharmacol 1965: 22; 93-8

- Barbiturates reduced the frequency and size of cerebral infarction,
  whereas halothane anesthesia increased both the frequency and the size of infarction.

  Smith AL, et al. Stroke 1974: 5; I-7
**Reduction of CMRO2 by different anesthetic conditions not associated with cerebral energy state (1960s-70s)**

Primary cerebral effect of anesthetics is on function and that the observed metabolic effects represent a passive, secondary response to the functional alterations.

<table>
<thead>
<tr>
<th></th>
<th>CMRO₂  (ml/min/100 g)</th>
<th>ATP (umol/g)</th>
<th>Lactate (umol/g)</th>
<th>Pyruvate/lactate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane (0.1%)</td>
<td>5.53 ± 0.26</td>
<td>2.30 ± 0.03</td>
<td>1.83 ± 0.18</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Halothane (0.8%)</td>
<td>4.65 ± 0.16</td>
<td>2.26 ± 0.03</td>
<td>2.20 ± 0.27</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>N₂O (70%)</td>
<td>5.88 ± 0.17</td>
<td>2.23 ± 0.05</td>
<td>2.63 ± 0.19</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>Thiopental (46mg/kg)</td>
<td>2.89 ± 0.19</td>
<td>2.21 ± 0.02</td>
<td>1.78 ± 0.17</td>
<td>17 ± 4</td>
</tr>
</tbody>
</table>


*Michenfelder JD, et al. Anaesthesiology 1970: 33; 315 -21*
Thiopental: not effective for global ischemia including TBI

- Thiopental treatment after global brain ischemia in pigtailed monkeys
  
  _Gisvold SE, et al. Anesthesiology 1984: 60; 88-96_

  Norepinephrine requirement for BP
  Lidocaine for control of arrhythmias
  No difference in mortality or neurologic outcome

- Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. Brain Resuscitation Clinical Trial I Study Group
  

  death: 77% vs 80%
  good recovery: 20% vs 17%
  sequela: 2% vs 5%

- No protection in acute TBI.
  
  _Cochrane library Systemic review 2009_

- Only function of reduction of CMR for protection in global ischemia.
Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia

Total infarct volume

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>Active EEG (15-23mg/kg)</th>
<th>BS EEG (45-60mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$163 \pm 66$mm$^3$</td>
<td>$124 \pm 68$mm$^3$</td>
<td>$128 \pm 54$mm$^3$</td>
</tr>
</tbody>
</table>

*Warner DS, et al. Anesthesiology 1996: 84; 1475-84*
A comparison of the effect of thiopental, methohexital and pentobarbital on the extent of injury after focal cerebral ischemia in rats

<table>
<thead>
<tr>
<th></th>
<th>Burst suppression</th>
<th>0.4 Burst suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>halothane</td>
<td>133 ± 17</td>
<td>124 ± 24</td>
</tr>
<tr>
<td>thiopentone</td>
<td>88 ± 14*</td>
<td>118 ± 15</td>
</tr>
<tr>
<td>methohexital</td>
<td>126 ± 19</td>
<td>70 ± 22*</td>
</tr>
<tr>
<td>pentobarbitone</td>
<td>130 ± 17</td>
<td>121 ± 20</td>
</tr>
</tbody>
</table>

*p<0.05 versus the other three groups.

Other proposed thiopental mechanisms along with uncovering focal ischemic injury mechanisms

- Decrease in CMR
- Improved distribution of rCBF
- Anti-seizure
- Decrease in ICP

- Decrease in cerebral edema
- FFA metabolism and scavenging of free radicals
- Blockade of calcium entry
- Etc.
A comfortable hypothesis reevaluated cerebral metabolic depression and brain protection during ischemia. Possible influence on thermoregulation.

Todd MM and Warner DS. Anesthesiology 1992: 76; 161-4
Small changes of brain temperature by anesthetics result in neuroprotection/neuroal damage
Ischemic cell counts within striatum (temp)

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Central Striatum</th>
<th>Dorsolateral striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-intra-post ischemic Brain temp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36-30-36</td>
<td>O **</td>
<td>O **</td>
</tr>
<tr>
<td>36-33-36</td>
<td>O **</td>
<td>12.5 ± 12.5 **</td>
</tr>
<tr>
<td>36-34-36</td>
<td>O **</td>
<td>11.6 ± 8.0 **</td>
</tr>
<tr>
<td>36-36-36</td>
<td>54.5 ± 4.8</td>
<td>56.8 ± 4.0</td>
</tr>
<tr>
<td>36-39-36</td>
<td>73.0 ± 7.0</td>
<td>71.0 ± 5.0</td>
</tr>
<tr>
<td>36-36-33</td>
<td>23.6 ± 10.7 *</td>
<td>39.7 ± 8.0</td>
</tr>
</tbody>
</table>

Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury

Small, clinically relevant changes in temperature (1 °C or 2 °C) resulted in significant alterations in both postischemic neurologic function and cerebral histopathology.

The relation between neurologic function rank and histopathology rank at 37 degrees Celsius, 38 degrees Celsius, or 39 degrees Celsius. Solid line = the line of identity (rs = 0.96; P < 0.001).

Temperature management in studies of barbiturate protection from focal cerebral ischemia – review article- (1974-2008)

<table>
<thead>
<tr>
<th>Neuroprotection</th>
<th>Present</th>
<th>Absent</th>
<th>Equivocal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Protocols published before 1987 (N=32)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature monitoring</td>
<td>(n=21; 66%)</td>
<td>(n=10; 31%)</td>
<td>(n=1; 3%)</td>
</tr>
<tr>
<td>None reported(n=10; 31%)</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inadequate (n=22; 69%)</td>
<td>13</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Adequate(n=0; 0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>B. Protocols published after 1987 (N=25)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature monitoring</td>
<td>(n=14; 56%)</td>
<td>(n=8; 32%)</td>
<td>(n=3; 12%)</td>
</tr>
<tr>
<td>None reported(n=0; 0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inadequate (n=10; 40%)</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Adequate(n=15; 60%)</td>
<td>9</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Protective effects of volatile anesthetics against ischemic injury


- **effect on CMR**:  
  No diff. of ATP (iso vs. pentobarbital)  
  max. depression at concentrations >2 MAC (iso, sevo and des).  
  Higher ATP and phosphocreatinine and reduced lactate (iso vs. N₂O)  
  Fast recovery of ATP and intracellular pH after IR (sevo. iso vs. hal)

- **Antiexcitotoxic effect**  
  reduce neuronal AMPA receptor-mediated responses (hal, iso)  
  inhibit NMDA receptors at 1 MAC (xenon> enfl, iso, des, hal> sevo)

- **Effect on catecholamine**: catecholamine promotes the propagation of brain injury.  
  Brain (↓) plasma (↔) catecholamine (sevo, propofol)
● **Anti-apoptosis**: Oxygen and glucose deprivation-induced neuronal apoptosis is attenuated by halothane and isoflurane.

● **Antioxidant:**
Few studies on volatile anesthetics as primary antioxidants in ischemic brain

● **rCBF:**
  - Sevo: minimal cerebral vasodilation (vs. iso. or des.)
  - Sevo: increased tolerance to lower CBF during carotid endarterectomy (vs. hal. or enf.)

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**Protective**
- focal, mild and brief incomplete ischemia
- prior to the insult

**Not protective**
- severe or prolonged global ischemia
- after the insult
Sevoflurane and halothane reduce focal ischemic brain damage in the rat. But, possible influence on thermoregulation

Optimal neuroprotective concentration

**Isoflurane**
1.0 MAC of isoflurane provided superior overall outcome relative to larger concentrations


**Sevoflurane**
Postischemic neuronal survival was increased with **1.8 MAC of sevoflurane** compared with 0.45 MAC.

*Laszuk I, et al. Neurocrit Care 2011: 15; 577-84*
Isoflurane delays but does not prevent cerebral infarction in rats subjected to focal ischemia

- **Methods:** MCA focal ischemia for 70 min, isoflurane (1.5 MAC)

Evidence of neuroprotection of general anesthetics in human trials?

3526 carotid stenosis (95 centres in 24 countries) + meta-analysis

(A) stroke or death

<table>
<thead>
<tr>
<th>Study</th>
<th>LA n/N</th>
<th>GA n/N</th>
<th>Peto odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binder, 1999</td>
<td>0/27</td>
<td>0/19</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Forrnell, 1989</td>
<td>4/56</td>
<td>3/55</td>
<td>1.33 (0.29-6.09)</td>
</tr>
<tr>
<td>Kazmierk, 2006</td>
<td>2/91</td>
<td>2/95</td>
<td>1.04 (0.14-7.54)</td>
</tr>
<tr>
<td>McCarthy, 2001</td>
<td>1/34</td>
<td>1/33</td>
<td>0.97 (0.06-15.83)</td>
</tr>
<tr>
<td>Ploskina, 1989</td>
<td>0/10</td>
<td>1/10</td>
<td>0.54 (0.00-6.62)</td>
</tr>
<tr>
<td>Proby, 1989</td>
<td>0/13</td>
<td>0/10</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Stangis, 1999</td>
<td>0/55</td>
<td>4/52</td>
<td>0.12 (0.02-0.88)</td>
</tr>
<tr>
<td>Total (without GALA)</td>
<td>286</td>
<td>274</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z=0.99</td>
<td>(p=0.32)</td>
<td></td>
</tr>
<tr>
<td>GALA</td>
<td>71/771</td>
<td>79/752</td>
<td>0.88 (0.64-1.13)</td>
</tr>
<tr>
<td>Total (with GALA)</td>
<td>2057</td>
<td>2026</td>
<td>0.85 (0.63-1.16)</td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z=1.02</td>
<td>(p=0.31)</td>
<td></td>
</tr>
</tbody>
</table>

(B) death

<table>
<thead>
<tr>
<th>Study</th>
<th>LA n/N</th>
<th>GA n/N</th>
<th>Peto odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Binder, 1999</td>
<td>0/27</td>
<td>0/19</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Forrnell, 1989</td>
<td>0/56</td>
<td>1/55</td>
<td>0.13 (0.00-6.70)</td>
</tr>
<tr>
<td>Kazmierk, 2006</td>
<td>0/91</td>
<td>1/95</td>
<td>0.14 (0.06-2.32)</td>
</tr>
<tr>
<td>McCarthy, 2001</td>
<td>1/34</td>
<td>1/33</td>
<td>0.67 (0.06-15.83)</td>
</tr>
<tr>
<td>Ploskina, 1989</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Proby, 1989</td>
<td>0/13</td>
<td>0/10</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Stangis, 1999</td>
<td>0/55</td>
<td>3/52</td>
<td>0.12 (0.03-1.21)</td>
</tr>
<tr>
<td>Total (without GALA)</td>
<td>286</td>
<td>274</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z=1.94</td>
<td>(p=0.05)</td>
<td></td>
</tr>
<tr>
<td>GALA</td>
<td>18/171</td>
<td>26/1752</td>
<td>0.72 (0.40-1.30)</td>
</tr>
<tr>
<td>Total (with GALA)</td>
<td>2057</td>
<td>2026</td>
<td>0.62 (0.36-1.07)</td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z=1.72</td>
<td>(p=0.08)</td>
<td></td>
</tr>
</tbody>
</table>
RESULTS:

178 patients also receiving supplemental protective drug (thiopental or etomidate) during temporary clipping.

Supplemental protective drug were associated with 3-month Glasgow Outcome Score ($P = 0.835$; odds ratio $= 1.048$, 95% CI $= 0.674$-1.631). The effect of supplemental protective drug did not significantly vary with temperature.
Endogenous dynamic (temporal and spatial) changes occur simultaneously for damage and protection in focal cerebral ischemia

Regression of the functional neurological deficit while the structural lesion grows (Dirnagl U, Trends Neurosci 1999)

(Dirnagl U, Trends Neurosci 2003)
Pre-exposure to hypoxia can prolong anoxic survival by preserving brain metabolism

(Dahl NA and Balfour WM. Am J Physiol 1964)

‘Ischemic preconditioning’ in ischemic myocardium


Cerebral ‘ischemic tolerance’

Types of conditioning
(Conditioning: stimulus below the threshold of damage)

Delayed preconditioning:
(1-7 days before ischemia)

Rapid preconditioning:
(0.5-3 hr before ischemia)

Rapid postconditioning:
(A few sec to min after reperfusion)

Delayed postconditioning:
(A few hrs to days after reperfusion)

- Rapid response such as ion channel permeability,
- Posttranslational modification of protein

* Remote conditioning: separate organs which are conditioned and protected (e.g. limb ischemia to induce protection of heart or brain)
Mechanism of inhalational anesthetics preconditioning in ischemic brain (preconditioning; protection; both under investigation)

- **Inhalational Anesthetics**
- **Perioperative Brain Ischemia**

**Cerebral Blood Vessel**
- Adenosine A1 Receptor Activation
- KATP Channel Activation
- p38 MAPK Activation
- iNOS → NO

**Mitochondria**
- Inhibition of Fomation
- Scavenging of free Radicals
- Calmodulin
- MAPK-ERK Pathway
- ↑Akt Activation
- Moderate ↑[Ca²⁺]i

**Axon Terminal**
- Inhibition of Glutamae Release
- AMPAR & NMDAR Antagonism
- ↓[Ca²⁺]i
- Inhibition of Membrane Degeneration and Lipid Peroxidation

- Catecholamine Release
- GABA Release

**CMR**

- Bax
- ↑Akt Activation
- Or Delay Apoptosis?

**KCCPD K1**
- GABA Receptor Potentiation
# Proposed mechanisms of volatile preconditioning

<table>
<thead>
<tr>
<th>Volatile anesthetics</th>
<th>In vitro/ in vivo experiments</th>
</tr>
</thead>
</table>
| isoflurane           | Anti-apoptosis  
                      Anti-excitotoxicity  
                      Mitochondrial $K_{ATP}$ activation  
                      iNOS activation  
                      Akt, MAPK activation  
                      Inhibition of ROS  
                      CBF                                                             |
| sevoflurane          | Anti-inflammation  
                      Anti-apoptosis  
                      Mitochondrial $K_{ATP}$ activation  
                      MARK activation  
                      BBB stabilization  
                      CBF                                                             |
| xenon                | Anti-apoptosis  
                      Anti-excitotoxicity  
                      Mitochondrial $K_{ATP}$ activation  
                      CREB transcription factor  
                      BNDF growth factor  
                      Inhibition of ROS                                                             |

1. **Increased substrate delivery**
2. **Antagonism of damaging mechanisms**
3. **Metabolic downregulation**
4. **Improved recovery**
Anesthetic preconditioning factors contributing to outcome: similar to protective effect

- **Protection**
  - ?
  - Shorter
  - Lower conc.
  - Milder

- **Injury**
  - ?
  - Prolonged
  - Higher conc.
  - Stronger

- Duration
- Timing
- Dose
- Severity of insult

- **Protection**
- **Injury**
### Preconditioning duration and interval between preconditioning and IR

<table>
<thead>
<tr>
<th>Animal</th>
<th>Stroke model</th>
<th>Preconditioning stimulus</th>
<th>Interval between preconditioning and ischemia</th>
<th>Histological and functional outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>rat</td>
<td>2 h of MCAO followed by 24 h of reperfusion</td>
<td>1.5% iso in 98% O₂ for 1 h</td>
<td>1 h</td>
<td>+</td>
</tr>
<tr>
<td>rat</td>
<td>pMCAO</td>
<td>2% iso for 30 min</td>
<td>24 h</td>
<td>+ at 6, 24, and 72 h after pMCAO</td>
</tr>
<tr>
<td>young rat</td>
<td>Lt CCA ligation followed by 8% O₂ for 1, 2, or 2.5 h</td>
<td>1% or 1.5% iso for 30 min</td>
<td>24 h</td>
<td>+ (2 or 2.5 hr ischemia)</td>
</tr>
<tr>
<td>rat</td>
<td>pMCAO</td>
<td>1.4 % (1 MAC) iso for 3 h</td>
<td>0, 12, 24, or 48 h</td>
<td>+ (0 ~ 24 h precond)</td>
</tr>
<tr>
<td>mice</td>
<td>1 h of MCAO followed by 48 h of reperfusion</td>
<td>1% or 1.4% iso for 3 h</td>
<td>0, 12, 24, or 48 h</td>
<td>+ (0~24 h precond)</td>
</tr>
<tr>
<td>rat</td>
<td>pMCAO</td>
<td>1.2% (1 MAC) hal for 3 h</td>
<td>24 h</td>
<td>+ at 4 day after pMCAO</td>
</tr>
<tr>
<td>rat</td>
<td>2 h of MCAO followed by 22 h of reperfusion</td>
<td>Reperfusion 1% to 2% hal for 1 or 8h</td>
<td>0 h</td>
<td>+ ( 1 hr precond)</td>
</tr>
<tr>
<td>rat</td>
<td>7 mins of cardiac arrest</td>
<td>2.4% (1 MAC) sevo for 30 mins once or on 4 consecutive days</td>
<td>15 min (single exposure, early) or 24 h (4 exposures, late)</td>
<td>+ at 7 days after cardiac arrest</td>
</tr>
</tbody>
</table>

Gender difference in ischemic injury and VA preconditioning

- Lower stroke incidence during **premenopause** and higher during **menopause**
  
  *Sudlow CL and Warlow CP. Stroke 1997: 28;491–9*

- Antiinflammatory effect of **Estrogen** attenuates iNOS expression resulting in protective effect.
  

- **IsoPC** (for 4h 1% isoflurane, 24 h before 2 h of MCAO) decreased ischemic damage in young and middle-aged male mice and markedly increased infarction in young female mice and had no effect in middle-aged female mice.
  
Few publications related to ‘anesthetic postconditioning’ from PubMed (2005-2011)

Weak evidence
Similar mechanism to preconditioning?

<table>
<thead>
<tr>
<th></th>
<th>Myocardium</th>
<th>Brain</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevoflurane</td>
<td>25</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>30</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Propofol</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Legend:
- Orange: Myocardium
- Light Blue: Brain
- Red: Others
- Isoflurane postconditioning induces neuroprotection via Akt activation and attenuation of increased mitochondrial membrane permeability.

  *Li L and Zuo Z. Neuroscience 2011: 199; 44-50*

- Isoflurane postconditioning reduces OGD-induced brain injury via mitochondrial $K_{ATP}$ channel.

Different gene expression hypoxic and anesthetic preconditioning

Despite sharing similar upstream signaling and neuroprotective outcomes, the genomic response to APC and HPC is different.


<table>
<thead>
<tr>
<th></th>
<th>Intracellular Ca$^{2+}$</th>
<th>Neuronal cell death</th>
<th>Signal transduction genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic Preconditioning</td>
<td>Increase to 50 nm</td>
<td>Decrease by 50% in CA1, CA3, dentate neuron</td>
<td>Increase more antiapoptosis/survival genes</td>
</tr>
<tr>
<td>Isoflurane preconditioning</td>
<td></td>
<td></td>
<td>Increase more cell cycle/ development/ growth genes</td>
</tr>
</tbody>
</table>
Combining preconditioning (CPC) with Hypoxia (HPC) + isoflurane (APC)

- Hypoxic preconditioning (95% N2+5% CO2 for 15 min, HPC), 1% isoflurane preconditioning for 15 min (APC) or their combination (CPC) for 15 min.

- OGD injury

- CPC decreased CA1, CA3 and dentate region death by 64–86% following OGD, more than HPC or APC alone (P<0.01).

Gene expression following CPC: an amalgam of gene expression in HPC and APC, with simultaneous increases in growth/development and survival/apoptosis regulation genes.
Combining conditioning with anesthetic pre- and post-conditioning

Additive neuroprotection with combination of isoflurane preconditioning and postconditioning than either alone.

- Preconditioning (2% isoflurane for 30 min at 24 h before insult)
- Ischemic insult (1-h OGD and a 24-h reperfusion)
- Postconditioning (2% isoflurane for 1 h) at 0-2 hr after the onset of OGD.

Combining different anesthetics

- Choice of Anesthetic Combination Determines Ca\(^{2+}\) Leak after Ischemia- Reperfusion Injury in the Working Rat Heart Favorable versus Adverse Combinations


- Alternative use of *isoflurane and propofol* confers superior cardioprotection than using one of them alone in a dog model of cardiopulmonary bypass.

  *Li T, et al. Eur J Pharmacol 2012: 677; 138-46*
Anesthesia: Could Early Use Affect the Brain Later?

By EBEN HARRELL  Tuesday, Nov. 03, 2009

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Glutamate and GABA act as trophic factors.

GABA’s effects are even excitatory in the very young brain.

Temporary interference by anesthetics during early brain development might interfere with proper CNS formation.

During brain development, apoptosis eliminate up to 70% of excessive neurons to ensure appropriate CNS structure and function.
Multi-exposure to anesthesia and developmental and behavioral disorders during early childhood

Retrospective cohort of younger than 3 years, 10,450 siblings (304 operated & 10416 matched) enrolled in the New York State Medicaid program,

All current anesthetic drugs induce neuronal cell death in the developing brain and potentially cause long-term neurological impairment.

- Painful stimuli without analgesia and anesthesia initiate a harmful stress response in young children and trigger neurotoxic effects in the developing brain.
- Anesthetic drugs may confer neuroprotection during hypoxic and ischemic insults.
Dexmedetomidine neuroprevention

- Postischemic dexmedetomidine reduce ischemic lesion by 50% in focal cerebral ischemia.  
  Maier C, et al. Anesthesiology 1993:79; 306-12

- Mechanisms:
  1) modulate ultra-early balance between pro- and antiapoptotic protein  
  2) reduce cortical lesion size in wild-type mice and adrenergic subtype $\alpha$2C-KO mice by 44% and 49%, but not in $\alpha$2A-KO mice in a perinatal excitotoxic brain damage model (Paris A, et al. Anesth Analg 2006: 102; 456-61)
  3) increases the expression of pERK1 and 2 involving synaptic plasticity and cell survival, via mechanisms independent of $\alpha$2AR activation.  

- Pro/fent’l sedation diminished cognitive scores by mean of -12.4 (p=0.001) while DEX/fent’l sedation improved cognitive scores by 6.8 (p=0.018) in NICU patients.  
Dexmedetomidine against neonatal anesthetic toxicity

α2 adrenoceptor signaling plays a trophic role during brain development. Dexmedetomidine prevented isoflurane-induced neonatal neurotoxicity.


Cognitive function assessment. Seven-day-old rat pups with 0.75% isoflurane or dexmedetomidine (1 μg/kg) treatment for 6 h.

Dexmedetomidine (1 μM) inhibits 0.75% isoflurane-induced neuroapoptosis in vitro.
## Benefit and detrimental effects of processes and molecules involved in ischemia

<table>
<thead>
<tr>
<th>Factor</th>
<th>Benefit</th>
<th>Detriments</th>
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<tbody>
<tr>
<td>Glutamate</td>
<td>Low levels: preconditioning effect through NMDA receptor activation</td>
<td>High levels: imbalance of ion flux due to receptor overstimulation</td>
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<tr>
<td>Calcium</td>
<td>Activate CREB, leading to activation of gene pathways leading to tolerance</td>
<td>High concentrations: in imbalance of ion flux and mitochondrial membrane permeabilization</td>
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<tr>
<td>Inflammation</td>
<td>Delivers more oxygen and glucose to affected area by increased BF</td>
<td>Cell damage caused by increased delivery of calcium and inflammatory cells secreting cytokines</td>
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<tr>
<td>Nitric oxide</td>
<td>Signaling leading to ERK activation. eNOS increases blood flow</td>
<td>Free radical can damage cell structures, reacts to form peroxynitirite, which does more damage</td>
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<tr>
<td>Caspase activity</td>
<td>Low levels of caspase 3: required for ischemic tolerance</td>
<td>Caspase activation: initiate apoptosis</td>
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</table>

Conclusions

Even though current anesthetics might show neuroprotective properties from in-vitro or in-vivo animal experiments, our believes toward anesthetic protection are still drifting because of lack of their clinical evidence.

We are looking forward getting a firm belief of anesthetic neuroprotection through more prospective, well designed, randomized clinical trials for at-risk surgical procedures, in which endogenous protective/repair machinery is expecting to afford valuable clues.