Anesthesia and Neurodegeneration

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Got Pain?
The drugs are not much different.
Common anecdote:

“My father (grandfather, uncle mother, brother, etc.) has never been the same after his surgery”


>65 yrs old, GA 250 patients, no controls. 7% severe dementia.
Post-Operative Cognitive Dysfunction

   >60 years age, all GA (~1200 pts, 300 controls).
   POCD 26% @ 1 week, 10% @ 3 months.
   Controls ~3% @ 3 months.

   40-60 years of age, all GA (~500 pts, 180 controls).
   POCD 20% @ 1 week, 6% @ 3 months.
   Controls 4% at 3 months. Subjective POCD 30% at 3 months.
Inhaled anesthetic binding sites are internal cavities.

Franks et al, Biophys J., 1998

Ishizawa et al, Mol. Pharm. 2003

Bhattacharya et al, JBC 2000

Liu et al, FASEB J., 2005

Cui et al, Biophys J. 2007
Cavities are found at interfaces and occupancy can modulate the oligomerization equilibrium.
A feature common to all the neurodegenerative diseases is protein oligomerization.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Proteins/Molecules</th>
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<tbody>
<tr>
<td>Alzheimer</td>
<td>$\beta$ amyloid peptide, tau</td>
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<tr>
<td>Parkinson</td>
<td>$\alpha$ synuclein</td>
</tr>
<tr>
<td>Huntington</td>
<td>polyglutamine peptides</td>
</tr>
<tr>
<td>J/C, Mad Cow</td>
<td>prions</td>
</tr>
</tbody>
</table>

How (or if) aggregated protein causes synaptic dysfunction or neurodegeneration is not yet clear.
Anesthesiology 2004;101:703

**Rank Order:**

- Haloalkanes > Haloethers > Injectable

bis-ANS binding, size exclusion and photocrosslinking all demonstrate enhanced intermediate population.

Carnini et al., *Curr Alz Res* 2007; 4:233-41
Biological Relevance: Cells

1. Exogenous Aβ + anesthetic more toxic to PC-12 cells than either alone. \(\text{(Eckenhoff et al, 2004)}\)
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2. Cells that over-produce Aβ exhibit greater anesthetic toxicity, a feature eliminated by Aβ oligomerization inhibitors (*Xie et al, 2006; Liang et al, 2008*)
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2. Cells that over-produce $\beta$ exhibit greater anesthetic toxicity, a feature eliminated by $\beta$ oligomerization inhibitors *(Xie et al, 2006; Liang et al, 2008)*

3. Isoflurane activates apoptotic pathways and enhances $\beta$ production. *(Wei et al, 2005; Xie et al, 2006-7)*

4. Anesthetic-induced apoptosis is calcium and agent dependent. *(Wei et al, 2005; Yang et al, 2008)*
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4. Anesthetic-induced apoptosis is calcium and agent dependent. (Wei et al, 2005; Yang et al, 2008)

5. Anesthetic-induced Aβ production is calcium and agent dependent. (Xie et al, 2008)
So this is more complicated than just oligomerization....

Inflammation

Loss of Memory

Cognition

Early Mortality

So this is more complicated than just oligomerization....

Calcium

Neuron Brain Animal

Neuron

Brain

Animal
The Tg2576 mouse overexpresses APPsw associated with early AD.

DESIGN: Exposed 12-month old mice to 2 hours of halothane or isoflurane in air (or air alone) every day for a week. Learning, memory evaluated before and starting three days after, then immunohistochemistry.
Mouse plaque

Halothane enhanced plaque load at 14d

Caspase 3 at 14d

Cx

CA1

DG

Working memory function evaluated starting ~1 week after exposures finished.

The Pre-symptomatic Patient

3XTg mice (APPsw, PS1, and tau transgenes) exposed to isoflurane or halothane (1 MAC for 5 hrs, 1/wk X 4 wks) at 1.5, 2.5 and 4 months of age. Learning and memory tested in water-maze 1 month later.
Is there a gender effect?
A central feature of human AD is intracellular NFT.
Tau, a microtubule-associated protein, is hyperphosphorylated by “anesthesia”.

So it may also reflect anesthetic management instead of just the anesthetic.

Inflammation

Aβ

APP

Cys-C

CTF

α products

tau

Calcium

microtubules

tubulin

tau-P

Aβ

oligomer

synaptic dysfunction

Aβ CTF

Cys-C

Calcium

tau

microtubules

tubulin

tau-P

NFT

Loss of Memory

Cognition

Early Mortality

Inflammation

Plaque

Calcium

Neuron

Brain

Animal

Single or many mechanisms?
Biological relevance: People


252 AD cases, *matched controls*.


252 AD cases.


115 AD vs 230 PD, 230 “controls”.

Mostly interpreted as negative, BUT……..
Impact of Prior Anesthesia History on AD
Silber & Rosenbaum analysis of Bohnen papers

**Number of Prior Anesthetics**

- None
- 1-5
- >6

**Hours of Prior Anesthesia**

- None
- <10 hr
- >10 hr

Odds Ratio

P=0.08 one sided

P=0.11 one sided
Alzheimer development in CABG vs PTCA

119 pts
Odds ratio = 1.71, p=0.04

What about other aggregating neurodegenerative disorders? Parkinson’s Disease
Anesthesiologists vs internists (n= 33,044)

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>Anesthesiologists</th>
<th>Internists</th>
<th>Comparison of anesthesiologists vs. internists</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>SMR*</td>
<td>95% CI** (P)</td>
</tr>
<tr>
<td>All periods</td>
<td>14</td>
<td>1.33</td>
<td>0.75–21.5 (0.29)</td>
</tr>
<tr>
<td>≤10 yr</td>
<td>3</td>
<td>0.60</td>
<td>0.15–1.57 (0.38)</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>11</td>
<td>2.22</td>
<td>1.15–3.80 (0.01)</td>
</tr>
</tbody>
</table>

**Likelihood ratio confidence interval.
Rotterdam Study:
5395 older (>55 yrs old) subjects, completed “food-frequency” questionnaires. Dementia screening, f/u by neurologist, 197 cases.

<table>
<thead>
<tr>
<th>Alcohol intake</th>
<th>None</th>
<th>Light</th>
<th>Mod</th>
<th>Heavy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Dementia</td>
<td>1.0*</td>
<td>0.8(0.6-1.2)</td>
<td>0.6(0.4-0.9)</td>
<td>1.0(0.4-2.6)</td>
</tr>
<tr>
<td>Alzheimer’s</td>
<td>1.0</td>
<td>0.9(0.6-1.4)</td>
<td>0.7(0.4-1.2)</td>
<td>1.2(0.4-3.6)</td>
</tr>
</tbody>
</table>

* = Hazard ratios

Nurses Health Study.

12,480 subjects, 70-81 years old.

Stampfer et al. NEJM 2005: 352:245
Alzheimer’s disease is a lifelong process. Detection of remote influences is difficult!

Small accelerations in symptom onset produces a large increase in prevalence.

Summary:

1. Anesthetics alone enhance amyloidopathy via multiple mechanisms.
2. Anesthetic-induced hypothermia enhances tauopathy.
3. Vulnerable populations most at risk.
5. Relationship between POCD and neurodegeneration?
6. Alternatives exist??

What next?

1. Epidemiology of AD and surgery/anesthesia.
2. Human studies essential – but we need good biomarkers.
3. Other anesthetics need to be studied.
Penn Collaborators

Anesthesia: Jonas Johansson
Maryellen Eckenhoff
Andrew Kofke
Renyu Liu
Jin Xi
Junxia Tang
Sean Garrity
Feras Mardini
Angelina Sylvestro

Chemistry: Mike Klein
Kent Blasie
Bill Dailey
Jeff Saven
Ivan Dmochowski

Pharmacology: Paul Axelsen

Path/Lab Med: John Trojanowski
Virginia Lee

Outcomes Ctr: Jeff Silber
Paul Rosenbaum

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“...the choice truths of medicine are frequently blended with a heap of rubbish.” John Morgan, 1765.