Are Anesthetics Toxic to the Brain: Do Our Drugs Kill Brain Cells?

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Outline

• Mechanisms of anesthesia and anesthetic neurotoxicity
• Developmental anesthetic neurotoxicity in the very young
• Anesthetics and age-related neurodegeneration in the elderly
• Concept of the vulnerable brain
General anesthetics produce a variety of potent neurobiological effects

Unconsciousness
Immobility
Amnesia

The essence of anesthesia: unconsciousness, amnesia, immobility
Specific anesthetic end points have distinct potencies and cellular sites of action

- **Amnesia**: frontal cortex/hippocampus
- **Unconsciousness**: thalamus, cortex
- **Immobility**: spinal cord (MAC)

*Perouansky et al., 2009*  
*Rudolph & Antkowiak, 2004*
Molecular mechanisms of anesthesia 101

General anesthetics act by **two** principal mechanisms:

- **Reduced excitatory transmission** (glutamate release, NMDA-type glutamate receptor block)

- **Enhanced inhibitory transmission** (GABA<sub>A</sub> receptor facilitation)
Anesthetic neurotoxicity: Are anesthetics toxic to the brain?

Anesthesia assumed reversible upon drug elimination for >160 years, but recent concerns for

• Neurodevelopmental toxicity
• Age-related neurodegeneration
Key developments in last decade

Detrimental effects of anesthesia at extremes of age detected in laboratory studies

- *Developing brain* - developmental neurotoxicity
- *Aged brain* – accelerated Alzheimer’s disease pathology

Bench to bedside scientific discovery; reverse of typical findings

Laboratory curiosity or clinical reality?
Developmental anesthetic neurotoxicity

relevance of anesthetic molecular mechanisms 101

- Neurotoxicity mechanisms are fundamentally the same as the mechanisms of anesthesia…

- NMDA receptor block or GABA$_A$ receptor potentiation during synaptogenesis leads to widespread cell death and neurodegeneration in immature rat brain (Ikonomidou et al., 2000)

- Activation of programmed cell death (apoptosis)

The same mechanisms involved in anesthesia contribute to developmental neurotoxicity…

Anesthesia and toxicity inseperable
Anesthetic Neurotoxicity

Precedent in fetal alcohol syndrome

Ethanol blocks NMDA receptors and potentiates GABA$_A$ receptors

Vulnerability coincides with peak synaptogenesis: 6 mo gestation to 3 yrs in humans

Transient ethanol exposure:

- kills millions of neurons
- reduces brain mass
- neurobehavioral deficits

Ikonomidou et al. Science 2000;287:1056-1060

Apoptosis in parietal and cingulate cortex of P8 rats treated 24 hours previously with saline, MK-801 (NMDA antagonist), phenobarbital, or ethanol
Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits
Jevtovic-Todorovic et al., J Neuroscience, 2003; 23:876–882

Midazolam/nitrous oxide/isoflurane to maintain surgical plane of anesthesia for 6 h in neonatal rats (P0-P14)

- widespread apoptotic neurodegeneration
- deficits in hippocampal synaptic transmission
- persistent memory/learning impairment
Do anesthetics harm the developing human brain? An integrative analysis of animal and human studies.
Summary of preclinical data for anesthetic neurotoxicity

- Evidence from multiple laboratories
- Widespread apoptotic degeneration in multiple species (mouse, rat, guinea pig, pig, primate)
- Occurs with both GABAergic and NMDA blocking drugs
- Associated with long-term behavioral changes in rodents and primates
Can you translate?

Problems with translating animal data:

- Converting development and exposure times between species; translatingtime.net
- Relevance of histopathological endpoints to neurobehavioral effects
- Physiological dysregulation in small animals
- Relevance to long-term outcome due to limited survival in animal models
Clinical evidence of neurotoxicity?

• Pressing questions for pediatric anesthesia
• Evidence for anesthetic neurotoxicity in preclinical models is unequivocal
• Need for prospective clinical studies
• Definitive clinical evidence in humans is lacking, and will be difficult to obtain
• Most studies are retrospective observational studies with heterogeneous populations and outcome measures
• Association vs. causation
• Results have been inconsistent (unsurprisingly)
Results of recent retrospective observational cohort studies:

Studies supporting behavioral deficits

- Association between >2 anesthetics before 4 years and **learning disabilities**; suggested risk for exposure > 2 hours (n=593; *Wilder*, 2009)
- Risk of **developmental and behavioral disorders** in children enrolled in a state Medicaid program greater if surgery at <3 years (n=383; 302) than for siblings with no surgery; risk greater for multiple surgeries (*DiMaggio*, 2009; 2011)
- Repeated exposure to anesthesia and surgery before the age 2 a significant independent risk factor for the later development of **learning disabilities** (n=8548) *Flick*, 2011)
- Repeated exposure to anesthesia and surgery before age 2 associated with development of **ADHD** as teen (n=5357; *Sprung*, 2012)
Results of recent retrospective observational cohort studies:

Studies **supporting** behavioral deficits

- Exposure to anesthesia before 3 years (n=321) increased odds for **language and cognitive deficits** in retrospective database analysis of Western Australia Pregnancy Cohort Study (Ing, 2012)
- Association between general anesthesia before 1 year and **learning disabilities** at age 12; no difference in standardized learning exam (n=100; Bong, 2013)
- Association between anesthesia before age 1 and **lower recollection scores**, confirmed in rat model (n=28; Stratmann et al., 2014)
- Association between preschool exposure to general anesthesia and small risk of **early developmental vulnerability** in large population-based cohort (188,557) study in Ontario (O’Leary et al., 2016)
- Surgery before age 4 associated with **long-term language and cognitive deficits** as well as gray matter defects on MRI (n=53; Backeljauw et al., 2016)
Results of recent retrospective observational cohort studies:

*No association* with deficits

- No association between urologic procedures <6 years and in neurobehavioral performance (n=243; *Kalkman*, 2009)
- No association between exposure <3 years and academic performance in a *twin study* (n=110; *Bartels*, 2009)
- No association between delivery by caesarean under general anesthesia and learning disability (*Sprung*, 2009)
- No association between exposure and academic performance at 15-16 years in 2689 Danish infants exposed during hernia repair at <1 year (*Hansen*, 2011)
GAS study
*Ongoing clinical trial*

- International prospective randomized controlled trial interim results
- Sevoflurane general anesthesia treatment group vs. awake spinal anesthesia control
- Neurodevelopmental results at 5 years
Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Dorris, Graham Bell, Robyn Stargatt, David C Bellinger, Tibor Schuster, Sarah J Arnup, Pollyanna Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium*

Summary
Background Preclinical data suggest that general anaesthetics affect brain development. There is mixed evidence from cohort studies that young children exposed to anaesthesia can have an increased risk of poor neurodevelopmental outcome. We aimed to establish whether general anaesthesia in infancy has any effect on neurodevelopmental outcome. Here we report the secondary outcome of neurodevelopmental outcome at 2 years of age in the General Anaesthesia compared to Spinal anaesthesia (GAS) trial.

- Interim results at 2 years
- Sevoflurane exposure for ~1 h in infants <60 weeks old does not increase risk of adverse neurodevelopmental outcomes
- Advantages: single agent, single procedure, but limited sensitivity of assessment at 2 years
- Primary endpoint 5 year analysis in 2017
PANDA (Pediatric Anesthesia Neurodevelopment Assessment) study

- Ambidirectional observational study
- Retrospective historical cohort with anesthesia exposure before age 3 yr (period of synaptogenesis in humans)
- Prospective follow-up for direct assessment of mean global IQ vs. no anesthesia sibling controls

https://clinicaltrials.gov/ct2/show/record/NCT00881764
105 sibling pairs from 4 AMCs for hernia surgery
Mean surgery time 80 min
No difference in mean global IQ at 8-15 years
Advantages: single exposure, healthy patients, single procedure
Disadvantages: 90% male
Questions: Role of repeated or longer exposure, comorbidities
MASK (Mayo Anesthetic Safety in Kids) trial

Prospective observational cohort of 1000 children in MN +/- single/multiple anesthesia exposure before age 3 yr
Neuropsychological and Behavioral Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia

The Mayo Anesthesia Safety in Kids (MASK) Study

David O. Warner, M.D., Michael J. Zaccariello, Ph.D., L.P., Slavica K. Katusic, M.D., Darrell R. Schroeder, M.S., Andrew C. Hanson, B.S., Phillip J. Schulte, Ph.D., Shonie L. Buenvenida, R.N., Stephen J. Gleich, M.D., Robert T. Wilder, M.D., Juraj Sprung, M.D., Danqing Hu, M.D., Robert G. Voigt, M.D., Merle G. Paule, Ph.D., John J. Chelonis, Ph.D., Randall P. Flick, M.D., M.P.H.
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- 997 children, general intelligence (IQ) tested at 8-12 or 15-20
- No significant differences between singly and multiply exposed children (primary endpoint)
- Processing speed and fine motor abilities decreased in multiply exposed (secondary endpoint) with parental reports of behavioral and learning difficulties

Anesthesiology, April 2018
The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains.

http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm
Recent perspective in *NEJM* recommends conversation with parents

Anesthesia and Developing Brains — Implications of the FDA Warning

Dean B. Andropoulos, M.D., M.H.C.M., and Michael F. Greene, M.D.

N Engl J Med. 2017 Feb 8
Is anesthetic neurotoxicity avoidable?

- Developmental stage – window of vulnerability
- Exposure dose and duration – 3-5 h threshold?
- Single vs. multiple exposures
- Drug combinations vs. monotherapy
  Synergy/antagonism
- Anesthetic-specific differences
- Mitigation by concurrent pain?
- Neuroprotective adjuvants
  Melatonin, Li⁺, L-carnitine, dexmedetomidine, xenon, bumetanide (NKCC1 inhibitor)
- Neuroplasticity and recovery
  Following damage, mammalian CNS is not hard-wired
Mitigation of toxicity by neuroplasticity: rats and nonhuman primates

• Sevoflurane induced memory impairment in P7 rats reversed by subsequent environmental enrichment

• No effect of 5h sevoflurane exposure in P6 monkeys on learning, memory or behavior with enriched environment (Zhou et al., 2015)
Unresolved questions regarding anesthetic neurotoxicity

• Does combination of GABAergic and NMDA blocking drugs cause more damage than a single agent?
• Is damage related to cumulative exposure time or number of exposures (suggested by retrospective clinical data)?
• Synaptic loss related to number of exposures in rats: 3 x 2h > 6h of sevoflurane (Amrock et al., 2015)
• Mitigation of toxicity by adjuvant drugs

• Strong signal, but…
• Currently no causal link between anesthesia exposure per se and long-term neurocognitive deficits
• No firm basis to delay necessary surgery

(smarttots.org/about/consensus-statement)
Anesthesia and the mature and aging brain
What is Alzheimer’s disease?

• Described by German psychiatrist Alois Alzheimer in 1906
• Loss of synaptic brain cell connections with neuronal degeneration and death, eventually destroying memory and other important mental functions
• Memory loss and confusion are the main symptoms
• Pathological diagnosis defined by plaques and tangles
Risk factors

- Age is the main risk factor (approaching 50% incidence >85 years)
- Other risk factors: diabetes, obesity, smoking, low fitness, low education, family history/genetics
Genetic factors

- Basis for up to 5% of cases; mutations in:
  - Amyloid precursor protein (APP); cleaved to Abeta
  - Presenilin-1 and -2 (PSEN); APP processing
  - Apolipoprotein E4 (APOE4): regulates Abeta levels
Mechanisms of Alzheimer’s disease

Aberrant processing of APP leads to *amyloid-β peptide* (Aβ42) formation

mutations that increase Aβ induce AD phenotype – *baptists*

extracellular *plaque* (amyloidopathy); toxic

Hyperphosphorylation of tau leads to self-association into paired helical filaments

*neurofibrillary tangles* (tauopathy) - *tauists*

disrupts cellular trafficking
Association with anesthesia and surgery? PubMed citations (as of April 2018)

AD: 134414
AD + anesthesia: 416
AD + surgery: 3096
AD + anesthesia and surgery: 153
Anaesthesia and Alzheimer’s disease: laboratory data – Abeta

In vitro experiment with isolated Abeta
Anesthetic effects on Alzheimer’s disease pathophysiology: summary

- Isoflurane alters APP processing to Aβ, and increases Aβ levels, caspase activation and apoptosis in neonatal mouse brain (Xie et al., 2006)
- Isoflurane worsens AD neuropathology, more so in AD model mice (Liu et al., 2010)
- Multiple anesthetics increase tau hyperphosphorylation and insoluble precipitates
- In AD model mice (Planel et al., 2009) and wild-type mice after repeated exposures (Le Freche et al., 2012)

**Problem: models do not use aged animals**
Human studies: CSF biomarkers

- CSF biomarkers measured with spinal drain
- Abnormal Abeta, tau, and phospho-tau in CSF up to 48 h after endoscopic surgery with propofol or sevoflurane (Tang et al., 2011)
Human studies: CSF biomarkers

The Effect of Propofol Versus Isoflurane Anesthesia on Human Cerebrospinal Fluid Markers of Alzheimer’s Disease: Results of a Randomized Trial

Miles Bergera,*, Jacob W. Nadlerb, Allan Friedmanc, David L. McDonaghd, Ellen R. Bennette, Mary Cootera, Wenjing Qif, Daniel T. Laskowitza,*,g,h, Vikram Ponnusamyh, Mark F. Newmana,1, Leslie M. Shaw, David S. Warnerg,k, Joseph P. Mathewa and Michael L. Jamesa,e for the MAD-PIA investigators1

Conclusion: Neurosurgery/otolaryngology procedures are associated with an increase in the CSF tau/Aβ ratio, and this increase was not influenced by anesthetic type. The increased CSF tau/Aβ ratio was largely driven by propofol/sevoflurane.

Open-heart surgery increases cerebrospinal fluid levels of Alzheimer-associated amyloid β

B. Reinsfelt1, A. Westerlind1, K. Blennnow2, H. Zetterbergb2,2 and S.-E. Ricksten1

At 24 h; propofol/sevoflurane
Up to 6 months after CABG with TIVA (Palotas et al., 2010)
CSF biomarker predicts POCD

Cerebrospinal Fluid Biomarker for Alzheimer Disease Predicts Postoperative Cognitive Dysfunction

Lisbeth Evered, B.Sc., M.Biostat., Ph.D., Brendan Silbert, M.B., B.S., F.A.N.Z.C.A.,
Paul Maruff, Ph.D., Kaj Blennow, M.D., Ph.D.

- Patients with low preoperative CSF Abeta, a biomarker for AD, had increased POCD at 3 months
- AD neuropathology may increase risk of POCD in presymptomatic individuals

Conclusions: Low CSF Aβ_{1-42} may be a significant predictor of POCD at 3 months. This indicates that patients with AD neuropathology even in the absence of clinically detectable AD symptoms may be susceptible to POCD. (Anesthesiology 2016; 124:353-61)
Epidemiological studies – meta-analysis

- No effect of anesthesia/surgery on AD

Seitz et al., 2011
Increased risk of dementia in people with previous exposure to general anesthesia: A nationwide population-based case–control study

Chia-Wen Chen\textsuperscript{a,b}, Che-Chen Lin\textsuperscript{c}, Kuen-Bao Chen\textsuperscript{b}, Yu-Cheng Kuo\textsuperscript{d,e}, Chi-Yuan Li\textsuperscript{a,b}, Chi-Jung Chung\textsuperscript{f,g,*}

- Large case-control study: >26,000 subjects; OR 1.34
Epidemiological studies - updated

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Q = 9.76, df = 14, p = 0.78; I² = 0.0

- Chen et al. 2014; OR 1.34 (1.24-1.42)
- Chen et al. 2013, HR 1.75 (1.59-1.92)
- Sprung et al. 2013, (OR 0.89 (0.73-1.1)
Prospective observation study of a registry for dementia in Seattle WA since 1994; analyzed in 2012

PARTICIPANTS: Community-dwelling members of the Adult Changes in Thought cohort aged 65 and older and free of dementia at baseline (N = 3,988).

MEASUREMENTS: Participants self-reported all prior surgical procedures with general or neuraxial (spinal or epidural) anesthesia at baseline and reported new procedures every 2 years. People undergoing high-risk surgery

Anesthetics and neurodegeneration - Summary

- Anesthetics activate pathological mechanisms of AD in animal models: 
  \textit{Abeta formation, oligomerization, neurotoxicity}
  \textit{tau hyperphosphorylation, aggregation, neurotoxicity}

- Anesthesia/surgery increases CSF biomarkers of AD in humans

- Observational studies in humans are inconclusive

- Not unlike the current situation for developmental neurotoxicity
AD develops over a long time course: cognitive trajectory

- Jack CR et al, Neuron, 2013
The vulnerable brain

- Brain is most sensitive to anesthesia/surgery at the extremes of age

The vulnerable brain

• Brain is most sensitive to anesthesia/surgery at the extremes of age
• Strong laboratory signal but unclear clinical translation (reproducibility striking)
• Identifying the vulnerable patient and mitigating risks:
  • Dosing, timing, agents, adjuvants