Anesthetic Neurotoxicity in the Developing Brain

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Disclosures
No commercial COI
Grant support from NIH
A fundamental premise of modern general anesthesia is that the brain is structurally left in the same condition that was prior to the administration of the anesthetic.

Is it time to modify this premise?
Anesthesia increased in cell death
Anesthesia led to poor performance on tests of learning and memory

“.. If surgery does not have to be performed early in life, it would be prudent to postpone it.”

J. W. Olney

Morgan K, Science News 2003;163:87
Anesthetic Effects on the Developing Nervous System

If You Aren’t Concerned, You Haven’t Been Paying Attention
Introduction

- Review of anesthetic neurotoxicity
- Pathology
- Relevance to humans and to clinical practice
Drugs with Developmental Neurotoxicity

- Anti-epileptic agents
  - Valproate, vigabatrin, phenytoin
  - Phenobarbital, diazepam, clonazepam
- Alcohol
- NMDA antagonists

Do anesthetics injure the brain?
Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits

- Isoflurane 0.75% to 1.5%
- Midazolam
- N₂O 80%

**Anesthetics cause widespread apoptotic neurodegeneration**

*Jevtovic-Todorovic et al, J Neuroscience 2003;23:876-882*
Vulnerability Greatest During Synaptogenesis

- About 6 hours of anesthesia required to demonstrate injury
- Exposure during synaptogenesis particularly deleterious

Rice D and Barone S Environ Health Persp 2000;108:S3
Chungani H, Preventive Medicine 1998;27:184-88
Isoflurane Neurotoxicity in Primates

Brambrink A et al, in press
Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys

M.G. Paule\textsuperscript{a,*}, M. Li\textsuperscript{a}, R.R. Allen\textsuperscript{b}, F. Liu\textsuperscript{a}, X. Zou\textsuperscript{a}, C. Hotchkiss\textsuperscript{c}, J.P. Hanig\textsuperscript{d}, T.A. Patterson\textsuperscript{a}, W. Slikker, Jr\textsuperscript{a}, C. Wang\textsuperscript{a}

\textit{Paule M et al, Neurotox Teratol 2011;33:220-230}
Effect of Propofol on Neurites

CNTR (0 hr) vs PPF (0 hr)
Effect of Propofol on Synaptic Density

Single exposure to propofol produces persistent changes in spine density
Effect of Propofol on Synaptic Density

Briner et al, Anesthesiology 2011;115:282-93
Propofol Induces Persistent Changes in Synaptic Density

Single exposure to propofol produces persistent changes in spine density

Briner et al, Anesthesiology 2011;115:282-93
Is any of this relevant to anesthesia in humans?
Early Exposure to Anesthesia and Learning Disabilities in a Population-based Cohort

- Population based retrospective cohort study
- Children anesthetized prior to 4 yr age
- Reading, written language, math learning disabilities

Wilder et al, Anesthesiology 2009;110:796-804
Attention-Deficit/Hyperactivity Disorder After Early Exposure to Procedures Requiring General Anesthesia

Juraj Sprung, MD, PhD; Randall P. Flick, MD, MPH; Slavica K. Katusic, MD; Robert C. Colligan, PhD; William J. Barbaresi, MD; Katarina Bojanić, MD; Tasha L. Welch, MD; Michael D. Olson, PA-C; Andrew C. Hanson, BS; Darrell R. Schroeder, MS; Robert T. Wilder, MD, PhD; and David O. Warner, MD

- GA before 2 years of age (n = 5357)
- ADHD diagnosis by 19 years of age (n = 341)

Multiple procedures under GA associated with increased risk of ADHD

Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship

Meike Bartels,¹* Robert R. Althoff,²* and Dorret I. Boomsma¹

- Monozygotic concordant – discordant twin design
- Anesthesia before age of 3 yr
- Anesthesia before age of 12 yr
- Results
  - Cognitive performance poor with anesthetic exposure
  - No difference between exposed and unexposed twin

No evidence for causal relationship between anesthesia exposure and learning difficulty

Inguinal hernia repair before 1 yr age under GA
Age matched control group
Test scores 9th grade

No difference in scores after adjusting for confounding variables

Hansen TG et al, Anesthesiology 2011;114:1076-85
Best studies have failed to demonstrate an adverse effect of anesthetics in infants

Single, brief anesthetic is unlikely to harm infants

Children who require more surgery are more likely to have problems

No data to suggest change in medical, surgical and anesthesia practice

Anesthetic neurotoxicity in children has become a modern day dragon in medicine. Dragons are very good at hiding from view, and they are hard to kill

Anesth Analg 2011; in press
Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia

- 2608 children Western Australia
  - 321 exposed; 2287 unexposed
- Language, cognition, behavior, motor function
  - Testing: 1, 2, 3, 5, 8, 10, 13, 16 yr
- Single exposure led to difficulty with:
  - Receptive language
  - Expression language
  - Abstract reasoning
- No motor or behavioral problems
- Multiple exposures did not exacerbate deficits

Ing C, et al. Pediatrics 2012;130;e476
Are Anesthesia and Surgery during Infancy Associated with Altered Academic Performance during Childhood?

Robert I. Block, Ph.D.,* Joss J. Thomas, M.D.,† Emine O. Bayman, Ph.D.,‡ James Y. Choi, M.D.,† Karolie K. Kimble, R.N., B.A.,§ Michael M. Todd, M.D.||

- Pyloromyotomy, inguinal herniorrhaphy, circumcision under GA
- Iowa tests of basic skills, educational development (7-10 yr age)

14% below 5th percentile

Longer anesthesia worse performance
Current Trials
FDA Funded Projects

- Childrens’ Hospital, Harvard University, Boston
  - General vs regional anesthesia

- Columbia University, New York
  - Cognitive, emotional and behavioral outcome after GA

- Mayo Clinic, Rochester
  - Long term cognitive development after GA
Anesthetic Effects on Developing Brain

- Multiple anesthetics, Long duration
- Single anesthetic, Brief Duration

Toxicity:
- Multiple agents: GABA-A agonism, NMDA antagonism
- Single agent, single anesthetic: isoflurane, sevoflurane, desflurane, propofol, midazolam, ketamine
- Dexmedetomidine, Opiates

Awake
Summary

- Dose dependent widespread neurodegeneration
  - Rodents
  - Subhuman primates
- Agents demonstrated to have toxicity:
  - Volatile anesthetics
  - Barbiturates
  - Benzodiazepines
  - Propofol
  - Ketamine
- Agents with no demonstrated toxicity
  - Dexmedetomidine
  - Opiates
- Vulnerability during synaptogenensis
- Requires prolonged exposure
- Damage associated with electrophysiologic abnormality
- Long term reduction in cognitive function
Summary

Anesthesia produces structural changes in brain

Clearly, more basic and clinical research is needed

There are, however, no data to indicate that anesthesia care providers should alter their practice