ANESTHETIC NEUROTOXICITY ON THE DEVELOPING BRAIN
From Aspen Anesthesia, presented by Holiday Seminars

Effects of Anesthetic Neurotoxicity in Animals

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Background: preliminary data from animals suggest common anesthetics neurotoxic; Food and Drug Administration (FDA) does not require evidence of neurologic safety of anesthetics at cellular level

Pathophysiology: apoptosis naturally occurring phenomenon in all growing organisms; humans born with third of total brain cells and approach 100% by young childhood; many cells and synapses form during growth period; some connections ineffective and nonfunctional; cells associated with nonfunctional connections die; mediators assist identification of effective connections; γ-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors affected by anesthetics; cells with decreased functionality undergo apoptosis; through interaction with receptors, anesthetics influence number of cells undergoing apoptosis

Mechanisms of cell death: necrosis and exocytosis — cells swell, explode, and release lysosomal enzymes; mediators left in vivo — apoptosis — cells shrink, break apart, undergo phagocytosis, and disappear

Research by Olney: identified anesthetics as causative mechanism for accelerated apoptosis; studies of brain trauma in rats — administration of anesthetics to rats found to increase apoptosis; exposure to anesthesia or ethanol postulated to trigger activation of GABA or NMDA, leading to involution of cells and apoptosis; final common pathway activation of caspase 3; caspase 3 used as metric for apoptosis

Effects of anesthetics: block NMDA receptors; activate glutamate receptors; block synaptogenesis and augment apoptosis during period of rapid brain growth in early infancy; additional structural changes mediated by NMDA and GABA can result in ineffective connections, leading to loss of brain tissue and neurocognitive dysfunction; all anesthetics cause accelerated apoptosis to varying degrees

Timing of maximal vulnerability: in rats, period of rapid synaptogenesis occurs within first 14 days of life, with maximum vulnerability at postnatal day (PND) 7; rhesus monkeys most vulnerable from second trimester until 2 mo after birth; in humans, rapid synaptogenesis occurs from third trimester until 3 yr of age

Studies evaluating damage: studies in rats demonstrate damage primarily on PND 7; additional studies demonstrate damage to other parts of brain at PND 21, after period of rapid synaptogenesis (ie, damage may occur in young adult rats); studies demonstrate damage occurs in all animals; speaker suggests all anesthetics involved

Studies by Stratmann et al: in rats, minimum alveolar concentration (MAC) of sevoflurane changes over time; in this model, one-third of animals died, suggesting stability of model precarious

Volatile anesthetics: similar levels of caspase 3 seen on PND 7 after one-half MAC of desflurane, isoflurane, or sevoflurane for 6 hr in littermate mice; xenon also shown to cause apoptosis

Intravenous (IV) agents: animals require larger dosages per kilogram than humans; apoptosis increases with increasing dosage and duration; in primates, 3-hr ketamine infusion had minimal effect on caspase 3 levels but large effect observed after 24 hr of infusion

Additional considerations: rats anesthetized for 1 day (ie, 7% of rat’s lifespan) of 14-day period of synaptogenesis; children anesthetized for few hours out of, eg, 3 yr raises questions about translatability of animal data; multiple agents produce compounding effect (giving medications in combination increases levels of caspase 3, compared with effects of individual agents); different anesthetics found to uniformly impair cognitive function

Lee study: after administration of 1 MAC of sevoflurane vs 1 MAC of sevoflurane plus nitrous oxide (N2O) to animals, performance in navigating maze similar; sevoflurane-alone group spent more time when presented with new object while sevoflurane plus N2O group did not, suggesting that addition of second agent caused learning disability (ie, decreased cognitive inquisitiveness)

Additional studies: studies of protective effect of anesthesia against inflammatory response to surgical incision have had contradictory results; magnesium, dexamethasone, and carbon dioxide cause apoptosis but not cognitive dysfunction; lithium, melatonin, and clonidine appear to have antiapoptotic properties

Traumatic brain injury (TBI): caused by dropping weights on heads of rats; in rats with TBI, arrival times delayed and path through maze impaired, compared with control group; third group (received brain trauma, followed by placement in enriched environment) performed almost as well as control group

Stratmann study: applied similar protocol to rats exposed to anesthetic instead of TBI; environmentally enriched group demonstrated faster recovery (ie, stimulating rats after anesthetic mitigates injury)

Zhang study: investigated socializing and cognitive function; used generation of progenitor cells as marker; progenitor cells demonstrate damage occurs in all animals; speaker suggests all anesthetics involved

Educational Objectives
The goal of this program is improve decision making and counseling of parents with regard to the use of anesthesia in children, in light of current data on anesthesia-induced neurotoxicity in developing animal and human brains. After hearing and assimilating this program, the clinician will be better able to:

1. Cite evidence linking exposure to anesthetics with the rate of apoptosis in the brain.
2. Assess data from animal models and studies on the effects of exposure to anesthesia during periods of rapid synaptogenesis.
3. Critically evaluate the literature addressing the effects of anesthesia on the developing human brain.
4. Identify gaps in current knowledge about anesthesia-induced neurotoxicity.
5. Provide appropriate information to parents concerned about the potential effects of anesthesia on the neurodevelopment of their children.

Faculty Disclosure
In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose. In his lecture, Dr. Lerman presents information related to the off-label or investigational use of a therapy, product, or device.
markedly reduced by exposure to sevoflurane; group exposed to sevoflurane followed by placement in enriched environment performed almost as well as controls; environmentally enriched group demonstrated superior performance, compared with rats exposed to sevoflurane without subsequent stimulation, and equally as well as controls at PND 49

**Preconditioning:** in rats, pretreatment with dose of ketamine before exposure to high-dose ketamine anesthetically dramatically reduced amount of apoptosis

**Suggested Reading**

**Brambrink AM et al:** Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. *Anesthesiology* 2012 Feb;116(2):372-84; **Creeley CE et al:** Isoflurane-induced apoptosis of neurons and oligodendrocytes in the fetal rhesus macaque brain. *Anesthesiology* 2014 Mar;120(3):626-38; **Creeley CE et al:** The young: neuroapoptosis induced by anesthetics and what to do about it. *Anesth Analg* 2010 Feb 1;110(2):442-8; **Shih J et al:** Delayed environmental enrichment reverses sevoflurane-induced memory impairment in rats. *Anesthesiology* 2012 Mar;116(3):586-602; **Stratmann G et al:** Isoflurane differentially affects neurogenesis and long-term neurocognitive function in 60-day-old and 70-day-old rats. *Anesthesiology* 2009 Apr;110(4):834-48; **Zhang MQ et al:** Neurobehavioural abnormalities induced by repeated exposure of neonatal rats to sevoflurane can be aggravated by social isolation and enrichment deprivation initiated after exposure to the anesthetic. *Br J Anaesth* 2015 Nov;115(5):752-60.

**Effects of Anesthetic Neurotoxicity in Humans**

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**Wilder et al (2009):** assessed learning disability in language, math, or reading (based on IQ and achievement test results) among 5000 children born in Olmsted County, MN, between 1976 and 1982 who received anesthetic at age ≤ 4 yr; 11% underwent one anesthetic, and 2% underwent >1 anesthetic; learning disability more common in children who underwent >1 anesthetic; risk increased with cumulative duration of anesthesia

Positive attributes of study: adjusted for age, sex, birth weight, maternal education, and known confounders for evaluating neurocognitive function; all children American Society of Anesthesiologists (ASA) Physical Status 1 and 2; learning disability persisted over time

Criticisms of study: neither patient characteristics nor cultural, racial, or ethnic diversity considered; used out-of-favor anesthetics (halothane and N₂O); learning disability not specific neuropsychological outcome; math, language, and reading reported as single outcome; follow-up of learning disability discontinued when disability detected

**Flick et al (2011):** evaluated behavior outcomes after early exposure; exposure group (350 children who underwent anesthesia at age < 2 yr) and 700 matched controls assessed for learning disability; adjusted for burden of illness; concluded repeated exposure to anesthesia and surgery independent risk factor for learning disability but not for emotional or behavioral disorder

Positive attributes: used 2 comprehensive independent methods to control for health status; children matched for factors associated with learning disability

Criticisms: halothane used; monitoring of hypoxia, hyperoxia, and hypcapnia not comprehensive; demographics not representative of entire United States

**Sprung et al (2012):** investigated attention-deficit/hyperactivity disorder (ADHD) in cohort of children born in Olmsted County, MN, from 1976 to 1982 and who remained there until age > 5 yr; ADHD diagnosed in 7.6% of overall cohort, 7.3% of children with no anesthetic exposure, 10.7% in children with single exposure, and 17.9% in children with ≥ 2 exposures

Positive attributes: risk stratified for comorbidities; adjusted for gestational age, sex, and birth weight

Criticisms: no distinction between effects of anesthesia vs surgery; no adjustment for familial factors; large overlap between ADHD and learning disability

**Sprung et al (2009):** same cohort; no difference seen in incidence of learning disability in children of mothers who underwent cesarean delivery under general vs regional anesthesia (RA); also found cumulative incidence of learning disability lower with cesarean delivery under RA than with vaginal delivery

**Kalkman et al (2009):** evaluated 243 children aged 0 to 6 yr who underwent anesthesia during different time periods; trend towards more clinically deviant behavior seen in children anesthetized at age < 2 yr (not statistically significant); underpowered retrospective pilot study

**DiMaggio et al (2009):** in retrospective cohort study, 383 children who underwent repair of inguinal hernia at age ≤ 3 yr compared with > 5000 controls (controlled for age, sex, race, and confounding diagnoses)

Findings: in exposed group, diagnoses of developmental neuroapoptosis, behavioral disorders, mental retardation, autism, or language and speech disorder 2.3-fold higher

Criticisms: outcome measures not standardized; homogenous population; anesthesia exposure in controls unknown

**Hansen et al (2011):** academic performance in 2689 Danish adolescents ages 15 to 16 yr who underwent inguinal hernia repair at age ≤ 1 yr compared with 14,000 matched controls; found no evidence of effect on academic achievement scores

Criticisms: homogeneous population; assessed only one neurobehavioral outcome; short duration of anesthesia

**Bartels et al (2009):** assessed 1100 monozygotic twin pairs; found no difference in educational achievement or cognitive problems in twin pairs discordant for anesthesia exposure at age < 3 yr

**DiMaggio et al (2011):** cohort of 10,450 twin siblings, not necessarily monozygotic; of 138 pairs discordant for anesthesia exposure, no problems noted with brain development in either twin in 107 problems; with both twins seen in 11, and no issues seen in either twin in 10 pairs; concluded no causal relationship exists between anesthesia exposure and brain dysfunction

**Ing et al (2012):** among 2800 children in Australia, lower scores in receptive and expressive language and abstract reasoning seen at age 10 yr in children exposed to anesthesia before age 3 yr, compared with unexposed children; study retrospective; demographics differed between exposed and unexposed group; indication for and type of surgery linked to cognitive deficits

**Ing et al (2014):** same Australian cohort; children exposed to anesthetic had greater deficits as indicated by neuropsychological testing and ICD-9 codes but no differences per academic achievement; study had numerous flaws

**Block et al (2012):** evaluated infants exposed to anesthesia at age < 1 yr; in infants with no additional risk factors for central nervous system problems, mean standardized achievement test scores did not differ from normal; however, association observed between test scores and duration of anesthesia exposure; flaws in study identified

**Hansen et al (2013):** evaluated educational outcomes in children who underwent pyloric stenosis repair at age < 3 mo; exposure group performed more poorly than controls, but no statistical difference found after adjustment for nonconfounders; birth weight most significant variable; exposed group predominantly male

**Stratmann et al (2014):** 28 children exposed to anesthesia at age < 1 yr had impaired recollection, compared with 28 matched controls; IQ scores not affected; same outcomes seen with once vs multiple anesthetics

**Backeljauw et al (2015):** cognition and brain structure in 53 children who underwent surgery at age < 4 yr compared with that in 53 controls; average test scores within population norms for all; exposed children scored lower in listening comprehension and performance IQ; lower gray matter density in occipital
cortex and cerebellum seen in exposed children, but no gross elimination of gray matter

Davidson et al (2015): multicenter study assessed neurodevelopmental outcomes at age 2 yr in children who underwent inguinal hernia repair at <60 wk postmenstrual age; children randomly assigned to awake RA or sevoflurane anesthesia; showed no evidence that <1 hr sevoflurane increased risk for adverse neurodevelopmental outcomes

Synaptogenesis: peaks at age 9 mo in parietal and temporal cortex (responsible for language and spatial attention); at age 2 to 3 yr, in prefrontal cortex controlling executive function, integration, and modulating brain function

Conclusions: mechanisms and significance of neurotoxicity not clear in pediatric population; change in clinical practice unwarrented based on currently available human literature and cannot be based on animal studies

SmartTots Initiative 2011 panel recommendations: minimize length of time child sedated; defercancel of surgery until age >4 yr possibly warranted if not harmful to child; further studies urgently needed

SmartTots 2015 consensus statement recommendations: for health care providers — answers to questions for parents and caregivers related to risks should highlight differences between research in animals and children; emphasize that, because most anesthetic medications have shown injury in animals, no medication or technique safer than any other; anesthetics necessary component of care for children requiring surgery, procedure, or test that cannot be delayed; decisions regarding timing of procedures should be discussed with all members of team and family; benefits of elective procedure should be weighed against risks associated with anesthesia and surgery; for parents and caregivers — discuss timing of planned procedures with health care team; concerns about unknown risk of anesthetic exposure to child's brain development must be weighed against potential harm of cancelling or delaying procedure; care of each child must be evaluated individually

Supplement to consensus statement: brain function complex and cannot be fully measured by single cognitive test; sevo-flurane only one of several commonly used anesthetic agents (unknown whether other agents produce similar results); many procedures require combination of ≥2 anesthetics, and effect of combinations unknown; different medical procedures may be combined with anesthetics to produce other outcomes; much brain development occurs throughout childhood; effects of exposure to anesthetics in subsequent months or years unknown; animal and epidemiologic data suggest risk of anesthetics to developing brain increases with longer or multiple exposures, but applicability to human children unclear

Suggested Reading


Acknowledgments

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- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
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- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes
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To test online, go to www.audiodigest.org and sign in to online services.
To submit a test form by mail or fax, complete Pretest section before listening and Posttest section after listening.

1. The final common pathway postulated for anesthesia-induced apoptosis is:
   (A) Activation of γ-aminobutyric acid (GABA)  (C) Activation of caspase 3
   (B) Activation of N-methyl-D-aspartate (NMDA)  (D) Release of lysosomal enzymes

2. Accelerated apoptosis has been observed with the use of:
   (A) Inhalational anesthetics only  (C) Combinations of ≥2 anesthetic agents
   (B) Intravenous anesthetics only  (D) All anesthetics

3. Animal studies have demonstrated that apoptosis increases with increasing _______ of ketamine infusion.
   (A) Dosage  (B) Duration  (C) A and B

4. Which of the following agents show evidence of antiapoptotic properties?
   1. Clonidine
   2. Dexamethasone
   3. Lithium
   4. Magnesium
   5. Melatonin
      (A) 1,2  (B) 3,4  (C) 1,3,5  (D) 2,3,4

5. Animals studies suggest which of the following about cognitive dysfunction caused by either brain trauma or exposure to anesthesia?
   (A) Resolves spontaneously over time
   (B) Remediated by subsequent exposure to an enriched environment
   (C) Exposure to an enriched environment produces only slight improvement
   (D) Cannot be remediated

6. Conclusions of Flick’s 2011 study of behavioral outcomes after exposure to anesthesia at age <2 yr included which of the following?
   (A) Repeated exposure to anesthesia was an independent risk factor for learning disability
   (B) Repeated exposure to anesthesia was an independent risk factor for emotional disorder
   (C) Repeated exposure to anesthesia was an independent risk factor for behavioral disorder
   (D) All the above

7. In Sprung’s 2012 cohort study assessing the potential link between exposure to anesthesia and attention-deficit/hyperactivity disorder (ADHD), rates of ADHD were:
   (A) More than 2-fold higher in children who had ≥2 exposures, compared with unexposed children
   (B) Not increased in children with only one exposure
   (C) Less than 3% in children with no exposure
   (D) Significantly higher in the overall cohort than in children with no exposure

8. In Backeljauw’s 2015 study, which of the following were observed in children who underwent surgery at age <4 yr, compared with controls?
   1. Lower scores in listening comprehension
   2. Lower scores in performance IQ
   3. Gross elimination of gray matter in the occipital cortex
   4. Gross elimination of gray matter in the cerebellum
   5. Equal gray matter density in the occipital cortex
      (A) 1,2  (B) 3,4  (C) 1,3,5  (D) 2,3,4

9. In human children, peak synaptogenesis occurs in the temporal cortex at age _______ and in the prefrontal cortex at age _______.
   (A) 3 mo; 9 to 12 mo  (C) 9 mo; 2 to 3 yr
   (B) 6 mo; 15 to 18 mo  (D) 12 mo; 3 to 4 yr

10. The 2015 SmartTots consensus statement includes which of the following recommendations?
    (A) Health care providers should highlight differences between research in animals and children
    (B) Health care providers should emphasize the safety advantages of regional techniques
    (C) Elective procedures should be deferred until after age 4
    (D) Anesthetics should be avoided for diagnostic tests

Answers to Audio Digest Anesthesiology Volume 58, Issue 16: 1-A, 2-A, 3-B, 4-C, 5-D, 6-A, 7-C, 8-D, 9-B, 10-C