Anesthetics and the Developing Brain
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Objectives
- Understand the recent literature about anesthesia and the developing brain
- Understand the limitations of the current literature
- Know the anesthetics and sedatives that are implicated in apoptosis and neurodegeneration
- Understand some of the strategies to mitigate apoptosis
- Know the current multicenter studies currently underway

Types of Studies
- Animal Studies
  - Rats
  - Guinea Pigs
  - Non-human Primates
- Population Cohort Studies
- Retrospective
- Cardiac Studies
- Case Based

Rats
- Scallet, A.C., et al., Developmental neurotoxicity of ketamine: morphometric confirmation, exposure parameters, and multiple fluorescent labeling of apoptotic neurons. Toxicol Sci 2004;81(2);364-70
- Jevtovic-Todorovic V, Benshoff N, Olney JW. Ketamine potentiates cerebrocortical damage induced by the common anaesthetic agent nitrous oxide in adult rats. Br J Pharmacol 2000;130;1692-8

Ketamine Induced Apoptosis in Rats
Young C, Jevtovic-Todorovic V, Qin YQ, et al. Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. Br J Pharmacol 2005;144:89-97
Guinea Pigs

- Pregnant Guinea Pigs: Brain development in guinea pigs occurs prenatally, and lasts longer than rat brain period of rapid brain growth.
- Isoflurane, Nitrous Oxide, Midazolam, compared to sham control (fentanyl infusion) and true control (no anesthesia).
- Arterial Line, Central Line, ETCO2, Oxygen Saturation, Temperature, PH, Bicarbonate, and Blood Glucose were monitored and controlled
- Sham control with fentanyl infusion and control with no anesthesia exposure
- Greatest amount of apoptosis in Isoflurane + Nitrous + Midazolam

Non-human Primate Studies


Animal Studies

- Anesthetics that are NMDA antagonists or GABA Agonists are associated with increased apoptosis in developing rat brains and that this association is dose responsive.
- The animals that had increased apoptosis showed signs of memory loss and cognitive dysfunction (less able to run a maze).
- The amount of neurologic damage was greatest at the time of maximum synaptogenesis (7 weeks gestation, 8-10 days postnatal in the non-human primate macaque).
- Virtually all anesthetics implicated with the exception of opiates, muscle relaxants, and possibly alpha 2 agonists.

Does Animal Data equal Human Data

- Different physiology and responses to anesthetics
- Different life spans
- Doses are different and larger in some of the studies
How can we study Humans?

- Cohort Studies
- Rochester Minnesota
- Western Australia
- Scandinavia
- New York
- Sibling and Twins

Cognitive and behavioral outcomes after early exposure to anesthesia and surgery

- Flick RP, Katusic SK, Colligan RC,
- Matched cohort study 8548 kids born between 1976 and 1982 in Olmstead County Minnesota
- 350 kids exposed to anesthesia (< 2 yo) vs 700 matched controls
- 286 exposed once 64 exposed more than once
- School records analyzed for learning disability and behavior
- Controlled for illness

Pediatrics. 2011;128:e1053–e1061

Educational outcome in adolescence following pyloric stenosis repair before 3 months of age

- Danish Birth cohort 1986-1990 examined for surgery for Pyloric Stenosis before 3 months of age and educational outcomes (age 15-16 yo)
- Exposure Group 779 compared against matched control group of 14,665
- No statistical difference found when adjusted for confounders except for academic non-attainment for PS (male predominance)


Anesthesia and cognitive performance in children: no evidence for a causal relationship

- Bartels M, Althoff RR, Boomsma DI
- 1134 Monozygotic twin pairs Netherlands 1986-1995
- Surgery before the age of 3 and educational scores near 12 yo
- MZ twins discordant for anesthesia exposure before age 3 showed no difference in Educational Achievement or Cognitive Problems
- Exposed children did have lower scores, however their MZ twin also showed lower scores


Long-term differences in language and cognitive function after childhood exposure to anesthesia.

- Ing C, DiMaggio C, Whitehouse A,
- Western Australia Pregnancy Cohort 2868 kids born between 1989 – 1992
- 321 Exposed to anesthesia before 3
- 2287 Unexposed
- Battery of Neuropsychological testing and outcomes of motor, language, and behavior assessed at age 10

Findings

- Children exposed to anesthesia before the age of 3 had an increased long term risk of clinical deficit in receptive and expressive language, as well as abstract reasoning. Children who only had a single exposure to anesthesia also had an increased risk of deficit.
- Outcome measure is important in determining the outcome

Neurotoxicity of sedative and analgesia drugs in young infants with congenital heart disease: 4-year follow-up

- García Guerra G; Robertson CM; Alton GY; Joffe AR; et al.
- 155 infants who underwent CHD 2000-2006, 10 died, 17 excluded, 8 lost to follow-up, 91 for analysis
- At two years of age, no difference detected
- At four years of age, statistically significant association between lower scores and cumulative Benzodiazepine dose and days on chloral hydrate.

Problems with existing data

- Cohort Studies are retrospective
- Impossible to separate surgery from the anesthetic
- Surgery and anesthesia are different today
- Many studies done when anesthesia delivered without pulse oximeter, ETCO₂, or with anesthetics no longer in use (Halothane, Pentothal)
- Humans are not rats or monkeys
- Different life spans, different biology, BGS occurs at different time.
Exercise inhibits neuronal apoptosis and improves cerebral function following rat traumatic brain injury


Delayed environmental enrichment reverses sevoflurane-induced memory impairment in rats


Two prospective multicenter anesthesia studies under way

* GAS infant hernia surgery randomized under GA vs Regional with robust follow up evaluation
* PANDA (Pediatric Anesthesia and Neurodevelopment) 500 sibling pairs one anesthetic exposure (ASA I or II) before 3 years with robust neuropsychological testing follow up