Anesthesia and the Developing Brain

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Introduction

- Anesthesia: safe intervention
- For more than 150 yrs: brain returns to the same state as before the anesthetic
- Recent yrs: neurotoxic effects of anesthetics
  - Long lasting
  - Cognitive defects

Animal Studies

- Combined anesthetic (Midazolam, N2O, Isoflurane)
- 7-day-old rats for 6 hours
- Impairment of long-term potentiation in the hippocampus
- Progressive deficit in spatial recognition tasks: 4 weeks and 4.5 months after anesthesia!!!

Jevtovic-Todorovic V, et al. J Neurosci 2003; 23:876-882

Factors Affecting the Toxicity of Anesthetics

- **Timing of Exposure:**
  - Neurons: especially vulnerable during the "brain growth spurt"
  - Varies by species:
    - Rats: 7th to 10th postnatal day
    - Rhesus monkeys: 5th to 16th postnatal day
    - Humans: last trimester until the 3rd year of life
- In rhesus monkeys:
  - Ketamine for 24 hrs at the end of pregnancy: apoptosis in the fetus
  - Same in 5-day-old
  - On day 35: no apoptosis

Slikker W Jr, et al. Toxilogical Sciences 2007; 98:145-158

Factors Affecting the Toxicity of Anesthetics

- **<u>Frequency and Duration of Anesthetic Exposure:</u>**
  - Apoptosis increases as a function of duration or repetition of the anesthetic
    - Single dose of ketamine in 7-day-old rats: no apoptosis
    - Repeated administration or for more than 6 hrs: increase in apoptosis

Pediatric Anesthesia 2002; 12:770-774

    - 1 hr Isoflurane: no neurotoxicity
    - 2 hr application: increase in neuronal apoptosis

Anesthesiology 2009; 110:849-861

    - Ketamine for 3 hrs in in 5-6-day-old monkeys: no apoptosis
    - 5, 9, 24 hr application: significant apoptosis

Anesthesiology 2012; 116:372-384

Factors Affecting the Toxicity of Anesthetics

- **Dose Dependency:**
  - Increasing the dose of anesthetic increases:
    - The number of apoptotic neurons
    - The degree of developmental impairment
    - The degree of cellular differentiation and synaptogenesis

Anesth Analg 2011;113:1161-1169

Anesthesiology 2005; 102:970-976

Possible Mechanisms of Anesthetic-Induced Neurodegeneration

- **Apoptosis:**
  - Intrinsic Pathway:
    - Initiated in response to signals from within the cell
    - Results in the release of pro-apoptotic proteins from the mitochondrium
  - Extrinsic Pathway: activated via "death" receptors (TNF receptor family)

Nature 1996; 384:368-372

Neuroscience 2005;135:815-827

Anesth Analg 2008; 106:1712-1714

Neuroscience Letters 2008; 447:109-114

Anesthesiology 2010; 112:1155-1163

Possible Mechanisms of Anesthetic-Induced Neurodegeneration

- **<u>Influence on Neuronal Differentiation, Synaptogenesis and Network Formation:</u>**
  - Isoflurane for 35 min on 4 consecutive days
  - Young mice and rats (14^{th} day), adult rats (60^{th} day)
  - Results:
    - Impaired memory performance in the young animals
    - More pronounced as the animals grew older
    - Reduction in hippocampal stem cells
    - Persistently reduced neurogenesis
    - Unaffected adult animals

Zhu C, et al. J Cereb Blood Flow Met 2010; 30:1017-1030

Possible Mechanisms of Anesthetic-Induced Neurodegeneration

- **Activation of Reactive Oxygen Species:**
  - By propofol, sevoflurane or isoflurane
  - Mitochondrial dysfunction
  - Energy breakdown of the neuron

Anesthesiology 2011; 115:992-1002

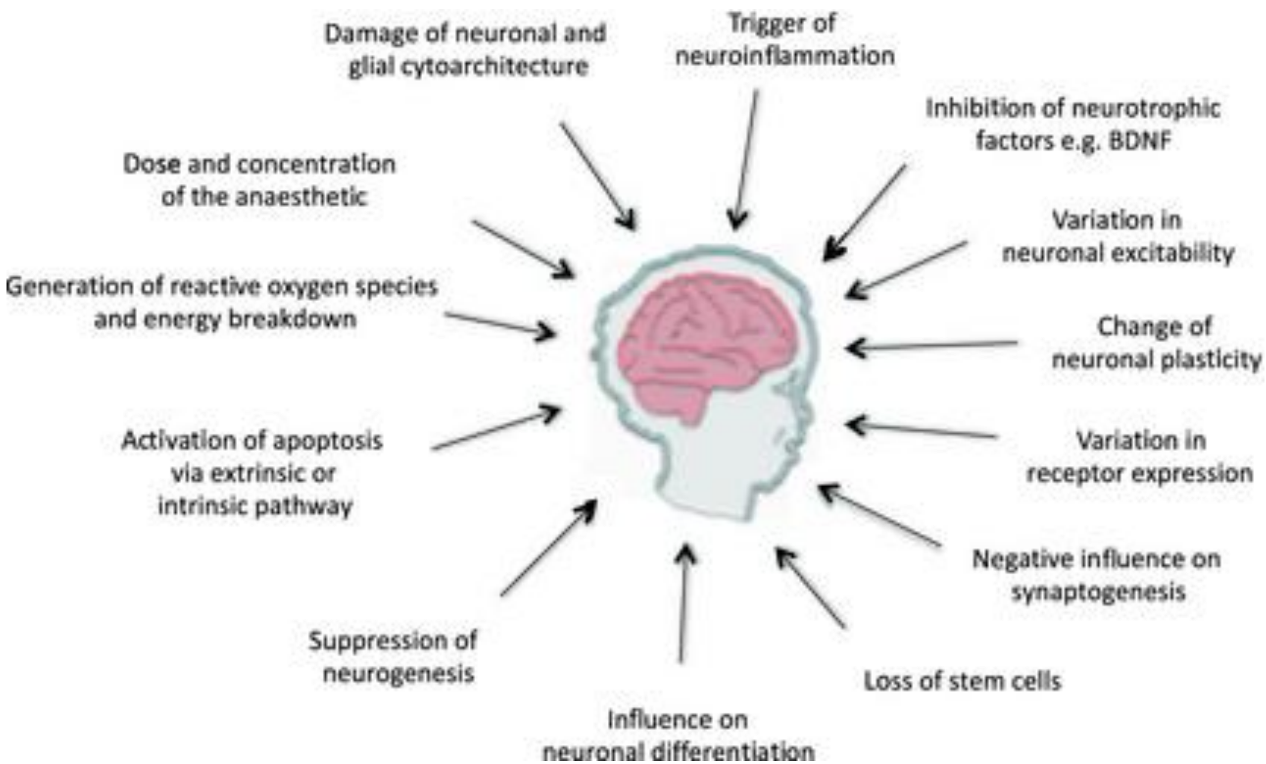
Neurobiology of Disease 2012; 45:1031-1041

Possible Mechanisms of Anesthetic-Induced Neurodegeneration

- **Anesthetic-Induced Neuroinflammation:**
  - Revealed as a further possible mechanism for cognitive impairment in newborn mice

Anesthesiology 2013; 118:502-515

Possible Mechanisms of Anesthetic-Induced Neurotoxicity in the Immature Brain



Anaesthesia 2014; 69:1009-1022

Translating Animal Data to Clinical Settings

- **Areas of uncertainty in translation to humans:**
  - The exact period of vulnerability
  - The dose required to cause injury
  - The clinical outcome likely to be seen
  - The role of anesthesia among the other factors
- **Dismissing** the laboratory findings: no more logical than blinding accepting them
- **Changes** seen in the laboratory are real

Clinical Data

- Essentially based on retrospective and observational studies
- The retrospective methodology presents limitations:
  - Initially sampled for different purposes and entities
  - Anesthetic agents may be obsolete
  - Study samples: representative of a fraction of the population
  - No way to control the indications for surgery
  - No way to control outcomes from the surgery itself
- Available evidence remains mixed

Clinical Retrospective Studies

Ing C, et al. Pediatrics 2012; 130:e476-485

- Originally, investigation of long-term effects of perinatal U/S exposure
- 2868 children
- 11% exposed to anesthesia before the age of 3
- Close early follow-up:1781 children
  - 206: single exposure
  - 52: multiple exposures
  - 1523: unexposed children
- Increased risk for disabilities in receptive language (tested at age 10)
- 75% increased risk of disability in abstract reasoning
- Behavioral and motor testing did not differ between groups

Clinical Retrospective Studies

Sprung J, et al. Mayo Clin Proc 2012; 87:120-129

- Birth-cohort from Minnesota
- 2-fold higher risk for ADHD by the age of 19
- If child exposed to 2 or more anesthetics before age 2
- No correlation between ADHD and a single exposure

- Association between anesthesia exposure and cognitive or behavioral issues: likely
- Effects: dose-related

Clinical Retrospective Studies

Hansen TG, et al. Anesthesiology 2011; 114:1076-1085

- National cohort of Danish adolescents
- Inguinal hernia repair at the age of 1 or less. N=2689
- Compared to 14,575 matched controls
- Same academic achievement scores
- Confounders such as gender, birth weight, parental age and education were controlled for

Clinical Retrospective Studies

Barteis M, et al. Twin Res Hum Genet 2009; 12:246-253

- Data taken from the Young Netherland Twin Register
- 1143 pairs of monozygotic twins
- Most pairs: both exposed or both not exposed to anesthesia
- 71 twin pairs discordant
- Nationwide standardized test at age 12:
  - Academic performance similar
- Teacher questionnaire:
  - Similar incidence of cognitive problems

Clinical Retrospective Studies

- Cardiovascular, **central nervous** and respiratory systems: extremely sensitive and vulnerable to hemodynamic and metabolic changes
- Outcome not chosen by the investigator
- Do not provide the most meaningful measure of the cognitive or behavioral effect
- Studies with <u>negative results</u>: broad measures of academic performance
- Studies with <u>positive results</u>: individual tests of cognitive performance

Conclusions

- Parents are aware!!
- No available scientific evidence to change pediatric anesthesia practice
- Not always possibility to postpone surgery or diagnostic test
- New organization: "Strategies Mitigating Anesthesia-Related Neurotoxicity in Tots" (SmartTots)
- Web site: http://www.smarttots.org
- Supports several prospective clinical trials

GAS Study
(General Anesthesia and Spinal)

- Children < 6 months
- Inguinal hernia repair
- General anesthesia or spinal anesthesia
- Neurodevelopmental outcome and apnea
- Preliminary results: 2015

PANDA Study
(Pediatric Anesthesia and NeuroDevelopmental Assessment)

- Multicenter study
- Age: up to 36 months
- Inguinal hernia repair
- Long-tem effects of anesthesia on cognitive function

MASK Study
(Mayo Safety in Kids)

- Cohort study
- Children in Rochester
- Children: <3 years
- One or more anesthetics