Neurotoxicity of Anesthetics in the Developing Brain: Summary Points

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1. The major excitatory neurotransmitter, glutamate, and the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are generally associated with neuronal communication in the adult brain.(1)

2. In the developing brain, these transmitters play a central role in brain morphogenesis, including synapse formation, proliferation, migration, differentiation and survival of neurons.(1)

3. Different types of glutamate and GABA receptors need to be expressed at the right time and place in the developing brain to produce normal brain structure and function.(1)

4. N-methyl-D-aspartate (NMDA)-type glutamate receptors are widely distributed in the CNS and play a key role in brain development including proliferation, migration, survival, and differentiation of neurons.(1)

5. Although GABA is an inhibitory neurotransmitter in adults, it acts as an excitatory transmitter in the developing CNS.(2)

6. During very early stages of normal brain development (i.e. neurogenesis), neurons are produced in excess and elimination of this excess (totaling as much as 50-70% of all of the neurons and progenitor cells produced) is critical for normal brain structure and function. In later stages of normal brain development (i.e. synaptogenesis), neuronal elimination is a very tightly controlled phenomenon during which a very small number of neurons are destined to die.(3)

7. The excess cells are eliminated by an inherent cell death program, termed apoptosis.(3)

8. In rats and mice, the peak period of synaptogenesis is the first two weeks of life.(4)

9. In humans, synaptogenesis starts during the third trimester and rapid brain growth occurs in different brain regions at different ages. By age 2 to 3 years, rapid brain growth in nearly all brain regions is mostly complete.(5)

10. In humans, normal brain development also importantly involves formation of neural circuits across different brain regions for functional connectivity. Neural circuit development slows after age 2 to 5 years, but it continues throughout childhood and adolescence.(6-8)

11. All anesthetics and sedatives used in infants and children including inhaled agents, benzodiazepines, barbiturates, ketamine, propofol, and etomidate are believed to block NMDA receptors and/or enhance GABA-A receptors to varying degrees.(9)

12. When anesthetic and sedative agents are administered to rodents during synaptogenesis or rapid brain growth, they cause widespread neuronal apoptosis, neurodegeneration, and changes in neuron growth and cell structure. In many of these studies, the rodents have subsequent learning and behavioral abnormalities as adults.(10-18)

13. In studies in which neonatal rodents are given ketamine in the presence of noxious stimuli, the degree of neuronal apoptosis is much reduced.(19)

14. Limited data are available from non-human primate studies. In neonatal monkeys, ketamine or isoflurane, given during the vulnerable period of rapid brain growth, causes widespread neuronal death and neurodegeneration. In one study, ketamine given to neonatal monkeys resulted in long-term behavioral abnormalities and impairments in learning and memory when the monkeys became adults.(20-23)

15. There are no studies that describe neuronal cell abnormalities in children attributed to anesthesia

16. Observational studies in humans have been mixed. Several studies report that anesthesia in infants and young children is associated with an increased risk of learning disabilities (with multiple anesthesia exposures, but not single), developmental and behavioral abnormalities, impaired language and abstract reasoning (with both single and multiple anesthetic exposures), and poor academic performance. Other studies do not find any association between anesthesia during early childhood and poor school academic performance or abnormal behavior later in life. Two studies in neonates report that there is no evidence that prolonged sedation, in and of itself, increases the risk of abnormal neurodevelopment.(24-34)

17. All of the human observational studies involve analyzing data originally collected for other purposes, either as studies to investigate other questions or data collected for reasons other than specifically for research. These studies use data already available on learning, academic performance, and behavior in children and infants with a history of anesthesia and surgery in the past, usually before age 3 to 4 years. Observational studies have significant weaknesses due to confounding factors that are both known (co-morbidity) and unknown, making interpretation of these studies difficult.

18. There are two key research approaches and techniques for detecting potential neuronal toxicity associated with anesthetic exposure, allowing scientists to bridge information between pre-clinical (rodents and non-human primates) and clinical (human) anesthesia projects. In pre-clinical research, in vivo imaging of rodent and non-human primate models by positron emission tomography (microPET) allows for an objective and quantitative assessment of functional and molecular targets in a longitudinal manner. When combined with cognitive and behavioral studies, PET offers a unique bridging approach allowing insight into "structure and function" issues that are not accessible via other methods. Additionally, scientists are able to use molecular tracers that label apoptotic neurons in the brain of anesthetic-exposed rodents, allowing one the ability to visualize and quantify neurotoxicity in nonhuman primate models of neonatal anesthetic exposure. Applying these tracers in human PET imaging will allow investigations of acute and chronic effects of anesthetics and consequences of potential therapeutic strategies.[35,36,37]

19. Recent advances in our understanding of stem cell biology and neuroscience have opened up new avenues of research for detecting anesthetic-induced neurotoxicity, dissecting underlying mechanisms, and developing potential protection/prevention strategies against anesthetic-induced neuronal injury.[38] The use of stem cell-derived models, especially human embryonic stem cells (in vitro) with their capacity for proliferation and potential for differentiation, have a great advantage for detecting potential anesthetic-induced neurotoxicity. Studies are currently underway to employ radioactive tracers (PET) designed to target specific stem cell ligands so that the anatomical locations of those cells can be determined and monitored. In addressing critical questions about the relationship between anesthetic-induced neurotoxicity and developmental stage at time of exposure, these molecular imagining tools can be utilized in vivo to monitor endogenous neural stem cell activity following exposure to general anesthetics.

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