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Neuronal Vulnerability to Anesthesia Neurotoxicity Depends on Age of Neurons

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Several clinical studies have examined anesthesia, surgery, and neurotoxicity in childhood.^{1–6} Among them, Wilder et al⁵ and Flick et al⁶ investigated thousands of children and found that those who had multiple (>3) and early (before the age of 4 years) exposures to anesthesia and surgery were at an increased risk of developing learning disabilities (the incidence reaches a plateau at age 12 years). DiMaggio et al² and Kalkman et al³ also found that anesthesia and surgery may lead to learning disabilities. Conversely, Sprung et al⁴ reported that fetal exposure to general anesthesia did not increase the risk of developing cognitive impairment. A study from the Netherlands also failed to show the effects of anesthesia exposure on long-term neurocognitive function.¹ A recent study by Hansen et al⁷ demonstrated that a single and relatively brief anesthetic exposure in infancy did not reduce academic performance at age 15 or 16 years, but led to a higher test score nonattainment rate. These collective findings, pending further research, suggest a possible causative relationship between anesthesia and/or surgery, and subtle selective impairment in neurodevelopment. Taken together, it is possible that children who undergo anesthesia and surgery may not achieve their cognitive potential to as great an extent as children who do not undergo anesthesia and surgery.

However, the underlying mechanisms of these effects remain unclear. Several preclinical studies have investigated the effects of anesthetics on neurotoxicity and neurobehavioral deficits, as well as the potential underlying mechanisms in young animals. These studies have shown that anesthetics may induce neuroapoptosis, neuroinflammation, synaptic dysfunction, and impairment of learning and memory.^{8–22}

In this issue of *Annals of Neurology*, a study by Hofacer et al assessed whether vulnerability to anesthetic-induced caspase activation and neuroapoptosis depended on the age of the neuron rather than the age of the organism.²³ Mice of different ages, postnatal day 7 (P7; newborn), P21 (juvenile), and P49 (young adult), received isoflurane (1.5%), a common inhalation anesthetic, for 6 hours. Neuroapoptosis was assessed in different brain regions of these mice. More importantly, neuroapoptosis in neurons of different ages, identified by various markers, was determined and compared.

The authors demonstrated that anesthesia with 1.5% isoflurane (in 30% oxygen) for 6 hours induced neuroapoptosis in the cortex but not in dentate granule cells of newborn (P7) mice. In contrast, isoflurane anesthesia resulted in neuroapoptosis in dentate granule cells but not in the cortex or midbrain of juvenile (P21) and young adult (P49) mice. Neurogenesis is delayed in dentate granule cells and continues to occur after birth.^{24,25} These findings suggest that isoflurane-induced neuroapoptosis may only occur at a certain stage of neuronal development, and is dependent on the age of the neuron, but independent of the age of the mouse.

In addition, by employing the S-phase marker bromodeoxyuridine to identify the birthdays of neurons, the authors found that more isoflurane-induced neuroapoptosis occurred in young granule cells than in old ones. The authors further demonstrated that neuroapoptosis appears in late progenitors (neuroD1-positive cells) and immature granule cells (calretinin-positive cells), but not in radial glialike progenitors (sox2-positive cells, the early stage progenitors) and mature granule cells (calbindin-positive cells), regardless of the age of the mice. Finally, the authors found that the pattern of vulnerability to the isoflurane-induced neuroapoptosis can also happen in the olfactory bulb, another brain region that has significant neurogenesis beyond the neonatal period.

In all of these well-designed and well-performed studies, the authors illustrated that cells in the dentate gyrus and olfactory bulb, the two brain regions that have predominantly postnatal neurogenesis, are vulnerable to anesthetic-induced neuroapoptosis, which may not occur in newborn (P7) mice, but does in juvenile (P21) mice, and can last through young adulthood (P49). These results provide new insights into the selectivity of anesthesia-induced neurotoxicity, including the relevant brain regions and neuron age-dependent nature of neuroapoptosis. These findings will certainly promote further studies to investigate anesthesia-induced neurotoxicity and neurobehavioral deficits. In particular, it is important to know the upstream mechanisms and downstream consequences of the selective anesthesia neurotoxicity that has been demonstrated by Hofacer et al. Several studies have shown that anesthetics may induce learning and memory impairment in young animals, but not in adult animals.^{13,26} Hopefully, the current study by Hofacer et al and follow-up studies will further elucidate the underlying mechanisms.

The widespread and growing use of anesthesia in children makes safety a major health concern.^{21,27} Safety is of even greater concern with the evidence that anesthesia and surgery may induce learning disabilities in children and that anesthetics may induce neurotoxicity, and learning and memory impairment in young animals. Therefore, research of anesthesia effects in the developing brain is important and timely. Previous studies have established the systems involved and demonstrated the phenomena of anesthesia-induced neurotoxicity in the developing brain; however, future efforts need to explore the multiple underlying mechanisms and the potential clinical relevance, which should be examined in collaboration with clinicians (eg, pediatric anesthesiologist) and basic scientists. Such joint efforts should ultimately lead to safer use of anesthesia and better postoperative outcomes for children. As an anesthesiologist and a researcher in neuroscience, this author certainly believes so.

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