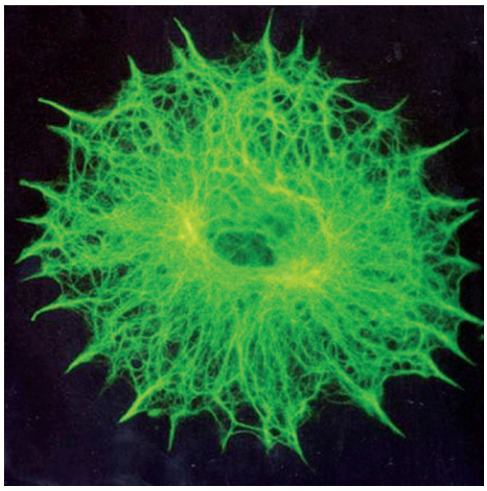
Postoperative Cognitive Effects in Newborns

The Role of Inflammatory Processes

MILLIONS of children have surgery under anesthesia each year in the United States. The majority of these children receive volatile anesthetics-based general anesthesia. However, the safety of general anesthetics, especially volatile anesthetics, in children has become an active research field in the last 10 yr because the detrimental effects of general anesthetics on brain cell survival and cognitive functions have been revealed in animals.[1] Although evidence for anesthetics-induced neurotoxicity in children has not been clearly demonstrated, some retrospective studies have shown that multiple surgeries under general anesthesia in young children may increase the risk of learning impairment later in life.[2,3] Thus, it is important to investigate the detrimental effects of general anesthetics on young brains and the mechanisms for these effects in animal studies so that potential interventions can be designed for humans if the harmful effects of general anesthetics in children are confirmed in future studies. In this issue of ANESTHESIOLOGY, two studies from Dr. Zhongcong Xie's laboratory have been provided as examples of the basic research in this field.[4,5]



"[These] studies from Xie's laboratory suggest an important role of neuroinflammation in sevoflurane-induced cognitive impairment in developing brains."

The first study by Shen *et al.*[4] showed that 6-day-old mice exposed to 3% sevoflurane for 2 h every day for 3 days had cognitive impairment assessed by the Morris Water Maze at 1 month of age. These mice also had neuroinflammation as evidenced by increased interleukin-6, tumor necrosis factor-α, and ionized calcium-binding adaptor molecule 1-positive cells (a marker of microglial activation) in the brain at the end of sevoflurane exposure (8-day-old mice). The cognitive impairment was attenuated by an enriched environment and ketorolac, an antiinflammatory agent. In contrast, exposure of 60-day-old mice to 2% sevoflurane for 2 h every day for 3 days did not induce cognitive impairment and neuroinflammation. Exposure of 6-day-old mice to 3% sevoflurane for 2 h once or to 9% desflurane for 2 h every day for 3 days also did not induce cognitive impairment and neuroinflammation.

The brain in the growth-spurt period (up to postnatal 36 months in humans and 3 weeks in rodents)[6] is particularly susceptible to various insults. Wilder *et al.*[2] have found that children who had three, but not one, exposures to anesthesia and surgery at an early age (before 4 yr of age) are at an increased risk to develop learning disabilities. The results of Shen's study[4] that three, but not one, exposures to sevoflurane anesthesia lead to cognitive impairment in young mice replicate the findings of the study by Wilder *et al.* in children, and suggest a potential role of sevoflurane anesthesia alone in the clinically observed learning disability in children after anesthesia and surgery. Also, Shen *et al.*[4] found that enriched environment reduced sevoflurane-induced cognitive impairment, suggesting that simple behavioral intervention(s) may be used to attenuate this potential detrimental effect of anesthetics on children.

The second study from Xie's group published in this issue of ANESTHESIOLOGY exposed pregnant mice at gestation stage day 14 to 2.5% sevoflurane for 2 h.[5] This exposure increased activated caspase-3 and interleukin-6 levels and reduced the levels of postsynaptic density-95, a synaptic protein, in the brain tissues of the fetal mice. Sevoflurane anesthesia in pregnant mice also increased interleukin-6 levels and reduced the levels of postsynaptic density-95 and synaptophysin, another synaptic protein, in the brain tissues of the offspring mice at postnatal day 31. More importantly, exposure of fetal mice to sevoflurane induced cognitive impairment assessed at postnatal day

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31. Interestingly, the authors showed that the sevoflurane-induced reduction of the postsynaptic density-95 levels was attenuated by interleukin-6 antibody in the primary mouse neurons. Finally, an enriched environment also attenuated the sevoflurane-induced cognitive impairment, neuroflammation, and reduction of postsynaptic density-95 and synaptophysin in the offspring mice at postnatal day 31. These findings clearly suggest that anesthetic exposure during second or third trimesters may cause significant detrimental effect on the brains of mice.

Both studies from Xie's laboratory suggest an important role of neuroinflammation in sevoflurane-induced cognitive impairment in developing brains.[4,5] This finding is consistent with previous studies showing that neuroinflammation is associated with cognitive impairment in humans[7–9] and in animals[10–12] and that neuroinflammation may contribute to cognitive impairment after isoflurane anesthesia or isoflurane anesthesia plus surgery in adult animals.[10,12–14] It is proposed that perioperative neuroinflammation plays an important role in postoperative cognitive dysfunction and therefore, the resolution of this neuroinflammation after surgery may result in cognitive improvement in adults.[15] Xie's studies extend this detrimental role of neuroinflammation in cognitive impairment to developing brains.

One issue related to the neuroinflammation theory for anesthetics-induced cognitive impairment is how anesthetics induce neuroinflammation. Anesthetics, including sevoflurane, have been shown to increase cytosolic calcium.[16] Increased cytosolic calcium level is associated with increased levels of proinflammatory cytokines,[17] potentially *via* activation of nuclear factor-κB signaling pathway.[18,19] Nuclear factor-κB is a key transcription factor that regulates cytokine expression.[18] Thus, the following mechanism can be proposed for volatile anesthetics to increase inflammatory cytokines in the brain: volatile anesthetics including sevoflurane increase cytosolic calcium, which then activates nuclear factor-κB signaling, leading to generation of proinflammatory cytokines.

One line of evidence to suggest the role of neuroinflammation in sevoflurane-induced cognitive impairment in Xie's studies is that ketorolac attenuated this cognitive impairment.[4] However, it is debatable whether ketorolac can be used routinely for this purpose in children because ketorolac can impair blood clotting and wound healing. However, lidocaine, a local anesthetic with antiinflammatory property, has been shown to reduce isoflurane-induced cognitive impairment and brain expression of inflammatory cytokines in adult animals.[13,14] Lidocaine has been commonly used clinically during general anesthesia and may be an alternative for ketorolac to reduce cognitive impairment in the developing brain should its effectiveness be established in the future studies.

A very interesting finding from Xie's studies is that exposure of 6-day-old mice to 9% desflurane for 2 h every day for 3 days did not induce cognitive impairment.[4] This result suggests that volatile anesthetics-induced cognitive impairment in the developing brain is agent specific. Agent-specific effects have been found previously for volatile anesthetics. For example, a prior short exposure of rats to isoflurane can reduce brain injury caused by brain ischemia-reperfusion occurring 24 h after the isoflurane exposure. This protective effect is difficult to be induced by desflurane.[20] Similarly, application of isoflurane, but not desflurane, after simulated ischemia and reperfusion provides protection in bovine pulmonary arterial endothelial cells.[21]

Currently, the potential detrimental effects of volatile anesthetics on developing brains constitute a very active research field. The studies from Xie's group focused on sevoflurane, an often-used volatile anesthetic in pediatric patients, and showed the role of neuroinflammation in cognitive impairment in young mice after sevoflurane exposure. These studies suggest potential interventions to reduce this effect if this anesthetic effect is confirmed in humans and, therefore, deserve our attention.

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