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REVIEW ARTICLE

Developmental anesthetic neurotoxicity: from animals to humans?

Deshui Yu · Bin Liu

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Abstract Several animal studies have demonstrated that most routinely used general anesthetics induce widespread neuroapoptosis and long-term neurocognitive impairment in the immature brain. These findings have generated great interest among pediatric anesthesiologists and other practitioners regarding the safe use of general anesthetics in pediatric patients. Several human retrospective studies failed to confirm whether or not anesthesia exposure during the crucial phase of brain development induces long-term neurocognitive deficits in humans. Since the clinical relevance of the results of general anesthesia in animal experiments is unknown, it is unreasonable to directly utilize the results derived from animals and retrospective human surveys to guide clinical practice at the present time. Clearly, additional prospective randomized controlled trials are needed in humans to determine the effects of general anesthesia on neurodevelopment. In this review, we summarize currently available laboratory and clinical evidence for anesthetic neurotoxicity. Furthermore, we discuss the implications of these results for clinical anesthesia.

Keywords Anesthesia · Brain · Neurotoxicity · Neuroapoptosis

Introduction

Advances in pediatric surgery have required the widespread and prolonged administration of general anesthetics to millions of neonates and young children in operating rooms and intensive care units (ICU). Conventionally, anesthesia effects are thought to be fully reversible and anesthetics are assumed to have no deleterious impact on the central nervous system (CNS). However, overwhelming experimental data in animal models suggest that early exposure to clinically-used general anesthetics could cause widespread neuroapoptosis and long-term neurocognitive deficits [1–4]. These experimental data raised considerable concerns about whether the same risk exists in humans and prompted researchers to search for clinical evidence [5]. Unfortunately, several recently published retrospective studies using different methodologies have failed to confirm or rule out the possibility of anesthetic neurotoxicity in humans. Because some inherent limitations exist in these epidemiological investigations, clinicians have not been able to draw definitive conclusions regarding the risk of anesthesia on human brain development [6]. Based on the lack of definitive data from controlled clinical trials, it is impossible to establish an association between early anesthesia and neurocognitive development. Thus, it would be inappropriate to withhold anesthesia from pediatric patients during surgery [7].

Experimental evidence for anesthesia-induced developmental neurotoxicity

Since their introduction, general anesthetics have been administered to neonates and young children, even though the exact mechanisms by which these drugs abolish the response to noxious stimulation remains largely unresolved. Common pathways of most clinically utilized general anesthetics include inhibition of *N*-methyl-D-aspartate (NMDA) receptors and/or activation of

D. Yu · B. Liu (✉)
Department of Anesthesiology, West China Hospital of Sichuan University, No.37 Wai Nan Guo Xue Xiang, Chengdu 610041, Sichuan, People's Republic of China
e-mail: benbinliu@sina.com

γ-aminobutyric acid (GABA) receptors [8]. Since NMDA and GABA-mediated neuronal activity are essential for normal functioning during mammalian brain development [9], it is conceivable that anesthetics also have other non-anesthetic actions that result in abnormalities of neuron survival and function.

Nearly 60 years ago, concerns regarding adverse effects of general anesthesia exposure on the developing brain were first raised. It was observed that administration of vinyl ether, cyclopropane or ethyl chloride to young children might cause personality changes, which was defined as the possible long-term neurological sequela of anesthesia [10]. Approximately three decades later, rodent studies suggested that prenatal exposure to prolonged sub-anesthetic doses of halothane led to decreased synaptic density and stunted behavioral development in postnatal rats [11]. In 1999, a landmark study demonstrated that treatment of neonatal rats with drugs that blocked NMDA receptors could trigger significant neuroapoptosis in the developing brain [1]. Subsequently, extensive investigations have shown that most currently used general anesthetics can induce significant neuroapoptosis and long-term neurocognitive deficits in immature animals.

Specifically, neuroapoptosis and neurocognitive deficits have been observed following exposure to midazolam [12, 13], ketamine [12, 14–20], propofol [4, 21–23], isoflurane [2, 3, 13, 24–35], desflurane [30, 31] or sevoflurane [30–32, 36, 37]. The toxic effects of most of these agents are dependent on dose and exposure time. Ketamine's ability to induce neurodegeneration was only observed at high doses, after prolonged exposure or with repeated administration [12, 14, 16, 18–20]. Similar dose-dependent effects have been demonstrated for propofol [21–23] and isoflurane [35]. Although combinations of different agents may allow smaller doses of each agent, more prominent neurotoxic effects were documented when anesthetics with both NMDAR and GABAR actions were administered simultaneously [2, 4, 12, 17, 28]. A notable exception is dexmedetomidine, which does not produce sedation via effects on GABA or NMDA receptors. This agent was not shown to have neurotoxic properties, and it could ameliorate isoflurane-induced neuroapoptosis when administered to neonatal rats [26].

In addition to general anesthetics, opioids are analgesics frequently used in pediatric anesthesia to decrease the dose requirement for anesthetics. Theoretically, their co-administration may mitigate anesthetic neurotoxicity. However, it has not yet been determined whether developmental exposure to opioids is safe. Some studies have suggested perinatal opioid administration can cause acute neuronal degeneration and long-term learning impairment extending into adulthood [38, 39].

Perhaps, the most intriguing evidence for the neurotoxicity of anesthetics comes from experiments using nitrous oxide or xenon, both NMDA antagonists. Even under hyperbaric conditions, nitrous oxide does not trigger massive neuroapoptosis by itself. However, when it was co-administered with isoflurane, nitrous oxide can exacerbate neurotoxicity induced by isoflurane [2, 24]. There is conflicting evidence on the potential of xenon, the noble gas, to induce or protect against neuroapoptosis in the developing brain. When administered as the sole anesthetic, the effect of xenon was deleterious in one study [40], but not so in another study [24]. In contrast to nitrous oxide, xenon was shown to alleviate isoflurane-induced neuroapoptosis [24, 40].

In addition to studies showing the neurotoxic effects of anesthetics, there are also some studies that observed a lack of deleterious effects following exposure to the anesthetic agents mentioned above [18, 23, 41, 42]. One study even noted that prenatal isoflurane exposure did not increase but rather decreased the rate of neurodegeneration and improved juvenile spatial learning/memory function in rats [29]. Moreover, several studies reported that neuroapoptosis was detected after neonatal anesthesia exposure, but animals did not demonstrate impaired neurocognitive dysfunction when tested in adulthood [3, 17]. Traditionally, anesthesia-induced neurocognitive deficits are thought to be permanent and irreversible, but a recent study suggested that the deleterious effects of anesthesia on memory could be attenuated (even completely eliminated) by delayed environmental enrichment [37].

Nonetheless, recent data suggests that the detrimental impact of early anesthesia on the immature brain is not limited to acute neuroapoptosis. We have found evidence of a relationship between anesthesia-induced long-term neurocognitive dysfunction and the reduction of excitatory neurotransmitter release in the cortex and hippocampus [43]. There is also evidence that anesthetics can fundamentally alter synaptogenesis [23, 44] and suppress neurogenesis [33], which raises the question as to whether long-term neurocognitive deficits should be attributed to suppressed neurogenesis and impaired synaptic transmission or to widespread neuroapoptosis (or to both).

It is important to recognize that general anesthetics are not the only agents in the human environment that can trigger a neurotoxic response. Neonatal exposure to a hypercarbia has been demonstrated to cause notable neuroapoptosis in brain areas previously shown to be susceptible to anesthesia-induced neuroapoptosis [45]. These results suggest that at least some of the neurotoxicity could be explained by anesthesia-induced respiratory depression. Other agents, such as magnesium (used in pre-eclampsia/eclampsia) [46] and dexamethasone [47] (commonly used in pre- or neonatal medicine) can also cause widespread neuroapoptosis and long-term neurocognitive deficits in immature rodents.

Another important feature of developmental anesthetic neurotoxicity is that the period of maximal susceptibility

coincides with the period of synaptogenesis, also known as the brain growth spurt period. This period is the most active phase of neuronal differentiation, synaptogenesis and functional network formation [48]. During this period, immature neurons are exquisitely sensitive to exogenous perturbations and pharmacological influences [49], and a transient disturbance might have an irreversible impact on brain development. The critical stage of synaptogenesis occurs in different species at different times, according to their life span and ontogeny. In rodents, which have relatively focused brain development, the period appears to be confined to the first 2 weeks after birth, peaking sharply on postnatal day 7 (P7) [48]. In humans, brain growth begins at the third trimester of gestation and continues for several years after birth [48]. Therefore, the 7-day-old rodents used in most studies might be equivalent to human neonates at approximately 32–36 weeks of gestation [50].

Although anesthesia may trigger neuroapoptosis, programmed cell death is also a normal phenomenon that occurs as the brain matures. During brain development, as many as 50–70 % of the entire neuronal population will undergo natural cell death to maintain the normal structure of the CNS [51]. Thus, it remains unclear whether anesthesia accelerates apoptosis of neurons that were obliged to die due to physiological degeneration, or if it destroys healthy neurons that were not destined to die. Both normal and decreased adult neuronal density could be observed after neonatal exposure to different anesthetic regimens, which may represent hastened physiological apoptosis and increased pathological cell death [3, 28].

Is anesthesia neurotoxic in infants and children?

Unfortunately, the clinical significance of the animal studies performed in this area remains controversial. Because of tremendous interspecies variations, it is extremely difficult to directly extrapolate experimental results to clinical practice. On a weight-based comparison, demonstration of anesthetic neurotoxicity in animals requires substantial exposure, both in dosage and duration. In some rodent studies, toxic doses of anesthesia are $\geq$20-fold greater than clinically used doses, even after allometric scaling is performed to account for differences in body size [52]. On the other hand, from a developmental perspective, rat brain development occurs in a matter of weeks, while it takes several years for a human brain to mature [48, 50]. In this regard, several hours of anesthesia in rodents may be equivalent to a month-long exposure in human neonates [14, 50]. Similar doses or durations of administration might never be used in clinical practice so that animal experiments might overestimate the human risk.

The direct extrapolation of laboratory findings to clinical anesthesia also has been seriously questioned, because of totally different circumstances between animal experiments and clinical management. Anesthesia in small rodents can cause progressive lactacidosis, hypercarbia and hypoglycemia, and all of these physiological disturbances during anesthesia have been shown to cause widespread neuroapoptosis in neonatal rodents [3, 45]. Other confounding variables, such as nutritional deprivation [3, 53] and repetitive maternal separation [53] following prolonged anesthesia, may also lead to learning disabilities and behavioral changes. Although most recent animal studies have performed arterial blood gas analysis to exclude the possibility that neuroapoptosis was induced by respiratory or metabolic distress during anesthesia, it is still possible that subtle and transient deficits were not detected. Furthermore, even normal blood gas values do not ensure adequate cerebral perfusion and oxygen saturation. In pediatric anesthesia, oxygenation, ventilation and other hemodynamic variables are continuously monitored and maintained within normal ranges. Human neonates routinely receive nutritional support in the perioperative period, which minimizes the risks of physiologic derangement and malnutrition. Another controversial issue is that many of the drugs that have been evaluated (midazolam, nitrous oxide and ketamine) are not the major agents used in current pediatric anesthesia.

Neuroapoptosis is observed in animals exposed to anesthesia without painful stimuli. Unlike animal studies, anesthesia in the clinical setting always includes significant noxious stimulation produced by surgical operations. It seems possible that noxious stimulation without proper analgesia/anesthesia would excessively activate NMDA or other excitatory receptors and lead to excitotoxicity in the developing brain, and therapeutic doses of anesthetic/analgesic drugs will reduce the degree of neuronal excitation [53]. In a recent study, tail-clamp injury had no effect on sevoflurane-induced histological and neurobehavioral changes in rodents [37]. It seems that surgical injury does not necessarily involve anesthetic neurotoxicity. Previous animal studies on the neurotoxicity of anesthetics have often been criticized for lacking a surgical stimulus. However, this study was the first to introduce tissue injury to the investigation of anesthetic neurotoxicity, and further studies with greater surgical stimuli should be done because cardiac surgery or other major procedures such as laparotomy definitely causes greater stress than tail-clamping.

The large number of animal experiments that have reported some degree of anesthetic neurotoxicity have promoted researchers to look for clinical evidence of the neurotoxic effects of anesthetics. Although no prospective studies have examined the effects of clinical doses of

anesthetics on brain structure or neurocognitive function, some retrospective studies have identified a significant association between early anesthesia and long-term brain development, whereas other studies have failed to demonstrate an association [54–59]. A population-based cohort study showed children (<4 years old) that received two or more periods of anesthesia had an increased risk of learning disabilities, whereas a single exposure to an anesthetic agent was not a risk factor [54]. These results are consistent with animal experiments that showed that repeated exposure, but not a single exposure, was associated with increased neuroapoptosis. Using the same methodology and cohort, this research group found that a brief fetal exposure to anesthesia at the time of cesarean delivery did not increase the risk of long-term learning disability compared with vaginal delivery without anesthesia [55]. Both of these studies [54, 55] suggest a relationship between early anesthesia and long-term learning disability, but there are also several limitations in the interpretation of these studies. First, these two studies followed patient cohorts that received anesthesia before 1982, and the agents commonly used at that time (halothane and nitrous oxide) are no longer used in clinical practice today. In addition, although the authors were careful to adjust for known confounders (e.g., sex, age, birth weight and maternal education), undetected hypoxia and hypercapnia may have affected the outcomes, because there was no pulse oximetry or capnography monitoring during anesthesia at that time. Therefore, according to the significant changes in anesthesia practice over the past 30 years, the results of these two retrospective studies may not be applicable to current pediatric anesthesia. The use of learning disability as an outcome measure may be another important limitation of these two studies. Learning disability is a categorical variable, and there is no standardized method for its assessment. Learning disability involves language, verbal and math, which clearly have divergent neurobiological bases in discrete brain regions. In these two studies, language, verbal, and math were lumped together into a single outcome measure, which is non-specific and the authors may have missed some other neurocognitive impairments.

To exclude underlying specific conditions that may impair neurocognitive development, two other studies that had divergent endpoints used a cohort of children who underwent inguinal hernia repair as the exposure group and an age-matched population as the control group [56, 57]. In the ethnically and socioeconomically homogeneous Danish population, a nationwide study found no connection between a single, relatively brief period of anesthesia (30–60 min) in infancy and reduced academic performance at age 15 or 16, after controlling for important confounding variables [56]. Although these results are reassuring, the authors also concluded that they can not exclude deficits in particular cognitive domains, and the effects of longer anesthetic durations could not be detected with this study design. Another study examined medical records for New York State using ICD-9 diagnostic codes for unspecific developmental delay or behavioral disorder. The authors found a 2.3-fold increase in the abnormal neurologic outcomes in children who had undergone herniorrhaphy under general anesthesia [57]. One important criticism is that the morbidity of birth complications such as low birth weight, congenital anomaly of the CNS and perinatal hypoxia were higher in the herniorrhaphy group, whereas the incidence of perinatal infection and hemorrhage was similar between the groups, but the authors treated them equally in the statistical analysis. It is apparent that these are not all equal in inducing neurocognitive impairment. Another criticism is that the authors defined a fairly wide range of abnormal neurologic outcomes, including mental retardation, autism and language or speech problems that are not seen in animal experiments.

In another retrospective study, parental questionnaires from children who had undergone urologic surgery at <2 years of age revealed an interesting trend towards a greater prevalence of learning deficits in children who had early surgery [58]. Although the results are alarming, the small number of patients makes it impossible to draw any definitive conclusions from this study. The authors also admitted that they would need approximately 10 times the number already studied to confirm or refute an effect of anesthesia on neurocognitive development.

Because monozygotic twins have identical genomes and similar socioeconomic environments, these pairs of children are thought to be the best-controlled study group for comparison. If the twin who receives anesthesia is more likely to have neurocognitive abnormalities than his genetic duplicate, it would provide strong evidence that surgery and anesthesia in early age is detrimental to brain development. A recent study examined educational attainment and cognitive problems/inattention of 1,143 monozygotic twins [59]. Although early exposure to anesthesia (<3 years) was associated with reduced educational achievement, there were no differences between twin pairs when they were discordant for anesthesia exposure. They attributed this result to comorbidity, but not surgery with anesthesia. This work also has some limitations. First, the authors didn't specify the types of anesthesia and data on the indications for surgery. Further, they used academic achievement scores but not direct assessment of learning disability as an objective outcome, and the former can be influenced by many different factors.

The human data derived from these nonrandomized pilot studies are still insufficient to either support or refute animal experiments because of substantial inherent limitations. First, it is extremely difficult to separate out the

contributions of anesthesia and surgical injury to cognitive outcome in these clinical studies, and it would not be surprising that young children that need one or more surgeries are at higher risk for learning disabilities than their age-matched peers. Second, these reports used very different outcome measures to assess the effects of anesthesia, such as learning disabilities, academic scores and parental questionnaires. These outcome measures may lack specificity and standardization in most cases. Another challenge inherent in these studies is the definition of a comparison group. Theoretically, the comparison group should be identical to the exposed group, except that the babies in the comparison group have never been anesthetized or received any other neurotoxic agents. This is impossible in retrospective studies because every child in the cohort is genetically different and has a different socioeconomic environment, which will fundamentally affect brain development. Other obstacles include the retrospective nature of the studies and the lack of precise information on the duration and dose of anesthetics.

Conclusions

On the basis of a large number of published findings, it is becoming wildly accepted that developmental anesthesia can induce significant and widespread neuroapoptosis and long-term neurocognitive dysfunction in immature animals. However, these results have not been confirmed in controlled clinical trials. Even if future epidemiologic studies indicate a strong association between early anesthesia and developmental dysfunction, it will still be difficult to prove that the dysfunction is a direct cause of anesthesia. In sum, the relationship between laboratory results and clinical anesthesia practice is a prominent but controversial question, based on currently insufficient available information, especially in humans. Therefore, it is unreasonable to withhold anesthesia from children who need surgery. Intense efforts should be made to obtain definitive data from well-designed prospective randomized controlled trials. Only then will it be possible to use existing anesthetics with minimum concern for their neurotoxic effects.

References

1. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vockler J, Dikeanian K, Tenkova TI, Stefovska V, Turski L, Olney JW. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 1999;283:70–4.
2. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 2003;23:876–82.
3. Loepke AW, Istaphanous GK, McAuliffe JJ, Miles L, Hughes EA, McCann JC, Harlow KE, Kurth CD, Williams MT, Vorhees CV, Danzer SC. The effects of neonatal isoflurane exposure in mice on brain cell viability, adult behavior, learning, and memory. Anesth Analg. 2009;108:90–104.
4. Fredriksson A, Ponten E, Gordh T, Eriksson P. Neonatal exposure to a combination of N-methyl-D-aspartate and γ-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology. 2007;107:427–36.
5. Loepke AW, McGowan FX Jr, Soriano SG. Con: the toxic effects of anesthetics in the developing brain: the clinical perspective. Anesth Analg. 2008;106:1664–9.
6. Wilder RT. Is there any relationship between long-term behavior disturbance and early exposure to anesthesia? Curr Opin Anesthesiol. 2010;23:332–6.
7. Stratmann G. Neurotoxicity of anesthetic drugs in the developing brain. Anesth Analg. 2011;113:1170–9.
8. Campagna JA, Miller KW, Forma SA. Mechanisms of actions of inhaled anesthetics. N Engl J Med. 2003;348:2110–24.
9. Lujan R, Shigemoto R, Lopez-Bendito G. Glutamate and GABA receptor signaling in the developing brain. Neuroscience. 2005;130:567–80.
10. Eckenhoff JE. Relationship of anesthesia to postoperative personality changes in children. Ame J Dis Child. 1953;86:587–91.
11. Uemura E, Levin ED, Bowman RE. Effects of halothane on synaptogenesis and learning behavior in rats. Exp Neurol. 1985; 89:520–9.
12. Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, Olney JW. Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. Br J Pharmacol. 2005;146: 189–97.
13. Olney JW, Wang H, Qin Y, Labruyere J, Young C. Pilocarpine pretreatment reduces neuroapoptosis induced by midazolam and isoflurane in infant mouse brain. Program NO. 28615 Neuroscience Meeting Planner Atlanta, GA: Society for Neuroscience, 2006.
14. Hayashi H, Dikkes P, Soriano SG. Repeated administration of ketamine may lead to neuronal degeneration in the developing rat brain. Paediatr Anaesth. 2002;12:770–4.
15. Scallet AC, Schmued LC, Slikker W Jr, Grunberg N, Faustino PJ, Davis H, Lester D, Pine PS, Sistare F, Hanig JP. Developmental neurotoxicity of ketamine: morphometric confirmation, exposure parameters, and multiple fluorescent labeling of apoptotic neurons. Toxicol Sci. 2004;81:364–70.
16. Zou XJ, Patterson TA, Sadovova N, Twaddle NC, Doerge DR, Zhang X, Fu X, Hanig JP, Paule MG, Slikker W, Wang C. Potential neurotoxicity of ketamine in the developing rat brain. Toxicol Sci. 2009;108:149–58.
17. Fredriksson A, Archer T, Alm H, Gordh T, Eriksson P. Neurofunctional deficits and potentiated apoptosis by neonatal NMDA antagonist administration. Behav Brain Res. 2004;153:367–76.
18. Slikker W Jr, Zou X, Hotchkiss CE, Divine RL, Sadovova N, Twaddle NC, Doerge DR, Scallet AC, Patterson TA, Hanig JP, Paule MG, Wang C. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci. 2007;98:145–58.
19. Zou XJ, Patterson TA, Divine RL, Sadovova N, Zhang X, Hanig JP, Paule MG, Slikker W Jr, Wang C. Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. Int J Dev Neurosci. 2009;27:727–31.
20. Wang C, Sadovova N, Hotchkiss C, Fu X, Scallet AC, Patterson TA, Hanig J, Paule MG, Slikker W Jr. Blockade of N-methyl-D-

aspartate receptors by ketamine produces loss of postnatal day 3 monkey frontal cortical neurons in culture. Toxicol Sci. 2006;91:191–201.
21. Cattano D, Young C, Straiko MMW, Olney JW. Subanesthetic doses of propofol induce neuroapoptosis in the infant mouse brain. Anesth Analg. 2008;106:1712–4.
22. Pesic V, Milanovic D, Tanic N, Popic J, Kanazir S, Jevtovic-Todorovic V, Ruzdijic S. Potential mechanism of cell death in the developing rat brain induced by propofol anesthesia. Int J Dev Neurosci. 2009;27:279–87.
23. Vutskits L, Gascon E, Tassonyi E, Kiss JZ. Clinically relevant concentrations of propofol but not midazolam alter in vitro dendritic development of isolated gamma-aminobutyric acid-positive interneurons. Anesthesiology. 2005;102:970–6.
24. Ma D, Williamson P, Januszewski A, Marie-Caroline N, Hossain M, Ong LP, Shu Y, Franks NP, Maze M. Xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain. Anesthesiology. 2007;106:746–53.
25. Yon JH, Daniel-Johnson J, Carter LB, Jevtovic-Todorovic V. Anesthesia induces neuronal cell death in the developing rat brain via the intrinsic and extrinsic apoptotic pathways. Neuroscience. 2005;135:815–27.
26. Sanders RD, Xu J, Shu Y, Januszewski A, Halder S, Fidalgo A, Sun P, Hossain M, Ma D, Maze M. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology. 2009;110:1077–85.
27. Palanisamy A, Baxter MG, Keel PK, Xie Z, Crosby G, Culley DJ. Rats exposed to isoflurane in utero during early gestation are behaviorally abnormal as adults. Anesthesiology. 2011;114:521–8.
28. Nikizad H, Yon JH, Carter LB, Jevtovic-Todorovic V. Early exposure to general anesthesia causes significant neuronal deletion in the developing rat brain. Ann NY Acad Sci. 2007;1122:69–82.
29. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creely CE, Olney JW. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology. 2010;112:834–41.
30. Istaphanous GK, Howard J, Nan X, Hughes EA, McCann JC, McAuliffe JJ, Danzer SC, Loepke AW. Comparison of neuroapoptotic properties of equipotent anesthetic concentrations of desflurane, isoflurane, or sevoflurane in neonatal mice. Anesthesiology. 2011;114:578–87.
31. Kodama M, Satoh Y, Otsubo Y, Araki Y, Yonamine R, Masui K, Kazama T. Neonatal desflurane exposure induces more robust neuroapoptosis than do isoflurane and sevoflurane and impairs working memory. Anesthesiology. 2011;115:979–91.
32. Liang G, Ward C, Peng J, Zhao Y, Huang B, Wei H. Isoflurane causes greater neurodegeneration than an equivalent exposure of sevoflurane in the developing brain of neonatal mice. Anesthesiology. 2010;112:1325–34.
33. Stratmann G, Bell JD, Alvi RS, Ku B, Saw L, Encarnacion A, Magnusson K, Bickler P, Liu J. Neonatal isoflurane anesthesia causes a permanent neurocognitive deficit in rats. J Neurosurg Anesthesiol. 2006;18:288.
34. Olney JW, Straiko MMW, Cattano D, Young C, Creely CE. Preventing anesthesia-induced developmental neuroapoptosis—temperature regulation approach. Anesthesiology. 2008;109:A1414.
35. Johnson SA, Young C, Olney JW. Isoflurane-induced neuroapoptosis in the developing brain of nonhypoglycemic mice. J Neurosurg Anesthesiol. 2008;20:21–8.
36. Zhang X, Xue Z, Sun A. Subclinical concentration of sevoflurane potentiates neuronal apoptosis in the developing C57BL/6 mouse brain. Neurosci Lett. 2008;55:429–36.
37. Shih J, May Laura DV, Gonzalez HE, Lee EW, Alvi RS, Sall JW, Rau V, Bickler PE, Lalchandani GR, Yusupova M, Woodward E, Kang H, Wilk AJ, Carlston CM, Mendoza MV, Guggenheim JN, Schaefer M, Rowe AM, Stratmann G. Delayed environmental enrichment reverses sevoflurane-induced memory impairment in rats. Anesthesiology. 2012;116:586–602.
38. Hammer RP Jr, Ricalde AA, Seatriz JV. Effects of opiates on brain development. Neurotoxicology. 1989;10:475–83.
39. Niu L, Cao B, Zhu H, Mei B, Wang M, Yang Y, Zhou Y. Impaired in vivo synaptic plasticity in dentate gyrus and spatial memory in juvenile rats induced by prenatal morphine exposure. Hippocampus. 2009;19:649–57.
40. Cattano D, Williamson P, Fukui K, Avidan M, Evers AS, Olney JW, Young C. Potential of xenon to induce or to protect against neuroapoptosis in the developing mouse brain. Can J Anaesth. 2008;55:429–36.
41. McClaine RJ, Uemura K, de la Fuente SG. General anesthesia improves fetal cerebral oxygenation without evidence of subsequent neuronal injury. J Cereb Blood Flow Metab. 2005;25:1060–9.
42. Wei H, Kang B, Wei W. Isoflurane and sevoflurane affect cell survival and BCL-2/BAX ratio differently. Brain Res. 2005;1037:139–47.
43. Yu D, Jiang Y, Gao J, Liu B, Chen P. Repeated exposure to propofol potentiates neuroapoptosis and long-term behavioral deficits in neonatal rats. Neurosci Lett. 2013;534:41–6.
44. Vutskits L, De Roo M, Klauser P, Adrian B, Muller D. Anesthetics impair dendritic spine development in the postnatal mouse somatosensory cortex. Anesthesiology. 2008;109:A325.
45. Stratmann G, May LD, Sall JW, Alvi RS, Bell JS, Ormerod BK, Rau V, Hilton JF, Dai R, Lee MT, Visrodia KH, Ku B, Zusmer EJ, Guggenheim J, Firouzian A. Effects of hypercarbia and isoflurane on brain cell death and neurocognitive dysfunction in 7-day-old rats. Anesthesiology. 2009;110:849–61.
46. Dribben WH, Creeley CE, Wang HH, Smith DJ, Farber NB, Olney JW. High dose magnesium sulfate exposure induces apoptotic cell death in the developing neonatal mouse brain. Neonatology. 2009;96:23–32.
47. Maloney SE, Noguchi KK, Wozniak DF, Fowler SC, Farber NB. Long-term effects of multiple glucocorticoid exposures in neonatal mice. Behav Sci. 2011;1:4–30.
48. Dobbing J, Sands J. Comparative aspects of the brain growth spurt. Early Hum Dev. 1979;3:79–83.
49. Olney JW. New insights and new issues in developmental neurotoxicology. Neurotoxicology. 2002;23:659–68.
50. Clancy B, Darlington RB, Finlay BL. Translating developmental time across mammalian species. Neuroscience. 2011;105:7–17.
51. Oppenheim RW. Cell death during development of nervous system. Annu Rev Neurosci. 1991;14:453–501.
52. Istaphanous GK, Ward CG, Loepke AW. The impact of the perioperative period on neurocognitive development, with a focus on pharmacological concerns. Best Pract Res Clin Anesthesiol. 2010;24:433–49.
53. Anand KJS, Soriano SG. Anesthetic agents and the immature brain: are these toxic or therapeutic? Anesthesiology. 2004;101:527–30.
54. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology. 2009;110:796–804.
55. Sprung J, Flick RP, Wilder RT, Katusic SK, Pike TL, Dingli M, Gleich SH, Schroeder DR, Barbaresi WJ, Hanson AC, Warner DO. Anesthesia for cesarean delivery and learning disabilities in a population-base birth cohort. Anesthesiology. 2009;111:302–10.

56. Hansen TG, Pedersen JK, Henneberg SW, Pedersen DA, Murray JC, Morton NS, Christensen K. Academic performance in adolescence after inguinal hernia repair in infancy: a nationwide cohort study. Anesthesiology. 2011;114:1076–85.
57. Diamaggio C, Sun LS, Kakavouli A, Byrne MW, Li G. A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and development disorders in young children. J Neurosurg Anesthesiol. 2009;21:286–91.
58. Kalkman CJ, Peelen L, Moons KG, Veenhuizen M, Bruens M, Sinnema G, de Jong TP. Behavior and development in children and age at the time of first anesthetic exposure. Anesthesiology. 2009;110:805–12.
59. Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet. 2009;12:246–53.