Anesthetic neurotoxicity in the newborn and infant

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Purpose of review
Every year, millions of children undergo anesthesia. Emerging evidence from experimental in-vitro and in-vivo models supports a role for neuropathologic injury and neurobehavioral deficits at older age after early exposure to various anesthetic regimens. Clinical studies have sought to identify a phenotype of developmental anesthesia neurotoxicity in humans, but the current evidence is limited to data from retrospective studies with their associated confounders. Experimental models have been used to further define the injury and to help identify potential mechanisms of this neurotoxicity.

Recent findings
A recent clinical trial from an Australian birth cohort suggests a single anesthesia exposure as a neonate or infant may increase the risk for language and abstract reasoning deficits later in life, though residual data confounders may remain. Several ongoing clinical trials like Mayo Safety in Kids, Pediatric Anesthesia NeuroDevelopment Assessment, and General Anesthesia and Apoptosis Study will likely offer more clear answers in the future. In the interim, experimental models have described roles for neuroinflammation, mitochondrial damage from reactive oxygen species, and the presence of several neuronal morphology changes from anesthesia exposure. Additionally, several potential neuroprotective agents and strategies have been tested in the laboratory.

Summary
Whether anesthesia-associated neurotoxicity affects the developing human brain and whether this leads to clinically measurable deficits remains unclear.

Keywords
anesthesia neurotoxicity, developmental neurotoxicity, infant, neonate

INTRODUCTION
Triggered by pioneering laboratory investigations in the first years of this millennium, human epidemiologic studies have documented a correlation between anesthetic exposure at young age and subsequent learning and academic performance impairments, or, most recently, even specific neurologic deficits and neuropsychological syndromes [1–5]. These findings are further raising concerns that anesthetic exposure may have deleterious effects on brain development [6].

The practical consequence for anesthesiologists, other healthcare providers, and particularly for families and society as a whole, is a profound dilemma: virtually all available anesthetic agents appear to cause harm in animal models, and clinical evidence is concerning but still ambiguous given its basis on retrospective studies. At the same time, it is accepted that infants and neonates indeed experience pain and stress, and that withholding adequate analgesia and sedation in these situations can cause hyperalgesia, structural alterations, and inappropriate behaviors in later development [7]. Thus, the appalling dilemma is that exposure to the very agents that can alleviate pain, provide sedation, and maintain anesthesia may be harmful to young children and may produce the very outcomes that occur following the experience of untreated pain and stress. This conundrum is further compounded by the fact that no proven safe alternatives are on the horizon, and stressful diagnostic tests or surgical interventions in even very young children often cannot be postponed until a later developmental stage.

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Despite inconclusive evidence, the discussion, which initially occurred amongst experts, has now left the laboratory to continue with families, within public groups, in the media, and with our surgical colleagues [8]. This discussion is particularly challenging to have when first forming the patient–physician relationship, when the goals are to simultaneously build trust and confidence in that relationship while caring for a sick child.

The review will explore new evidence regarding anesthesia-induced brain injury to the developing brain, as provided from clinical or laboratory studies during the annual period of review. When necessary, we will briefly reflect on previous work in order to provide the context for new data. Our aim is to inform the provider about the latest progress in the field, and provide facts and needed explanations for interactions with other healthcare providers and families of young children.

CLINICAL EVIDENCE
Retrospective studies suggest an association between anesthesia exposure in the developing brain and an increased risk of cognitive or behavioral disorders. DiMaggio et al. [1] evaluated a birth cohort of New York Medicaid patients exposed to inguinal hernia repair (IHR) (under anesthesia) prior to age 3. These patients had more than twice the risk of a behavioral or developmental disorder when compared to age-matched controls. In a follow-up study, they evaluated for risk of similar cognitive and behavioral disorders in this same cohort after any exposure to surgery prior to age 3, as compared to sibling-matched controls [2]. Exposed siblings had a greater than 60% increased risk of these disorders, and the risk increased as the number of surgical (and anesthetic) exposures increased.

Wilder et al. [3], from the Mayo Clinic, investigated a birth cohort from Minnesota to evaluate for an association between anesthesia exposure prior to age 4 and diagnosis of learning disabilities by age 19. There was no association between one anesthesia exposure and learning disabilities, though there was an increased risk of learning disabilities with two exposures, and an even greater risk with three. Further, they evaluated risk versus length of anesthesia, and showed a trend towards increased learning disabilities with increasing length of exposure, with a statistically significant increase in learning disabilities in exposures of 120 min or greater. Further database analysis designed to control for potential confounders with matched controls evaluated for the risk of learning disabilities versus anesthesia exposure prior to age 2 [4]. They showed no significant increase in learning disabilities with one exposure, but a greater than two-fold higher association of learning disabilities with multiple anesthesia exposures. Moreover, they assessed for an association between one or multiple anesthesia exposures prior to age 2 and the diagnosis of attention-deficit hyperactivity disorder (ADHD) by age 19 [5]. There was no increased risk of ADHD with a single exposure, but a nearly two-fold increased risk with two or more anesthesia exposures.

The fact that multiple studies have suggested an association between anesthesia exposure and cognitive or behavioral issues, and that these effects appear to be dose-related, argues for scientific plausibility. However, these studies are limited by their retrospective design, with the associated inability to rule out residual confounders (e.g. patient factors regarding indication for surgery, outcomes directly related to the surgical stimulus, etc.). The anesthesia exposures studied do not necessarily reflect current practice either, as they were conducted many years ago. For example, in Wilder et al.’s study, 88% of the anesthetics included halothane [3]. As such, there has been great emphasis on pursuing randomized and prospective clinical studies.

The US Food and Drug Administration and the International Anesthesia Research Society (IARS) started a formal partnership in 2010 called ‘Strategies for Mitigating Anesthesia-Related Neuro-Toxicity in Tots’ (SmartTots) to support further basic science and clinical research addressing the safety of anesthesia in neonates and young children (www.smarttots.org [9], reviewed by Ramsay and Roizen [10]). Their December 2012 consensus statement continues to state that current evidence does not support a change in practice, and that further research on this subject is needed. There are several...
SmartTots-supported prospective clinical trials currently in process, including the General Anesthesia and Apoptosis (GAS) study, the Pediatric Anesthesia Neuromotor Development Assessment (PANDA) project, and the Mayo Safety in Kids (MASK) study.

The GAS study is an ongoing prospective, randomized, multicenter, international trial comparing regional anesthesia and general anesthesia for IHR in neonates [11]. Inclusion criteria are 26 weeks gestational age or greater and postconceptual age of 60 or less. Primary outcomes include several immediate postoperative physiologic variables including presence of apnea and neurocognitive testing at 2 and 5 years of age. General anesthesia is defined as exposure to sevoflurane with a bupivacaine single shot caudal or ilioinguinal block. Regional anesthesia is defined as a bupivacaine caudal or spinal block alone, caudal and spinal block, or spinal and ilioinguinal block (all single-shot techniques). Enrollment completed in January 2013 with 722 total participants (Davidson A, personal communication). Several sites have begun 5-year follow-up testing.

The PANDA project is a multicenter study seeking to compare American Society of Anesthesiology physical status of 1 or 2 children exposed to any type of anesthetic for IHR prior to 36 months old to unexposed siblings. The study participants are identified retrospectively; then they undergo prospective neurocognitive and behavior testing at age 8–15 years. A pilot feasibility study including 28 sibling pairs was recently completed [12**]. The study coordinators project enrollment of 960 participants in the formal study, which is ongoing [12**].

The MASK study is a collaborative effort between the National Center for Toxicological Research (NCTR) and the Mayo Clinic [9]. They are evaluating a large cohort of children from Minnesota to identify those with one, multiple, or no anesthesia exposures prior to age 3. These children will undergo extensive prospective neurocognitive testing, including the operant test battery (OTB). The OTB is an array of cognitive tests involving positive reinforcement that has been extensively used in neurotoxicology research. These tests assess several cognitive modalities, and have been validated in humans as well as nonhuman primates (NHPs) [13]. The MASK study started recruitment in January 2013, as of June recruited about 70 individuals, and expects to report results in 3 years (Flick R, personal communication).

A most recent and highly interesting study from several researchers in New York and Australia suggests an association between exposure to anesthesia prior to age 3 and language and abstract reasoning deficits detected at age 10, even with a single anesthesia exposure [14**]. They analyzed a prospectively obtained Australian database, which was originally created to investigate long-term effects of perinatal ultrasound exposure, and included children who received perinatal care in and around Perth, Western Australia. Out of 2868 identified children, about 9% were lost to follow-up by age 10, and 11% were exposed to anesthesia prior to age 3. The remainder were unexposed. As with similar studies, anesthesia exposure was defined by identifying those children who had to undergo surgery or specific procedures requiring anesthesia.

When comparing single and multiple exposures before age 3, the authors use more strict follow-up criteria for inclusion, to avoid misclassifying one with multiple exposures as a single exposure due to limited early follow-up. This method yielded 206 single exposures, 52 multiple exposures, and 1523 unexposed children.

Neurocognitive testing evaluated expressive and receptive language ability, cognition, behavior, and motor function. After adjusting for confounders, they found a 2.4-fold increased risk for disabilities in receptive language when comparing children with a single exposure versus unexposed children, and a 3.5-fold increased risk when comparing children with multiple exposures to unexposed children. Cognition testing revealed a 75% increased risk of disability in abstract reasoning in the single-exposure group versus the unexposed group, but no statistically significant difference when comparing those with multiple exposures. The remaining testing modalities did not differ between groups.

To summarize, the available clinical data probing for associations between anesthesia exposure and cognitive and behavioral outcomes remain mixed. Some studies suggest a single exposure to anesthesia may be ‘safe’ compared to multiple exposures [3–5], whereas other studies suggest significant deficits with a single exposure [1,2,14**]. These studies remain limited by their retrospective and observational designs, and the presence of largely out-of-date anesthetic agents. The upcoming results from ongoing randomized and prospective trials will provide further perspective on this important issue.

EXPERIMENTAL EVIDENCE

In-vivo and in-vitro experimental models continue to build on our understanding of anesthesia-associated neurotoxicity in the developing brain. Previous studies show that this neurotoxicity occurs around the period of rapid synaptogenesis or the ‘brain growth spurt’ and across several species including...
rats, mice, guinea pigs, and NHPs [15–34,35**]. Further, the damage has been associated with lasting cognitive and behavioral deficits [19,21,26,32], is dose-dependent, and, in some models, present even with exposure to sub-anesthetic doses [20,23–25].

Some of the earliest studies in fetal and neonatal rodents directly implicated N-methyl-D-aspartate (NMDA) receptor antagonism and γ-aminobutyric acid (GABA<sub>A</sub>) receptor potentiation as causes of widespread neurodegeneration, with a pattern of cell toxicity that resembles programmed cell death [15–17]. Further, combining NMDA antagonism and GABA<sub>A</sub> potentiation, for example, through exposure to ethanol, caused even more widespread neurodegeneration [16]. This synergistic toxicity has also been shown with combinations of NMDA antagonist and GABAergic drugs [20–22,31], with robust neurodegeneration seen after exposure to a balanced anesthetic of midazolam, isoflurane, and nitrous oxide, as compared to either agent alone [17].

The supportive literature continues to grow, implicating several NMDA antagonists (ketamine [15,19–21,30] and nitrous oxide [17,29,31]), GABA<sub>A</sub> receptor-potentiating drugs (midazolam [17,20,29], diazepam [16,18,19], clonazepam [16,18], pentobarbital [16], phenobarbital [16,18], thiopenal [21], isoflurane [17,23,27–29,31]), sevoflurane [25–28], and desflurane [28], and those with mixed activity (propofol [21,24] and ethanol [16]) are neurotoxic in fetal and neonatal animal models. Several antiepileptic drugs have been linked to similar neurotoxicity [18].

During the year in review, many facets of this complex subject were further investigated. We have highlighted several of these reports including those addressing the comparative toxicity of agents, morphological changes to neurons and astrocytes from anesthesia exposure, and potential neuroprotective strategies.

**Differential toxicity of agents**

Groups have attempted to identify whether one anesthetic is more or less toxic than another, for example, isoflurane versus sevoflurane, though with mixed results [27,28]. Most recently, Ramage et al. [36*] showed differences in neurocognitive outcomes when comparing one minimum alveolar concentration (MAC) of sevoflurane anesthesia to isoflurane anesthesia in neonatal rats. Postnatal day 7 (P7) rats were exposed to one MAC of sevoflurane or isoflurane for 4 h. MAC was carefully titrated by tail clamp testing every 15 min. As adults, age P75 and greater, the rats underwent neurocognitive testing. Isoflurane-exposed rats demonstrated deficits in short-term and early long-term memory, whereas those exposed to sevoflurane had only early long-term memory deficits, each compared to unexposed controls.

Our group of collaborators recently published results describing the pattern of neuroapoptosis in fetal and neonatal rhesus macaques exposed to propofol anesthesia [37**] and compared the toxicity to that of a previous study with isoflurane [33]. The NHP fetuses were exposed in utero for 5 h at gestational age 120 days (out of 165 days total gestation) or immediately after birth (P6), similar to previous studies evaluating ketamine [34] and isoflurane [33]. These developmental stages in a Rhesus macaque correspond to a slightly preterm to mature human neonate, or a 4–6-month-old human infant, respectively. Propofol was carefully titrated to a plane of moderate anesthesia by assessing for response to a painful stimulus every 30 min. After exposure, animals were given time to recover, then were euthanized and processed for analysis.

Widespread neuroapoptosis was noted. The propofol-exposed fetal group had 2.4-fold more neuroapoptosis, whereas the neonatal group had 3.8-fold more, both versus controls. Neurons comprised about 50% of the dying cells and the remaining 50% were oligodendrocytes. The dying oligodendrocytes were noted to be in a maturation stage where myelination was just beginning, similar to results after isoflurane exposure [35**,38**]. However, when comparing the magnitude of cell death with the prior isoflurane study in P6 neonatal macaques [33], there was four times more apoptosis in the isoflurane group than the propofol group.

**Neuronal architecture changes**

Mintz et al. [39] investigated the effects of anesthesia on the developing axon. As an immature neuron grows, neurites, or ‘out-growths’ from the cell body, lengthen and contract. One of these neurites will eventually outgrow the others, rapidly elongate, and become the axon in the process of neuron polarization. This process is important for developing a neuronal network, ensuring connections between axons and neighboring dendrites [40]. The experiments by Mintz et al. involved dissociated neurons from embryonic mouse neocortex cultured in vitro under either control conditions, or exposed to varying concentrations of isoflurane for 4 h (0.6, 1.2, 1.8, 2.4, or 3.0%) or at 2.4% isoflurane for varying lengths of time (2, 4, 6, or 8 h). The percentage of polarized neurons decreased in cells treated for 4 h in 1.2% isoflurane or higher and in 2.4% isoflurane treated for 4 h or longer, indicating a time and concentration-dependent effect.
Neuronal polarity also decreased after exposure to propofol. The fact that both of these GABA<sub>A</sub>-potentiating drugs led to decreased neuron polarization led the authors to assess whether the effect was dependent on the GABA<sub>A</sub> receptor. However, using the potent, selective GABA<sub>A</sub> receptor agonist muscimol, which clinically produces sedative-hypnotic effects, they were unable to show differences in the percentage of polarized neurons in comparison to untreated cultures, arguing against a selectively GABA<sub>A</sub>-mediated mechanism for decreased neuron polarization in this experimental model. The functional consequences of delayed neuron polarization are unclear, though the authors surmise ‘if the axon “misses” the window when the appropriate cue is present, the parent neuron may not be incorporated into key circuits’ ([39], p. 373).

In a separate set of experiments, Mintz et al. [41*] describe alterations in axon growth in reference to guidance cues, also in a model of embryonic mouse neocortex neuronal culture, as well as slices of neocortex from P3 rats. The neuronal cultures were used to assess axonal growth cone (AGC) collapse, a normal response to guidance cues in the growing axon. The authors showed concentration-dependent inhibition of AGC collapse with clinically relevant concentrations of isoflurane and propofol. There are similar inhibitions of AGC collapse after exposure to other GABA<sub>A</sub>-associated anesthetics such as thiopental and midazolam, with little inhibition from ketamine and nitrous oxide, which may have weak GABAergic properties [42,43], and no inhibition by fentanyl and dexmedetomidine, which do not have GABAergic properties. This trend argues that anesthetic-associated inhibition of AGC collapse could be GABA<sub>A</sub>-receptor-mediated.

Similarly, in neuronal slices, an 8-h exposure to 1.2% isoflurane caused completely random axonal growth trajectory as opposed to proper guidance cue mediated ventral growth in controls. These anesthesia-associated abnormal responses to growth cues could be a morphologic phenotype of anesthesia-related injury that is distinct from neuronal apoptosis.

The majority of literature on anesthesia-associated neurotoxicity focuses on neuron-specific toxicity, with the exception of our most recent study evaluating effects on oligodendrocytes in a NHP model [35**,37**,38**], and that of Culley et al. [44*] evaluating the effects of isoflurane on the cytoskeleton of cultured rat astrocytes. Culley et al. exposed these cultures to 4 h of 1.4% isoflurane or 4 h of air (control), and assessed for cell viability, proliferation, and expression of cytoskeletal proteins, both immediately after exposure and 48 h later. Isoflurane exposure had no effect on cell viability or proliferation. However, isoflurane-exposed astrocytes exhibited less α-tubulin and glial fibrillary acidic protein (GFAP), two cytoskeletal proteins, though their gross motility was not impaired. Further, culture medium from these control and exposed astrocytes was transferred to primary rat neuronal cultures to assess for the ability of this ‘astrocyte-conditioned medium’ to nourish growing neurons and support synaptic formation. There was no difference in synaptogenesis between these two groups. Altogether, their findings argue that astrocytes may be more resistant to anesthesia-associated neurotoxicity than neurons.

Others have focused on identifying changes to organelles, especially mitochondria, and intracellular mechanisms that could be part of the process of anesthesia-associated apoptosis or may be complementary to it. Within the past year, groups have further identified associations between this apoptosis and increased reactive oxygen species with associated changes in mitochondrial morphology [45*,46*] (and presumably changes to mitochondrial function), or up-regulated inflammatory markers [47*]. It remains to be determined whether these changes are components of the process towards apoptosis triggered by an as yet identified proximal trigger, or if these represent the initial changes upstream from the final apoptosis pathway leading to cell death.

**Neuroprotective strategies**

Several drugs have previously been identified as possibly neuroprotective against anesthesia-associated toxicity, specifically in neonatal rodent models. Among these are erythropoietin [48], bumetanide [49], L-carnitine [50], xenon [51,52], dexmedetomidine [53,54], melatonin [55], and lithium [56]. Also, erythropoietin [48], xenon [52], and dexmedetomidine [53] have been associated with improvements in the negative cognitive effects of neonatal anesthesia exposure in rodents.

Within the year in review, Liu et al. [57**] published further data supporting the use of L-carnitine as a neuroprotective agent when testing ketamine exposures in rat primary forebrain cultures. They note that ketamine-treated cells exhibited oxidative stress-associated DNA damage, and this damage essentially disappeared when L-carnitine was administered along with ketamine.

Similarly, Liu et al. [58**] demonstrated increased neuroapoptosis in neonatal rats exposed to ketamine that was mitigated by concomitant lithium administration. They further show that this ketamine exposure led to decreased phosphorylated protein kinase B (phosph-AKT) and thus increased
unphosphorylated glycogen synthase kinase-3β (GSK-3β). GSK-3β is a protein implicated in several neurodegenerative diseases that is inactivated by phosphorylation [59]. Lithium also mitigates these changes to phospho-AKT and GSK-3β, suggesting a possible mechanism for lithium’s protective effects [58**].

Yonamine et al. [60**] recently evaluated hydrogen gas as a potential neuroprotective agent, while using this agent as part of the carrier gas for an inhaled anesthetic. They applied a neonatal mouse model to test groups exposed to varying concentrations of sevoflurane with or without hydrogen in the carrier gas mix. The authors found less apoptosis and signs of less oxidative stress in those exposed to hydrogen gas, arguing for an antioxidant mechanism of neuroprotection [60**]. A separate cohort of mice underwent testing for sociability at 12 weeks and fear conditioning (memory) at 13 weeks postnatal age. Animals exposed to sevoflurane alone scored significantly worse on both behavioral measures as compared to unexposed controls, and the deficits were ameliorated in the group with concomitant hydrogen gas exposure.

Zhao et al. [61**], using a model of immortalized human neuroprogenitor cells (NPCs), demonstrated that a short period of isoflurane ‘preconditioning’ (pretreatment) can mitigate the toxic effects of a more prolonged exposure to isoflurane, interpreted by the authors as evidence for a mechanism involving altered calcium signaling. In the absence of pretreatment, a 2.4% isoflurane exposure for 6 h did not cause increased NPC death, whereas a 12 or 24-h exposure did. This injury was mitigated with a 1-h 2.4% isoflurane pretreatment.

Lastly, pramipexole, a drug noted to restore mitochondrial integrity, was tested by Boscolo et al. [62**] in a neonatal rat model exposed to midazolam, isoflurane, and nitrous oxide. As adults, rats in the anesthesia-only group had significant cognitive impairment, whereas those exposed as neonates to anesthesia with pramipexole appeared to be protected from these effects in adulthood.

CONCLUSION

Scientific evidence published during the annual period of review, both from laboratory and epidemiologic investigations, augments rather than alleviates concerns for toxic effects of anesthetics and sedatives to the developing brain. Anesthetic neurotoxicity has been described to affect a variety of morphologic elements within the neuropil of mammalian brain, including that of NHPs. Several concepts for a potential pathomechanism have been further defined or newly suggested. However, exact knowledge about the details of both phenotype and mechanism is still scarce. The discussion continues regarding whether human infants and children are at risk for a similar injury since clinical evidence thus far is only available from retrospective studies and such data do not allow identification of causal relationships. Results from the ongoing prospective clinical trials are thus anticipated with considerable excitement. Nevertheless, several key issues have not yet been systematically approached, for example, the differential effects of anesthetics versus those of the simultaneous surgical intervention.

Similar to previous work, the material published during the annual period in review has not produced the evidence needed to trigger change in clinical practice. Accordingly, experts in the field initiated by the FDA and SmartTots continue to support this view in their consensus statement to the public, which has received endorsement by a number of key organizations in the field (www.smarttots.org).

In the meantime, it is imperative to further expand research efforts through well designed human trials as well as highly relevant translational research in the laboratory.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 639).

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Anesthesia Neurodevelopment Assessment (PANDA) project. PANDA sym-
13. This study describes the PANDA study design and reports preliminary results.
and cognitive function after childhood exposure to anesthesia. Pediatrics
15. This cohort study evaluated a prospectively obtained database to assess for an
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25. Zhang X, Xue Z, Sun X. Subcortical cell of sevoflurane potentiates neuroapop-
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57. Liu F, Patterson TA, Sadovova N, et al. Ketamine-induced neuronal damage and altered N-Methyl-D-Aspartate receptor function in rat primary forebrain culture. Toxicol Sci 2013; 131:548–557. This culture model demonstrates that a 24-h ketamine exposure causes a compensatory increase in the NMDA receptor NRT1 subunit. Further, when ketamine is removed from the system, these neurons have exaggerated responses (calcium influx) to NMDA activation that appear dependent on extracellular calcium, generate reactive oxygen species, and result in neuronal death. These changes can be mitigated with L-carnitine.

58. Liu JR, Baek C, Han XH, et al. Role of glycogen synthase kinase-3β in ketamine-induced developmental neuroapoptosis in rats. Brit J Anaesth 2013; 110 (S1):i3–i9. This group implicates a role for ketamine’s effects on protein kinase B (AKT) and glycogen synthase kinase-3β in anesthesia-associated developmental neurotoxicity. Further, lithium mitigates these negative effects.


60. Yonamine R, Satoh Y, Kodama M, et al. Co-administration of hydrogen gas as part of the carrier gas mixture suppresses neuronal apoptosis and subsequent behavioral deficits caused by neonatal exposure to sevoflurane in mice. Anesthesiology 2013; 118:105–113. This group shows that adding hydrogen gas as part of the carrier gas for an inhaled anesthetic can decrease apoptosis and behavioral effects from sevoflurane exposure in neonatal mice, perhaps through an antioxidant mechanism.

61. Zhao X, Yang Z, Liang G, et al. Dual effects of isoflurane on proliferation, differentiation, and survival in human neuroprogenitor cells. Anesthesiology 2013; 118:537–549. These studies show a 1-h “preconditioning” exposure with isoflurane can mitigate the neurotoxic effects of a future more prolonged exposure. Through an elegant set of experiments, they show that several calcium receptors are implicated in these responses, with a fine balance in calcium homeostasis likely linked to both neuroprotection and apoptosis. This may explain how isoflurane can be both neuroprotective and neurotoxic.