Anesthesia for the young child undergoing ambulatory procedures: current concerns regarding harm to the developing brain

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Purpose of review Sedation and anesthesia are often necessary for children at any age, and are frequently provided in ambulatory settings. Concerns have mounted, based on both laboratory studies including various mammalian species and retrospective human clinical studies, that the very drugs that induce sedation and anesthesia may trigger an injury in the developing brain, resulting in long-lasting neurobehavioral consequences.

Recent findings New retrospective studies further augment these concerns. Specifically, recent studies support that a single anesthesia exposure before age 3 may increase the risk for long-term disabilities in language acquisition and abstract reasoning, and that exposure to two or more anesthetics before age 2 nearly doubles the risk for an attention-deficit hyperactivity disorder diagnosis by age 19. However, methodological limitations preclude final conclusions or change in practice based on these reports, as retrospective studies cannot prove causation. Ongoing prospective clinical studies such as ‘General Anesthesia and Apoptosis Study’, ‘Pediatric Anesthesia NeuroDevelopment Assessment’, and ‘Mayo Safety in Kids’ trials will offer more answers in the future. Meanwhile, laboratory experiments continue to describe differential morphologic injury to individual structures in the neuropil, and have identified mitochondrial dysfunction and neuroinflammation as potential links in the injury process. Additionally, concepts for protection against anesthesia-induced neurotoxicity continue to be tested in the laboratory.

Summary Results from ongoing prospective clinical trials and translational research will help clarify whether anesthesia-associated neurotoxicity affects the developing human brain, including whether it causes long-term disability, and may further identify the injury mechanisms and potential strategies for protection. Currently, the available evidence does not support a change in practice.

Keywords ambulatory anesthesia, children, developmental anesthesia neurotoxicity, infants, pediatric anesthesia

INTRODUCTION

At this time, anesthesia and adequate pain control can be so effectively provided that children who need to undergo a surgical procedure can frequently be sent home the same day, to further recover from the intervention in the familiar home environment.

Moreover, providing general anesthesia to young children has become so safe that families and caregivers have little to worry about in terms of the immediate risks of the anesthetic and the immediate postoperative period.

However, debate has ensued over mounting evidence suggesting that exposure to anesthetics at a young age may impair subsequent brain development and cause long-term behavior and learning impairments [1–4]. The most recent epidemiologic studies suggest that even specific neurologic deficits and neuropsychological syndromes are more frequently encountered in children and young adults.
who were exposed to anesthesia at a young age [5,6]. A large body of experimental literature, which ignited the field and triggered human studies about 10 years ago, now clearly documents anesthesia-associated neurotoxicity and its behavioral consequences in multiple mammalian species, and provides the first insights into potential mechanisms in these injury models. Nevertheless, critics challenge the relevance of the available retrospective epidemiologic studies, which, by design, cannot establish a causal relationship between the drugs used to induce anesthesia and sedation and the suspected injury in the developing human brain.

Not surprisingly, the discussion has spread from expert circles [7] to public groups, the media, and families [8]. Now families and clinicians, both surgeons and anesthesiologists, are increasingly involved in this discussion prior to procedures that require sedation or anesthesia in a young child. It is a difficult discussion to have while simultaneously trying to build trust and confidence with the sick child and his family. It is a particularly difficult situation because virtually all currently used anesthetics and sedatives are under scrutiny, and safe alternatives are not available. Moreover, many diagnostic tests or surgical interventions that require sedation or anesthesia frequently cannot be postponed until a later developmental state.

This fundamental, and only partially elucidated, problem is challenging clinicians on a day-to-day basis, as well as the healthcare system as a whole. An important step forward was the foundation of a new organization in 2010 that is solely dedicated to the cause of funding the development of ‘Strategies for Mitigating Anesthesia-Related NeuroToxicity in Tots’ (SmartTots). This initiative, the product of a strategic partnership between the US Food and Drug Administration (FDA) and the International Anesthesia Research Society, raises funds to support further basic science and clinical research addressing the safety of anesthesia in neonates and young children (www.smarttots.org [9,10]). SmartTots also gathers experts to help inform the public; for example, their most recent consensus statement, from December 2012, advises that current evidence does not support a change in practice, and that further research on this subject is needed. SmartTots currently supports several prospective clinical trials, including the ‘General Anesthesia and Apoptosis Study’ (GAS) study, Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) project, and Mayo Safety in Kids (MASK) study.

This ongoing discussion will be better informed by the results of these and other clinical trials along with systematic insights from translational laboratory research. Thus, in the next few years we will hopefully see answers to the most urgent and clinically relevant questions as to how the safest sedation or anesthesia plan can be provided to infants and children.

This review will provide an update about the newest evidence pertaining to anesthesia-induced brain injury in the developing brain. Clinical or laboratory studies that were published during the annual period of review will be highlighted and discussed in the context of previous work as necessary.

CLINICAL STUDIES
As of today, clinical evidence regarding negative long-term cognitive and behavioral effects of anesthetics in young children is based on retrospective and observational studies. Despite very careful analysis, this retrospective methodology with several potential confounders presents limitations. Specific concerns include that the analyzed data were initially sampled for different purposes and entities (school administration, health insurance, and public health authorities), the anesthetic agents at the time of exposure may not be in use today, the study samples are representative of only a fraction of the population (e.g., Medicaid database), or that there is no way to control for factors leading to the need for surgery or outcomes from the surgery itself.

It is, therefore, no surprise that the currently available evidence remains mixed. Some studies suggest significant cognitive and behavioral deficits
even with a single anesthesia exposure [1,2,6**], whereas others saw no such effects after a single short exposure [11,12]. In contrast, multiple or longer exposures may be injurious enough such that a long-term functional deficit results [3–4,5*].

Ongoing prospective trials

Although the results from retrospective studies were critical in informing the field about the potential for an anesthetic toxicity phenotype in humans, based on prior methodologic concerns, the expectations are high that ongoing prospective trials will provide more definitive evidence on the issue.

Potentially, the earliest results from a prospective randomized clinical trial on this issue will come from the GAS study. This is a multicenter, international trial that compares general anesthesia (sevoflurane with a bupivacaine single shot caudal or ilioinguinal block) and regional anesthesia (bupivacaine caudal, spinal, or spinal and ilioinguinal block alone) for inguinal hernia repair (IHR) in neonates [13]. The study enrollment has been complete since January 2013 (n = 722; age 26–60 postconceptual weeks). Primary outcomes include postoperative variables such as the incidence of apnea, and neurocognitive testing at 2 and 5 years of age, which has started at several study sites (A. Davidson, Australia, personal communication).

Another ongoing large multicenter study is the PANDA project. Children are enrolled when exposed to any type of anesthetic for IHR before 36 months of age together with their nonexposed siblings, and are prospectively evaluated for cognitive and behavior abilities between age 8 and 15. The pilot study showed feasibility in 28 sibling pairs. Planned enrollment for the large trial is 960 participants [14**].

The most recently initiated large prospective clinical trial, the MASK study, is a collaborative effort between the Mayo Clinic and the National Center for Toxicological Research [9]. By way of this collaboration, the study effectively utilizes testing methods that are validated in human participants and are sensitive for the anesthesia-toxicity cognitive phenotype in nonhuman primates [15]. MASK, therefore, is uniquely poised to provide highly valuable clinical information to the field.

Enrollment of children that were exposed to either one, multiple, or no anesthetics prior to age 3 started in January 2013. The study participants will be tested prospectively for neurocognitive modalities using, among others, an operant test battery that, as described above, has been validated in humans as well as nonhuman primates [15]. As of June 2013, the team has recruited about 70 individuals and expects to report results in 3 years (R. Flick, Rochester, Minnesota, personal communication).

Key findings of recent retrospective clinical studies

Three very important contributions from recent retrospective studies are further highlighted: an association between exposure to anesthesia at young age and language and abstract reasoning deficits in later childhood [6**], an association between exposure to anesthesia at young age and the diagnosis of attention-deficit hyperactivity disorder (ADHD) later in life [5*], and evidence for dose effects suggesting that one exposure may not, but longer exposures or multiple exposures may result in learning disabilities later in the teenage years [3].

The first observation was recently published by a team of collaborators from Australia and the USA [6**]. They report an increased risk for disabilities in language acquisition and abstract reasoning when tested at age 10 in children that received one or more anesthetics before age 3. The team analyzed data that were prospectively obtained, originally to investigate long-term effects of perinatal ultrasound exposure in Perth, Western Australia. Eleven percent of the children in this database (n = 2868) were exposed to anesthesia at a young age (receiving surgery before age 3). They also identified single versus multiple exposures before age 3 among a subset of patients with very close early follow-up, yielding 206 single exposures, 52 multiple exposures, and 1523 unexposed children. They found an increased risk for disabilities in receptive language, when tested at age 10, that was 2.4-fold (single exposure) or 3.5-fold (multiple exposures) higher when compared with unexposed children, even after adjusting for confounders. Additionally, they detect a 75% increased risk of disability in abstract reasoning in single-exposed versus nonexposed children, although the comparison between multiple-exposed and nonexposed children was not statistically significant. Behavioral and motor testing did not differ between groups [6**].

Secondly, ADHD may be more likely to develop when a very young child receives multiple anesthetics. This was recently published by a team of researchers from the Mayo Clinic in Rochester [5*]. Analyzing a birth cohort from Minnesota, the investigators observed a nearly two-fold higher risk for a diagnosis of ADHD by age 19 when the child was exposed to two or more anesthetics before age 2. In contrast, their data suggested no correlation between an ADHD diagnosis and a single exposure [5*].
Thirdly, functional deficits following exposure to general anesthesia may be dose-dependent. The same group at the Mayo Clinic was also the first to investigate potential dose effects of early anesthesia exposure with long-term changes in learning and behavior [3]. In an earlier analysis of the same database, they found that children with only one anesthesia exposure prior to age 4 had no statistically increased risk of being diagnosed with a learning disability by age 19. However, they observed a significant increase in the diagnosis of learning disability after two exposures, an even higher risk after three exposures, and elevated risk if the anesthesia exposure was 2 h or longer. More recent results were obtained in a repeated cohort analysis that better controlled for potential confounders by using matched controls, and again showed increased risk for learning disability diagnosis with repeated exposures [4].

Controversies and limitations of current clinical evidence

On the basis of these reports, it is reasonable to consider that an association between anesthesia exposure and cognitive or behavioral issues is likely, and that the effects are dose-related. Nevertheless, at least two retrospective studies were unable to find such an association when analyzing different populations. Researchers in Denmark found no difference between the academic performances of teenagers (age 15–16) that were exposed to anesthesia for IHR as infants versus unexposed age-matched controls [11]. An analysis of data from the Young-Netherlands Twin Register echoed the above findings [12]; academic performance on a nationwide standardized test at age 12 was not different when comparing twins exposed to anesthesia by either age 3 or age 12 to their unexposed twin sibling.

Apart from the previously mentioned general methodology-specific limitations of a retrospective study design, and in contrast to the above work from the Mayo Clinic, the last two studies do not consider anesthesia-specific information such as agents used, type of anesthesia (general versus regional, etc.), and length of anesthesia exposure. In addition, the study from Denmark [11] enrolled ‘anesthesia-exposed’ individuals as those who underwent IHR, although both exposed and unexposed groups could have had anesthesia for other indications. Further, the study from the Netherlands [12] identified ‘anesthesia exposure’ by survey results from parents, representing another opportunity for potential individual misclassification. Such misclassification could result in diluting any true difference in outcome between the groups.

EXPERIMENTAL STUDIES

Laboratory investigations, involving multiple experimental models and different mammalian species, are a critical step in identifying cellular targets, mechanisms, and potential interventions relevant to anesthesia-associated neurotoxicity in the developing brain. It is well documented that the brains of rats, mice, guinea pigs, and nonhuman primates [16–35,36] are particularly sensitive to the apparent toxic effects of sedatives and anesthetics, as well as alcohol and antiepileptic drugs, specifically around the period of rapid synaptogenesis or the ‘brain growth spurt’. Further, this morphologic damage seen in animal models has been shown to be dose-dependent, at times occurring with exposure to subanesthetic doses [21,24–26], and often associated with lasting cognitive and behavioral deficits [20,22,29,33].

Fetal and neonatal animal models within the experimental literature implicate a role for two familiar drug classes in this observed neurotoxicity, including n-methyl-D-aspartate (NMDA) receptor antagonists (ketamine [16,20–22,31] and nitrous oxide [18,30,32]) and GABA<sub>A</sub> receptor potentiating drugs (midazolam [18,21,30], diazepam [17,19,20], clonazepam [17,19], pentobarbital [17], phenobarbital [17,19], thiopental [22], isoflurane [18,24,28–30,32], sevoflurane [26–29], and desflurane [29]), as well as those with mixed activity (propofol [22,25] and ethanol [17]). Likewise, comparable neurotoxicity has been seen with several antiepileptic drugs [19]. Some studies have suggested that xenon, which has anesthetic properties, and dexmedetomidine, which is clinically used as a sedative, have no neurotoxic effects and may in fact be protective against anesthesia-associated neurotoxicity [37–40].

During the annual period of review, many avenues of this complicated experimental subject have been further explored. Of these many avenues, we have highlighted a few, including studies comparing the differential toxicity of agents, morphological changes to the neuropil after anesthesia exposure, and possible neuroprotective strategies.

Anesthetics, analgesics, and sedatives have different neurotoxic potential in the laboratory

It remains unclear whether anesthetics differ in their toxicity [28,29]. A new study in neonatal rats (exposed at postnatal day 7 (P7); 1 minimum alveolar concentration (MAC) × 4 h) demonstrated neurocognitive deficits as adults (age P75) in both short-term and early long-term memory in those exposed to isoflurane, whereas those exposed to sevoflurane had only early long-term memory
deficits, both compared with unexposed controls [41\(^a\)]. A study in nonhuman primates demonstrated less neuronal and glial apoptosis in both fetal (gestational age 120 of 165 days; G120) and neonatal (P6) rhesus macaques exposed to 5 h of propofol [42\(^a\)] as compared to isoflurane anesthesia in a previous study using the same model [34]. Of note, the neuro-developmental stage of a G120 versus P6 rhesus macaque corresponds with a slightly preterm to mature human neonate, or a 4–6-month-old human infant, respectively. For both age groups, the above propofol study [42\(^a\)] also demonstrated that apart from neurons (50% of the apoptotic cell load), 50% of the cells undergoing apoptosis were from the pool of young oligodendrocytes (just beginning myelination). Similar cell-specific injury was seen after isoflurane anesthesia [36\(^a\),43\(^a\)].

Two recent studies evaluated the effects of repeated morphine exposures in the developing mammal brain and reported conflicting results. One group [44\(^a\)] observed that neonatal rats given a single morphine injection at P7 or P15 (10 mg/kg) did not have evidence of cortical neuronal apoptosis, as opposed to rats that received propofol. Similarly, neonatal rats given daily morphine injections for a week (P7-P15 and P15-P20) did not have evidence of altered neuronal dendritic spine density, whereas those given a single propofol exposure at P7 or P15 did. A separate group [45\(^a\)] observed increased neuroapoptosis after repeated morphine injections in neonatal rats (P1-P7) given a more frequent dosing interval (10 mg/kg twice daily).

**Anesthesia-induced toxicity affects multiple cell types and cell structures in the brain**

As mentioned above, new evidence suggests that anesthetics not only affect neurons in the developing brain, but also target certain other cell types and specific sub-cellular structures. Recent work evaluates anesthetic effects on oligodendrocytes in a non-human primate model [36\(^a\),42\(^a\),43\(^a\)]; postmitotic neurons, GABAergic interneurons, and astrocytes of neonatal mice [46\(^a\)]; and on the cytoskeleton of cultured rat astrocytes [47\(^a\)].

Although evidence suggests oligodendrocytes are particularly sensitive to toxicity from isoflurane and propofol, especially when they are just beginning to myelinate axons [36\(^a\),42\(^a\),43\(^a\)], astrocytes may be more resistant to anesthesia-associated neurotoxicity than neurons [46\(^a\),47\(^a\)] and presumably as compared to these young oligodendroglia.

Anesthetics apparently also specifically affect the developing axon [48\(^a\)]. Recent in-vitro experiments found that the percentage of developing axons (polarized neurons) decreased in cultured embryonic mouse neurons treated for 4 h under moderate-to-higher isoflurane concentrations (1.2–3.0%) and when exposed to 2.4% isoflurane for 4–8 h, indicating a time and concentration-dependent effect. Similarly, neuronal polarity decreased after exposure to propofol, and both the isoflurane and propofol effects were independent of GABAA receptor mediation. [48\(^b\)].

A second report from the same group describes altered responses to guidance cues during axonal growth in another in-vitro mouse model exposed to isoflurane or propofol [49\(^a\)]. Further, they demonstrate this with clinically relevant concentrations of these drugs and show a concentration-dependent effect. Additionally, they show similar inhibited responses to growth cues with thiopental or midazolam, less inhibition with ketamine or nitrous oxide, and none with fentanyl or dexmedetomidine. Anesthesia-associated abnormal axonal growth could be a morphologic phenotype of anesthesia-related injury that is separate from neuronal apoptosis.

New evidence from the laboratory suggests that exposure to anesthetics also affects cell organelles, especially mitochondria, and changes cellular mechanisms. A recent study in neonatal rats exposed to a mixed anesthetic of midazolam, nitrous oxide, and isoflurane demonstrated increased mitochondrial fission within neurons and associated increases in brain reactive oxygen species (ROS) after exposure [50\(^a\)]. Another group used a human neural stem cell model to show similar increases in mitochondrial fission and ROS with associated apoptosis after exposure to ketamine [51\(^a\)], with less apoptosis if ketamine was given concomitantly with a ROS scavenger. Another study reported up-regulated inflammatory markers following serial sevoflurane exposures in neonatal mice [52\(^a\)]. Future experiments should seek to identify whether these changes are the results of a more proximal injury mechanism, or if they are the ultimate triggers leading to cell death.

**Experimental strategies to protect the brain from anesthesia-induced toxicity**

Potential neuroprotective agents for anesthesia exposure in neonatal rodent models have been previously identified, including co-administration of erythropoietin [53], bumetanide [54], L-carnitine [55], xenon [37,38], dexmedetomidine [39,40], melatonin [56], and lithium [57]. Some studies also observed an improvement in functional outcome in rodents when erythropoietin [53], xenon [38], or dexmedetomidine [39] was applied in conjunction with the anesthetic exposure.

During the year in review, several studies were published testing new potential neuroprotective strategies against anesthesia-induced toxicity in the developing brain, and furthering the literature...
on lithium and L-carnitine as protective agents, but complicating the view of xenon as protective.

Xenon, which others have described as neuroprotective [37, 38], was found to be neurotoxic following exposure to this anesthetic gas using a neonatal rat hippocampal slice model [58**]. The slice preparations were exposed to xenon, isoflurane, or sevoflurane (0.75, 1, or 2 MAC each) for 6h. Although 0.75 MAC of xenon (normobaric conditions) did not cause significant apoptosis, exposure to xenon at both 1 and 2 MAC (hyperbaric conditions) resulted in significant neuronal death in several hippocampal regions. At 1 MAC, the injury was smaller with xenon compared with isoflurane or sevoflurane.

A preconditioning (or ‘stress’-inducing pretreatment) paradigm was tested in a model of immortalized human neuroprogenitor cells. The data demonstrated that a short period of isoflurane ‘pre-conditioning’ can mitigate the toxic effects of a more prolonged exposure to isoflurane [59**]. Similar results were noted with isoflurane pretreatment in the neonatal rat hippocampal slice model experiments with xenon listed above [58**].

L-carnitine was again tested as a possible neuroprotective agent, using a neuronal culture model of anesthesia toxicity [60**]. The data showed that ketamine-treated neurons demonstrated oxidative stress-associated DNA damage, and when L-carnitine was administered with ketamine this damage was completely abolished.

Another study described increased neuroapoptosis in neonatal rats given ketamine that was reduced by joint lithium administration [61**]. They further suggest a potential mechanism for this protection, which involves diminishing the ketamine-induced activation of signaling elements (phospho-AKT and GSK-3β), whereby the activation of these elements has been associated with neurodegenerative disease [62].

The neuroprotective potential of adding hydrogen gas to the carrier gas of an inhaled anesthetic was tested in a neonatal mouse model [63**]. The mice with concomitant hydrogen exposure demonstrated less oxidative stress, reduced apoptosis, and improved functional outcomes at 13 weeks, as compared with those exposed to sevoflurane alone. Importantly, the association with less oxidative stress suggests a possible antioxidant mechanism for these effects [63**].

Lastly, co-administration of pramipexole, a drug known to protect mitochondrial integrity, was tested in the neonatal rat. Animals exposed to a mix of midazolam, isoflurane, and nitrous oxide in addition to pramipexole had much improved cognitive capacity as adults compared with those that received the anesthetic without pramipexole [64**].

**CONCLUSION**
We have ample evidence that untreated pain is bad for the developing brain, and an ethical obligation to provide safe anesthesia and sedation for our pediatric patients. The currently available clinical evidence suggests lasting cognitive effects may result from anesthesia exposure during the critical brain maturation period from infancy into childhood, and may be more likely with longer or repeated exposures. This latter concept seems especially important for our ambulatory population who often undergo multiple anesthetics (e.g., myringotomy tubes; lumbar punctures, bone marrow aspirations, and neuroimaging for cancer patients). It remains difficult to reconcile the observed neurocognitive effects with those that could be related to the indication for surgery, the surgery itself, or other genetic or environmental factors. Continued experimental evidence from several fetal and neonatal mammalian models argues that such an injury phenotype in humans is scientifically plausible. That being said, we still do not have discrete proof that such an entity exists in humans receiving modern anesthesia care.

We look forward to results expected from the GAS, PANDA, and MASK studies, which should shed further light on a possible injury phenotype in humans.

The SmartTots website (http://www.smarttots.org) remains an excellent resource for up-to-date information on this subject both for providers and families.

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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


This study analyzes a birth cohort from Minnesota and reports a nearly two-fold higher risk for a diagnosis of ADHD by age 19 when the child was exposed to two or more anesthetics before age 2. The data suggest no increased risk for an ADHD diagnosis with a single exposure. The retrospective design, by principle, limits broader interpretation of these results.


This is an observational cohort study involving a prospectively obtained database, comparing neurocognitive testing in children exposed to either one or multiple anesthetics before age 3. Although confounders remain, they note deficits in abstract reasoning and language, even after a single exposure.


PANDA study design and preliminary results are reported in this article.


This neonatal rat study compared equivalent sevoflurane and isoflurane exposures, and detected differences in cognitive testing at adulthood.


A comprehensive analysis of the associated giall and neuronal injury from propofol exposure is presented in this evaluation of fetal and neonatal rhesus macaques. Further, the propofol-related injury is compared with similar exposures in the same nonhuman primate model with isoflurane (References [35] and [36] above), demonstrating significantly more injury following equitant exposure iso-flurane anesthesia at this stage of brain development, which corresponds to that of a human neonatal primate.


Giall and neuronal injury in fetal rhesus macaques from isoflurane exposure was first described in this report. As the same group described in neonatal rhesus after similar isoflurane exposure, young oligodendroglia appear highly vulnerable to the injurious effects of isoflurane at this earlier stage of brain development.


This group evaluated neuroapoptosis in the somatosensory and medial prefrontal cortices in neonatal rats exposed to single or multiple morphine doses. Further, they carefully evaluated changes to the dendritic architecture of pyramidal neurons. They did not appreciate differences in apoptosis or dendritic spine density when comparing the groups. Of note, propofol exposure was used as a positive control.

Bajic D, Commons KG, Soniano SG. Morphine-enhanced apoptosis in selective brain regions of neonatal rats. J Dev Neurosci 2013; 31:258–266.

This group carefully evaluated the brains of neonatal rats exposed to twice daily morphine for the first week of life, and noted increased apoptosis in several brain regions.


This group comprehensively evaluated for neuronal apoptosis in neonatal rat (P7) exposed to 6% isoflurane, when assessed immediately postexposure. They report the involvement of several specific cell types including GABA-ergic interneurons and postsynaptic neurons.
Different studies have examined the effects of general anesthesia on neural development and function, primarily using rodent models. Isoflurane, a commonly used inhalation anesthetic, has been shown to affect the cytoskeleton in developing neural tissue 


Using a model of cultured rat astrocytes, these authors show decreases in cytoskeletal proteins with unaltered gross motility after exposure to isoflurane. They were also able to show that the growth medium from these exposed cells could still nourish the growth of a neuronal culture.


The authors use a model of dissociated neurons obtained from mouse neocortex, and demonstrate disruption in the neuronal processes (polarization) after isoflurane or propofol treatment.


This group demonstrated disrupted responses to guidance cues in the growing axon in response to several anesthetic agents, in this in-vitro mouse model.


The authors demonstrate that neonatal rats exposed to midazolam, nitrous oxide, and isoflurane have increased mitochondrial fission and ROS.


Using a model of human neural stem cells, this group demonstrates an increase in ROS and mitochondrial fission after ketamine exposure.


This group shows that neonatal mice given several sevoflurane exposures have signs of neuroinflammation and cognitive impairment.


This effect is mitigated when preceded by a 0.75 MAC isoflurane pretreatment.


Using a model of human neuroprogenitor cells, this group demonstrates that a 1-hour pretreatment with isoflurane can decrease the neurotoxic effects of a more prolonged and future exposure. They also carefully show that several calcium receptors are likely behind this observed effect, and theorize how isoflurane could logically be both neuroprotective and neurotoxic.


This group demonstrates in cultured neurons that a 24-h exposure to ketamine causes an increase in the NR1 subunit of the NMDA receptor. Also, when one then removes ketamine from the system, the receptors have an exaggerated response (calcium influx) to NMDA activation that may lead to cell death. Specifically, this response appears extracellular calcium dependent and is also associated with increases in ROS. They further show that these responses are mitigated with L-carnitine.


Using a neonatal rat model, this group demonstrates a role for two specific cell-signaling proteins (protein kinase B (AKT) and glycogen synthase kinase-3β) in anesthesia-associated neurotoxicity. Further, these cell signal changes are mitigated with concomitant lithium exposure.


58. Brosnan H, Bickler PE. Xenon neurotoxicity in rat hippocampal slice cultures is similar to isoflurane and sevoflurane. Anesthesiology 2013; 119:335–344.

These experiments evaluate for cell death in a neonatal rat hippocampal slice culture model exposed to 0.75, 1, and 2 MAC of xenon, isoflurane, or sevoflurane for 4 h. Importantly, they are the first to demonstrate that xenon at 1 MAC and above is neurotoxic. Significant apoptosis results after 1 and 2 MAC of each agent.


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This group demonstrates less neurotoxicity in neonatal mice given sevoflurane when hydrogen is added to the carrier gas. They suggest a potential antioxidant mechanism for this effect.


These experiments suggest that pramipexole could potentially protect against the negative cognitive effects of an anesthesia exposure in a neonatal rat model. Further, they suggest a possible mitochondrial mediated and/or ROS quenching mechanism for this effect.