NEURAL REGENERATION RESEARCH
www.nrronline.org

Dual effects of $GABA_AR$ agonist anesthetics in neurodevelopment and vulnerable brains: From neurotoxic to therapeutic effects

Dihan Lu, Wen Zhang, Keyu Chen, Xia Feng*

https://doi.org/10.4103/NRR.NRR-D-24-00828

Date of submission: September 4, 2024

Date of decision: September 30, 2024

Date of acceptance: November 10, 2024

Date of web publication: December 7, 2024

From the Contents

Abstract

Debates regarding the specific effects of general anesthesia on developing brains have persisted for over 30 years. A consensus has been reached that prolonged, repeated, high-dose exposure to anesthetics is associated with a higher incidence of deficits in behavior and executive function, while single exposure has a relatively minor effect on long-term neurological function. In this review, we summarize the dose-dependent neuroprotective or neurotoxic effects of gamma-aminobutyric acid type A receptor agonists, a representative group of sedatives, on developing brains or central nervous system diseases. Most preclinical research indicates that anesthetics have neurotoxic effects on the developing brain through various signal pathways. However, recent studies on low-dose anesthetics suggest that they may promote neurodevelopment during this critical period. These findings are incomprehensible for the general "dose-effect" principles of pharmacological research, which has attracted researchers' interest and led to the following questions: What is the threshold for the dual effects exerted by anesthetics such as propofol and sevoflurane on the developing brain? To what extent can their protective effects be maximized? What are the underlying mechanisms involved in these effects? Consequently, this issue has essentially become a "mathematical problem." After summarizing the dose-dependent effects of gamma-aminobutyric acid type A receptor agonist sedatives in both the developing brain and the brains of patients with central nervous system diseases, we believe that all such anesthetics exhibit specific threshold effects unique to each drug. These effects range from neuroprotection to neurotoxicity, depending on different brain functional states. However, the exact values of the specific thresholds for different drugs in various brain states, as well as the underlying mechanisms explaining why these thresholds exist, remain unclear. Further in-depth exploration of these issues could significantly enhance the therapeutic translational value of these anesthetics.

Key Words: brain; central nervous system; cognition; gamma-aminobutyric acid type A receptor agonist; general anesthetics; neurogenesis; neurological disorders; neuroprotection; neurotoxicity; signal pathways

Introduction

The advancements in modern anesthesia have enabled more infants and young children to undergo necessary surgeries or procedures based on their medical conditions. During early postnatal development, the developing brain of mammals are in a dynamic and critical state, which influences future neurological function and renders the brain highly vulnerable to various stimuli—a condition often referred to as the "fragile brain" (Jevtovic-Todorovic and Brambrick, 2018; Kelly et al., 2023). The exuberant neural regeneration process during this period has sparked increased attention and debate regarding the impact of general anesthesia on the developing brain (Vutskits and Xie, 2016; McCann and Soriano, 2019; Ing et al., 2022). In 1999, *Science* reported the potential neurotoxicity associated with anesthetic agents (Ikonomidou et al., 1999), leading to a surge of foundational research focusing on the effects of anesthesia drugs, particularly gamma-aminobutyric acid type A receptor ($GABA_AR$) agonist sedatives (such as sevoflurane, midazolam, and propofol), on the immature mammalian brain (Jevtovic-Todorovic et al., 2003; Cattano et al., 2008; Satomoto et al., 2009; Wang et al., 2020; Sun et al., 2022; Zhang and Li, 2023). Early laboratory studies often concluded that exposure to general anesthesia shortly after birth can induce long-term morphological and functional changes in the central nervous system (CNS), resulting in impaired neurocognitive function (Hudson and Hemmings, 2011). However, these studies typically used dosages based on equivalence, resulting in significantly higher plasma and effect-site concentrations in rodents—nearly 10-fold higher—than in humans (Shortal et al., 2018; Anderson and Bagshaw, 2019). This approach has resulted in uncertainty about the applicability of these findings to clinical practice. To date, comprehensive studies observing the effects of anesthesia on neurodevelopment under varying anesthesia states and drug dosages are lacking. $GABA_AR$ agonists are a class of sedative drugs that enhance the inhibitory effects of the neurotransmitter gamma-aminobutyric acid (GABA) on the CNS. By binding to $GABA_ARs$, these drugs promote the opening of chloride channels, which hyperpolarizes neurons and reduces their activity, leading to sedation, anxiolysis, and, at higher doses, anesthesia. Well-known $GABA_AR$ agonists include benzodiazepines (e.g., diazepam, midazolam), barbiturates (e.g., phenobarbital) and commonly used anesthetics such as propofol and sevoflurane. In recent years, newer drugs targeting $GABA_ARs$ with improved safety profiles and reduced side effects have emerged. One example is remimazolam, an ultra-short-acting benzodiazepine approved for procedural sedation, which offers more controlled sedation with rapid recovery in comparison with traditional benzodiazepines and is widely used in current general anesthesia as a sedative drug.

Currently, widely used sedatives in clinical practice include $GABA_AR$ agonists, N-methyl-D-aspartate receptors (NMDAR) antagonists, and α2-adrenergic receptor agonists. Due to the differences in the specific receptor-binding processes, the effects of different types of anesthetics under the same conditions vary, limiting the scope for a unified discussion. Moreover, other vital drugs (such as ketamine and dexmedetomidine) have already been thoroughly reviewed recently. Accordingly,

Department of Anesthesiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong Province, China
***Correspondence to:** Xia Feng, MD, PhD, fengxia@mail.sysu.edu.cn.
https://orcid.org/0000-0001-8182-9803 (Xia Feng)

How to cite this article: *Lu D, Zhang W, Chen K, Feng X (2026) Dual effects of $GABA_AR$ agonist anesthetics in neurodevelopment and vulnerable brains: From neurotoxic to therapeutic effects. Neural Regen Res 21(1):81-95.*

since the anesthetics discussed here are mainly $GABA_AR$ agonists, we will explore the translational potential of existing $GABA_AR$ agonist sedatives from the developing brain to aging, as well as different CNS disease models, which are together recognized as "vulnerable brains," based on their roles in various aspects of neurological function.

In this review, we will first outline the specific effects and underlying mechanisms of anesthesia on the neurological development of the brain, discuss the current research landscape, and highlight valuable avenues for future investigation.

Search Strategy

The articles cited in this review were published between January 1, 1997 and September 1, 2024 and were retrieved from the PubMed database using the following words and phrases to maximize search specificity and sensitivity: "anesthesia OR anaesthesia OR anesthetic OR anaesthetic OR $GABA_AR$ agonist," "neurotoxicity," "neurogenesis," "brain," "development OR developing OR develop," "cognitive function," "dose," "dual effect," "neonate OR young OR child OR children," "aged," "neuroprotective OR neuroprotection," "apoptosis," "mechanism," "synaptic plasticity," "neuroinflammation," "single or once," "repeated," "ferroptosis," "autophagy," "neuron OR nerve OR neuro OR neuronal," "signal OR signaling pathway," "clinical OR clinic," "CNS diseases," "cerebral ischemia–reperfusion injury," "traumatic brain injury," "neonatal hypoxic-ischemic brain injury," "ischemic stroke," "middle cerebral artery occlusion," "controlled cortical impact," "intracerebral hemorrhage," "subarachnoid hemorrhage," "delayed cerebral ischemia," "brain injury," "autism spectrum disorders," "attention deficit and hyperactivity disorder," "neural developmental disorder," "Alzheimer's disease," "Parkinson's disease," "neurodegeneration disease," "aging OR aged OR age OR old OR elder or elderly." Various combinations of these keywords were used to comprehensively retrieve full-text articles, and all papers were screened by titles and abstracts. A total of 191 articles related to our research objectives were included. No restrictions related to language were applied. All authors were involved in the literature search.

Neurotoxicity and Mechanisms of $GABA_AR$ Agonist Sedatives in Developing Brain

Since the publication of a study describing the potential widespread neurotoxicity of NMDAR antagonists in the developing brain in 1999 (Ikonomidou et al., 1999), clinicians and researchers have raised profound concerns regarding the neurotoxicity of anesthetics. Answering this question requires high-quality, convincing clinical studies, but such clinical studies require extensive time and large sample sizes. Therefore, early published researches were predominantly preclinical studies (**Figure 1**).

Preclinical studies

Animal studies

Numerous animal studies have demonstrated that early-life exposure to general anesthesia can result in structural brain damage and short- or long-term cognitive impairments (Sun et al., 2022; Wang et al., 2020; Zhang and Li, 2023). In these experiments, researchers primarily focused on isoflurane, ketamine, sevoflurane, propofol, and etomidate (Yang et al., 2020; Bleeser et al., 2023b). Overall, the findings of these studies indicated that increased exposure time and dose are correlated with more significant neurotoxic effects on the nervous system. Studies investigating the neurotoxicity of $GABA_AR$ agonists have used young mice, rats, and rhesus monkeys as models (Chinn et al., 2020; Bleeser et al., 2023a). For instance, newborn postnatal day 7 (P7) mice treated with three doses of 200 mg/kg of propofol showed anxiety-like and compulsive behaviors at 4 months (Zhou et al., 2021). Similarly, P7 rats exposed to 0.75% isoflurane for 6 hours exhibited emotional behavioral changes at around 11 weeks of age (Diana et al., 2020). Additionally, P6 mice exposed to 3% sevoflurane for 6 hours developed learning deficits at 8 weeks of age and showed social behavioral abnormalities at 14 weeks of age (Satomoto et al., 2009). Moreover, newborn rhesus monkeys exposed to three sessions of 0.7%–1.5% isoflurane anesthesia for 5 hours displayed motor reflex deficits after 1 month and increased anxiety responses to new social environments at 12 months (Coleman et al., 2017). These studies indicate that exposure to these levels of anesthesia during the neonatal period can have enduring effects on learning, emotional, and social cognitive behaviors.

The typical related neurotoxic effects studied were as follows: (1) Apoptosis: Anesthetics can induce neuronal apoptosis through intrinsic and extrinsic pathways (Yon et al., 2005). Susceptibility to anesthesia-induced neuronal apoptosis varies with age at exposure, showing peaks in neurogenesis and natural cell death that can extend into adulthood for certain regions (Deng et al., 2014). (2) Synaptic plasticity: Exposure of P7 rats to 2.5% isoflurane reduces synaptic density, and a single 2-hour exposure alters synaptic postsynaptic density lengths and dendritic spine morphology (Amrock et al., 2015). Newborn rats exposed to 2% sevoflurane for 2 hours exhibit synaptic ultrastructural damage in the hippocampal CA3 region (Sun et al., 2019). Isoflurane and sevoflurane can also inhibit synaptic transmission and long-term potentiation (LTP) in a concentration-dependent manner (Haseneder et al., 2009). (3) Neuroinflammation: Repeated exposure of newborn mice to 3% sevoflurane for 2 hours induces neuroinflammation, including

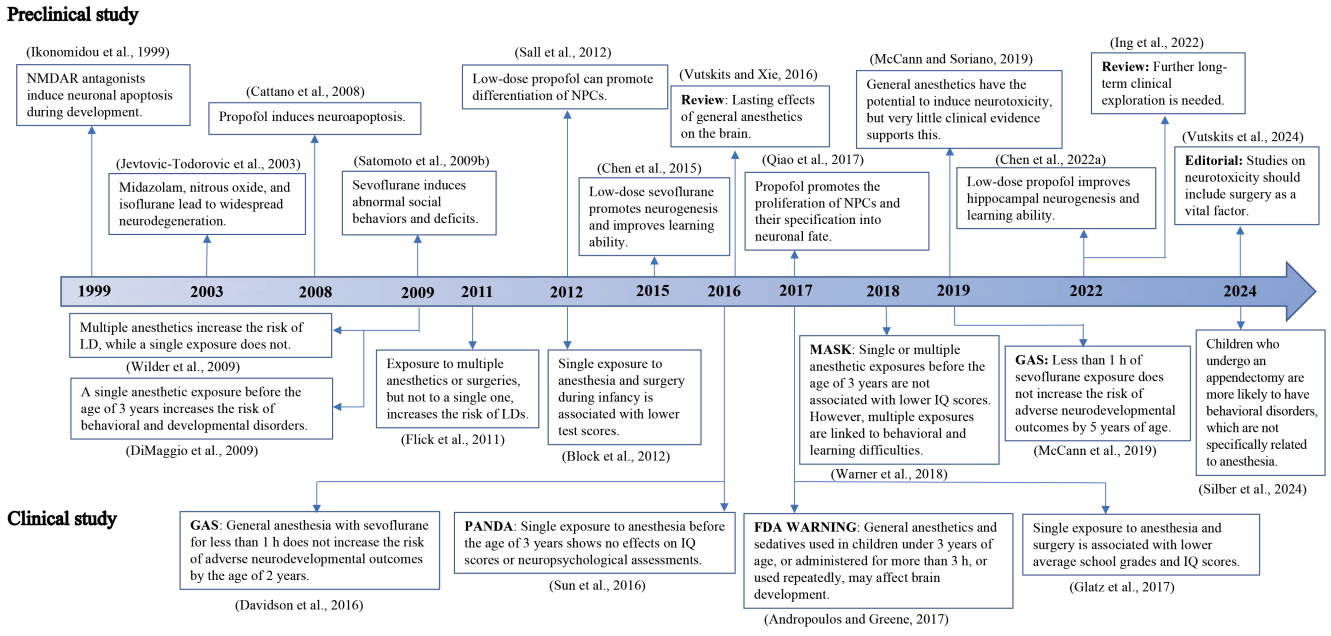

Figure 1 | **Timeline illustrating the neurological effects of anesthetics on development in research.**
FDA: The Food and Drug Administration; GAS: The general anesthesia compared with spinal anesthesia; IQ: intelligence quotient; LD: learning disability; MASK: Mayo Anesthesia Safety in Kids; NMDAR: N-methyl-D-aspartate receptors; NPCs: neural progenitor cells; PANDA: the pediatric anesthesia neurodevelopment assessment.

microglial activation and increased levels of pro-inflammatory cytokines (Shen et al., 2013), which are possibly related to enhanced transcriptional activity of nuclear factor-κB (NF-κB) and microglial polarization (Zhang et al., 2013a; Xu et al., 2023). In addition, sevoflurane can also inhibit M2 activation (Pei et al., 2017). (4) Ferroptosis: Recent studies have shown that sevoflurane leads to cytoplasmic and mitochondrial iron accumulation in the hippocampal neurons of newborn rats (Wu et al., 2020; Kang et al., 2024). Isoflurane enhances cytochrome c oxidase/complex IV activity in a dose- and time-dependent manner, inducing ferroptosis in hippocampal neurons (Liu et al., 2021). (5) Autophagy: Exposure to 3.4% sevoflurane for 4 hours daily for 3 days in newborn rats increases autophagic vacuoles in hippocampal neurons (Xu et al., 2018b), potentially inducing cognitive impairment in young mice (Wang et al., 2019) that is possibly related to endoplasmic reticulum stress (Zhang et al., 2023). In conclusion, the toxic effects associated with the neurotoxicity of anesthetics include but are not limited to the above aspects, with the related research being relatively comprehensive.

In vitro studies

The establishment of *in vitro* cell culture systems has provided further evidence of the developmental neurotoxicity of $GABA_AR$ agonists (Chinn et al., 2020). An early study using primary hippocampal neuron cultures found that exposure to 100 μmol/L propofol for 3 hours increased neuronal apoptosis and significantly reduced neuron viability (Tu et al., 2019). Similar results were observed after exposure to 3.4% sevoflurane for 1, 2, or 5 hours (Xu et al., 2018c). Additionally, rat cortical primary neurons exposed to 1.8% isoflurane for 6 hours showed a significant decrease in the levels of pre- and postsynaptic proteins synapsin-1 and Homer-I (Xu et al., 2018a).

With advancements in stem cell research, one study utilized *in vitro* cultured neural stem cells (NSCs) and found that treatment with 1.4% and 2.8% isoflurane for 6 hours resulted in a reduction in the number of $BrdU^+Sox2^+$ cells 6 or 24 hours after treatment, indicating decreased levels of cell proliferation post-treatment (Culley et al., 2011). Additionally, mouse NSCs exposed to 100 μmol/L propofol for 6 hours exhibited increased apoptosis, along with elevated levels of apoptosis-related proteins (Zhang et al., 2022).

Organoid models provide physiological systems that can effectively simulate various diseases and indicate tissue responses to drugs and injuries (Lee et al., 2017, 2022; Chhibber et al., 2020; Li et al., 2024; Zhou et al., 2024). One study reported that human-induced pluripotent stem cell (hiPS)-derived midbrain organoids exhibited significantly reduced cell proliferation after exposure to 2% sevoflurane for 6 hours, including premature differentiation of dopamine neurons (Shang et al., 2022). This evidence partially confirms that $GABA_AR$ agonists exhibit neurotoxic effects *in vitro* at specific exposure levels.

Related molecular mechanisms

Anesthetics such as $GABA_AR$ agonists are widely believed to directly act on $GABA_ARs$ in the CNS to induce reversible loss of consciousness, amnesia, and sedation (Yin et al., 2019; Muheyati et al., 2024). However, the broad spectrum of developmental neurotoxicity observed in earlier studies exhibits significant dose and concentration dependencies that cannot be solely explained by the action of $GABA_ARs$ (Ji et al., 2019; Xu et al., 2023). Therefore, numerous studies have speculated that these effects are likely mediated through the induction of shared signaling pathways (Friese et al., 2023), including the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) (Perluigi et al., 2015; Xu et al., 2018a; Liang et al., 2022a; Friese et al., 2023), c-Jun N-terminal kinase (JNK)/c-Jun (Li et al., 2013; Bi et al., 2018; Liang et al., 2020), and wingless-type mouse mammary tumor virus integration site (Wnt)/β-catenin pathways (Zhang et al., 2013c; Fang et al., 2017; Ma et al., 2017; Liu et al., 2018; Wang et al., 2021a) and certain microRNAs (miRNAs) (Xu et al., 2019a; Wang et al., 2021b; Zhang et al., 2022). Given the wealth of research in this area, a detailed discussion of these studies is beyond the scope of this review.

In addition to the aforementioned pathways, recent attention has also focused on changes in mitochondrial homeostasis regulation (Feng et al., 2024; Jia et al., 2024). A previous study has shown that exposure of P7 rats to 0.75% sevoflurane for 6 hours leads to long-term alterations in mitochondrial morphology and distribution and neuronal damage (Sanchez et al., 2011). Furthermore, propofol-induced inhibition of mitochondrial membrane potential promotes hippocampal neuronal mitochondrial damage in a dose-dependent manner (Liang et al., 2022b). Additionally, exposure to 1.4% isoflurane in mice leads to imbalances in mitochondrial dynamics, resulting in oxidative stress and energy deficiency and ultimately leading to neurotoxicity (Lu et al., 2020). Moreover, propofol-induced neuronal cell death via cyclin-dependent kinase 1 (CDK1)/dynamin-related protein 1 (Drp1)-mediated mitochondrial fission and mitochondrial permeability transition pore (mPTP) opening can be partially reversed by mitochondrial fission inhibitors (Twaroski et al., 2015).

Furthermore, ongoing research is investigating whether $GABA_AR$ agonists exert neurotoxic effects through $GABA_AR$-related mechanisms (Gascoigne et al., 2021). Wang et al. (2024) demonstrated that the $GABA_AR$ α5 subunit in mice is related to sevoflurane-induced partial impairments in long-term learning and memory. Additionally, isoflurane disrupts axonal growth cone guidance through $GABA_ARs$, affecting neuronal circuit assembly and neural circuit formation and thereby exerting detrimental effects on developing brains (Mintz et al., 2013). The effects of sevoflurane on growth cone sensing are also believed to be mediated by the $GABA_AR$ α2 subunit, and this process depends on developmental chloride ion gradients (Xu et al., 2019b). Additionally, $GABA_AR$ depolarization-mediated activation of voltage-gated calcium channels, which leads to increased intracellular calcium levels, is thought to be involved in sevoflurane-induced developmental neurotoxicity and cognitive impairments (Zeng et al., 2022) as well as stress-related cognitive impairments (Liu et al., 2016).

In summary, multiple preclinical studies on the developmental neurotoxicity of $GABA_AR$ agonists have been conducted over the past few decades, and have yielded exceptionally fruitful research outcomes. However, clinical research is essential when discussing how anesthetics affect developmental neurofunction. Therefore, as research progresses, influential clinical studies will continue to be published, playing a crucial role in advancing this field of study.

Clinical studies

The aforementioned foundational studies largely suggest that specific exposures during anesthesia procedures can impair developmental brain neurofunction. Meanwhile, several meta-analyses have shown that children with single or multiple exposure to anesthetics show more behavioral problems, worse executive function, and higher incidences of neurodevelopmental disorder diagnoses than those without exposure to anesthetics (Reighard et al., 2022). Since clinical research holds greater practical value closer to human scenarios, this section will first analyze and discuss the clinical studies describing "developmental neurotoxicity."

Among the studies that used academic performance as an outcome, a retrospective study conducted in 2012 focused on 287 children in Iowa who underwent surgery during infancy. The study found that the average exam scores of the participants were significantly lower than the expected normative values, with a higher proportion performing poorly academically (Block et al., 2012). Additionally, in 2017, a retrospective cohort study in Sweden found that children who underwent a single instance of anesthesia and surgery had lower average school grades and intelligence quotient test scores at military conscription at 18 years of age in comparison with unexposed children (Glatz et al., 2017).

Furthermore, among studies that utilized clinical diagnoses, a retrospective birth cohort study conducted in Olmsted County involving 5357 children born between 1976 and 1982 found no increased risk of learning disabilities associated with a single exposure to anesthesia. However, children who were exposed to two or more anesthetic drugs showed an increased risk of learning disabilities, with the risk rising in proportion to the cumulative duration of anesthesia exposure (Wilder et al., 2009). A subsequent matched-cohort study, which accounted for health status, confirmed this conclusion (Flick et al., 2011). Additionally, a study by DiMaggio et al. involving children enrolled in the New York State Medicaid program between 1999 and 2001 found that children under 3 years of age who underwent hernia repair were more than twice as likely to be diagnosed with developmental or behavioral disorders than those in the control group (DiMaggio et al., 2009).

Neuropsychological testing is also used as a highly valued evaluation indicator (Block et al., 2012). In terms of IQ score, a 2017 study based on the Netherlands' 'Generation R Study' found that children who underwent anesthesia before the age of 5 years had a lower IQ at 6 years of age than those who did not undergo anesthesia (de Heer et al., 2017). Additionally, a study of healthy volunteers aged 5 to 18 years who were

grouped into those who underwent surgery with anesthesia before the age of 4 years and those who did not revealed that the exposed group scored significantly lower in IQ and listening comprehension (Backeljauw et al., 2015). Prospective neuropsychological testing studies are currently limited, but Warner et al.'s *Mayo Anesthesia Safety in Kids* (*MASK*) study on children in 2018 categorized children into unexposed, single-exposure, and multiply exposed groups on the basis of anesthesia exposure before the age of 3 years and conducted neuropsychological testing at the ages of 8–12 years or 15–20 years (Warner et al., 2018). The results indicated that children in the multiply exposed group showed decreased processing speed and fine motor skills than those in the unexposed group, although this phenomenon was not observed in the single-exposure group. Moreover, parents of children in the multiply exposed group reported more problems of executive function, behavioral, and reading-related issues.

In conclusion, early clinical studies on the neurotoxic effects of anesthetics during neurodevelopment were primarily retrospective cohort studies. These studies are susceptible to confounding factors, such as incomplete data collection and the developmental impact of the surgeries themselves. Additionally, other factors, including underlying neurodevelopmental conditions like prematurity, low birth weight, chromosomal abnormalities, or congenital heart disease, may have also influenced the outcomes. As research in this field has progressed, large-scale prospective clinical studies with high-quality evidence have emerged. In 2016, the Food and Drug Administration (FDA) issued drug safety warnings that echoed the conclusions of foundational research, indicating that general anesthesia and sedation drugs used in children younger than 3 years of age for more than 3 hours or with repeated exposure may affect brain development (Andropoulos and Greene, 2017). While the intensity of the debate surrounding this clinical issue has gradually decreased, the direction of scientific inquiry remains a critical concern for clinical practitioners and researchers, warranting further exploration.

Relative Low-Dose Exposure to $GABA_AR$ Agonist Sedatives Has Minimal Impact on Developing Vulnerable Brain Function

The preceding discussion confirms that the developmental neurotoxicity caused by $GABA_AR$ agonists is concentration- and dose-dependent, and the risk of neurotoxicity increases significantly with longer exposure times. However, several large-scale clinical studies conducted in the early 21st century concluded that a single exposure to anesthesia during surgery has no significant impact on the neurological development of children, particularly with regard to intelligence (Liu et al., 2020; Ing et al., 2021). Thus, the alarming results observed in basic research may not accurately reflect the real-life scenarios observed in children. These findings have led to the need to understand the appropriate approach for drug selection to meet surgical needs as well as determination of drug dosages and administration methods. Subsequent studies are now beginning to investigate $GABA_AR$ agonist administration methods that appear to have no effects on neurodevelopment, potentially offering valuable guidance for clinical drug application.

Clinical studies: single surgery and anesthesia exposure show no effects on neurological function

To further explore the potential neurotoxicity of anesthetics in clinical settings, researchers conducted several large-scale human cohort studies aimed at addressing previous shortcomings such as insufficient sample sizes, non-standardized trial designs, and inadequate consideration of confounding factors. The results of these studies indicate that early, single exposures to general anesthetics do not lead to long-term neurological changes in humans. The studies supporting this conclusion are summarized as follows:

The pediatric anesthesia neurodevelopment assessment study

This study used a sibling-matched cohort design involving 105 pairs of siblings aged 8 to 15 years. The exposed children had a single exposure to anesthesia during inguinal hernia surgery within the first 36 months of life. The results indicated no significant differences in mean IQ scores or neuropsychological assessments between the exposed and unexposed siblings (Sun et al., 2016).

The general anesthesia compared with spinal anesthesia study

This was an international, assessor-masked, randomized controlled equivalence trial conducted in infants. The results at 2 and 5 years of age showed no increased risk of adverse neurodevelopmental outcomes associated with sevoflurane general anesthesia in comparison with awake regional anesthesia (Davidson et al., 2016; McCann et al., 2019).

Mayo anesthesia safety in kids study

A propensity-guided approach was used in this study involving children born in Olmsted County, Minnesota. The results indicated that single or multiple anesthetic exposures before the age of 3 years were not associated with deficits in general intelligence. However, multiple exposures or longer durations of anesthesia may have been linked to decreased processing speed and fine motor abilities (Warner et al., 2018).

Additionally, a subsequent meta-analysis showed that a single exposure to general anesthesia in children was associated with statistically significant increments in parent-reported behavioral problems, but the children showed no difference in general intelligence (Ing et al., 2021). Furthermore, recent research indicates that children who undergo appendectomy are more likely to experience behavioral disorders that are not specifically linked to anesthesia (Silber et al., 2024). Thus, studies on neurotoxicity should consider surgery as a crucial factor (Vutskits and Davidson, 2024).

Preclinical studies: single, short-term, relatively low-dose anesthesia exposure shows no adverse effects on developing mammal brains

The findings of the aforementioned clinical studies indicate that the developmental neurotoxicity associated with pediatric anesthesia may have been overestimated or misunderstood. Therefore, this issue needs to be studied in more detail in basic research studies, and the findings indicate that the appropriate anesthesia exposure does not adversely affect the neurofunction of the vulnerable brain. Although these studies are relatively limited and may be subject to publication bias, a thorough investigation is essential for guiding pediatric anesthesia practices in a clinical setting. In the following paragraphs, we have analyzed these studies, focusing particularly on the effects of different dosages, durations, and frequencies of $GABA_AR$ agonist anesthetics on neurodevelopment.

Drug dosage

The dosage of anesthetic drugs used has been shown to be relevant to neurological outcomes. Studies have demonstrated that exposure to 2% sevoflurane for 2 hours inhibits hippocampal LTP in P7 rats, whereas exposure to 1% sevoflurane for the same duration does not produce this effect (Kato et al., 2013). Additionally, an intraperitoneal injection of 60 mg/kg of propofol in P7 mice resulted in a reduction of $BrdU^+Sox2^+$ cells in the dentate gyrus, significantly inhibiting early neurogenesis in this region, while 30 mg/kg of propofol did not lead to any changes (Huang et al., 2016). Furthermore, treatment with 1.4% and 2.8% isoflurane for 6 hours suppressed the proliferation levels of rat NSCs, but 0.7% isoflurane did not exhibit this toxicity (Culley et al., 2011). These findings suggest that when using the same anesthetics and exposure durations, appropriately reducing the dosage of $GABA_AR$ agonist sedatives may have no significant neurotoxic effect on the developing brain.

Duration

Exposure duration is another key factor influencing neurodevelopmental outcomes. Studies have reported that exposure of P7 rats to 3% sevoflurane for 6 hours resulted in reduced spine density, increased expression of synaptic vesicle-related proteins, damage to the hippocampal synaptic ultrastructure, and impairments in both hippocampal-dependent spatial and non-spatial learning and memory. In contrast, exposure to 3% sevoflurane for just 1 hour did not produce these changes (Xiao et al., 2016). Furthermore, in another study comparing durations, P6 rhesus monkey infants exposed to isoflurane for 3 hours exhibited significantly reduced levels of neuron apoptosis in their brains in comparison with those exposed for 5 hours (Noguchi et al., 2017). These findings suggest that shorter exposure durations may not result in significant neurotoxic effects from $GABA_AR$ agonist sedatives on the vulnerable developing brain.

Frequency

The frequency of exposure is another important aspect that distinguishes neurotoxic effects. Repeated exposure of P7 rats to 2.5% sevoflurane for 2 hours on P7, P10, and P13 resulted in significant synaptic loss and other toxic effects, while single exposures lasting 2 or 6 hours did not produce relevant changes (Amrock et al., 2015). Similarly, newborn rhesus monkeys that

received three 5-hour exposures to isoflurane exhibited motor reflex defects after one month and increased anxiety responses to new social environments at 12 months, whereas single exposures to isoflurane did not lead to significant behavioral changes (Coleman et al., 2017). Additionally, repeated exposure of P7 rats to 75 mg/kg of propofol resulted in significant neuron apoptosis and alterations in excitatory synaptic transmission in various brain regions, while single treatments did not elicit comparable toxic responses (Yu et al., 2013). Furthermore, repeated administration of 200 mg/kg of etomidate to newborn P7 mice led to more pronounced cognitive and behavioral deficits in adulthood in comparison with the deficits observed with single treatments (Zhou et al., 2021). These findings suggest that, in experiments involving the same anesthetic agent, dosage, and duration, single exposures to $GABA_AR$ agonist sedatives during developmental periods do not exhibit significant neurotoxic effects.

After conducting an in-depth review of the published literature on the effects of $GABA_AR$ agonist sedative exposure on the vulnerable brain, we have arrived at a preliminary conclusion: the potential damage caused by general anesthetics during developmental periods is closely linked to various aspects of the treatment strategies, including drug dosage, exposure duration, and frequency. Accordingly, single, short-term, relatively low-dose exposure to $GABA_AR$ agonist sedatives does not significantly affect neurofunction. Thus, the specific role of $GABA_AR$ agonist sedatives in neural development may represent a mathematical "dose-effect" relationship. Consequently, other effects may be observable at lower exposure levels where toxicity is not observed, and additional findings highlighting these effects may be of value.

Sub-Threshold Exposures to $GABA_AR$ Agonist Sedatives May Promote Neurodevelopment

Considering the fact that the doses of $GABA_AR$ agonist sedatives required to achieve anesthesia effects in rodents and even rhesus monkeys (50 to 200 mg/kg) are significantly higher than those needed for clinical infants and young children (1 to 3 mg/kg; Shortal et al., 2018; Anderson and Bagshaw, 2019), the conclusions drawn from basic research cannot be directly applied to the conditions in pediatric procedures. The equivalent drug doses calculated based on body surface area yield blood or effect-compartment concentrations much higher than those observed in the brains of infants and young children undergoing clinical procedures. Consequently, studies have begun to apply $GABA_AR$ agonists at concentrations relevant to clinical sedation, exploring their effects on the developing brain and suggesting that these agents may have a protective effect.

As early as 2012, Philip et al. reported that propofol at a concentration of 7.1 μM can promote the differentiation of neural progenitor cells (NPCs) into neurons *in vitro*, while concentrations greater than 7.1 μmol/L lead to cell death (Sall et al., 2012). Qiao et al. (2017) obtained similar results, demonstrating that 10 μmol/L of propofol promotes NPC proliferation and neural fate specification, whereas 200 μmol/L inhibits NPC proliferation and increases glial fate. However, these studies have not received much attention. Subsequent research showed that a single low dose of propofol (4 mg/kg) can enhance hippocampal neurogenesis in P7 mice, improving their hippocampus-related learning and memory abilities, while a high dose of propofol (50 mg/kg) produced detrimental effects (Chen et al., 2022a). These findings highlight the importance of dose–response relationships in the effects of propofol on the developing brain: high doses have clear damaging effects, while low doses can promote beneficial outcomes.

Similar results have been observed with inhalational anesthetics. Alkire et al. (2005) found that exposure to low concentrations of sevoflurane (0.11%) can enhance memory retention in rats 24 hours later, a phenomenon closely associated with the amygdala. In 2015, Chen et al. reported that low concentrations (1.8%) of sevoflurane anesthesia promote neurogenesis in the hippocampus of newborn rats and enhance learning ability in the hippocampal dentate gyrus. A subsequent study in 2018 corroborated these findings, demonstrating that exposure to low concentrations of sevoflurane (1.2%) in newborn rats improved their learning and memory abilities, which is closely related to synaptic formation (Chen et al., 2018).

Due to the limited attention received by this area of research, the mechanisms underlying the neuroprotection offered by low-dose $GABA_AR$ agonists remain in the early stages of exploration. A previous study investigating the use of low-dose propofol (4 mg/kg) have shown that peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α-mediated oxidative phosphorylation (OXPHOS) activation is involved in promoting neuronal differentiation and enhancing hippocampal-related learning and memory abilities (Chen et al., 2022a). Another study suggests that both low (10 μmol/L) and high (200 μmol/L) doses of propofol exert dual protective effects on neurons by regulating the inositol-1,4,5-trisphosphate receptor (InsP3R) (Qiao et al., 2017). Additionally, different concentrations of isoflurane may influence the survival and neurogenesis of NPCs through differential activation of inositol 1,4,5-trisphosphate (InsP3) or ryanodine receptors located on the endoplasmic reticulum membrane (Zhao et al., 2013). The upregulation of hippocampal NMDAR subunit 2B (NR2B) expression and the activation of extracellular regulated kinase 1/2 (ERK1/2) are also believed to enhance spatial learning without inducing neuronal apoptosis when low concentrations (0.7%) of isoflurane are used (Liu et al., 2014).

Interestingly, although these sedatives are widely recognized to specifically activate $GABA_ARs$, most mechanistic studies have not directly investigated $GABA_ARs$. We believe this oversight may be attributable to several factors: (1) Activation of $GABA_ARs$ alone cannot fully explain the neurofunctional effects produced by low-dose $GABA_AR$ agonists. (2) These drugs are highly lipophilic small molecules that can easily cross lipid bilayers, allowing for a variety of potential effects. Thus, further research is needed to clarify the specific targets and relevant modes of action of these drugs, which will significantly guide future research efforts.

In conclusion, $GABA_AR$ agonist sedatives exhibit dual effects on the developing brain: as the total anesthetic dose increases, their effects transition from protective to neutral and ultimately to damaging (**Figure 2** and **Tables 1–3**). However, the limited number of researchers currently investigating the neuroprotective effects of low-dose $GABA_AR$ agonists has resulted in a scarcity of studies, with no unified definition of the specific threshold for this transition in effects. Moreover, these thresholds are likely to vary across clinical pediatric settings, animal models, and *in vitro* culture systems. We speculate that the diverse mechanisms reported for $GABA_AR$ agonist sedatives, combined with their systemic effects on the human body, contribute to the complex interplay of factors influencing their specific effects on neurofunction at different anesthetic doses. Thus, this issue can be viewed as a "mathematical problem." Future research should focus on assessing thresholds, developing specific effect models, and conducting indicator analyses to further explore this topic.

Neuroprotective Effects of $GABA_AR$ Agonist Sedatives in Central Nervous System Diseases

In the previous section, $GABA_AR$ agonist sedatives were shown to influence the normal neurodevelopmental state of the CNS. Thus, unless studies examining these effects account for the exposure dosage, frequency, and duration, they can be considered to be incomplete. Additionally, beyond the developing brain, other stages of brain function—including aging, brain injury, and neurodevelopmental diseases—should also be included in the definition of "vulnerable brains," which may be at the highest risk of anesthetic-induced neurotoxicity.

Earlier research has suggested that anesthetics may have neuroprotective effects in certain neurological disorders, such as cerebral ischemia-reperfusion injury (CIRI) and traumatic brain injury (TBI) (Yamaguchi et al., 1999; Engelhard et al., 2004). This leads to the reasonable speculation that a certain "threshold" of effect change must exist. However, since the prototypes of exposure in this field are significantly different from the normal neurodevelopmental state mentioned earlier, the corresponding thresholds differ considerably from those observed during normal neurodevelopment. Since clinical studies have paid limited attention to dosage discussions, this section focuses solely on preclinical studies to more clearly elucidate dose-related effects.

In the following sections, we will analyze the research on anesthetics in neurological disorders, focusing on the differences in effects based on the dosage and frequency of exposure to $GABA_AR$ agonist sedatives. We aim to determine whether their protective or toxic effects show any gradient changes in various disease models and to explore strategies for maximizing their neuroprotective

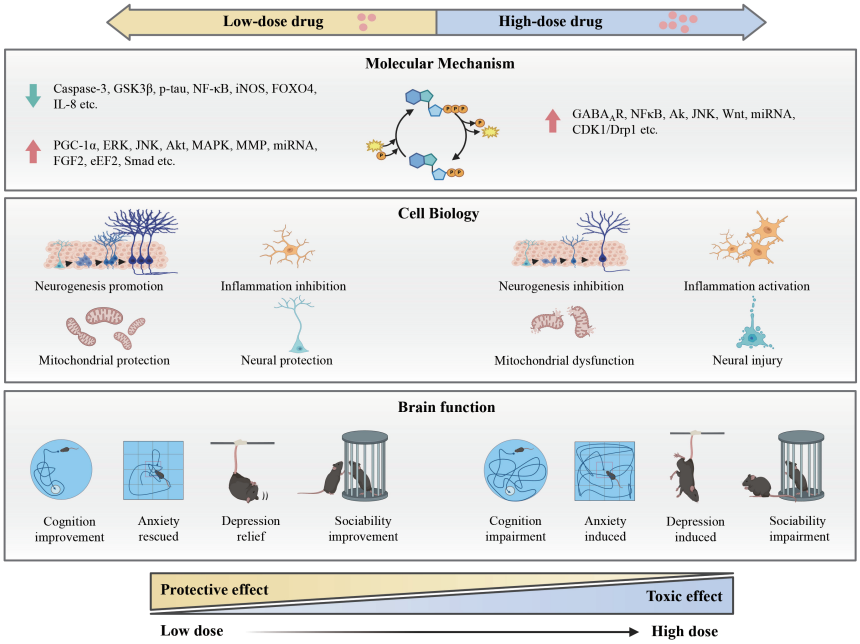

Figure 2 | **Overview of the dual effects of GABA$_A$R agonist anesthetics on neurodevelopment.**
GABA$_A$R agonist anesthetics present dose-dependent dual effects on neurodevelopment. As we mentioned above, low-dose GABA$_A$R agonist anesthetics may interact with multiple molecular signaling pathways to promote neurogenesis, reduce neuroinflammation, enhance mitochondrial metabolism, and protect neurons. Thus, they provide neuroprotective benefits, including improvements in cognitive function, alleviation of anxiety and depression, and enhancements in social abilities. In contrast, high-dose GABA$_A$R agonist anesthetics activate signaling pathways that inhibit neurogenesis, promote neuroinflammation, impair mitochondrial metabolism, and damage neurons, leading to neurotoxicity effects. Created with BioRender.com. Akt: Protein kinase B; CDK1/Drp1: cyclin-dependent kinase 1/dynamin-related protein 1; eEF2: eukaryotic elongation factor 2; ERK: extracellular regulated kinase 1/2; FGF2: fibroblast growth factor 2; FOXO4: forkhead box O4; GABA$_A$R: gamma-aminobutyric acid type A receptor; GSK3β: glycogen synthase kinase-3beta; IL-8: interleukin-8; iNOS: inducible NOS; JNK: Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; miRNA: microRNA; MMP: matrix metalloproteinase; NF-κB: nuclear factor-κB; PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator-1α; Smad: Sma- and Mad-related protein; Wnt: wingless-type mouse mammary tumor virus integration site.

benefits. Furthermore, given the fact that GABA$_A$R agonist sedatives have been shown to promote neurodevelopmental effects at low exposure doses, we will discuss their potential therapeutic applications in current models of intractable neurodevelopmental disorders.

Central nervous system injury models

As early as the last century, propofol and isoflurane were reported to exhibit neuroprotective effects, including inhibition of neuronal death, increased cerebral blood flow, and suppression of excitotoxicity, in models of CIRI and TBI (Yamaguchi et al., 1999; Statler et al., 2000). GABA$_A$R agonist sedatives are now widely accepted to provide certain protective effects in models of neuronal injury; however, further discussion is needed to evaluate the optimal exposure dosage.

Neonatal hypoxic–ischemic brain injury

In neonatal hypoxic-ischemic brain injury (HIBI), excitotoxicity and oxidative stress can lead to delayed cell death and subsequent neurological deficits. Despite the availability of several effective treatment methods for this condition, the mortality and disability rates associated with HIBI remain high (Arnautovic et al., 2024; Yang et al., 2024). Encouragingly, preclinical data suggest that treatment with GABA$_A$R agonist sedatives can improve neurological outcomes in neonatal HIBI models.

Pre-treatment with anesthetics is considered to offer certain protective effects. Pre-exposure to 8.4% desflurane, 1.8% isoflurane, or 3.1% sevoflurane for 3 hours improved adult-like object recognition and performance in water maze tasks in P10 hypoxic–ischemic mice (McAuliffe et al., 2009). Other studies have demonstrated that pretreating postnatal day 6 (P6) mice with 1.5% isoflurane for 30 minutes can mitigate the neuronal damage following HIBI and enhance motor coordination 1 month after ischemia (Zhao et al., 2007). Additionally, pre-treatment with 1.8% isoflurane for 2 hours can reduce mortality rates following HIBI in P9 neonatal mice and improve striatal function in adulthood (McAuliffe et al., 2007).

Furthermore, early intervention following injury also has significant protective effects. In P7 rats subjected to HIBI, exposure to 2.4% sevoflurane for 30 minutes significantly improves learning and memory function, reduces astrocyte proliferation and glial scar formation, increases dendritic spine density, and preserves hippocampal tissue morphology (Gao et al., 2021). The underlying mechanisms suggest that sevoflurane may exert neuroprotective effects by inhibiting autophagy through the inositol-requiring enzyme-1 (IRE1)-JNK-beclin1 signaling pathway (2.4%, 30 minutes) (Niu et al., 2021) or by regulating the enhancer of zeste homolog 2 (Ezh2)-modulated phosphatase and tensin homolog deleted on chromosome 10 (Pten)/Akt/mTOR signaling pathway (2.5%, 30 minutes) (Xue et al., 2019).

Anesthetic exposure in the early post-treatment phase is also considered to be protective. In P7 rats, administration of 1.5% or 2% isoflurane for 30 minutes within 6 hours of left common carotid artery ligation can reduce the decrease in weight and neuron density in both the left and right hemispheres. However, this protective effect is not observed with 1% isoflurane administered within 6 hours or with 1.5% or 2% isoflurane administered after 6 hours (Xu et al., 2016). This suggests that isoflurane post-treatment in neonatal HIBI induces concentration-dependent neuroprotection, with the optimal dosage and timing being crucial. Similarly, a previous study has shown that post-treatment with 2% isoflurane for 1 hour can reduce infarct volume after HIBI in rats via the sphingosine-1-phosphate (S1P)/phosphatidylinositol-3-kinase (PI3K)/Akt pathway, providing long-term neuroprotection (Zhou et al., 2010). Likewise, post-treatment with 15 μM propofol for 1 hour can alleviate the decrease in cell viability and the increase in apoptosis caused by hypoxia in hippocampal neurons, likely through enhanced expression of the glial glutamate transporter-1 (GLT-1) and modulation of the JNK/Akt signaling pathway (Gong et al., 2016).

In summary, the preclinical studies described above indicate that GABA$_A$R agonist sedatives provide concentration-dependent neuroprotective effects in neonatal HIBI, akin to the "mathematical problem" encountered in developing brains. However, due to the lack of studies examining higher doses, the potential toxic effects of these higher doses remain unclear.

Cerebral ischemia–reperfusion injury

CIRI is a critical factor contributing to the poor prognosis in ischemic stroke patients, and the protective effects of GABA$_A$R agonist sedatives against CIRI have been extensively studied (Jurcau and Simion, 2021; Chen et al., 2022b). The following paragraphs provide detailed explanations based on the type of drug.

Propofol is one of the earliest compounds identified to possess neuroprotective effects against CIRI (Young et al., 1997). A previous study demonstrated that intravenous administration of 5 mg/kg of propofol 10 minutes prior to cerebral ischemia, followed by a continuous infusion at 20 mg/kg/h post-reperfusion, can suppress the elevation of interleukin-8 (IL-8), endothelin-1, and malondialdehyde levels following CIRI (Wei et al., 2012). Higher doses, ranging from 20 to 50 mg/kg/h, can improve neurological outcomes and reduce both infarct volume and apoptosis (Liang et al., 2013). In contrast, lower doses (10 mg/kg/h) have been found to be ineffective. Doses between 50 and 150 mg/kg administered before or after ischemia have been shown to alleviate CIRI by reducing oxidative stress, inflammation, and neuronal death, while also protecting mitochondrial structure and function (Chen and Li, 2021; Hu et al., 2021; Fan et al., 2023).

Isoflurane is also recognized for its significant neuroprotective effects against CIRI (Chen et al., 2022b). Administering 1.5% isoflurane for 60 minutes in rats following 90 minutes

Table 1 | **The relationship between propofol and vulnerable brain**

Model	Propofol	Drug, age of exposure or duration of exposure	Outcome	Influence	Reference
Mouse	4 mg/kg	P7	Spatial cognitive ability↑ Neurogenesis↑ Memory ability–	↑	Chen et al., 2022a
Mouse	30 mg/kg	P7	Proliferation– Neurogenesis↓	↓	Huang et al., 2016
Mouse	50 mg/kg	P7	Spatial cognitive ability↓ Memory ability–	↓	Chen et al., 2022a
Mouse	60 mg/kg	P7	Proliferation↓ Neurogenesis↓	↓	Huang et al., 2016
Rat	75 mg/kg	P7	Apoptosis and neuronal loss↑	↓	Yu et al., 2013
			Spatial learning and memory ability–	–	
			Excitatory amino acid neurotransmitter–	–	
Rat		P7, P8, P9, P10, P11, P12, P13	Apoptosis and neuronal loss↑ Spatial learning and memory ability↓ Excitatory amino acid neurotransmitter↓	↓	Yu et al., 2013
Thy1.2-GCaMP6 transgenic mouse	200 mg/kg	P7	Cognitive and behavioral function–	–	Zhou et al., 2021
Thy1.2-GCaMP6 transgenic mouse		P7, P9, P11	Neuronal activity, cognitive and behavioral function↓	↓	Zhou et al., 2021
NSPC	1 μM	3 h	Mitochondrial function–	–	Liang et al., 2022b
Hippocampal precursor cell	2.1 μM	6 h	Neuronal differentiation↑	↑	Sall et al., 2012
Hippocampal precursor cell		24 h	Neuronal differentiation↑	↑	Sall et al., 2012
Hippocampal precursor cell	< 7.1 μM	6 h	LDH–	–	Sall et al., 2012
Hippocampal precursor cell		24 h	LDH–	–	Sall et al., 2012
Hippocampal precursor cell	> 7.1 μM	6 h	LDH↑	↓	Sall et al., 2012
Hippocampal precursor cell		24 h	LDH↑	↓	Sall et al., 2012
NSPC	10 μM	3 h	Mitochondrial function↓	↓	Liang et al., 2022b
NSPC		6 h	Cell viability↑	↑	Qiao et al., 2017
NSPC			Apoptosis↑	↓	Zhang et al., 2022
NSPC			Proliferation–	–	Huang et al., 2016
NSPC		24 h	Proliferation↑ Neuronal fate↑ Cell viability↑	↑	Qiao et al., 2017
NSPC			Proliferation, neuronal differentiation, mitochondrial metabolism↑	↑	Chen et al., 2022a
NSPC			Apoptosis–	–	Huang et al., 2016
NSPC		48 h	Apoptosis–	–	Huang et al., 2016
HESC-derived neuron	2 μg/mL	6 h	Neuron death↑ Mitochondrial fission↑	↓	Twaroski et al., 2015
NSPC	50 μM	6 h	Apoptosis↑	↓	Zhang et al., 2022
NSPC			Apoptosis–	–	Huang et al., 2016
NSPC		24 h	Apoptosis↑	↓	Huang et al., 2016
NSPC		48 h	Apoptosis↑	↓	Huang et al., 2016
NSPC	100 μM	3 h	Mitochondrial function↓ Apoptosis↑	↓	Liang et al., 2022b
Hippocampal neuron			Apoptosis↑	↓	Tu et al., 2019
NSPC		6 h	Cell viability–	–	Qiao et al., 2017
NSPC			Apoptosis–	–	Huang et al., 2016
NSPC		24 h	Apoptosis↑	↓	Zhang et al., 2022
NSPC			Apoptosis↑	↓	Huang et al., 2016
NSPC			Cell viability– Autophagy↑	↓	Qiao et al., 2017
NSPC		48 h	Apoptosis↑	↓	Huang et al., 2016
NSPC	200 μM	6 h	Cell viability↓	↓	Qiao et al., 2017
NSPC		24 h	Cell viability↓ Proliferation↓ Glial fate↑	↓	Qiao et al., 2017
NSPC		2-24 h	Autophagy↑	↓	Qiao et al., 2017
NSPC	300 μM	6 h	Cell viability↓	↓	Qiao et al., 2017
NSPC		24 h	Cell viability↓	↓	Qiao et al., 2017

On the column of outcome, the arrows indicate the following meaning: ↑: Increase ; ↓: Decrease; –: No significant effect; On the column of influence, the arrows indicate the following meaning: ↑: Neuroprotective effect; ↓: Neurotoxic effect; –: No significant effect. LDH: Lactate dehydrogenase; NSPC: neural stem/progenitor cell.

of arterial occlusion reduces cerebral infarct volume, improves neurological deficit scores, and decreases neuronal damage and apoptosis (Ge et al., 2021). The neuroprotective effects of isoflurane are associated with the activation of the bone morphogenetic protein 7 (BMP7)/Sma- and Mad-related protein 1/5/9 (Smad1/5/9) and p38 mitogen-activated protein kinase (p38MAPK) signaling pathways. Additionally, post-treatment administration of 1.5% and 3.0% isoflurane significantly reduces neurobehavioral defect scores and decreases the infarct area in CIRI rats. In contrast, post-treatment administration of 4.5% isoflurane does not show significant differences in behavioral defect scores and results in a lesser reduction in infarct area compared with the lower doses (Wang et al., 2016).

Studies involving sevoflurane have demonstrated that administering 2% sevoflurane for 15 minutes during middle cerebral artery occlusion modeling in 8- to 10-week-old rats upregulates the expression of microRNA 203, leading to reduced inflammation, neuronal apoptosis, and infarct area (Zhong et al., 2020). Furthermore, pre-treatment with 2% sevoflurane for 2 hours significantly reduces neuronal degeneration in CIRI rats, while pre-treatment with 1% or 4% sevoflurane for the same duration is less effective (Wen et al., 2016). Additionally, pre-treatment with 2.5% sevoflurane for 30 minutes, administered three times, or 4% sevoflurane for 1 hour can provide neuroprotection against CIRI by reducing inflammation, minimizing oxidative stress, and inhibiting apoptotic pathways (Su et al., 2021; Yang et al., 2022).

Desflurane has also been reported to have neuroprotective effects against CIRI. Administering desflurane anesthesia at 1.0, 1.25, or 1.5 minimum alveolar concentration (MAC) after inducing cerebral infarction in rats reduces infarct area and plasma lactate dehydrogenase (LDH) activity, with 1.25 MAC being more effective than 1.5 MAC (Tsai et al., 2004). Thus, desflurane provides dose-dependent neuroprotection against CIRI, indicating the possibility of a threshold effect.

A newly approved sedative, remimazolam, administered at 5–20 mg/kg during CIRI, improves neurological function, reduces infarct volume, and alleviates neuron damage, with the best observed effects at 10 mg/kg (Shi et al., 2022).

Overall, these research findings suggest that most $GABA_AR$ agonist sedatives exhibit an "optimal exposure dosage" for neuroprotection against CIRI, with the protective effect diminishing from high to low doses beyond this threshold. Drug use within this threshold demonstrates dose-dependent neuroprotective effects, while doses above this

Table 2 | **The relationship between isoflurane and vulnerable brain**

Model	Isoflurane	Age or duration of each exposure	Outcome	Influence	Reference
Mouse	0.50%	6 h, P7	Ferroptosis↑ Spatial learning and memory abilities↓	↓	Liu et al., 2021
Rat	0.75%	6 h, P7	Mitochondrial morphogenesis and function↓	↓	Sanchez et al., 2011
			Synaptic transmission↓	↓	
Rat		6 h, P7	Neuron death↑ Spatial learning and memory abilities↓	↓	Ma et al., 2017
Rat		6 h, P7	Social and emotional development↓	↓	Diana et al., 2020
Mouse	1.00%	6 h, P7	Ferroptosis↑ Spatial learning and memory abilities↓	↓	Liu et al., 2021
Rat	1.10%	4 h, P7	Apoptosis ↑	↓	Li et al., 2013
Mouse	1.50%	2 h, P7	Ferroptosis↑ Spatial learning and memory abilities↓	↓	Liu et al., 2021
Mouse		4 h, P7	Ferroptosis↑ Spatial learning and memory abilities↓	↓	Liu et al., 2021
Mouse		6 h, P7	Ferroptosis↑ Spatial learning and memory abilities↓	↓	Liu et al., 2021
Rhesus macaque	0.7%–1.5%	3 h, P6	Apoptosis↑	↓	Noguchi et al., 2017
Rhesus macaque		5 h, P6	Motor and behavioral development–	–	Coleman et al., 2017
Rhesus macaque		5 h, P6; P9; P12	Motor and behavioral development↓	↓	Coleman et al., 2017
NSPC	0.60%	1 h	Proliferation↑ Cytotoxicity–	↑	Zhao et al., 2013
NSPC	0.70%	6 h	Proliferation–	–	Culley et al., 2011
NSPC	1.20%	1 h	Proliferation– Cytotoxicity–	–	Zhao et al., 2013
Dissociated neuron		8 h	Axon guidance↓	↓	Mintz et al., 2013
NSPC	1.40%	6 h	Proliferation↓	↓	Culley et al., 2011
primary neuron	1.80%	6 h	Synapse formation↓	↓	Xu et al., 2018a
H4 cell, microglia, primary neuron	2.00%	6 h	Neuroinflammation↑	↓	Zhang et al., 2013a
NSPC	2.40%	1 h	Proliferation↓ Cytotoxicity– Glial cell fate–	↓	Zhao et al., 2013
primary neuron		6 h	Synapse formation↓	↓	Xu et al., 2018a
NSPC		24 h	Cytotoxicity↑ Glial cell fate↑	↓	Zhao et al., 2013
NSPC	2.80%	6 h	Proliferation↓	↓	Culley et al., 2011

On the column of outcome, the arrows indicate the following meaning: ↑: Increase ; ↓: Decrease; –: No significant effect; On the column of influence, the arrows indicate the following meaning: ↑: Neuroprotective effect; ↓: Neurotoxic effect; –: No significant effect. NSPC: Neural stem/progenitor cell.

level may diminish that protective effect. Although not yet reported, further increasing the dose could lead to potential neurotoxicity and damage, particularly in developing brains. Additionally, various drugs appear to show differing effects: propofol primarily exhibits concentration-dependent protective effects within the reported exposure doses, whereas inhaled anesthetics tend to have an "intermediate value" as the optimal exposure dose.

Traumatic brain injury

Traumatic brain injury (TBI) is a risk factor for the development of chronic traumatic brain disease, all-cause dementia, Parkinson's disease, and various neurodegenerative diseases (Brett et al., 2022; Zhang et al., 2025). $GABA_AR$ agonist sedatives have also been reported to exhibit protective effects against TBI.

Statler et al. (2000) demonstrated that administering 1% isoflurane anesthesia for 4 hours after controlled cortical impact (CCI) in adult male Sprague–Dawley rats improved long-term neurological outcomes and reduced damage to CA1 hippocampal neurons by increasing cerebral blood flow and decreasing excitotoxicity following TBI. Another study found that rats treated with 1% isoflurane for 30 minutes prior to TBI performed better in beam balance, beam walking, and Morris water maze tests, and exhibited increased survival of hippocampal neurons (Statler et al., 2006b). Additionally, a comparative study of various anesthetics and sedatives—including diazepam, fentanyl, isoflurane, ketamine, morphine, pentobarbital, and propofol—after CCI revealed that rats treated with 1% isoflurane for 1 hour demonstrated the best cognitive recovery and survival of hippocampal neurons (Statler et al., 2006a). Post-treatment with 1%, 3%, and 5% sevoflurane for 1 hour has also been shown to mitigate neuronal apoptosis induced by TBI in rats through the activation of the enhancer of zeste homolog 2 (EZH2)/Krüppel-like factor 4 (KLF4) axis and the p38-MAPK signaling pathway in a dose-dependent manner (Wang et al., 2021c). Furthermore, administering 2.4% sevoflurane for 1 hour after CCI can improve brain edema, neurological deficits, and neuronal autophagy and apoptosis by activating the fibroblast growth factor 2 (FGF2)/EZH2 axis and downregulating hairy and enhancer of split 1 (HES1) (Wang et al., 2022).

Propofol is a frontline sedative for TBI patients in clinical practice (Oddo et al., 2016). A previous study has shown that incubating organotypic hippocampal brain slices with 10–400 μmol/L propofol for 72 hours after focal mechanical injury can dose-dependently reduce both total tissue damage and secondary tissue damage (Rossaint et al., 2009). Another study demonstrated that administering 50 or 100 mg/kg of propofol 10 minutes after TBI modeling in mice can dose-dependently decrease brain water content following TBI, which is associated with the inhibition of aquaporin-4 (AQP-4) expression (Ding et al., 2013). Furthermore, intravenous injection of 12.5 mg/kg propofol within 5 minutes of TBI, followed by a continuous infusion at 40 mg/kg/h for 2 hours, can maintain the balance of interleukin-17 (IL-17)-producing T helper (Th17) and regulatory T (Treg) cells through the microRNA-145-3p/nuclear factor of activated T cells c2 (NFATc2)/NF-κB axis in rats. This mechanism attenuates the inflammatory response and reduces brain damage in TBI rats (Cui et al., 2021a).

Other drugs, such as etomidate and thiopental, also exhibit similar protective effects. Administering 2 mg/kg of etomidate intravenously 5 minutes before or after injury in male Sprague–Dawley rats that had undergone CCI can mitigate secondary damage caused by TBI, with more pronounced effects observed on pre-treatment exposure (Dixon et al., 2003). Additionally, administering 0.01–2 mM of thiopental after hypoxia treatment of human SK-N-SH neurons or primary mouse cortical neurons—used to simulate TBI—can inhibit protein synthesis and prevent hypoxic neuronal cell death by promoting the phosphorylation of eukaryotic elongation factor 2 (eEF2) (Schwer et al., 2013). However, comparative studies examining different drug doses are currently lacking.

The research findings suggest that $GABA_AR$ agonist sedatives exhibit dose-dependent neuroprotective effects within a specific range against TBI. However, due to the limited number of reported studies, determination of a threshold effect related to drug dosage is currently challenging.

Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) can lead to brain dysfunction through inflammatory reactions, hemoglobin breakdown, complement activation, and other processes, among which the activation of microglia plays a crucial role (Lan et al., 2017). A previous study has shown that anesthesia with 2.2% sevoflurane significantly delays the activation of microglia and reduces their level following ICH in adult rats (Karwacki et al., 2006). Additionally, research has demonstrated that 2% sevoflurane alleviates hippocampal neuron apoptosis in mice after ICH by upregulating miR-133b, inhibiting forkhead box O4 (FOXO4), and activating the B-cell lymphoma/leukemia 2 (BCL2) (Li et al., 2023).

Table 3 | **The relationship between sevoflurane and vulnerable brain**

Model	Sevoflurane	Age or duration of each exposure	Outcome	Influence	Reference
Rat	0.85%	6 h, P7	Neuron death↑ Spatial learning and memory abilities↓	↓	Ma et al., 2017
Rat	1.00%	1 h, P7	Apoptosis↑ Spatial learning and memory abilities↓	↓	Xu et al., 2019a
Rat		2 h, P7	LTP–	–	Kato et al., 2013
	1.20%	6 h, P7	Neurogenesis, synaptic plasticity↑	↑	Chen et al., 2018
			Spatial learning and memory ability↑	↑	
Rat	1.80%	6 h, P4–6	Proliferation, survival of newborn cell↑	↑	Chen et al., 2015
			Motor system and emotion– DG-dependent learning ability↑	↑	
Rat	2.00%	1 h, P7	Apoptosis↑ Spatial learning and memory abilities↓	↓	Xu et al., 2019a
Rat		2 h, P7	LTP↓	↓	Kato et al., 2013
		2 h, P7	Synaptic ultrastructure↓ Temporary spatial working memory↓	↓	Sun et al., 2019
Rat		4 h, P7; P8; P9	Inflammation↑ Spatial learning and memory abilities↓	↓	Wang et al., 2021
Rat	2.40%	6 h, P7	Neurogenesis, synaptic plasticity–	–	Chen et al., 2018
			Spatial learning and memory abilities–	–	
Rat	2.50%	2 h, P7	Synaptic density, presynaptic mitochondrial density–	–	Amrock et al., 2015
Mouse		2 h, G15.5–G17.5	Neurogenesis↓ Cognitive function↓	↓	Fang et al., 2017
Rat			Synaptic density, presynaptic mitochondrial density↓	↓	Amrock et al., 2015
Rat		6 h, P7	Synaptic density, presynaptic mitochondrial density↓	↓	Amrock et al., 2015
Rat	3.00%	1 h, P7	Synaptic plasticity– LTP– Spatial learning and memory abilities–	–	Xiao et al., 2016
Mouse		2 h, P6	Neuroinflammation, cognitive function–	–	Shen et al., 2013
Rat		2 h, P7	Autophagy↑ Spatial learning and memory abilities↓	↓	Zhang et al., 2023
Rat		2 h, P4; P5; P6	Stress response↑ Spatial learning and memory abilities↓	↓	Liu et al., 2016
Rat		2 h, P6; P7; P8	Iron overload↑ Cognitive function↓	↓	Wu et al., 2020
Rat			Synapse formation↓ Spatial and fear memory, anxiety behavior↓	↓	Liang et al., 2020a
Mouse			Neuroinflammation, cognitive function↓	↓	Shen et al., 2013
Mouse			Neuroinflammation, cognitive function↓	↓	Kang et al., 2024
Mouse			Autophagy↑ Spatial learning and memory abilities↓	↓	Wang et al., 2019
Mouse			Inflammation, apoptosis↑ Spatial learning and memory abilities↓	↓	Zeng et al., 2022
Rat		4 h, P7	Apoptosis↑ Spatial learning and memory abilities↓	↓	Bi et al., 2018
Rat		4 h, P7; P8; P9	Inflammation↑ Spatial learning and memory abilities↓	↓	Wang et al., 2021a
Mouse		6 h, P6	Apoptosis↑ Long-term memory, social behavior↓	↓	Satomoto et al., 2009
Rat		6 h, P7	Synaptic plasticity↓ LTP↓ Spatial learning and memory abilities↓	↓	Xiao et al., 2016
Rat	3.40%	4 h, P7	Autophagy↑	↓	Xu et al., 2018b
Rat		4 h, P7; P8	Autophagy↑	↓	Xu et al., 2018b
Rat		4 h, P7; P8; P9	Autophagy↑	↓	Xu et al., 2018b
Rat	4.00%	1 h, P7	Apoptosis↑ Spatial learning and memory abilities↓	↓	Xu et al., 2019a
NSPC	2.00%	6 h	Proliferation–	–	Zhang et al., 2013c
			Ferroptosis↑	↓	Kang et al., 2024
		12 h	Ferroptosis↑	↓	Kang et al., 2024
		24 h	Ferroptosis↑	↓	Kang et al., 2024
Hippocampal neuron	3.00%	6 h	Iron overload↑	↓	Wu et al., 2020
Hippocampal neuron	3.40%	1 h	Autophagy, apoptosis↑	↓	Xu et al., 2018b
Hippocampal neuron		3 h	Autophagy, apoptosis↑	↓	Xu et al., 2018b
Hippocampal neuron		5 h	Autophagy, apoptosis↑	↓	Xu et al., 2018b
Hippocampal neuron	4.00%	6 h	Ferroptosis↑	↓	Kang et al., 2024
Hippocampal neuron		12 h	Ferroptosis↑	↓	Kang et al., 2024
Hippocampal neuron		24 h	Ferroptosis↑	↓	Kang et al., 2024
NSPC	4.10%	2 h, for 3 d	Neurogenesis↓	↓	Fang et al., 2017
NSPC		6 h	Proliferation↓	↓	Zhang et al., 2013
Hippocampal neuron			Apoptosis↑	↓	Liang et al., 2022
NSPC			Cell cycle↓	↓	Liu et al., 2018
H4 cell			Neuroinflammation↑	↓	Zhang et al., 2013
Hippocampal neuron	8.00%	6 h	Ferroptosis↑	↓	Kang et al., 2024
Hippocampal neuron		12 h	Ferroptosis↑	↓	Kang et al., 2024
Hippocampal neuron		24 h	Ferroptosis↑	↓	Kang et al., 2024

On the column of outcome, the arrows indicate the following meaning: ↑: Increase ; ↓: Decrease; –: No significant effect; On the column of influence, the arrows indicate the following meaning: ↑: Neuroprotective effect; ↓: Neurotoxic effect; –: No significant effect. DG: Dentate gyrus; LTP: Long-term potentiation; NSPC: Neural stem/progenitor cell.

Furthermore, treatment with 30 and 60 mg/kg propofol after ICH in rats dose-dependently suppresses the release of inflammatory factors, upregulates matrix metalloproteinase-9 (MMP-9) expression in the brain, and induces neurogenesis to alleviate the condition, whereas the effect of 15 mg/kg propofol is less pronounced (Han et al., 2015). These results suggest that $GABA_AR$ agonist sedatives have a dose-dependent neuroprotective effect on ICH within a certain range.

Subarachnoid hemorrhage

Delayed cerebral ischemia (DCI) has been identified as a significant factor contributing to a poor prognosis following subarachnoid hemorrhage (SAH) caused by aneurysms (Wolfert et al., 2022). Pre-treatment with 2% isoflurane for 1 hour at 1 hour after SAH was shown to downregulate inducible nitric oxide synthase (iNOS) levels and provide protection against DCI following SAH in mice (Liu et al., 2023b). Additionally, a previous study has indicated that administering 2% isoflurane for 1 hour post-SAH can protect against DCI by inhibiting microglial activation and reducing NF-κB levels (Liu et al., 2023a). In adult male rats with acute SAH, sedation with 4% sevoflurane for 4 hours maintains hemodynamic stability without increasing intracranial pressure, enhances membrane stability, and reduces brain water content by lowering β-chain protein levels, thereby alleviating the formation of early brain

edema (Beck-Schimmer et al., 2020). Furthermore, propofol has been shown to mitigate early brain injury induced by SAH by activating the PI3K/Akt signaling pathway, which suppresses inflammation and oxidative stress (Zhang et al., 2019). However, comprehensive dosage studies to determine the optimal exposure levels for these treatments are currently lacking.

Due to the previously discussed models of neurological damage, particularly in certain reversible conditions such as ICH and TBI, established clinical treatment strategies exist. However, the role of anesthetic drugs in the rehabilitation process has not been sufficiently emphasized. In contrast, for diseases with long-term and significant sequelae, such as neonatal HIBI and CIRI, current treatment methods aimed at improving prognosis remain inadequate. Therefore, the neuroprotective effects of anesthetic drugs warrant greater attention. This article examines these diseases individually, with the goal of summarizing and exploring the "threshold effect" of anesthetics on the vulnerable brain on the basis of existing knowledge.

In summary, $GABA_AR$ agonist sedatives exhibit varying effects across different models of drug- and injury-induced neurological damage. Extensive research in this area indicates that anesthetic drugs have a therapeutic threshold for neuroprotection in CIRI, and that differences exist among various drugs, as detailed above. In contrast, for neonatal HIBI and TBI, current dose–response studies primarily revealed concentration-dependent protective effects, although the number of studies in this area is somewhat limited. Research on hemorrhagic diseases is even more scarce, making it challenging to draw relevant conclusions. Considering the effects of $GABA_AR$ agonist sedatives in the context of the developing and vulnerable brain, we can speculate that in different disease models and with different drugs, there exists an exposure threshold where these agents exhibit a "protective—neutral—toxic" effect.

Neural developmental disorders

Autism spectrum disorder

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by social deficits, for which there are currently no definitive treatment options beyond behavioral interventions (Lord et al., 2020; Roy and Strate, 2023). Basic research suggests that impairments in GABAergic synaptic transmission leading to excitatory/inhibitory imbalance within specific cortical circuits may account for many of the behavioral symptoms observed in ASD. Thus, $GABA_AR$ agonist sedatives may have neuroprotective effects in individuals with ASD (Port et al., 2017), leading to a growing body of research focused on this phenomenon.

Cui et al. (2021b) found that exposing P16-17 BTBR T+ Itpr3tf/J (BTBR) mice to 2.5% sevoflurane for three sessions of 1 hour each, with a 2-hour interval between exposures, can reduce autism-like behaviors, improve excitatory/inhibitory balance, and enhance mitochondrial respiration and brain-derived neurotrophic factor (BDNF) signaling in these mice. Similarly, a previous study demonstrated that administering 25 and 50 mg/kg of propofol can improve social deficits in 8-week-old BTBR mice, with higher doses reducing repetitive self-grooming behaviors and marble burying (Cai et al., 2017). However, due to the unclear pathogenesis of ASD and the challenges in standardizing animal models, the applicability of these conclusions remains debatable. Although the number of relevant studies is limited, the recent discovery of the protective effects of these anesthetic agents has generated excitement among researchers in the field of ASD. Further in-depth research could potentially provide new options and directions for the treatment of ASD.

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a common, highly heritable condition characterized by symptoms of inattention, impulsivity, and hyperactivity (Posner et al., 2020). In clinical research, a study of all children born in Rochester, Minnesota, between 1976 and 1982 found that repeated exposure to surgeries requiring general anesthesia before the age of 2 years was associated with an increased risk of developing ADHD later in life (Sprung et al., 2012). Conversely, a retrospective matched-cohort study of children born in Taiwan, China between 2001 and 2005 found no increased risk of ADHD among children exposed to anesthesia (either single or multiple times) before the age of 3 years in comparison with those who were not exposed (Ko et al., 2014).

However, basic research studies have yielded contradictory findings regarding the potential risk of ADHD development associated with early exposure to $GABA_AR$ agonist sedatives (Xu et al., 2019c). One study exposed P6 mice to 3% sevoflurane for 2 hours per day over 3 days, and the findings showed that adult mice exhibited increased jumping time and significantly shortened latency to the first jump in the cliff avoidance response test. This phenomenon was associated with chemogenetic activation of excitatory neurons in the medial prefrontal cortex (mPFC), suggesting that multiple exposures to sevoflurane may induce impulsive behaviors resembling ADHD in adulthood (Xie et al., 2020). In contrast, another study exposed P7 mice to 2.5% sevoflurane for 2 hours, or to sevoflurane at P7, P10, and P13 for 2 hours each, and found that this exposure during early development did not impair attention in adult mice (Murphy et al., 2017).

ADHD, as a refractory condition, has been receiving increasing attention within the field (Posner et al., 2020). Currently, the role of $GABA_AR$ agonist sedatives in ADHD is believed to primarily fall within the "neutral-to-toxic" spectrum. Further research is needed to determine whether lower concentrations of these sedatives can have neuroprotective effects in individuals with ADHD.

In addition to the aforementioned studies related to ASD and ADHD, no other reports have described the application of $GABA_AR$ agonist sedatives in neurodevelopmental disorders such as cerebral palsy, developmental delays, intellectual disabilities, Down syndrome, or amyotrophic lateral sclerosis. Furthermore, reports on the neuroprotective effects of $GABA_AR$ agonist sedatives in developmental disorders are also scarce. However, as researchers increasingly focus on this area, $GABA_AR$ agonist sedatives are believed to hold potential for breakthroughs in the treatment of developmental diseases.

Neurodegenerative disease

Alzheimer's disease

Alzheimer's disease (AD) is a multifactorial and heterogeneous neurodegenerative disease that occurs in older adults and is characterized by progressive cognitive impairment and behavioral deficits (Scheltens et al., 2021). Currently, no confirmed effective drugs are available for the treatment of AD. Previous studies have suggested that $GABA_AR$ agonist sedatives have neurotoxic effects on AD, accelerating its neurodegenerative progression (Tian et al., 2021; Eun et al., 2022); however, other studies indicate that $GABA_AR$ agonist sedatives do not cause neurological damage in AD and may even exhibit neuroprotective effects (Shao et al., 2014; Borgstedt et al., 2022).

A study investigating the effects of isoflurane found that exposure to 1.6% isoflurane for 2 hours did not affect amyloid biomarkers or cognitive behavior in mice (Borgstedt et al., 2022). In contrast, another study demonstrated that 1.7% isoflurane improved cognitive ability and learning and reduced anxiety (Eckel et al., 2013). Among studies investigating the influence of exposure duration, one study exposed 5xFAD mice to 8% desflurane, 2.8% sevoflurane, or 1.4% isoflurane for either 30 minutes or 6 hours. The findings indicated that short-term exposure to inhaled anesthetics did not affect hippocampal-dependent memory or amyloid-β (Aβ) deposition in the brain. However, long-term exposure resulted in a significant increase in Aβ deposition in the hippocampus and activation of glial cells in the amygdala (Han et al., 2021). Thus, while short-term exposure to anesthetics has no effect on AD, long-term exposure may have neurotoxic effects. Additionally, *in vitro* treatment with 0.5% isoflurane reduced Aβ-induced caspase-3 activation, whereas 2% isoflurane had the opposite effect. *In vivo*, exposure to 0.7% isoflurane for 30 minutes was protective, while exposure to 1.4% isoflurane for 6 hours was damaging, indicating a dose-dependent dual effect (Xu et al., 2011).

Similar effects have been observed with propofol. Administration of 250 mg/kg propofol showed no effects on MWM testing, plaque formation, tau aggregation, or neuroinflammation in AD mice (Mardini et al., 2017). Additionally, another study found that repeated exposure to 200 mg/kg propofol did not alter plaque deposition or synaptic degeneration in amyloid precursor protein (APP)/presenilin 1 (PS1) mice (Woodhouse et al., 2018). Furthermore, in a toxicity model using pheochromocytoma (PC12) cells induced by $A\beta_{25-35}$ for 6 hours, treatment with 20 μmol/L propofol protected PC12 cells from $A\beta_{25-35}$-induced apoptosis and inhibited tau protein hyperphosphorylation via the glycogen synthase kinase-3 beta (GSK-3β) pathway. Thus, propofol may have a neuroprotective effect that could slow disease progression in AD (Zhang et al., 2013b). Moreover, intraperitoneal injection of 50 mg/kg propofol once a week for 12 weeks in 19-month-old AD transgenic mice reduced Aβ-induced mitochondrial permeability transition pore (mPTP) opening, decreased caspase-3

activation, and improved cognitive function (Shao et al., 2014). Overall, these studies indicate that short-term, low-dose exposure to $GABA_AR$ agonist sedatives such as isoflurane and propofol has neuroprotective effects in AD; however, due to limited research in this area, the specific optimal exposure threshold cannot be determined at present.

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder (Bloem et al., 2021). A previous study has suggested that exposure to $GABA_AR$ agonist sedatives could either induce or accelerate the progression of PD (Mastrangelo et al., 2013). However, research involving pre-symptomatic Parkinsonian rat models (DJ-1 rats) aged 6–7 months showed that exposure to 1.2% isoflurane anesthesia for 2 hours on three separate occasions did not result in any differences in motor or cognitive function in comparison with the control group (Xu et al., 2021). Additionally, no long-term changes were observed in the density of dopamine neurons or glial cells, indicating that the use of isoflurane does not accelerate the onset of PD. Furthermore, another study demonstrated that 20 minutes of anesthesia with 2% isoflurane in an animal model resembling early-stage PD could regulate the striatal AKT-GSK3β pathway and improve motor deficits (Leikas et al., 2017).

In summary, contrary to previous views, our findings indicate that the effects of $GABA_AR$ agonist sedatives on neurodegenerative diseases vary depending on the dosage and duration of exposure. Low-dose, short-term exposure to these sedatives exhibits neuroprotective effects, thereby indirectly supporting our proposed "threshold effect" of "protection—neutral—toxicity," which also applies to neurodegenerative diseases.

Aging

Aging is characterized by functional decline and reduced multisystem reserve (Guo et al., 2022). Older adult surgical patients were previously believed to be more susceptible to cognitive dysfunction and increased mortality rates (Chen et al., 2020; Lim and Lee, 2020). However, a previous study suggested that $GABA_AR$ agonist sedatives have no detrimental effects on aging and may even contribute to delaying the aging process (Culley et al., 2006).

Research indicates that administering 1.5% isoflurane to 16-month-old elderly rats does not lead to differences in hippocampal neural progenitor cell proliferation, neuronal differentiation, new neuron survival, or any long-term outcomes in hippocampal functional tests (Stratmann et al., 2010). In contrast, in 16–18-month-old elderly rats, single (4 hours) or repeated (2 hours daily for 5 days) exposure to 1.5% or 2.5% sevoflurane resulted in extended escape latency and impaired spatial memory, with more significant effects observed following repeated exposure (Guo et al., 2018). Thus, sevoflurane exposure can negatively impact learning and memory abilities in elderly rats, with the effects correlated to the exposure dose. Additionally, research has shown that exposure to 1.5 MAC desflurane significantly impaired task acquisition in 16–18-month-old elderly rats, while exposure to 1 MAC desflurane did not result in this impairment. Thus, the effects of desflurane on learning and memory in rats are dose-dependent and related to age (Callaway et al., 2015).

In another study, treatment with intraperitoneal propofol (50 mg/kg, once a week for 8 weeks) in 18-month-old mice improved cognitive function and attenuated aging-related caspase-3 activation. The treatment also reduced brain tissue levels of beta-site APP-cleaving enzyme and increased neprilysin levels, leading to lower Aβ levels (Zhang et al., 2014). Furthermore, intraperitoneal injection of propofol (50 mg/kg, once a week for 8 weeks) in 18-month-old wild-type mice enhanced spatial learning function and attenuated caspase-3 activation via the mitochondrial pathway (Shao et al., 2014). On the basis of these findings, we can similarly conclude that exposure to $GABA_AR$ agonist sedatives exhibits a "protection—neutral—toxicity" threshold effect in the context of aging.

After summarizing and compiling comprehensive data on neurological disorders from our screening of the mathematically dose-dependent dual effects of anesthetics on the developing brain, we can preliminarily conclude that $GABA_AR$ agonist sedatives exhibit a dual effect on different states of the CNS. However, different thresholds exist for various diseases and medications, necessitating separate studies to explore these thresholds and compile the relevant data. The consistency of results in clinical and basic research (animal and cellular studies) is an important consideration in this regard. Although exploration of the "threshold" in clinical settings presents significant challenges, addressing this "mathematical problem" represents both a crucial opportunity and challenge for the field of anesthesia.

Limitations

One of the limitations of this discussion is that we have not covered sedative anesthetics beyond $GABA_AR$ agonists, such as NMDAR antagonists (e.g., ketamine) or alpha-2 adrenergic agonists (e.g., dexmedetomidine), which also play crucial roles in anesthesia and sedation. Additionally, the mechanisms of action for these drugs, including $GABA_AR$ agonists, remain complex and not fully understood, as various studies report different pathways and interactions at the molecular level. This lack of consensus on the precise mechanisms has led to gaps in our understanding of how these drugs exert their effects on the brain. Furthermore, large-scale clinical studies exploring the comparative efficacy and safety of these agents across diverse patient populations are lacking, limiting the generalizability of these findings and our ability to make evidence-based recommendations for optimal sedation and anesthesia practices. More research is needed to address these gaps and provide a clearer understanding of the full spectrum of sedative anesthetics.

Conclusions

The significance of $GABA_AR$ agonist sedatives in current clinical anesthesia, particularly in pediatric anesthesia, is undeniable. Over more than 30 years of exploration, the dose-dependent dual effects of these drugs on the developing brain have become increasingly clear. Contrary to previous notions of "neurotoxicity in the developing brain," "neuroprotection in brain injury diseases," and the "varied protective/toxic effects of different drugs," our extensive research in this area has led us to propose an innovative conclusion in this review. We assert that all $GABA_AR$ agonist sedatives exhibit specific threshold effects ranging from neuroprotection to neurotoxicity that are unique to each drug and depend on different brain functional states. In the vulnerable developing brain, anesthesia, particularly at high doses, may be detrimental, while in cases of CNS injury or neurological diseases, it may provide protective benefits. Additionally, we believe that anesthesia has associated thresholds in neurodegenerative diseases and developmental disorders currently lacking effective treatment options. By expanding the existing understanding of $GABA_AR$ agonist sedatives and leveraging this understanding, clinicians can achieve remarkable neuroprotective effects that may alleviate and even partially treat such diseases.

The term "vulnerable brain" refers to a specific stage in which the brain is particularly susceptible to anesthetic-induced neurotoxicity. This vulnerability encompasses a wide range of conditions. From an age-related perspective, it includes the immature brain and aging brain. In terms of pathological states, it encompasses the injured brain, neurological disorders, and abnormally developed brains. In vulnerable brains, by identifying the mathematical threshold of anesthetic effects, the optimal dose and administration method to achieve the best protective outcomes can be determined. By fine-tuning anesthetic dosage and timing, anesthetics may not only offer neuroprotection but also potentially promote recovery and function in various vulnerable states. This approach could lead to personalized anesthetic strategies that maximize protective or therapeutic benefits while minimizing the risks of neurotoxicity, opening new therapeutic avenues for conditions such as developmental disorders, neurodegenerative diseases, and brain injuries.

Studies of the target sites of general anesthesia sedatives remain a fascinating area of research. A review of the currently published literature on the molecular mechanisms of sedative drugs revealed the involvement of various cell surface receptors (e.g., $GABA_AR$, dopamine receptors) and associated downstream intracellular signaling pathways (e.g., Akt, ERK, JNK, Wnt), along with changes at the level of nuclear transcription factors. The sedatives discussed in this review are small-molecule compounds, similar to metformin, and are highly lipophilic, which conferred a wide range of potential action sites and targets based on their chemical properties. While additional exploration of these mechanisms is warranted, further investigation into the specific molecular mechanisms that lead to the final effects is required. This includes starting with the relevant compounds, designing probes for intracellular distribution, targeting associated proteins, and examining different modes of action at varying concentrations. Such efforts could significantly enhance our understanding of the action patterns of anesthetic drugs.

In summary, addressing this "mathematical problem" from various angles may present a historic opportunity for the field of anesthesia to gain prominence, enabling anesthesiologists to demonstrate their unique value in anesthesia treatment.

Author contributions: *Conceptualization and writing - review & editing: DL. Manuscript writing: DL, WZ, KC. Visualization: WZ. Supervision: XF. All authors approved the final version of this manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Data availability statement: *Not applicable.*

References

Alkire MT, Nathan SV, McReynolds JR (2005) Memory enhancing effect of low-dose sevoflurane does not occur in basolateral amygdala-lesioned rats. Anesthesiology 103:1167-1173.
Amrock LG, Starner ML, Murphy KL, Baxter MG (2015) Long-term effects of single or multiple neonatal sevoflurane exposures on rat hippocampal ultrastructure. anesthesiology 122:87-95.
Anderson BJ, Bagshaw O (2019) Practicalities of total intravenous anesthesia and target-controlled infusion in children. Anesthesiology 131:164-185.
Andropoulos DB, Greene MF (2017) Anesthesia and developing brains- Implications of the FDA warning. N Engl J Med 376:905-907.
Arnautovic T, Sinha S, Laptook AR (2024) Neonatal hypoxic-ischemic encephalopathy and hypothermia treatment. Obstet Gynecol 143:67-81.
Backeljauw B, Holland SK, Altaye M, Loepke AW (2015) Cognition and brain structure following early childhood surgery with anesthesia. Pediatrics 136:e1-12.
Beck-Schimmer B, Restin T, Muroi C, Roth Z'Graggen B, Keller E, Schlapfer M (2020) Sevoflurane sedation attenuates early cerebral oedema formation through stabilisation of the adherens junction protein beta catenin in a model of subarachnoid haemorrhage: a randomised animal study. Eur J Anaesthesiol 37:402-412.
Bi C, Cai Q, Shan Y, Yang F, Sun S, Wu X, Liu H (2018) Sevoflurane induces neurotoxicity in the developing rat hippocampus by upregulating connexin 43 via the JNK/c-Jun/AP-1 pathway. Biomed Pharmacother 108:1469-1476.
Bleeser T, Hubble TR, Van de Velde M, Deprest J, Rex S, Devroe S (2023a) Introduction and history of anaesthesia-induced neurotoxicity and overview of animal models. Best Pract Res Clin Anaesthesiol 37:3-15.
Bleeser T, Brenders A, Hubble TR, Van de Velde M, Deprest J, Rex S, Devroe S (2023b) Preclinical evidence for anaesthesia-induced neurotoxicity. Best Pract Res Clin Anaesthesiol 37:16-27.
Block RI, Thomas JJ, Bayman EO, Choi JY, Kimble KK, Todd MM (2012) Are anesthesia and surgery during infancy associated with altered academic performance during childhood? Anesthesiology 117:494-503.
Bloem BR, Okun MS, Klein C (2021) Parkinson's disease. Lancet 397:2284-2303.
Borgstedt L, Bratke S, Blobner M, Potzl C, Ulm B, Jungwirth B, Schmid S (2022) Isoflurane has no effect on cognitive or behavioral performance in a mouse model of early-stage Alzheimer's disease. Front Neurosci 16:1033729.
Brett BL, Gardner RC, Godbout J, Dams-O'Connor K, Keene CD (2022) Traumatic brain injury and risk of neurodegenerative disorder. Biol Psychiatry 91:498-507.
Cai Y, Wang L, Xiao R, Li X, He X, Gao J, Xu H, Fan X (2017) Autism-like behavior in the BTBR mouse model of autism is improved by propofol. Neuropharmacology 118:175-187.
Callaway JK, Jones NC, Royse AG, Royse CF (2015) Memory impairment in rats after desflurane anesthesia is age and dose dependent. J Alzheimers Dis 44:995-1005.
Cattano D, Young C, Straiko MM, Olney JW (2008) Subanesthetic doses of propofol induce neuroapoptosis in the infant mouse brain. Anesth Analg 106:1712-1714.
Chen C, Shen FY, Zhao X, Zhou T, Xu DJ, Wang ZR, Wang YW (2015) Low-dose sevoflurane promotes hippocampal neurogenesis and facilitates the development of dentate gyrus-dependent learning in neonatal rats. ASN Neuro 7:1759091415575845.
Chen K, Lu D, Yang X, Zhou R, Lan L, Wu Y, Wang C, Xu X, Jiang MH, Wei M, Feng X (2022a) Enhanced hippocampal neurogenesis mediated by PGC-1alpha-activated OXPHOS after neonatal low-dose propofol exposure. Front Aging Neurosci 14:925728.
Chen SJ, Yuan XQ, Xue Q, Lu HF, Chen G (2022b) Current research progress of isoflurane in cerebral ischemia/reperfusion injury: a narrative review. Med Gas Res 12:73-76.
Chen X, Zhou X, Yang L, Miao X, Lu DH, Yang XY, Zhou ZB, Kang WB, Chen KY, Zhou LH, Feng X (2018) Neonatal exposure to low-dose (1.2%) sevoflurane increases rats' hippocampal neurogenesis and synaptic plasticity in later life. Neurotox Res 34:188-197.
Chen Y, Zhang P, Lin X, Zhang H, Miao J, Zhou Y, Chen G (2020) Mitophagy impairment is involved in sevoflurane-induced cognitive dysfunction in aged rats. Aging 12:17235-17256.
Chen Y, Li Z (2021) Protective effects of propofol on rats with cerebral ischemia-reperfusion injury via the PI3K/Akt pathway. J Mol Neurosci 71:810-820.
Chhibber T, Bagchi S, Lahooti B, Verma A, Al-Ahmad A, Paul MK, Pendyala G, Jayant RD (2020) CNS organoids: an innovative tool for neurological disease modeling and drug neurotoxicity screening. Drug Discov Today 25:456-465.
Chinn GA, Pearn ML, Vutskits L, Mintz CD, Loepke AW, Lee JJ, Chen J, Bosnjak ZJ, Brambrink AM, Jevtovic-Todorovic V, Sun LS, Sall JW (2020) Standards for preclinical research and publications in developmental anaesthetic neurotoxicity: expert opinion statement from the SmartTots preclinical working group. Br J Anaesth 124:585-593.
Coleman K, Robertson ND, Dissen GA, Neuringer MD, Martin LD, Cuzon Carlson VC, Kroenke C, Fair D, Brambrink AM (2017) Isoflurane anesthesia has long-term consequences on motor and behavioral development in infant rhesus macaques. Anesthesiology 126:74-84.
Cui C, Zhang D, Sun K, Li H, Xu L, Lin G, Guo Y, Hu J, Chen J, Nong L, Cai Y, Yu D, Yang W, Wang P, Sun Y (2021a) Propofol maintains Th17/Treg cell balance and reduces inflammation in rats with traumatic brain injury via the miR-145-3p/NFATc2/NF-kappaB axis. Int J Mol Med 48:135.
Cui J, Park J, Ju X, Lee Y, Hong B, Ahn J, Kim YH, Ko Y, Yoon SH, Lim C, Lee SY, Huh SO, Heo JY, Chung W (2021b) General anesthesia during neurodevelopment reduces autistic behavior in adult BTBR mice, a murine model of autism. Front Cell Neurosci 15:772047.
Culley DJ, Loguinov A, Yukhananov R, Crosby G (2006) General anesthesia does not reduce life expectancy in aged rats. Anesth Analg 102:956-959.
Culley DJ, Boyd JD, Palanisamy A, Xie Z, Kojima K, Vacanti CA, Tanzi RE, Crosby G (2011) Isoflurane decreases self-renewal capacity of rat cultured neural stem cells. Anesthesiology 115:754-763.
Davidson AJ, et al. (2016) Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 387:239-250.
de Heer IJ, Tiemeier H, Hoeks SE, Weber F (2017) Intelligence quotient scores at the age of 6 years in children anaesthetised before the age of 5 years. Anaesthesia 72:57-62.
Deng M, Hofacer RD, Jiang C, Joseph B, Hughes EA, Jia B, Danzer SC, Loepke AW (2014) Brain regional vulnerability to anaesthesia-induced neuroapoptosis shifts with age at exposure and extends into adulthood for some regions. Br J Anaesth 113:443-451.
Diana P, Joksimovic SM, Faisant A, Jevtovic-Todorovic V (2020) Early exposure to general anesthesia impairs social and emotional development in rats. Mol Neurobiol 57:41-50.
DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G (2009) A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. J Neurosurg Anesthesiol 21:286-291.
Ding Z, Zhang J, Xu J, Sheng G, Huang G (2013) Propofol administration modulates AQP-4 expression and brain edema after traumatic brain injury. Cell Biochem Biophys 67:615-622.
Dixon CE, Ma X, Kline AE, Yan HQ, Ferimer H, Kochanek PM, Wisniewski SR, Jenkins LW, Marion DW (2003) Acute etomidate treatment reduces cognitive deficits and histopathology in rats with traumatic brain injury. Crit Care Med 31:2222-2227.
Dou Y, Fei X, He X, Huan Y, Wei J, Wu X, Lyu W, Fei Z, Li X, Fei F (2024) Homer1a reduces inflammatory response after retinal ischemia/reperfusion injury. Neural Regen Res 19:1608-1617.
Eckel B, Ohl F, Starker L, Rammes G, Bogdanski R, Kochs E, Blobner M (2013) Effects of isoflurane-induced anaesthesia on cognitive performance in a mouse model of Alzheimer's disease: a randomised trial in transgenic APP23 mice. Eur J Anaesthesiol 30:605-611.
Engelhard K, Werner C, Eberspacher E, Pape M, Stegemann U, Kellermann K, Hollweck R, Hutzler P, Kochs E (2004) Influence of propofol on neuronal damage and apoptotic factors after incomplete cerebral ischemia and reperfusion in rats: a long-term observation. Anesthesiology 101:912-917.
Eun JD, Jimenez H, Adrien L, Wolin A, Marambaud P, Davies P, Koppel JL (2022) Anesthesia promotes acute expression of genes related to Alzheimer's disease and latent tau aggregation in transgenic mouse models of tauopathy. Mol Med 28:83.
Fan GB, Li Y, Xu GS, Zhao AY, Jin HJ, Sun SQ, Qi SH (2023) Propofol inhibits ferroptotic cell death through the Nrf2/Gpx4 signaling pathway in the mouse model of cerebral ischemia-reperfusion injury. Neurochem Res 48:956-966.
Fang F, Song R, Ling X, Peng M, Xue Z, Cang J (2017) Multiple sevoflurane anesthesia in pregnant mice inhibits neurogenesis of fetal hippocampus via repressing transcription factor Pax6. Life Sci 175:16-22.
Feng L, Sun J, Xia L, Shi Q, Hou Y, Zhang L, Li M, Fan C, Sun B (2024) Ferroptosis mechanism and Alzheimer's disease. Neural Regen Res 19:1741-1750.
Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, Warner DO (2011) Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics 128:e1053-1061.
Friese MB, Gujral TS, Palanisamy A, Hemmer B, Culley DJ, Crosby G (2023) Anesthetics inhibit phosphorylation of the ribosomal protein S6 in mouse cultured cortical cells and developing brain. Front Aging Neurosci 15:1060186.
Gao QS, Zhang YH, Xue H, Wu ZY, Li C, Zhao P (2021) Brief inhalation of sevoflurane can reduce glial scar formation after hypoxic-ischemic brain injury in neonatal rats. Neural Regen Res 16:1052-1061.

Gascoigne DA, Serdyukova NA, Aksenov DP (2021) Early development of the GABAergic system and the associated risks of neonatal anesthesia. Int J Mol Sci 22:12951.

Ge M, Yin J, Qin X, Zhai J, Shao X, Wang R, Fan S, Dai Z, Wang S, Li Y (2021) Isoflurane post-conditioning attenuates cerebral ischemia/reperfusion injury by reducing apoptotic through activating the BMP7/SMAD signaling pathway in rats. J Chem Neuroanat 112:101916.

Glatz P, Sandin RH, Pedersen NL, Bonamy AK, Eriksson LI, Granath F (2017) Association of anesthesia and surgery during childhood with long-term academic performance. JAMA Pediatr 171:e163470.

Gong HY, Zheng F, Zhang C, Chen XY, Liu JJ, Yue XQ (2016) Propofol protects hippocampal neurons from apoptosis in ischemic brain injury by increasing GLT-1 expression and inhibiting the activation of NMDAR via the JNK/Akt signaling pathway. Int J Mol Med 38:943-950.

Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, Li J (2022) Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduct Target Ther 7:391.

Guo S, Liu L, Wang C, Jiang Q, Dong Y, Tian Y (2018) Repeated exposure to sevoflurane impairs the learning and memory of older male rats. Life Sci 192:75-83.

Han D, Li S, Xiong Q, Zhou L, Luo A (2015) Effect of propofol on the expression of MMP-9 and its relevant inflammatory factors in brain of rat with intracerebral hemorrhage. Cell Biochem Biophys 72:675-679.

Han F, Zhao J, Zhao G (2021) Prolonged volatile anesthetic exposure exacerbates cognitive impairment and neuropathology in the 5xFAD mouse model of Alzheimer's disease. J Alzheimers Dis 84:1551-1562.

Haseneder R, Kratzer S, von Meyer L, Eder M, Kochs E, Rammes G (2009) Isoflurane and sevoflurane dose-dependently impair hippocampal long-term potentiation. Eur J Pharmacol 623:47-51.

Hu Y, Ye C, Cheng S, Chen J (2021) Propofol downregulates lncRNA MALAT1 to alleviate cerebral ischemia-reperfusion injury. Inflammation 44:2580-2591.

Huang J, Jing S, Chen X, Bao X, Du Z, Li H, Yang T, Fan X (2016) Propofol administration during early postnatal life suppresses hippocampal neurogenesis. Mol Neurobiol 53:1031-1044.

Hudson AE, Hemmings HC, Jr. (2011) Are anaesthetics toxic to the brain? Br J Anaesth 107:30-37.

Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vockler J, Dikranian K, Tenkova TI, Stefovska V, Turski L, Olney JW (1999) Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 283:70-74.

Ing C, Jackson WM, Zaccariello MJ, Goldberg TE, McCann ME, Grobler A, Davidson A, Sun L, Li G, Warner DO (2021) Prospectively assessed neurodevelopmental outcomes in studies of anaesthetic neurotoxicity in children: a systematic review and meta-analysis. Br J Anaesth 126:433-444.

Ing C, Warner DO, Sun LS, Flick RP, Davidson AJ, Vutskits L, McCann ME, O'Leary J, Bellinger DC, Rauh V, Orser BA, Suresh S, Andropoulos DB (2022) Anesthesia and developing brains: unanswered questions and proposed paths forward. Anesthesiology 136:500-512.

Jia Q, Li J, Guo X, Li Y, Wu Y, Peng Y, Fang Z, Zhang X (2024) Neuroprotective effects of chaperone-mediated autophagy in neurodegenerative diseases. Neural Regen Res 19:1291-1298.

Jevtovic-Todorovic V, Brambrick A (2018) General anesthesia and young brain: what is new? J Neurosurg Anesthesiol 30:217-222.

Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF (2003) Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 23:876-882.

Ji C, Ni Q, Chen W, Yang Z, Ma D (2019) General anesthetic neurotoxicity in the young: Mechanism and prevention. Neurosci Biobehav Rev 107:883-896.

Jurcau A, Simion A (2021) Neuroinflammation in cerebral ischemia and ischemia/reperfusion injuries: from pathophysiology to therapeutic strategies. Int J Mol Sci 23:14.

Kang L, Piao M, Liu N, Gu W, Feng C (2024) Sevoflurane exposure induces neuronal cell ferroptosis initiated by increase of intracellular hydrogen peroxide in the developing brain via ER stress ATF3 activation. Mol Neurobiol 61:2313-2335.

Karwacki Z, Kowianski P, Dziewiatkowski J, Domaradzka-Pytel B, Ludkiewicz B, Wojcik S, Narkiewicz O, Morys J (2006) Quantitative analysis of influence of sevoflurane on the reactivity of microglial cells in the course of the experimental model of intracerebral haemorrhage. Eur J Anaesthesiol 23:874-881.

Kato R, Tachibana K, Nishimoto N, Hashimoto T, Uchida Y, Ito R, Tsuruga K, Takita K, Morimoto Y (2013) Neonatal exposure to sevoflurane causes significant suppression of hippocampal long-term potentiation in postgrowth rats. Anesth Analg 117:1429-1435.

Kelly CE, Shaul M, Thompson DK, Mainzer RM, Yang JY, Dhollander T, Cheong JL, Inder TE, Doyle LW, Anderson PJ (2023) Long-lasting effects of very preterm birth on brain structure in adulthood: a systematic review and meta-analysis. Neurosci Biobehav Rev 147:105082.

Ko WR, Liaw YP, Huang JY, Zhao DH, Chang HC, Ko PC, Jan SR, Nfor ON, Chiang YC, Lin LY (2014) Exposure to general anesthesia in early life and the risk of attention deficit/hyperactivity disorder development: a nationwide, retrospective matched-cohort study. Paediatr Anaesth 24:741-748.

Lan X, Han X, Li Q, Yang QW, Wang J (2017) Modulators of microglial activation and polarization after intracerebral haemorrhage. Nat Rev Neurol 13:420-433.

Lee CT, Bendriem RM, Wu WW, Shen RF (2017) 3 d brain organoids derived from pluripotent stem cells: promising experimental models for brain development and neurodegenerative disorders. J Biomed Sci 24:59.

Lee JA, Bae DH, Choi WH, Cho CH, Bang YS, Yoo J (2022) Effects of sevoflurane exposure on fetal brain development using cerebral organoids. J Mol Neurosci 72:2440-2450.

Leikas JV, Kohtala S, Theilmann W, Jalkanen AJ, Forsberg MM, Rantamäki T (2017) Brief isoflurane anesthesia regulates striatal AKT-GSK3β signaling and ameliorates motor deficits in a rat model of early-stage Parkinson's disease. J Neurochem 142:456-463.

Li L, Zhan Y, Xia H, Wu Y, Wu X, Chen S (2023) Sevoflurane protects against intracerebral hemorrhage via microRNA-133b/FOXO4/BCL2 axis. Int Immunopharmacol 114:109453.

Li M, Yuan Y, Hou Z, Hao S, Jin L, Wang B (2024) Human brain organoid: trends, evolution, and remaining challenges. Neural Regen Res 19:2387-2399.

Li Y, Wang F, Liu C, Zeng M, Han X, Luo T, Jiang W, Xu J, Wang H (2013) JNK pathway may be involved in isoflurane-induced apoptosis in the hippocampi of neonatal rats. Neurosci Lett 545:17-22.

Liang C, Cang J, Wang H, Xue Z (2013) Propofol attenuates cerebral ischemia/reperfusion injury partially using heme oxygenase-1. J Neurosurg Anesthesiol 25:311-316.

Liang L, Xie R, Lu R, Ma R, Wang X, Wang F, Liu B, Wu S, Wang Y, Zhang H (2020) Involvement of homodomain interacting protein kinase 2-c-Jun N-terminal kinase/c-Jun cascade in the long-term synaptic toxicity and cognition impairment induced by neonatal Sevoflurane exposure. J Neurochem 154:372-388.

Liang L, Fan Z, He D, Zhao Y, Zeng T, Liu B, Ma T, Kang J, Zhang H (2022a) Sevoflurane-induced neurotoxicity in the developing hippocampus via HIPK2/AKT/mTOR signaling. Neurotox Res 40:803-813.

Liang Y, Huang Y, Shao R, Xiao F, Lin F, Dai H, Pan L (2022b) Propofol produces neurotoxicity by inducing mitochondrial apoptosis. Exp Ther Med 24:630.

Lim BG, Lee IO (2020) Anesthetic management of geriatric patients. Korean J Anesthesiol 73:8-29.

Liu G, Zhu T, Zhang A, Li F, Qian W, Qian B (2016) Heightened stress response and cognitive impairment after repeated neonatal sevoflurane exposures might be linked to excessive GABAAR-mediated depolarization. J Anesth 30:834-841.

Liu J, Wang P, Zhang X, Zhang W, Gu G (2014) Effects of different concentration and duration time of isoflurane on acute and long-term neurocognitive function of young adult C57BL/6 mouse. Int J Clin Exp Pathol 7:5828-5836.

Liu M, Jayaraman K, Mehla J, Diwan D, Nelson JW, Hussein AE, Vellimana AK, Abu-Amer Y, Zipfel GJ, Athiraman U (2023a) Isoflurane conditioning provides protection against subarachnoid hemorrhage induced delayed cerebral ischemia through NF-kB inhibition. Biomedicines 11:1163.

Liu M, Jayaraman K, Norris AJ, Hussein A, Nelson JW, Mehla J, Diwan D, Vellimana A, Abu-Amer Y, Zipfel GJ, Athiraman U (2023b) Isoflurane conditioning-induced delayed cerebral ischemia protection in subarachnoid hemorrhage-role of inducible nitric oxide synthase. J Am Heart Assoc 12:e029975.

Liu P, Yuan J, Feng Y, Chen X, Wang G, Zhao L (2021) Ferroptosis contributes to isoflurane-induced neurotoxicity and learning and memory impairment. Cell Death Discov 7:72.

Liu S, Fang F, Song R, Gao X, Jiang M, Cang J (2018) Sevoflurane affects neurogenesis through cell cycle arrest via inhibiting wnt/beta-catenin signaling pathway in mouse neural stem cells. Life Sci 209:34-42.

Liu X, Ji J, Zhao GQ (2020) General anesthesia affecting on developing brain: evidence from animal to clinical research. J Anesth 34:765-772.

Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, Jones EJH, Jones RM, Pickles A, State MW, Taylor JL, Veenstra-VanderWeele J (2020) Autism spectrum disorder. Nat Rev Dis Primers 6:5.

Lu Y, Chen L, Ye J, Chen C, Zhou Y, Li K, Zhang Z, Peng M (2020) Surgery/Anesthesia disturbs mitochondrial fission/fusion dynamics in the brain of aged mice with postoperative delirium. Aging 12:844-865.

Luo X, Shu XZ, Liu DN, Tan JQ, Peng T, Huang XR, Sun GH, Peng XK, Wang JL, Zhou J (2024) Effects of electroacupuncture on Toll-like receptor 4/nuclear factor κB signalling pathway in cerebral ischemia-reperfusion injury rats. Zhonguo Zuzhi Gongcheng Yanjiu 28:2186-2190.

Ma JF, Li CG, Sun MY, Shao GF, Li KZ (2017) Isoflurane and sevoflurane affects Wnt/beta-catenin signaling pathways in hippocampal formation of neonatal rats. Eur Rev Med Pharmacol Sci 21:1980-1989.

Mardini F, Tang JX, Li JC, Arroliga MJ, Eckenhoff RG, Eckenhoff MF (2017) Effects of propofol and surgery on neuropathology and cognition in the 3xTgAD Alzheimer transgenic mouse model. Br J Anaesth 119:472-480.

Mastrangelo G, Comiati V, dell'Aquila M, Zamprogno E (2013) Exposure to anesthetic gases and Parkinson's disease: a case report. BMC Neurol 13:194.

McAuliffe JJ, Joseph B, Vorhees CV (2007) Isoflurane-delayed preconditioning reduces immediate mortality and improves striatal function in adult mice after neonatal hypoxia-ischemia. Anesth Analg 104:1066-1077, tables of contents.

McAuliffe JJ, Loepke AW, Miles L, Joseph B, Hughes E, Vorhees CV (2009) Desflurane, isoflurane, and sevoflurane provide limited neuroprotection against neonatal hypoxia-ischemia in a delayed preconditioning paradigm. Anesthesiology 111:533-546.

McCann ME, et al. (2019) Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. Lancet 393:664-677.

McCann ME, Soriano SG (2019) Does general anesthesia affect neurodevelopment in infants and children? BMJ 367:l6459.

Mintz CD, Barrett KMS, Smith SC, Benson DL, Harrison NL (2013) Anesthetics interfere with axon guidance in developing mouse neocortical neurons in vitro via a γ-aminobutyric acid type A receptor mechanism. Anesthesiology 118:825-833.

Muheyati A, Jiang S, Wang N, Yu G, Su R (2024) Extrasynaptic GABA (A) receptors in central medial thalamus mediate anesthesia in rats. Eur J Pharmacol 972:176561.

Murphy KL, McGaughy J, Croxson PL, Baxter MG (2017) Exposure to sevoflurane anesthesia during development does not impair aspects of attention during adulthood in rats. Neurotoxicol Teratol 60:87-94.

Niu J, Wu Z, Xue H, Zhang Y, Gao Q, Li C, Zhao P (2021) Sevoflurane post-conditioning alleviated hypoxic-ischemic brain injury in neonatal rats by inhibiting endoplasmic reticulum stress-mediated autophagy via IRE1 signalings. Neurochem Int 150:105198.

Noguchi KK, Johnson SA, Dissen GA, Martin LD, Manzella FM, Schenning KJ, Olney JW, Brambrink AM (2017) Isoflurane exposure for three hours triggers apoptotic cell death in neonatal macaque brain. Br J Anaesth 119:524-531.

Oddo M, Crippa IA, Mehta S, Menon D, Payen JF, Taccone FS, Citerio G (2016) Optimizing sedation in patients with acute brain injury. Crit Care 20:128.

Pei Z, Wang S, Li Q (2017) Sevoflurane suppresses microglial M2 polarization. Neurosci Lett 655:160-165.

Perluigi M, Di Domenico F, Butterfield DA (2015) mTOR signaling in aging and neurodegeneration: at the crossroad between metabolism dysfunction and impairment of autophagy. Neurobiol Dis 84:39-49.

Port RG, Gaetz W, Bloy L, Wang DJ, Blaskey L, Kuschner ES, Levy SE, Brodkin ES, Roberts TPL (2017) Exploring the relationship between cortical GABA concentrations, auditory gamma-band responses and development in ASD: evidence for an altered maturational trajectory in ASD. Autism Res 10:593-607.

Posner J, Polanczyk GV, Sonuga-Barke E (2020) Attention-deficit hyperactivity disorder. Lancet 395:450-462.

Qiao H, Li Y, Xu Z, Li W, Fu Z, Wang Y, King A, Wei H (2017) Propofol affects neurodegeneration and neurogenesis by regulation of autophagy via effects on intracellular calcium homeostasis. Anesthesiology 127:490-501.

Reighard C, Junaid S, Jackson WM, Arif A, Waddington H, Whitehouse AJO, Ing C (2022) Anesthetic exposure during childhood and neurodevelopmental outcomes: a systematic review and meta-analysis. JAMA Netw Open 5:e2217427.

Rossaint J, Rossaint R, Weis J, Fries M, Rex S, Coburn M (2009) Propofol: neuroprotection in an in vitro model of traumatic brain injury. Crit Care 13:R61.

Roy M, Strate P (2023) Autism spectrum disorders in adulthood-symptoms, diagnosis, and treatment. Dtsch Arztebl Int 120:87-93.

Sall JW, Stratmann G, Leong J, Woodward E, Bickler PE (2012) Propofol at clinically relevant concentrations increases neuronal differentiation but is not toxic to hippocampal neural precursor cells in vitro. Anesthesiology 117:1080-1090.

Sanchez V, Feinstein SD, Lunardi N, Joksovic PM, Boscolo A, Todorovic SM, Jevtovic-Todorovic V (2011) General anesthesia causes long-term impairment of mitochondrial morphogenesis and synaptic transmission in developing rat brain. Anesthesiology 115:992-1002.

Satomoto M, Satoh Y, Terui K, Miyao H, Takishima K, Ito M, Imaki J (2009) Neonatal exposure to sevoflurane induces abnormal social behaviors and deficits in fear conditioning in mice. Anesthesiology 110:628-637.

Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chetelat G, Teunissen CE, Cummings J, van der Flier WM (2021) Alzheimer's disease. Lancet 397:1577-1590.

Schwer CI, Lehane C, Guelzow T, Zenker S, Strosing KM, Spassov S, Erxleben A, Heimrich B, Buerkle H, Humar M (2013) Thiopental inhibits global protein synthesis by repression of eukaryotic elongation factor 2 and protects from hypoxic neuronal cell death. PLoS One 8:e77258.

Shang J, Li B, Fan H, Liu P, Zhao W, Chen T, Chen P, Yang L (2022) Sevoflurane promotes premature differentiation of dopaminergic neurons in hiPSC-derived midbrain organoids. Front Cell Dev Biol 10:941984.

Shao H, Zhang Y, Dong Y, Yu B, Xia W, Xie Z (2014) Chronic treatment with anesthetic propofol improves cognitive function and attenuates caspase activation in both aged and Alzheimer's disease transgenic mice. J Alzheimers Dis 41:499-513.

Shen X, Dong Y, Xu Z, Wang H, Miao C, Soriano SG, Sun D, Baxter MG, Zhang Y, Xie Z (2013) Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. Anesthesiology 118:502-515.

Shi M, Chen J, Liu T, Dai W, Zhou Z, Chen L, Xie Y (2022) Protective effects of remimazolam on cerebral ischemia/reperfusion injury in rats by inhibiting of NLRP3 inflammasome-dependent pyroptosis. Drug Des Devel Ther 16:413-423.

Shortal BP, Reitz SL, Aggarwal A, Meng QC, McKinstry-Wu AR, Kelz MB, Proekt A (2018) Development and validation of brain target controlled infusion of propofol in mice. PLoS One 13:e0194949.

Silber JH, Rosenbaum PR, Reiter JG, Jain S, Hill AS, Hashemi S, Brown S, Olfson M, Ing C (2024) Exposure to operative anesthesia in childhood and subsequent neurobehavioral diagnoses: a natural experiment using appendectomy. Anesthesiology 141:489-499.

Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanic K, Welch TL, Olson MD, Hanson AC, Schroeder DR, Wilder RT, Warner DO (2012) Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc 87:120-129.

Statler KD, Kochanek PM, Dixon CE, Alexander HL, Warner DS, Clark RS, Wisniewski SR, Graham SH, Jenkins LW, Marion DW, Safar PJ (2000) Isoflurane improves long-term neurologic outcome versus fentanyl after traumatic brain injury in rats. J Neurotrauma 17:1179-1189.

Statler KD, Alexander H, Vagni V, Dixon CE, Clark RS, Jenkins L, Kochanek PM (2006a) Comparison of seven anesthetic agents on outcome after experimental traumatic brain injury in adult, male rats. J Neurotrauma 23:97-108.

Statler KD, Alexander H, Vagni V, Holubkov R, Dixon CE, Clark RS, Jenkins L, Kochanek PM (2006b) Isoflurane exerts neuroprotective actions at or near the time of severe traumatic brain injury. Brain Res 1076:216-224.

Stratmann G, Sall JW, Bell JS, Alvi RS, May L, Ku B, Dowlatshahi M, Dai R, Bickler PE, Russell I, Lee MT, Hrubos MW, Chiu C (2010) Isoflurane does not affect brain cell death, hippocampal neurogenesis, or long-term neurocognitive outcome in aged rats. Anesthesiology 112:305-315.

Su G, Qu Y, Li G, Deng M (2021) Sevoflurane protects against cerebral ischemia/reperfusion injury via microrna-30c-5p modulating homeodomain-interacting protein kinase 1. Bioengineered 12:11858-11871.

Sun GY, Xie K, Sun ZY, Sun MY, Li N (2019) Sevoflurane induces temporary spatial working memory deficits and synaptic ultrastructure impairments in the hippocampus of neonatal rats. Eur Rev Med Pharmacol Sci 23:2620-2629.

Sun LS, Li G, Miller TL, Salorio C, Byrne MW, Bellinger DC, Ing C, Park R, Radcliffe J, Hays SR, DiMaggio CJ, Cooper TJ, Rauh V, Maxwell LG, Youn A, McGowan FX (2016) Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA 315:2312-2320.

Sun M, Xie Z, Zhang J, Leng Y (2022) Mechanistic insight into sevoflurane-associated developmental neurotoxicity. Cell Biol Toxicol 38:927-943.

Tang X, Yan T, Wang S, Liu Q, Yang Q, Zhang Y, Li Y, Wu Y, Liu S, Ma Y, Yang L (2024) Treatment with β-sitosterol ameliorates the effects of cerebral ischemia/reperfusion injury by suppressing cholesterol overload, endoplasmic reticulum stress, and apoptosis. Neural Regen Res 19:642-649.

Tian D, Xing Y, Gao W, Zhang H, Song Y, Tian Y, Dai Z (2021) Sevoflurane aggravates the progress of alzheimer's disease through NLRP3/caspase-1/gasdermin D pathway. Front Cell Dev Biol 9:801422.

Tsai SK, Lin SM, Hung WC, Mok MS, Chih CL, Huang SS (2004) The effect of desflurane on ameliorating cerebral infarction in rats subjected to focal cerebral ischemia-reperfusion injury. Life Sci 74:2541-2549.

Tu Y, Liang Y, Xiao Y, Lv J, Guan R, Xiao F, Xie Y, Xiao Q (2019) Dexmedetomidine attenuates the neurotoxicity of propofol toward primary hippocampal neurons in vitro via Erk1/2/CREB/BDNF signaling pathways. Drug Des Devel Ther 13:695-706.

Twaroski DM, Yan Y, Zaja I, Clark E, Bosnjak ZJ, Bai X (2015) Altered mitochondrial dynamics contributes to propofol-induced cell death in human stem cell-derived neurons. Anesthesiology 123:1067-1083.

Vutskits L, Xie Z (2016) Lasting impact of general anaesthesia on the brain: mechanisms and relevance. Nat Rev Neurosci 17:705-717.

Vutskits L, Davidson AJ (2024) Developmental anesthesia neurotoxicity research in humans: moving the concept. Anesthesiology 141:431-433.

Wang F, Li C, Shao J, Ma J (2021a) Sevoflurane induces inflammation of microglia in hippocampus of neonatal rats by inhibiting Wnt/beta-Catenin/CaMKIV pathway. J Pharmacol Sci 146:105-115.

Wang J, Sun P, Liang P (2020) Neuropsychopharmacological effects of midazolam on the human brain. Brain Inform 7:15.

Wang Q, Luo J, Sun R, Liu J (2021b) MicroRNA-1297 suppressed the Akt/GSK3beta signaling pathway and stimulated neural apoptosis in an in vivo sevoflurane exposure model. J Int Med Res 49:300060520982104.

Wang S, Yin J, Ge M, Dai Z, Li Y, Si J, Ma K, Li L, Yao S (2016) Transforming growth-beta 1 contributes to isoflurane postconditioning against cerebral ischemia-reperfusion injury by regulating the c-Jun N-terminal kinase signaling pathway. Biomed Pharmacother 78:280-290.

Wang S, Wang S, Wang Z, Dong J, Zhang M, Wang Y, Wang J, Jia B, Luo Y, Yin Y (2024) The changing of alpha5-GABAA receptors expression and distribution participate in sevoflurane-induced learning and memory impairment in young mice. CNS Neurosci Ther 30:e14716.

Wang X, Dong Y, Zhang Y, Li T, Xie Z (2019) Sevoflurane induces cognitive impairment in young mice via autophagy. PLoS One 14:e0216372.

Wang Z, Li J, Wang A, Wang Z, Wang J, Yuan J, Wei X, Xing F, Zhang W, Xing N (2021c) Sevoflurane inhibits traumatic brain injury-induced neuron apoptosis via ezh2-downregulated KLF4/p38 axis. Front Cell Dev Biol 9:658720.

Wang Z, Wang Z, Wang A, Li J, Wang J, Yuan J, Wei X, Xing F, Zhang W, Xing N (2022) The neuroprotective mechanism of sevoflurane in rats with traumatic brain injury via FGF2. J Neuroinflammation 19:51.

Warner DO, Zaccariello MJ, Katusic SK, Schroeder DR, Hanson AC, Schulte PJ, Buenvenida SL, Gleich SJ, Wilder RT, Sprung J, Hu D, Voigt RG, Paule MG, Chelonis JJ, Flick RP (2018) Neuropsychological and behavioral outcomes after exposure of young children to procedures requiring general anesthesia: the mayo anesthesia safety in kids (MASK) study. Anesthesiology 129:89-105.

Wei X, Wan X, Zhao B, Hou J, Liu M, Cheng B (2012) Propofol inhibits inflammation and lipid peroxidation following cerebral ischemia/reperfusion in rabbits. Neural Regen Res 7:837-841.

Wen XR, Fu YY, Liu HZ, Wu J, Shao XP, Zhang XB, Tang M, Shi Y, Ma K, Zhang F, Wang YW, Tang H, Han D, Zhang P, Wang SL, Xu Z, Song YJ (2016) Neuroprotection of sevoflurane against ischemia/reperfusion-induced brain injury through inhibiting JNK3/Caspase-3 by enhancing Akt signaling pathway. Mol Neurobiol 53:1661-1671.

Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO (2009) Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 110:796-804.

Wolfert C, Maurer CJ, Berlis A, Schneider H, Steininger K, Motov S, Krauss P, Sommer B, Shiban E (2022) Hydrocephalus, cerebral vasospasm, and delayed cerebral ischemia following non-aneurysmatic spontaneous subarachnoid hemorrhages: an underestimated problem. Neurosurg Rev 46:23.

Woodhouse A, Fernandez-Martos CM, Atkinson RAK, Hanson KA, Collins JM, O'Mara AR, Terblanche N, Skinner MW, Vickers JC, King AE (2018) Repeat propofol anesthesia does not exacerbate plaque deposition or synapse loss in APP/PS1 Alzheimer's disease mice. BMC Anesthesiol 18:47.

Wu J, Yang JJ, Cao Y, Li H, Zhao H, Yang S, Li K (2020) Iron overload contributes to general anaesthesia-induced neurotoxicity and cognitive deficits. J Neuroinflammation 17:110.

Xiao H, Liu B, Chen Y, Zhang J (2016) Learning, memory and synaptic plasticity in hippocampus in rats exposed to sevoflurane. Int J Dev Neurosci 48:38-49.

Xie L, Liu Y, Hu Y, Wang B, Zhu Z, Jiang Y, Suo Y, Hu M, Gao J, Ullah R, Hu Z (2020) Neonatal sevoflurane exposure induces impulsive behavioral deficit through disrupting excitatory neurons in the medial prefrontal cortex in mice. Transl Psychiatry 10:202.

Xu C, Niu JJ, Zhou JF, Wei YS (2019a) MicroRNA-96 is responsible for sevoflurane-induced cognitive dysfunction in neonatal rats via inhibiting IGF1R. Brain Res Bull 144:140-148.

Xu DA, DeYoung TP, Kondoleon NP, Eckenhoff RG, Eckenhoff MF (2021) Anesthetic effects on the progression of parkinson disease in the rat DJ-1 model. Anesth Analg 133:1140-1151.

Xu F, Han L, Wang Y, Deng D, Ding Y, Zhao S, Zhang Q, Ma L, Chen X (2023) Prolonged anesthesia induces neuroinflammation and complement-mediated microglial synaptic elimination involved in neurocognitive dysfunction and anxiety-like behaviors. BMC Med 21:7.

Xu J, Mathena RP, Xu M, Wang Y, Chang C, Fang Y, Zhang P, Mintz CD (2018a) Early developmental exposure to general anesthetic agents in primary neuron culture disrupts synapse formation via actions on the mTOR pathway. Int J Mol Sci 19:2183.

Xu J, Xu M, Wang Y, Mathena RP, Wen J, Zhang P, Furmanski O, Mintz CD (2019b) Anesthetics disrupt growth cone guidance cue sensing through actions on the GABA (A) alpha2 receptor mediated by the immature chloride gradient. Neurotoxicol Teratol 74:106812.

Xu L, Shen J, Yu L, Sun J, Yan M (2018b) Autophagy is involved in sevoflurane-induced developmental neurotoxicity in the developing rat brain. Brain Res Bull 140:226-232.

Xu L, Shen J, Yu L, Sun J, McQuillan PM, Hu Z, Yan M (2018c) Role of autophagy in sevoflurane-induced neurotoxicity in neonatal rat hippocampal cells. Brain Res Bull 140:291-298.

Xu L, Hu Y, Huang L, Liu Y, Wang B, Xie L, Hu Z (2019c) The association between attention deficit hyperactivity disorder and general anaesthesia- a narrative review. Anaesthesia 74:57-63.

Xu Y, Xue H, Zhao P, Yang Y, Ji G, Yu W, Han G, Ding M, Wang F (2016) Isoflurane postconditioning induces concentration- and timing-dependent neuroprotection partly mediated by the GluR2 AMPA receptor in neonatal rats after brain hypoxia-ischemia. J Anesth 30:427-436.

Xu Z, Dong Y, Wu X, Zhang J, McAuliffe S, Pan C, Zhang Y, Ichinose F, Yue Y, Xie Z (2011) The potential dual effects of anesthetic isoflurane on Aβ-induced apoptosis. Curr Alzheimer Res 8:741-752.

Xue H, Xu Y, Wang S, Wu ZY, Li XY, Zhang YH, Niu JY, Gao QS, Zhao P (2019) Sevoflurane post-conditioning alleviates neonatal rat hypoxic-ischemic cerebral injury via Ezh2-regulated autophagy. Drug Des Devel Ther 13:1691-1706.

Yamaguchi S, Midorikawa Y, Okuda Y, Kitajima T (1999) Propofol prevents delayed neuronal death following transient forebrain ischemia in gerbils. Can J Anaesth 46:593-598.

Yang F, Zhao H, Zhang K, Wu X, Liu H (2020) Research progress and treatment strategies for anesthetic neurotoxicity. Brain Res Bull 164:37-44.

Yang L, Chen H, Guan L, Xu Y (2022) Sevoflurane offers neuroprotection in a cerebral ischemia/reperfusion injury rat model through the E2F1/EZH2/TIMP2 regulatory axis. Mol Neurobiol 59:2219-2231.

Yang M, Wang K, Liu B, Shen Y, Liu G (2024) Hypoxic-ischemic encephalopathy: pathogenesis and promising therapies. Mol Neurobiol. doi: 10.1007/s12035-024-04398-9.

Yin L, Li L, Deng J, Wang D, Guo Y, Zhang X, Li H, Zhao S, Zhong H, Dong H (2019) Optogenetic/chemogenetic activation of gabaergic neurons in the ventral tegmental area facilitates general anesthesia via projections to the lateral hypothalamus in mice. Front Neural Circuits 13:73.

Yon JH, Daniel-Johnson J, Carter LB, Jevtovic-Todorovic V (2005) Anesthesia induces neuronal cell death in the developing rat brain via the intrinsic and extrinsic apoptotic pathways. Neuroscience 135:815-827.

Young Y, Menon DK, Tisavipat N, Matta BF, Jones JG (1997) Propofol neuroprotection in a rat model of ischaemia reperfusion injury. Eur J Anaesthesiol 14:320-326.

Yu D, Jiang Y, Gao J, Liu B, Chen P (2013) Repeated exposure to propofol potentiates neuroapoptosis and long-term behavioral deficits in neonatal rats. Neurosci Lett 534:41-46.

Zeng S, Zhu R, Wang Y, Yang Y, Li N, Fu N, Sun M, Zhang J (2022) Role of GABA (A) receptor depolarization-mediated VGCC activation in sevoflurane-induced cognitive impairment in neonatal mice. Front Cell Neurosci 16:964227.

Zhang H, Sun X, Li J, Shan W, Yang J, Zuo Z (2023) Endoplasmic reticulum stress-activated neuronal and microglial autophagy contributes to postoperative cognitive dysfunction in neonatal rats. Neurochem Res 48:1835-1847.

Zhang HB, Tu XK, Chen Q, Shi SS (2019) Propofol reduces inflammatory brain injury after subarachnoid hemorrhage: involvement of PI3K/Akt pathway. J Stroke Cerebrovasc Dis 28:104375.

Zhang J, Li Y (2023) Propofol-induced developmental neurotoxicity: from mechanisms to therapeutic strategies. ACS Chem Neurosci 14:1017-1032.

Zhang L, Zhang J, Yang L, Dong Y, Zhang Y, Xie Z (2013a) Isoflurane and sevoflurane increase interleukin-6 levels through the nuclear factor-kappa B pathway in neuroglioma cells. Br J Anaesth 110 Suppl 1:i82-91.

Zhang R, Xu J, Liu YY, Zuo PP, Yang N, Ji C, Wang Y, Wang H, Wu AS, Yue Y (2013b) Propofol may protect PC12 cells from beta-amyloid (2) (5) (-) (3) (5) induced apoptosis through the GSK-3beta signaling pathway. Chin Med J (Engl) 126:1884-1889.

Zhang W, Liu Q, Zhu H, Ma C, Luo Q, Ji M, Liu L (2022) Propofol induces the apoptosis of neural stem cells via microRNA-9-5p / chemokine CXC receptor 4 signaling pathway. Bioengineered 13:1062-1072.

Zhang Y, Shao H, Dong Y, Swain CA, Yu B, Xia W, Xie Z (2014) Chronic treatment with anesthetic propofol attenuates beta-amyloid protein levels in brain tissues of aged mice. Transl Neurodegener 3:8.

Zhang Y, Dong Y, Zheng H, Shie V, Wang H, Busscher JJ, Yue Y, Xu Z, Xie Z (2013c) Sevoflurane inhibits neurogenesis and the Wnt-catenin signaling pathway in mouse neural progenitor cells. Curr Mol Med 13:1446-1454.

Zhang Z, Li Z, Li S, Xiong B, Zhou Y, Shi C (2025) Hyperbaric oxygen for moderate-to-severe traumatic brain injury: outcomes 5-8 years after injury. Med Gas Res 15:156-163.

Zhao P, Peng L, Li L, Xu X, Zuo Z (2007) Isoflurane preconditioning improves long-term neurologic outcome after hypoxic-ischemic brain injury in neonatal rats. Anesthesiology 107:963-970.

Zhao X, Yang Z, Liang G, Wu Z, Peng Y, Joseph DJ, Inan S, Wei H (2013) Dual effects of isoflurane on proliferation, differentiation, and survival in human neuroprogenitor cells. Anesthesiology 118:537-549.

Zhou G, Pang S, Li Y, Gao J (2024) Progress in the generation of spinal cord organoids over the past decade and future perspectives. Neural Regen Res 19:1013-1019.

Zhong H, Chen H, Gu C (2020) Sevoflurane post-treatment upregulated mir-203 expression to attenuate cerebral ischemia-reperfusion-induced neuroinflammation by targeting MyD88. Inflammation 43:651-663.

Zhou H, Xie Z, Brambrink AM, Yang G (2021) Behavioural impairments after exposure of neonatal mice to propofol are accompanied by reductions in neuronal activity in cortical circuitry. Br J Anaesth 126:1141-1156.

Zhou Y, Lekic T, Fathali N, Ostrowski RP, Martin RD, Tang J, Zhang JH (2010) Isoflurane posttreatment reduces neonatal hypoxic-ischemic brain injury in rats by the sphingosine-1-phosphate/phosphatidylinositol-3-kinase/Akt pathway. Stroke 41:1521-1527.

C-Editor: Zhao M; S-Editors: Wang J, Li CH;
L-Editor: Song LP;T-Editor: Jia Y