Journal of Integrative Neuroscience

J. Integr. Neurosci. **2025**; 24(3): 26388
https://doi.org/10.31083/JIN26388

Review

Effects of Xenon on the Developing Brain: Current Insights from Pre-clinical and Clinical Studies

Qinfang Shi[1,2,3], Gerhard Rammes[4], Ping Wang[5], Chengkun Xia[1,2,3], Fangfang Mou[6], Jing Zhu[6], Haidong Guo[6,*], Shuijin Shao[6,*], Xingxing Wang[6,*]

[1]Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 430022 Wuhan, Hubei, China
[2]Institute of Anesthesia and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 430022 Wuhan, Hubei, China
[3]Key Laboratory of Anesthesiology and Resuscitation (Huazhong University of Science and Technology), Ministry of Education, 430022 Wuhan, Hubei, China
[4]Department of Anesthesiology and Intensive Care Medicine, School of Medicine and Health, Klinikum Rechts der Isar, Technical University of Munich, 81675 Munich, Germany
[5]Department of Anesthesiology, Shenzhen University General Hospital, 518071 Shenzhen, Guangdong, China
[6]School of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, 201203 Shanghai, China
*Correspondence: hdguo@shutcm.edu.cn (Haidong Guo); shaoshuijin@163.com (Shuijin Shao); xingxingwang@shutcm.edu.cn (Xingxing Wang)
Academic Editor: Bettina Platt
Submitted: 1 September 2024 Revised: 19 October 2024 Accepted: 31 October 2024 Published: 4 March 2025

Abstract

Research has indicated that general anesthetics may potentially induce neuroapoptosis, resulting in long-term neurological deficits in the developing brain. Fortunately, xenon, a noble gas, emerges as a promising candidate for an ideal anesthetic due to its favorable properties, offering neuroprotection and mitigating the neurotoxic effects of other general anesthetics during early life stages. Nevertheless, it is important to highlight that xenon has also been observed to cause neuroapoptosis in the neonatal brain, suggesting that xenon possesses both neuroprotective qualities (as evidenced by pre-clinical and clinical studies) and neurotoxic potential (based mainly on pre-clinical evidence) during brain development. To gain a comprehensive understanding the effects xenon, this review will explore the anesthetic properties of xenon, examine its effects on anesthesia, and elucidate its mechanisms of potential neuroprotection and neurotoxicity in the developing brain. The primary emphasis will be on xenon's application in the context of anesthetic-induced developmental neurotoxicity (AIDN), hypoxic-ischemic encephalopathy (HIE), and teratogenicity, aiming to provide valuable insights for pediatricians, pediatric anesthesiologists, and other healthcare professionals involved in the use and study of xenon anesthesia.

Keywords: general anesthesia; xenon; neuroprotection; neuroapoptosis; synaptic transmission

1. Introduction

Each year, roughly 1 to 2% of pregnant women require non-obstetric surgery and anesthesia to address various medical conditions [1]. Simultaneously, millions of infants and young children necessitate general anesthesia for essential or life-preserving surgeries. While it was initially believed that anesthesia induces a safe and reversible state of unconsciousness, recent studies indicate that exposure to general anesthetics could result in long-term morphological and functional changes in the developing brain, potentially causing permanent neurocognitive deficits [2–5]. In light of this, the Food and Drug Administration (FDA) has issued a warning to inform the public that prolonged or repeated exposure to general anesthetics may have a detrimental effect on the brains of children under the age of three [6].

The process of brain development is a complex and ongoing journey. Typically, it begins with the differentiation of neural progenitor cells during the third week of gestation and continues until the third decade of life [7]. Throughout this process, one of the most significant phenomena observed is synaptogenesis, encompassing axon growth, target recognition, and synapse elimination, which are critical for the formation of neural networks [8]. The neural networks thus formed are highly sensitive to a range of environmental stimuli, notably the neurotransmitter glutamate and its corresponding receptors [9–11].

The neuroprotective properties of xenon on the developing brain have recently attracted considerable interest [12–20]. This noble gas was first discovered by William Ramsay in 1898 [21], and its anesthetic properties were initially reported in 1951. Approximately half a century later, xenon received approval as an anesthetic agent in Russia in 2000, with this approval subsequently being extended to Germany in 2005 and Europe in 2007 [13,22]. Over the years, extensive research has demonstrated the safety and efficacy of xenon in both pre-clinical and clinical studies, including in infants and young children [12,19,22–24]. In particular, several studies have highlighted the potential neuroprotective effects of xenon on the developing brain [14,25,26]. However, it has also been observed that xenon

may induce neuroapoptosis in the neonatal brain [17,27]. Consequently, it appears that xenon exhibits both neuroprotective properties and neurotoxic effects during brain development. To tackle this, the present review brings together the latest information on the effects of xenon on the developing brain, focusing particularly on its impact on hypoxic-ischemic encephalopathy (HIE), anesthetic-induced developmental neurotoxicity (AIDN), and obstetric anesthesia.

2. Xenon's Property and Mechanisms as an Anesthetic

Xenon, a noble gas celebrated for its complete valence shell and minimal reactivity, derives its name from the Greek term signifying "foreigner" or "stranger", reflecting its scarcity—it constitutes merely one part per 20 million in the atmospheric air. Discovered in 1898 by William Ramsay and Maurice Travers [21], xenon was isolated via fractional distillation of liquefied air. In 1951, xenon was first utilized as a clinical anesthetic by the American anesthesiologist Stuart C. Cullen, who successfully administered it to an 81-year-old man in good health [22]. Later, extensive clinical and laboratory studies have highlighted xenon as a potent anesthetic possessing numerous desirable properties, including rapid onset and expiration, low blood/gas partition coefficients [28], non-toxicity, effective analgesia [12], minimal hemodynamic depression [29], and organ protection, particularly neuroprotection [30,31] and cardioprotection [32].

Nonetheless, the mechanism of xenon as an anesthetic remained largely a mystery until 1998, when Franks *et al*. [33] discovered that in rat hippocampal neuronal cultures, exposure to 80% xenon resulted in a non-competitive reduction of N-methyl-D-aspartic acid (NMDA) receptor-induced currents by roughly 60%. Subsequently, in 2007, Dickinson *et al*. [34] conducted further research and demonstrated that xenon not only acted as a noncompetitive antagonist of NMDA receptors but also competed with glycine on the GluN1 subunit of the NMDA receptor. This revealed that xenon inhibited NMDA receptors via both competitive and noncompetitive mechanisms.

The additional research conducted by Haseneder *et al*. [35] revealed that in basolateral amygdala slices, xenon depressed another ionotropic glutamate receptor, α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) receptor-mediated synaptic transmission. In this study, xenon concentration-dependently reduced NMDA and AMPA receptor-mediated synaptic currents with similar potency [35]. Moreover, at a liquid phase concentration of 1.9 mM, xenon is a weak antagonist against NMDA and AMPA receptors by reducing synaptic responses in slices of various brain regions only to approximately 65–58% and 67–56%, respectively [36,37]. At this concentration, xenon reversibly blocked CA1-long-term potentiation (LTP) due to the impact of NMDA receptor activation on synaptic plasticity [38].

Cyclic nucleotide-gated cation channel Type 2 (HCN2) channels are a special class of ion channels that play multiple important roles in the nervous system, mainly including the regulation of neuron excitability, synaptic plasticity, spontaneous rhythmic activities of neurons (such as the sleep-wake cycle), and synchrony of neural networks [39]. Thalamic HCN channels are pivotal targets for the influence of anesthetics on consciousness levels and may play a significant role in the process of anesthesia recovery [40]. In acute brain slices from adult wild-type mice, xenon reduced thalamocortical signal transmission in a concentration-dependent manner. In contrast, in HCN2 knockout mice, xenon neither attenuated thalamocortical signal transmission nor exhibited sedative effects [41]. Subsequently, they confirmed that the hypnotic properties of xenon are mediated by impairing HCN2 channel function through interference with the cyclic nucleotide-binding domain (CNBD) of HCN2 channels [42].

Other mechanisms also contribute to the anesthetic properties of xenon. Subsequent research revealed that at clinically relevant concentrations, xenon inhibited nicotinic acetylcholine (nACh) receptors in a non-competitive and voltage-independent manner, which suggested that xenon functions via the suppression of nACh receptors [43]. In addition, two-pore-domain potassium (TREK-1) channels belong to the two-pore domain K+ channels (K2P) and displays sensitivity to physical and chemical stimuli, including volatile anesthetics [44]. Gruss *et al*. [45] evaluated the currents of mock-transfected human embryonic kidney cells (HEK-293 cells) and found that xenon markedly activated TREK-1 channels in HEK-293 cells.

In conclusion, xenon, as an inhaled anesthetic, exerts its effects by suppressing NMDA, AMPA, and nACh receptors, activating K2P-TREK-1 channels, and inhibiting HCN2 channels (refer to Table 1, Ref. [33–37,41–43,45]).

3. Neuroprotection Mechanisms of Xenon

3.1 Cellular and Molecular Candidates

As demonstrated previously, xenon has been utilized as an inhaled anesthetic with various mechanisms of action. Among these, certain candidates are believed to contribute to xenon's neuroprotective properties. The neuroprotective effect of xenon is potentially due to its antagonistic effect on the NMDA receptor. This mechanism enables xenon to counteract the excitotoxicity resulting from the over-release of glutamate, which is implicated in various neuropathological conditions. Preclinical studies have demonstrated that xenon exhibits neuroprotective properties across a variety of models, including those of hypoxic-ischemic injury [31], traumatic brain injury [46], and AIDN [47]. However, the precise mechanisms underlying these neuroprotective effects have not yet been fully elucidated. Current observations suggest that these effects primarily involve the antagonism of the NMDA, AMPA, and HCN receptors [13,14],

Table 1. Molecular mechanisms of xenon's anesthetic effect.

Experimental subjects	Concentration	Mechanisms
Cultured rat hippocampal neurons	80%	Noncompetitive antagonist of NMDA receptors [33].
Hippocampal neurons	5%, 20%, 40%, 60%, and 80%	Competitive antagonist of NMDA receptors for glycine binding site on the GluN1 subunit [34].
Neurons in the acute basolateral amygdala slices	18%, 30%, and 65%	Concentration-dependently inhibited NMDA and AMPA receptors with similar potency [35].
Acute basolateral amygdala brain slices	65% (1.9 mM)	No selective antagonist of NR2A- or NR2B subunit of NMDA receptors [36].
Acute prefrontal cortex and substantia gelatinosa slices	65% (1.9 mM)	Inhibition of NMDA and AMPA receptor-mediated synaptic transmission to approximately 65–58% and 67–56%, respectively, in slices of various brain regions via postsynaptic mechanisms; reversibly blockage of CA1-LTP due to the impact of NMDA receptor activation on synaptic plasticity [37].
Acute thalamocortical slices from adult mice	18%, 30%, and 65%	Concentration-dependent inhibition of HCN2 channel functions depending on intracellular cyclic adenosine monophosphate levels [41].
HEK-293 cells transfected with murine HCN2	65%	Decreasing maximum I_h current amplitude by 33.4 $\pm$ 12.2% [41].
Acute thalamocortical slices from adult mice	65%	Impaired HCN2 channel function via interfering with the CNBD [42].
Xenopus Oocyte	35%, 70%, and 100%	Concentration-dependent inhibition of (α7) 5 nACh receptor in a non-competitive and voltage-independent manner [43].
Modified HEK-293 cells	80%	Concentration-dependent activation of K2P-TREK-1 [45].

NMDA, N-methyl-D-aspartic acid; AMPA, α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid; LTP, long-term potentiation; HCN2, Cyclic nucleotide-gated cation channel Type 2; HEK-293 cells, human embryonic kidney cells; CNBD, cyclic nucleotide-binding domain; nACh, nicotinic acetylcholine; K2P, two-pore domain K+ channels; TREK-1, two-pore-domain potassium; GluN1, Glutamate Receptor NMDA Type Subunit 1; NR2A, Glutamate Receptor NMDA Type Subunit 2A; NR2B, Glutamate Receptor NMDA Type Subunit 2B.

the modulation of K2P-TREK-1 [48], and the upregulation of the hypoxia-inducible factor 1 alpha (HIF-1α) pathway [49].

3.1.1 NMDA Receptors Antagonism

As previously stated, NMDA receptors are essential ionotropic glutamate receptors within the central nervous system (CNS), playing a critical role in most excitatory neurotransmission, synaptic plasticity, and learning and memory. Excessive activation of these receptors can lead to excitotoxicity, a phenomenon first identified by Olney in 1969 [50]. Excitotoxicity plays a role not only in acute neural injuries such as those caused by hypoxia-ischemia and traumatic brain injury, but also closely linked to neurodegenerative disorders like Alzheimer's disease [51]. Noncompetitive NMDA receptor antagonists have the capacity to avert the excessive activation of NMDA receptors, thereby demonstrating significant potential in maintaining their normal physiological function and offering neuroprotective benefits for the management of neurological conditions. Unsurprisingly, xenon, as a specific NMDA receptor antagonist, has been demonstrated to partially restored amyloid β 1–42 (Aβ_{1-42})-induced impairment of LTP at subanesthetic concentrations in acute mice brain slices [52]. Furthermore, xenon exhibited a concentration-dependent neuroprotective effect at subanesthetic levels without inducing neurotoxicity [14].

In the developing brain, NMDA receptors and their agonists are necessary for synaptogenesis, synaptic development and synapse stabilization [53]. In neonatal animal models, it has been confirmed drugs that blocking NMDA receptors has been shown to trigger widespread apoptotic neurodegeneration during early postnatal brain development [54–56]. Although xenon has been demonstrated to provide neuroprotective effects in various preclinical models [31]. However, as an NMDA receptors antagonist, xenon can also trigger neurotoxicity in the developing brain [16]. It seems that xenon may have dual effects to the developing brain depending on the duration of exposure. That is exposure for a short period is protective, whereas prolonged exposure may exert toxicity to the developing brain.

3.1.2 Activation of Two-pore-domain Potassium-TREK-1

The distinctive subunit architecture of the K2P channel renders it a compelling target for general anesthetics. Comprising four transmembrane segments and two pore-forming domains configured in tandem, K2P channels operate as either homo- or hetero-dimeric entities. This structural configuration is linked to basal channel activity and responsiveness to membrane tension. Specifically, when K2P channels are stimulated, they produce basal K+ currents, which assist in sustaining the membrane in a hyperpolarized condition, thereby modulating neuronal excitability [57,58]. TREK-1, a subtype of K2P channels distributed throughout the CNS, responds to mechanical stimuli, temperature fluctuations, pH variations, voltage changes, and lipid interactions. Upon activation, TREK-1 facilitates the efflux of potassium ions (K+), leading to neuronal hyperpolarization. This process can diminish cellular excitability and safeguard the brain against excitotoxic damage [48,59,60]. The research team led by Franks employed electrophysiological techniques to investigate human HEK-293 cells that had been transfected with TREK-1 and TASK-3 channels. They discovered that TREK-1 channels were activated by clinically relevant concentrations of xenon, whereas TASK-3 channels remained unresponsive to the gas. This finding corroborates the potential of TREK-1 channels as a significant target for xenon, which may play a role in its neuroprotective effects [45].

3.1.3 Hypoxia-inducible Factor 1α

HIF-1α, a critical subunit of the heterodimeric transcription factor HIF-1, plays a central role in modulating cellular and developmental responses to low oxygen levels [61]. Under normoxic conditions, the expression levels of HIF-1α are typically minimal; however, they surge significantly when oxygen levels drop. Notably, HIF-1α has the capacity to induce the expression of genes crucial for cellular repair and restoration, such as erythropoietin (EPO) and vascular endothelial growth factor (VEGF). EPO and VEGF play a vital role in improving oxygen delivery to hypoxic regions via angiogenesis and erythropoiesis. Furthermore, they are critical in protecting neurons during conditions of hypoxia, ischemia, and preconditioning events [62]. Interestingly, xenon significantly enhanced HIF-1α transcription and translation even under normal oxygen conditions. This finding indicates that xenon might confer neuroprotective advantages by increasing the expression of HIF-1α and promoting cellular responses to hypoxia [49,63].

3.2 Modulation of Dendritic Spines and Neural Activity

Neurons play a crucial role in the transmission of chemical and electrical signals. Dendritic spines, which are found along the dendrite shafts of neurons, offer essential morphological support for synaptic transmission and plasticity. Under normal conditions, these dendritic spines undergo a highly dynamic process of pruning, which is vital for integrating neurons into functional circuits. A prior study that compared equipotent concentrations of xenon, isoflurane, and sevoflurane demonstrated that only xenon maintained the normal structure and density of CA1-dendritic spines, whereas a decrease in spine subtypes was noted with the other two anesthetics [20]. This suggests a potential mechanism by which xenon, as an inhaled anesthetic, may provide neuroprotection.

Xenon has been demonstrated to mitigate the neurotoxic effects of Aβ on dendritic spine morphology. In acute hippocampal slices pre-incubated with Aβ, exposure to 1.9 mM xenon counteracted the deleterious impact of Aβ_{1-42} on dendritic spines, whether in the dentate gyrus region [64] or throughout the entire hippocampus [65]. Furthermore, the replenishment of xenon in dentate gyrus (DG) dendritic spines played a role in augmenting synaptic pruning through MEGF10-mediated astrocytic phagocytosis [64]. The revival of neural function by xenon was noted in hippocampal slices pretreated with Aβ isoforms. In this research, hippocampal slices were pre-incubated with four Aβ species, namely Aβ_{1-40}, Aβ_{1-42}, AβpE3, and 3NTyrAβ, followed by the introduction of 65% xenon. Remarkably, xenon exposure led to a partial or complete restoration of neural activity, as evidenced by voltage-sensitive dye imaging [65].

3.3 Modulation of Mitochondrial Function

Mitochondria are highly plastic and dynamic organelles that are essential for cellular metabolism, cell signaling, stress response, and homeostasis maintenance [66]. Increasing data suggest that mitochondria are a potential key target of anesthetic damage, and general anesthetics can cause mitochondrial dysfunction through multiple pathways, including oxidative stress, impaired mitochondrial dynamics, imbalance of calcium homeostasis, and mitochondria-dependent apoptotic pathways [67,68]. Xenon was reported to alleviate isoflurane-induced apoptosis in neonatal rats, which could partially attributed to the inhibition of mitochondria-induced activation of the caspase-3 pathway [26,47]. Furthermore, in a neonatal hypoxia-induced seizures preclinical model, xenon was demonstrated to enhance neuronal protection by decreasing mitochondrial oxidative stress [69]. Moreover, in one prolonged febrile seizures study, 70% xenon application was shown to alleviate oxidative stress and attenuate mitochondrial defects, and subsequently reduce the level of mitophagy [70].

In summary, the neuroprotective benefits of xenon observed in recent studies are primarily ascribed to its ability to inhibit the overstimulation of NMDA receptors in excitotoxic scenarios, activate K2P channels and the HIF-1α pathway, preserve dendritic spine structure and neuronal function, and alleviate mitochondrial dysfunction.

4. Effects of Xenon on the Developing Brain

The development of the brain is a complex and protracted process, during which NMDA receptors are of paramount importance [9–11]. Exposure to substances that inhibit NMDA receptors during the late fetal stage or the early postnatal period can induce extensive neurodegeneration via apoptosis [54–56]. Nevertheless, there is a significant exception: the NMDA antagonist xenon has proven to be an effective neuroprotective agent for the developing brain in various pre-clinical models, including those for HIE [15,71–73], AIDN [26,47], and obstetric anesthesia [74–76] (refer to Table 2, Ref. [14,15,31,71–73,77], Table 3, Ref. [24,78], Table 4, Ref. [26,47,79]).

4.1 Hypoxic-ischemic Encephalopathy (HIE)

HIE is one of the leading causes of neonatal brain injury, often resulting from acute perinatal asphyxia. It affects roughly 1.5 infants per 1000 live births, with a mortality rate ranging between 15% and 20% [80]. Survivors frequently experience severe neurodevelopmental deficits. The neuropathology of HIE is an evolving process that begins with an acute hypoxic-ischemic event and progresses into a reperfusion phase, which can exacerbate the injury. Acute hypoxia-ischemia causes a deprivation of glucose and oxygen supply, leading to energy failure and a cascade of biochemical events that result in cell dysfunction and, ultimately, cell death through mechanisms such as excitotoxicity, inflammation, and oxidative stress [81,82].

Therapeutic hypothermia has emerged as the standard treatment for moderate to severe cases of HIE in numerous countries, substantially improving the overall prognosis for affected infants. However, approximately one-third of patients do not respond favorably to therapeutic hypothermia, and the mortality and disability rates persist at an alarmingly high level among infants with HIE [83,84]. As a result, there is a pressing need for supplementary therapies. In a neonatal rat model of hypoxic-ischemia, xenon has been observed to demonstrate both short- and long-term neuroprotective effects [25,85]. Furthermore, xenon's advantageous properties, such as its swift onset and offset of action, non-toxicity, and minimal hemodynamic depression, make it an appealing candidate for improving the outcomes of HIE treatment.

4.1.1 Pre-clinical Studies

Studies have shown that the combination of xenon with hypothermia can amplify the neuroprotective effects of hypothermia when used alone in models of HIE [15,71–73]. In a neonatal rat model of hypoxia-ischemia, Ma *et al.* [15] observed that four hours post-injury, the synergistic neuroprotective effects of xenon combined with hypothermia were evident both *in-vitro* and -*vivo*. This combined therapy was effective in reducing excitotoxicity by diminishing neurotransmitter release and blocking receptors [15]. Similarly, Hobbs *et al.* [71] conducted a study that illustrated the enduring neuroprotective benefits of the xenon-hypothermia combination in HIE cases. Their research indicated that a combination of 50% xenon with 32 °C hypothermia yielded the most significant improvement and nearly fully restored function. Subsequently, they found that pairing 50% xenon with 24 hours of hypothermia at 33.5 °C resulted in global neuroprotection with substantially reduced histological damage compared to either treatment administered individually [73]. The additional neuroprotective benefits of the xenon-hypothermia combination were corroborated in a neonatal global hypoxia-ischemia porcine model that closely mirrored clinical HIE. These findings imply that the xenon-hypothermia combination could offer a more efficacious therapeutic option for individuals with HIE. However, further research is urgently required to fully comprehend the potential advantages and risks associated with this treatment strategy.

However, in a rat model of severe hypoxia-ischemia at seven days old, the addition of 50% xenon to 32 °C hypothermia for a duration of 5 hours did not yield the anticipated neuroprotective effects of therapeutic hypothermia [77]. The discrepancy in results may be attributed to several factors. Firstly, the concentration of xenon might have been insufficient, or the exposure period could have been too brief. When xenon is used in conjunction with hypothermia, its efficacy in reducing brain injury is contingent upon its concentration, with significant effects observed at levels exceeding 40% [15]. Secondly, in this model of severe hypoxia-ischemia, a hypothermia level of 32 °C may not represent the optimal therapeutic temperature.

4.1.2 Clinical Trials

Increasing experimental evidence suggest that xenon can amplify the neuroprotective effects of hypothermia to hypoxic–ischemic injury. Nonetheless, clinical trials remain essential to validate this effect. The initial human trial, named CoolXenon, took place from March 2010 to April 2011. This study involved the inhalation of xenon alongside 72 hours of cooling in 14 neonates diagnosed with HIE. While the study did not confirm the enhanced neuroprotective effect of xenon, an 18-month follow-up study showed the safety and feasibility to administer 50% xenon and hypothermia to term infants with perinatal asphyxia [24].

Shortly after the initiation of the CoolXenon study, the Total Body hypothermia plus Xenon (TOBY-Xe) trial—the first randomized clinical trial—was conducted to assess the efficacy of xenon in conjunction with hypothermia for treating birth asphyxia in 4 neonatal intensive-care units across the UK. In this trial, 92 infants with moderate to severe HIE were randomized to receive hypothermia at 33.5 °C for 72 hours or hypothermia combined with 30% xenon for 24 hours, initiated within 6 hours of birth [78]. Despite promising results from preclinical trials, the study found that the addition of xenon to hypothermia did not enhance neuroprotective effects, as measured by magnetic resonance spec-

Table 2. Neuroprotection of xenon in hypoxic-ischemic model from pre-clinical studies.

Age	Model and xenon	Molecular mechanisms of neuroprotection of xenon	Outcomes
Organotypic hippocampal brain slices from 7-day-old C57/BL6 mice	Hypoxia-ischemia Xenon (0.5 atm) with 20% O_2/75% N_2/5% (1 atm) for 24 h	Blockage of NMDA receptors via binding to its glycine site.	Xenon was neuroprotective when applied up to 3 h after oxygen-glucose deprivation (OGD) [31].
(1) A mouse neuronal-glial cell co-culture (2) Female Sprague-Dawley (SD) rats (weight, 240–260 g)	Hypoxia-ischemia (*in vitro* with neuronal-glial cell co-culture) Xenon: 20%, 40%, 60%, 75%	(1) Lactate dehydrogenase (LDH) release was reduced ① to baseline by xenon (60%) with oxygen deprivation; ② by 80% with either NMDA- or glutamate-induced injury with xenon (75% atm). (2) The degenerated neurons in both arcuate nuclei were reduced by 45% by xenon (75% atm).	Xenon was concentration-dependently protective against neuronal injury provoked by oxygen deprivation, NMDA, or glutamate [14].
(1) Glial-neuronal cocultures from early postnatal and fetal BALB/c mice (2) Seven-day-old SD rats	Hypoxic-ischemic injury Xenon (12.5–75%) and hypothermia (33 °C) 4 h after injury	*In-vitro* with glial-neuronal cocultures: (1) Xenon (75%) obtained dendritic network after 75 min OGD. (2) During OGD and recovery, xenon (12.5–75%) decreased LDH release in a concentration-dependent manner (IC_{50}: 36 ± 3% atm). (3) Xenon (10, 20, 50, 75%) + hypothermia (33 °C) or xenon (12.5%) + hypothermia (30–35 °C) reduced LDH release. (4) xenon (75%, 24 h) did not harm uninjured cells: increased cell viability and reduced apoptotic cell death by cytometry of annexin V (for apoptosis) and propidium iodide (for necrosis). *In-vivo* with SD rats: (1) Xenon (≥40%) + hypoxia increased ratio of right-to-left hemispheric weight (R/L ratio); xenon (70%, 90 min–6 h) increased R/L ratio after the hypoxic-ischemic insult; xenon (≥60%) increased R/L ratio 4 h after the hypoxic-ischemic insult. (2) Xenon (70%, 16, 24, and 48 h) decreased apoptotic cell death and increased the viable cell count (cerebral cortex and dentate gyrus); xenon (70%, 48 h) reduced necrotic cell death (cortex); xenon (20%) + hypothermia (35 °C) decreased cell apoptosis and increased cell viability 4 h after hypoxic insult. (3) 30 days after injury, xenon (70%) improved the motor and coordination; xenon (20%) + hypothermia (35 °C) restored neurological function. (4) Xenon (70%/20%) + hypothermi (35 °C) suppressed Bcl-2-Associated X Protein (Bax) expression.	Combination of xenon and hypothermia synergistically enhanced individual neuroprotective properties [15].
Neonatal rat	Hypoxic/ischemic model Xenon (50%) with hypothermia (32 °C) after injury	Complete restoration of long-term function.	Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia [71].

Table 2. Continued.

Age	Model and xenon	Molecular mechanisms of neuroprotection of xenon	Outcomes
Seven-day-old Wistar rat	Hypoxic–ischemic model Xenon (50%) with hypothermia (32 °C) 5 h after injury	Adding 50% xenon to 5 h delayed hypothermia significantly improved functional outcome as compared to delayed hypothermia alone.	Adding 5 h delayed xenon to delayed hypothermia treatment improves long-term function in neonatal rats surviving to adulthood [72].
Newborn pigs	Hypoxic–ischemic mode Xenon (50%, 18 h) with hypothermia (33.5 °C, 12/24 h)	Combination of xenon with 12/24 h hypothermia produced additive neuroprotective effect.	Xenon enhances hypothermic neuroprotection in asphyxiated newborn pigs [73].
Seven-day-old rat pups	Severe hypoxic–ischemic insult mode Xenon (50%) with hypothermia (32 °C) for 5 h after hypoxic–ischemia	Adding 50% inhaled xenon with hypothermia didn't provide neuroprotection 1 week after severe hypoxic–ischemic brain injury.	Xenon combined with therapeutic hypothermia is not neuroprotective after severe hypoxia-ischemia in neonatal rat [77].

Table 3. Effects of xenon on the developing brain-clinical trials.

Age	Model	Treatment	Outcomes
Newborns	14 newborns with moderate to severe neonatal encephalopathy	Up to 18 h xenon inhalation with 72 h 33.5 °C hypothermia (1 received 25% and 13 received 50% xenon)	(1) 50% xenon for up to 18 h with 72 h of cooling was feasible; (2) No adverse effects with 18 months follow-up [24].
36–43 weeks gestational age	moderate to severe encephalopathy	Within 12 h of birth, 33.5 °C hypothermia for 72 h in combination with 30% xenon for 24 h	Administration of xenon is safe but didn't enhance the neuroprotection of cooling after birth asphyxia [78].
CoolXenon2 + CoolXenon3	Newborns at high risk of brain injury following poor condition at birth	33.5 °C hypothermia for 72 h starting within 3 h after birth, combining 50% xenon for 18 h starting within 5 h after birth in neonates of Hypoxic-ischemic Encephalopathy (HIE)	Cooling+xenon was safe but did not improve the cognition, language, and motor abilities of the infants (CoolXenon3–Health Research Authority (https://www.hra.nhs.uk/))

Table 4. Effects of xenon in combination with other anesthetics.

General anesthetics	Model	Effects of xenon	Molecular mechanisms
0.75% isoflurane plus 30% or 60% xenon for 6 h	P7 SD rat pups	Xenon (both 30% and 60%) mitigates isoflurane-induced neonatal apoptosis.	Downregulated the expressions apoptotic pathways indicators: caspase-3, caspase-8, caspase-9, cytochrome cc [26].
Pretreatment with 70% xenon/70% nitrous oxide for 2 h, 24 h later exposed to the combination of 70% nitrous oxide with 0.75% isoflurane for 6 h	P7 SD rat pups	Xenon pretreatment prevented nitrous oxide- and isoflurane-induced neuroapoptosis and cognitive deterioration.	Partly attributed to the inhibition of mitochondria-induced activation of the caspase-3 pathway since xenon up-regulated the expression of antiapoptotic Bcl-2 and down-regulated proapoptotic tumor suppressor transcription factor P53 [47].
Exposed to propofol (50 μM) for 16 h in the presence or absence of 33% xenon	Human neural stem cells	33% xenon effectively protect neurons from propofol-induced downregulation of polysialic acid (PSA) expression.	Xenon recovered the expression of PSA neural cell adhesion molecule (NCAM) on human neural stem cell differentiated neurons [79].

troscopy and magnetic resonance imaging (MRI), beyond 6 hours after birth compared to hypothermia alone [78,86]. The lack of a positive effect from xenon could be attributed to a suboptimal dose, duration, and timing of xenon administration (the mean age at which xenon was started was nearly 10 hours); the severity of encephalopathy in the participants; the low sensitivity of the cerebral biomarkers used in the study; and the low power of the follow-up study. Despite the absence of a beneficial effect from the combination of xenon in the TOBY-Xe study, it confirmed the suitability of cerebral magnetic resonance biomarkers as predictors of outcomes following neuroprotective therapy after birth asphyxia.

Two additional randomized clinical trials, CoolXenon2 and CoolXenon3, were also conducted in the UK. These trials aimed to determine if adding 50% xenon for 18 hours to 33.5 °C hypothermia for 72 hours could further reduce movement and cognitive disabilities. Efforts were made to initiate xenon and cooling as soon as possible, with xenon starting within 5 hours and hypothermia within 3 hours after birth. From March 2012 to March 2018, 82 newborns were enrolled, and no significant differences were found in the primary outcomes of death and disability with the additional use of xenon (CoolXenon3 - Health Research Authority (https://www.hra.nhs.uk/)).

In summary, despite promising pre-clinical results indicating that xenon may enhance neuroprotection in HIE, clinical evidence remains only modest. There is an urgent need for further research, particularly focusing on the dosage, timing, and duration of xenon administration. Consequently, while xenon may hold potential to augment the neuroprotective effects of hypothermia in HIE, it is too soon to consider its routine application in human newborns.

4.2 Teratogenicity in Obstetric Anesthesia

During pregnancy, a woman might need non-obstetric surgery at any stage. Statistics indicate that roughly 1.5% to 2.0% of expectant mothers undergo anesthesia for such procedures [1,87]. At this time, the fetus's CNS is especially susceptible and fragile. Consequently, it is imperative to pay close attention to the potential teratogenic and other adverse effects of anesthetics [88]. Recent research indicates that exposure to xenon during pregnancy does not appear to have any detrimental impact on fetal development or reproductive function [74–76]. For instance, one study on rats exposed to 70–75% xenon for 24 hours on the ninth day of pregnancy did not exhibit any birth defects [74]. Likewise, an 80% xenon concentration did not affect fertility, pregnancy outcomes, embryo survival rates, body weight, or the overall development of newborns [75,76]. These findings suggest that xenon does not present a significant risk to expectant mothers or their developing fetuses. While clinical data on the administration of xenon to pregnant women is scarce, the safety profile of xenon as shown in pre-clinical studies provides an optimistic perspective for its use in obstetric anesthesia.

4.3 Anesthesia-induced Developmental Neurotoxicity (AIDN)

Each year, millions of young children undergo general anesthesia to undergo critical surgeries. At present, all general anesthetic agents either inhibit NMDA receptors (such as nitrous oxide, ketamine, and xenon), enhance Gamma-Aminobutyric Acid (GABA) receptors (including midazolam and propofol), or influence both (as with volatile anesthetics isoflurane and sevoflurane). However, exposure to drugs that block NMDA receptors during the late fetal or early postnatal period can induce widespread apop-

totic neurodegeneration [89,90]. Furthermore, numerous preclinical studies involving rodents and non-human primates have shown that prolonged exposure to general anesthetics, especially during periods of rapid brain growth, is linked to widespread neuroapoptosis and long-term neurocognitive deficits [2,4,91]. In 2003, Vesna Jevtovic-Todorovic and her team [2] assessed the impact of anesthesia on the developing brain using 7-day-old rats. They administered a combination of three commonly used pediatric anesthetics—midazolam, nitrous oxide, and isoflurane—at clinically relevant doses for 6 hours. Their findings indicated widespread neuroapoptosis, programmed brain cell death, and enduring learning and memory deficits. Since then, a burgeoning body of research suggests that prolonged exposure to anesthetics early in life disrupts neuronal development and synaptogenesis [92–94]. For instance, isoflurane exposure led to the loss of neural stem cells and persistent, progressive memory impairment in young rodents [92]; propofol, the most commonly used intravenous anesthetic, resulted in significant apoptosis of neurons and glia in the young rhesus macaque brain [93].

Therefore, nearly all pediatric anesthetics currently in clinical use have been shown to exhibit neurodegenerative effects on the developing brain. In comparison to the commonly used volatile anesthetics, xenon stands out as a superior option, offering unique benefits as an ideal anesthetic for the developing brain. Nevertheless, research has demonstrated that xenon provides neuroprotection against neuroapoptosis induced by other general anesthetics [26,47,79], although there is limited evidence to suggest that xenon may also have apoptotic effects on the neonatal brain [16,17,27].

4.3.1 Animal Studies

The neuroprotective properties of xenon have been documented in numerous studies. In 2007, Ma and colleagues [26] demonstrated that exposing 7-day-old rats to a combination of xenon and isoflurane did not lead to deterioration but instead offered concentration-dependent protection against isoflurane-induced neuronal apoptosis. Subsequently, in 2010, they delved deeper into the effects of xenon on neuronal apoptosis triggered by isoflurane and nitrous oxide during the critical period of synaptogenesis. Their research revealed that preconditioning with xenon safeguarded against neurodegeneration and cognitive decline caused by nitrous oxide and isoflurane in 7-day-old rats. These findings indicated that xenon also conferred protection against the neurotoxic effects of nitrous oxide [47]. An additional study, which utilized human neural stem cells, showed that the co-administration of a subclinical dose of xenon with propofol effectively shielded neurons from propofol-induced damage [79].

In contrast, the neurotoxic effects of xenon on the developing brain have also been observed [16,17,27]. In 2011, Dr. Cattano *et al*. [17] discovered that administering a mixture of 75% xenon and 25% oxygen to newborn rats for 2 hours increased the transcriptional activity of genes associated with protein kinase B (PKB) and c-Jun N-terminal kinase kinase 1 (JNKK1), which were linked to heightened neuronal apoptosis in the neonatal rat brain. Similarly, a study by Brosnan and Bickler [27], utilizing postnatal rat hippocampal slice cultures, demonstrated that xenon's neurotoxicity was comparable to that of isoflurane and sevoflurane at equivalent concentrations. Additionally, neuroapoptosis was observed in newborn mice after exposure to 70% xenon for 4 hours. Despite these instances of neuroapoptosis, xenon remains a relatively safe inhaled anesthetic when compared to others; for instance, its propensity to promote neural apoptosis is significantly less than that of isoflurane [16]. However, when xenon is administered in conjunction with isoflurane, it retains its neurotoxic properties and suppresses isoflurane's apoptogenic effects [16]. Therefore, xenon's impact on neurodevelopment may hinge on the delicate balance between neuroprotection and neurodegeneration. Furthermore, xenon's efficacy as a neuroprotective agent seems to rely on its capacity to prevent the neurotoxicity of other co-administered anesthetics.

4.3.2 Clinical Trials

The minimal alveolar concentration (MAC) indicates the potency of an anesthetic required to prevent 50% of subjects from experiencing pain during surgery. Xenon's MAC in adults is approximately 63.1%, whereas the value for children remains undetermined [95]. However, extrapolating from the MAC values of other volatile anesthetics, it is anticipated that xenon's MAC in children would exceed that of adults. A meta-analysis has estimated that xenon's MAC at one year of age could be as high as 92% [96]. Consequently, in pediatric anesthesia, xenon should be administered in conjunction with other anesthetics to guarantee that the inspiratory oxygen concentration does not fall below 30%.

In 2014, a phase-II clinical trial was conducted to evaluate the efficacy of xenon in children aged between 4 and 12 years. During this pilot study, the group receiving xenon-augmented sevoflurane anesthesia exhibited quicker emergence compared to those receiving sevoflurane alone. Nonetheless, no significant variations were observed in neurocognitive assessments [19,97]. In a parallel clinical trial involving children under the age of 4, the administration of 50–65% xenon as an adjunct to sevoflurane anesthesia was shown to be safe and practicable in preschoolers. Additionally, the co-administration of xenon was associated with enhanced hemodynamic stability, improved cerebral oxygen saturation, faster recovery times, and a reduced incidence of emergence delirium [18]. Currently, an ongoing clinical trial is assessing the safety and feasibility of combining dexmedetomidine with xenon anesthesia in children aged 1 month to 3 years undergoing elective car-

Table 5. Neurotoxicity of xenon on the developing brain from pre- and clinical studies.

Age	Treatment	Mechanisms
Postnatal day 7 rats	75% xenon/25% oxygen for 2 h	Xenon was neuroapoptotic for the developing rodent forebrain [17].
Organotypic hippocampal cultures from 7-day-old rats	0.75, 1, and 2 minimal alveolar concentration (MAC) of xenon, isoflurane and sevoflurane	At 1 MAC, xenon increased cell death 40% above baseline, and the neurotoxicity of xenon in rat hippocampal slice cultures is similar to isoflurane and sevoflurane [27].
Postnatal day 7 C57BL/6 mice	0.75% isoflurane, 70% xenon; or 0.75% isoflurane + 70% xenon for 4 h	(1) Xenon and isoflurane alone induced a significant increase in neuroapoptosis. (2) When xenon was administered with isoflurane, the apoptosis was reduced to a level lower than that for isoflurane alone [16].
Children less than 4 with cardiac catheterization	50–65% xenon plus sevoflurane or sevoflurane alone	50–65% xenon plus sevoflurane has better cerebral oxygen saturation, leading toa faster recovery and a reduction of emergence delirium [18].
Children between 4 to 12 years old undergoing elective cardiac catheterization	50% xenon plus sevoflurane or sevoflurane alone	No significant difference was observed in neurocognitive test [19].

diac catheterization [98]. The results of this study are anticipated to furnish essential data for future clinical trials investigating the neurodevelopmental impacts of xenon and dexmedetomidine (Table 5, Ref. [16–19,27]).

Based on preclinical studies, we must recognize that xenon can exert dual effects on the developing brain, namely neuroprotection and neurodegeneration [18,19]. The equilibrium between these two effects is of paramount importance. Furthermore, the degree of xenon's neurotoxicity in the developing brain is contingent upon various factors, including dosage, the timing of application, and the duration of exposure. Significantly, xenon has the potential to mitigate developmental neurotoxicity caused by other anesthetics. Consequently, xenon's impact on the developmental brain may hinge on its capacity to safeguard against the neurotoxicity induced by concurrently administered anesthetics.

It is essential to remember that the preclinical model functions as an experimental tool and should not be confused with clinical pediatric anesthesia. Although xenon has shown encouraging outcomes in laboratory research, its use in clinical pediatric anesthesia is still in the early stages. The precise timing and scope of exposure, including frequency and total dosage of anesthesia, have not yet been determined for humans. Therefore, further well-structured studies are imperative to investigate the potential benefits and drawbacks of xenon and to enhance the safety of pediatric anesthetic procedures.

5. Conclusion

Numerous fetuses, infants, and young children necessitate anesthesia annually. Additionally, the developing brain undergoes highly dynamic processes and is particularly susceptible to the effects of anesthesia. Therefore, it is imperative for anesthesiologists to utilize safer anesthetic techniques for these vulnerable subjects. General anesthetics such as isoflurane and sevoflurane have been shown to induce widespread neuroapoptosis and neurodegeneration. Hence, xenon emerges as an extraordinary candidate, as numerous studies have demonstrated its neuroprotective effects.

As an inhaled anesthetic, xenon functions by suppressing NMDA, AMPA, and nACh receptors, activating K2P-TREK-1 channels, and inhibiting HCN2 channels. Moreover, during anesthesia, xenon exhibits both neuroprotective and neurotoxic properties. According to the present review, xenon's neuroprotective effects are generally mediated by (1) modulation of molecules—the antagonism of the NMDA, AMPA, and HCN receptors, the activation of K2P-TREK-1 channels, and the upregulation of the HIF-1α pathway; (2) maintenance of dendritic spine structure and neuronal function; and (3) alleviation of mitochondrial dysfunction.

Most pre-clinical and clinical studies have reported xenon's neuroprotective effects in the context of HIE, obstetric anesthesia, and AIDN. HIE is one of the leading causes of neonatal brain injury. For moderate to severe cases of HIE, therapeutic hypothermia is considered the most promising treatment option. Moreover, the combination of xenon has been shown to significantly improve therapeutic outcomes. Pre-clinical studies have reported the short- and long-term neuroprotective effects of xenon, with mechanisms including antagonism of NMDA receptors, reduction of apoptosis through modulation of lactate dehydrogenase (LDH) and Bcl-2-Associated X Protein (Bax), and increased cell survival. Despite these encouraging stud-

ies, clinical trials are only just beginning. Two out of three clinical trials have indicated positive effects of xenon co-application with hypothermia, while the third is still ongoing. Further evidence from clinical observations is urgently needed. Teratogenicity in obstetric anesthesia poses a significant concern for the fragile and susceptible fetal CNS. Fortunately, the application of xenon has shown no obvious deficits in fetal development or reproduction.

The developmental neurotoxicity associated with inhaled anesthetics is a significant side effect. On one hand, xenon has been shown to directly preserve neural morphology and function. On the other hand, xenon also offers protection against the neural function impairment caused by other general anesthetics; for example, it has been observed to mitigate neuroapoptosis induced by isoflurane. In reality, most of the general anesthetics commonly used in clinical settings, such as isoflurane and sevoflurane, possess neurotoxic properties, which positions xenon as an exceptional candidate for anesthesia. A recent study may have illuminated the mechanism behind this phenomenon. Researchers compared the equipotent concentrations of isoflurane, sevoflurane, and xenon on synaptic transmission and morphologic plasticity, and found that xenon maintained dendritic spine morphology in contrast to isoflurane and sevoflurane. We hypothesize that this protective effect of xenon may primarily stem from its markedly different chemical structure compared to other general anesthetics. For instance, isoflurane and sevoflurane are members of the ether class of organic compounds, characterized by an oxygen atom bonded to two alkyl or aryl groups, whereas xenon is a chemical element with the atomic number 54 (consisting of 54 protons and 54 electrons in its atomic structure). Nevertheless, due to the scarcity of literature, the precise mechanism underlying xenon's neuroprotective effects compared to other general inhaled anesthetics remains to be clarified.

It is also noteworthy that, according to limited studies, xenon has been reported to induce neuroapoptosis. In neurodevelopmental studies, xenon directly caused neural death in forebrain or hippocampal slice cultures. In a clinical study, the rate of hemodynamic instability among children under 4 was similar for isoflurane, sevoflurane, and xenon. Despite these findings from animal models and clinical trials, additional results indicated that xenon generally reduced the neurotoxicity from both isoflurane and sevoflurane to a lesser degree. Moreover, compared to sevoflurane, xenon decreased vasopressor requirements, maintained higher cerebral oxygen saturation, and led to a quicker recovery in children under 4 undergoing cardiac catheterization. Therefore, from the current literature, it appears that xenon generally produces mild neurotoxicity. Further studies are warranted to fully elucidate the specific neuroapoptotic mechanisms of xenon and to ascertain its safety for use in the developing brain.

In conclusion, both pre-clinical and clinical studies have clearly demonstrated the neuroprotective effects of xenon on the developing brain, positioning it as a promising anesthetic for use in late fetal or early postnatal life. Nonetheless, it is important to note the potential neurodegenerative effects that xenon may induce, as suggested by limited evidence. There are still uncertainties regarding xenon's precise role in anesthesia and its underlying mechanisms, including issues with delayed administration, suboptimal dosing, and the use of insensitive biomarkers. Consequently, further research into improved application methodologies and the precise mechanisms of xenon's neuroprotective and neurotoxic effects is highly desirable. Despite these challenges, existing evidence indicates that xenon may provide superior neurological outcomes compared to standard care in specific clinical scenarios. Moreover, the safety and practicality of xenon use in young children and neonates, as shown in clinical trials, offer a solid basis for future investigations. Although data on pediatric patients, particularly young children, are currently limited and variable, these studies have established a foundation for upcoming clinical trials. The potential for xenon in pediatric applications is indeed promising. Therefore, it is crucial to ascertain the optimal administration protocols to maximize neuroprotection and minimize any potential risks. This proactive approach will be essential in shaping the design of human trials and improving the safety of pediatric clinical practices.

Author Contributions

QFS, HDG, SJS, GR and XXW designed the research. PW, CKX, FFM, and JZ collected and sorted references, and provided help and advice on the writing of the manuscript. QFS, GR, and XXW wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

The work was supported by a. the Postdoctoral Fellowship Program of CPSF under Grant Number GZC20231694. b. Shanghai Mental Health Center, Traditional Chinese Medicine Institute of Mental Disorders, grant number: SZB2023205. c. Research Grant of Key Laboratory of Anesthesiology and Resuscitation (Huazhong University of Science and Technology), Ministry of Education, grant No. 2024MZFS003.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Tolcher MC, Fisher WE, Clark SL. Nonobstetric Surgery During Pregnancy. Obstetrics and Gynecology. 2018; 132: 395–403. https://doi.org/10.1097/AOG.0000000000002748

[2] Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, *et al*. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2003; 23: 876–882. https://doi.org/10.1523/JNEUROSCI.23-03-00876.2003

[3] Sinner B, Becke K, Engelhard K. General anaesthetics and the developing brain: an overview. Anaesthesia. 2014; 69: 1009–1022. https://doi.org/10.1111/anae.12637

[4] Raper J, Alvarado MC, Murphy KL, Baxter MG. Multiple Anesthetic Exposure in Infant Monkeys Alters Emotional Reactivity to an Acute Stressor. Anesthesiology. 2015; 123: 1084–1092. https://doi.org/10.1097/ALN.0000000000000851

[5] Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. Nature Reviews. Neuroscience. 2016; 17: 705–717. https://doi.org/10.1038/nrn.2016.128

[6] Administration, U.F.a.D., Drug safety communication: FDA approves label changes for use of general anesthetic and sedation drugs in young children. 2017. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm554634.htm (Accessed: 5 November 2018).

[7] Stiles J, Jernigan TL. The basics of brain development. Neuropsychology Review. 2010; 20: 327–348. https://doi.org/10.1007/s11065-010-9148-4

[8] Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? Neuroscience and Biobehavioral Reviews. 2003; 27: 3–18. https://doi.org/10.1016/s0149-7634(03)00005-8

[9] Komuro H, Rakic P. Modulation of neuronal migration by NMDA receptors. Science (New York, N.Y.). 1993; 260: 95–97. https://doi.org/10.1126/science.8096653

[10] Luján R, Shigemoto R, López-Bendito G. Glutamate and GABA receptor signalling in the developing brain. Neuroscience. 2005; 130: 567–580. https://doi.org/10.1016/j.neuroscience.2004.09.042

[11] Wu C, Sun D. GABA receptors in brain development, function, and injury. Metabolic Brain Disease. 2015; 30: 367–379. https://doi.org/10.1007/s11011-014-9560-1

[12] Lachmann B, Armbruster S, Schairer W, Landstra M, Trouwborst A, Van Daal GJ, *et al*. Safety and efficacy of xenon in routine use as an inhalational anaesthetic. Lancet (London, England). 1990; 335: 1413–1415. https://doi.org/10.1016/0140-6736(90)91444-f

[13] Ma D, Wilhelm S, Maze M, Franks NP. Neuroprotective and neurotoxic properties of the 'inert' gas, xenon. British Journal of Anaesthesia. 2002; 89: 739–746.

[14] Wilhelm S, Ma D, Maze M, Franks NP. Effects of xenon on in vitro and in vivo models of neuronal injury. Anesthesiology. 2002; 96: 1485–1491. https://doi.org/10.1097/00000542-200206000-00031

[15] Ma D, Hossain M, Chow A, Arshad M, Battson RM, Sanders RD, *et al*. Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. Annals of Neurology. 2005; 58: 182–193. https://doi.org/10.1002/ana.20547

[16] Cattano D, Williamson P, Fukui K, Avidan M, Evers AS, Olney JW, *et al*. Potential of xenon to induce or to protect against neuroapoptosis in the developing mouse brain. Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2008; 55: 429–436. https://doi.org/10.1007/BF03016309

[17] Cattano D, Valleggi S, Cavazzana AO, Patel CB, Ma D, Giunta F. Xenon exposure in the neonatal rat brain: effects on genes that regulate apoptosis. Minerva Anestesiologica. 2011; 77: 571–578.

[18] Devroe S, Meeusen R, Gewillig M, Cools B, Poesen K, Sanders R, *et al*. Xenon as an adjuvant to sevoflurane anesthesia in children younger than 4 years of age, undergoing interventional or diagnostic cardiac catheterization: A randomized controlled clinical trial. Paediatric Anaesthesia. 2017; 27: 1210–1219. https://doi.org/10.1111/pan.13230

[19] Devroe S, Lemiere J, Van Hese L, Gewillig M, Boshoff D, Poesen K, *et al*. The effect of xenon-augmented sevoflurane anesthesia on intraoperative hemodynamics and early postoperative neurocognitive function in children undergoing cardiac catheterization: A randomized controlled pilot trial. Paediatric Anaesthesia. 2018; 28: 726–738. https://doi.org/10.1111/pan.13444

[20] Wang X, Shi Q, Pradhan AK, Ziegon L, Schlegel M, Rammes G. Beta-Site Amyloid Precursor Protein-Cleaving Enzyme Inhibition Partly Restores Sevoflurane-Induced Deficits on Synaptic Plasticity and Spine Loss. International Journal of Molecular Sciences. 2022; 23: 6637. https://doi.org/10.3390/ijms23126637

[21] Ramsay W. An attempt to estimate the relative amounts of krypton and of xenon in atmospheric air. Proceedings of the Royal Society of London. 1902; 71: 421–426. https://doi.org/10.1098/rspl.1902.0121

[22] CULLEN SC, GROSS EG. The anesthetic properties of xenon in animals and human beings, with additional observations on krypton. Science (New York, N.Y.). 1951; 113: 580–582. https://doi.org/10.1126/science.113.2942.580

[23] Rossaint R, Reyle-Hahn M, Schulte Am Esch J, Scholz J, Scherpereel P, Vallet B, *et al*. Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. Anesthesiology. 2003; 98: 6–13. https://doi.org/10.1097/00000542-200301000-00005

[24] Dingley J, Tooley J, Liu X, Scull-Brown E, Elstad M, Chakkarapani E, *et al*. Xenon ventilation during therapeutic hypothermia in neonatal encephalopathy: a feasibility study. Pediatrics. 2014; 133: 809–818. https://doi.org/10.1542/peds.2013-0787

[25] Ma D, Hossain M, Pettet GKJ, Luo Y, Lim T, Akimov S, *et al*. Xenon preconditioning reduces brain damage from neonatal asphyxia in rats. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2006; 26: 199–208. https://doi.org/10.1038/sj.jcbfm.9600184

[26] Ma D, Williamson P, Januszewski A, Nogaro MC, Hossain M, Ong LP, *et al*. Xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain. Anesthesiology. 2007; 106: 746–753. https://doi.org/10.1097/01.anes.0000264762.48920.80

[27] Brosnan H, Bickler PE. Xenon neurotoxicity in rat hippocampal slice cultures is similar to isoflurane and sevoflurane. Anesthesiology. 2013; 119: 335–344. https://doi.org/10.1097/ALN.0b013e31829417f0

[28] Goto T, Suwa K, Uezono S, Ichinose F, Uchiyama M, Morita S. The blood-gas partition coefficient of xenon may be lower than generally accepted. British Journal of Anaesthesia. 1998; 80: 255–256. https://doi.org/10.1093/bja/80.2.255

[29] Luttropp HH, Romner B, Perhag L, Eskilsson J, Fredriksen S, Werner O. Left ventricular performance and cerebral haemodynamics during xenon anaesthesia. A transoesophageal echocardiography and transcranial Doppler sonography study. Anaesthesia. 1993; 48: 1045–1049. https://doi.org/10.1111/j.

1365-2044.1993.tb07522.x
[30] Dickinson R, Franks NP. Bench-to-bedside review: Molecular pharmacology and clinical use of inert gases in anesthesia and neuroprotection. Critical Care (London, England). 2010; 14: 229. https://doi.org/10.1186/cc9051
[31] Banks P, Franks NP, Dickinson R. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor mediates xenon neuroprotection against hypoxia-ischemia. Anesthesiology. 2010; 112: 614–622. https://doi.org/10.1097/ALN.0b013e3181cea398
[32] Smit KF, Weber NC, Hollmann MW, Preckel B. Noble gases as cardioprotectants - translatability and mechanism. British Journal of Pharmacology. 2015; 172: 2062–2073. https://doi.org/10.1111/bph.12994
[33] Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR. How does xenon produce anaesthesia? Nature. 1998; 396: 324. https://doi.org/10.1038/24525
[34] Dickinson R, Peterson BK, Banks P, Simillis C, Martin JCS, Valenzuela CA, *et al*. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor by the anesthetics xenon and isoflurane: evidence from molecular modeling and electrophysiology. Anesthesiology. 2007; 107: 756–767. https://doi.org/10.1097/01.anes.0000287061.77674.71
[35] Haseneder R, Kratzer S, Kochs E, Eckle VS, Zieglgänsberger W, Rammes G. Xenon reduces N-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated synaptic transmission in the amygdala. Anesthesiology. 2008; 109: 998–1006. https://doi.org/10.1097/ALN.0b013e31818d6aee
[36] Haseneder R, Kratzer S, Kochs E, Höfelmann D, Auberson Y, Eder M, *et al*. The xenon-mediated antagonism against the NMDA receptor is non-selective for receptors containing either NR2A or NR2B subunits in the mouse amygdala. European Journal of Pharmacology. 2009; 619: 33–37. https://doi.org/10.1016/j.ejphar.2009.08.011
[37] Haseneder R, Kratzer S, Kochs E, Mattusch C, Eder M, Rammes G. Xenon attenuates excitatory synaptic transmission in the rodent prefrontal cortex and spinal cord dorsal horn. Anesthesiology. 2009; 111: 1297–1307. https://doi.org/10.1097/ALN.0b013e3181c14c05
[38] Kratzer S, Mattusch C, Kochs E, Eder M, Haseneder R, Rammes G. Xenon attenuates hippocampal long-term potentiation by diminishing synaptic and extrasynaptic N-methyl-D-aspartate receptor currents. Anesthesiology. 2012; 116: 673–682. https://doi.org/10.1097/ALN.0b013e3182475d66
[39] He C, Chen F, Li B, Hu Z. Neurophysiology of HCN channels: from cellular functions to multiple regulations. Progress in Neurobiology. 2014; 112: 1–23. https://doi.org/10.1016/j.pneurobio.2013.10.001
[40] Schwerin S, Westphal C, Klug C, Schneider G, Kreuzer M, Haseneder R, *et al*. Sedative Properties of Dexmedetomidine Are Mediated Independently from Native Thalamic Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel Function at Clinically Relevant Concentrations. International Journal of Molecular Sciences. 2022; 24: 519. https://doi.org/10.3390/ijms24010519
[41] Mattusch C, Kratzer S, Buerge M, Kreuzer M, Engel T, Kopp C, *et al*. Impact of Hyperpolarization-activated, Cyclic Nucleotide-gated Cation Channel Type 2 for the Xenon-mediated Anesthetic Effect: Evidence from In Vitro and In Vivo Experiments. Anesthesiology. 2015; 122: 1047–1059. https://doi.org/10.1097/ALN.0000000000000635
[42] Kassab NED, Mehlfeld V, Kass J, Biel M, Schneider G, Rammes G. Xenon's Sedative Effect Is Mediated by Interaction with the Cyclic Nucleotide-Binding Domain (CNBD) of HCN2 Channels Expressed by Thalamocortical Neurons of the Ventrobasal Nucleus in Mice. International Journal of Molecular Sciences. 2023; 24: 8613. https://doi.org/10.3390/ijms24108613
[43] Suzuki T, Ueta K, Sugimoto M, Uchida I, Mashimo T. Nitrous oxide and xenon inhibit the human (alpha 7)5 nicotinic acetylcholine receptor expressed in Xenopus oocyte. Anesthesia and Analgesia. 2003; 96: 443–8, table of contents. https://doi.org/10.1097/00000539-200302000-00028
[44] Vivier D, Bennis K, Lesage F, Ducki S. Perspectives on the Two-Pore Domain Potassium Channel TREK-1 (TWIK-Related K(+) Channel 1). A Novel Therapeutic Target? Journal of Medicinal Chemistry. 2016; 59: 5149–5157. https://doi.org/10.1021/acs.jmedchem.5b00671
[45] Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP. Two-pore-domain K+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. Molecular Pharmacology. 2004; 65: 443–452. https://doi.org/10.1124/mol.65.2.443
[46] Harris K, Armstrong SP, Campos-Pires R, Kiru L, Franks NP, Dickinson R. Neuroprotection against traumatic brain injury by xenon, but not argon, is mediated by inhibition at the N-methyl-D-aspartate receptor glycine site. Anesthesiology. 2013; 119: 1137–1148. https://doi.org/10.1097/ALN.0b013e3182a2a265
[47] Shu Y, Patel SM, Pac-Soo C, Fidalgo AR, Wan Y, Maze M, *et al*. Xenon pretreatment attenuates anesthetic-induced apoptosis in the developing brain in comparison with nitrous oxide and hypoxia. Anesthesiology. 2010; 113: 360–368. https://doi.org/10.1097/ALN.0b013e3181d960d7
[48] Franks NP, Honoré E. The TREK K2P channels and their role in general anaesthesia and neuroprotection. Trends in Pharmacological Sciences. 2004; 25: 601–608. https://doi.org/10.1016/j.tips.2004.09.003
[49] Valleggi S, Patel CB, Cavazzana AO, Ma D, Giunta F, Cattano D. Xenon Upregulates Hypoxia Inducible Factor 1 Alpha in Neonatal Rat Brain under Normoxic Conditions. International Scholarly Research Notices. 2011; 2011: 510297. https://doi.org/10.5402/2011/510297
[50] Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science (New York, N.Y.). 1969; 164: 719–721. https://doi.org/10.1126/science.164.3880.719
[51] Doble A. The role of excitotoxicity in neurodegenerative disease: implications for therapy. Pharmacology & Therapeutics. 1999; 81: 163–221. https://doi.org/10.1016/s0163-7258(98)00042-4
[52] Bürge M, Kratzer S, Mattusch C, Hofmann C, Kreuzer M, Parsons CG, *et al*. The anaesthetic xenon partially restores an amyloid beta-induced impairment in murine hippocampal synaptic plasticity. Neuropharmacology. 2019; 151: 21–32. https://doi.org/10.1016/j.neuropharm.2019.03.031
[53] Gambrill AC, Barria A. NMDA receptor subunit composition controls synaptogenesis and synapse stabilization. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 5855–5860. https://doi.org/10.1073/pnas.1012676108
[54] Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, *et al*. Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. British Journal of Pharmacology. 2005; 146: 189–197. https://doi.org/10.1038/sj.bjp.0706301
[55] Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, Dikranian K, *et al*. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science (New York, N.Y.). 1999; 283: 70–74. https://doi.org/10.1126/science.283.5398.70
[56] Hansen HH, Briem T, Dzietko M, Sifringer M, Voss A, Rzeski W, *et al*. Mechanisms leading to disseminated apoptosis follow-

ing NMDA receptor blockade in the developing rat brain. Neurobiology of Disease. 2004; 16: 440–453. https://doi.org/10.1016/j.nbd.2004.03.013

[57] Honoré E. The neuronal background K2P channels: focus on TREK1. Nature Reviews. Neuroscience. 2007; 8: 251–261. https://doi.org/10.1038/nrn2117

[58] Patel AJ, Honoré E. Anesthetic-sensitive 2P domain K+ channels. Anesthesiology. 2001; 95: 1013–1021. https://doi.org/10.1097/00000542-200110000-00034

[59] Heurteaux C, Guy N, Laigle C, Blondeau N, Duprat F, Mazzuca M, *et al*. TREK-1, a K+ channel involved in neuroprotection and general anesthesia. The EMBO Journal. 2004; 23: 2684–2695. https://doi.org/10.1038/sj.emboj.7600234

[60] Buckler KJ, Honoré E. The lipid-activated two-pore domain K+ channel TREK-1 is resistant to hypoxia: implication for ischaemic neuroprotection. The Journal of Physiology. 2005; 562: 213–222. https://doi.org/10.1113/jphysiol.2004.077503

[61] Iyer NV, Kotch LE, Agani F, Leung SW, Laughner E, Wenger RH, *et al*. Cellular and developmental control of O2 homeostasis by hypoxia-inducible factor 1 alpha. Genes & Development. 1998; 12: 149–162. https://doi.org/10.1101/gad.12.2.149

[62] Lee JW, Bae SH, Jeong JW, Kim SH, Kim KW. Hypoxia-inducible factor (HIF-1)alpha: its protein stability and biological functions. Experimental & Molecular Medicine. 2004; 36: 1–12. https://doi.org/10.1038/emm.2004.1

[63] Jelkmann W. Xenon misuse in sports – Increase of Hypoxia-Inducible Factors and erythropoietin, or nothing but „Hot air“? German Journal of Sports Medicine/Deutsche Zeitschrift fur Sportmedizin. 2014; 65: 267–271. https://doi.org/10.5960/dzsm.2014.143

[64] Shi D, Wong JKY, Zhu K, Noakes PG, Rammes G. The Anaesthetics Isoflurane and Xenon Reverse the Synaptotoxic Effects of Aβ_{1-42} on Megf10-Dependent Astrocytic Synapse Elimination and Spine Density in Ex Vivo Hippocampal Brain Slices. International Journal of Molecular Sciences. 2023; 24: 912. https://doi.org/10.3390/ijms24020912.

[65] Hofmann C, Sander A, Wang XX, Buerge M, Jungwirth B, Borgstedt L, *et al*. Inhalational Anesthetics Do Not Deteriorate Amyloid-β-Derived Pathophysiology in Alzheimer's Disease: Investigations on the Molecular, Neuronal, and Behavioral Level. Journal of Alzheimer's Disease: JAD. 2021; 84: 1193–1218. https://doi.org/10.3233/JAD-201185

[66] Chen W, Zhao H, Li Y. Mitochondrial dynamics in health and disease: mechanisms and potential targets. Signal Transduction and Targeted Therapy. 2023; 8: 333. https://doi.org/10.1038/s41392-023-01547-9

[67] Hogarth K, Tarazi D, Maynes JT. The effects of general anesthetics on mitochondrial structure and function in the developing brain. Frontiers in Neurology. 2023; 14: 1179823. https://doi.org/10.3389/fneur.2023.1179823

[68] Li L, Yu Q, Liang W. Molecular pathways of mitochondrial dysfunctions: possible cause of cell death in anesthesia-induced developmental neurotoxicity. Brain Research Bulletin. 2015; 110: 14–19. https://doi.org/10.1016/j.brainresbull.2014.10.011

[69] Zhang M, Cui Y, Zhu W, Yu J, Cheng Y, Wu X, *et al*. Attenuation of the mutual elevation of iron accumulation and oxidative stress may contribute to the neuroprotective and antiseizure effects of xenon in neonatal hypoxia-induced seizures. Free Radical Biology & Medicine. 2020; 161: 212–223. https://doi.org/10.1016/j.freeradbiomed.2020.09.030

[70] Cheng Y, Zhai Y, Yuan Y, Li H, Zhao W, Fan Z, *et al*. Xenon inhalation attenuates neuronal injury and prevents epilepsy in febrile seizure Sprague-Dawley pups. Frontiers in Cellular Neuroscience. 2023; 17: 1155303. https://doi.org/10.3389/fncel.2023.1155303

[71] Hobbs C, Thoresen M, Tucker A, Aquilina K, Chakkarapani E, Dingley J. Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. Stroke. 2008; 39: 1307–1313. https://doi.org/10.1161/STROKEAHA.107.499822

[72] Liu X, Dingley J, Scull-Brown E, Thoresen M. Adding 5 h delayed xenon to delayed hypothermia treatment improves long-term function in neonatal rats surviving to adulthood. Pediatric Research. 2015; 77: 779–783. https://doi.org/10.1038/pr.2015.49

[73] Chakkarapani E, Dingley J, Liu X, Hoque N, Aquilina K, Porter H, *et al*. Xenon enhances hypothermic neuroprotection in asphyxiated newborn pigs. Annals of Neurology. 2010; 68: 330–341. https://doi.org/10.1002/ana.22016

[74] Lane GA, Nahrwold ML, Tait AR, Taylor-Busch M, Cohen PJ, Beaudoin AR. Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. Science (New York, N.Y.). 1980; 210: 899–901. https://doi.org/10.1126/science.7434002

[75] Burov NE, Arzamastsev EV, Kornienko LI, Kudimova LA. Investigation of the teratogenic and embryotoxic action of xenon. Anesteziologiia i Reanimatologiia. 2002; 69–70.

[76] Burov NE, Arzamastsev EV, Kornienko LI, Kudimova LA. Influence of xenon on reproductive function. Anesteziologiia i Reanimatologiia. 2002; 71–72.

[77] Sabir H, Osredkar D, Maes E, Wood T, Thoresen M. Xenon Combined with Therapeutic Hypothermia Is Not Neuroprotective after Severe Hypoxia-Ischemia in Neonatal Rats. PloS One. 2016; 11: e0156759. https://doi.org/10.1371/journal.pone.0156759

[78] Azzopardi D, Robertson NJ, Bainbridge A, Cady E, Charles-Edwards G, Deierl A, *et al*. Moderate hypothermia within 6 h of birth plus inhaled xenon versus moderate hypothermia alone after birth asphyxia (TOBY-Xe): a proof-of-concept, open-label, randomised controlled trial. The Lancet. Neurology. 2016; 15: 145–153. https://doi.org/10.1016/S1474-4422(15)00347-6

[79] Liu F, Liu S, Patterson TA, Fogle C, Hanig JP, Slikker W, Jr, *et al*. Effects of Xenon-Based Anesthetic Exposure on the Expression Levels of Polysialic Acid Neural Cell Adhesion Molecule (PSA-NCAM) on Human Neural Stem Cell-Derived Neurons. Molecular Neurobiology. 2020; 57: 217–225. https://doi.org/10.1007/s12035-019-01771-x

[80] Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. JAMA Pediatrics. 2015; 169: 397–403. https://doi.org/10.1001/jamapediatrics.2014.3269

[81] Perlman JM. Summary proceedings from the neurology group on hypoxic-ischemic encephalopathy. Pediatrics. 2006; 117: S28–33. https://doi.org/10.1542/peds.2005-0620E

[82] Allen KA, Brandon DH. Hypoxic Ischemic Encephalopathy: Pathophysiology and Experimental Treatments. Newborn and Infant Nursing Reviews: NAINR. 2011; 11: 125–133. https://doi.org/10.1053/j.nainr.2011.07.004

[83] Shankaran S. Outcomes of hypoxic-ischemic encephalopathy in neonates treated with hypothermia. Clinics in Perinatology. 2014; 41: 149–159. https://doi.org/10.1016/j.clp.2013.10.008

[84] Pedroza-García KA, Calderón-Vallejo D, Quintanar JL. Neonatal Hypoxic-Ischemic Encephalopathy: Perspectives of Neuroprotective and Neuroregenerative Treatments. Neuropediatrics. 2022; 53: 402–417. https://doi.org/10.1055/s-0042-1755235

[85] Dingley J, Tooley J, Porter H, Thoresen M. Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxia-ischemia. Stroke. 2006; 37: 501–506. https://doi.org/10.1161/01.STR.0000198867.31134.ac

[86] Azzopardi D, Chew AT, Deierl A, Huertas A, Robertson NJ, Tusor N, *et al*. Prospective qualification of early cerebral biomarkers in a randomised trial of treatment with xenon combined with moderate hypothermia after birth asphyxia. EBioMedicine.

2019; 47: 484–491. https://doi.org/10.1016/j.ebiom.2019.08.034

[87] Fisher SC, Siag K, Howley MM, Van Zutphen AR, Reefhuis J, Browne ML, *et al*. Maternal surgery and anesthesia during pregnancy and risk of birth defects in the National Birth Defects Prevention Study, 1997-2011. Birth Defects Research. 2020; 112: 162–174. https://doi.org/10.1002/bdr2.1616

[88] Kuczkowski KM. Nonobstetric surgery during pregnancy: what are the risks of anesthesia? Obstetrical & Gynecological Survey. 2004; 59: 52–56. https://doi.org/10.1097/01.OGX.0000103191.73078.5F

[89] Hwang JY, Kim YH, Ahn YH, Wie MB, Koh JY. N-Methyl-D-aspartate receptor blockade induces neuronal apoptosis in cortical culture. Experimental Neurology. 1999; 159: 124–130. https://doi.org/10.1006/exnr.1999.7126

[90] Ikonomidou C, Bittigau P, Ishimaru MJ, Wozniak DF, Koch C, Genz K, *et al*. Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science (New York, N.Y.). 2000; 287: 1056–1060. https://doi.org/10.1126/science.287.5455.1056

[91] Istaphanous GK, Howard J, Nan X, Hughes EA, McCann JC, McAuliffe JJ, *et al*. Comparison of the neuroapoptotic properties of equipotent anesthetic concentrations of desflurane, isoflurane, or sevoflurane in neonatal mice. Anesthesiology. 2011; 114: 578–587. https://doi.org/10.1097/ALN.0b013e3182084a70

[92] Zhu C, Gao J, Karlsson N, Li Q, Zhang Y, Huang Z, *et al*. Isoflurane anesthesia induced persistent, progressive memory impairment, caused a loss of neural stem cells, and reduced neurogenesis in young, but not adult, rodents. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2010; 30: 1017–1030. https://doi.org/10.1038/jcbfm.2009.274

[93] Creeley C, Dikranian K, Dissen G, Martin L, Olney J, Brambrink A. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. British Journal of Anaesthesia. 2013; 110 Suppl 1: i29–38. https://doi.org/10.1093/bja/aet173

[94] Soriano SG, Liu Q, Li J, Liu JR, Han XH, Kanter JL, *et al*. Ketamine activates cell cycle signaling and apoptosis in the neonatal rat brain. Anesthesiology. 2010; 112: 1155–1163. https://doi.org/10.1097/ALN.0b013e3181d3e0c2

[95] Nakata Y, Goto T, Ishiguro Y, Terui K, Kawakami H, Santo M, *et al*. Minimum alveolar concentration (MAC) of xenon with sevoflurane in humans. Anesthesiology. 2001; 94: 611–614. https://doi.org/10.1097/00000542-200104000-00014

[96] Mapleson WW. Effect of age on MAC in humans: a meta-analysis. British Journal of Anaesthesia. 1996; 76: 179–185. https://doi.org/10.1093/bja/76.2.179

[97] Devroe S, Lemiere J, Van de Velde M, Gewillig M, Boshoff D, Rex S. Safety and feasibility of xenon as an adjuvant to sevoflurane anaesthesia in children undergoing interventional or diagnostic cardiac catheterization: study protocol for a randomised controlled trial. Trials. 2015; 16: 74. https://doi.org/10.1186/s13063-015-0587-3

[98] Devroe S, Devriese L, Debuck F, Fieuws S, Cools B, Gewillig M, *et al*. Effect of xenon and dexmedetomidine as adjuncts for general anesthesia on postoperative emergence delirium after elective cardiac catheterization in children: study protocol for a randomized, controlled, pilot trial. Trials. 2020; 21: 310. https://doi.org/10.1186/s13063-020-4231-5