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From Neurotoxicity to Neuroprotection: Rethinking GABA_AR-

Targeting Anesthetics

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18 **ABSTRACT**

19 The brain growth spurt (BGS) represents a pivotal window in neurodevelopment, defined by rapid
20 neurogenesis, heightened synaptogenesis, and the dynamic establishment of neural networks. During this
21 phase, heightened brain plasticity significantly enhances learning and memory abilities, while also
22 increasing the brain's susceptibility to disruptions. Anesthetics, particularly those targeting γ -
23 aminobutyric acid type A receptors (GABA_ARs), interfere with GABAergic and glutamatergic systems,
24 disrupt brain-derived neurotrophic factor (BDNF) signaling, and exacerbate neurotoxic effects. These
25 agents activate glial cells, induce inflammation, and contribute to oxidative stress, while also disrupting
26 calcium homeostasis and triggering endoplasmic reticulum stress. Furthermore, anesthetics alter the
27 expression of non-coding RNAs, which affects gene regulation and long-term memory formation. The
28 extent of neurotoxic effects is contingent upon a constellation of factors, including the timing, dosage,
29 and frequency of anesthetic exposure, as well as individual susceptibility. Notably, perioperative
30 administration of anesthetic agents has been implicated in long-term cognitive dysfunction, thereby
31 emphasizing the critical importance of precisely modulated dosing regimens and temporally optimized
32 delivery strategies to mitigate potential neurodevelopmental risks. In contrast, neuroactive steroids
33 demonstrate promising neuroprotective potential by modulating GABA_AR activity, enhancing BDNF
34 release, and regulating oxidative stress and inflammation. New strategies for preventing and reversing
35 anesthetic-induced neurotoxicity could include novel anesthetic combinations, anti-apoptotic agents,
36 antioxidants, or nutritional supplements. These findings underscore the complex and multifactorial
37 effects of anesthetic agents on the developing brain and emphasize the urgent need to establish and refine
38 anesthetic strategies that safeguard neural integrity during vulnerable windows of neurodevelopment.
39 **Keywords** Anesthetics Targeting GABAARs; Neurodevelopment; Neurotoxicity; Neuroprotective;
40 Neuroactive Steroids

1. Introduction

A growing body of evidence derived from both animal models and clinical research suggests that the postnatal BGS represents a critical period in neurodevelopment, during which the central nervous system displays exceptional plasticity and heightened susceptibility to external perturbations. During this critical developmental window, neuronal circuits are sculpted through the rapid generation and remodeling of trillions of synapses, accompanied by dynamic neuronal migration, connectivity establishment, and functional maturation (Maksimovic et al., 2022). This crucial period is characterized by an accelerated process of neurogenesis, gliogenesis, and synaptogenesis, which collectively contribute to the brain's high plasticity and vulnerability (Fan et al., 2021; Vanderhaeghen & Polleux, 2023). At this developmental stage, the brain exhibits heightened sensitivity to disturbances arising from both environmental stimuli and pharmacological exposures.

An expanding corpus of evidence derived from both invertebrate and vertebrate models indicates that administration of general anesthetics during the BGS period can elicit extensive neurodevelopmental disruptions. These include the induction of neuronal apoptosis, inhibition of dendritic arborization, impairment of synaptogenesis, and disruption of synaptic plasticity, collectively contributing to persistent deficits in learning, memory, and long-term neurological function (Schaefer et al., 2019; Xu et al., 2018). It is now well-recognized that such adverse neurodevelopmental outcomes are mechanistically linked to the modulation of synaptic signaling by anesthetic agents. In particular, these drugs enhance inhibitory neurotransmission via GABA_ARs and/or suppress excitatory activity by antagonizing N-methyl-D-aspartate (NMDA) receptors—alterations that critically impair synaptic formation and stability during key developmental periods (Forcelli et al., 2011; Zhou et al., 2011). In clinical practice, GABA_AR agonists are more commonly administered than NMDA receptor antagonists such as ketamine or nitrous oxide. Frequently utilized GABA_AR-targeting anesthetics encompass inhalational agents—such as sevoflurane, isoflurane, and desflurane—as well as intravenous drugs including propofol, etomidate, and a range of benzodiazepines (e.g., midazolam, diazepam, remimazolam) and barbiturates (e.g., thiopental, pentobarbital).

GABA_AR agonists such as propofol disrupt a critical developmental process in which GABA transitions from depolarizing to inhibitory action. By enhancing inhibitory signals, these agents disturb the balance between excitatory and inhibitory signaling, thereby compromising neural network stability and causing long-term damage to developing brain networks. Consequently, these drugs have been included on the FDA's warning list due to their potential neurotoxic risks to children (Food & Administration, 2017).

Neuroactive steroids (NAS), a subclass of endogenous steroid compounds, act as powerful allosteric modulators of GABA_ARs and play a pivotal role in modulating inhibitory neurotransmission within the central nervous system. While NAS agents such as CDNC, alphaxalone, and 3 β -hydroxyandrostanes share sedative and anesthetic properties akin to propofol, they differ significantly in their neurotoxicity profiles. Notably, even at equivalent or supratherapeutic concentrations, these compounds do not elicit neuroapoptotic responses. In contrast, conventional anesthetics including isoflurane and propofol have

83 been shown to induce widespread neuronal apoptosis when administered during critical windows of brain
84 development. These neurotoxic effects are intimately linked to enduring impairments in synaptogenesis,
85 reduced neural plasticity, and cognitive decline (Xu et al., 2018; Zhao et al., 2023). Such findings
86 underscore the distinctive neurodevelopmental safety profile of NAS agents relative to traditional
87 anesthetics like propofol (Atluri et al., 2018; Tesic et al., 2020). Furthermore, NAS agents demonstrate
88 more pronounced neuroprotective properties, such as preventing neuronal apoptosis, protecting against
89 neurodegenerative diseases, and exerting anti-neuroinflammatory effects (Diviccaro et al., 2022).

90
91 Given the divergent mechanisms of action and neurodevelopmental consequences observed
92 between traditional intravenous anesthetics and emerging NAS, this review systematically examines the
93 neurotoxic risks and neuroprotective potential of GABAergic intravenous anesthetics during early brain
94 development. Particular attention is devoted to the reversibility and long-term consequences of
95 developmental impairments resulting from anesthetic exposure. This discussion provides deeper insights
96 into the molecular and cellular pathways implicated in anesthetic-induced neurotoxicity, while also
97 exploring critical factors that modulate individual susceptibility to these adverse effects. Lastly, we
98 evaluate emerging strategies aimed at preventing or attenuating anesthetic-related neurodevelopmental
99 harm.

100 101 **2. Neurotoxic Mechanisms of Anesthetics Targeting GABA_ARs**

102
103 During key stages of neurodevelopment, the precisely coordinated activity of GABAergic and
104 glutamatergic signaling cascades is essential for orchestrating neural stem cell proliferation, directing
105 lineage-specific differentiation, and ensuring neuronal survival and maturation. General anesthetics, by
106 profoundly modulating these excitatory and inhibitory neurotransmitter systems, have been demonstrated
107 to disrupt the finely tuned synaptic equilibrium essential for normal brain development during these
108 sensitive periods. This dysregulation is partially mediated by alterations in the NKCC1/KCC2 expression
109 ratio, which governs intracellular chloride gradients and GABAergic polarity (see section 2.1), as well
110 through direct interference with the functional integrity of GABA_ARs and NMDA receptors (Cabrera
111 et al., 2020). In addition, anesthetic agents have been reported to modulate the expression patterns of
112 BDNF, a key neurotrophin involved in synaptic regulation, thereby influencing neuron–glia crosstalk
113 and initiating downstream neuroinflammatory responses (Wan et al., 2021). Moreover, anesthetic agents
114 influence the expression of brain-derived neurotrophic factor (BDNF), thereby modulating the functional
115 dynamics of both neurons and glial cells, and eliciting neuroinflammatory responses. This leads to
116 calcium overload, enhanced oxidative stress, mitochondrial damage, endoplasmic reticulum stress, and
117 alterations in non-coding RNAs (ncRNAs). These interacting mechanisms impair the proper assembly
118 of neural circuits during development and may exert enduring detrimental effects on overall brain
119 function (Fig. 1).

120 121 **2.1 Disruption of Neurotransmitter Balance by Anesthetics**

122
123 During early brain development, GABA is released prior to the functional maturation of
124 glutamatergic synapses. In the neonatal cortex, high expression of the sodium–potassium–chloride
125 cotransporter 1 (NKCC1) establishes a depolarizing chloride gradient, thereby rendering GABAergic

126 signaling excitatory during this critical developmental window. As the brain matures, the expression of
 127 potassium–chloride cotransporter 2 (KCC2) progressively increases, replacing NKCC1 activity and
 128 resulting in a developmental transition in GABA function—from excitatory to inhibitory. This dynamic
 129 transition between excitatory and inhibitory signals ensures that neurons receive sufficient excitatory
 130 inputs during development while progressively establishing inhibitory neural networks (Oh et al., 2016;
 131 Watanabe & Fukuda, 2015). GABA_AR agonists, such as propofol and etomidate, may disrupt the
 132 excitation/inhibition (E/I) balance by increasing NKCC1 expression or inhibiting the maturation of
 133 KCC2 (Ju et al., 2017). This disruption leads to chloride extrusion and membrane depolarization,
 134 ultimately resulting in neuronal hyperexcitability and cognitive dysfunction (DiGruccio et al., 2015). In
 135 addition to modulating neurotransmitter systems, general anesthetics have been shown to activate
 136 voltage-gated calcium channels—particularly L-type channels—thereby elevating intracellular calcium
 137 concentrations. This abnormal calcium influx disrupts neuronal calcium homeostasis, a fundamental
 138 regulator of cell viability and intracellular signaling, and initiates a cascade of pathological events that
 139 ultimately lead to neuronal degeneration. These observations underscore calcium dysregulation as a central
 140 pathogenic mechanism in anesthetic-induced neurotoxicity (Miao et al., 2022; Schaefer et al., 2019;
 141 Soyalp et al., 2022). BZDs like midazolam and diazepam enhance central GABAergic function by
 142 binding to GABA_ARs and modulating downstream signaling pathways, including those involving protein
 143 kinase G and synaptic marker interactions (Fredriksson et al., 2007; Jevtovic-Todorovic et al., 2003).
 144 For instance, midazolam requires higher doses to induce sedation in neonatal animals because, at elevated
 145 concentrations, the anesthetic's effect on KCC2 surpasses its impact on NKCC1, ultimately achieving
 146 sedation through neuronal hyperpolarization (Doi et al., 2021). However, excessive dosages increase the
 147 risk of neurotoxicity, particularly in infants, as anesthetic doses often exceed those used in adults,
 148 rendering them more susceptible to neuronal injury. In contrast, remimazolam, with its lower equivalent
 149 dosage, short half-life, and minimal accumulation, results in less memory impairment. This is attributed
 150 to the reduced affinity of its metabolites for GABA_ARs, which is approximately 1/400 of remimazolam's
 151 affinity, thereby decreasing NMDAR overexpression and alleviating synaptic damage (Shi et al., 2024).

153 During intense synaptic activation, Glutamate (GLU) induces postsynaptic membrane
 154 depolarization by activating AMPA receptors, which relieves the magnesium block on NMDA receptors
 155 and allows calcium ions to enter, triggering long-term potentiation (LTP). Subsequently, Postsynaptic
 156 density protein 95 (PSD95) functions as a pivotal structural scaffold at the synapse, anchoring NMDA
 157 AMPA receptors at the postsynaptic membrane, facilitating AMPA receptor insertion, and enabling
 158 the induction of long-term potentiation (LTP) and synaptic plasticity, thereby strengthening synaptic
 159 connectivity. Conversely, GABA_AR activation has been shown to impair LTP induction—a fundamental
 160 cellular mechanism underpinning learning and memory—by attenuating GLU release at excitatory
 161 synapses. This inhibition of excitatory neurotransmission disrupts synaptic strengthening mechanisms
 162 essential for cognitive development. In vitro experiments indicate that propofol inhibits GLU release by
 163 suppressing presynaptic membrane depolarization, which reduces Na⁺ influx while its effect on
 164 presynaptic Ca²⁺ influx and the reverse transport of transporters is not significant (Bademosi et al., 2018;
 165 Karunanithi et al., 2020). Evidence from animal models indicates that propofol, at concentrations
 166 consistent with clinical use, exerts direct modulatory effects on postsynaptic GABA_ARs, thereby
 167 enhancing inhibitory neurotransmission during critical stages of brain development (Li et al., 2020). At
 168 clinically relevant concentrations, both propofol and etomidate have been shown to interact with the

169 vesicle docking protein syntaxin1A, thereby restricting its lateral mobility and impairing glutamate
170 (GLU) exocytosis from glutamatergic neurons in the basal forebrain of mice (Bademosi et al., 2018;
171 Karunanithi et al., 2020). This molecular interaction diminishes neuronal excitability and contributes to
172 functional impairment in cortical networks. Thiopental, another intravenous anesthetic, has been
173 implicated in neonatal neurodegeneration by inhibiting GLU synthesis and promoting apoptotic signaling
174 via upregulation of pro-apoptotic proteins (Naseri et al., 2017). Concurrently, gestational exposure to
175 sevoflurane has been linked to sustained downregulation of key synaptic proteins—most notably PSD95
176 and synaptophysin—in the hippocampus of both fetal and postnatal offspring, suggesting long-lasting
177 impairments in synaptic architecture and integrity (Zheng et al., 2013). This effect may involve
178 modulation of the ubiquitin–proteasome pathway. Impaired PSD95 expression destabilizes postsynaptic
179 AMPA receptor anchoring, enhancing receptor internalization through clathrin-mediated endocytosis.
180 These alterations compromise hippocampal synaptic potentiation and are associated with memory
181 deficits in rodent behavioral paradigms (Liao et al., 2021; Lu et al., 2017).

182 183 2.2 Impact of Anesthetics on BDNF

184
185 BDNF, a pivotal modulator of neurodevelopment, governs fundamental processes including
186 neuronal differentiation, axonal and dendritic growth, and synaptic plasticity. Initially synthesized as the
187 precursor protein proBDNF, BDNF is predominantly stored within synaptic vesicles and subsequently
188 converted into its mature form (mBDNF) through proteolytic processing—a transformation essential for
189 synaptic remodeling and the refinement of neural circuits during critical windows of brain development.
190 Binding of proBDNF to its receptor p75^{NTR} activates the RhoA signaling cascade, resulting in axonal
191 elongation and growth cone collapse (Head et al., 2009). During neurodevelopment, BDNF regulates the
192 development of GABAergic, glutamatergic, and other synaptic types to ensure the precise establishment
193 and stability of neural networks in the brain (Szymanski & Minichiello, 2022).

194
195 General anesthetics such as propofol significantly affect BDNF and its associated signaling
196 pathways by modulating GABAergic and glutamatergic neurotransmission, thereby disrupting
197 neuroplasticity (Cohen-Cory et al., 2010). Experimental studies have demonstrated that propofol
198 attenuates the signaling cascade of BDNF and its receptor TrkB, thereby leading to reduced expression
199 of PSD95 and impairing synaptic plasticity (Wan et al., 2021). Simultaneously, propofol activates the
200 P75^{NTR}/RhoA/ROCK pathway and GABA_ARs, increasing the ratio of proBDNF to mBDNF, disrupting
201 the homeostasis of neurotrophic factor signaling, and exacerbating neuronal apoptosis, leading to
202 neurological dysfunction (Kahraman et al., 2008). Furthermore, propofol significantly suppresses the
203 expression of BDNF, B-cell lymphoma 2 (BCL-2), and phosphorylated cAMP response element-
204 binding protein (p-CREB) in hippocampal neurons, thereby intensifying its neurotoxic impact (Wei
205 et al., 2016).

206
207 Within the context of early neural development, repeated exposure to sevoflurane disrupts the
208 equilibrium between tissue plasminogen activator and its endogenous inhibitor PAI-1, thereby impairing
209 the fibrinolytic cascade and compromising synaptic plasticity. This dysregulation subsequently hinders

the activation of TrkB signaling and reduces the proteolytic processing of proBDNF into mBDNF (Dong et al., 2020). In parallel, sevoflurane engages the proBDNF-p75 neurotrophin receptor (p75^{NTR}) axis to trigger the JNK/c-JUN/AP-1 cascade (Bi et al., 2018), while simultaneously promoting neurodegenerative signaling via β -arrestin 1/2-mediated stimulation of metabotropic GLU receptors, leading to ERK1/2-MAPK activation and downstream NRF2/BACH1 transcriptional modulation (Wang et al., 2016; F. Yang et al., 2020). Disruption of the BDNF-TrkB-Pi3K-Akt-mTOR signalling cascade in both cortical and hippocampal circuits is increasingly recognised as a key contributor to the neurotoxic effects observed following exposure to general anaesthetics (Wang & Wang, 2019). In postnatal day 6 (P6) mice, exposure to sevoflurane induces pathological activation of GSK-3 β , resulting in aberrant tau hyperphosphorylation, upregulation of IL-6 in the hippocampus, and diminished expression of the synaptic scaffolding protein PSD95. These molecular alterations converge to impair cognitive performance, suggesting a mechanistic link between anesthetic exposure, neuroinflammation, and synaptic dysfunction (Faraco et al., 2019; Tao et al., 2014).

Furthermore, Repeated exposure to benzodiazepines, including remimazolam and midazolam, has been demonstrated to disrupt short-term cognitive processes such as learning and memory in juvenile rodent models. This cognitive impairment may be mechanistically attributed to a reduction in BDNF, upregulated caspase-3 expression, diminished phosphorylation of PSD95, and suppression of LTP within the hippocampus, culminating in the exacerbation of hippocampal neuronal cell death. (Shi et al., 2024).

2.3 Effects of Anesthetics on Glial Cells and Inflammation

Anesthetic agents exert their effects not only on neurons but also extensively influence glial populations in the developing brain, with notable impacts on astrocytes, microglia, and oligodendrocytes. Amplified inflammatory activity within astrocytes and microglia is a defining feature of neuroinflammation, marked by glial cell activation or infiltration of immune cells that subsequently drive the upregulation of pro-inflammatory mediators (Mendiola & Cardona, 2018). Oligodendrocytes further influence neurodevelopment through their role in myelination (Fig. 3).

Microglial activation is broadly acknowledged as a central driver of pro-inflammatory cytokine and chemokine production within the central nervous system. Persistent or excessive activation of these immune mediators is intimately linked to neuronal injury and is thought to underlie anaesthesia-related neuroinflammatory pathologies (Chen et al., 2018). Repeated exposure to sevoflurane during the neonatal stage has been demonstrated to markedly stimulate microglial activation, leading to heightened expression of pivotal neuroinflammatory mediators such as TNF- α , IL-6, and IL-1 β (M. Yang et al., 2020). Moreover, prenatal anaesthetic exposure via maternal administration disrupts fetal glial cell signaling, prominently increasing IL-6 production through extracellular signal-regulated kinase (ERK) phosphorylation (Hirotsu et al., 2019). Concurrently, neonatal exposure to sevoflurane significantly upregulates sirtuin 2 (SIRT2) in the hippocampus, promoting microglial polarization towards a pro-inflammatory M1 phenotype (Z. Wu, Y. Zhang, et al., 2020). Beyond inhalational anesthetics, intravenous agents such as propofol and midazolam have also been associated with microglial activation, leading to an upsurge in the release of inflammatory mediators, notably IL-1 β and TNF- α (Popić et al., 2015; Ramirez et al., 2016). These responses contribute to neuroinflammatory cascades and interfere

with developmental neurogenesis (Milanovic et al., 2016). Exposure to propofol during early postnatal development significantly elevates the expression of pro-inflammatory markers—including caspase-1 and interleukin-1 β —in both cortical and thalamic regions of postnatal day 7 (PND7) rats (Milanovic et al., 2016). Importantly, microglial activation induced by sevoflurane has likewise been linked to the pathogenesis of various neurodegenerative conditions (Yeh et al., 2017).

Astrocytes are essential regulators of neural circuit formation and play a fundamental role in sustaining synaptic architecture and functionality throughout neurodevelopment. Anesthetics may disrupt astrocyte density and function, thereby impairing BDNF secretion and indirectly affecting neuronal survival. For example, in high-density co-cultures of astrocytes, BDNF secretion effectively rescues propofol-induced neuronal death, whereas low-density astrocytes, which secrete insufficient BDNF, fail to provide the same protection (Y. Liu et al., 2017). These observations may offer mechanistic insight into the heightened susceptibility of the developing brain to anesthetic-induced neurotoxicity. Within the hippocampus, astrocytes enriched in phosphoprotein enriched in astrocytes 15 (PEA15) are prominently represented, with PEA15 expression shown to increase progressively as astrocytes undergo maturation... Mounting evidence indicates that propofol interferes with neurodevelopment by suppressing the expression of PEA15, thereby perturbing the ERK/CREB/RSK2 signaling axis. This disruption ultimately results in diminished neuronal proliferation alongside an increase in programmed cell death (Xian et al., 2019).

Oligodendrocytes are central mediators of myelin sheath formation, facilitating efficient axonal conduction and supporting the maturation of neural circuits (Choi et al., 2019; Thompson et al., 2020). Myelination, a tightly regulated and temporally coordinated process occurring during early postnatal development, plays a pivotal role in the emergence of higher-order cognitive capacities and is intimately associated with the dynamic remodeling of both structural and functional neural circuitry (Deoni et al., 2018). Oligodendrocytes are not fully mature during the neonatal period, and anesthetic-induced inflammation may permanently damage myelination, hindering normal neurodevelopment. Studies have shown that anesthetic drugs have a far greater impact on oligodendrocyte apoptosis than on neurons, with apoptosis occurring at twice the rate in oligodendrocytes, representing 59% of all apoptotic cells (Schenning et al., 2017). Administration of propofol during vulnerable windows of early neurodevelopment markedly amplifies apoptotic activity in both neuronal and oligodendrocyte populations, concurrently triggering a substantial upregulation of pro-inflammatory cytokine expression. These molecular and cellular disruptions exhibit a strong association with enduring behavioural impairments manifesting in later stages of life (Milanovic et al., 2016; Ye et al., 2013). Moreover, gestational exposure to sevoflurane has been shown to impair myelination in offspring by inducing iron deficiency, thereby compromising myelin structure and reducing overall myelin content (Zuo et al., 2020). Similarly, exposure to high concentrations of sevoflurane during the early postnatal phase has been linked to impaired oligodendrocyte maturation and disruption of the normal trajectory of white matter myelination in the developing rat brain. These disturbances in oligodendrocyte lineage development contribute to central nervous system dysmyelination, a pathological process that may underlie long-term cognitive impairments (Z. Wu, H. Xue, et al., 2020).

2.4 Effects of Anesthetics on Calcium Overload, Oxidative Stress, and Endoplasmic Reticulum Stress

Appropriate calcium ion (Ca^{2+}) levels are crucial for regulating oxidative phosphorylation in the mitochondrial matrix, thereby maintaining normal ATP production rates. Nevertheless, excessive calcium influx—particularly originating from the cytosol or the endoplasmic reticulum (ER)—can compromise mitochondrial respiratory chain function, thereby promoting the overproduction of reactive oxygen species (ROS). The resulting elevation in intracellular ROS levels ultimately culminates in oxidative DNA damage (Piao et al., 2020). Excessive generation and accumulation of ROS compromise the structural integrity of the mitochondrial membrane, disrupt cellular energy homeostasis by impairing ATP synthesis, and increase mitochondrial outer membrane permeability (MOMP), collectively triggering signaling cascades that culminate in cellular dysfunction (Calvo-Rodriguez & Bacskaï, 2021; Marchi et al., 2018).

General anesthetics have been shown to induce excessive activation of inositol 1,4,5-trisphosphate (IP_3) receptors, leading to a pronounced increase in cytosolic Ca^{2+} levels while simultaneously depleting calcium stores within the endoplasmic reticulum. This disruption in intracellular calcium homeostasis may represent a key mechanistic link underlying anesthesia-induced neurotoxicity during brain development (Yang & Wei, 2017). For instance, the combination of propofol and midazolam significantly increases mitochondrial ROS levels, inhibits antioxidant enzyme activity, and impairs synaptic function (Boscolo et al., 2013). Propofol uncouples oxidative phosphorylation, disrupting mitochondrial function and increasing ROS production, thereby exacerbating neurotoxicity, which is difficult to mitigate through pretreatment (Shibuta et al., 2022). When midazolam is combined with nitrous oxide and isoflurane, ROS levels increase by approximately 30%, and antioxidant enzyme activity is notably reduced (Boscolo et al., 2013). Anesthetic compounds—particularly benzodiazepines such as midazolam and diazepam—have been associated with detrimental neurodevelopmental consequences, primarily through the disruption of synaptic architecture, impairment of synaptic transmission, and induction of neuronal apoptosis (Lee et al., 2015).

Exposure to sevoflurane has been demonstrated to activate the PI3K/Akt signaling cascade, thereby perturbing the balance between pro-survival and pro-apoptotic pathways and triggering apoptotic cell death. This dysregulation enhances MOMP, ultimately triggering intrinsic apoptotic pathways and contributing to long-term cognitive impairments observed during adolescence (Hu et al., 2019; Yu et al., 2020). In parallel, mounting evidence implicates ER stress as a key mediator of sevoflurane-induced neurotoxicity, primarily via the PERK-eIF2 α -ATF4-CHOP signaling pathway (B. Liu et al., 2017). In the developing brain, exposure to sevoflurane has also been shown to upregulate the expression of protein tyrosine phosphatase 1B within the ER, thereby initiating ER stress responses and promoting neurodegenerative alterations (Liu et al., 2019).

2.5 Effects of Anesthetics Targeting GABA_A Rs on Non-Coding RNAs (ncRNAs)

Emerging evidence highlights the pivotal influence of ncRNAs in orchestrating diverse neurobiological processes through intricate post-transcriptional regulatory mechanisms. General

anesthetics modulate the expression profiles of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in the developing brain, forming complex molecular regulatory networks that may perturb critical neural pathways. Such dysregulation is implicated in the induction of acute neuronal apoptosis persistent memory deficits, potentially resulting in irreversible neurodevelopmental alterations (Jiang et al., 2021; Rodrigues et al., 2020; Shu et al., 2019).

With respect to apoptotic mechanisms, sevoflurane has been shown to upregulate the expression of caspase-3 and Bax, while concurrently downregulating Bcl-2, BDNF, and nerve growth factor (NGF). These changes are accompanied by alterations in long non-coding RNA (lncRNA) expression and a reduction in hippocampal neuronal density, collectively leading to ultrastructural abnormalities and neuronal apoptosis (Hu et al., 2019) (Hu et al., 2019). Moreover, the long non-coding RNA LRCF has been identified as a pivotal regulatory element in mediating isoflurane-induced apoptosis of oligodendrocytes. In neonatal mice, expression levels of LRCF are significantly elevated relative to those in adults. This upregulation promotes apoptotic signaling through activation of the HIF-1 α /caspase-3 axis. Conversely, reduced LRCF expression appears to exert neuroprotective effects by recruiting the alternative HIF-1 α /miR-138-5p/caspase-3 pathway. These expression-dependent regulatory divergences may account for the heightened susceptibility of the developing brain to anesthesia-induced neurotoxicity during the neonatal period. Consequently, high LRCF expression may serve as a high-risk biomarker for OLG damage caused by anesthesia (Zeng et al., 2021). Exposure to sevoflurane has been demonstrated to influence synaptic plasticity by upregulating the expression of synaptophysin mRNA, a key presynaptic marker, via a mechanism dependent on N6-methyladenosine RNA modification. Paradoxically, this post-transcriptional modification contributes to a subsequent decline in synaptophysin protein abundance, which is associated with disrupted motor coordination and impaired cognitive performance in juvenile mice (L. Zhang et al., 2022). Isoflurane anesthesia has been reported to downregulate the expression of microRNA-132, thereby reducing dendritic spine density in the hippocampus, a morphological alteration that contributes to impaired learning and memory performance in rodent models (Zhang et al., 2017).

3. Neuroprotective Potential of Anesthetics

NAS, as sedatives and anesthetics, demonstrate significant neuroprotective potential (Tateiwa & Evers, 2024). By modulating both inhibitory and excitatory neurotransmitter systems, NAS maintain the stability of neural networks. Additionally, NAS promote the release of BDNF, a molecule essential for supporting neuronal growth, viability, and synaptic plasticity. Furthermore, NAS regulate inflammation and oxidative stress, alleviating neuroinflammation and reducing oxidative damage, thereby effectively protecting neuronal cells from injury. These multiple mechanisms collectively highlight the potential of NAS agents as neurodevelopmental protective compounds (Fig. 3).

3.1 Modulation of the Inhibitory Neurotransmitter System

While most NAS serve as potent allosteric modulators of GABA_AR, enhancing or inhibiting GABA-induced currents via subtype-specific binding—such as potentiation by 3 α -hydroxylated neurosteroids and suppression by 3 β -sulfated derivatives—emerging evidence indicates a divergence in neurotoxic potential among GABA_AR-activating agents (Chen et al., 2019; Laverty et al., 2017). Notably,

compounds like propofol, CDNC24, and alphaxalone all activate GABA_ARs, yet only propofol has been consistently associated with significant neurotoxicity during brain development, whereas NAS such as alphaxalone exhibit negligible or no overt neurotoxic effects(Tesic et al., 2020). Further investigations revealed that NAS compounds, such as alphaxalone and 3 β -OH, do not induce neuronal apoptosis, regardless of their activation of GABA_ARs. The neuroprotective properties of these compounds may be partially attributed to their ability to inhibit T-type calcium channels, particularly Cav3.1, thereby diminishing presynaptic GABA release(Tesic et al., 2020; Timic Stamenic et al., 2021). Intriguingly, the mechanism of action of 3 β -OH appears to operate independently of classical modulation of GABAergic or NMDA receptor pathways(Atluri et al., 2018; Timic Stamenic et al., 2021). NAS enhances neuronal regeneration. For instance, allopregnanolone binds to the transmembrane domain of the GABA_AR complex, activating the receptor and increasing intracellular Ca²⁺ concentrations. This calcium influx subsequently activates CaMK IV, which phosphorylates and activates the transcription factor CREB1. Once activated, CREB1 enhances the transcription of genes involved in cell cycle regulation, thereby promoting mitotic activity in neural stem cells and oligodendrocyte precursor cells(G. F. Li et al., 2018). Moreover, NAS demonstrates significant potential for selective regulation of different GABA_AR subtypes. These compounds can modulate receptor tonic currents by enhancing GABA_AR-mediated current activity. At moderate concentrations, NAS compounds inhibit GABA_AR function, whereas at lower and higher concentrations, they enhance GABA regulation. This suggests that NAS compounds exert a complex bidirectional effect on GABA_ARs within different concentration ranges, potentially providing a new therapeutic strategy for neuroprotection by modulating neural activity (Fig. 4).

400

401 3.2 Modulation of the Excitatory Neurotransmitter System

402

NAS, such as 3 β -OH, reduces presynaptic AMPA receptor-mediated excitatory synaptic currents but does not affect NMDAR-mediated excitatory currents, thus modulating the glutamatergic system(Atluri et al., 2018). Gonadal steroids, such as estradiol (E2) and 17 β -estradiol, potentiate NMDAR-mediated synaptic transmission and facilitate the release of GLU from primary afferent terminals, thereby increasing dendritic spine density in dorsal horn neurons of the spinal cord(Zhang et al., 2012). Estradiol not only enhances the binding of NMDAR agonists and competitive antagonists(Kow et al., 2005) but may also exert a dual action by enhancing cognitive function, promoting synaptic transmission while offering neuroprotective effects(Nilsen et al., 2002). The enantiomer of 17 β -estradiol exhibits neuroprotective properties against glutamate-induced toxicity in cultured neuronal cells, implying that its protective effects may be mediated through pathways independent of classical nuclear estrogen receptors(Green et al., 2001). These studies suggest that NAS drugs exhibit neuroprotective potential by modulating NMDARs and the GLU transport system within a specific concentration range(Fig. 4).

416

417 3.3 Promotion of BDNF Release

418

Many studies have indicated that NAS can bind to and regulate various proteins involved in cell protection, including estrogen receptors α/β (ER α/β), the orphan nuclear receptor pregnane-X receptor (PXR), and the GPER1, thereby modulating BDNF levels (Briz & Baudry, 2014; Jakab et al., 2001; Serrao & Goodchild, 2022). For example, the enantiomer of 17 β -estradiol regulates BDNF levels through an ER β -mediated mechanism (Jakab et al., 2001). This modulatory action not only contributes to improved learning and memory performance but also serves a pivotal role in mitigating cognitive impairments induced by anesthesia (Taylor et al., 2017). Additionally, neurosteroid drugs such as alphaxalone activate PXR, further promoting the secretion of BDNF and exerting neuroprotective effects (Frye et al., 2014; Serrao & Goodchild, 2022). Clinical randomized controlled trials (RCTs) have demonstrated that patients treated with alphaxalone during hip replacement surgery show better cognitive performance postoperatively, with significantly higher plasma levels of BDNF than patients treated with propofol and sevoflurane (Serrao & Goodchild, 2022). These findings suggest that NAS, by modulating BDNF and associated pathways, exhibits significant neuroprotective effects, particularly in the recovery of cognitive function following anesthesia and surgery.

3.4 Regulation of Inflammation and Oxidative Stress

NAS, such as pregnenolone, exert anti-inflammatory effects through multiple signaling pathways, including Toll-like receptor signaling, the TRAM-TRIF pathway, BDNF, and CX3CL1 signaling pathways. NAS suppress the initiation of pro-inflammatory signaling cascades by disrupting the binding of Toll-like receptors—specifically TLR2, TLR4, and TLR7—to their adaptor proteins such as MyD88, MD2, and TIRAP, thereby reducing downstream synthesis of pro-inflammatory mediators (Balan et al., 2019; Balan, Grusca, et al., 2023; Balan, Patterson, et al., 2023). In addition to its established role in suppressing pro-inflammatory signaling, NAS activate the TLR4-TRAM-TRIF pathway, leading to the upregulation of key anti-inflammatory mediators such as IL-17 and BDNF, thereby contributing to neuroprotection (Aurelian & Balan, 2019). NAS also promote the expression of the anti-inflammatory chemokine CX3CL1, which is essential for maintaining the equilibrium between pro- and anti-inflammatory responses within the central nervous system, ultimately alleviating neuroinflammation. Furthermore, NAS have been shown to attenuate microglial pro-inflammatory activation by engaging GABA_ARs and modulating the BDNF-TrkA/TrkB signaling cascade, while concurrently regulating the transcription of pro-inflammatory genes (Alexaki et al., 2018; S. Y. Wu et al., 2020). Beyond anti-inflammatory action, NAS support neuronal repair and regeneration through diverse neuroprotective mechanisms, offering potential therapeutic benefits in the context of neurodegenerative conditions and traumatic brain injury. Collectively, these findings underscore the central role of inflammation and oxidative stress in anesthetic-induced neurotoxicity. Importantly, NAS modulate antioxidant and anti-inflammatory processes not only through GABAergic pathways but also via alternative non-GABAergic mechanisms, highlighting their promise in mitigating the adverse neurodevelopmental effects associated with anesthetic exposure.

4. Susceptibility Factors for Anesthetic-Induced Neurotoxicity

4.1. Dose-, Time-, and Frequency-Dependent Effects of Anesthetics

Anesthetic-induced neurotoxicity demonstrates marked dependence on dose, exposure duration, and administration frequency. Evidence from both cellular and animal models indicates that anesthetic agents, such as propofol, may facilitate the differentiation of neural progenitor cells into neurons when administered at very low concentrations (Qiao et al., 2017). However, at subclinical or medium-to-high doses, these anesthetics inhibit neuronal proliferation, increase pro-inflammatory factor levels, and trigger widespread neuronal apoptosis, with the extent of apoptosis gradually increasing with higher doses (K. Chen et al., 2022; Han et al., 2015). Anesthetic neurotoxicity also demonstrates a clear time dependence, with neuronal apoptosis worsening as the exposure duration increases (Huang et al., 2012; Zhang et al., 2016). In rodent models, brief exposure to propofol (2 or 4 hours) induced marked activation of caspase-3, a key executor of apoptosis. Notably, a more prolonged exposure of 6 hours elicited not only a pronounced increase in caspase-3 but also elevated calpain activity within the cerebral cortex and thalamus. These molecular alterations were concomitant with the emergence of apoptotic neuron profiles, indicating that extended anesthetic exposure may potentiate neurodegenerative processes in specific brain regions (Milanovic et al., 2010). Prolonged exposure to sevoflurane impairs the maturation of neural circuits by inhibiting synaptogenesis and destabilizing dendritic spine development. This anesthetic disruption is further characterized by structural synaptic alterations, including increased expression of synaptic vesicle-related proteins, reduced density of apical dendritic spines, and ultrastructural disorganization within hippocampal synapses, which collectively contribute to cognitive deficits observed in juvenile rats (Yu et al., 2020). Moreover, a study comparing single-dose versus seven-dose administrations of propofol with the same total dose showed that rats exposed multiple times exhibited significant impairments in spatial learning and hippocampal function, suggesting that frequent exposures may have a more severe impact on neurological function than a single cumulative dose (Gao et al., 2014). Recurrent administration of sevoflurane during critical periods of cortical development has been implicated in long-term synaptic dysfunction, accompanied by structural synaptic anomalies and persistent cognitive deficits manifesting in adulthood (G. Li et al., 2019; Zhou et al., 2019).

4.2 Synergistic Effects of Combined Anesthesia

Emerging evidence indicates that the combined administration of anesthetic agents may markedly potentiate neuronal apoptosis and disrupt hippocampal synaptic integrity, thereby impairing learning and memory through synergistic neurotoxic effects (Jevtovic-Todorovic et al., 2003). For instance, during critical windows of brain maturation, the combined administration of ketamine with thiopental or propofol significantly amplifies neuronal cell death in neonatal animals and results in enduring functional impairments in adulthood, whereas the administration of these agents individually tends to produce only modest neurodevelopmental effects (Fredriksson et al., 2007). The combined use of anesthetics such as isoflurane, midazolam, and nitric oxide (NO) in a "triple cocktail" may reduce synaptic density (Lunardi et al., 2010), destabilize mitochondria (Sanchez et al., 2011), and increase autophagic activity (Fredriksson et al., 2007), which could contribute to neurodegenerative changes. Combined exposure to midazolam and nitrous oxide perturbs the homeostasis of mitochondrial dynamics by dysregulating key modulators such as Mfn-2 and Drp-1. This imbalance leads to pronounced mitochondrial morphological alterations, compromised bioenergetic function, and subsequent impairments in neuronal integrity and performance (Boscolo et al., 2013).

4.3 Region-Specific Sensitivity to Anesthetics During Critical Periods of Brain Development

During BGS, exposure to anesthetic drugs can lead to widespread neuronal apoptosis and result in persistent behavioral deficits (Gentry et al., 2013). The temporal window of the BGS varies significantly across mammalian species. In rodents, this critical phase of neurodevelopment unfolds within the first two weeks following birth (Semple et al., 2013), whereas in rhesus macaques, it spans from gestational day 115 to approximately postnatal day 60 (Brambrink et al., 2012); and in humans, the growth spurts occur at varying times across different brain regions, with most regions peaking in the second year after birth and typically reaching their maximum between 3 and 10 years of age (Andropoulos & Greene, 2017). Neuronal apoptosis induced by anesthetic drugs exhibits significant regional specificity at different time points during the BGS. In rodents, postnatal day 0 (P0) is the peak period of early apoptosis, primarily occurring in neurons of the hypothalamus and certain thalamic nuclei; day 3 (P3) marks the peak of intermediate apoptosis, affecting regions such as the Subiculum, Hilar, caudate nucleus, and thalamic nuclei; day 7 (P7) represents the peak of late apoptosis, predominantly affecting cortical neurons (Maloney et al., 2019). Similarly, In a comparable model using rhesus monkeys, prenatal exposure to propofol predominantly induces apoptosis in neurons and oligodendrocytes within the cerebellum, hypothalamus, and additional posterior and anterior brain regions, whereas exposure during the neonatal period primarily affects the cerebral cortex (Creeley et al., 2013) (Fig. 4).

4.4 Vulnerable Populations for Anesthetic-Induced Neurotoxicity

Neonates—particularly those born prematurely, with low birth weight, reduced gestational age, or complex congenital anomalies—constitute a highly vulnerable population, exhibiting an elevated susceptibility to anesthesia-related neurodevelopmental impairment. Neuroimaging studies have revealed that preterm infants frequently display structural abnormalities in both gray and white matter following neonatal surgery. These alterations, detectable by MRI, have been strongly correlated with subsequent cognitive deficits and delays in neurodevelopmental milestones (Filan et al., 2012; Stolwijk et al., 2017). Weiss et al. noted that neonatal brains are highly sensitive to ischemic injury, placing these groups at a higher risk for neurodevelopmental disorders during the perioperative period. Specifically, during anesthesia, changes in hemodynamics, respiration, and metabolism may have a greater impact on neurodevelopment than the anesthetic drugs themselves (Weiss et al., 2016). Furthermore, factors such as increased surgical frequency, prolonged hospital stays, and prolonged respiratory support further exacerbate the risk of neurodevelopmental disorders. These impairments are not only related to the direct effects of surgery and anesthesia, but may also be closely associated with hemodynamic instability, improper respiratory control, and metabolic imbalance during anesthesia, compounded by surgical stress and primary diseases (Stolwijk et al., 2016).

5 Potential Strategies to Prevent and Reverse Neurotoxicity

5.1 Combination of Newer Anesthetic Agents

Dexmedetomidine (DEX), a highly selective α_2 -adrenergic receptor agonist, has emerged as a potent neuroprotective agent against isoflurane-induced neurotoxicity, primarily due to its robust anti-apoptotic

properties. Mechanistically, DEX exerts its neuroprotective effects through engagement with several converging molecular cascades. These include the DNMT3a-miR-377-5p-Arc axis and the ERK1/2-CREB-BDNF signaling pathway (Xiao et al., 2018), along with activation of the PI3K-Akt cascade. Concurrently, it inhibits pro-apoptotic processes by downregulating the GSK-3 β -CRMP2 and CDK5-CRMP2 pathways (Z. Chen et al., 2022). Pretreatment with DEX has also been shown to counteract the isoflurane-mediated repression of neurotrophic mediators such as BDNF mRNA, phosphorylated ERK1/2, CREB, and BDNF protein, thereby preserving synaptic homeostasis under anesthetic-induced stress (Tu et al., 2019). Additional studies have confirmed that the suppression of the GSK-3 β /CRMP2 and CDK5/CRMP2 pathways by DEX contributes to reduced neuronal apoptosis and cognitive decline in neonatal models (J. Li et al., 2019). Moreover, the neuroprotection afforded by DEX extends beyond apoptosis, encompassing antioxidative and anti-inflammatory actions that mitigate sevoflurane-induced cognitive impairments (Wang et al., 2015). In neonatal rats, DEX may also confer protection via modulation of glutamatergic transmission (Wang et al., 2019). Activation of α_2 -adrenergic receptors by DEX and related agonists like clonidine has additionally been found to attenuate tau hyperphosphorylation and its associated cognitive sequelae in neonatal mice exposed to sevoflurane (Sun et al., 2021). Notably, the neuroprotective efficacy of DEX in anesthetic regimens appears dose-dependent: at low concentrations, co-administration with sevoflurane enhances neuroprotection; however, higher doses paradoxically increase apoptosis and mortality, potentially due to reduced α_2 receptor selectivity and inadvertent α_1 receptor activation (Liu et al., 2016; Perez-Zoghbi et al., 2020) (Perez-Zoghbi et al., 2017) (Fig. 4).

Novel BZDs such as remimazolam, when combined with sevoflurane, significantly reduce the incidence of postoperative delirium, suggesting a neuroprotective potential that may be linked to reduced overall anesthetic exposure (Yang et al., 2022). The combined use of anesthetics might also protect the brain by balancing excitatory and inhibitory pathways. For example, midazolam could facilitate the reuptake of excess GLU via EAAT2 and enhance GABA_AR activity, inhibiting the release of glutamate transporters, thereby effectively alleviating excitotoxicity caused by the upregulation of NMDAR NR1 subunits after ketamine withdrawal (Y. Li et al., 2018; Slikker et al., 2007). Moreover, NAS such as 17 β -estradiol may enhance AKT phosphorylation, increase p-GSK-3 β levels, and stimulate BDNF release (W. Li et al., 2019; Yang et al., 2022), effectively mitigating the apoptosis induced by combinations of triple cocktails (Lu et al., 2006) or ketamine (Li et al., 2014). Alphaxalone has been reported to mitigate the neurotoxic effects elicited by isoflurane exposure in neonatal rats, highlighting its potential as a neuroprotective agent during early brain development (Zhao et al., 2023).

5.2 Neuroprotective Agents

5.2.1 Anti-Apoptotic Agents

Neuronal apoptosis is a major mechanism of developmental neurotoxicity induced by GABA_AR receptor agonists. Inhibiting apoptotic pathways may serve as a potential intervention. The histamine H₃ receptor antagonist Clobenpropit has been shown to activate the PI3K/Akt signaling cascade, thereby mitigating isoflurane-induced apoptotic injury in hippocampal neurons in vitro (He et al., 2018) (He et al., 2018). Complementarily, the TNF- α inhibitor Etanercept significantly reduced neuronal apoptosis in

the developing rat brain following isoflurane exposure (Chen et al., 2016) (Chen et al., 2016), suggesting a role for inflammatory modulation in anesthetic-induced neurotoxicity. In a separate study, Straiko and colleagues demonstrated that the co-administration of lithium with either ketamine or propofol did not significantly alter caspase-3 activation levels compared to control conditions, indicating a limited effect of lithium in modulating anesthetic-induced apoptosis via this pathway (Straiko et al., 2009). Moreover, erythropoietin (EPO) can partially reverse the decrease in BDNF and Bcl-2 levels caused by general anesthetics, thereby mitigating neuronal damage (Pellegrini et al., 2014).

5.2.2 Anti-Inflammatory Agents

Neuroinflammation has emerged as a critical mediator of anesthetic-induced neurotoxicity, making it a compelling target for therapeutic intervention. Recent findings indicate that edaravone confers neuroprotection against isoflurane-induced neuronal injury by attenuating inflammatory and apoptotic responses via activation of the mBDNF–TrkB–PI3K signaling axis (Yang et al., 2021). These beneficial effects have been validated across both in vitro neuronal culture systems and in vivo preclinical models, highlighting the therapeutic promise of neurotrophic pathway modulation in mitigating anesthesia-related neural damage. In parallel, doxycycline—a semi-synthetic tetracycline antibiotic—has demonstrated potent neuroprotective capabilities beyond its antimicrobial function. Through engagement of the PI3K/Akt pathway, doxycycline has been shown to exert significant anti-inflammatory and anti-apoptotic effects, supporting its candidacy as a therapeutic agent for inflammation-related neurodevelopmental pathologies (Möller et al., 2016).

5.2.3 Anti-Oxidative Stress Neuroprotective Agents

Recent advances in neuropharmacology underscore the neuroprotective potential of natural antioxidants against anesthesia-induced neurotoxicity. Melatonin, for instance, has been shown to activate the PKC α /Nrf2 signaling cascade, upregulate the anti-apoptotic protein Bcl-xL, suppress cytochrome c release, and inhibit mitochondrial-dependent apoptotic pathways. Through these mechanisms, melatonin markedly reduces neuronal apoptosis triggered by combined exposure to diazepam, nitrous oxide, and isoflurane, suggesting a protective role in anesthetic neurotoxicity (B. Li et al., 2018; Yon et al., 2006). Similarly, curcumin (Ji et al., 2015) and resveratrol (Tang et al., 2021), both known for their antioxidant properties, have been demonstrated to attenuate sevoflurane-induced oxidative stress by neutralizing ROS and suppressing associated inflammatory responses. Acetyl-L-carnitine (L-Ca), a mitochondria-targeted antioxidant, has been identified as neuroprotective in aging and neurodegenerative conditions (Robinson et al., 2019; Yan et al., 2014). Notably, co-administration of L-Ca with propofol has been reported to alleviate propofol-induced cytotoxicity in embryonic neural stem cells, primarily by reducing ROS production and downregulating oxidative stress-related signaling pathways (Liu et al., 2014). These findings highlight the promise of L-Ca as a potential adjunct in anesthetic protocols, particularly those involving agents with known oxidative liabilities.

5.2.4 Nutritional Supplements for Neuroprotection

Calcium homeostasis disruption is a key mechanism underlying anesthetic-induced neurotoxicity, involving mitochondrial dysfunction as well as damage to astrocytes and neurons. Emerging evidence indicates that stabilizing intracellular calcium dynamics may represent a promising strategy to counteract the neurodevelopmental toxicity associated with sevoflurane exposure (Zhu et al., 2024). Iron deficiency has been recognized as a pivotal determinant of impaired myelination within the central nervous system, exerting its most detrimental effects during the fetal period and early stages of postnatal development. Disruptions in iron homeostasis during these sensitive periods may compromise oligodendrocyte function and hinder the proper formation of myelin sheaths (Ward et al., 2014). Sevoflurane exposure has been implicated in disrupting myelin development during early brain maturation, potentially through mechanisms involving oligodendrocyte apoptosis, as well as deficiencies in iron and folate metabolism. Supplementing with iron and folate and inhibiting OL apoptosis could be effective preventive measures, although further research is needed.

These findings suggest that strategies aimed at preventing apoptosis and inflammation, reducing oxidative stress, and restoring calcium homeostasis and nutrient balance may offer promising interventions against sevoflurane-induced neurotoxicity (Fig. 3).

6. Concluding Remarks and Future Directions

During the BGS, the finely tuned interplay between the GABAergic and glutamatergic (GABA/GLU) systems is essential for proper neural development, with the developmental switch from NKCC1 to KCC2 transporters serving as a pivotal mechanism in establishing the balance between E/I signaling. Anesthetics, particularly intravenous agents targeting GABA_ARs, may disrupt this transition, thereby destabilizing neural networks (Cabrera et al., 2020). Additional mechanisms include the imbalance of the BDNF signaling pathway, oxidative stress responses, and inflammatory reactions, all of which exacerbate neurotoxicity. Compared with traditional anesthetics, newer agents such as NAS (Tesić et al., 2020; Timić Stamenić et al., 2021), remimazolam (Shi et al., 2024), and DEX (Wei et al., 2016) exhibit milder mechanisms of action, maintaining sufficient anesthetic effects while minimizing interference with the nervous system. However, our understanding remains limited regarding how novel NAS and similar compounds may modulate T-type calcium channels and selectively bind to specific sites on GABA_AR, thereby facilitating endogenous regenerative processes in the brain and mitigating the neurotoxic effects of anesthetic agents. Further investigation is essential to elucidate their potential in alleviating neurotoxicity. Concurrently, significant strides are being made in the development of neuroprotective pharmacotherapies. Agents such as melatonin (B. Li et al., 2018), erythropoietin (EPO) (Pellegrini et al., 2014), and resveratrol (Tang et al., 2021)—all of which exhibit potent antioxidant, anti-inflammatory, and neuroprotective properties—have been investigated as promising candidates for mitigating anesthetic-induced neurotoxicity (Fig. 3). Accordingly, the development of next-generation anesthetic agents should prioritise strategies that minimise neurotoxicity, enhance intrinsic neuroprotective mechanisms, and facilitate post-injury repair and functional recovery—thereby ensuring both the safety and therapeutic efficacy of anaesthesia in paediatric and other high-risk populations.

Since the 2016 advisory issued by the FDA regarding the potential neurotoxic effects of anesthetic agents in pediatric populations, there has been a marked increase in clinical investigations evaluating the

neurodevelopmental consequences of anesthetic exposure in children. Findings from key studies such as the PANDA study (Sun et al., 2016) and the GAS trial (Davidson et al., 2016; McCann et al., 2019) have shown that a single, brief exposure—typically under one hour—to general anesthesia in children younger than five years of age is not associated with significant long-term neurodevelopmental deficits. However, the MASK study provided evidence that multiple exposures prior to age three may be linked to slower cognitive processing, impaired fine motor coordination, and increased risk of behavioral and learning difficulties. Supporting this, recent data suggest that general anesthesia administered to infants under one year of age is associated with an elevated risk of developmental delays, with risk escalating as the number of surgical procedures increases (Kobayashi et al., 2020). While the majority of clinical studies suggest that isolated anesthetic exposure is relatively safe, the literature remains inconclusive due to ethical constraints, methodological limitations, and perioperative confounders. Notably, the combined neurotoxic effects of multiple anesthetic agents and their potential protective mechanisms remain underexplored. Future research should adopt an integrative approach, combining mechanistic molecular studies, behavioral analyses in animal models, and rigorously designed clinical trials. Prospective randomized controlled trials (RCTs) with long-term neurodevelopmental follow-up are essential. Moreover, the establishment of standardized dosing frameworks and exposure durations, alongside anesthesia protocols tailored to regional brain vulnerability across developmental stages, will be critical to advancing this field.

Clinical investigations into the long-term cognitive and behavioral consequences of anesthetic exposure in children employ heterogeneous methodologies. However, a significant proportion of these studies rely predominantly on subjective outcome assessments (Maloney et al., 2019), with limited incorporation of objective neuroimaging techniques or biomarker analyses, thereby straining a comprehensive evaluation of anesthetic-induced neurodevelopmental effects (Bethlehem et al., 2022; Hwang et al., 2022). Notably, quantitative ultrasound imaging has revealed increased apoptotic activity in the developing brains of non-human primates following sevoflurane exposure, highlighting the potential neurotoxic impact of this agent during vulnerable periods of brain maturation (Rosado-Mendez et al., 2019). Complementary neuroimaging studies suggest that pediatric exposure to inhalational anesthetics such as isoflurane and sevoflurane is associated with cognitive impairments and disruptions in white matter integrity (Banerjee et al., 2019; Bethlehem et al., 2022). Moreover, prospective investigations report that as many as 75% of infants undergoing non-cardiac surgery for congenital anomalies exhibit mild to moderate neuroimaging abnormalities postoperatively (Mongerson et al., 2019; Moran et al., 2019). To delineate the precise neurodevelopmental impact of anesthetic agents, future studies should adopt an integrative approach—combining MRI and diffusion tensor imaging (DTI) with high-resolution ultrasound and biomarker profiling (e.g., inflammatory cytokines, BDNF)—in conjunction with longitudinal assessments of cognitive and behavioral function across defined developmental windows. This will help establish preventive or reversal strategies, such as the use of antioxidants, calcium channel blockers, or agents that promote myelination, or through environmental stimulation and functional training to restore the function of impaired neural networks.

7. conclusion

718 With the widespread clinical application of intravenous anesthetics targeting GABA_ARs, their
719 potential impact on the developing nervous system has increasingly become a focal point of academic
720 attention. Although extensive research has elucidated the neurodevelopmental impact of GABA_AR–
721 targeting agents via modulation of both GABA_ARs and NMDA receptors, the specific influence of
722 anesthetic drugs on synaptogenesis remains a complex and multilayered phenomenon. Deciphering the
723 long-term consequences of such agents, alongside the identification of potential neuroprotective
724 strategies and the refinement of their clinical applicability, continues to pose substantial challenges for
725 future investigations.

726 **Statements & Declarations**

727

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734 **Conflict of interest**

735 The authors declare no competing interests.

736 **Contributors**

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744 **Data availability**

745 No new datasets were generated or analyzed in the course of this review. As such, data sharing is not
746 applicable.

747 **Ethical Approval**

748 This work is a synthesis of previously published literature and does not involve any original research
749 involving human participants or animals conducted by the authors. All referenced studies received
750 appropriate ethical approvals as documented in their respective publications.

751 **Sources and Data Illustration Strategy**

752 To illustrate the mechanisms of anesthetic-induced neurotoxicity, all pathway diagrams and synaptic
753 models presented in this review were created using BioRender and manually curated from previously
754 published peer-reviewed literature. No new experimental or clinical data were generated or analyzed
755 for this work.

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FIGURES LEGENDS

Fig. 1 Mechanisms of Developmental Neurotoxicity Induced by Anesthetics Targeting GABA_A Receptors

Anesthetic drugs target GABA_A receptors (GABA_AR) in immature neurons, leading to developmental neurotoxicity. Black arrows represent the direct effects of anesthetic drugs on immature neurons, while red arrows indicate the subsequent effects triggered by the inhibition of relevant signaling pathways. The underlying mechanisms include: GA upregulating NKCC1 and downregulating KCC2, thereby enhancing GABA-mediated excitatory signaling, which leads to excessive calcium influx and calcium overload. This overload then triggers neuroinflammation and exacerbates oxidative stress. Through NMDAR-mediated excitatory/inhibitory imbalance (E/I imbalance), synaptic plasticity is disrupted, with a reduction in PSD95 and related proteins, as well as inhibition of long-term potentiation (LTP). Furthermore, GA affects the BDNF signaling pathway by enhancing BDNF/ P75^{NTR}, inhibiting BDNF/TrkB signaling, and causing BDNF dysregulation. Simultaneously, it interferes with abnormal ncRNA and PTP-1B signaling pathways, inducing endoplasmic reticulum stress, which ultimately results in neuronal damage.

Fig. 2 The Effects of Anesthetics Targeting GABA_A Receptors on Different Neuronal Populations

Anesthetic agents activate microglia, triggering the release of pro-inflammatory cytokines and M1 markers, which in turn exacerbate neuroinflammation. These drugs induce massive apoptosis in oligodendrocytes, leading to neuronal demyelination. Notably, iron and folate have been shown to mitigate this demyelination process. Furthermore, anesthetics interfere with astrocyte function via the ERK pathway, disrupting BDNF metabolism and ultimately leading to neuronal apoptosis. This cascade of events underscores the harmful effects of anesthetics on neurodevelopment, particularly in the context of inflammation-induced apoptosis in both neurons and glial cells.

Fig. 3 Neuroprotective Mechanisms of NAS

NAS exerts neuroprotective effects through multiple pathways. The mechanisms are as follows: black arrows indicate the direct effects of anesthetics on immature neurons, while red arrows represent subsequent effects induced by the inhibition of related signaling pathways. NAS interacts with TLR2, TLR4, and TLR7 and their adaptor proteins to reduce the production of inflammatory factors, thereby alleviating neuronal inflammation. NAS also regulates the synthesis of mBDNF through receptors such as GPER1, ERα/β, and PXR. mBDNF activates MEK/ERK, PI3K/AKT, and PLCγ/PKC signaling pathways through TrkA/B receptors, inhibiting ROS production, alleviating mitochondrial dysfunction, reducing neuronal apoptosis, enhancing neurotransmitter release, and activating NMDAR to promote LTP formation, thus increasing synaptic plasticity. Additionally, NAS may exert anesthetic effects by modulating GABA_ARs and calcium ions while enhancing neuronal regeneration to further protect the nervous system. NAS, DEX, and EPO reduce neuroinflammation and exhibit anti-apoptotic and neuroprotective effects through the BDNF/TrkB pathway, while Clobenpropit, Edaravone, and Doxycycline act through the BDNF/PI3K pathway. Melatonin increases BDNF production through Nrf2, while L-Ca, Curcumin, and Resveratrol reduce oxidative stress, and Etanercept reduces the production of inflammatory factors.

Fig. 4. The Impact of Anesthetic Agents on Different Brain Regions During Development

Neurodevelopmental trajectories based on global pediatric MRI data are presented, with the y-axis representing the percentage of maximum volume attained by each brain region during development, and

1377 the x-axis representing age. The yellow shaded region highlights the period of anesthesia vulnerability,
1378 in comparison to the critical peak developmental periods for various brain functions. The impact of
1379 anesthetic drugs on different brain regions is shown, with highlighted areas indicating regions
1380 particularly vulnerable to anesthesia-induced damage. BGS: brain growth spurt; GMV: total cortical grey
1381 matter volume; WMV: total white matter volume; CSF: total ventricular cerebrospinal fluid volume
1382 (ventricles or cerebrospinal fluid); MCT: mean cortical thickness; TSA: total surface area; TCV: total
1383 cerebrum volume.

1384 **Fig. 5 Graphical Abstract: Mechanisms of Anesthetic-Induced Neurotoxicity Targeting GABA_A**
1385 **Receptors and Associated Susceptibility Factors**

1386 Neonatal brain development occurs during a critical period, and anesthetic-induced neurotoxicity during
1387 this time is influenced by multiple complex factors, including the mechanisms of anesthetic drugs
1388 targeting GABA receptors and associated susceptibility factors. The interplay of these factors contributes
1389 to the formation of a complex mechanism underlying neonatal neurotoxicity induced by anesthesia.

1390

1391 **Fig. 1 Mechanisms of Developmental Neurotoxicity Induced by Anesthetics Targeting GABA_A**
1392 **Receptors**

1393

1394 **Fig. 2** The Effects of Anesthetics Targeting GABA_A Receptors on Different Neuronal Populations

1395 **Fig. 3 Neuroprotective Mechanisms of NAS**

1396 **Fig. 4 The Impact of Anesthetic Agents on Different Brain Regions During Development**

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1399 **Fig. 5 Graphical Abstract: Mechanisms of Anesthetic-Induced Neurotoxicity Targeting GABA_A**

1400 **Receptors and Associated Susceptibility Factors**

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