Hang et al. *Zool. Res.* 2024, 45(3): 691−703
https://doi.org/10.24272/j.issn.2095-8137.2023.413

ZR | Zoological Research

Review Open Access

General anesthetic agents induce neurotoxicity through oligodendrocytes in the developing brain

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ABSTRACT

General anesthetic agents can impact brain function through interactions with neurons and their effects on glial cells. Oligodendrocytes perform essential roles in the central nervous system, including myelin sheath formation, axonal metabolism, and neuroplasticity regulation. They are particularly vulnerable to the effects of general anesthetic agents resulting in impaired proliferation, differentiation, and apoptosis. Neurologists are increasingly interested in the effects of general anesthetic agents on oligodendrocytes. These agents not only act on the surface receptors of oligodendrocytes to elicit neuroinflammation through modulation of signaling pathways, but also disrupt metabolic processes and alter the expression of genes involved in oligodendrocyte development and function. In this review, we summarize the effects of general anesthetic agents on oligodendrocytes. We anticipate that future research will continue to explore these effects and develop strategies to decrease the incidence of adverse reactions associated with the use of general anesthetic agents.

Keywords: Oligodendrocytes; General anesthetic agents; Neurotoxicity; Central nervous system; Perioperative neurocognitive disorders

INTRODUCTION

General anesthetic agents (GAAs) confer a range of benefits for medical procedures, including analgesia, amnesia, loss of consciousness, reflex suppression, and moderate muscle relaxation. These agents facilitate the induction of reversible brain states, essential for performing surgical or invasive medical procedures. GAAs achieve unconsciousness by altering neurotransmission across multiple regions of the brain, including the cerebral cortex, brainstem, and thalamus (Brown et al., 2010). By targeting γ-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA) receptors (NMDAR), ion channels, enzymes, and other proteins, GAAs inhibit excitatory neurons and/or facilitate inhibitory neurons to exert sedative and anesthetic effects (Wong-Kee-You et al., 2023). Notably, in addition to acting on neurons in the brain, GAAs also act on glial cells, which provide critical support for proper neuronal function. Consequently, there is growing interest in understanding the effects of GAAs on glial cells (Yang et al., 2024a, 2024b).

Approximately 50% of cells within the central nervous system (CNS) are neuroglia, primarily tasked with safeguarding, regulating, and supporting neuronal activities (Allen & Lyons, 2018). Oligodendrocytes, constituting 45%–75% of all glial cells in the human brain (Ortinski et al., 2022), play a critical role in myelin formation and axonal maintenance in the CNS. The proliferation and differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes and subsequent myelin formation are governed by various molecular mechanisms, including the mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) signaling pathways, extrinsic extracellular signals, intrinsic transcription factors of oligodendrocytes, epigenetic regulators, and microRNAs (miRNAs) (Elbaz & Popko, 2019). Several of these

Received: 06 March 2024; Accepted: 01 April 2024; Online: 02 April 2024
Foundation items: This work was supported by the Natural Science Foundation of Zhejiang Province (LZ22H090002, 2014C33170) and National Natural Science Foundation of China (82171260, 81641042, 81471240)
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mechanisms could serve as targets for GAAs, impairing oligodendrocyte differentiation and proliferation, as well as myelin production. Mature oligodendrocytes possess the capacity to rapidly synthesize, organize, and transport a vast array of proteins, including myelin basic protein (MBP) and proteolipid protein (PLP)/DM20, crucial for constructing myelin sheaths (Simons & Nave, 2015). White matter in the brain consists predominantly of axons wrapped in myelin sheaths. In addition to multiple sclerosis, myelin sheath abnormalities have been linked to disorders such as depression (Zhou et al., 2021) and attention deficit hyperactivity disorder (ADHD) (Wu et al., 2014).

Repetitive exposure to GAAs has been shown to induce a series of pathological alterations in the developing brain, disrupting the growth and maturation of neurons and glial cells, potentially leading to emotional and social behavioral impairments in later life (Glatz et al., 2017; Raper et al., 2018; Walkden et al., 2020). Oligodendrocytes are vulnerable to apoptosis when exposed to GAAs (Brambrink et al., 2012; Creeley et al., 2013), especially during the phase in which they begin myelin formation around axons. GAAs can influence the function of oligodendrocytes by acting on their NMDA and GABA receptors (Hamilton et al., 2017; Lundgaard et al., 2013), as well as impacting various pathways, such as the mTOR (Li et al., 2019) and Wnt/β-catenin (Liang et al., 2021) signaling pathways. This disruption in myelin sheath construction can potentially lead to the development of postoperative learning, behavioral, and emotional disorders. Furthermore, oligodendrocyte proliferation and differentiation are also impacted by neuroinflammation, metabolic disorders, and changes in gene expression induced by GAAs. These effects can result in developmental disorders and dysfunctions in oligodendrocytes, as well as compromised myelin sheath formation. Thus, to prevent neurotoxicity induced by GAAs, it is crucial to explore the precise mechanisms by which they target oligodendrocytes.

This article provides a comprehensive review of the mechanisms through which GAAs impact oligodendrocytes and their effects on myelin formation. It summarizes findings from both clinical and animal studies investigating the relationship between general anesthesia and oligodendrocytes and discusses how GAAs damage myelin sheaths and oligodendrocytes, leading to neurotoxic consequences. This review also provides recommendations for future research and potential therapeutic approaches to mitigate the neurotoxic effects induced by GAAs.

PHYSIOLOGICAL CHARACTERISTICS OF OLIGODENDROCYTES

There has been an increasing focus on oligodendrocytes as important targets for GAAs, primarily owing to their inherent physiological characteristics. Oligodendrocyte lineage cells can be sequentially categorized as OPCs, pre-myelinating/immature oligodendrocytes, and myelinating/mature oligodendrocytes (Simons & Nave, 2015). Various transcription factors, such as oligodendrocyte transcription factor 1 (Olig1), oligodendrocyte transcription factor 2 (Olig2), and SRY-Box transcription factor 10 (SOX10), are crucial for promoting the growth, maturation, and differentiation of oligodendrocytes throughout their life cycle (Elbaz & Popko, 2019). Pre-myelinating oligodendrocytes initiate the process of myelin production, which continues during the myelinating oligodendrocyte stage. Oligodendrocytes express several myelin-related proteins, including MBP, PLP, myelin-associated glycoprotein (MAG), and myelin oligodendrocyte glycoprotein (MOG) throughout this process. GAAs can inhibit the activity of these transcription factors, subsequently reducing the production of proteins associated with myelin, altering myelin development, and leading to neurotoxic effects (Liu et al., 2018). In addition, many molecular mechanisms are involved in the process of myelin formation, including multiple signaling pathways, such as the mTOR signaling pathway, epigenetic regulators, and microRNAs, all of which are impacted by GAAs to varying extents.

Most GAAs exhibit either NMDAR antagonist or GABA receptor (GABAR) agonist properties. Oligodendrocytes are known to express a variety of glutamate receptor types. Using calcium microfluorimetry, Cavaliere et al. (2012) demonstrated that glutamate activation of NMDAR increases cytoplasmic calcium levels and facilitates the formation of myelin sheaths when oligodendrocytes are co-cultured with neurons during differentiation. Additionally, stimulation of oligodendrocyte NMDAR promotes the translocation of glucose transporter 1 (GLUT1) (Saab et al., 2016). As glucose is the primary carbon source for fat precursor metabolites, its availability is a rate-limiting factor in myelin formation. Consequently, GAAs that inhibit NMDAR may adversely impact myelin formation during development.

Excitotoxicity is a common cause of glutamate receptor-mediated oligodendrocyte death in strokes involving white matter (Fern & Matute, 2019). Research has demonstrated that exposure to sevoflurane can also cause glutamate-induced excitotoxicity. Overactivation of glutamate receptors can lead to an inward influx of calcium ions (Ca^{2+}) and the accumulation of Ca^{2+} within the mitochondria (Butt et al., 2014), resulting in oligodendrocyte death through mitochondrial depolarization, increased free radical oxidation, and the release of pro-apoptotic proteins. Oligodendrocytes also possess GABAR, even though the majority of known GABAergic synapses are found in gray matter. GABAR influence oligodendrocytes primarily by modulating neuronal activity and protecting neurons from excitotoxicity (Butt et al., 2014). Following hypoxia, enhanced GABA signaling stimulates OPC progression, myelin production, and oligodendrocyte development (Zonouzi et al., 2015), suggesting potential neuroprotective strategies after general anesthesia.

GABA initially acts as an excitatory neurotransmitter in the developing brain. Exposure to GAAs with GABAR agonist properties at this stage can induce aberrant proliferation and differentiation of OPCs, thus impacting myelin sheath formation and potentially resulting in neurodevelopmental abnormalities and cognitive deficits (Li et al., 2022). Therefore, the impact of GAAs on the brain can vary significantly with age.

EVIDENCE FROM PRE-CLINICAL AND CLINICAL STUDIES

Pre-clinical studies

In vivo and *in vitro* experiments have demonstrated that commonly used GAAs can induce oligodendrocyte apoptosis, disrupt myelin formation, and lead to emotional and social behavioral deficits (Table 1). For instance, Wu et al. (2020) reported that two-day-old postnatal (P2) Sprague-Dawley rats exposed to 4.9% sevoflurane (approximately 1.5 minimum

Table 1 Summary of changes in oligodendrocytes induced by general anesthetic agents (GAAs) in various studies

GAAs	Experimental subjects	Exposure period	Concentration or dose	Exposure time	Mechanisms	Effects	References
Sevoflurane	Rats	P7	3%	4 h	Increased expression of cleaved-caspase-3 by activating JNK/c-Jun signaling pathway.	Reduced learning and memory ability.	Bi et al., 2018
	Mice	P7–P9	3%	2 h/day; 3 days	Activated $GABA_A$ receptor, leading to depolarization of cell membranes, and Ca^{2+} influx through NCX.	Caused spatial learning and memory deficits.	Li et al., 2022
	Mice	P6	3%	2 h/day; 3 days	Induced microglial activation and increased levels of proinflammatory cytokines, particularly IL-6 and TNF-α.	Caused learning and memory impairment.	Shen et al., 2013
	Mice	P6	3%	2 h/day; 3 days	Increased secretion of IL-1β and IL-6.	Affected hippocampal-dependent learning and memory.	Xia et al., 2017
	Rats	P2	4.9%	2 h	Caused widespread reactive astrogliosis.	Decreased explorative activity and increased anxiety-like behavior, as well as learning and memory impairments.	Wu et al., 2020
	Primary cultured mouse neurons	7 DIV	2.7%/3.6%/4.5%	–	Up-regulated mTOR pathway.	–	Xu et al., 2018
	Mice	P6–P8	3%	2 h/day; 3 days	Suppressed Wnt signaling and up-regulated MT1 receptor.	Induced long-term impairment of cognition and learning/memory.	Liang et al., 2021
	Rhesus macaques; Mice	–	2.5%/3%	3 days	Induced disrupted folate metabolism and reduced expression of *TYMS* and *ERMN*.	Increased anxiety-like behavior and induced cognitive impairment.	Zhang et al., 2019
	Rats	P7	3.2%	1–2 h	Decreased expression of genes associated with myelination and up-regulated expression of V-Glut1.	Induced anxiety, impacted various aspects of exploratory behaviors, resulted in object recognition deficits and compromised hippocampal-dependent memory.	Jimenez-Tellez et al., 2023
Isoflurane	Mice	P7	1.5%	4 h	Decreased expression of DNMT1 in oligodendrocyte lineage cells by targeting mTOR signaling pathway and reduced number of excitatory axon-oligodendrocyte progenitor cell synapses in hippocampus.	Caused impaired spatial learning.	Li et al., 2019
	Mice	5–8 months	1.4%	2 h	Increased protein and mRNA levels of TNF-α, IL-6, and IL-1β in brain tissue.	–	Wu et al., 2012
	Bees	–	2%	6 h	Caused substantial shift in circadian clock by acting on expression of clock genes.	Caused persistent and marked shift in clock.	Cheeseman et al., 2012
Propofol	Rhesus macaques	G120/P6	–	5 h	Induced apoptosis of oligodendrocytes by up-regulating expression of caspase-3 gene and decreasing expression of MBP.	–	Creeley et al., 2013
	Zebrafish embryos	24–120 hpf	1, 2 and 3 μg/mL	–	Up-regulated expression of caspase gene and inhibited expression of myelin basic protein.	–	Guo et al., 2015
	Zebrafish embryos	6–48 hpf	20 μg/mL; 30 μg/mL	–	Reduced MBP expression at both mRNA and protein levels in zebrafish embryos by decreasing mRNA expression of Olig1, Olig2, and SOX10.	–	Liu et al., 2018
	Neonatal mouse neurons	4–7 DIV	3 μmol/L	6 h	Activated $p75^{NTR}$-RhoA-ROCK pathway.	–	Pearn et al., 2012
	Rats	P7	20 mg/kg	2–6 h	Activated Fas/FasL-mediated extrinsic and Bcl-2-dependent intrinsic apoptotic pathways, resulting in caspase-8 and caspase-9 activation.	Affected long-term memory and increased motor activities.	Milanovic et al., 2016

Continued

GAAs	Experimental subjects	Exposure period	Concentration or dose	Exposure time	Mechanisms	Effects	References
	Primary oligodendrocytes	–	10, 25 and 50 μg/mL	48 h	Up-regulated expression of HIF-1α, miR138-5p, and caspase-3 in oligodendrocytes.	–	Zeng et al., 2021
Ketamine	Mice	P7	40 mg/kg	–	Disrupted mitochondrial membrane permeability, allowing extramitochondrial leakage of cytochrome *c*, followed by sequence of changes culminating in activation of caspase-3.	Contributed to neurodevelopmental disturbances.	Olney et al., 2004
	Mice	6–8 weeks	3 mg/kg	–	Blockade of NMDAR at rest deactivated eEF2, resulting in reduced eEF2 phosphorylation and de-suppression of translation of BDNF.	Produced antidepressant responses.	Autry et al., 2011

P7: Postnatal day 7; JNK: c-Jun N-terminal kinase; GABA: γ-aminobutyric acid; NCX: Na^+-Ca^{2+} exchanger; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin-1 beta; DIV: Days *in vitro*; mTOR: Mechanistic target of rapamycin; MT1: Melatonin receptor 1; *TYMS*: Thymidylate synthase; V-Glut1: Vesicular glutamate transporter 1; DNMT1: DNA methyltransferase 1; G120: Gestational day 120; MBP: Myelin basic protein; hpf: Hours post-fertilization; Olig1/2: Oligodendrocyte transcription factor 1/2; SOX10: SRY-Box transcription factor 10; $p75^{NTR}$: p75 neurotrophin receptor; RhoA: Ras homolog family member A; ROCK: Rho kinase; Fas: Fas cell surface death receptor; Bcl-2: B-cell lymphoma 2; HIF-1α: Hypoxia-inducible factor 1α; NMDAR: N-methyl-D-aspartate receptor; eEF2: Eukaryotic elongation factor 2; BDNF: Brain-derived neurotrophic factor. –: Not available.

alveolar concentration) for 2 h exhibited decreased exploratory activity, heightened anxiety-like behavior, and impaired learning and memory, along with extensive reactive astrogliosis in brain tissue 12 h post-anesthesia. The excessive generation of free radicals and inflammatory mediators resulting from astrogliosis can be detrimental to neurons and oligodendrocytes, impacting their survival and maturation (Pekny & Pekna, 2014). While GAAs can induce apoptosis in oligodendrocytes, the extent to which they influence these cells varies with developmental stage. Creeley et al. (2014) observed that after 5 h of isoflurane anesthesia, fetal rhesus macaques at gestational day 120 (G120) exhibited significant neuronal and oligodendrocyte death, with a degenerating neuron to glial cell ratio of 41:59. Immunofluorescence double-staining using MBP for pre-myelinating and myelinating oligodendrocytes and activated caspase-3 (AC3) for apoptosis indicated susceptibility of oligodendrocytes to apoptosis during anesthesia, particularly during the initial stages of myelin formation (Creeley et al., 2014). Extensive apoptosis in both neurons and glial cells was also observed in P6 rhesus macaques after similar exposure to isoflurane, with a degenerating neuron to glial cell ratio of 48:52. Oligodendrocytes were specifically affected during pre-myelinating and myelinating oligodendrocyte stages, while the OPC stage remained unaffected (Brambrink et al., 2012). Schenning et al. (2017) extended these findings by demonstrating that in P20 or P40 juvenile rhesus monkeys exposed to 5 h of isoflurane anesthesia, oligodendrocyte apoptosis was nearly twice that of neurons. These findings imply a persistent susceptibility of oligodendrocytes in postnatal non-human primates (NHP) to apoptosis from GAAs throughout all stages of brain development, despite a decrease in neuronal vulnerability with age.

Clinical studies

Inhalational anesthetics can potentially trigger significant apoptotic responses in the brains of infants and children. Children anesthetized with halothane and nitrous oxide have been shown to exhibit asymmetric brain shrinkage, severe demyelination, and depletion of oligodendrocytes in the midbrain, medulla, and cerebellum (Selzer et al., 2003). These findings suggest that inhalational anesthetics may exert an inhibitory effect on the survival and function of oligodendrocytes. Given that over half of the brain's volume is white matter, composed of nerve fiber bundles sheathed in myelin produced and maintained by oligodendrocytes (Wu et al., 2023), the implications of this inhibition are considerable. Studies have revealed a correlation between repeated exposure to anesthesia for surgery and an increased risk of ADHD in children (Warner et al., 2018), a disorder linked to myelin degradation in white matter microstructures (Ameis et al., 2016). Structural neuroimaging has demonstrated that children who underwent surgery or anesthesia in infancy exhibit a widespread reduction in white matter integrity and volume distribution across multiple brain regions, including the brainstem, parietal and occipital lobes, and infratentorium (Block et al., 2017). Furthermore, investigations into survivors of childhood acute lymphoblastic leukemia have shown that repeated exposure to general anesthesia, particularly with propofol and longer cumulative duration, can lead to a decrease in white matter integrity, notably in the corpus callosum (Banerjee et al., 2019). Thus, these studies suggest that exposure to GAAs may lead to oligodendrocyte apoptosis during myelin formation, ultimately impacting white matter integrity and volume. Various clinical studies have shown that children who have undergone anesthesia for surgery are at a higher risk of cognitive impairment and alterations in brain structures (Block et al., 2017; Hu et al., 2017). Therefore, it is plausible that structural damage to white matter caused by oligodendrocyte apoptosis may be a significant factor contributing to postoperative cognitive impairment in children.

MECHANISMS UNDERLYING GAA-OLIGODENDROCYTE INTERACTIONS

Sevoflurane

Sevoflurane, the most commonly used inhalation anesthetic in pediatric patients, has been shown to induce oligodendrocyte apoptosis in brains of infant rhesus macaques (Rosado-

Mendez et al., 2019). One of the main mechanisms behind this is sevoflurane induction of mitochondrial outer membrane permeabilization (MOMP). Activation of Jun amino-terminal kinase (JNK), casein kinase II (CKII), and p38 MAPK can antagonize anti-apoptosis and promote MOMP, leading to intracellular apoptosis (Green & Llambi, 2015). Therefore, by triggering JNK/c-JUN/activator protein-1 (AP-1) signaling, repeated exposure to sevoflurane can lower the anti-apoptotic/pro-apoptotic ratio and increase MOMP (Bi et al., 2018).

Regulation of Ca^{2+} can influence the development and function of oligodendrocytes and OPCs (Paez & Lyons, 2020). Sevoflurane anesthesia has been shown to induce an imbalance in calcium homeostasis within OPCs (Li et al., 2022). Oligodendrocytes and their progenitor cells express various neurotransmitter receptors, including those for glutamate and GABA, two central neurotransmitters (Habermacher et al., 2019). These receptors are critical targets for GAAs and play an important role in connecting neurons and oligodendrocytes. Although GABA typically acts as an inhibitory neurotransmitter, during early brain development, Na-K-2Cl cotransporter 1 (NKCC1) is highly expressed, while K-Cl cotransporter 2 (KCC2) is less expressed due to an elevated intracellular concentration of Cl^-. As a result, GABA functions as an excitatory neurotransmitter during this period. The binding of $GABA_A$ receptors ($GABA_AR$) can cause Cl^- efflux, which depolarizes cell membranes (Pfeffer et al., 2009). As a $GABA_AR$ agonist, sevoflurane can act on $GABA_AR$ in the postsynaptic membrane of OPCs, causing membrane depolarization, Na+ efflux, and subsequent Ca^{2+} influx through the Na^+-Ca^{2+} exchanger (NCX), leading to intracellular Ca^{2+} accumulation. These events disrupt normal OPC proliferation and differentiation and interfere with myelin sheath formation, ultimately leading to neurodevelopmental abnormalities and cognitive impairment (Li et al., 2022).

The mTOR signaling pathway is located downstream of the growth factor-stimulated phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathways. This pathway plays a crucial role in regulating protein synthesis, cell proliferation, differentiation, and survival. Moreover, it is a key regulator of myelin sheath formation in oligodendrocytes (Lebrun-Julien et al., 2014). Studies have shown that exposure to sevoflurane increases mTOR pathway activity, leading to abnormal proliferation and differentiation of OPCs (Xu et al., 2018). The mTOR complex 1 (mTORC1), formed by the interaction of mTOR with several proteins, plays a crucial role in coordinating the synthesis of proteins and lipids essential for myelin formation in the CNS (Lebrun-Julien et al., 2014). Both *in vivo* and *in vitro* studies have also shown that mTOR signaling plays an important role in the later stages of oligodendrocyte development, regulating the transition from pre-myelinating to myelinating oligodendrocytes and determining the extent of myelin formation (Dai et al., 2014; Guardiola-Diaz et al., 2012; Wahl et al., 2014). In addition, extracellular signal-regulated kinase 1 and 2 (Erk1/2) signaling, which controls the shift from early to late OPCs, is vital for oligodendrocyte development in both *in vivo* and *in vitro* contexts. Sevoflurane-induced up-regulation of mTOR signaling disrupts the delicate balance and timing of mTORC1 activation in oligodendrocytes, leading to abnormal oligodendrocyte proliferation and differentiation, and ultimately resulting in myelin hypoplasia. Furthermore, the PI3K/Akt/mTOR pathway can interact with the MAPK pathway via insulin receptor substrate 1 (IRS-1), negatively affecting the Erk 1/2 pathway (Dai et al., 2014). Consequently, excessive activation of mTORC1 may have an inhibitory feedback effect on the Erk1/2 and/or PI3K-Akt pathways, reducing MBP expression in oligodendrocytes and impairing myelin synthesis. As such, sevoflurane exposure may impact myelin development by activating the mTOR pathway, resulting in the inhibition of oligodendrocyte proliferation and differentiation (Figure 1).

Liang et al. (2021) reported that repeated exposure to sevoflurane during the neonatal phase can lead to long-term inhibition of Wnt/β-catenin signaling in hippocampal neurons and oligodendrocytes in adult mice. The Wnt signaling pathway plays a crucial role in oligodendrocyte proliferation and differentiation, as well as the formation and maintenance of myelin sheaths in the nervous system (Guo et al., 2015a). Activation of this pathway induces the accumulation of β-catenin protein in the cytoplasm, which then translocates to the nucleus and activates transcription factor 4 (TCF4),

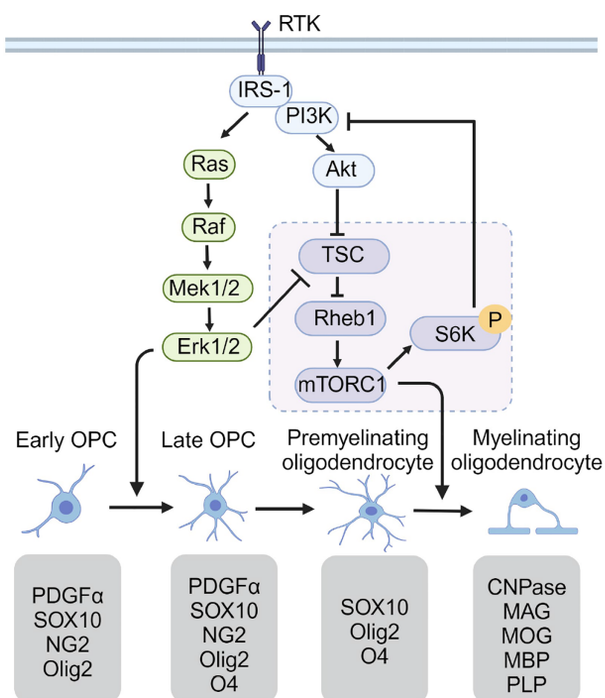

Figure 1 mTORC1 affects oligodendrocyte development

Activation of mTORC1 promotes pre-myelinating to myelinating oligodendrocyte transition. Overactivation by GAAs disrupts this process and impedes Erk1/2 signaling in the transition from early to late OPCs by linking to the Ras/Raf/Mek/Erk pathway through IRS-1. Created with BioRender.com. RTK: Receptor tyrosine kinase; IRS-1: Insulin receptor substrate 1; Ras: Rat sarcoma; Raf: Rapidly accelerated fibrosarcoma; Mek1/2: Mitogen-activated protein kinase 1 and 2; Erk1/2: Extracellular signal-regulated kinase 1 and 2; PI3K: Phosphoinositide 3-kinase; Akt: Protein kinase B; TSC: Tuberous sclerosis complex; Rheb1: Ras homolog enriched in brain 1; mTORC1: Mammalian target of rapamycin complex 1; S6K: Ribosomal protein S6 kinase; OPC: Oligodendrocyte precursor cell; PDGFα: Platelet-derived growth factor α; SOX10: SRY-Box transcription factor 10; NG2: Neural glial antigen 2; Olig2: Oligodendrocyte transcription factor 2; CNPase: 2',3'-cyclic nucleotide 3'-phosphodiesterase; MAG: Myelin-associated glycoprotein; MOG: Myelin oligodendrocyte glycoprotein; MBP: Myelin basic protein; PLP: Proteolipid protein.

promoting oligodendrocyte maturation (Fu et al., 2009). Sevoflurane up-regulates soluble frizzled-related protein 1 (SFRP1), a Wnt signaling inhibiting peptide, and glycogen synthase kinase 3β (GSK-3β), which is involved in the degradation of β-catenin (Liang et al., 2021). Axis inhibition protein 2 (Axin2), which serves as a negative regulator of the Wnt signaling pathway, is important for the moderate activation of the Wnt signaling pathway (Guo et al., 2015a). Normal expression of Axin2 in neurons and oligodendrocyte progenitor cells is essential for normal development and functional maintenance of the nervous system (Liang et al., 2021). Sevoflurane exposure has been shown to significantly down-regulate both the protein and mRNA expression levels of Axin2 (Liang et al., 2021). Increased expression of melatonin receptor 1 (MT1) signaling in hippocampal neurons and oligodendrocytes has been reported in neonatal mice (P6–P8) exposed to 3% sevoflurane for 3 consecutive days (Liang et al., 2021), suggesting that sevoflurane may up-regulate MT1 (a membrane G-protein-coupled receptor that specifically binds to melatonin). Notably, melatonin pretreatment has shown significant long-term protective effects against repeated sevoflurane-induced synaptotoxicity in neonatal mice. Under normal circumstances, MT1 co-expresses with β-catenin and Axin2 in the hippocampal regions. However, the connection between MT1 and β-catenin is disrupted under sevoflurane exposure (Liang et al., 2021). In contrast, melatonin pretreatment appears to enhance this interaction, restoring levels of key molecules (including Axin2, β-catenin, and GSK-3β) involved in the Wnt signaling pathway affected by sevoflurane treatment. These finding imply that melatonin may play a protective role in preventing sevoflurane-induced neurotoxicity by modulating Wnt/β-catenin signaling. Studies have also linked overactivation of the Wnt/β-catenin signaling pathway in older mice with perioperative neurocognitive disorders (PND) (Wu et al., 2021). Hyperactivation of this pathway can lead to a decrease in Olig2 (Huang et al., 2020), impacting the developmental regulation of OPCs and their early differentiation into oligodendrocytes. Therefore, avoiding disruption of the Wnt/β-catenin signaling pathway, which is crucial for oligodendrocyte growth, development, and myelin sheath formation, holds promise for preventing perioperative neurotoxicity induced by sevoflurane (Figure 2).

Sevoflurane-induced metabolic disruptions may also negatively impact maturation of oligodendrocytes and synthesis of myelin in the developing brain. The folate-mediated one-carbon metabolism pathway, which involves the thymidylate synthase (*TYMS*) gene, participates in DNA methylation by providing a methyl donor (Yuan et al., 2007). As *TYMS* is a crucial folate-dependent enzyme, an imbalance in DNA methylation will result from low folate and low *TYMS* expression. Research has shown that repeated exposure to sevoflurane in young rhesus monkeys and mice can lead to decreased blood folate levels, reduced *TYMS* levels in the prefrontal cortex, increased methylation of the *ERMN* promoter region, and decreased expression of *ERMN* mRNA (Zhang et al., 2019). *ERMN*, a crucial gene involved in myelin sheath formation, is located in the outer tongue of the myelin sheath and paranodal loops of oligodendrocytes and encodes Ermin, an oligodendrocyte-specific cytoskeletal molecule crucial for myelin sheath maintenance and stabilization in adults (Brockschnieder et al., 2006). Thus, the reduction in folate after sevoflurane anesthesia may induce abnormal DNA methylation in the brain, disrupt *TYMS* and *ERMN* expression, and impair myelin formation. Interestingly, restoration of impaired myelin formation and attenuation of cognitive deficits induced by sevoflurane anesthesia have been achieved with folate supplementation or increased *ERMN* expression (Zhang et al., 2019). These findings suggest that the folate-*ERMN*-myelination cascade may be a potential mechanism by which inhalation anesthetics cause postoperative neurotoxicity in young animals. Myelin, formed by oligodendrocytes in an iron-

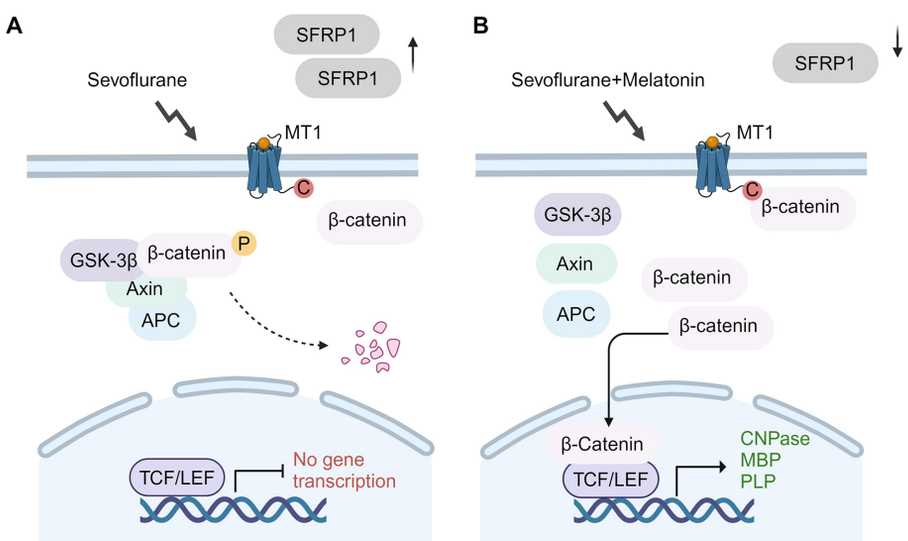

Figure 2 Effects of sevoflurane exposure on Wnt signaling pathway

By influencing the β-catenin destruction complex, which includes APC, Axin2, and GSK-3β, sevoflurane prevents myelin production in oligodendrocytes. Sevoflurane exposure induces an up-regulation in GSK-3β and down-regulation in Axin2, as well as an increase in SFRP1. Furthermore, melatonin exerts a neuroprotective effect by restoring levels of Wnt signaling molecules reduced during sevoflurane administration. Created with BioRender.com. SFRP1: Secreted frizzled-related protein 1; GSK-3β: Glycogen synthase kinase 3β; Axin: Axis inhibition protein; APC: Adenomatous polyposis coli; TCF/LEF: T-cell factor/lymphoid enhancer factor; CNPase: 2',3'-cyclic nucleotide 3'-phosphodiesterase; MBP: Myelin basic protein; PLP: Proteolipid protein.

dependent manner, wraps the axons of neurons (Ward et al., 2014). Research on gestational mice has shown that sevoflurane treatment significantly reduces brain iron levels in offspring, leading to oligodendrocyte dysfunction and reduced myelin formation (Zuo et al., 2020).

Exposure to sevoflurane has been shown to alter the expression of several genes involved in myelination, including MAG, PLP1, and MBP (Jimenez-Tellez et al., 2023), which are essential for normal oligodendrocyte development and myelin formation. Additionally, genes such as vesicular glutamate transporter 1 (V-Glut1) are up-regulated in response to sevoflurane. Overexpression of V-Glut1 may trigger glutamate-induced excitotoxicity, which not only promotes cell death through excessive glutamate release from neurons and glial cells but also activates NMDAR in the postsynaptic membrane, leading to prolonged Ca^{2+} influx and loss of synaptic structure (Jimenez-Tellez et al., 2023).

Isoflurane

Exposure to isoflurane has been shown to reduce the number of V-Glut1-positive synapses in mouse hippocampal fimbria (Li et al., 2019), suggesting a reduction in the number of axon-OPC synapses on each OPC after isoflurane exposure. This synaptic connection is essential for both the formation and maintenance of myelin, as well as for the release of signaling molecules and intercellular connections. Therefore, the reduction of this synaptic connection may also be a significant mechanism for decreased myelin development induced by GAAs. Isoflurane has also been shown significantly promotes inflammation and increases proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), in mouse brain tissue (Wu et al., 2012), leading to neuroinflammation and detrimental impacts on immature oligodendrocyte survival, proliferation, and differentiation.

Isoflurane is reported to target the mTOR signaling pathway by reducing the expression of DNA methyltransferase 1 (DNMT1) in oligodendrocyte lineage cells, thereby impacting the proliferation and differentiation of OPCs (Li et al., 2019). DNA methylation plays a critical role in controlling the proliferation and development of OPCs. A genome-wide study of differentially methylated genes during the differentiation of OPCs to oligodendrocytes revealed that DNA methylation promotes this transition by regulating cell cycle exit and potentially influencing neuronal lineage determination (Moyon et al., 2016). DNMT1 is essential for maintaining DNA methylation (Lyko, 2018). Therefore, up-regulation of the mTOR signaling pathway induced by isoflurane exposure may inhibit the differentiation of OPCs to oligodendrocytes by negatively regulating DNA methylation through DNMT1.

Isoflurane has been shown to influence clock gene expression, circadian activity rhythms, timed foraging, and orientation behavior in honeybees (Cheeseman et al., 2012). Additionally, the expression of oligodendrocyte genes varies considerably between the waking and sleeping states in animals, with OPC proliferation also higher during sleep than wakefulness, showing a positive correlation with the duration of rapid eye movement (REM) sleep (Bellesi et al., 2013). Several genes expressed at higher levels during sleep are associated with cell membrane synthesis and maintenance, especially those related to myelin. Conversely, wakefulness is associated with to active expression of genes linked to apoptosis, cellular stress response, and cell differentiation and development. Given their potential to disrupt sleep, cause fatigue, and induce symptoms of temporal disorientation and sleep disturbance following general anesthesia, GAAs may inhibit OPC proliferation and differentiation by interfering with the biological clock.

Propofol

Propofol has been found to cause neuronal and oligodendrocyte apoptosis in fetal and neonatal rhesus macaque brains after 5 h of exposure (Creeley et al., 2013). Notably, propofol appears to selectively act on oligodendrocytes when they begin to produce MBP in preparation for the formation of axonal myelin sheaths. MBP, the second most abundant protein in CNS myelin sheaths, is synthesized and secreted by oligodendrocytes and serves as a membrane actin-binding protein, transmitting extracellular signals into the cytoskeleton and myelin sheaths of oligodendrocytes (Boggs, 2006). Abnormal expression of MBP can lead to impaired, reduced, or even absent myelin formation, affecting neural information transmission and potentially contributing to neurodegenerative disease development. Experiments in fetal and newborn NHPs (Creeley et al., 2013) and zebrafish (Guo et al., 2015b) have reported that propofol can cause increased oligodendrocyte and neuronal apoptosis as well as decreased MBP expression. Apoptosis involves both intrinsic and extrinsic pathways, culminating in the activation of caspase family members and their cleavage of more than 400 substrates, including kinases, DNA repair enzymes, and proteins involved in mRNA splicing, DNA replication, and cell survival, thereby triggering the entire process of cell death (Green & Llambi, 2015). Studies have also confirmed that propofol up-regulates caspase-3 gene expression and apoptosis in oligodendrocytes (Creeley et al., 2013). As oligodendrocyte numbers can directly affect MBP expression, it is hypothesized that propofol-induced down-regulation of MBP gene and protein levels is likely triggered by oligodendrocyte apoptosis. Transcription factors such as Olig1, which is involved in late maturation and myelin formation of oligodendrocytes, Olig2, which is essential for oligodendrocyte precursor cell differentiation, and SOX10, which is crucial in the terminal developmental stage of oligodendrocytes (Elbaz & Popko, 2019), can be inhibited by propofol. Exposure during the embryonic stage disrupts multiple developmental periods of oligodendrocytes by inhibiting these transcription factors, down-regulating MBP expression, and exerting neurotoxic effects (Liu et al., 2018). These findings suggest that propofol reduces MBP expression at the molecular protein level.

Although the mechanism by which propofol induces apoptosis in oligodendrocytes is unknown, several studies have indicated that the p75 neurotrophin receptor ($p75^{NTR}$)-RhoA-Rho kinase (ROCK) pathway plays an important role in propofol-induced neurotoxicity. Brain-derived neurotrophic factor (BDNF) regulates the formation and differentiation of oligodendrocytes by playing significant roles in pro-survival and pro-apoptotic signaling pathways (Geraghty et al., 2019; Pearn et al., 2012). BDNF is stored in synaptic vesicles as proneurotrophin (proBDNF). ProBDNF is hydrolyzed and cleaved to mature BDNF (mBDNF) by fibrinolytic enzymes (a protease-activated by tissue plasminogen activator (tPA)), which bind to tropomyosin receptor kinase B (TrkB), trigger pro-survival signals, and promote neural synaptic development, maturation, and stabilization (Pang et al., 2004).

Uncleaved proBDNF preferentially binds to $p75^{NTR}$, activating RhoA and triggering cell death (Bai, 2003). Thus, a possible mechanism by which propofol induces neurotoxicity is by inhibiting tPA release and blocking the conversion of proBDNF to mBDNF, leading to preferential signaling by $p75^{NTR}$, RhoA activation, actin cytoskeleton depolymerization, and subsequent apoptosis of neurons. Propofol also stimulates Fas/FasL death receptor proteins (Milanovic et al., 2016), which activate the Fas/FasL signaling pathway and caspase cascade, both of which lead to apoptosis. Thus, this may also be one of the mechanisms by which propofol causes oligodendrocytes to undergo apoptosis.

The long non-coding RNA (lncRNA) LRCF, which is associated with cognitive function, is significantly expressed in the brains of neonatal mice, decreasing as they age. Notably, research has demonstrated that lncRNA-LRCF is involved in propofol-induced proliferation and apoptosis of oligodendrocytes, with propofol exposure leading to an up-regulation of hypoxia-inducible factor 1α (HIF-1α), caspase-3 protein, and miRNA138-5p in neonatal mouse oligodendrocytes (Zeng et al., 2021). HIF-1α binds to the miRNA138-5p promoter and positively regulates its transcription via the transcription factor binding site (TFBS). Furthermore, miRNA138-5p binds to the 3'UTR prediction site of caspase-3 to negatively regulate the production of proteins. Therefore, propofol disrupts the caspase-3/miRNA138-5p/HIF-1α pathway to prevent apoptosis. However, elevated levels of lncRNA-LRCF in the brains of neonatal mice block the HIF-1α/miR138-5p/caspase-3 pathway by binding to miRNA138-5p to form a miRNA sponge, leading to propofol-induced cellular damage in oligodendrocytes via the HIF-1α/caspase-3 pathway (Zeng et al., 2021).

Ketamine

Ketamine, a non-competitive NMDAR inhibitor, acts on oligodendrocytes to decrease myelin production and increase cell death. It increases MOMP, causing cytochrome *c* to leak from the mitochondria, triggering a series of reactions that culminate in caspase-3 activation and apoptosis (Dimaggio et al., 2009; Olney et al., 2004). In addition, by blocking synaptic NMDAR, ketamine inhibits eukaryotic elongation factor-2 kinase (eEF2K), which then up-regulates BDNF translation (Autry et al., 2011). This action triggers TrkB signaling, leading to transphosphorylation, downstream activation of Erks and Akt, inhibition of GSK-3β, and activation of mTOR (Zanos & Gould, 2018) (Figure 3). In addition to inducing synaptogenesis, this mechanism may also enhance oligodendrocyte proliferation and differentiation. The antidepressant effects of ketamine may influence the ability of oligodendrocyte lineage cells to proliferate and differentiate, particularly under stress, which significantly impacts oligodendrogliogenesis and myelin development in the prefrontal cortex. In mice with stress-induced depression, 69% of the most significantly down-regulated genes are associated with myelin, including *MOG* and *ERMN* (Lehmann et al., 2017). Furthermore, in depressed humans, oligodendrocyte development and myelin formation are influenced by a variety of mechanisms, including abnormal dopaminergic transmission and 5-hydroxytryptamine (5-HT) levels in the brain (Zhou et al., 2021).

Ketamine also exhibits anti-inflammatory effects. Notably, sepsis model research has indicated that ketamine can reduce the binding affinity of lipopolysaccharide (LPS) to LPS-binding

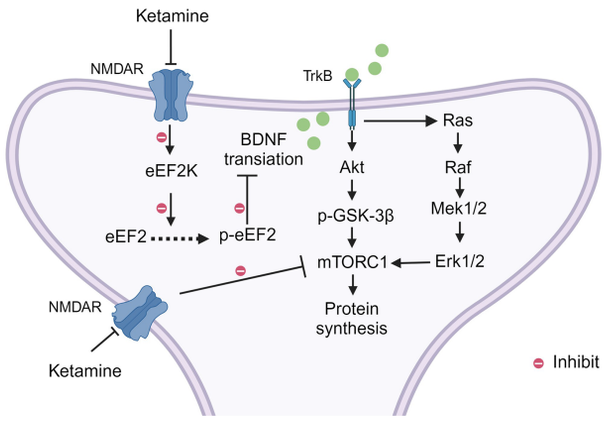

Figure 3 Neurotoxic effects of ketamine mediated by NMDAR

By acting on NMDAR on postsynaptic neurons, ketamine may reduce eEF2K activation, which causes dephosphorylation of eEF2 and deregulation of the inhibitory effects on BDNF. Activation of TrkB receptors by BDNF results in downstream activation of Mek-MAPK/Erk and PI3K-Akt signaling pathways. Through mTORC1 activation, these two mechanisms can promote protein translation. Created with BioRender.com. NMDAR: N-Methyl-D-Aspartate receptor; TrkB: Tropomyosin receptor kinase B; eEF2K: Eukaryotic elongation factor 2 kinase; BDNF: Brain-derived neurotrophic factor; Akt: Protein kinase B; GSK-3β: Glycogen synthase kinase 3β; mTORC1: Mammalian target of rapamycin complex 1; Ras: Rat sarcoma; Raf: Rapidly accelerated fibrosarcoma; Mek1/2: Mitogen-activated protein kinase 1 and 2; Erk1/2: Extracellular signal-regulated kinase 1 and 2.

proteins and inhibit phosphorylation of several protein kinases and transcription factors, including NF-κB and AP-1, through toll-like receptor (TLR)-mediated signaling (Hirota & Lambert, 2018). This anti-inflammatory effect somewhat ameliorates the negative impact of inflammatory factors on oligodendrocyte proliferation and differentiation.

INTERACTIONS AMONG GLIAL CELLS

Neuroinflammation induced by microglial activation can have substantial effects on oligodendrocyte survival, proliferation, and differentiation. Both animal models and humans with PND show elevated levels of proinflammatory cytokines. Neuroinflammation likely plays a key role in the development of PND by mediating oligodendrocyte damage. Activated microglia release a range of proinflammatory cytokines and chemokines in the CNS. Studies have shown that repeated neonatal exposure to sevoflurane activates microglia in the mouse brain, leading to an increase in proinflammatory cytokines (TNF-α, IL-6, and IL-1β) and induction of neurocognitive deficits (Shen et al., 2013; Xia et al., 2017). Furthermore, in mouse models simulating premature brain inflammation induced by systemic exposure to IL-1β, there is a notable reduction in oligodendrocyte proliferation at P10 and MBP and MAG levels at both P10 and P15 (Klein et al., 2022). Oligodendrocyte damage is primarily caused by an increase in microglial presence and activity, with notable proinflammatory marker enrichment in certain regions. Additionally, overexpression of microglial miRNA-146b-5p has been shown to significantly reduce LPS-induced activation of microglial cells, thereby attenuating IL-1β-induced reduction of oligodendrocyte myelin formation (Bokobza et al., 2022), highlighting the critical role of microglial activation in both oligodendrocyte and myelin damage. TNF-α produced by

microglia activation can directly target developing oligodendrocytes, impairing mitochondrial function and enhancing susceptibility to excitotoxic injury (Adén et al., 2010; Bonora et al., 2014), and also indirectly damage immature oligodendrocytes by activating astrocytes. However, the increased release of proinflammatory cytokines by microglial activation can also promote the survival of mature oligodendrocytes *in vitro* (Taylor et al., 2010), suggesting that OPCs may be more susceptible to damage from neuroinflammation induced by GAA exposure relative to mature oligodendrocytes.

Repeated exposure to sevoflurane can cause widespread reactive astrogliosis in certain regions of the brain (Wu et al., 2020). Astrocytes participate in OPC proliferation and differentiation by secreting substances that either promote or inhibit these processes (Rawji et al., 2020). Reactive astrogliosis plays a dual role in the proliferation and differentiation of OPC. On the one hand, it enhances the activity of signal transducer and activator of transcription 3 (STAT3) (Nobuta et al., 2012), leading to increased expression of anti-apoptotic proteins B-cell lymphoma 2 (Bcl-2), MBP, and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase), an enzyme involved in myelin formation mainly found in oligodendrocytes. This activation potentially enhances the survival and differentiation of oligodendrocytes (Steelman et al., 2016). On the other hand, bone morphogenetic proteins (BMPs), endothelin-1, and proinflammatory cytokines such as TNF-α and IL-1β, which are released during reactive astrogliosis, exert toxic effects on oligodendrocytes, impacting their maturation and survival (Van Tilborg et al., 2016). GAAs can inhibit the number and maturation of astrocytes by interfering with signaling pathways essential for their growth and proliferation in the developing brain (Wang et al., 2016; Zhou et al., 2019). Although some evidence suggests that sevoflurane exposure does not cause widespread reactive astrogliosis, this discrepancy could be attributed to variations in GAA dosage, exposure duration, and animal models employed. While there is ongoing debate regarding the effects of GAAs on astrocytes, it is clear that oligodendrocytes are susceptible at all developmental phases and remain vulnerable to the impacts of GAAs even as a patient ages.

POTENTIAL NEUROPROTECTIVE STRATEGIES

Given the significance of oligodendrocytes as a target for GAAs and their role in the development of PNDs, we propose several potential neuroprotective measures. Research suggests that oligodendrocytes are particularly susceptible during the period of myelin sheath production, with children under 3 years of age who have undergone more than three surgeries requiring exposure to GAAs facing a higher risk of cognitive deficits by age 15 (Hu et al., 2017). In contrast, single, short-term exposures have not been linked to increased risk (Sun et al., 2016). Therefore, at crucial neurodevelopmental stages, such as those in infants and toddlers, careful consideration should be given to the choice of anesthetic, as well as the dosage and duration of exposure.

While accumulating evidence suggests that conventional GAAs may exert neurotoxic effects on the developing brain, the use of medications with neuroprotective qualities may help mitigate these effects. For example, dexmedetomidine (DEX), which targets α2-adrenergic receptors, offers multiple neuroprotective benefits. Notably, it reduces the negative impact of proinflammatory cytokines on oligodendrocyte proliferation and differentiation by inhibiting the production of inflammatory mediators, such as TNF-α and IL-6, and preventing NF-κB activation and LPS-induced cytokine release, thereby reducing inflammation (Li et al., 2020). Additionally, DEX can partially reverse isoflurane-induced cognitive impairment and attenuate apoptosis by up-regulating anti-apoptotic effectors like Erk and Bcl-2 signaling (Alam et al., 2017). It also promotes cell survival through increased BDNF levels and effectively induces sedation in children without causing negative side effects or cardiorespiratory instability (Koroglu et al., 2005), providing a potential protective strategy to reduce neonatal GAA-induced apoptosis. Xenon, another anesthetic, inhibits activation of the caspase-3 pathway induced by mitochondria, thereby reducing apoptosis (Alam et al., 2017). As an NMDAR inhibitor, xenon exhibits milder neurotoxicity and more neuroprotective properties compared to ketamine (Sanders et al., 2013), potentially due to the up-regulation of survival proteins such as Bcl-2. Xenon anesthesia is also associated with superior circulatory stability, reduced analgesic requirements, decreased adrenergic levels, and enhanced perfusion of individual organs compared to commonly used anesthetic agents (Wu et al., 2019), making it a promising neuroprotective agent. Propofol also produces some anti-inflammatory effects by inhibiting the expression of IL-6 and IL-1β through the $GABA_AR$ and nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated signaling pathways (Kochiyama et al., 2019).

Exposure to general anesthesia can alter the expression levels of certain myelin-related genes. Several animal studies have shown that DEX preconditioning can partially reverse these changes (Jimenez-Tellez et al., 2023), although further research is needed to determine its clinical applicability. Another possible therapeutic strategy is the use of erythropoietin (EPO), which has been shown to enhance oligodendrocyte development, survival, maturation, and myelin synthesis *in vitro* (Jantzie et al., 2013). Additionally, insulin-like growth factor 1 (IGF-1), which activates the Erk and Akt/mTOR pathways (Bibollet-Bahena & Almazan, 2009), may promote oligodendrocyte and OPC differentiation and myelin formation *in vitro*. Given that continuous exposure to GAAs affects oligodendrocyte proliferation, differentiation, and survival, targeting oligodendrocyte receptors and signaling pathways may serve as a viable treatment strategy.

CHALLENGES AND FUTURE DIRECTIONS

While the effects of GAAs on oligodendrocytes have been extensively investigated in animal experiments, clinical data linking GAAs to oligodendrocyte apoptosis remain limited. Evidence that GAAs induce oligodendrocyte apoptosis primarily relies on imaging studies showing damage to white matter structures following GAA exposure. Furthermore, diffusion tensor imaging has revealed common interhemispheric brain damage in children diagnosed with ADHD, obsessive-compulsive disorder (OCD), and autism spectrum disorder (ASD) (Ameis et al., 2016). These observations suggest that changes in white matter integrity and volume in children may be associated with neurodevelopmental disorders (NDDs), implying GAA-induced abnormalities in oligodendrocyte development and dysfunction, as well as compromised myelin formation, may significantly contribute to childhood NDDs. To validate the

accuracy and significance of these anesthesia-related changes, additional prospective clinical trials are required. Further complementary laboratory research is also needed to identify the precise mechanisms involved and to develop suitable therapeutic interventions.

The susceptibility of oligodendrocytes to apoptosis from GAAs spans from the initiation of myelin-forming protein production to the development of myelinated axons. GAAs can markedly inhibit both oligodendrocytes and neurons during the fetal stage in NHPs, with the vulnerable period lasting throughout the neonatal stage and toxic potential increasing significantly between the fetal (G120) and neonatal (P6) periods (Brambrink et al., 2012; Creeley et al., 2014). Furthermore, the vulnerability of oligodendrocytes persists into later developmental stages at P20 and P40, corresponding to human infants with brain development approaching 9.5 months, even as neuronal vulnerability diminishes (Schenning et al., 2017). These findings exemplify the prolonged sensitivity of oligodendrocytes to GAAs and the persistence of their pharmacological effects. Considering that myelin sheath formation continues into late adolescence in humans, the potential for anesthesia-induced toxicity also likely continues into adolescence. The toxic impacts of GAAs on oligodendrocytes in the developing brain may play a critical role in the onset of NDDs following anesthetic exposure in early childhood. However, as these conclusions are predicated on NHP experiments, further research and human trials are necessary to validate these findings.

As a type of neuroglial cell, oligodendrocytes are interconnected with astrocytes and microglia. GAA-induced activation of microglia triggers the release of high concentrations of proinflammatory cytokines, adversely affecting the survival, differentiation, and proliferation of immature oligodendrocytes. Conversely, microglia with an anti-inflammatory phenotype can promote the differentiation of oligodendrocytes *in vitro*. Astrocytes also exhibit a dual effect on oligodendrocyte proliferation and differentiation. Thus, further research is required to fully understand the complex interactions and mechanisms of action between GAAs and glial cells. Furthermore, the specific pathways through which GAAs impact neurons via oligodendrocytes remain unclear. However, animal studies suggest that treatments targeting oligodendrocytes may ameliorate neurotoxicity caused by GAAs. A deeper understanding of the role of oligodendrocytes in the interactions between GAAs and neurons is anticipated to lead to innovative therapeutic approaches for treating neurological and psychiatric disorders.

An increasing number of studies have shown how crucial oligodendrocytes are to CNS function. In addition to influencing myelin formation, oligodendrocytes express a variety of immunomodulatory molecules associated with neuroinflammation. Oligodendrocyte lineage cells also indirectly regulate inflammation-induced mood disorders through a variety of signaling pathways (Zhou et al., 2021). Thus, oligodendrocytes may play a greater role in GAA-induced neurotoxicity than previously thought, with many questions remaining to be answered.

CONCLUSIONS

Oligodendrocytes express abundant GABAR and NMDAR. Most anesthetics with NMDAR antagonist or GABAR agonist properties can trigger widespread apoptotic neurodegeneration in the developing brain. The interaction of GAAs with $GABA_AR$ on the postsynaptic membranes of OPCs disrupts calcium homeostasis, resulting in abnormal OPC proliferation and differentiation. GAA-induced changes in MOMP can result in leakage of cytochrome *c* and the subsequent activation of caspase-3, a key mediator of apoptosis in oligodendrocytes. As a significant target of GAAs, the PI3K/Akt/mTOR pathway influences oligodendrocytes by up-regulating their activity and negatively regulating the Erk 1/2 pathway, which, in turn, affects oligodendrocyte proliferation and differentiation. GAAs can inhibit Wnt/β-catenin signaling, which may be regulated by melatonin. Many proinflammatory cytokines adversely affect the proliferation, differentiation, and survival of immature oligodendrocytes. Therefore, some anesthetics with anti-inflammatory properties could offer neuroprotection by decreasing neuroinflammation. GAAs also have the potential to induce metabolic disorders and alter gene expression, impacting the maturation and development of oligodendrocytes. Conversely, ketamine, by inhibiting eEF2 and up-regulating BDNF translation, exhibits antidepressant and anti-inflammatory properties that may support the development and differentiation of oligodendrocytes. In this review, we explored the mechanisms underlying the impact of GAA on oligodendrocytes and their consequent neurotoxic effects, aiming to enhance our understanding of GAA-induced neurotoxicity and stimulate new research that could lead to clinically applicable strategies to minimize the adverse neurocognitive effects associated with GAA use.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

W.X.H., J.H.L., and Z.Y.H. designed and conceived the manuscript. W.X.H. wrote the manuscript. Y.C.Y. and Y.H.H. conducted the literature search. F.Q.F. and X.H.Q. designed and prepared the figures and tables. L.W. and P.M.M. edited the manuscript. H.X., J.H.L., and Z.Y.H. reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors acknowledge Yu-Dong Zhou and Yi Shen (Zhejiang University School of Brain Science and Brain Medicine, Hangzhou, China) for their support to our team and assistance in revising this manuscript. Figures were created with BioRender.com (Toronto, Ontario, Canada).

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