General anesthetic agents induce neurotoxicity through astrocytes

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From the Contents

Abstract

Neuroscientists have recognized the importance of astrocytes in regulating neurological function and their influence on the release of glial transmitters. Few studies, however, have focused on the effects of general anesthetic agents on neuroglia or astrocytes. Astrocytes can also be an important target of general anesthetic agents as they exert not only sedative, analgesic, and amnesic effects but also mediate general anesthetic-induced neurotoxicity and postoperative cognitive dysfunction. Here, we analyzed recent advances in understanding the mechanism of general anesthetic agents on astrocytes, and found that exposure to general anesthetic agents will destroy the morphology and proliferation of astrocytes, in addition to acting on the receptors on their surface, which not only affect Ca^{2+} signaling, inhibit the release of brain-derived neurotrophic factor and lactate from astrocytes, but are even involved in the regulation of the pro- and anti-inflammatory processes of astrocytes. These would obviously affect the communication between astrocytes as well as between astrocytes and neighboring neurons, other neuroglia, and vascular cells. In this review, we summarize how general anesthetic agents act on neurons via astrocytes, and explore potential mechanisms of action of general anesthetic agents on the nervous system. We hope that this review will provide a new direction for mitigating the neurotoxicity of general anesthetic agents.

Key Words: astrocytes; brain-derived neurotrophic factor; general anesthetic agents; neuron; neurotoxicity; N-methyl-D-aspartate receptor; perioperative neurocognition; Toll-like receptor; γ-aminobutyric acid receptor

Introduction

General anesthetic agents (GAAs) can reversibly inhibit central nervous system (CNS) function, induce loss of consciousness, amnesia, analgesia, and muscle relaxation, while maintaining a stable physiological state. Despite their different chemical structure, GAAs target multiple sites through a variety of mechanisms. It is generally believed that GAAs produce their anesthetic effects by interacting with various receptors and ion channels including γ-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA), glycine, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, and neuronal nicotinic acetylcholine receptors, as well as voltage-dependent Na^+, K^+, and Ca^{2+} channels (Joo et al., 2001; Ward and Loepke, 2012).

Neuroglia are groups of cells in the CNS that include astrocytes, microglia, and oligodendrocytes which account for 19–40%, 5–10%, and 45–75% of all cells in the CNS, respectively (Ortinski et al., 2022). In the past, the function of glial cells was thought to be limited to mechanical and nutritional support, neuronal repair, creating barriers, and participating in the immune response. It has been shown that in addition to their support functions, glial cells, particularly astrocytes, are also widely involved in regulating neuronal physiological activities such as controlling synapse formation and growth (Allen and Lyons, 2018), regulating synaptic transmission (Schummers et al., 2008), releasing glial transmitters to regulate neuronal activity (Volterra and Meldolesi, 2005), and participating in metabolism to provide lactate energy supply (Magistretti and Allaman, 2018).

GAAs can not only cause disruption to the morphology of astrocytes, but also affect the proliferation of astrocytes and inhibit the connexins between astrocytes. These disrupt the balance of the astrocyte network. In addition, GAAs affect Ca^{2+} signaling in astrocytes, inhibit the release of brain-derived neurotrophic factor (BDNF) and lactate from astrocytes, and are even involved in mediating anti-inflammatory and pro-inflammatory processes in astrocytes, which will inevitably have a significant impact on signaling from astrocytes to astrocytes as well as from astrocytes to neighboring neurons, other neuroglial cell populations, and vascular cells (**Table 1**).

Astrocytes form a reticulum of neural tissue which acts as a support and divider and regulates nerve function by forming close contact with synapses, secreting neuroactive substances, or eliminating neurotransmitters (Valori et al., 2019). Astrocytes are endowed with a variety of voltage and ligand-dependent ion channels such as hemichannels (HCs), bestrophin-1 channels, and volume-regulated anion channels (Verkhratsky and Steinhauser, 2000). In addition, many different types of neurotransmitter receptors and transporters (glutamate transporter 1, glutamate aspartate transporter, and GABA transporter) are expressed on the surface membrane of astrocytes (Danbolt, 2001). Astrocytes are capable of transmitting information via ionic changes in the extracellular space that accompany nerve impulse activity as well as through the release of neurotransmitters, growth factors, and other glial signaling molecules (Kim et al., 2020; Brandebura et al., 2023; **Figure 1**). These ion channels and transmitter receptors are diverse, and many of them are targets of GAAs (Allen and Lyons, 2018). GAAs not only inhibit neuronal excitation, leading to sedation, analgesia, and amnesia, but also act directly on astrocytes, affecting their proliferation and apoptosis as well as their secretory and regulatory functions. Therefore, it is important to further understand the pharmacological effects of GAAs on astrocytic function and to explore how GAAs act on neurons via astrocytes.

In this review, we discuss the physiological aspect of GAAs interaction with astrocytes as well as the role of astrocytes in GAA-induced adverse drug reactions and neurotoxicity.

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Table 1 | **Summary of the changes in astrocytes induced by GAAs in various studies**

GAAs	Experimental subjects	Exposure period	Concentration or dose	Exposure time	Mechanisms
Sevoflurane	Rats	P7	2.50%	6 h	Reduces the expression of GFAP and GLAST (Wang et al., 2016).
	Mice	P21–27	532 μM	/	Increases the function of astrocytic $GABA_A$-Rs in the hippocampus (Chung et al., 2021).
	Mice	P7	2.50%	4 h	Disrupts the Ca^{2+} homeostasis of astrocytes and down-regulates ezrin (Zhou et al., 2019).
	Rats	2 wk	2.50%	2 h	Enhances the clearance of $A\beta_{1-40}$ via up-regulating aquaporin-4 expression in astrocytes (Gao et al., 2019).
	Rats	P85–90	3%	2 h	Evaluates the signaling of hippocampal pro-inflammatory factors and NF-κB (Hwang et al., 2017).
Isoflurane	Rats and mice	P14; P60	1.70%	35 min; 4 d	Decreases the number of astrocytes in the early stage and increases the number in the later stage (Zhu et al., 2010).
	NHPs	P6	0.7–1.5%	5 h; once or three times	Increases in GFAP-positive area in specific brain regions (Neudecker et al., 2021).
	Rats	DIV4; DIV15	3%	24 h	Delays morphological differentiation and impairs the growth of the immature astrocytes (Lunardi et al., 2011).
	Rats	DIV14	1.40%	4 h	Decreases α-tubulin and GFAP and redistributes F-actin (Culley et al., 2013).
	Mice	1–4 mon	0.7%; 1.3%	20 min; 1 h	Triggers a persistent increase in tonic current and cell-surface expression of α5GABAA-Rs (Zurek et al., 2014).
	Mice	6–12 wk	1.0–1.5%	/	Suppresses calcium transients in neocortical astrocytes (Thrane et al., 2012).
	Rats	P7-12	0.5–5%	/	Inhibits a Kir4.1/5.1-like conductance in neonatal rat brainstem astrocytes (Ou et al., 2020).
	Mice	P1	0.7–2.1%	2 h	Decreases the cell viability and BDNF expression of astrocytes via upregulation of TREK-1 (Zhou et al., 2017).
	Mice	E18; P1–3	1.2%–3.6%	5 h	Neurons co-cultured with astrocytes exposed to isoflurane show reduced axonal outgrowth (Ryu et al., 2014).
	Mice	4 mon	1.50%	6 h	Decreases GJs-Cx43 expression in the hippocampus and enhances hemichannel activity (Dong et al., 2022).
	Rats	/	2%	1 h; 24 h	Inhibits the activation of astrocytes and protein expression of TLR4, MyD88, and NF-κB (Xiao et al., 2015).
Propofol	Rats	P1	30 μM	6 h	Decreases BDNF secretion from astrocytes (Liu et al., 2017).
	Mice	P15–25	50–150 μM	/	Inhibits both gap junctional communication and hemichannel activity (Liu et al., 2016).
	Mice	P14–21	150 μM	/	Induces changes in Cx43 phosphorylation in murine cortical astrocytes (Nuriya et al., 2018).
	Rats	P1–3	0–100 μM	/	Inhibits the TLR4/MyD88-dependent NF-κB, ERK1/2, and p38 MAPK pathways (Zhou et al., 2015).
	Rats	P2–3	0.33–300 μM	/	Increases the secretion of TNF-α from astrocytes at 300 μM, but inhibits secretion at 10 μM (Liu et al., 2012).
	Rats	P7	10 μg/mL; 0.9 μg/mL	1 h; 48 h	Up-regulates rno-miR-665 which can suppress BCL2L1 and elevates cleaved caspase-3 expression (Sun et al., 2015).
Ketamine	Rats	P21–40	3–1200 μM	/	Inhibits the frequency of SICs in a concentration-dependent manner (Zhang et al., 2019).
	Mice	6–12 wk	0.12 mg/g	/	Suppresses calcium transients in neocortical astrocytes (Thrane et al., 2012).
	Human	/	0–150 μM	6 h	Decreases BDNF secretion and increases BDNF-AS and pro-BDNF secretion (Penning et al., 2021).
	Mice	P15–25	50–300 μM	/	Inhibits hemichannel activity and shows a weak effect on GJs communication (Liu et al., 2016).
Etomidate	Mice	P21–27	100 μM	/	Increases the function of astrocytic $GABA_A$-Rs in the hippocampus (Chung et al., 2021).
	Mice	1–4 mon	8 and 20 mg/kg	/	Increases a tonic inhibitory current generated by $\alpha5GABA_A$-Rs (Zurek et al., 2014).
Dexmedetomidine	Mice	8–9 wk	25 μg/kg	/	Prevents excessive cell-surface expression and function of $\alpha5GABA_A$-Rs after anesthesia (Wang et al., 2018).

BCL2L1: Bcl-2-like protein 1; BDNF: brain-derived neurotrophic factor; BDNF-AS: BDNF-antisense; Cx: connexin; DIV: day-*in-vitro* treatment; E: embryonic day; ERK: extracellular signal-regulated protein kinases; GAAs: general anesthetic agents; GABAA-R: type A γ-aminobutyric acid receptor; GFAP: glial fibrillary acidic protein; GJ: gap junction; GLAST: glutamate-aspartate transporter; Kir: inwardly rectifying K^+; MAPK: mitogen-activated protein kinase; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor-kappa B; NHP: non-human primate; P: postnatal day; SICs: slow inward currents; TLR: Toll-like receptor; TREK-1: TWIK-related potassium channel-1; $\alpha5GABA_A$-Rs: α5 subunit-containing $GABA_A$ receptors.

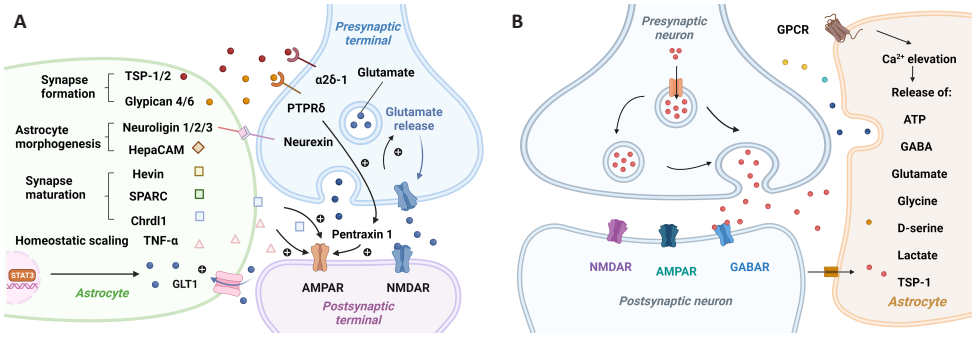

Figure 1 | **Astrocyte processes contact synapses.**
(A) TSP-1 released by astrocytes could act on neuronal α2δ-1 receptors to induce aggregation of synaptic proteins and cause synaptic proliferation and differentiation. Astrocyte glypicans 4 and 6 promote the formation of excitatory synapses via GluA1 AMPARs. Glypican 4 induces the release of pentraxin 1 from presynaptic terminals by signaling through presynaptic PTPRδ. Pentraxin then accumulates AMPARs on the postsynaptic terminal forming functional synapses. Neuroligins and neurexins are essential synaptic components that determine synapse specification through trans-synaptic interactions with each other. Hevin, SPARC, and Chrdl1 are involved in regulating synaptic maturation. Meanwhile, astrocytes also express glutamate transport via GLT1. (B) Activation of GPCRs induce the release of neuroactive substances such as ATP, GABA, glutamate, glycine, D-serine, lactate, and TSP-1 from astrocytes through elevated Ca^{2+}, which act on neurons and synapses. Created with BioRender.com. AMPAR: Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; GABA: γ-aminobutyric acid; GABAR: gamma-aminobutyric acid receptor; GLT1: glutamate transporter 1; GPCR: G-protein coupled receptor; NMDAR: N-methyl-D-aspartate receptor; PTPRδ: protein tyrosine phosphatase receptor δ; STAT3: signal transducer and activator of transcription 3; TSP-1: thrombospondin-1.

Retrieval Strategy

In this narrative review, we included articles discussing the effects of various general anesthetic drugs on astrocytes. Supplementary databases include the Web of Science, Embase, CNKI, and Wanfang. In January 2023, we searched the PubMed database for articles published from 1990 to 2023 by using different combinations of the following keywords: astrocyte, neuroglia, sevoflurane, desflurane, isoflurane, ether, enflurane, inhalation anesthetic agent, inhalation anesthetic, volatile anesthetic, gas anesthetic, propofol, etomidate, ketamine, dexmedetomidine, intravenous anesthetic agent, intravenous anesthetic, general anesthetic agent, general anesthetic, and anesthesia. Further screening was carried out by reading the abstracts and full texts of the literature. We cited the most recent articles whenever possible, but also retained some original publications with significant findings and a certain number of older citations.

Effects of General Anesthetic Agents on Astrocytes

Astrocyte proliferation and morphology

Astrocyte proliferation

GAAs induce alterations in astrocytic expression and secretory function that affect how astrocytes support neuronal development. These alterations include impaired expression of glutamate-aspartate transporters (GLAST), glial fibrillary acidic protein (GFAP; Wang et al., 2016), and brain-derived neurotrophic factor (BDNF; Liu et al., 2017).

GFAP is a marker of mature astrocytes, and its expression is elevated following astrocytic proliferation or injury (Yang and Wang, 2015). After stimulation with lipopolysaccharide (LPS), the expression of GFAP in astrocytes was significantly up-regulated. Propofol (10 μM) can inhibit the expressions of GFAP and significantly attenuate the activation of astrocytes induced by LPS (Zhou et al., 2015). Studies on rats exposed to sevoflurane (2.5% for 6 hours) after day 7 of birth showed a significant reduction in the expression of GFAP and GLAST in the hippocampal tissue, and a decrease in astrocytic numbers from days 1 to 14. This is the result of sevoflurane-induced inactivation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, which is essential for astrocytic proliferation, maturation, and positive response to injury (Wang et al., 2016). This indicates that GAAs inhibit the number and maturation of astrocytes by interfering with the signaling pathway related to the growth and proliferation of astrocytes in the developing brain.

Exposure of rats and mice (postnatal day 14) to 1.7% isoflurane for 35 minutes daily for 4 successive days revealed a significant reduction in SOX-2/GFAP-positive cells by dual labeling with SOX-2 and GFAP in young animals, but astrocytic hyperplasia in adults (Zhu et al., 2010). This study suggests that juvenile exposure to inhaled anesthetics reduces astrocyte numbers in the early stage and astrocytic hyperplasia in the late stage of development. A study of the brains of rhesus monkey pups (postnatal day 6) exposed to single or multiple doses of isoflurane (0.7–1.5%, 5 hours) showed an increased density of GFAP and proliferation of astrocytes in the primary visual cortex, perirhinal cortex, and the subiculum (brain regions associated with visual recognition memory), and the amygdala (brain region associated with emotional and social behavior) 2 years after exposure (Neudecker et al., 2021). Because activation and chronic proliferation of astrocytes is a typical nonspecific response to CNS injury (Brandebura et al., 2023), this suggests that astrocytic proliferation is likely a response to a chronic injury produced by inhaled anesthetic exposure during early childhood. The proliferation of reactive astrocytes or the increase of GFAP is helpful to isolate the damaged brain regions from intact nerve tissue, thereby preventing the spread of the injury. Thus, this plays a role in the corresponding nerve protection and repair of various CNS injuries (Sofroniew, 2009). However, the proliferation of astrocytes can also lead to hyperactivity of neurons and diseases of the CNS. The long-term activation of astrocytes induced by GAAs seems to be diffuse and chronic, which will adversely affect the connectivity of brain regions and changes in synaptic structure and function, resulting in cognitive and social behavior defects (Zhu et al., 2010; Neudecker et al., 2021).

Astrocyte morphology

Astrocytes are involved in synapse formation and elimination. They mediate normal neural function by helping form efficient synaptic connections. Repeated exposure to inhaled anesthetics during the critical period of synapse development causes neuronal apoptosis and damages the cytoskeleton of astrocytes. This, in turn, affects brain development and has been linked to behavioral and cognitive deficits (Xie et al., 2020). RhoA, a member of the Rho family of GTP-binding proteins, controls the formation of actin stress fibers that are involved in the regulation of microtubule formation (Stern et al., 2021). Animal experiments have shown that isoflurane (3% for 24 hours) induces disruption of the astrocytic cellular actin network by downregulating the RhoA/myosin light chain protein signaling. This will lead to serious morphological changes in astrocytes, destroy astrocytic function, and delay the morphological differentiation of immature astrocytes (Lunardi et al., 2011), accompanied by a decrease of astrocytes. *In vitro* studies have shown that isoflurane exposure (1.4% for 4 hours) decreases the expression of α-tubulin and GFAP and redistributes F-actin (Culley et al., 2013). Interestingly, this did not affect the survival, proliferation, and synaptogenesis of astrocytes. The reason for different results after exposure to isoflurane is likely because of different research methods and administration schemes *in vitro* and, but both reveal the destruction of GAAs on the astrocyte skeleton.

Anti-/pro-inflammatory effects

The inflammatory cytokines in the CNS are mainly released by glial cells (Uddin and Lim, 2022; Zhou et al., 2023). After activation due to surgical or anesthetic stress, astrocytes accelerate the secretion and release of chemokines and inflammatory mediators, triggering neuroinflammation and cognitive dysfunction (Mayo et al., 2014). Nuclear factor-kappa B (NF-κB) signaling is critical in immune and inflammatory responses, and both inhaled anesthetics and intravenous anesthetics can activate this pathway (Zhang et al., 2013). Sevoflurane (3% for 2 hours) exposure in adult rats increased the release of pro-inflammatory factors TNF-α, IL-1β, and IL-6 from hippocampal astrocytes and induced activation of NF-κB signaling involved in the expression of inflammatory genes (Zhu et al., 2017). The JAK/STAT signaling pathway is one of the key factors promoting neuroinflammation in neurodegenerative diseases. Astrocytes activate inflammatory programs involving STAT3 activation in a JAK1-dependent manner (Yan et al., 2018). Interestingly, sevoflurane exposure inhibited astrocyte maturation and function by inducing JAK/STAT inactivation, a pathway that may be a novel target for the treatment of general anesthesia-induced neurotoxicity in the developing brain (Wang et al., 2016).

Propofol (10 μM) significantly inhibited LPS-induced pro-inflammatory factors (TNF-α, IL-1β, and IL-6) in astrocytes (Zhou et al., 2015). Toll-like receptor 4 (TLR4) is a transmembrane receptor protein associated with the immune response and is expressed in astrocytes (Li et al., 2021b). Upon induction of LPS, TLR4 receptors are activated and myeloid differentiation factor 88 (MyD88) can be recruited to TLR4 receptors, which activates NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways to mediate the expression of pro-inflammatory genes (Gorina et al., 2011). Propofol and isoflurane exert anti-inflammatory effects by inhibiting this signaling pathway (Xiao et al., 2015; Zhou et al., 2015).

GABA receptors

$GABA_A$ receptors

$GABA_A$ receptors ($GABA_A$-Rs), the main targets of GAAs, contain pentameric channels with multiple subunits (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, π, and ρ_{1-3}) and are categorized as either intrasynaptic or extrasynaptic. These two groups of receptors show great differences in subunit composition, channel dynamics, affinity to GABA, desensitization rate, and pharmacological properties (Zhu et al., 2018). In response to high-concentration GABA released from the presynaptic terminal, intrasynaptic $GABA_A$-Rs generate fast and transient inhibitory currents. In contrast, high-affinity extrasynaptic $GABA_A$-Rs generate persistent (tonic) inhibitory currents in response to a low concentration of GABA (Engin et al., 2018).

Astrocytic GABA receptors are widely expressed in the soma, the synapse-surrounding processes, and brain vessel-contacting endfeet (Liu et al., 2022). A human brain study reported the expression of genes encoding α_2, β_1, and γ_1 subunits in astrocytes (Sequeira et al., 2019). This indicates the abundant presence of $GABA_A$-Rs in astrocytes. Recent studies have shown that etomidate and sevoflurane can increase the function of $GABA_A$-Rs in astrocytes by increasing the peak amplitude of the current and/or by prolonging its decay, thus increasing intracellular Ca^{2+} and inducing the release of various signal molecules (Chung et al., 2021). It is worth noting that etomidate (but not sevoflurane) increases the peak amplitude of the current, which suggests that the results of GAAs on $GABA_A$-Rs are inconsistent, which is closely related to drug bioavailability, the effects of the drugs on $GABA_A$-Rs kinetics, and the subunit composition of the underlying receptors.

Extrasynaptic $GABA_A$-Rs play an important role in producing anesthetic effects (Wang and Orser, 2011). Extrasynaptic $GABA_A$-Rs containing the α5 subunit (α5$GABA_A$-Rs) are closely associated with acute amnesia produced by GABAergic GAAs (Zurek et al., 2014). Elevated activity of α5$GABA_A$-Rs decreases neuronal excitability, interferes with synaptic plasticity, and is involved in GABAergic GAAs-induced memory impairment, which is one of the causative mechanisms of anterograde amnesia (Wang and Orser, 2011). GAAs can also trigger deficits in persistent memory, which continue even after elimination of the GAAs (Whissell et al., 2016). Such long-term memory changes are closely related to the transport and expression of extrasynaptic $GABA_A$-Rs. Furthermore, glial cells, especially astrocytes, play an irreplaceable role in modulating the expression of extrasynaptic $GABA_A$-Rs (Chung et al., 2021). Following brief exposure to intravenous (etomidate) and inhaled (isoflurane) anesthetics, tonic currents were generated in cells containing α5$GABA_A$-Rs in the hippocampus and trigger a sustained increase in cell surface expression of α5$GABA_A$-Rs (Zurek et al., 2014). This change is not because of the direct action of GABAergic GAAs on neurons, rather because of the stimulation of astrocytes by GABAergic GAAs to release soluble factors that can interfere with neurons, thereby triggering alterations in receptor function (Zurek et al., 2014).

Alterations in the expression and function of $GABA_A$ receptors, which may persist after GAAs are eliminated from the body, appear to be associated with long-term cognitive deficits after anesthesia. Dexmedetomidine reduces the expression of cell surface α5$GABA_A$-Rs and prevents anesthetic-induced increases in neuronal tonic currents (Wang et al., 2018). It also attenuates behavioral deficits associated with postoperative delirium by targeting the α_2 adrenergic receptors in astrocytes (Hertz et al., 2010; Wang et al., 2018). This crosstalk between glial cells and neurons is being studied in an effort to better understand, prevent, and treat cognitive deficits after anesthesia.

$GABA_B$ receptors

$GABA_B$ receptors ($GABA_B$-Rs) are class C heterodimers of G-protein coupled receptors. $GABA_B$-Rs are primarily coupled to the Gi/o class of heterotrimeric G proteins, leading to a prolonged decrease in neuronal excitability via inhibition of adenylyl cyclase, voltage-gated calcium ion channels, and opening of the potassium ion channels (Yang et al., 2022). Astrocytes express $GABA_{B1a}$, $GABA_{B1b}$, and $GABA_{B2}$ receptors (Charles et al., 2003).

In the cortex, exogenous GABA acts only on $GABA_B$-Rs in astrocytes, not $GABA_A$-Rs, thus triggering changes in the level of Ca^{2+} (Mariotti et al., 2016). Calcium signals mediated by hippocampal astrocytic $GABA_B$-Rs are preferentially established in the postnatal hippocampal network (Ishibashi et al., 2019). Multiple exposures of neonatal mice to sevoflurane (3%) triggered activation of the medial prefrontal cortex excitatory neurons and induced impulsive behavior in mice, while inhibition of medial prefrontal cortex excitatory neurons partially alleviated this behavioral deficit (Xie et al., 2020). Sevoflurane acts as a GABA receptor agonist and enhances synaptic inhibition in the CNS via $GABA_B$-Rs. It has been found that altered intracellular calcium signaling in astrocytes induced thrombospondin-1 release, which acts on neuronal α2δ-1 receptors to induce aggregation of synaptic proteins and cause synaptic proliferation and differentiation (Nagai et al., 2019). Upregulation of thrombospondin-1 has been closely associated with attention-deficit hyperactivity disorder-like hyperactive behavior.

NMDA receptors

NMDA receptors are glutamate-gated calcium-permeable ion channels that exist as heterotetramers. They play a key role in synaptic transmission and plasticity (Zhang et al., 2021). The function of intracellular expression of NMDA receptors in glial cells has been controversial. The expression of NMDA receptor subunits (NR1 and NR2) was detected at the mRNA and protein levels. Furthermore, both membrane currents and cytosolic Ca^{2+} increases were observed in astrocytes from cortical slices in response to slice superfusion with solutions supplemented with NMDA (Verkhratsky and Kirchhoff, 2007). In addition, astrocytes under acutely isolated cortical slices showed NMDA-activated currents sensitive to NMDA receptor antagonists (Lalo et al., 2006). These studies confirm NMDA receptor expression in astrocytes. Indeed, stimulation of presynaptic terminals induces electrical responses in cortical astrocytes, which are mediated by NMDA receptors and electrogenic Na^+/glutamate transporters, thus playing a role in synaptic signal transmission (Verkhratsky and Kirchhoff, 2007).

Unfortunately, most current studies have focused on the effects of GAAs on neuronal NMDA receptor regulation of function and proliferation of glial cells through altered neuronal signaling; however, studies on the effects of GAAs on astrocytic NMDA receptors are still scarce. Whole-cell recordings of neurons in a prefrontal cortex slice preparation from rats showed that ketamine inhibited astrocyte-mediated slow inward currents (SICs) synchronization in a concentration-dependent manner. This is most likely mediated by extrasynaptic NMDA receptors containing N1 or NR2B subunits (Zhang et al., 2019). SICs are essential in promoting synchronized neural activity and cognitive formation (Li et al., 2013). Thus, this would inhibit glutamatergic transmission from astrocytes to neurons, thereby decreasing neuronal activity, which may be involved in ketamine-induced loss of consciousness.

Ca^{2+} signals

It has been shown that elevated Ca^{2+} concentrations in astrocytes could propagate in glial cells and also induce elevated Ca^{2+} concentrations in adjacent neurons, leading to the concept of gliotransmission from astrocytes to neurons (Bazargani and Attwell, 2016). Neurons transmit information to astrocytes primarily through the release of synaptic transmitters and factors that bind to astrocytic G-protein-coupled receptors (Durkee et al., 2019), triggering inositol 1,4,5-trisphosphate production and Ca^{2+} release from the endoplasmic reticulum (Woll and Van Petegem, 2022). Activation of this signaling pathway can generate a wide range of Ca^{2+} signaling oscillations (Semyanov et al., 2020). In some brain regions, increases in intracellular astrocytic Ca^{2+} can be triggered by stimulation of Ca^{2+} permeable ionotropic receptors; whereas, transient increases in astrocytic Ca^{2+} can also be induced by neurotransmitters or specialized pumps (Volterra et al., 2014). The net result of this intracellular Ca^{2+} increase is that astrocytes then rapidly release glial transmitters that promote or inhibit synaptic transmission resulting in either long-term potentiation or long-term depression (Halassa and Haydon, 2010). It is important to note that this finding is controversial. Agulhon et al. (2010) found no correlation between astrocytic $[Ca^{2+}]_i$ and hippocampal synaptic transmission and plasticity by manipulating astrocytic $[Ca^{2+}]_i$. This may be attributed to different astrocyte types and activation patterns as well as the environment in which the synapses are located.

Most GAAs in clinical use inhibit calcium transients *in vitro* and *in vivo* (Thrane et al., 2012). Both the maintenance of neuronal homeostasis and synaptic communication are closely linked to intra-astrocytic Ca^{2+} commands (Sobolczyk and Boczek, 2022). The maintenance of many normal physiological functions depends on the tight regulation of homeostatic function and Ca^{2+} dynamics in astrocytes (Shigetomi et al., 2016; Lin et al., 2022). Thus, alterations in Ca^{2+} signaling in astrocytes may be a common pathway for the action of GAAs. Sevoflurane administration eliminated transient Ca^{2+} and reduced baseline Ca^{2+} levels in astrocytes, resulting in the down-regulation of the actin-binding membrane binding protein Ezrin, abnormal synaptogenesis, and defective astrocytic morphology (Zhou et al., 2019). Altered Ca^{2+} signaling in astrocytes may be involved in GAAs-induced social behavioral and cognitive dysfunction in mice.

Thrane et al. (2012) showed that ketamine and isoflurane significantly inhibited spontaneous calcium transients and desynchronized calcium transients in neocortical astrocytes of mice by using doses that did not affect neuronal activity. Calcium transients produced by anesthesia are mediated by inositol 1,4,5-trisphosphate type 2 receptors, and blocking neuronal activity with tetrodotoxin did not affect the calcium signaling in astrocytes (Thrane et al., 2012; Zhou et al., 2019). This suggests that astrocytes can respond to the effects of GAAs independent of neurons through altered calcium signaling. GAAs can directly affect astrocyte function through their effects on calcium signaling. This spontaneous, rapid, and highly synchronized calcium signal that is eliminated by anesthesia induction may be a non-neuron-sensitive indicator of waking cortical activity and is associated with arousal from the anesthetized state (Thrane et al., 2012). Therefore, astrocytes are likely involved in anesthesia-induced sedation or loss of consciousness.

K^+ channels

The K^+ conductance of astrocytes dominates the membrane potential, which is determined by the transmembrane K^+ gradient. This determines the important role of astrocytes in buffering excess K^+ in the extracellular space, regulating neuronal membrane potential and excitability as well as the homeostasis of the internal environment by absorbing K^+ released during neuronal activity and distributing it to sites of lower concentration (Hertz and Chen, 2016). Extracellular accumulation of K^+ promotes chronic pain, and the activation of K^+ channels in astrocytes induced by GAAs should promote K^+ uptake and contribute to analgesia (Mulkey et al., 2022).

Inwardly rectifying K^+ (Kir) channels in astrocytes plays an important role in K^+ buffering. Kir4.1 is an inwardly rectifying potassium channel expressed explicitly in astrocytes (Nwaobi et al., 2016). Kir4.1 and Kir4.1/5.1 channels mediate K^+ buffering through the uptake of excess extracellular potassium ions, thereby regulating both the concentration of extracellular potassium ions at the synapse and the excitability of the neuron (Li et al., 2021a). A recent study showed that the anesthetic and ventilatory effects of isoflurane are mediated by Kir4.1/5.1 channels in astrocytes of the retrotrapezoid nucleus, a brainstem region associated with respiratory control (Ou et al., 2020). The channel effects are closely related to its ability to reduce K^+ buffering, resulting in increased extracellular K+ and glutamate levels. The specific outcome depends on the extracellular environment and the combined effects of the anesthesia-induced opening of TWIK-related potassium channel-1 (TREK-1).

Inhaled anesthetics selectively open two-pore-domain potassium channels in humans, including TREK-1, TREK-2, TASK-1, TASK-2, TASK-3, and TALK-2 channels (Honore, 2007). TREK-1 is the most thoroughly studied anesthesia-sensitive two-pore-domain potassium channel, which is widely expressed in astrocytes and neurons (Honore, 2007). TREK-1 is activated in response to inhaled anesthetics (chloroform, diethyl ether, halothane, and isoflurane), leading to hyperpolarization of the resting membrane potential involved in the anesthetic effect, with carboxy (C)-terminal regions being critical in the activation process (Pavel et al., 2020). Meanwhile, TREK-1 knockout mice have been shown to exhibit reduced sensitivity to inhaled anesthetics. Although the neural pathways involved have not been clarified (Mathie et al., 2021), TREK-1 opening is involved in the cellular mechanisms of general anesthesia. Isoflurane significantly reduced the expression of BDNF and induced apoptosis by upregulating TREK-1 in astrocytes of neonatal mice (Zhou et al., 2017). This could be reversed by knocking out TREK-1. TREK-1 plays a role in anesthesia-induced sleep/unconsciousness, as well as cerebral ischemia and emotional disorders such as depression, epilepsy, and nociception, and it is promising as a potential therapeutic approach for various pathological states (Steinberg et al., 2015).

The current superposition of Kir4.1 and TREK channels constitutes the "passive" current mode of hippocampal astrocytes (Seifert et al., 2009). In addition, the Kir4.1 channel is a regulator of BDNF expression in astrocytes. Inhibition of this channel attenuates K^+ buffering and enhances BDNF expression and neuronal excitability (Ohno et al., 2018).

BDNF

GAAs induce neurotoxicity through a variety of molecular mechanisms, including alterations in apoptosis-related genes and the secretion of cytokines and neurotrophic factors (Zuo et al., 2016). BDNF is a crucial regulator of neural circuit development and brain function, neuronal differentiation and growth, synapse formation and plasticity, and higher cognitive functions such as learning and memory (Park and Poo, 2013).

BDNF exerts its opposite effects by acting on two receptor systems, tropomyosin-related kinase B (TrkB) and p75 neurotrophin receptor (P75NTR) (Liu et al., 2021). Mature BDNF promotes synapse formation, maintains synaptic stability, and mediates long-term potentiation by activating the TrkB receptors (Notaras and van den Buuse, 2019). A study found that propofol reduced BDNF secretion from astrocytes and induced neuronal death through the Akt/GSK3β/mitochondrial fission signaling pathway. BDNF supplementation alleviated this alteration (Liu et al., 2017). The neuroprotective function of astrocytes is mediated through BDNF-TrkB signaling that attenuates propofol-induced neuronal death. BDNF induces PI3K activity via TrkB receptors and activates Akt signaling to protect developing neurons (Sossin and Barker, 2007). These findings suggest that BDNF increased cell survival through enhancing Akt phosphorylation and its downstream p-GSK3β (Liu et al., 2017). Although this is not the only pathway through which propofol exerts multiple effects, it also provides a potential strategy to study anesthetic-induced neurotoxicity in the developing brain.

ProBDNF is unprocessed BDNF that induces long-term depression and postsynaptic neuronal death after binding to neuronal P75NTR (Gibon and Barker, 2017). Expression of p75NTR is low under normal physiological conditions and upregulated under pathological conditions such as inflammation or epilepsy (Podyma et al., 2021). GAAs induce neurotoxicity in the developing brain by reducing proteolytic cleavage of proBDNF, enhancing postsynaptic proBDNF/p75NTR binding, and causing synaptic abnormalities and neuronal death (Head et al., 2009). Astrocytes express p75NTR, which rapidly internalizes proBDNF removing it from the extracellular space (Bergami et al., 2008). *In vitro* studies have found that co-culture with astrocytes reduced neuronal death after exposure to isoflurane, while proBDNF levels and neuronal death were increased after inhibition or knockout of astrocytic p75NTR. Thus, astrocytic p75NTR may exert a neuroprotective effect by binding to proBDNF to reduce neuronal p75NTR binding to proBDNF, thereby preventing isoflurane related neurotoxicity in the immature brain (Stary et al., 2015).

Co-culture of astrocytes exposed to isoflurane (2.4% for 5 hours) with unexposed neurons demonstrated a significant reduction in BDNF levels and a 30% reduction in axonal growth (Ryu et al., 2014). By contrast, exogenous supplementation of BDNF eliminated this effect on axons. Isoflurane may indirectly induce neurological dysfunction by acting on astrocytes to reduce BDNF levels and inhibit axonal growth in co-cultures. Another study showed that astrocytes exposed to isoflurane (1.4% for 4 hours) had reduced astrocytic skeletal protein expression, but no reduction in BDNF levels (Culley et al., 2013). This difference is likely attributable to the concentration and dose of GAAs as well as cell culture medium conditions.

Energy (lactate) metabolism

Astrocyte-derived lactate drives neuronal activity and is the primary neuronal energy substrate (Barros et al., 2023). Our current understanding is that glial cells process glucose mainly by glycolysis, a process triggered by glutamate, $NH4^+$, NO, and K^+, producing lactate and pyruvate (Magistretti and Allaman, 2018). In contrast, during hypermetabolic activity, stimulation by neuromodulators such as noradrenaline, vasoactive intestinal peptide, adenosine, and K^+, glycogen stored in astrocytes can be broken down into L-lactic acid providing an energy substrate for neurons (Suzuki et al., 2011).

After anesthesia induction in neonatal mice, lactate levels in cortical astrocytes decreased rapidly (Sotelo-Hitschfeld et al., 2015; Ramadasan-Nair et al., 2019). A similar study has been reported in adult rats, where examination of cortical and brainstem slices showed that etomidate, thiopental, and propofol decreased the rate of glycolysis and the amount of lactate released (Hadjihambi et al., 2020). These data confirm that GAAs interfere with glycolysis and lactate production/release from astrocytes. Release of lactate from astrocytes plays a vital role in forming long-term memory and maintaining synaptic long-term potentiation (Suzuki et al., 2011). Thus, this may explain the involvement of astrocytes in inducing amnesia during anesthesia. Lactate is supplied to neurons by adjacent astrocytes after glycolysis and can be released through transmembrane monocarboxylate transporters (MCT1 and MCT4), high-capacity cation channels, and pannexins (Magistretti and Allaman, 2018). Therefore, GAAs may inhibit lactate release by acting on these lactate release pathways. NADH and ATP can be produced after lactic acid metabolism. NADH can regulate the activity of NMDA receptors, affect the Ca^{2+} signal and intracellular signal cascade, and the expression of genes related to cellular plasticity (including cytoskeleton-related genes and BDNF; Yang et al., 2014). These mechanisms reinforce the concept of GAAs interacting with glial cells described in our review.

HCs and gap junctions

Astrocytes are coupled to each other through gap junctions (GJs) to form a syncytium-like network (Totland et al., 2020). Connexin 43 (Cx43) functions as a transmembrane protein that is the primary component of HCs and GJs. It is responsible for intercellular electrical coupling and allows diffusion of nutrients and ions between astrocyte networks (Martins-Marques et al., 2019; **Figure 2**).

It has been reported that GAAs inhibit the function of GJs in astrocytes. Propofol and etomidate significantly reduced the permeability of GJs. Halothane, enflurane, and isoflurane induced closure of GJs in a dose-dependent and reversible manner (Mantz et al., 1993). GAAs significantly inhibit the activity of HCs and gap junctional intercellular communication in astrocytes induced by endotoxin LPS and proinflammatory cytokines. In addition, it was shown that propofol produced a more substantial inhibitory effect than ketamine and dexmedetomidine in this regard (Liu et al., 2016). An autogenous orthotopic liver transplantation study found that propofol protected BEAS-2B cells from LPS-induced injury by inhibiting GJs-Cx43 (Yuan et al., 2016). This suggests that GAAs have a protective effect on the organism during organ transplantation by inhibiting GJs.

Astrocytes can release gliotransmitters and neuromodulators, including glutamate, D-serine, and lactate, via functional HCs, a pathway known to be involved in memory formation (Pan et al., 2015; Karagiannis et al., 2016). Blocking Cx43-HCs can cause short- and long-term fear memory deficits (Linsambarth et al., 2022). Thus, inhibition of Cx43-HCs in astrocytes by GAAs may contribute to the induction of amnesia during anesthesia. Inflammatory factors and transmitters released by astrocytes during chronic pain can be released via HCs (Huang et al., 2021), and the expression of connexins in astrocytes increases after nerve damage (Ji et al., 2019).

Cx43-HCs induce neuroinflammation by releasing inflammatory mediators, and inflammation-induced cognitive dysfunction is closely associated with elevated IL-6 and IL-1β (Osso and Chan, 2015; Patterson, 2015). Long-term exposure to isoflurane reduced GJs-Cx43 in the hippocampus and primary astrocytes, increased the activity of Cx43-HCs, elevated the release of IL-1β and IL-6, and induced cognitive dysfunction in mice (Dong et al., 2022). This suggests that the astrocyte network mediated by GJs-Cx43 is involved in isoflurane-induced cognitive dysfunction.

MicroRNAs and related signaling pathways

MicroRNAs, small endogenous non-coding RNAs, negatively regulate target gene expression (Abe and Bonini, 2013; Martinez and Peplow, 2023). MicroRNAs play a vital role in regulating ketamine and propofol-induced neurotoxicity (Bosnjak et al., 2016). Thirteen miRNAs demonstrate significant differences in expression in hippocampal astrocytes of the developing brain after short-term exposure to high concentrations of propofol (10 μg/mL for 1 hour), and long-term exposure to low concentrations of propofol (0.9 μg/mL for 48 hours). Among them, the expression of miR-665 was significantly increased, which is involved in inducing astrocyte death by inhibiting the expression of the anti-apoptotic gene Bcl-2-like protein 1 (BCL2L1) and increasing the expression of caspase-3 in immature astrocytes *in vitro* (Sun et al., 2015). BCL2L1 is cleaved by caspase in the loop region inducing the apoptotic process. Thus, miR-665 negatively regulates the regulation of BCL2L1 and is involved in propofol-induced astrocyte apoptosis through a caspase-3-mediated mechanism. In addition, regulation of microRNA in astrocytes by propofol induced upregulation of miR-206 in glioma cells (Wang et al., 2020). MiR-206 has been shown to silence the expression of Cx43 by targeting the 3' un-translated region of Cx43 (Li et al., 2017).

Inhalation Anesthetic Agents

Sevoflurane

The effects of sevoflurane on astrocytes are reflected in its disruption of morphology and proliferation of astrocytes on the one hand and the regulation of astrocytes function on the other. Sevoflurane can not only inhibit the expression of ezrin by disrupting the homeostasis of Ca^{2+} in astrocytes and thereby affecting the morphological maturation of astrocytes (Zhou et al., 2019) but also inhibit the proliferation and maturation of astrocytes by interfering with the JAK/STAT pathway (Wang et al., 2016). All of these adversely affect astrocyte development and maturation as well as synaptogenesis and even neurobehavior.

$GABA_A$ receptors, an important target of sevoflurane in neurons, are also expressed in astrocytes (Garcia et al., 2010; Verkhratsky and Nedergaard, 2018). Evidence suggests that sevoflurane can increase the function of astrocytic $GABA_A$ receptors in the hippocampus (Chung et al., 2021). This increases the likelihood that $GABA_A$ receptors in astrocytes will interact with GAAs and become upstream signals to trigger the release of soluble factors and alterations in ion signaling. The glutamate transporter protein GLAST is predominant in astrocytes, and disruption of glutamate homeostasis is responsible for the pathogenesis of many neurological disorders. Sevoflurane (2.5% for 6 hours) exposure significantly reduced the number of astrocytes and the expression of GLAST (Wang et al., 2016). Inhibition of astrocytes by sevoflurane will lead to increased extracellular glutamate concentration that, in turn, can induce excitatory neurotoxicity, enhance the effects of GAAs on developing neurons, and induce neuronal death.

Surgery may be the main cause of Aβ increase, and sevoflurane (2.5% for 2 hours) increases the elimination of Aβ by up-regulating aquaporin-4 in astrocytes, which is the key component in the glymphatic system (Gao et al., 2019). Similarly, sevoflurane (3% for 2 hours) reduced the release of pro-inflammatory factors through inhibition of the TLR4/NF-κB pathway in rats with transient cerebral ischemia (Hwang et al., 2017). These evidences suggest that sevoflurane has some neuroprotective effects, which may be closely related to the anti-inflammatory effects of sevoflurane. The same GAAs produce both protective and neurotoxic effects, suggesting that despite the same signaling pathway, the effects on the pathway may not be identical at different concentrations of GAAs or under different physiological or pathological conditions.

Isoflurane

Similar to sevoflurane, isoflurane interferes with the morphology and formation of astrocytes and astrocyte network, mainly by damaging the actin cytoskeletons to damage the development of immature astrocyte α-tubulin and redistributed F-actin (Lunardi et al., 2011). However, evidence suggests that repeated developmental exposures to isoflurane are strongly associated with impaired visual recognition memory, learning disabilities, and attention-deficit/hyperactivity disorder, as well as reduced social behavior and increased anxiety-related behaviors that correspond to astrocyte proliferation in the corresponding brain regions, respectively, that may impair normal functioning by affecting the development of key brain regions and their connections (Neudecker et al., 2021). The reasons for the different results of changes in the number of astrocytes may be closely related to the dose of isoflurane, age of exposure, and animal model used. In addition, isoflurane interfered with astrocyte network communication promoting neuroinflammation and cognitive deficits by decreasing GJs-Cx43 expression in the hippocampus and enhanced HCs activity (Dong et al., 2022).

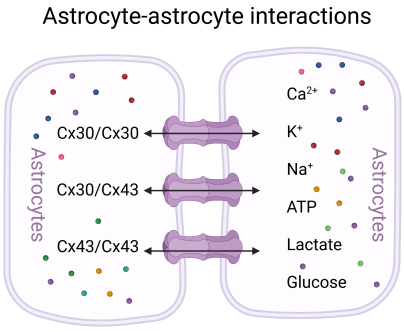

Figure 2 | **Communications between astrocytes.**
Information transfer between astrocytes can take place through the exchange of Ca^{2+}, K^+, Na^+, ATP, lactate, and glucose via channels composed of connexin (Cxs). Created with BioRender.com.

Isoflurane can significantly inhibit induced calcium transients in astrocytes at sub-anesthetic doses, but neurons showed low sensitivity to isoflurane (Schummers et al., 2008). The high sensitivity of astrocytes to isoflurane determines complex changes in Ca^{2+} activity. Spontaneous Ca^{2+} activity of astrocytes in the somatosensory cortex was reduced by approximately 85% under isoflurane anesthesia and by 55% in the hippocampal and cortical brain slices when compared to awake mice (Mulkey et al., 2022).

Intra-astrocytic Ca^{2+} signaling exists in the form of intrinsic oscillatory, propagating waves, and dynamic alterations in Ca^{2+} in the microdomains (Khakh and McCarthy, 2015). Thus, the effects of anesthesia on this primary mode of communication will inevitably interfere with the communication between astrocytes and astrocytes and between astrocytes and corresponding neurons. as well as corresponding neuronal signaling and other changes in the extracellular environment. Isoflurane affects the expression of membrane receptors and channels in astrocytes, not only triggering cell-surface expression of $\alpha5GABA_A$-Rs but also inhibiting Kir4.1/5.1 and up-regulating TREK-1 channels, which would further disrupt the astrocyte functional expression (Zurek et al., 2014; Zhou et al., 2017; Ou et al., 2020). Isoflurane can be indirectly involved in cognitive dysfunction by inhibiting axonal growth through decreased BDNF expression in astrocytes, a process that may be mediated through TREK-1 channels (Zhou et al., 2017).

For established neurodegenerative lesions, GAAs may exert neuroprotective properties. Astrocytes use the multiple EGF-like domains 10 pathway to assist in the elimination of synapses through a phagocytic mechanism (Chung et al., 2015). Recent research shows that isoflurane can attenuate the enhancement of $A\beta_{1-42}$-induced synaptic elimination in hippocampal brain slices *ex vivo*, possibly through the downregulation of multiple EGF-like domains 10 (Shi et al., 2023). These results provide evidence that isoflurane does not trigger or promote the pathogenesis of Aβ-derived Alzheimer's disease and provides a new direction for the protective role of isoflurane.

Intravenous Anesthetic Agents

Propofol

Propofol exerts its anesthetic effects primarily through agonism of GABA and NMDA receptors. These two types of receptors expressed in astrocytes may determine that astrocytes have an important role in propofol anesthesia (Liu et al., 2017). In addition, propofol promotes neuronal death at least in part by reducing the secretion of BDNF in astrocytes, and astrocyte BDNF-mediated cell survival pathways may have significant potential in attenuating propofol-induced neurotoxicity (Liu et al., 2017).

Propofol protects astrocytes from LPS and related inflammatory factors by inhibiting Cx43 including GJs and HCs in astrocytes (Yuan et al., 2016). One hypothesis on the protective effects of propofol suggests that propofol promotes the degradation of Cx43 resulting in the attenuation of the transport of intercellular reactive oxygen species (Yuan et al., 2019). Propofol has also been demonstrated to prevent oxidative stress-induced apoptosis by inducing autophagy (Yoon et al., 2017). Therefore, whether propofol promotes the degradation of Cx43 in damaged astrocytes by inducing autophagy is worth exploring. Another hypothesis suggested that propofol interferes with post-translational Cx43 modifications. Biochemical and immunohistochemical analyses have demonstrated that propofol did not alter protein expression levels of Cx43 or its incorporation into GJ plaques (Nuriya et al., 2018). It did, however, change the migration pattern of Cx43. This confirms that post-translational modifications occurred (Nuriya et al., 2018).

Propofol has an anti-inflammatory effect that attenuates LPS-induced astrocyte activation and subsequent inflammatory response by inhibiting TLR4/MyD88-dependent NF-κB, extracellular signal-regulated protein kinases 1/2, and p38 mitogen-activated protein kinase pathways (Zhou et al., 2015). Interestingly, this anti-inflammatory effect was only significant when using clinically relevant concentrations (10 μM) of propofol. The same result was confirmed in another study (Liu et al., 2012). High concentrations of propofol (300 μM), on the other hand, increased astrocyte TNF-α secretion (Liu et al., 2012). Paradoxically, propofol (30 and 300 μM) did not affect LPS-induced nitrite or TNF-α production in primary cultures of rat glial cells (Shibakawa et al., 2005). The reasons for these contradictions may be attributed to the different concentrations of propofol and LPS and the use of different types of cell models. It is also worth noting that propofol induces apoptosis and necrosis in astrocytes by affecting interference with micoRNA expression, and the mechanism needs to be further explored (Sun et al., 2015).

Ketamine

Ketamine, an NMDA receptor antagonist, may inhibit astrocyte-mediated synchronization of SICs through extrasynaptic NMDA receptors (Zhang et al., 2019). It is noteworthy that low doses of ketamine were sufficient to inhibit spontaneous calcium transients and SICs in astrocytes without affecting neuronal activity, further suggesting that astrocytes appear to be more sensitive to ketamine (Thrane et al., 2012; Zhang et al., 2019). Similar to the significant inhibitory effect of propofol on GJs and HCs, ketamine has a stronger inhibitory effect on HCs at 50 μM rather than at clinical doses (< 50 μM), with a reduction of approximately 60% (Liu et al., 2016). Since GJs and HCs are involved in the propagation of calcium waves between astrocytes (Scemes and Giaume, 2006; Leybaert and Sanderson, 2012), this may be one of the mechanisms by which high doses of anesthetics affect calcium signaling in astrocytes.

Ketamine reduced secretion of BDNF in neurons and astrocytes and increased the expression of BDNF-antisense and the secretion of pro-BDNF in astrocytes (Penning et al., 2021). Briefly, BDNF-antisense is closely associated with CNS damage, Parkinson's disease, and other CNS pathology (Ghafouri-Fard et al., 2021). This suggests that BDNF is involved in ketamine-induced neurotoxic effects in the developing brain. In addition, ketamine treatment of astrocytes induced alterations in the function of extracellular vesicles. Abnormalities in extracellular vesicle function will play a role in neuronal death by altering neurotransmitter release (Penning et al., 2021). Dexmedetomidine, however, promotes the release of BDNF from astrocytes and alleviates memory and cognitive deficits after etomidate anesthesia (Wang et al., 2018). These results emphasize the complexity of the effects of GAAs on astrocytes.

Limitations

This review has some limitations. First, the topic of the effects of GAAs on astrocytes has attracted the attention of neuroscientists, and therefore there is a massive amount of related literature already available with great potential for further accelerated growth. Second, in this review we have mainly focused on the neurotoxicity pathways of GAAs through astrocytes; in fact, the effect of GAAs on astrocytes is not only limited to neurotoxicity but also contributes to the induction and maintenance of the anesthetic state, but there is still a lack of research on this aspect. Third, glial cells are crucial for the formation and maintenance of homeostasis in the CNS, and the various types of glial cells are so closely connected that the fulfillment of their functions is often the result of interactions; however, GAAs do not only act on astrocytes, rather also on other glial cells with different results. Therefore, it is important to categorize and discuss the effects of GAAs on different glial cells.

Conclusion

GAAs not only disrupt the morphology and proliferation of astrocytes but also affect connexins and intracellular Ca^{2+} signaling, thereby interfering with cell-to-cell signaling. GAAs can also affect the release of gliotransmitters, cytokines, and neurotrophic factors by acting on GABA, NMDA receptors, and K^+ channels in astrocytes. For example, GAAs can interfere with cognition and memory formation by affecting the release of BDNF and lactate. In addition, GAAs may be involved in mediating the pro-inflammatory/anti-inflammatory processes in astrocytes as well as promoting astrocyte apoptosis by affecting the expression of microRNAs. Numerous *in vivo* and *in vitro* studies have demonstrated that commonly used anesthetics can target astrocytes through multiple signaling pathways, thereby participating in anesthetic effects or inducing neurotoxicity (**Figure 3** and **Table 1**).

Future Directions

Astrocytes are not simply a homogeneous population of cells in the brain. They are an integral part of the structure and function of the CNS. Alterations in their messaging and homeostasis can trigger a pathological cascade. Currently, most studies involving astrocytes have chosen to broadly target molecular markers such as GFAP, GLAST, glutamate transporter 1, and Cx43. Astrocytic transcriptome analysis has confirmed the region-specific nature of astrocytes, with different stimuli altering the transcriptional profile of astrocytes. Astrocytes have multiple phenotypes in the central nervous system. Examination of their function in specific brain regions, under a variety of conditions (anesthesia, disease, and pathological states) will help to reveal the molecular basis of astrocyte responses. This information has great potential in preventing disease progression. Thus, an in-depth understanding of specific astrocytic transcription factors and subpopulations will aid the emerging field of research on astrocyte diversity. The emerging human-induced pluripotent stem cell is being applied as a new tool for astrocyte research promising a better understanding of astrocyte differentiation, heterogeneity, and function. It is also an excellent target for drug discovery and development.

Although the mechanisms by which GAAs interact with neurons via astrocytes have not been fully explained, it is undeniable that interventions targeting astrocytes hold promise for reducing anesthetic-induced neurotoxicity as well as potential applications for the treatment of neurological and psychiatric disorders.

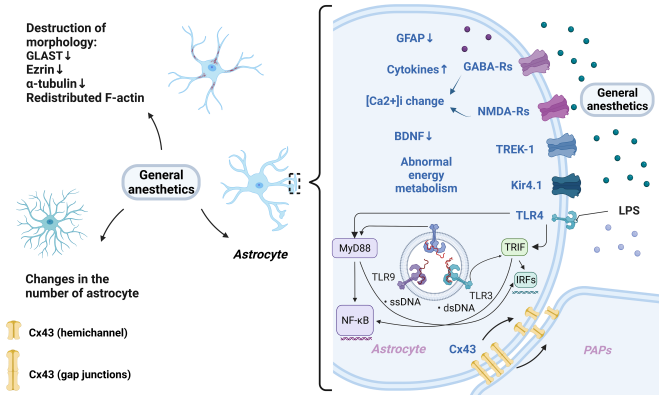

Figure 3 | **Diagrammatic representation of functional changes in astrocytes after general anesthetic agents (GAAs) exposure.**
GAAs can destroy the morphology of astrocytes and change their number. They not only decrease the expression of GLAST and GFAP but also act on a variety of receptors (GABA and NMDA receptors) and channels (TREK-1 and Kir4.1) in astrocytes. Activation of receptors triggers altered calcium signaling, affecting the release of glial transmitters, cytokines, and BDNF. GAAs can induce inhibition of glycolysis and production/release of lactate in astrocytes and interfere with memory function. And they are involved in activation/inhibition of NF-κB signaling to induce pro-inflammatory/anti-inflammatory effects in astrocytes. In addition, exposure to GAAs induces down-regulation of Cx43 gap junctions and impairs the astrocyte network. Created with BioRender.com. BDNF: Brain-derived neurotrophic factor; Cx: connexin; GABA-R: γ-aminobutyric acid receptor; GFAP: glial fibrillary acidic protein; GLAST: glutamate-aspartate transporter; IRF: interferon regulatory factor; Kir: inwardly rectifying K^+; LPS: lipopolysaccharide; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor-kappaB; NMDA-R: N-methyl-D-aspartate receptor; PAP: peripheral astrocyte process; TLR: Toll-like receptor; TREK-1: TWIK-related potassium channel-1; TRIF: Toll/IL-1R domain-containing adaptor-inducing IFN-beta.

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