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REVIEW ARTICLE

The Effects of General Anesthetics on Synaptic Transmission

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Abstract: General anesthetics are a class of drugs that target the central nervous system and are widely used for various medical procedures. General anesthetics produce many behavioral changes required for clinical intervention, including amnesia, hypnosis, analgesia, and immobility; while they may also induce side effects like respiration and cardiovascular depressions. Understanding the mechanism of general anesthesia is essential for the development of selective general anesthetics which can preserve wanted pharmacological actions and exclude the side effects and underlying neural toxicities. However, the exact mechanism of how general anesthetics work is still elusive. Various molecular targets have been identified as specific targets for general anesthetics. Among these molecular targets, ion channels are the most principal category, including ligand-gated ionotropic receptors like γ-aminobutyric acid, glutamate and acetylcholine receptors, voltage-gated ion channels like voltage-gated sodium channel, calcium channel and potassium channels, and some second massager coupled channels. For neural functions of the central nervous system, synaptic transmission is the main procedure for which information is transmitted between neurons through brain regions, and intact synaptic function is fundamentally important for almost all the nervous functions, including consciousness, memory, and cognition. Therefore, it is important to understand the effects of general anesthetics on synaptic transmission *via* modulations of specific ion channels and relevant molecular targets, which can lead to the development of safer general anesthetics with selective actions. The present review will summarize the effects of various general anesthetics on synaptic transmissions and plasticity.

Keywords: Neuropharmacology, general anesthetics, ion channels, neurotransmitter, synaptic transmission, synaptic plasticity.

1. INTRODUCTION

General anesthetics are an important kind of therapeutic medicine in clinical practice. The Lancet reports more than 300 million people to receive general anesthesia under various conditions every year all over the world [1]. While general anesthetics produce many similar endpoints and side effects such as loss of consciousness, immobilization, and amnesia, their chemical structures are quite varied (Fig. **1**). Besides the diversity of general anesthetic structure, the multiple potential molecular targets and the complex binding sites and interaction in a single target contribute to the main obstacles of uncovering the molecular mechanism of general anesthetics. General anesthetics can be divided into subcategories like volatile anesthetics (*e.g.* ether, halothane, isoflurane and sevoflurane) and intravenous general anesthetics (*e.g.* propofol, etomidate and ketamine). Despite the differential administration approach, both the volatile and intravenous general anesthetics are easy to cross the blood-brain barrier. The volatile anesthetics is barely metabolized and exhaled *via* respiratory airway, but the intravenous general anesthetics is mainly metabolized and eliminated from the body *via* the liver and kidney. Because almost all the general anesthetics are highly lipid-soluble, at the early stage of research, a non-specific theory such as the Meyer-Overton rule was the predominant hypothesis for a mechanism of action for general anesthetics, which indicated that actions of general anesthetics were mediated by interfering the neural membrane because of their lipid solubility [2]. However, the lipid theory cannot explain many facts of general anesthetic pharmacology. In fact, clinically relevant concentrations of general anesthetics minimally affect lipid bilayer properties while significantly interfering with the actions of various molecular targets [3, 4]. In addition, some general anesthetic derivatives such as non-immobilizers (Fig. **1B**, structurally similar to volatile anesthetics but cannot produce typical anesthetic actions like unconsciousness and immobility) are

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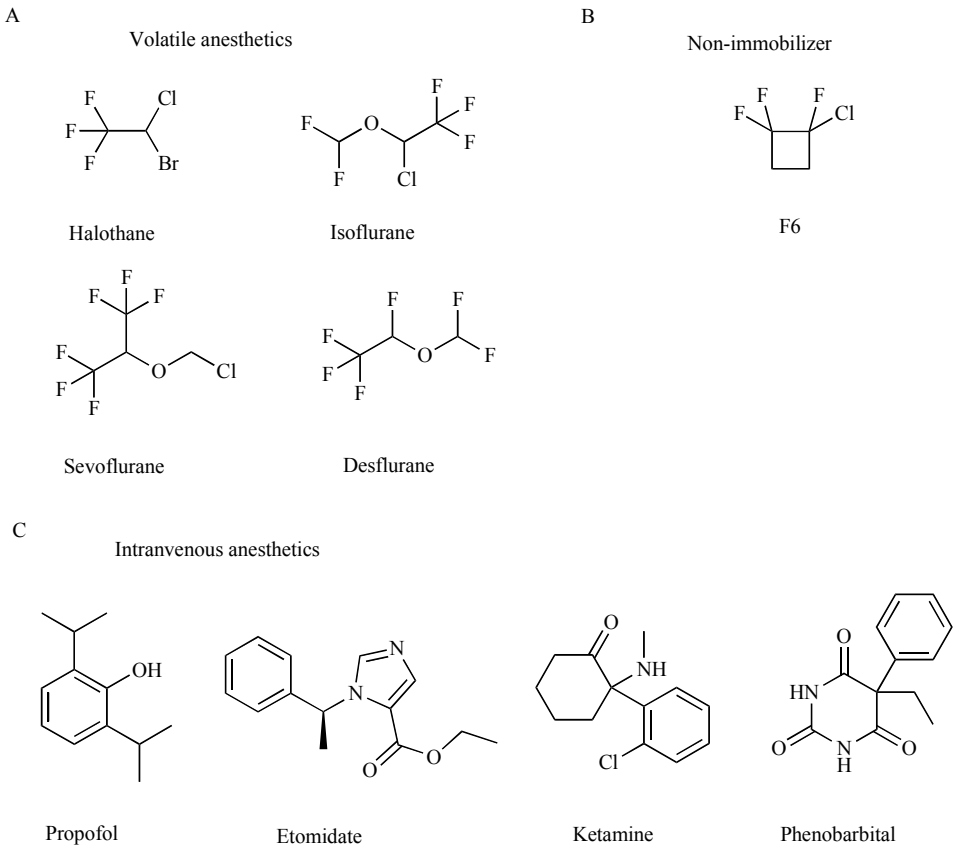

Fig. (1). Diverse structures of general anesthetics. A: Volatile anesthetics including halothane, isoflurane, sevoflurane and desflurane. The chemical name of halothane is 2-bromo-2-chloro-1,1,1-trifluoroethane, belongs to a different class of compounds than fluorinated ether for isoflurane, sevoflurane and desflurane. But they produce similar pharmacological actions including amnesia, hypnosis, unconsciousness and immobility. **B:** Commonly used tool drug for anesthetic research F6. F6 has similar physicochemical properties to volatile anesthetics, but F6 cannot produce general anesthetic actions including unconsciousness and immobility. These facts indicate that physicochemical property (*e.g.* lipid solubility) is not the determined mechanism for general anesthesia. **C:** Commonly used intravenous general anesthetics, including propofol, etomidate, ketamine and phenobarbital. The structures of these intravenous general anesthetics are varied while all induce unconsciousness. Nevertheless, the discrepancy in structure determined various mechanisms of general anesthesia by enhancing inhibitory neuron or inhibiting excitatory neuron, and even might be associated with other effect, such as sympathetic suppression or activation.

also highly lipid-soluble [5]. All these facts indicate that actions of general anesthetics involve specific neural substrate and/or molecular targets.

General anesthetics can affect various neural functions of the central nervous system and produce general anesthesia [5, 6]. Among the relevant functions of central nervous system, synaptic transmission is the main procedure for information transmission between neurons and/or other cells [7, 8]. Plasticity of synapses is the most important property for synaptic transmission, which is crucial for memory and other higher brain functions [9]. Typical transmission of the chemical synapse involves presynaptic and postsynaptic components. During a presynaptic action potential, voltage-gated Ca^{2+} channels at the active zone open, allowing Ca^{2+} to enter the presynaptic terminal. The rise in intracellular Ca^{2+} concentration triggers a biochemical reaction that causes the vesicles to fuse with the presynaptic membrane and release neurotransmitter into the synaptic cleft, a process termed exocytosis [10, 11] (Fig. **2A**). The transmitter molecules then diffuse across the synaptic cleft and bind to their receptors on the postsynaptic cell membrane, leading to the opening or closing of ion channels. The resulting flux of ions alters the membrane conductance and potential of the postsynaptic cell [12].

Specific actions of general anesthetics on synaptic transmission of different parts of the central nervous system can contribute to the differential pharmacological actions of general anesthetics as well as their underlying neural toxicities [13, 14]. Therefore, it is important to understand the exact actions of general anesthetics on synaptic transmission *via* modulations of specific ion channels and relevant molecular targets. Many efforts have been devoted to exploring how general anesthetics modulate synaptic transmission in defined neural pathways. The present review will briefly summarize the effects of various clinical used general anesthetics on synaptic transmissions and synaptic plasticity, which can contribute to development of novel general anesthetics.

2. PRESYNAPTIC ACTIONS OF GENERAL ANESTHETICS

Most general anesthetics depress excitatory transmission at clinical concentrations [15]. Synaptic actions of general anesthetics involve depression of fast excitatory and en-

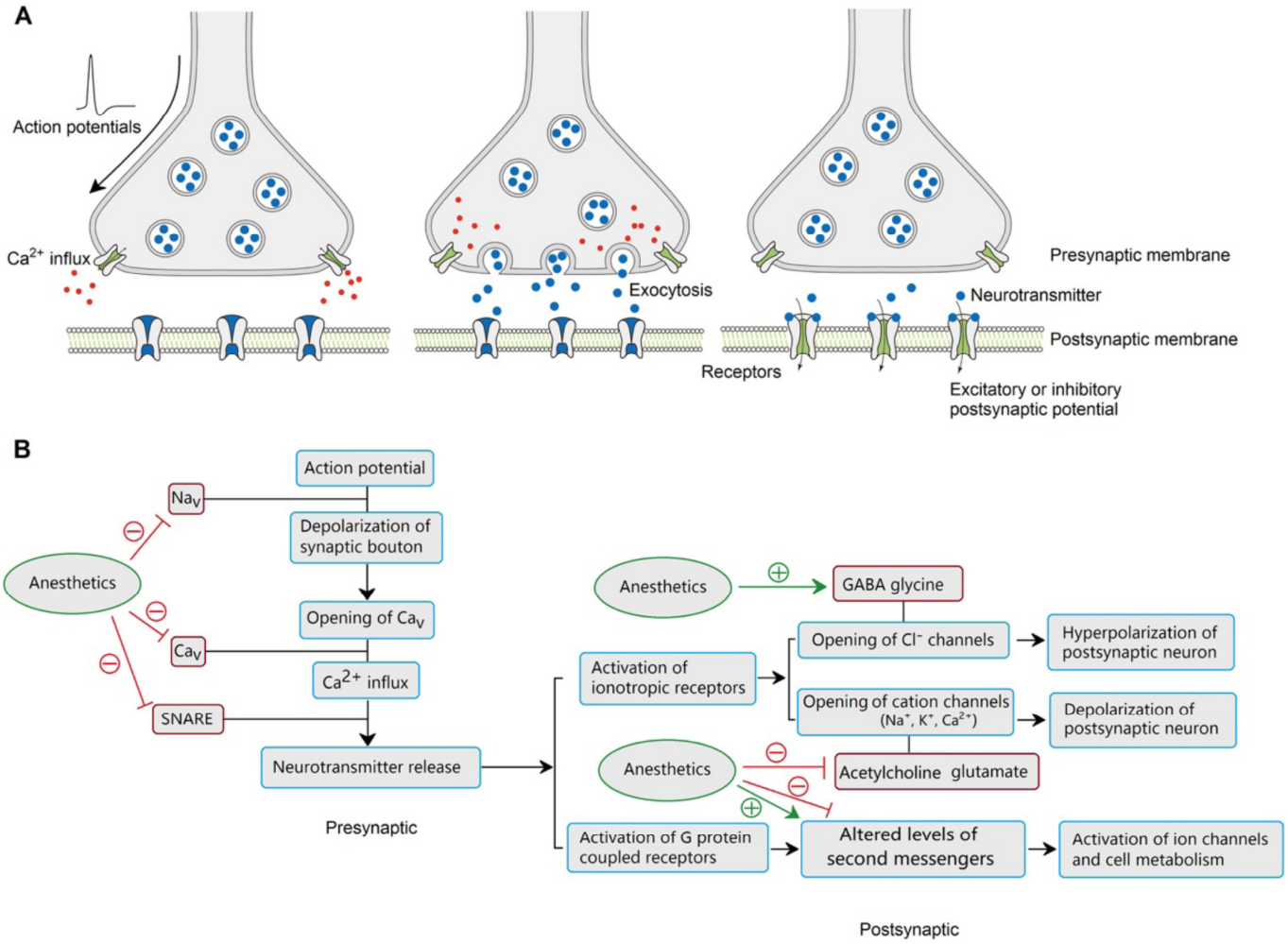

Fig. (2). Physiological process of synaptic transmission and possible synaptic targets for general anesthetics. A: Main process of chemical synaptic transmission in physiological condition. Action potentials mediated by voltage-gated sodium channel propagate to terminal boutons and depolarize the presynaptic membrane. The depolarization results in calcium influx and exocytosis for neurotransmitter release by vesicles fusion with presynaptic membrane. The released neurotransmitter binds and activates postsynaptic receptors, further lead to excitatory or inhibitory postsynaptic potential. **B**: Underlying targets for general anesthetics on synaptic transmission. Theoretically, all the components participating the synaptic transmission are possible targets of general anesthetics. General anesthetics modulate synaptic actions by both pre- (release) and post-synaptic (receptor) mechanisms. At presynaptic part, voltage-gated sodium channel (Na_v), voltage-gated calcium channel (Ca_v) and the soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) are key targets of general anesthetics to inhibiting neurotransmitter release. At postsynaptic part, general anesthetics act mainly by enhancing inhibitory neuronal receptor, such as γ-aminobutyric acid (GABA) and glycine receptors, or suppressing excitatory neuronal receptors such as glutamate and acetylcholine receptors [25]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

hancement of fast inhibitory synaptic transmissions [5]. Several effects of general anesthetics have been found to explain the depressant action on excitatory transmission, such as reduced membrane excitability [16, 17], reduced presynaptic action potential conduction [18, 19] and inhibition of transmitter release [20]. Postsynaptic receptors are also found as candidate targets of general anesthetics. Volatile anesthetics block postsynaptic glutamate receptors at some synapses [21]. Electrophysiological evidence supports that general anesthetics act on synapses by both pre- (release) and postsynaptic (receptor) mechanisms (Fig. **2B**) [22-25]. Although both pre- and post-synaptic targets are important to general anesthetic actions, it is not very clear about the relative importance between pre- and post-synaptic actions [26].

For pre-synaptic action, a decrease in the amount of transmitter secreted in response to each action potential can result from a number of different factors: general anesthetics could prevent action potentials fully invading the axonal arbour and thereby decrease the synaptic drive to the postsynaptic neurons [27, 28]. This can lead to the silencing of a proportion of the normal synaptic contacts and result in decreased excitation of the postsynaptic neurons. Alternatively, their effects might result from direct action on the process of exocytosis, either by inhibiting calcium entry into the presynaptic bouton or by direct action on the exocytotic machinery.

Presynaptic and postsynaptic effects might be differentially important in varied regions and actions of different

categories of general anesthetic effects in the central nervous system (CNS) [29-31]. Volatile anesthetics decrease excitatory postsynaptic potentials (EPSPs) in spinal and hippocampal neurons and decrease cortical neuron sensitivity applied glutamate due to a presynaptic mechanism [32]. For glutamatergic synaptic transmission, the presynaptic site might be the main target for general anesthetics [33]. Presynaptic effects are also important for intravenous general anesthetics in some conditions. Intravenous general anesthetics act on γ-aminobutyric acid (GABA) terminals at presynaptic sites to increase inhibitory postsynaptic currents (IPSC) frequency and GABA release [34]. By investigation of the effects of propofol and the barbiturate pentobarbital on neurotransmitter release by measuring Ca^{2+} concentration in the presynaptic nerve terminals (boutons), these intravenous general anesthetics were found to inhibit neurotransmitter release from the excitatory presynaptic nerve terminals by inhibition of Ca^{2+} influx evoked by high potassium [35].

In summary, both presynaptic and postsynaptic effects of general anesthetics are important for their synaptic actions. This section summarizes the presynaptic actions of general anesthetics on their cellular and molecular targets.

2.1. Presynaptic Effects of General Anesthetics on Neurotransmitter Release

Do general anesthetics inhibit the intracellular machinery that controls exocytosis? The basic mechanisms of different neurotransmitters release are relatively conserved [36]. Previous studies have found that general anesthetics did not alter the basal secretion of catecholamine or the neurotransmitter release evoked by calcium [37]. Consistent with this, Hemmings *et al*. reported that halothane did not inhibit the release of glutamate evoked by ionomycin (which directly raises the intracellular calcium concentration) from isolated synaptic terminals, although it did inhibit the secretion evoked by 4-aminopyridine (which induces secretion by depolarizing the nerve terminals) [38]. Recently, isoflurane was found to inhibit synaptic vesicle exocytosis through reduced Ca^{2+} influx, and not Ca^{2+}-exocytosis coupling [39]. These results suggest that general anesthetics inhibit Ca^{2+} influx rather than interfering with calcium influx induced intracellular events. Isolated neurohypophysial nerve terminals have been used to investigate the electrophysiological effects of general anesthetics on nerve terminals using whole-terminal patch-clamp recordings [19, 40]. These studies indicate that isoflurane inhibits Na^+ currents and action potential amplitude of nerve terminals by inhibiting voltage-gated sodium channel (Na_v) in isolated rat neurohypophysial nerve terminals [40], by which isoflurane can depress action potential-evoked synaptic vesicle exocytosis and excitatory postsynaptic current (EPSC) amplitude [41].

General anesthetics may also alter major neurotransmitter release in the central nervous system. Exocytosis imaging showed that isoflurane inhibits action potential evoked synaptic vesicle exocytosis in cultured rat hippocampal neurons [42]. This inhibition of glutamate release by volatile anesthetics may due to blockade of presynaptic Na^+ channels [43, 44]. The model drug non-immobilizer F6 (Fig. **1B**) produces no effect on neurotransmitter release and inhibition of Na_v at predicted anesthetic concentrations [44]. These results indicate the role of presynaptic Na_v in the modulation of glutamate release by volatile anesthetics. Voltage-gated calcium channels (Ca_v) in the hippocampus are relatively insensitive to isoflurane compared to Na_v [45, 46]. However, there is a study reporting that volatile anesthetics including isoflurane, enflurane, and halothane can also decrease Ca^{2+} transients and glutamate release possibly by specific Ca_v modulation in isolated cerebral synaptosomes [20]. In addition, other possible presynaptic mechanisms of general anesthetics may include the enhancement of glutamate uptake and the effects on vesicle fusion [47, 48]. Intravenous general anesthetics can also affect glutamate release. Propofol, thiopental, and ketamine were found to decrease K^+-evoked glutamate release from rat cortical slices [22]. General anesthetics, including halothane, enflurane, and sodium thiopental but not propofol were found to inhibit glutamate release from cortical slices during anoxia at clinical concentrations [49].

The effects of volatile anesthetics vary between transmitter types, which may contribute to the differential actions of volatile anesthetics on specific neural functions. Volatile anesthetics can inhibit evoked GABA release of rat cortical nerve terminals [50]. The volatile anesthetic isoflurane has greater selectivity for modulating glutamate release compared with GABA, acetylcholine, dopamine, and norepinephrine release, partly due to presynaptic specializations of ion channel expression, regulation, and coupling to exocytosis [39, 42, 51]. However, the exact mechanism for this selectivity is not fully clear yet. The intravenous general anesthetics, including propofol, etomidate, pentobarbital, but not ketamine, increase K^+-evoked GABA release in a concentration-dependent manner [34]. Halothane and isoflurane increase the basal release of dopamine while decrease the N-methyl-D-aspartate (NMDA)-evoked dopamine release by directly acting at dopamine terminals in striatal slices [52]. These effects may be mediated by both depression of presynaptic NMDA receptor responses and enhancement of GABA receptor responses. Volatile anesthetics, thiopental, and ketamine can affect both spontaneous and depolarization-evoked ^{3H}-dopomine (^{3H}-DA) release in the rat striatum, and enflurane uniquely increases dopamine release mediated by NMDA-receptor [53]. In contrast, halothane produces pre-synaptic inhibition of dopamine release, probably by modulation of the dopamine-2 receptor (D2-receptor) [54]. Dopamine transporters have also been suggested as possible targets of volatile anesthetics. Sevoflurane increases dopamine release in cortical brain slices, which is mediated by dopamine transporters located at the plasma membrane [55]. The dopamine transport of synaptosomes is reversibly inhibited by halothane and isoflurane [56]. In rat striatal slices, halothane increases acetylcholine release by decreasing dopamine release [57]. In addition, halothane and isoflurane differentially alter the presynaptic regulation of dopamine and GABA release mediated by presynaptic acetylcholine receptors in the rat striatum, suggesting that cholinergic transmission may be a potential presynaptic target for volatile anesthetics in the CNS [58]. The effects of classical volatile anesthetic isoflurane on GABA and glutamate release are shown in Fig. **3** and the summary of presynaptic effects of general anesthetics on neurotransmitter release is listed in Table **1**.

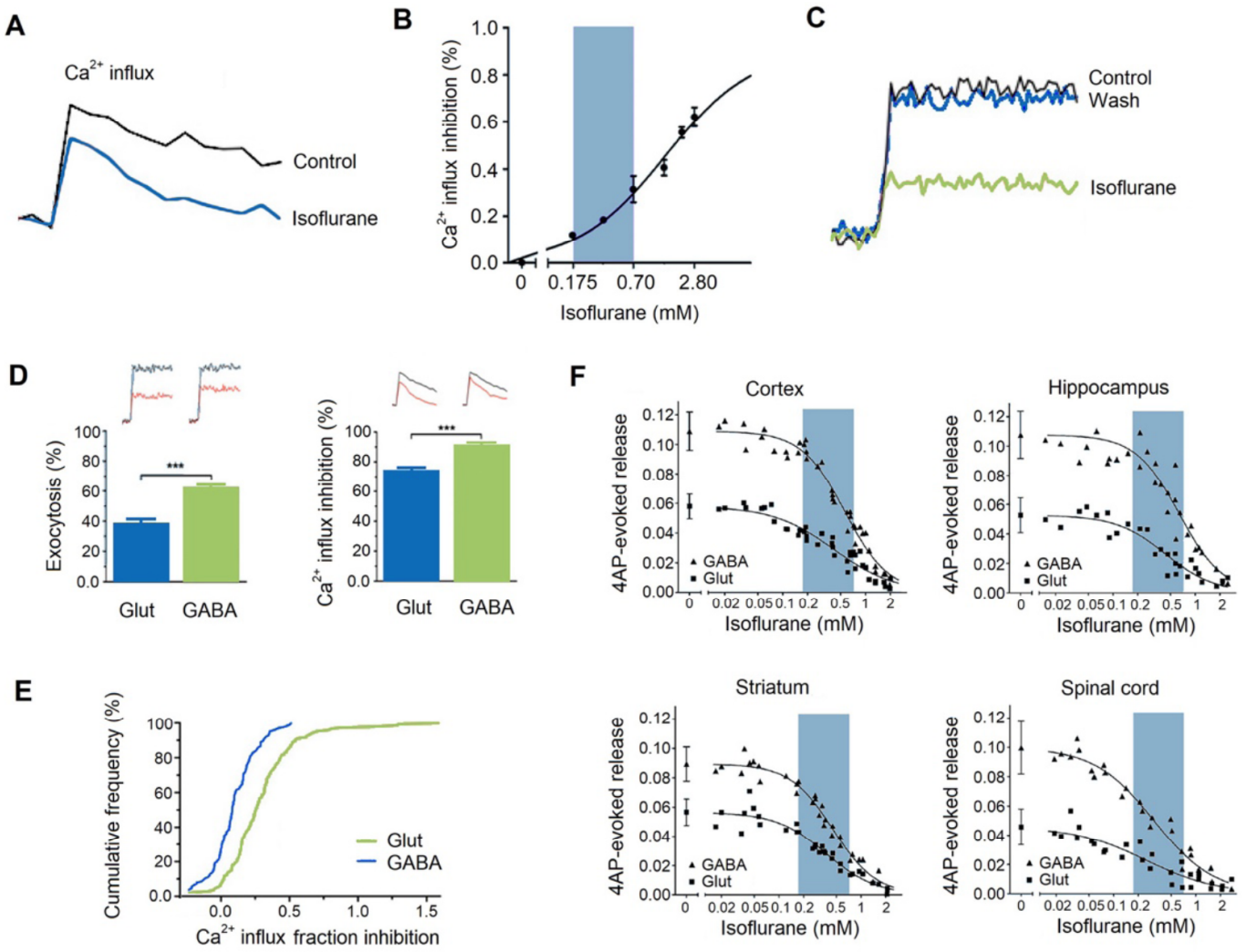

Fig. (3). Effects of isoflurane on GABA and glutamate release. A-B: Isoflurane inhibits calcium influx measured by fluorescence imaging of GCaMP3 **(A)**. Calcium influx is inhibited by isoflurane in a concentration-dependent manner. The blue bar indicates the clinically relevant concentrations of isoflurane (0.175-0.7 mM) **(B)**; **C**: Fluorescence imaging experiment demonstrated that isoflurane significantly depress exocytosis as measured by vGlut-pHlourin; **D-E**: The depression of isoflurane on exocytosis and Ca^{2+} influx is more potent for glutamate (Glut) than GABA [39]; **F**: The depression of isoflurane on 4AP-evoked release of glutamate and GABA are different in various part of central nervous system including cortex, hippocampus, striatum and spinal cord. The blue bar indicates the clinically relevant concentrations of isoflurane (0.175-0.7 mM) [62]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.2. Pre-synaptic Target of Na_v

Although early studies failed to demonstrate the significant role of Na_v for general anesthetics in myelinated axons [26], it has been identified that smaller diameter unmyelinated fibers and bare nerve terminals are more sensitive to Na_v block and do not retain conduction velocity as seen in myelinated nerves. It is now evident that clinical concentrations of volatile anesthetics inhibit Na_v in isolated rat nerve terminals [40, 72] and neurons [73-75], as well as in heterologously expressed mammalian Na_v subunits [76-80]. General anesthetics inhibit excitatory transmitter release in a Na_v dependent way. The action potential simulation evoked transmitter release is sensitive to volatile anesthetics, while high K^+-evoked transmitter release is relatively insensitive [50, 51], indicating that depressions in neurotransmitter release by volatile anesthetics involve inhibition of presynaptic action potentials as a result of Na_v blockade. There is also evidence to support that multiple sites of the Na_v are affected by general anesthetics [81, 82], which may contribute to the state-dependent modulation of Na_v by general anesthetics. This section will briefly review the role of Na_v mediating the anesthesia effects.

2.2.1. Na_v Channel Pharmacology

A variety of drugs and toxins, including local anesthetics, class I anti-arrhythmic drugs, and class I anti-epileptic drugs, exhibit a voltage-dependent and frequency-dependent block of Na_v [83]. These properties are conferred by different drug affinities for the various functional states of the Na_v: resting, open, and inactivated (Fig. **4A**). The Na_v family consists of nine homologous pores forming a subunit ($Na_v1.1$-$Na_v1.9$) with distinct cellular and subcellular distributions [84]. The

Table 1. Presynaptic effects of general anesthetics on neurotransmitter release.

			Volatile Anesthetics				Intravenous General Anesthetics			
			Sevoflurane	**Isoflurane**	**Halothane**	**Enflurane**	**Propofol**	**Etomidate**	**Ketamine**	**Thiopental**
	Brain region									
Glutamate	Cortex	Basal release		- [59]	- [59]	- [59]	N/A [49]			N/A [49]
		K^+-evoked release		- [20]	- [20]	- [20]	- [22]		- [22]	- [22]
		4AP-evoked release		- [51]	- [60]	- [60]	- [61]			
	Hippocampus	4AP-evoked release		- [62]						
		K^+-evoked release		- [63]			- [63]			
	Striatum	K^+-evoked release		- [63]			- [63]			
		4AP-evoked release		- [62]						
GABA	Cortex	Basal release	+ [64]	+ [59]	N/A [59]	N/A [59]	+ [34]			
		K^+-evoked release		N/A [62]			+ [34]	+ [34]	N/A [34]	
		4AP-evoked release		- [51]			- [50]			
	Hippocampus	4AP-evoked release		- [62]						
		K^+-evoked release		N/A [62]						
	Striatum	K^+-evoked release		N/A [62]						
		4AP-evoked release		- [62]						
Dopamine	Cortex	Basal release	+ [55]							
	Striatum	Basal release		+ [52]	+ [52]	+ [53]	- [65]		N/A [53]	N/A [53]
		NMDA-evoked release		+ [52]	+ [52]	+ [53]			- [53]	- [53]
		K^+-evoked release		- [51]			- [65]			
		4AP-evoked release		- [51]						
Acetylcholine	Cortex	Basal release		+ [66]	+ [57]		- [67]			
	Hippocampus	Basal release					- [67]		+ [68]	
	Striatum	Basal release					- [67]		N/A [68]	
		K^+-evoked release								
		4AP-evoked release								
Norepinephrine	Cortex	Basal release	+ [69]	+ [69]	+ [70]		+ [70]	N/A [70]	N/A [70]	
		Stimulus-evoked release			N/A [70]		- [70]	N/A [70]	N/A [70]	
	Hippocampus	K^+-evoked release		N/A [51]						
		4AP-evoked release		- [51]						
		Nicotinic evoked release		- [71]						
	Striatum	K^+-evoked release					- [65]			

4AP: 4-Aminopyridine; "+": Enhancement; "-": Inhibitory effect; "N/A": No effect.

gene names are referred to as SCN1A through SCN11A [84, 85]. The individual Na_v is distinguished not only by differences in their sequence but also by their kinetics and expression profiles. Most excitatory neurons express a high density of $Na_v1.6$ and $Na_v1.2$ [86, 87], while $Na_v1.1$ is preferentially expressed in inhibitory GABAergic interneurons [88, 89]. The differential inhibition of neuronal Na_v subtypes by general anesthetics might, therefore, lead to differential anesthetic effects on neurotransmitter release between excitatory and inhibitory synapses [39, 59, 79].

2.2.2. Testing the Relevance of Na_v as an Anesthetic Target

Axonal action potentials were initially reported to be relatively resistant to clinical concentrations of volatile anesthetics [90]. This is consistent with the relative insensitivity of sodium currents in squid [91] and crayfish giant axons

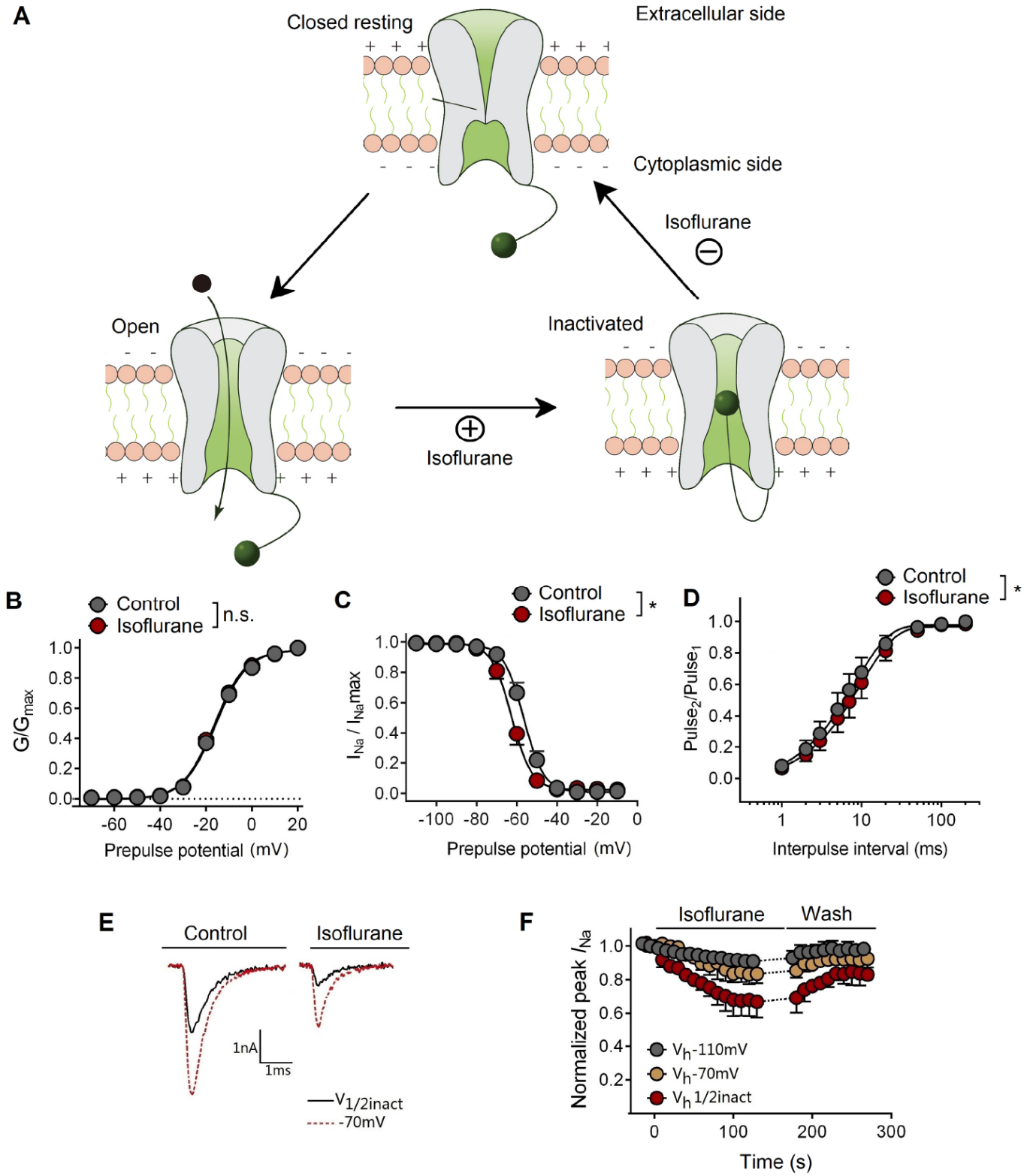

Fig. (4). Effects of isoflurane on voltage-gated sodium channels. A: Effects of isoflurane on voltage-gated sodium channel (Na_v) gating. Na_v typically exists in three states, resting, open and inactivated. Isoflurane can significantly stabilize inactivated state of sodium channels by facilitating voltage-dependent inactivation and delaying recovery from inactivation [79]; **B**: The effect of isoflurane on voltage-dependent activation of Na_v is insignificant; **C**: Isoflurane significantly hyperpolarized voltage-dependent inactivation curve of Na_v; **D**: Isoflurane significantly delay recovery of Na_v from steady-state inactivation; **E-F**: Voltage- and use-dependent inhibition of isoflurane on sodium peak currents. The inhibition of isoflurane on sodium peak currents is more potent from the depolarized holding potential ($V_{1/2inact}$) than physiologically relevant potential (-70 mV) [80]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

[92] to volatile anesthetics. These results established a widespread notion that clinical concentrations of general anesthetics do not act by blocking Na_v or any other voltage-gated ion channels [93]. However, axonal conduction in small (0.1-0.2 mm) unmyelinated hippocampal axons is significantly depressed by volatile anesthetics, and other small diameter structures such as nerve terminals might also be sensitive [18, 27]. Patch-clamp recordings of accessible nerve terminals have shown that isoflurane reduces action potential amplitude [19] and that reductions in nerve terminal action potential amplitude have significant effects on transmitter release and hence on synaptic transmission [46]. Potent volatile anesthetics inhibit native Na_v from isolated nerve terminals [40, 94], dorsal root ganglion (DRG) neurons and hippocampal neurons [75] while the non-immobilizer F6 is ineffective [44]. Isoflurane and other volatile anesthetics inhibit multiple mammalian Na^+ channel isoforms [77] including $Na_v1.2$ [79, 95], $Na_v1.4$ and $Na_v1.6$ [78, 96], $Na_v1.5$ [97], and $Na_v1.8$ [76]. Interestingly, recent studies indicate that the volatile anesthetic isoflurane differentially inhibits CNS Na_v subtypes: inhibition of peak I_{Na} by isoflurane is less pronounced for $Na_v1.1$ compared to $Na_v1.2$ or $Na_v1.6$ [80]. Because of the differential expression of specific Na_v subtypes between and within neurons, greater inhibition of $Na_v1.2$ and $Na_v1.6$ compared to $Na_v1.1$ could contribute to the region- and neurotransmitter-selective effects of volatile anesthetics on synaptic transmission. Volatile anesthetics suppress Na_v mainly by stabilization of inactivated state of Na_v and delay recovery from steady-state inactivation (Fig. **4B-D**) [80]. In addition to transit components of the Na_v current, isoflurane at clinically relevant concentrations also inhibits persistent component of Na_v currents on hippocampal pyramidal neurons, indicating that volatile anesthetics might directly modulate instinct excitability of presynaptic neurons [75].

Differently with the local anesthetics binding to the central cavity and causing open channel block of Na_v [82], molecular dynamics (MD) modeling studies with the tool of bacterial voltage-gated sodium channel (NaChBac) indicate that multiple sites of the channel are affected by volatile anesthetics, at least including the central cavity, channel S4-S5 linker, S6 interface and the selectivity filter [81, 98]. Notably, the volatile anesthetics interaction with the binding sites in the channel is conformation and concentration-dependent. Sevoflurane interactions in the S4-S5 linker were found only in partially activated/closed and activated/open states. The interaction in S4-S5/S6 interface affects inactivation and voltage-dependent activation by altering the coupling between the voltage sensor domain (VSD) and the pore [81, 99]. Occupying the central cavity and interacting with residues are suggested to be involved in the mechanism underlying the general anesthetics blocking the open channel, which act in higher concentration. The effect of potentiation at low concentrations (< 0.5 mM) and inhibition at high concentrations (> 1 mM) caused by sevoflurane indicates differential affinity of the interaction regions and an inhibitory combined net impact of these interactions [81]. Intravenous general anesthetics also inhibit Na_v. Generally, propofol has several mechanisms of actions [100], mainly including potentiation of the $GABA_A$ receptor by slowing the channel-closing kinetics [101, 102]. Propofol has also been identified to inhibit Na_v in a dose-dependent and reversible manner, which is known to inhibit glutamate release in synaptosomes, contributing to its anesthetic, anticonvulsant, and neuroprotective effects [40, 103]. Propofol inhibits brain Na_v expressed in a stably transfected Chinese hamster ovary cell line [104]. Besides the transient component of Na_v currents, propofol reduces both the duration and the number of spikes recorded from isolated cortical neurons, and consistently inhibits persistent Na_v currents with an IC_{50} at relatively low concentrations [105]. These results indicate that propofol may directly modulate neuronal excitability by inhibiting Na_v and preferably suppressing persistent Na_v currents [105]. Computational docking and MD simulation study revealed that a fluorinated propofol analogue, 4-fluoropropofol interacts in four binding sites of NaChBac, including the activation gate and selectivity filter in the pore, the voltage sensing domain, and the S4-S5 linker, however the extracellular interface of the pore domain might not be involved [106].

Etomidate can suppress the activity of cortical neurons [107]. However, the contribution of Na_v for etomidate anesthesia is somewhat controversial. Etomidate can dose-dependently inhibit Na_v currents of primary somatosensory cortex pyramidal neurons, while shifting the steady-state inactivation curve towards the left and prolonging the recovery time of Na_v from inactivation [108]. However, the effects of etomidate on neurotransmitter release mediated by sodium channels have not been demonstrated. Another study suggests that etomidate interacts with the sodium-conducting pathway of the channel causing a concentration-dependent block of the time-averaged sodium conductance with EC_{50} of 0.19 mM [109], which is above the clinically relevant concentrations of serum etomidate (up to 0.01 mM), suggesting a limited role for human sodium channels in the mechanisms of etomidate during clinical anesthesia.

Ketamine produces local anesthetic-like actions [110, 111]. Thus, Na_v is recognized as a molecular target of ketamine [112]. However, whether the effects of ketamine on Na_v are involved in its general anesthetic actions or merely for local anesthetic-like actions are unclear. Ketamine inhibits its Na_v conductance in a concentration-dependent manner in human neuroblastoma SH-SY5Y cells and on single human CNS sodium channels [113, 114]. Ketamine blocks tetrodotoxin (TTX)-resistant (TTX-r) Na_v on small DRG neurons in dose-dependent and use-dependent manner. The activation and inactivation properties of both TTX-sensitive (TTX-s) and TTX-r Na_v are sensitive to ketamine [115]. However, ketamine is less effective than lidocaine-like local anesthetics in stabilizing the inactivated state of Na_v.

2.3. Presynaptic Targets of Calcium Channels

Presynaptic calcium channels are important for the regulation of intracellular calcium concentration and calcium influx. The increase of intracellular free calcium levels gives rise to a range of calcium-dependent vital cellular processes such as neurotransmitter release, hormone secretion, and gene transcription [116-118]. The control of calcium homeostasis is precisely and complexly regulated by several important mechanisms, including voltage and ligand-gated calcium channels, sodium-calcium exchangers, calcium-ATPase, and

endoplasmic reticulum and mitochondrial calcium sequestration proteins [119, 120].

2.3.1. Testing the Relevance of Ca_v as an Anesthetic Target

There are at least five major classes of Ca_v (voltage-gated calcium channel), which are known as the L, N, P/Q, R and T subtypes [121]. Based on the degree of membrane depolarization required for activation, two main subtypes of voltage-gated calcium channels (Ca_v) are divided into: low voltage-activated (LVA, also T type) channels and high voltage-activated (HVA, also L type) channels [122]. According to distinct Ca_v subunits, T-type Ca_v is classified into $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$ isoforms at the sub-cellular level [123-125], which can act as a pacemaker to help trigger action potentials after membrane hyperpolarization [126, 127]. T-type Ca_v also contributes to repetitive spiking and bursting to regulate the normal physiological function, such as deep sleep [128]. L-type Ca_v is classified into $Ca_v1.1$ to 1.4 and mediates excitation-contraction coupling in cardiac, smooth, and skeletal muscle, involving regulation of transcription, endocrine secretion, and neuronal Ca^{2+} transients in cell bodies and dendrites. For other Ca_v subtypes, $Ca_v2.1$, $Ca_v2.2$, $Ca_v2.3$ are the representative subtypes of N-type, P/Q- type, R-type Ca_v, correspondingly, which are involved in the regulation of neurotransmitter release and dendritic Ca^{2+} transients [121].

Inhibition of Ca_v to reduce transmitter release has long been considered as plausible mechanism for general anesthesia [20]. Both volatile and intravenous general anesthetics can alter intracellular calcium concentration in various samples, including hepatocytes [129], mouse whole-brain synaptosomes [130], and rodent hippocampal slices [131]. Alteration of intracellular calcium concentrations induced by general anesthetics may increase potassium conductance that hyperpolarizes the cell and thus reducing the excitability of cells [120, 132]. However, the role of Ca_v in the effects of volatile anesthetics is controversial. Some researches point out either N or L calcium channels are insensitive to general anesthetics, while others found that Ca_v may be putative sites of intravenous general anesthetic action. In this section, we will focus on the function of neuronal Ca_v in mediating the effects of currently used general anesthetics.

Direct measurements of the calcium transients recorded from synaptic boutons have shown that Ca_v responsible for synaptic transmission are predominantly of the P/Q and N subtypes [133]. This is consistent with other pharmacological studies of synaptic transmission [134]. Do general anesthetics inhibit the activity of Ca_v for synaptic neurotransmission? There is no evidence to suggest a selective action of general anesthetics on either N or L calcium channels. P-type calcium channels are also relatively insensitive to a variety of general anesthetics [45]. Giving the importance of P/Q and N type calcium channels on the neurosecretion, these results suggest that depressant effects of general anesthetics on excitatory synaptic transmission are more likely to be caused by direct effects on other targets. However, three studies using quantal analysis have provided evidence that general anesthetics depress excitatory synaptic transmission by decreasing the action potential-evoked secretion of neurotransmitter [135-137]. These conclusions have been supported recently by direct measurement of the effect of pentobarbital on the amplitude of the calcium transients recorded in the presynaptic boutons [138]. This study shows a greater reduction in the calcium transients than expected, and probably reflects the involvement of calcium-induced calcium release in the presynaptic boutons [139]. As this is a positive feedback process, a small reduction in calcium entry could lead to a substantial decrease in the probability of transmitter release from a given synaptic bouton. Eventually, this would lead to a decrease in the excitatory synaptic drive to the postsynaptic neuron. To resolve the matter fully, there needs to be a closer examination of the relationship between the presynaptic calcium transients and the release of neurotransmitter.

The effects of volatile anesthetics on Ca_v were first described in cardiac papillary muscle where halothane inhibited slow calcium currents [140]. Other halogenated anesthetics including enflurane and isoflurane have been subsequently shown to inhibit electrically evoked calcium transients in the sinoatrial node [141]. Apart from cardiac L-type channels, neuronal calcium channels are proposed as important targets for the action of general anesthesia by the effects of volatile anesthetics on cell excitability and neurotransmission in the nervous system [20, 142, 143]. Halothane alters the intracellular free calcium concentration and glutamate release in Guinea pig cerebrocortical synaptosomes, thus depressing presynaptic transmitter release [20]. Isoflurane inhibits the peak amplitude of T-type calcium currents of native thalamocortical neurons in acute rat brain slices and decreases the activity of thalamic cells that might be pivotal to induce loss of consciousness and hypnosis of general anesthetics [144]. T-type calcium channel currents in thalamic neurons play a critical role in the generation of low-amplitude oscillatory bursting and are associated with the state of arousal and sleep, as well as seizures. Enflurane has been reported to block the T-type Ca_v current in nucleus reticularis thalami neurons [145]. Nitrous oxide completely blocks native T channels currents in reticular thalamic neurons with an IC_{50} of 20%, but does not affect Ca_v 3.3 calcium currents at higher concentrations [146]. In the mutant mice knockout T-type calcium channels, the median effective concentration (minimum alveolar concentration) of halothane for loss of righting reflex is not altered, although the onset of anesthesia is delayed [147]. Thus, the role that T-type channels play in the effects of volatile anesthetics is not clear.

For neuronal L-type Ca_v, halothane can reduce L-type currents in human neuronal cells primarily by decreasing the channel opening and enhancing the rate for channel closing and inactivation [148]. Isoflurane at concentration of 0.6 mM (~2 MAC) can inhibit $Ca_v1.1$ and $Ca_v1.2$ channels but not the non-immobilizer F6 in isolated cultured adult rat spinal cord motor neurons, suggesting that these channels may contribute to isoflurane-induced immobility [149]. Halothane (0.45 and 0.9 mM), isoflurane (0.54 and 1.23 mM), and enflurane (0.65 and 1.48 mM) reduce L-type Ca_v peak currents to a similar extent, but do not shift the current-voltage (I-V) relationship for L-type current activation [150]. In rat DRG neurons, isoflurane can (~1 MAC) inhibit L-, N- and P/Q-type Ca_v currents through enhancing current inactivation and prolonging recovery time after inactivation [151]. Since P/Q-

and N-type channels are the most important voltage-gated calcium channels involved in synaptic transmission in the mammalian brain, it is important to establish their sensitivity to clinically relevant concentrations of general anesthetics [152]. In mice lacking the N-type calcium channel, the sensitivity to halothane is significantly increased compared with the wild-type mice [153]. Recently study found that isoflurane inhibits exocytosis from dopaminergic neurons by a mechanism distinct from that in non-dopaminergic neurons involving reduced Ca^{2+} entry through $Ca_V2.1$ and/or $Ca_V2.2$ [154]. Isoflurane at a concentration of 0.31 mM (~1 MAC) only inhibited peak currents of N-type Ca_v by 14%, while the gas anesthetic xenon has no effect on N-type channels at a concentration of 3.4 mM (approximately 1 MAC) [155]. Halothane and isoflurane can also substantially inhibit the P-type channels currents on acutely dissociated cerebellar Purkinje neurons, but at concentrations much greater than those that are clinically relevant [45]. However, a research study reported that specific calcium antagonists of L-, N-, and P-type channels produced little effect on reversal of the actions of isoflurane and halothane on inhibition of calcium currents [156]. Therefore, the precise role of inhibition of HVA calcium channels by the actions of volatile anesthetics in the central nervous system is unknown. Interestingly, decreased sensitivity to halothane was found in mutant mice lacking the R-type channels both *in vivo* and in hippocampal slices, implying a possibility that this channel may be involved in cellular mechanisms underlying the effects of general anesthesia [157].

Propofol also produces significant inhibition of T-type calcium currents in the rat hippocampal neurons and in stably expressed HEK293 cells [158]. L-type calcium channels are also regarded as molecular target for intravenous general anesthetics, as propofol interacts with the L-type Ca_v alpha-subunit 1, 4-dihydropyridine binding site on rat's cerebrocortical membranes [159]. In spinal cord, propofol reduces the excitability of sensorimotor neurons by depressing plateau potentials mediated by L-type currents, which might contribute to the reduction of spinal activity during general anesthesia [160]. At clinically relevant concentrations, propofol inhibits glutamate release mainly due to direct suppression of P/Q-type voltage-sensitive calcium channels currents [45, 161]. However, another study showed that the substantial inhibition for P/Q-type channel currents is only found at a concentration much greater than clinically relevant, thus indicating that the P/Q-type channels may not play a major role in the mechanism of general anesthesia, including both volatile and intravenous anesthetics [45]. In knockout mice lacking the N-type Ca_v, the sensitivity to propofol is significantly decreased compared with the wild-type ones, suggesting that the inhibition of the N-type channel counteracts propofol anesthesia [157]. The role of R-type ($Ca_v2.3$) calcium channel was also indicated by the study of Takei *et al.*, which revealed that $Ca_v2.3$ knockout decreased the anesthetic sensitivity of propofol [157].

Several studies have found that ketamine can also act as a calcium channel antagonist to induce cerebral and pulmonary vasodilation [162-164]. Ketamine inhibits voltage-gated calcium channels to depress excitatory transmission through the P/Q-type calcium channels [161]. Ketamine blocks T-type calcium channels currents in transfected HEK293 cells and dorsal root ganglion [158]. Etomidate has been found to inhibit calcium channel currents in a concentration-dependent manner with a reduction in the probability of calcium channel opening and an increase in the rate of channel inactivation [142]. L- and T-type Ca_v are both the probable targets for etomidate [158, 159]. The anesthetic barbiturate thiopental at clinically relevant concentrations directly inhibits P/Q-type calcium [161]. Etomidate and thiopental interact with L-type channels alpha-subunit 1,4-dihydropyridine binding site, but not the verapamil-binding site in rat cerebrocortical membranes [159, 165]. Although voltage-gated calcium channels may be putative sites of intravenous anesthetic action, the neuronal calcium channels subtypes are less sensitive to intravenous general anesthetics.

In summary, varied general anesthetics including volatile anesthetics and intravenous general anesthetics have been found to modulate Ca_v (Table **2**). However, whether the effects of general anesthetics on neurotransmitter release are directly *via* inhibition of Ca_v is not fully clear. The involvement of Ca_v may differ among general anesthetics and between different brain regions and neurotransmitter types.

2.4. Presynaptic Targets of Potassium and other Ion Channels

Potassium channels stabilize the membrane potential by drawing the membrane potential closer to the K^+ equilibrium potential. General anesthetics can promote the opening of K^+ channels, enhancing K^+ currents, and thus producing a reduction in neuronal excitability that contributes to the transition to unconsciousness [183]. Generally, potassium channels can be divided into four subfamilies based on their similarity of amino acid sequences, including voltage-gated potassium channels (K_v), calcium-activated potassium channels (K_{Ca}), inward rectifier potassium channels (K_{ir}) and tandem pore domain potassium channels (K2P) [184]. Previous studies indicate that K2P and K_v are modulated by general anesthetics, which may contribute to the effect of immobilization and loss of consciousness of general anesthetics [185, 186]. However, the binding sites and molecular mechanism underlying general anesthetics modulating these potassium channels are not fully clear.

K2P channels expressed widely in the CNS contribute to background membrane conductance. TASK (Tandem of P-domains weak inward rectifying K^+ channel-related acid-sensitive K^+ channel) and TREK-1 (TWIK-related K^+ channel-1) are important mammalian K2P channels and activated by volatile anesthetics [186, 187]. Chloroform, diethyl ether, halothane and isoflurane activate TREK-1, whereas only halothane and isoflurane activate TASK. Activation of TASK-1 and TASK-3 potassium channels by volatile anesthetics and transmitter inhibition by these channels require a region at the interface between the final transmembrane domain and the cytoplasmic C terminus [188-190]. TASK channels in cholinergic neurons are molecular substrates for immobilization actions of volatile anesthetics [186]. TASK channels also contribute to the regulation of breathing during general anesthesia and may have therapeutic potential for treating breathing disorders [191].

Table 2. The effects of general anesthetics on Ca_v.

			Volatile Anesthetics				Intravenous Anesthetics			
Type	**Channel**	**Localization**	**Halothane**	**Isoflurane**	**Sevoflurane**	**Enflurane**	**Propofol**	**Ketamine**	**Etomidate**	**Thiopental**
T (LVA)	$Ca_v3.1$, $Ca_v3.2$, $Ca_v3.3$	Neuronal cell bodies and dendrites, cardiac and smooth muscles	- [147, 150, 166]	- [146, 147, 150, 158, 166-168]	- [147, 168]	- [146, 150, 166]	- [146, 158]	- [158]	- [146, 158]	- [169]
L (HVA)	$Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$	Neuronal cell bodies and proximal dendrites, cardiac and smooth muscles, and neuroendocrine cells	- [150, 156, 170-172]	- [150, 151, 156, 167, 168, 170, 173-177]	- [168, 171, 178]	- [150]	- [159, 160, 165, 179]	- [159, 165]	- [159, 165]	- [159, 165]
P/Q (HVA)	$Ca_v2.1$	Nerve terminals and dendrites, neuroendocrine cells	- [45, 156]	- [45, 151, 156, 173]	N/A	- [143]	- [45, 65, 161]	- [161]	- [180]	- [45, 161]
N (LVA)	$Ca_v2.2$	Nerve terminals and dendrites, neuroendocrine cells	- [156]	- [143, 151, 156, 173, 174, 181]	N/A	- [143]	- [182]	- [182]	- [182]	- [182]
R (LVA)	$Ca_v2.3$	Neuronal cell bodies and dendrites	- [157]	- [143]	N/A	- [143]	- [157]	N/A	N/A	N/A

"-": Inhibitory effect; "N/A": Not determined; Ca_v: voltage-gated calcium channel.

K_v has been proven to be the molecular targets for general anesthetics. Li *et al*. reported that isoflurane increases the open probability and unitary conductance of K_v channel (*ShakerB*) in Drosophila, mediating the potentiation of channel conductance [192]. Another Drosophila Shaker B K_v channel, K-Shaw2 is demonstrated to be inhibited by isoflurane, halothane, and propofol [193, 194]. However, sevoflurane was found to potentiate the K-Shaw2 conductance *via* shifting the conductance-voltage relation toward negative voltages and increasing the maximum conductance [195]. This discrepancy in modulating the K_v was suggested to be associated with differences in anesthetic structure and K_v channel structure and conformation [196]. The S4-S5 linker, S6-tail, and the S5 segment have been reported to be major interaction regions of K_v to general anesthetics [196]. The S4-S5 linker mutations of T330G in K-Shaw2 and G329T in $K_v1.2$ eliminate and enhance the sevoflurane-induced potentiation of the K-Shaw2, respectively [196, 197].

Besides above-mentioned ion channels, HCN (Hyperpolarization and cyclic nucleotide-gated) channels also contribute to the effects of general anesthetics [198]. HCN channels contribute to the sensitivity of general anesthetics, including volatile anesthetics, propofol and ketamine [185, 199, 200]. On molecular level, isoflurane inhibits HCN channel currents in motor and cortical pyramidal neurons. With this inhibition to HCN channels, isoflurane can increase temporal summation of EPSPs (Excitatory postsynaptic potentials) in cortical neurons in wild-type mice, while anesthetic-induced EPSP summation is not observed in cortical cells from HCN1 knockout mice [201]. The isoflurane-mediated inhibition of HCN1-containing channels was postulated to contribute to synaptically drive slow-wave oscillations in thalamocortical circuits which might be associated with hypnosis [202, 203]. The potency of volatile anesthetics, including isoflurane and sevoflurane to produce anterograde amnesia and hypnosis are attenuated in HCN1 knockout mice *in vivo* [185]. Ketamine causes a subunit-specific inhibition of recombinant HCN1-containing channels at clinically relevant concentrations [204]. HCN1 channels are more potently inhibited by S-(+)-ketamine than racemic ketamine, consistent with its anesthetic actions *in vivo* [204]. In cortical pyramidal neurons, ketamine induces membrane hyperpolarization and enhanced synaptic coupling, promoting cortical synchronization and supporting slow cortical rhythms [204]. The potency for ketamine to provoke a loss-of-righting reflex can be strongly reduced in overall HCN1 knockout mice [204] and forebrain HCN1 knockout mice [205], indicating forebrain HCN1 channel is the neural substrate for hypnosis induced by ketamine.

2.5. Presynaptic Targets of SNARE

SNARE (soluble N-ethylmaleimide-sensitive fusion attachment protein receptor) proteins are key components of protein complexes that drive neurotransmitter vesicle docking, priming and fusion [206]. Synaptic vesicles dock at the presynaptic membrane before release and undergo a priming reaction for exocytosis [12]. Neurosecretion is induced after Ca_v open, Ca^{2+} influx, and arising of action potentials in presynaptic membrane [12, 206]. The SNARE complex, the core proteins, is comprised of three proteins: syntaxin, SNAP-25/23, and synaptobrevin [207, 208]. Both the ternary SNARE complex and/or syntaxin only, particularly syntaxin-1A, are underlying candidates to bind volatile anesthetics because they are thought to form a parallel four-stranded helical bundle with large hydrophobic cavities [209-211].

2.5.1. SNARE Proteins as Potential Molecular Targets for General Anesthetics

A neomorphic Caenorhabditis elegans mutation in the gene unc-64, which encodes the presynaptic protein syn-

taxin-1A, confers resistance to isoflurane and halothane [48]. The result indicates that resistant syntaxin mutant directly blocks isoflurane and halothane binding to presynaptic targets that suppresses the effects of general anesthesia [48]. These results are also shown in the Drosophila melanogaster model system, suggesting that isoflurane also targets synaptic release mechanisms in flies [212]. Altered syntaxin-1A mobility on the plasma membrane of neurosecretory cells is associated with the changes of synaptic activity [213, 214]. Syntaxin-1A, the key membrane-bound component of the SNARE complex and required for neurotransmitter release in all neurons, normally acts to mediate fusion of vesicles with the presynaptic membrane [211, 215]. Using nuclear magnetic resonance imaging, isoflurane and halothane at clinically relevant concentrations are found to bind to both syntaxin and the SNARE complex proteins, thereby presenting evidence that syntaxin and syntaxin-binding proteins are both candidate anesthetic targets [216]. The volatile anesthetic isoflurane inhibits the neurotransmitter release machinery in wild-type PC12 cells as well as hippocampal neurons [217]. Knockdown of synaptotagmin I, a protein on presynaptic vesicles and considered to be a calcium sensor, mediates the fast-synchronous component of release, or co-knockdown SNAP-25 and SNAP-23, components of SNARE complex, both attenuate the inhibitory effects of isoflurane on neurotransmitter release [218]. These data suggest that multiple SNARE and SNARE-associated proteins of the neurotransmitter release machinery might be the targets of volatile anesthetics.

Propofol and etomidate can suppress the synaptic release machinery in neurosecretory cells and hippocampal neurons at clinically relevant concentrations [219]. Over-expressing a mutant form of syntaxin completely eliminates the reduction in synaptic release produced by propofol [219]. Knocking down synaptotagmin I, or SNAP-25/SNAP-23, can replicate this result, indicating that both etomidate and propofol can inhibit neurotransmitter release by direct interaction with SNAREs and SNARE-associated proteins [218]. However, there is no direct evidence to suggest the effect of ketamine on the synaptic release processes by SNARE. Ketamine significantly reduces the accumulation of SNARE complex in neuronal synaptic membranes at a sub-anesthetic dose (15 mg/kg) [220], although the effects of higher doses of ketamine at clinical anesthetic levels are unclear. This result indicates that the regulation of SNARE complex might be involved in post-anesthetic effects associated with ketamine anesthesia. In summary, synaptic transmitter release machinery might be the target of general anesthetics for presynaptic inhibition of neurotransmitter release.

3. POSTSYNAPTIC EFFECTS OF GENERAL ANESTHETICS

The postsynaptic effects of general anesthetics on synaptic transmission are mostly mediated through postsynaptic receptor manipulation. Among postsynaptic receptors, γ-aminobutyric acid, NMDA glutamate and glycine receptors are the most fundamental targets for general anesthetics [5] (Table **3**). Of note, voltage-gated ion channels such as Na_v and K2P in postsynaptic neuron may also contribute to general anesthetic effects [221], which is not summarized in this review.

3.1. γ-aminobutyric Acid (GABA) Receptors

γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system, with fast synaptic inhibition mediated by postsynaptic $GABA_A$ receptors [222, 223]. $GABA_A$ receptors are members of the superfamily of ligand-gated ion channels and are thought to consist of a variety of subunits (α1-6, β1-3, γ1-3, δ, ε, θ, and ρ1-3) (Fig. **5**) [223, 224]. A major target of most, if not all, general anesthetics at clinically relevant concentrations are the $GABA_A$ receptor, which is a ligand-gated chloride ion channel receptor for the neurotransmitter GABA and universally inhibits neuronal excitability by synaptic phasic currents and extrasynaptic tonic currents [225, 226]. Most effects of general anesthetics on GABAergic synaptic transmission are postsynaptic or extrasynaptic on $GABA_A$ receptors, compared to presynaptic glutamatergic transmission modulation [227, 228].

Propofol potentiates the action of the GABA responses at the $GABA_A$ receptors and directly activates $GABA_A$ receptor function [229]. All subunits of $GABA_A$ receptors including α, β and γ contribute to the sensitivity of propofol to the $GABA_A$ receptors [230-232]. Mutations within either $GABA_A$ α2 (S270 or A291) or β1 (S265 or M286) subunits have little or no effect on the actions of propofol [233]. However, a point mutation in the β1 subunit (M286W) abolished potentiation of GABA by propofol but did not alter direct activation of the receptor by high concentrations of propofol [233]. Propofol can activate α1β3 $GABA_A$ receptors by interactions with the β-β, α-β, and β-α interfaces [226, 234]. Specific postsynaptic effects of propofol on $GABA_A$ receptors indicate that propofol prolongs the decay phase of miniature IPSCs (Inhibitory postsynaptic potentials) without affecting the frequency of mIPSCs and had little effect on EPSC kinetics [228]. Of note, as mentioned previously, propofol can also influence presynaptic mechanisms of GABAergic transmission, such as GABA uptake and GABA release [227].

Etomidate enhances the actions of innate GABA transmission [235]. Clinically relevant concentrations of etomidate slow the inhibitory postsynaptic current decay mediated by synaptic $GABA_A$ receptors, prolonging postsynaptic inhibition and reducing the frequency response of neuronal circuits [236]. Enhanced activation of extrasynaptic $GABA_A$ receptors by etomidate is also found at clinical concentrations, which can increase the tonic inhibitory "leak" current, reducing neuronal excitability [237]. Effects of etomidate on tonic currents mediated by extrasynaptic $GABA_A$ receptors might be even more important than the effects on synaptic currents [238]. Etomidate at supra-clinical concentrations also directly activates synaptic $GABA_A$ receptor channels in the absence of GABA; an action termed as direct activation, GABA-mimetic activity, or allosteric agonism [239]. α-β subunit region of the $GABA_A$ receptors M2 domain has been found to affect etomidate sensitivity. A point mutation replacing β1S265 with N (β1S265N) increases etomidate sensitivity, while replacing β2N265 with S (β2N265S), dramatically reducing etomidate sensitivity [240]. At position 286 in the M3 domains of all $GABA_A$ receptor β subunits is a methionine and βM286 mutations also influence etomidate sen-

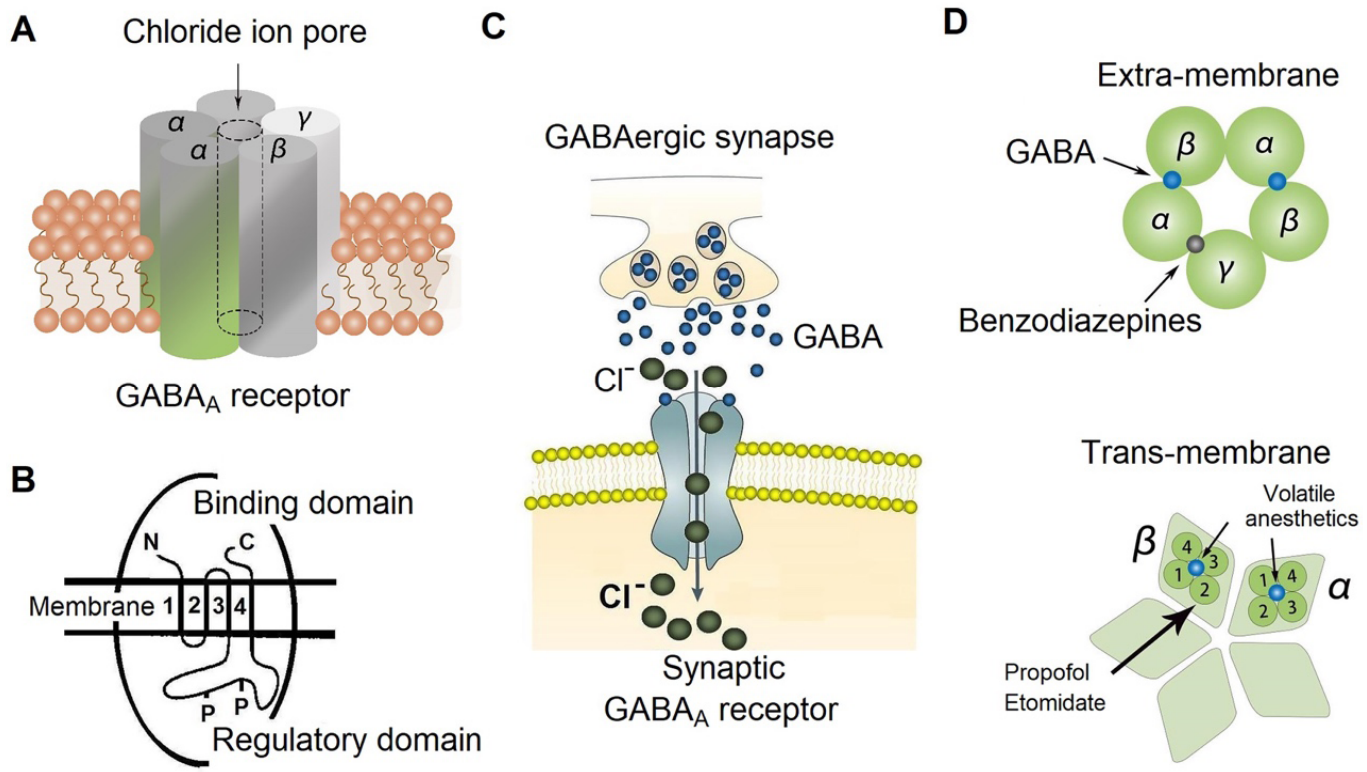

Fig. (5). Structure of GABA$_A$ receptors and general anesthetics binding sites. A-B: Brief structures of GABA$_A$ receptor, which contains five subunits and four transmembrane domains for each subunit. Each subunit has a binding domain extracellularly and regulatory domain intracellularly. **C**: The released GABA from presynaptic membrane activates GABA$_A$ receptors, which then leading to chloride influx and hyperpolarization of postsynaptic membrane; **D**: The possible binding sites for benzodiazepines (upper), propofol and etomidate (lower) on GABA$_A$ receptor. Benzodiazepines binds GABA$_A$ receptors at extra-membrane site between α and γ subunits. However, propofol and etomidate can bind the α and β subunits at their transmembrane domains. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

sitivity [240]. The βM286W mutation eliminates etomidate modulation of receptors, whereas the αA291W mutation has no effect on etomidate actions [241, 242].

Although the effects of volatile anesthetics are relatively complex, synaptic GABA$_A$ receptor also contributes to the effects of volatile anesthetics on the central nervous system [31, 242, 243]. Most volatile anesthetics enhance the amplitude of the responses to GABA and prolong the duration of GABA induced synaptic inhibition [31]. A reduced sensitivity to isoflurane in enhancing GABA$_A$ receptor current is found in α1 S270H mutant [244]. Volatile anesthetics including isoflurane, enflurane and sevoflurane produce heterogeneous effects on miniature inhibitory postsynaptic currents (mIPSCs) and evoked inhibitory postsynaptic currents (eIPSCs) with different modulations of synaptic and extrasynaptic GABA$_A$ receptors [245]. These results suggest that the extrasynaptic GABA$_A$ receptors mainly contribute to the enhancement of the inhibitory responses in the presence of volatile anesthetics at clinically relevant concentrations. More recently, there is increasing interest in extrasynaptic receptors in generating the anesthetized state [246-251]. The extrasynaptic GABA-induced receptors might be the major site of volatile anesthetic-induced GABA transmission, exhibiting higher affinities for GABA and decreased desensitization [102, 225, 226].

3.2. Glutamate Receptors

Glutamate acts on a diverse set of membrane receptors: ionotropic and metabotropic [252]. Ionotropic receptors are ligand-gated ion channels and are divided into two major categories: NMDA and non-NMDA receptors. The latter receptor category includes AMPA and kainate receptors [253, 254]. In cultured hippocampal neurons, isoflurane blocked NMDA-stimulated currents, which is potentially mediated by its interference with NMDA receptor channel function [255]. Mutations of two transmembrane segments in GluN1 and GluN2A subunits (F639A and A85W, respectively) significantly reduce the sensitivity of recombinant NMDA receptors to halothane, isoflurane, cyclopropane and xenon, but have no effects on their sensitivity to ketamine or nitrous oxide, indicating that the mechanisms of inhibition of NMDA receptors among various anesthetics may differ [256]. Higher brain centers are probably involved in anesthetic-induced unconsciousness [257], but the target site responsible for anesthetic-induced immobility is mainly the spinal cord [258]. In rats, the administration of NMDA receptor antagonists intrathecally has been shown to reduce the MAC of isoflurane, and this MAC-sparing effect can be reversed by administration of NMDA receptor agonists [259, 260]. GluN2A knockouts showed normal sensitivity to sevoflurane and isoflurane, but they were resistant to the

hypnotic effect of nitrous oxide [261]. However, some studies questioned the role of NMDA receptors in mediating immobility by volatile anesthetics and suggested that NMDA receptors may not be significantly involved in the immobilizing effect of volatile anesthetics [261, 262]. The volatile anesthetic isoflurane has been reported to induce caspase activation and accumulation of β-amyloid (Aβ), which lead to facilitation of synaptic NMDA receptor endocytosis and potentially result in the isoflurane-induced impairment of learning and memory [263].

Distribution of AMPA receptors may alter during exposure to general anesthetics [264]. The total protein levels of three AMPA receptor subunits (GluR1-3) in the surface pool are reduced, and these proteins in the intracellular pool of cortical neurons are elevated by an anesthetic dose of pentobarbital. The similar phenomenon of redistribution of GluR1/3 was also observed in mouse striatal neurons. The effect of pentobarbital on sub-cellular distribution of AMPA receptors is reversible; AMPA receptor redistribution returned to normal levels after the anesthesia was withdrawn [264]. For kainate receptors, general anesthetics, including isoflurane and sevoflurane have been found to potentiate synaptic kainate receptors such as GluK2, which may lead to excitatory effects in general anesthesia induction and recovery [228, 265].

3.3. Glycine Receptor

Glycine synapses are the principal inhibitory synapse in the spinal cord. Propofol enhances the function of glycine receptors at the spinal cord level, which might contribute to propofol-induced analgesia [266]. Propofol potentiates glycine-activated Cl^- currents recorded from spinal neurons of mice [230, 267, 268]. The large intracellular loop of both the glycine receptor and $GABA_A$ receptor has a conserved single phenylalanine residue (F380 and F385, respectively) that influences its sensitivity to propofol [269]. However, propofol does not require a structural transition of subunits in the transmembrane domain, which is the functional part of glycine receptors [270]. Propofol acts at both the presynaptic glycine release machinery and the postsynaptic glycine receptor [271].

Two specific amino-acid residues in transmembrane domains 2 and 3 (TM2 and TM3) of glycine receptors are critical for the modulation by volatile anesthetics [243]. Volatile anesthetics are positive regulators to glycine receptor function in the presence of glycine and enhance glycine receptor channel opening without dependence on neurotransmitter binding [272]. Halothane, chloroform, and ether potentiate the response to glycine at clinically relevant doses [273]. Recent studies have demonstrated that amino acid (S267) in TM2 provides a specific site for anesthetic binding, which provides strong evidence that the actions of anesthetics are induced by binding on a single site in these receptors [274]. However, Cecilia *et al*. indicate that glycine receptors may not mediate anesthetic immobility produced by isoflurane and other volatile anesthetics *in vivo* [275].

3.4. Nicotinic Acetylcholine Receptors (nAChR)

Nicotinic acetylcholine receptors are members of the ligand-gated ion channel superfamily, which compromise muscle-type nAChR and neuronal-type nAChR [276]. Located at the neuromuscular junction, the muscle-type nAChR is the target of neuromuscular blockers and local anesthetics to prevent muscle contraction. General anesthetics mainly affect the neuronal-type nAChR by inhibiting functions of the central nervous system, including memory formation [277, 278]. The major neuronal nicotinic acetylcholine receptors are heterologous pentamers of α4β2 subunits (brain), or α3β4 subunits (autonomic ganglia) [279]. Volatile anesthetics and ketamine are the most potent inhibitors both at α4β2 and α3β4 receptors at clinically relevant doses [276, 280]. Molecular dynamic simulation studies revealed that three main sites in the nAChR transmembrane domain interact with isoflurane: an isoflurane dimer occludes the pore with contract residues ranging from those in 6′ (a serine ring) to those in 16′ (a hydrophobic ring), αδ-δ and αγ-γ subunit interfaces below the M2-M3 loop, subunit centers of α chain [281]. Even though the pentameric ligand-gated ion channel from Gloebacter violaceus (GLIC) is considered to be a prokaryotic tool for the study of pentameric ion channel Cys-loop receptors (including the $GABA_A$, glycine, and nACh receptors), the interaction of GLIC with general anesthetic is not completely consistent with nACh. Klein *et al*. reported that the subunit interfaces and α chains of GLIC did not interact with isoflurane [281]. Photolabeling study revealed that tyrosine site at extracellular and transmembrane domains, GammaTyr-111 in ACh binding site segment E, alphaTyr-213 within alphaM1 and deltaTyr-228 within deltaM1 were photo-labeled by 14C-labeled halothane [282]. TDBzl-etomidate (a photoreactive etomidate analog) was demonstrated to inhibit the Torpedo nAChR *via* interacting at M2-9 and -13 of the ion channel and potentiate the nAChR *via* interacting at interface between the alpha and gamma subunits (labeling of alphaM2-10 and gammaMet-299) [283]. Although nicotinic acetylcholine receptors are not directly involved in the hypnotic component of anesthesia, it is possible that modulation of central acetylcholine transmission by volatile anesthetics contributes to analgesia [276]. The main effect of anesthetic agents on nicotinic acetylcholine receptors is inhibitory [276]. Intravenous general anesthetics, including propofol and etomidate, exert an inhibitory effect on the nicotinic acetylcholine receptors, but only at concentrations higher than those necessary for anesthesia, which is potentially one of the factors involved in arterial hypotension during general anesthesia [284]. nAChR is now also considered to be inhibited by ketamine to induce unconsciousness [285, 286].

4. SYNAPTIC PLASTICITY AFFECTED BY GENERAL ANESTHETICS

Reversible unconsciousness and amnesia induced by general anesthetics during the perioperative phase act as a core component of general anesthesia [294]. Nevertheless, in the developing or elderly brain, exposure to general anesthetics is considered a potential risk for long-lasting cognitive function deficit [295]. Synaptic plasticity, driven by synaptic or neuronal activity, is critical for high-level functions of the brain, including learning, memory, cognitive function, and emotion [9]. Most excitatory synapses exhibit various forms of plasticity modes that last from milliseconds to weeks [9].

Table 3. Postsynaptic effects of general anesthetics on receptors.

	Volatile Anesthetics			Intravenous General Anesthetics			
	Halothane	**Enflurane**	**Isoflurane**	**Propofol**	**Etomidate**	**Ketamine**	**Thiopental**
$GABA_A$	+ [102, 287]	+ [102, 233, 287]	+ [102, 287]	+ [229, 231, 287]	+ [287, 288]		+ [225, 287, 289]
α1β2γ			+ [225]				
α5β2γ2s			+ [225]				
α6β2γ2s			+ [225]				
α-subunit			+ [244, 290]	+ [230-232]			
β-subunit			+ [225]	+ [230-232]	+ [240-242]		+ [225, 289]
γ-subunit			+ [291]				
NMDA glutamate	- [256]		- [255]			- [292]	
AMPA glutamate			-[263]				
Glycine		+ [293]	+ [275]	+ [266]			
N-Ach (neuronal receptor)				- [284]	- [284]	- [276]	

"+": Potentiation; "-": inhibitory effect.

Thereinto, long-term synaptic plasticity functionally manifested by long-term potentiation (LTP) and long-term depression (LTD) has been shown to be critical for information coding and learning/memory formation or cognitive function by numerous studies [296]. In terms of morphology, long-term synaptic plasticity is associated with up- or down-regulated expression of synapse related protein, including AMPA receptor, F actin, synaptophysin or the alterations of the synapse shape [297]. Multiple mechanisms have been disclosed to underlie the LTP/LTD, involving modulating the transmitter release presynaptically and regulating the expression or function of receptor postsynaptically [298]. The NMDA receptor-dependent and AMPA receptor-mediated LTP/LTD is one of the well elucidated and representative postsynaptic mechanisms [299]. Briefly, the excitatory activity of the postsynaptic membrane activates the NMDA receptor, which mediates Ca^{2+} influx [300]. Intracellular Ca^{2+} activates various substrates, including protein kinase, phosphatase, transcription regulators, which modulate the phosphorylation or expression levels of AMPA receptor subunits on the cell membrane [301]. As the main functional receptor sensing the glutamate, the alteration of the AMPA receptor on the membrane mediates the change of the synaptic transmission efficacy [302]. The synaptic plasticity is vulnerable to be modulated by various factors. The synaptic or neural activity is an important driving force for synaptic plasticity, and the general anesthetic undoubtedly affects the activity of neuron or synapse. Thus, uncovering the modulatory effect of general anesthetics on the synaptic plasticity is important for understanding the anesthesia-related reversible amnesia and post-anesthetic change in cognitive functions.

4.1. Volatile Anesthetics on Synaptic Plasticity

In hippocampus slices from juvenile and adult mice, clinically relevant concentrations of isoflurane depressed the field excitatory postsynaptic potentials (fEPSP) and occluded the LTP or LTD induction after tetanic or low-frequency stimulus [303]. Clinically relevant concentrations of sevoflurane were also revealed to inhibit the fEPSP and LTP in the hippocampal slice [304]. Antagonism of $GABA_A$ receptor by picrotoxin prevented the inhibitory effect of isoflurane on LTP by sevoflurane [303]. In addition, inhibition of α4β2N-AChR in the hippocampus impaired LTP [305]. Given the effect of nAchR in regulating the glutamatergic system, it is suggested that disrupting the excitatory-inhibitory balance might be the main mechanism underlying volatile anesthetic modulating synaptic plasticity.

However, other mechanisms may also be involved. In rat hippocampus, the expression levels of multiple proteins were changed immediately after or 3 days after 3-hour isoflurane anesthesia including synapsin-2, glutathione S-transferase ω1, and purine nucleoside phosphorylase, which are associated with synaptic communication and plasticity [306]. Maternal rats exposed to isoflurane during late pregnancy caused impairment of spatial learning and memory in offspring, which were suggested to be associated with up-regulating the expression of histone deacetylase-2 and down-regulating the cAMP response element binding protein (CREB) and NMDA receptor 2B subunit (NR2B) expression [307]. Notably, an assumption of synaptic plasticity saturation was demonstrated [308]. Other studies have found that inhibitory avoidance learning and long-term potentiation in the hippocampus were impaired seven days after exposure to 1.8% isoflurane for 2 hours, which was suggested to be associated with saturation of LTP by increased expression and decreased ubiquitination of GluA1 in the synaptoneurosomes [308]. Antagonism of H3 receptors can abolish the effect of isoflurane exposure on synaptic plasticity and memory defects [309]. In addition, the role of inhibitory neural activity was also revealed by early exposure to isoflurane and N_2O at postnatal day 7 (P7) which depressed the amplitude and enhanced the decays of eIPSCs while decreasing the paired-

pulse ratio of eIPSCs at postnatal day 14 (P14) in thalamus [310].

Besides the functionally inhibitory effect, clinical concentrations of isoflurane exposure resulted in rapid and non-uniform shrinkage and loss of dendritic spines in cultured rat hippocampal neurons, associated with inducing the spine F-actin disassembly [311]. More importantly, the isoflurane-induced spine shrinkage and loss were reversible upon isoflurane elimination, suggesting an insight of the morphological plasticity for the mechanism of general anesthesia. Even though, to date, there is little evidence about selective targets for volatile anesthetic affecting synaptic plasticity. Further studies should be conducted to explore the relationship between anesthesia actions with synaptic plasticity.

4.2. Propofol and Etomidate on Synaptic Plasticity

Propofol reduced polychronous group size in a dose-dependent manner in a network model of hippocampus [312]. This effect was suggested to disrupt the balance between excitation and inhibition induced by propofol or $GABA_A$ receptor potentiation. An *in vivo* study reported that a low dose of propofol impaired the maintenance of LTP but enhanced the induction of LTD without affecting the basal transmission in the CA1 region of hippocampus of phenobarbitone anesthetized rats [313]. Consistently, in Schaffer-collateral pathway of rat hippocampal slices, propofol inhibited the LTP induction but showed less impact on the LTP maintenance and no effect on LTD [314]. In addition to the hippocampus, propofol impairment of LTP induction was also found in the parallel fiber to Purkinje cell synapses in cerebellum, indicating a potential explanation for propofol caused prolonged movement disorders [315].

Long-term neurocognitive abnormalities after propofol exposure in developing or elderly brains have also been explored by multiple studies [316]. Propofol showed different effects in the developing hippocampus, indicated by more effective suppression on whole-cell EPSC and lower concentrations needed to facilitate the NMDA receptor-dependent LTD in 21 days old rats compared to 7 days old rats [317]. Interestingly, despite the frequently discussed neural damage, under specific conditions, propofol shows protective effects on synaptic plasticity. Electroconvulsive therapy (ECT) is one of the effective tools for antidepressant treatment but reported to impair the learning, memory, and LTP in the hippocampus [318, 319]. Propofol alleviated the ECT caused spatial memory impairment and LTP inhibition in the hippocampus of depressed model rats, which might act through regulating synaptic plasticity-related proteins and/or NMDA receptor subunits, GluA1, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and brain-derived neurotrophic factor (BDNF)/proBDNF [320-322]. Although propofol is shown to have protective effects on cerebral ischemia-induced neuronal death by several studies, research in the hippocampus of rats revealed no significant protective effect of propofol on the LTP impairment caused by ischemic injury [323].

Similar to propofol, the etomidate mechanism of action is proposed to work through enhancing $GABA_A$ receptor-mediated tonic inhibition. There have been reports on the effect of blocking memory via enhancement of inhibitory neural activity and inhibiting LTP [324]. Etomidate at concentrations corresponding to one-half to four times the half-maximal effective concentration impairs hippocampus-dependent learning and memory, prolongs the time constant of decay for $GABA_A$, and increases the speed of IPSCs without significant effects on the amplitudes [325]. Molecular biological studies reveal that the phosphorylation level of CREB, one of the core components of synaptic plasticity and memory function, could be reduced by etomidate and propofol. This effect was reversible after removal of etomidate or propofol, suggesting a potential molecular target for general anesthetics [326].

In addition to the acute effect, etomidate has been reported to result in a sustained increase of $\alpha5$-$GABA_A$ receptor for at least one week. The increased $\alpha5$-$GABA_A$ function was suggested to impair memory performance and synaptic plasticity in the hippocampus after general anesthesia, and inhibiting the $\alpha5$-$GABA_A$ receptor could reverse this effect [327]. Similarly, propofol, as well as the isoflurane, were also found to increase the cell-surface expression of $GABA_A$ receptors, suggesting a mechanism for persistent memory deficits after general anesthetics exposure [327, 328].

4.3. Ketamine on Synaptic Plasticity

As a non-competitive antagonist of NMDA receptor, ketamine possesses a potent effect on synaptic plasticity in the NMDA receptor-dependent manner. Various regions of the central nervous system are affected by ketamine, including the hippocampus, thalamus, visual cortex, and spinal cord [329-333]. The direct inhibition of synaptic plasticity contributes to impaired learning and memory [334]. Ketamine infusion resulted in the impairment in working memory, verbal learning, and memory in healthy subjects [335]. A recent study showed that pre-training administration of ketamine impaired the extinction of the conditioned fear response in rats [336]. However, potentially protective effects of ketamine for Alzheimer's disease were revealed by inhibiting the NMDA receptor-dependent LTD in the hippocampus to protect gamma oscillations [337]. In addition, similar to other general anesthetics, exposure to ketamine anesthesia at a neonatal period also resulted in long-term impairment of synaptic plasticity in the anterior cingulate cortex of rats [338].

Even as an old general anesthetic, ketamine is showing a new application for antidepressant treatment in recent decades [339]. A randomized study consistently found that the antidepressant effect of ketamine revealed 2 hours after administration and lasted for as long as 7 days [340]. The seemingly contradictory effect of ketamine on learning/memory or antidepressant treatment is associated with its biphasic effect at sub-anesthetic dose, which inhibits the NMDA receptor acutely and modulates the synaptic plasticity chronically after administration [341, 342]. Twenty-four hours after a low dose of ketamine administration, the spine number, especially the mushroom or mature spines, and the synaptic plasticity-related proteins (postsynaptic density-95, GluR1, synapsin 1) in the prefrontal cortex (PFC) significantly increased [343]. In addition, activating the mammalian target of rapamycin (mTOR) signaling has been identified as the mechanism for ketamine-induced enhancement of

synaptic protein synthesis [343]. In addition, several studies on synaptic plasticity have revealed that activation of mTOR signaling and synaptic protein synthesis is dependent on activation of the AMPA receptors. The metabolism of (R, S)-ketamine to (2S, 6S; 2R, 6R)-hydroxynorketamine (HNK), rather than ketamine, is essential for antidepressant and synaptogenesis effects, by inhibiting the NMDA receptor [344]. Early and sustained activation of AMPA receptor is involved in the effect of ketamine metabolites [344]. Nevertheless, controversy has recently been raised from a study which demonstrated that with pretreatment of cytochrome P450 (CYP) inhibitors to decrease the production, the (2R, 6R)-HNK did not alleviate the antidepressant efficacy of R-ketamine but enhanced it, indicating that the unmetabolized (R)-ketamine itself rather than the metabolite (2R, 6R)-HNK is necessary for the antidepressant action of (R)-ketamine [345].

5. SIDE EFFECTS OF GENERAL ANESTHETICS RELATED TO SYNAPTIC TRANSMISSION

General anesthetics produce clinically demanded pharmacological actions like amnesia, hypnosis, unconsciousness, immobility and analgesia. However, general anesthetics may also induce side effects like respiratory depressions. Meanwhile, the actions of general anesthetics on synaptic transmission and plasticity can also exert underlying side effects or even toxicity to sensitive central nervous systems in patient populations such as newborns and the elderly. This section will briefly summarize such side effects of general anesthetics.

5.1. Cognitive and Post-Memory

Accumulating evidence suggests that exposure to general anesthetics during a brain growth-spurt period can induce neurotoxicity and long-term cognitive deficits [346, 347]. Isoflurane induced the activation and translocation of dynamin-related protein, which was closely associated with synaptic degeneration in neurodegenerative diseases, causing excessive mitochondrial fission and subsequently synaptic injury and long-term cognitive deficits [348]. Sevoflurane exposure on the developing brain impaired learning, memory, and synaptic plasticity in the hippocampus of rats where the degree of impairment depended on the duration of exposure [349]. However, the underlying mechanism for long-lasting learning and cognitive impairment caused by general anesthesia remains unknown. The GluA1 subunit of AMPA receptor is considered as a key molecule for learning and synaptic plasticity, which requires trafficking of GluA1-containing AMPA receptors into the synapse. After exposure to 1.8% isoflurane for 2 h in rats, the inhibitory avoidance learning and long-term potentiation were impaired, and GluA1 was temporarily increased in the synaptoneurosomes. Increased levels of GluA1 may reduce the synaptic capacity for additional trafficking of GluA1-containing AMPA receptors [308].

5.2. Brain Development

The exposure to commonly used volatile anesthetics and intravenous general anesthetics causes biochemical and morphological changes in immature and aging neurons [346]. Both animal and human data suggest that commonly-used general anesthetics could damage the developing brain [15]. General anesthetics may cause significant and widespread neuroapoptosis of developing neurons in various mammalian species [350-353]. It has been observed that the peak of vulnerability to anesthesia-induced neuroapoptosis coincides with the peak of synaptogenesis; neurons are much less vulnerable during the late stages of synaptogenesis [353]. Early exposure to general anesthetics at the peak of their synaptogenesis (rat postnatal day 7) causes long-term impairments in synaptic transmission in the hippocampus of adolescent rats (postnatal day 27-33) [350]. Although the precise mechanisms for the long-term changes in synapses after exposure to general anesthetics remain to be known, recent studies suggest that anesthetics inhibit axonal growth cone collapse, reducing proper response to guidance cues, thus causing errors in axon targeting [354].

In the developing striatum, tonic GABA currents exist in medium-sized spiny projection neurons and have an important function in the balance of excitatory/inhibitory and maturation of striatal neural circuits. Sevoflurane affects the tonic GABA inhibition in a developing striatal neural network [355]. In rat models, exposure to sevoflurane for 6 hours at postnatal days 4 (P4) induced activation of caspase-3 and impairment of long-term potentiation at P5 and P18-21, respectively. Pretreatment with bumetanide, an Inhibitor of NKCC1 (Na^+-K^+-$2Cl^-$ transporter isoform 1) blocked the increased activation of caspase-3 but did not alleviate the impairment of long-term potentiation. These results suggest that sevoflurane affects GABA systems, which may result in epileptogenic and neurotoxic effects in neonatal rats [356].

5.3. Depression of Respiration

All volatile and most intravenous general anesthetics currently used clinically cause respiratory depression at surgical concentrations [357]. Volatile anesthetics primarily inhibit multiple components of the respiratory center in the brainstem, *via* enhancing the GABAergic or glycinergic inhibition or reducing the glutamatergic receptors activity [358]. The depressive effect of volatile anesthetics on muscular tension can also contribute to the respiratory depression of general anesthetics. Sevoflurane and isoflurane can cause muscle relaxation and potentiate the effects of neuromuscular blocking agents, whereas the neuromuscular junction is the action site. It was reported that the enhancement of muscle relaxation by isoflurane and sevoflurane was mediated by increasing the activity of nicotinic acetylcholine receptors [359]. Presynaptic mechanisms are also suggested to be involved in this action. Sevoflurane and isoflurane inhibited presynaptic exocytosis evoked by sodium-dependent depolarization and may act on tetrodotoxin-sensitive sodium channels at the mouse neuromuscular junction [360].

5.4. Synaptic Morphology

In addition to inducing neuroapoptosis, general anesthetics can also affect synaptogenesis during brain development [361]. Isoflurane reversibly destabilized dendritic spines in the hippocampus in an activity-dependent mechanism. This effect may contribute to the acute anesthetic effects on excitatory synaptic transmission and anesthetic-induced amnesia [311]. The effect on the dendritic spine density of volatile anesthetics during synaptogenesis varies with the duration of

exposure time [362]. In addition, a recent study demonstrated that early exposure to general anesthesia with isoflurane alone or in combination with N_2O induced plasticity of eIPSCs in neurons of the thalamic reticular nucleus by both presynaptic and postsynaptic mechanisms. The changes of inhibitory synaptic transmission in the thalamus induced by general anesthetics may affect the neuronal excitability and consequently cause abnormal thalamocortical oscillations in later life [310]. Although these alterations were initially considered deleterious, several studies suggest that they may eventually improve neural function under some specific conditions. Interestingly, in a recent study, it was reported that exposure of the developing brain to a low concentration (1.2%) of sevoflurane for 6 h could improve spatial learning and memory function, along with increased hippocampal neurogenesis and synaptic plasticity in later life [363]. Thus, general anesthetics should not merely be considered as neurotoxic drugs but rather acknowledged as robust, context-dependent modulators of neural plasticity [364].

CONCLUSION

In summary, synaptic transmission is the main procedure for information transmission between neurons and/or other cells in the central nervous system and intact synaptic function is fundamental for almost all the nervous functions, including consciousness, memory and cognition. Specific effects of general anesthetics on synaptic transmission contribute to their pharmacological actions. Therefore, it is important to understand the effects of general anesthetics on synaptic transmission *via* modulation of specific ion channels and relevant targets, which may contribute to the development of safer general anesthetics with selective actions. General anesthetics can modulate synaptic transmission in both presynaptic and postsynaptic sides and targeting varied ion channels and receptors. The differential effects on multiple targets involved in synaptic transmission among general anesthetics may contribute to their specifically pharmacological actions, which is one of the most important purposes for anesthetic mechanism research. With the rapid progress of neuroscience methods, further researches of general anesthetic mechanism are required to explain the pharmacological actions and/or overall effects of general anesthetics on physiological functions like EEG (electroencephalogram) by their specific modulations in synaptic transmission or molecular targets.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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