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REVIEW ARTICLE

Effects of General Anesthetics on Synaptic Transmission and Plasticity

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Abstract: General anesthetics depress excitatory and/or enhance inhibitory synaptic transmission principally by modulating the function of glutamatergic or GABAergic synapses, respectively, with relative anesthetic agent-specific mechanisms. Synaptic signaling proteins, including ligand- and voltage-gated ion channels, are targeted by general anesthetics to modulate various synaptic mechanisms, including presynaptic neurotransmitter release, postsynaptic receptor signaling, and dendritic spine dynamics to produce their characteristic acute neurophysiological effects. As synaptic structure and plasticity mediate higher-order functions such as learning and memory, long-term synaptic dysfunction following anesthesia may lead to undesirable neurocognitive consequences depending on the specific anesthetic agent and the vulnerability of the population. Here we review the cellular and molecular mechanisms of transient and persistent general anesthetic alterations of synaptic transmission and plasticity.

Keywords: Anesthesia, synaptic plasticity, presynaptic function, postsynaptic structure, ion channels, synaptic transmission.

1. INTRODUCTION

The first public demonstration of a surgical procedure with general anesthesia was performed in 1846 using sulfuric ether. Since that time, various chemically diverse structures have been identified to have potent and selective effects on neuronal transmission to produce the cardinal features of general anesthesia: amnesia, unconsciousness, and immobility. General anesthetic agents are categorized based on whether they are administered by inhalation (*e.g.*, volatile) or intravenously, but their chemical structures, molecular targets, and binding sites are quite diverse. Although mechanistically distinct, general anesthetics depress fast excitatory and/or enhance fast inhibitory synaptic transmission mediated primarily by glutamate and GABA, respectively [1, 2]. The relative importance of anesthetic effects on excitatory *vs* inhibitory synapses to potentiate overall synaptic inhibition varies among anesthetic agents [3]: modulation of postsynaptic NMDA or postsynaptic and extrasynaptic $GABA_A$ receptors is a major contributor to the effects of intravenous anesthetics like ketamine or propofol, respectively; presynaptic and postsynaptic inhibition of excitatory glutamatergic transmission contributes to the depressant effects of volatile anesthetics [3-7]. The mechanisms for the acute anti-excitatory effects of volatile anesthetics include depression of neuronal excitability [8] or action potential conduction [9-12], inhibition of Ca^{2+} influx [13, 14] and synaptic vesicle exocytosis [15-17], and/or blockade of postsynaptic glutamate receptors [18]. Excitatory glutamate receptors are largely targeted to dendritic spines [19]; their identification as a cellular substrate for anesthetic action [20, 21] highlights their influence on advanced functions such as synaptic plasticity, learning, memory and suggests a role for spine plasticity in the acute and enduring neurocognitive effects of general anesthetics. Here we highlight some of the critical targets involved in the modulation of synaptic transmission and plasticity and the neurophysiological effects of general anesthetics as well as their role in lasting cognitive changes.

Unless indicated otherwise, the agent-specific cellular and pharmacological differences described here occur at clinical concentrations of anesthetics, defined as concentrations measured *in vivo* required for therapeutic endpoints of general anesthesia.

2. PRESYNAPTIC ANESTHETIC EFFECTS

2.1. Neuronal Excitability

2.1.1. Sodium Channels

Volatile anesthetics reduce excitatory postsynaptic potentials (EPSPs) primarily through presynaptic actions [3, 5, 22]. Reports in the 1970s and 1980s implicated the effects of volatile anesthetics on modulation of protein function, shifting attention away from direct interactions with the lipid bilayer [23]. In fact, clinically relevant concentrations of various general anesthetics only minimally affect lipid bilayer properties [24]. Voltage-gated Na^+ channels (Na_v) control neuronal excitability, action-potential (AP) driven Ca^{2+} influx, and Ca^{2+}-dependent neurotransmitter release [25, 26]. At least three states have been identified for neuronal Na_v depending on membrane potential: resting (closed), activated

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(open), and inactivated [27]. Upon neuronal depolarization, sodium channels rapidly activate and initiate an AP, followed by fast inactivation and return of baseline sodium conductance within a few milliseconds [28]. Both local and volatile anesthetic exhibit a voltage- and frequency-dependent block of Na_v [29-31]. Volatile anesthetics reduce peak Na^+ currents in two ways: 1) preferential interaction with inactivated states of Na_v to shift steady-state inactivation toward more negative membrane potentials, reducing channel availability and slowing recovery from fast- inactivation, and 2) interaction with the open and/or resting state to produce tonic block [30, 31]. Substantial neurochemical and electrophysiological evidence supports direct inhibition of presynaptic Na_v and subsequent depression of APs and nerve terminal depolarization by volatile anesthetics in heterologous expression systems [32] as well as in more physiologically relevant neuronal preparations, including isolated nerve terminals from rat cerebral cortex [33], rat neurohypophysis, and giant calyx of Held slices [11, 12, 34]. Alternatively, prolonged depolarization or repetitive depolarization drives Na_v into a distinct slow-inactivated state from which recovery is very slow [35, 36]; slowly inactivating Na_v or resurgent sodium currents that occur with repolarization can enhance repetitive firing and modulate overall neuronal excitability as opposed to AP initiation and propagation [27, 37]. In acute mouse brain slices, these persistent neuronal sodium currents are also inhibited by isoflurane to reduce hippocampal pyramidal neuron excitability [38].

Na_v blockade may also contribute to the actions of propofol, a structurally distinct intravenous anesthetic that attenuates increases in Na^+ flux, intracellular free Na^+ levels and Na^+ channel-dependent glutamate release in isolated rat cerebrocortical nerve terminals [39] and calyx of Held [40]. Like volatile anesthetics, propofol primarily enhances inactivation of Na_v, with some contribution of reduced activation at higher concentrations in neurohypophysial nerve terminals [34] and isolated nerve terminals [41]. Similarly, higher than clinically relevant plasma concentrations of ketamine, another commonly used intravenous anesthetic, also inhibit Na_v conductance in human neuroblastoma cells [42] and isolated nerve terminals prepared from human cortical tissue [43].

Na_v channels consist of a large, pore-forming α subunit in association with auxiliary β subunits [44, 45]. Of the nine subtypes of α subunit ($Na_v1.1$-$Na_v1.9$), $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, and $Na_v1.6$ are highly expressed in the central nervous system [46, 47], with $Na_v1.3$ preferentially expressed during development [44]. Multiple expression systems have identified neuronal Na_v subtype- and agent-specific effects of inhaled anesthetics to reduce peak Na_v current at clinically relevant concentrations in a voltage-dependent manner. At physiologic holding potentials, isoflurane induces fast inactivation and inhibition of peak Na^+ currents of $Na_v1.2$ and $Na_v1.6$ compared with $Na_v1.1$ expressed in a mammalian cell line [48, 49]. Reduced sensitivity of $Na_v1.1$ to isoflurane is consistent with previous findings reported in Chinese hamster ovary cells [31] and *Xenopus* oocytes [50]. Distinct gating properties contribute to these sensitivity differences as similar voltage-dependence of activation, but a positive shift in the voltage-dependence of inactivation was revealed for $Na_v1.1$ compared to $Na_v1.2$ and $Na_v1.6$ [49]. In contrast, suppression of $Na_v1.2$ (50-70%) by propofol in various expression systems requires supratherapeutic concentrations [34, 50, 51]. Furthermore, Na_v subtypes show subcellular-, regional-, and neurotransmitter-selective expression [52-55], and distinct sensitivity differences may further contribute to selective anesthetic effects on synaptic transmission.

Regulation of neuronal excitability by Na_v supports their roles in the behavioral endpoints of anesthesia. Intrathecal and intravenous administrations of Na_v blockers in rats and humans increase the potencies of isoflurane, halothane, or sevoflurane [56-59], while drugs that activate Na_v antagonize general anesthesia as reflected in increased MAC (minimum alveolar concentration of anesthetic that eliminates movement in response to noxious stimulation in 50% of subjects) and reduced potency [59-61]. This finding is consistent with a role for Na_v as a mediator of immobility produced by anesthetics. Additional reports have also observed reduced activity of a specific Na_v to increased sensitivity to volatile anesthetics in transgenic mice. Mutant mice with reduced $Na_v1.6$ activity exhibit reduced theta power in the waking state, suggestive of decreased arousal and neuronal excitability [62]. These mice exhibit increased sensitivity to isoflurane and sevoflurane during induction of unconsciousness [62], exemplifying how reductions in AP conduction by anesthetics at the neuronal level leads to alterations in oscillatory activity at the neural network level [63], influencing disruptions in signal propagation and cortical communication involved in higher-order functions like consciousness which rely on precisely tuned integration of inputs [64].

Na_v function is also regulated by second messenger-mediated protein phosphorylation, an important neuromodulation mechanism and an additional target for volatile anesthetics. Phosphorylation of Na_v by protein kinase A (PKA) and protein kinase C (PKC) reduces Na^+ channel activity by altering channel kinetics [65-67] with differential subtype sensitivity: $Na_v1.2$ is more sensitive to PKA and PKC modulation compared to $Na_v1.6$ [68, 69]. In turn, anesthetics can mediate PKC phosphorylation to indirectly affect Na_v inhibition as brain PKC activity is increased by halothane and/or propofol purified from rat brain or in isolated nerve terminals [70, 71].

2.2. Calcium Dynamics

2.2.1. Calcium Channels

Presynaptic voltage-gated Ca^{2+} channels (Ca_v) are essential to neurotransmission by mediating Ca^{2+} influx to trigger synaptic vesicle exocytosis. Over the course of an AP, membrane Ca_v open at the presynaptic terminal, allowing Ca^{2+} entry. The increase in Ca^{2+} influx, along with efflux from store-operated Ca^{2+} channels (SOCs), increases intracellular free calcium concentrations regulating crucial second messenger-mediated biochemical processes, including neurotransmitter release [72, 73]. In the CNS, there are five major classes of Ca^{2+} currents: L-, N-, P/Q-, R-, and T- type, with the latter characterized as low voltage-activated channels (LVA) based on the degree of membrane depolarization required for activation [74, 75]. This section will largely focus on the function of presynaptic Ca_v (N-, P/Q-, R-type currents) in anesthetic effects.

As ion channels are a principal target of general anesthetics, inhibition of Ca_v to reduce AP-evoked exocytosis is a

plausible action of general anesthetics [76, 77]. However, early observations of anesthetic inhibition of synaptic Ca_V were often conflicting. Volatile anesthetics such as halothane were found to increase resting cytoplasmic Ca^{2+} in isolated mouse brain nerve terminals [78] and hippocampal brain slices [79], but likely resulted in depressed neuronal excitability *via* potassium channel- [80] or $GABA_A$-mediated chloride conductance [79] as later work observed significant reductions in the frequency of miniature excitatory postsynaptic currents (mEPSCs) and miniature inhibitory postsynaptic currents (mIPSCs) [81]. With electrical or chemical depolarization, halothane, enflurane, and isoflurane cause a marked and reversible suppression of inward Ca^{2+} current and synaptic excitation in rat hippocampal slices [82] and cultured neurons [83, 84]. Intracellular Ca^{2+} dynamics are further perturbated due to delayed clearance by volatile anesthetics. Clinical concentrations of halothane not only reduce AP amplitude, but also prolong the repolarization phase 2-to 4-fold by inhibition of plasma membrane Ca^{2+}-ATPase, an ion pump that ejects Ca^{2+} from the cell following influx into the cytoplasm [85]. Impaired synaptic transmission contributed by Ca^{2+}-dependent presynaptic mechanisms is also produced by supratherapeutic concentrations of propofol as inhibition of EPSCs due to reduced Ca^{2+} influx was observed by an increased paired-pulse ratio (PPR) and prolonged slowing of endocytosis [40]. Voltage-gated Ca_V are heteromultimeric protein complexes composed of α_1, α_2-δ, β, and γ subunits, with the α_1 subunit containing an ion-conducting pore, voltage sensor, gating machinery and drug-binding sites that determine channel subtype [44]. There are three major presynaptic Ca_V family subtypes: P/Q- ($Ca_V2.1$), N- ($Ca_V2.2$), and R-type (Ca_V-2.3), with P/Q- and N-types primarily coupled to neurotransmitter release with distinct physiological and pharmacological characteristics [86-88]. Anesthetics alter Ca^{2+} currents contributed by multiple subtypes of Ca_V, but detailed analysis of the influence on individual channel types was inconclusive in multiple physiological systems [89, 90]. For example, P-type channels, named from their initial discovery in cerebellar Purkinje cells, were found to be insensitive to inhibition by volatile (halothane, isoflurane) and intravenous (propofol, thiopental) anesthetics [91], although they contribute to ~80% of voltage-gated Ca^{2+} uptake in nerve terminals based on inhibition by ω-Aga-IVA, a specific P-channel blocker [92, 93]. However, these studies were conducted in dissociated Purkinje neurons and the possibility of heterogenous subpopulations of Ca_V could not be ruled out [91]. Separate expression of specific neuronal Ca_V in *Xenopus* oocytes in later studies revealed inhibition of P/Q- and N-mediated Ca^{2+} currents by both halothane and isoflurane in a concentration dependent manner *via* steady-state inactivation [94], an effect further modulated by PKC translocation and activation [95]. Further examination of excitatory neurotransmitter release by specific Ca_V blockers in rat hippocampal neurons revealed a larger contribution by P/Q-type compared to N-type currents, but again with no significant differences in their functional sensitivities to isoflurane [14]. Behaviorally, N-type channels participate in both excitatory and inhibitory synaptic transmission which are sensitive to the actions of anesthetics. Mutant mice lacking $Ca_V2.2$ show increased sensitivities to halothane-induced immobility and hypnosis consistent with reduced field excitatory postsynaptic potentials (fEPSPs) recorded from Schaffer collateral CA1 synapses, while displaying decreased sensitivity to propofol possibly due to reduced GABA release from inhibitory presynaptic terminals [96]. Similar findings were also reported for $Ca_V2.3$ [96], a subtype that contributes to transmitter release with lower efficacy compared to $Ca_V2.1$ and $Ca_V2.2$ [97].

2.2.2. Intracellular Calcium Stores

With critical influence over cytoplasmic free Ca^{2+}, intracellular Ca^{2+} stores provide an additional target for anesthetics. The endoplasmic reticulum (ER) is the largest intracellular store of releasable Ca^{2+} [98], regulating intracellular Ca^{2+} critical to neuronal excitability [99] *via* Ca^{2+} influx pumps [sarcoplasmic/ER Ca^{2+} ATPase (SERCA)] and receptor-gated Ca2+ efflux channels [inositol 1,4,5-triphosphate receptors (IP3R), ryanodine receptors (RyR)] [100-102]. Axonal ER Ca^{2+} controls presynaptic intracellular Ca^{2+} through Ca^{2+} sensing proteins and decreased ER Ca^{2+} is linked to reduced presynaptic Ca^{2+} influx [103], providing possible targets of anesthetic action; efflux of Ca^{2+} *via* IP_3R or RyR have been implicated in sevoflurane- or halothane-induced increase in intracellular Ca^{2+}, respectively [104, 105]. Furthermore, volatile anesthetics have several significant side effects, with some individuals developing malignant hyperthermia (MH), a potentially fatal pharmacogenetic disorder triggered by uncontrolled Ca^{2+} release from the SR mediated by RyR1 [106, 107].

2.3. Synaptic Vesicle Exocytosis

2.3.1. Small Vesicle Exocytosis

Neurotransmitter release is primarily determined by Ca^{2+} entering the bouton [108]. General anesthetics differentially act on presynaptic Ca^{2+} *via* actions on ion channels or vesicle fusion mechanisms to inhibit evoked synaptic vesicle (SV) exocytosis [109, 110] and reduce EPSCs [11] associated directly with attenuated release probability and a number of functional release sites [81, 111]. AP-evoked depolarization can be pharmacologically mimicked by 4- aminopyridine (4AP) and veratridine, a K^+ channel blocker and a Na_V agonist, respectively, while elevated K^+ elicits Na_V-independent depolarization [25]. Although one study reported that isoflurane, enflurane, and halothane can directly act on Ca_V in isolated nerve terminals to decrease glutamate release [76], Ca_V are relatively insensitive to isoflurane compared to Na_V [11, 91]. Considerable evidence supports inhibition of Na_V as a major contributor to the presynaptic effects of anesthetics on veratridine-4AP-evoked glutamate release from nerve terminals isolated from several species and brain regions, including from rat, mouse, or guinea pig cerebral cortex and rat striatum and hippocampus [110, 112]. These findings are consistent with a target upstream of Ca^{2+} entry as they were not reproduced for release evoked by elevated K^+, a mechanism that directly opens Ca_V [113]. Inhibition of evoked GABA release also occurs for isoflurane [13, 114], but is balanced by potentiation of $GABA_A$ receptors and increased asynchronous GABA release [115], leading overall to enhanced net inhibition [3, 116]. Moreover, isoflurane inhibits Na_V-dependent glutamate release with greater potency than GABA release from cerebral cortex, striatum, and hippocampus [15, 16, 113]. Consistent with selective inhibition of excitatory synaptic transmission, isoflurane inhibition

of Ca^{2+} influx was also greater in glutamatergic compared with GABAergic boutons assayed using genetically encoded Ca^{2+} biosensors [13]. These effects are not dependent on differential sensitivities to isoflurane or variable expression or coupling of presynaptic Ca_V subtypes to synaptic vesicle exocytosis [14]. Neurotransmitter release is supra-linearly dependent on presynaptic Ca^{2+} influx due to the highly cooperative binding of Ca^{2+} to synaptotagmin 1, the principal neuronal Ca^{2+} sensor for triggering synaptic vesicle fusion [117, 118]. Clinical concentrations of isoflurane inhibit single AP-evoked glutamate exocytosis; lowering external Ca^{2+} to mimic the isoflurane-induced reduction in Ca^{2+} leads to an equivalent reduction in exocytosis, suggesting that anesthetic inhibition of neurotransmitter release occurs primarily through reduced axon terminal Ca^{2+} entry without significant direct effects on Ca^{2+}-exocytosis coupling or on the vesicle fusion machinery [13].

The diversity of GABAergic interneurons makes comparing differences in presynaptic anesthetic pharmacology between glutamatergic and GABAergic neurons difficult, as these interneurons vary in their expression of key neurotransmission-related proteins [119] including ion channels, Ca^{2+}-binding proteins involved in modulating intracellular Ca^{2+}, and intracellular signaling proteins [120]. For example, hippocampal parvalbumin (PV^+) interneurons are distinguished by a supra-critical density of $Na_V1.1$ at distal and terminal axons thought to enable their fast-spiking phenotype [121], while excitatory pyramidal neurons express more $Na_V1.2$ and $Na_V1.6$ [53, 54, 122]. Expression of presynaptic Na_V subtypes coupled to neurotransmitter release not only differs between transmitter types, but also between CNS regions in a nerve terminal-specific manner [113, 123] as inhibition of Na_V-dependent glutamate release occurs with ~50% greater potency than inhibition of GABA release in cortical, striatal, and hippocampal nerve terminals [123]. Differential pre- and post-synaptic expression of Na_V subtypes in rat hippocampus [55] further contributes to variations in neurotransmitter suppression as Na_V subtypes are differentially inhibited by volatile anesthetics $Na_V1.1 < Na_V1.2/1.6$; [49], determining cell-specific inhibition of synaptic vesicle exocytosis. For example, $Na_V1.1$ is less sensitive to isoflurane than $Na_V1.2$ and $Na_V1.6$ are due to its unique gating properties [49], suggesting that $Na_V1.1$ expression in GABAergic boutons underlies their reduced sensitivity to isoflurane inhibition. Like volatile anesthetics, propofol, thiopental, and ketamine also reduce glutamate release from rat cortical slices, while GABA release was increased *via* an Na_V-independent mechanism by propofol, etomidate, or pentobarbital [115, 124].

2.3.2. Large Vesicle Exocytosis

Monoamine neurotransmitters such as dopamine are packaged into both small synaptic vesicles and large dense core vesicles (LDCV) for release. However, only small synaptic vesicles localize to synaptic boutons, while LDCVs engage primarily in extrasynaptic exocytosis [125, 126]. Aminergic neurons have distinct mechanisms of LDCV exocytosis [127] and play central roles in wakefulness and arousal [128]. Stimulation of dopaminergic neurons in the rat ventral tegmental area (VTA), a principal midbrain dopaminergic region [129], induces emergence from isoflurane in rats [130]. Conversely, inhibitors of the dopamine transporter restore conscious behaviors in rats anesthetized with isoflurane, propofol, or sevoflurane [131-133]. Early reports on basal and chemically evoked dopamine release by various anesthetics have been inconsistent, showing increased or decreased release based on the type of anesthetic agent and stimulation [134-136]. Recent work using fluorescence imaging, under electrically evoked action potentials in cultured rat VTA neurons, show that isoflurane inhibits exocytosis in dopaminergic neurons with intermediate potency compared to glutamate and GABA synaptic vesicle exocytosis [17]. Although considerable evidence supports that presynaptic Ca^{2+} channels are not the principal targets involved in inhibition of glutamate and GABA release by volatile anesthetics [123, 137], exocytosis in dopaminergic neurons evoked by elevated KCl is inhibited, a mechanism mediated exclusively by reduced Ca^{2+} entry through both $Ca_V2.1$ (P/Q-type) and $Ca_V2.2$ (N-type) and is independent of Na_V activation [17]. Halothane and isoflurane also alter the presynaptic regulation of dopamine and GABA release mediated by presynaptic acetylcholine receptors in rat striatum, suggesting that cholinergic transmission is a presynaptic target for volatile anesthetics [138].

Brain-derived neurotrophic factor (BDNF), a secreted growth factor packaged in LDCV, plays a critical role in modulating excitatory synaptic transmission. Activity-dependent presynaptic BDNF signaling *via* its receptor, TrkB, potentiates glutamate release by multiple mechanisms: activation of the phospholipase Cγ (PLCγ) pathway increases intracellular Ca^{2+} [139]; phosphorylation of synapsin 1 by mitogen-activated protein kinase (MAPK) and increased Rab3 expression act directly on vesicle machinery [140, 141]; and activation of an actin motor complex increases neurotransmitter replenishment and release [142, 143]. Synapses in BDNF knockout mice have fewer docked vesicles [144] and reduced probability of neurotransmitter release [145]. Based on stimulation frequency, BDNF can be released from axons or dendrites [146, 147] and have diverse pre- and post-synaptic modulatory effects on mature glutamatergic synapses, indicating a plausible presynaptic target for volatile anesthetics. BDNF release evoked by tetanic high-frequency stimulation (16 bursts of 50 action potentials @ 50 Hz) was significantly inhibited by clinical concentrations of isoflurane (unpublished data), suggesting a novel contribution to isoflurane-induced reductions of excitatory transmission.

2.4. Additional Targets

2.4.1. Potassium and Hyperpolarization-activated and Cyclic Nucleotide-gated Channels

Other anesthetic-sensitive ion channels or presynaptic proteins critical to CNS excitability and synaptic transmission include two-pore domain K^+ channels (K_{2P}), hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels, and SNARE proteins. Potassium channels regulate the passive flow of K^+ ions to maintain the membrane potential following changes in transmembrane potential. Out of the four subfamilies of potassium channels, K_{2P} and K_V channels are modulated by general anesthetics [57, 148-150]. K_{2P} channels are widely expressed in the nervous system and contribute to background membrane conductance [151]. Electro-

physiological measurements show that isoflurane opens K_{2P} channels leading to reduced neuronal excitability [152, 153], altering network oscillations [154], underlying loss of consciousness and immobilization [155-158]. HCN channels also contribute to sensitivity to general anesthetics [159-161], as slow-wave oscillations within the thalamocortical circuits, indicative of the anesthetized state, are associated with isoflurane-mediated inhibition of HCN channels [162]. Induction of both anterograde amnesia and hypnosis under isoflurane and sevoflurane are attenuated in HCN1 knockout mice [160]. Comparably, K_{2P} and HCN channels are also targeted by propofol and ketamine to mediate anesthetic endpoints [163-165].

2.4.2. Synaptic Vesicle Machinery

Downstream of ion channel regulation, the synaptic vesicle release machinery itself may also be involved in anesthetic inhibition of exocytosis. Recent findings support distinct dual mechanisms based on the frequency of input. With short depolarizing pulses in calyx of Held slices, isoflurane inhibits exocytosis by reducing Ca^{2+} influx without altering Ca^{2+}- exocytosis coupling as previously reported in hippocampal neurons [13, 111], whereas with long presynaptic depolarizations associated with greater exocytosis, isoflurane directly inhibits exocytic machinery downstream of Ca^{2+} influx [111]. Moreover, in simultaneous recordings of pre- and post-synaptic APs, as well as in unit recordings from cerebral cortical neurons in mice *in vivo*, isoflurane preferentially inhibits monosynaptic transmission evoked by higher-frequency stimulation [111], further suggesting a critical role for exocytic machinery.

The SNARE complex, comprised of syntaxin 1, SNAP-25/23, and synaptobrevin [166, 167] regulates synaptic vesicle docking, priming, and fusion [168]. Mutations in the syntaxin homolog in *Caenorhabaditis elegans* confer resistance to the behavioral effects of isoflurane and halothane [169], results that are recapitulated in *Drosophila melanogaster* [170]. In rodent model systems, clinical concentrations of isoflurane and halothane directly bind rat synaptic SNARE proteins [171] and inhibit neurotransmitter release in hippocampal neurons, an effect abolished by overexpression of syntaxin 1 [172] or knockdown of SNAP-25/23 [173]. Interference with SNARE complex formation by direct interaction with syntaxin 1 [174] and inhibition of neurotransmitter release were also observed at clinical concentrations of propofol and etomidate in neurosecretory cells and rat hippocampal neurons [175], although these effects occur at higher anesthetic concentrations.

2.4.3. Gap Junctions

Gap junctions provide electrical coupling of neurons and glial cells to mediate direct cell-to-cell communication and synchronized activation of cellular networks [176]. Volatile anesthetics like halothane, enflurane, sevoflurane, and isoflurane at high supratherapeutic concentrations inhibit gap-junction-mediated neural activities by reducing gap junction conductance [177] and permeability *in vitro* [178, 179], and contribute to anesthetic-induced immobilization *in vivo* [180]. These effects are largely observed under higher than clinical concentrations, unlike depression of intercellular communication *via* gap junctions by intravenous anesthetics like propofol and thiopental [181]. Preclinically, based on the loss or recovery of righting reflex, used as a proxy for conscious states, genetic deletion of connexin 36, a gap-junction protein, increases sensitivity to the hypnotic effects of both isoflurane and propofol [182]. These studies indicate that desynchronization of saltatory conduction between clustered neurons contributes to reduced overall cortical network excitation by anesthetics.

3. POSTSYNAPTIC ANESTHETIC EFFECTS

The neurophysiological effects of general anesthetics involving postsynaptic modulation are largely mediated through ligand-gated ion channels that play essential physiological roles in inhibitory and excitatory synaptic transmission: $GABA_A$, nicotinic acetylcholine, and AMPA- and NMDA-type glutamate receptors [77, 183]. Glutamate receptors are anchored by actin filaments, mostly in dendritic spines, postsynaptic structures that compartmentalize biochemical and cell biological processes critical for excitatory synaptic transmission and plasticity [19, 184, 185]. Transient alterations in spine structure and function and the underlying actin dynamics also provide plausible mechanisms for acute anesthetic action [20, 21, 186].

3.1. Receptor Signaling

3.1.1. g-Aminobutyric Acid Receptors

Considerable evidence indicates that the neurodepressive actions of general anesthetics involve enhancement of inhibitory synaptic transmission [1, 187-191]. GABA, the major inhibitory neurotransmitter in the mammalian brain, activates two distinct receptor subtypes: $GABA_A$ receptors, pentamers composed of multiple subunits that form a Cl^--selective ion channel; and $GABA_B$ receptors, single subunit receptors that couple to G-proteins and modulate K^+ and Ca^{2+} channels [192]. $GABA_A$ receptors mediate both phasic synaptic (fast) and tonic extrasynaptic (slow) inhibitory transmission; they are sites of action for most general anesthetics [116, 193, 194].

The halogenated ethers enflurane, halothane, and isoflurane [195-198] as well as the intravenous anesthetics propofol [199] and etomidate [200] all enhance $GABA_A$ receptor function at clinically relevant concentrations shown by enhancement of $GABA_A$-mediated currents and Cl^- flux in cells, brain slices and brain homogenates (reviewed in [201, 202]). Intracerebroventricular picrotoxin, a $GABA_A$ receptor antagonist, increases isoflurane MAC, requiring higher doses to achieve a surgical plane [203]. $GABA_A$ receptor modulation by propofol or pentobarbital has distinct dose-dependent effects likely involving multiple sites of action [204]; clinical concentrations of propofol potentiate GABA-activated currents, increase open channel frequency, and reduce the rate of desensitization, while intermediate concentrations directly activate $GABA_A$ channels, and even higher concentrations inhibit receptor function [205-209]. Electrophysiological and radioligand binding experiments suggest that etomidate shares this ability to interact with $GABA_A$ receptors [210-212], potentiating synaptic and extrasynaptic $GABA_A$- mediated currents by increased channel open time and probability of channel opening [213, 214]. Similarly, most volatile anesthetics enhance the amplitude of $GABA_A$-

mediated currents and prolong synaptic inhibition [215] by direct effects on channel gating, as suggested by the use of partial agonists [216]. Heterogenous effects on miniature-IPSCs and evoked-IPSCs suggest a larger contribution by extrasynaptic receptors [194, 217]. Modulation of extrasynaptic $GABA_A$-mediated tonic conductance by volatile anesthetics was first demonstrated in CA1 pyramidal neurons [218], followed by single synapse preparations from CNS slices [215].

$GABA_A$ receptors are pentamers formed by different glycoprotein subunits (α1-6, β1-3, γ1-3, δ, ρ1-3, and ε, φ, π), providing numerous potential combinations with distinct pharmacological profiles [219-221] that show variable sensitivity to allosteric modulators [222]. Subunit requirements for the formation of functional recombinant $GABA_A$ receptors in cell lines and *Xenopus* oocytes are various [223-226], but most $GABA_A$ receptors *in vivo* consist of α, β,and γ subunit complexes [227]. Receptors composed of α1β3 can be expressed *in vitro* and form functional GABA- activated channels [228-231] that are fully sensitive to general anesthetics [232, 233]. Differences in β subunits maybe species-specific; rodent β1 and murine β2 and β3 form homomeric receptors that are selectively opened by pentobarbital, etomidate, and propofol, but are less sensitive to GABA [234-237], unlike human and bovine β1 subunits expressed in oocytes [235, 238], suggesting distinct drug- and neurotransmitter-bound states [239]. Site-directed mutagenesis has identified key subunits involved in the anesthetic modulation of $GABA_A$ receptors. A point mutation in the β1 subunit (M286W) abolishes potentiation of GABA effect by propofol, without altering direct activation by higher concentrations [240]. Replacing the asparagine residue at position 265 on either β2 or β3 subunits inhibits the modulatory actions of enflurane and isoflurane [241, 242] as well as both the modulatory and direct effects of etomidate and propofol [243], findings that are further substantiated in mouse models. Cultured hippocampal neurons or cortical brain slices from β2 (N265S) mice show diminished potentiation of GABA-induced Cl^- currents by etomidate or less effective reduction of spontaneous firing by etomidate and enflurane, respectively [244]. Direct *in vivo* measurements of anesthetic endpoints show that selective agonism of receptors containing the β3 subunit contributes to etomidate anesthesia, with both β2 and β3 subunits contributing to sedation [245, 246] and loss of righting reflex (LORR) [244, 245]. Thus, $GABA_A$ receptors containing the β2 and β3 subunits are sufficient for most anesthetic endpoints, but potentiation caused by volatile anesthetics are smaller compared to intravenous anesthetics at equi-anesthetic concentrations, suggesting additional targets. Genetically engineered mice that lack the β3 subunit are more resistant to the immobilizing effects of enflurane, isoflurane, and halothane, but not loss of consciousness, suggesting separate anesthetic states may also be mediated by regional $GABA_A$ receptor heterogeneity [247-250]. In the neocortex, both α1 and β2 subunit-containing $GABA_A$ receptors contribute to the sedative effects of volatile anesthetics [191], including depression of action potential firing correlated with increased GABAergic inhibition by isoflurane, enflurane, and halothane [251].

The $GABA_A$ receptor is made up of five subunits, each of which is proposed to contain four transmembrane segments (TM1-4), including a short extracellular loop between TM2 and TM3 that is involved in channel gating [252]. Chimeric studies demonstrate that transmembrane domains of α and β subunits are essential for positive modulation of GABA binding and modulation by anesthetics. The GABA-potentiating action of propofol is influenced by the α1 subunit, particularly the TM2 region [253], while the TM3 domains of the α2 and β2 subunits are associated with binding [254, 255] and increased affinity for etomidate and propofol [240]. In contrast, enhancement of submaximal GABA-activated currents by intravenous anesthetics are eliminated by mutation of the G219 residue in the TM1 region of the β2 subunit [256]. Moreover, residues within TM2 and TM3 of $GABA_A$ α2 and β1 subunits are necessary for positive receptor modulation by isoflurane [240, 257, 258] with some evidence of α1 and α4 involvement in isoflurane binding [259] and its hypnotic [260, 261] and amnestic actions [262], respectively. In the dentate gyrus, levels of α1 and γ2 subunits are higher at the synapse compared to α4 and δ subunits that are expressed more extrasynaptically [263], suggesting further regional and cellular specificity as the γ2 subunit can influence pharmacologic sensitivity as effects of isoflurane on peak amplitude and on the kinetics of deactivation and desensitization are substantially reduced in γ2-containing receptors [264].

Impaired memory is a potent effect of anesthetics and was initially thought to involve tonic inhibitory conductance generated primarily by α5 subunit-containing $GABA_A$ receptors [265]; hippocampal slices and primary hippocampal neurons exhibit a tonic conductance generated by α5 $GABA_A$ receptors that is enhanced by several classes of anesthetics, including propofol [116], isoflurane [265], and etomidate [266]. Subsequent studies support differential modulation of both synaptic and extrasynaptic $GABA_A$ receptors in effects of anesthetic on memory [267-269]. In hippocampal slices, long-term potentiation, normally impaired by etomidate, remains intact in mice with a null mutation of the α5 subunit compared to wild-type littermates [266]. Correspondingly, wild-type mice exhibit increased sensitivity to the amnestic effects of etomidate as well as impaired performance in hippocampal-dependent learning and memory tasks compared to α5-subunit-deficient mice [266, 270].

3.1.2. Nicotinic Acetylcholine Receptors

$GABA_A$ receptors are members of the pentameric ligand-gated ion channel superfamily that also includes muscle- and neuronal-type nicotinic acetylcholine receptors (nAChR; [271]. Due to their greater accessibility, initial studies focused on anesthetic inhibition of muscle-type nAChRs at the neuromuscular junction, a target of local anesthetics [272]. However, neuronal nAChRs that play a crucial role in synaptic transmission, both as postsynaptic mediators of fast synaptic responses and at presynaptic sites, were later found to have greater anesthetic sensitivity, particularly to volatile anesthetics [273]. Neuronal receptors are expressed as homomeric or heteromeric complexes [274, 275] with repeating α7-α9 subunits or heteromers of two or three α and β subunits in different stoichiometries, respectively [275, 276]. The different subunit combinations enable functional diversity in ion conductance, selectivity, and kinetics in both native and heterologous systems [275, 277].

Initially, the effects of general anesthetics were tested on nicotinic receptors in mollusks [278, 279] and bovine adrenal chromaffin cells [280, 281], which showed inhibition by inhalational agents. Voltage-clamp studies on acetylcholine-activated currents of rodent α4β2 nAChR expressed in *Xenopus* oocytes confirmed high sensitivity to inhalational anesthetics including halothane, isoflurane, and sevoflurane at anesthetic and sub-anesthetic doses, with higher concentrations required for inhibition by propofol [273]. Heteromeric human neuronal nAChRs (α2β4, α3β4, α4β2) expressed in oocytes or human embryonic kidney cells were also inhibited by isoflurane, sevoflurane, halothane and ketamine with subunit-specific sensitivities [282-284], largely determined by a single amino acid residue (β2-Val 253; β4-Phe 255) identified by chimeric and single amino acid mutants of nAChR [285]. In contrast, α7 subunits directly interact with anesthetics [286, 287], but homomeric α7 receptors were mostly insensitive to isoflurane or propofol at clinical concentrations, requiring supraclinical doses for inhibition [288, 289]. However, native channels in dissociated rat cortical neurons exhibit inhibition by clinical concentrations of halothane for both α4β2-type and α7-type currents, with lower sensitivity for the latter, by accelerating the decay phase of α7-type currents while slowing decay of α4β2-type currents [290]. Complementary dynamic simulation models further propose multiple putative binding sites for halothane interaction with α4β2 nAChR in the open confirmation [291]. nAChR modulation by various anesthetics possibly contributes to analgesia [272], but is not directly involved in producing hypnosis or immobility [292-294]. However, specific loss of cholinergic basal forebrain neurons increases time to emergence from propofol and pentobarbital, and reduces behavioral excitation during halothane exposure [295].

3.1.3. Glutamate Receptors

Two major classes of ionotropic glutamate receptors have been identified: *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors [296]. The NMDA receptor is blocked in a voltage-dependent manner by physiologic concentrations of Mg^{2+} and requires binding of both glutamate and the co-agonist glycine for activation, allowing influx of Ca^{2+} and Na^{+} [297]. Considerable evidence suggests interactions between anesthetics and NMDA receptors: volatile anesthetic potency is increased by NMDA receptor antagonism [298, 299], and NMDA-stimulated currents are inhibited by isoflurane in cultured hippocampal neurons, decreasing both the frequency of channel opening and channel open time [300]. In rat brain homogenates, disruption of glutamate-stimulated binding of the NMDA pore blocker, MK-801, with reversal by the NMDA receptor positive modulator, glycine, show direct interaction of enflurane and halothane with NMDA receptors and subsequent ion channel inhibition [301, 302]. Volatile anesthetic effects on glutamatergic synaptic transmission are most likely heterosynaptic as both NMDA and AMPA receptor antagonists, administered intrathecally, can reduce the MAC of isoflurane in rats [303, 304] , and they preferentially block AMPA over NMDA receptor-mediated currents at high doses of halothane [22, 305, 306].

Unlike volatile anesthetics, ketamine and propofol have opposing effects on NMDA receptors. Ketamine directly blocks NMDA receptors to produce anesthetic and analgesic effects [307-309] by two mechanisms: an open-channel block and closed-channel block characterized by a decrease in open frequency with no change in open time [310]. In contrast, clinical concentrations of propofol do not show significant effects on excitatory transmission based on effects on NMDA and AMPA glutamate receptors expressed in *Xenopus* oocytes [311] or on the release of glutamate from rat synaptosomes [39, 312]; any direct effects of propofol on NMDA receptors occur only at supratherapeutic concentrations [313].

NMDA receptors are heteromeric protein complexes comprising at least two of seven known subunit types: GluN1, GluN2 (A-D), and GluN3 (A-B), with proper assembly requiring GluN1 and at least one GluN2 subunits [314]. The functional AMPA receptor is usually a homomeric or heteromeric tetrameric complex with various compositions of four different subunits: GluA1-4 [315]. Using recombinant GluN1/GluN2A and GluN1/GluN2B glutamate receptors, [316] showed that clinical concentrations of isoflurane, sevoflurane, and desflurane inhibit NMDA receptors in a reversible, dose-dependent, and voltage-insensitive manner. Comparing wild-type and mutant GluN1/GluN2A receptors extend these findings to show that amino acid substitutions in TM3 of GluN1 and TM4 of GluN2A subunits reduce the action of various anesthetics [317]. Although equi-anesthetic concentrations of most anesthetics inhibit NMDA receptors to some extent [318], genetic deletion of NMDA receptor subunits does not show specificity to ketamine in reducing sensitivity to anesthesia/hypnosis [319] or to volatile anesthetics in producing immobilization [320].

Glutamate receptors are functionally modulated by signaling that regulates their state of phosphorylation and, in turn, activity [321]. Although direct channel effects are lacking, investigation of propofol effects on GluN1 subunit phosphorylation in cultured neurons found reduced phosphorylation and activation of ERK leading to alterations in intracellular Ca^{2+} and transcription [322-324] at amnestic concentrations of propofol [325]. Moreover, propofol increases phosphorylation of GluA1, although it is unclear whether this contributes to any specific pharmacological action of propofol [326]. Similarly, both *in vitro* [327, 328] and *in vivo* studies [329] show alterations of NMDA GluN1 and AMPA GluA1 subunit phosphorylation by ketamine and isoflurane, with a possible role in analgesia [330].

3.2. Dendritic Spine Dynamics

Modulation of neurotransmission by general anesthetics produces both therapeutic and undesirable effects, including neurotoxicity and cognitive dysfunction. Multiple targets have been identified for the neurophysiological effects of general anesthetics (*vida supra*), but cumulative and downstream effects on synaptic plasticity can lead to acute or delayed cognitive dysfunction [331-333]. Dendritic spines form the postsynaptic contact sites for most excitatory synapses and represent the structural basis of glutamatergic synaptic plasticity [19]. They are of significant interest as a subcellular substrate for anesthetic action and enduring cognitive effects as alterations in spine number and shape are associated with cognitive and developmental dysfunction in various neurological disorders [334].

Spine changes following anesthetic exposure depend on neuronal age: during development, anesthetic exposure can increase or decrease dendritic spine and filopodial density depending on the stage of synaptogenesis [335-338]. Synaptogenesis is a critical period of development, shaping connectivity and regulating the balance between excitatory and inhibitory synaptic function [339]. In the mouse somatosensory cortex and hippocampus, anesthesia with propofol or ketamine increased the density of dendritic spines [335, 340]; similar structural modifications are also observed in rat prefrontal cortex after treatment with isoflurane, sevoflurane, or desflurane [336]. In mature neurons, there is transient and reversible anesthetic-induced disruption of spine structure [20, 21]. Intravital imaging of young adult mouse cortical neurons showed that ketamine/xylazine or isoflurane had no effects on spine formation or elimination but temporarily reduced elimination of filopodia, precursors of established spines [20].

3.2.1. Actin Dynamics

Spine stability and structure are directly regulated by dynamic changes in the actin cytoskeleton that help anchor glutamate receptors to postsynaptic sites [184, 185] and modulate learning and memory [341-343]. Previous studies have implicated filamentous actin in anesthetic effects on neurons and astrocytes [344, 345]. In developing neurons, sevoflurane can reduce the length of filopodia by an actin-dependent mechanism [346], and inhibition of Rho-A activated kinase (ROCK), a kinase involved in actin dynamics, attenuates the effects of high concentrations of ketamine [347]. Similarly, Matus and colleagues [186] demonstrated that volatile anesthetics, including isoflurane and enflurane, reversibly block rapid actin-based spine motility in the spine head (often called ''morphing''). Dendritic spines undergo transient reductions in area and number following isoflurane exposure in the hippocampus, effects that are prevented by actin filament stabilization [21].

3.2.2. BDNF Signaling

As a key modulator of synaptic plasticity, the mature form of brain derived neurotrophic factor (mBDNF), cleaved from its precursor proBDNF, regulates spine structure [348, 349]. ProBDNF and mBDNF signal *via* distinct receptors to mediate divergent actions on neuronal survival, structure, and synaptic plasticity [350, 351]. Cleavage of proBDNF to mBDNF is developmentally regulated; in the early postnatal brain, high levels of proBDNF activate p75 receptors to promote cell death and attenuate synaptic transmission [352, 353]. Quantitative histology and evidence from immunofluorescence microscopy suggest that isoflurane [344], propofol [354] and a cocktail of general and local anesthetics [355] produce neurotoxicity in the developing brain *via* proBDNF signaling. Upregulating cleavage of proBDNF to mBDNF or direct pharmacological inhibition of p75 receptors attenuates both isoflurane- and propofol-induced neuronal apoptosis [354] and isoflurane-induced destabilization of dendritic filopodia [344]. In contrast, in the adult brain, mBDNF regulates the density and morphology of dendritic spines [348, 349], promoting neuronal survival and enhancing synaptic plasticity *via* TrKB signaling [356-358]. *In vivo* studies support a role for down-regulation of mBDNF by anesthetics. In humans, propofol or isoflurane significantly reduces plasma BDNF concentration intraoperatively and 24 h after surgery [359]. Moreover, epigenetic enhancement of BDNF signaling improves cognitive impairments induced by isoflurane in aged rats [360].

Collectively, these studies identify dendritic spines as a structural target for acute anesthetic action on hippocampus-dependent memory, and possibly persistent effects on network function if original connections are not restored.

4. FUNCTIONAL OUTCOMES OF ANESTHETIC-INDUCED SYNAPTIC PLASTICITY

4.1. Preclinical Assessments of Cognitive Function

4.1.1. Synaptic Potentiation and Depression

Synaptic plasticity is the strengthening or weakening of synapses in response to activity patterns; it involves complex modulation by distinct signaling proteins that alter cellular activity. The two main types of synaptic plasticity are either a persistent decrease [long-term depression (LTD)] or increase [long-term potentiation (LTP)] in synaptic efficiency [361], involving in part Ca^{2+} entry and depolarization. LTP and LTD are critically dependent on excitatory synaptic transmission through hippocampal dendritic spines, which are modulated during memory consolidation [351] and blocked by anesthetics [362, 363] both acutely [364, 365] and chronically [366-368], and following anesthetic exposure during critical periods of neurodevelopment [369, 370].

In CA1 pyramidal neurons of rodent hippocampal slices, clinical concentrations of halothane, isoflurane, and sevoflurane reduce the probability of LTP induction likely associated with decreased postsynaptic depolarization [362, 371, 372], while ketamine blocks LTP [373] *via* inhibition of NMDA receptor-mediated Ca^{2+} influx [374, 375] or AMPA receptor signaling [376]. Isoflurane-induced persistent changes in synaptic strength have been attributed to potentiation of $GABA_A$ and glycine receptor function [269], as well as inhibition of nAChR [377-379], AMPA and NMDA receptors [18, 380, 381]; modulations that contribute to reduced overall glutamatergic transmission and decreased postsynaptic Ca^{2+} currents [382]. *In vivo,* depression of LTP induction is recapitulated in electrophysiological recordings of adult rats with exposure to clinical concentrations of sevoflurane [383], although confounding effects of halothane cannot be completely ruled out here. Effects of propofol on synaptic plasticity in the CA1 region are variable and dose-dependent: low doses of propofol enhance the development of LTD and impair maintenance of LTP by an NMDA receptor-dependent mechanism [366], while supratherapeutic concentrations inhibit LTP mediated by $GABA_A$ receptors [384-386]. $GABA_A$ receptors on non-pyramidal, inhibitory neurons also play a role in impairing LTP by etomidate [387].

4.1.2. Animal Behavior

These functional deficits in synaptic plasticity intersect the cellular and behavioral changes described in preclinical studies [331, 368, 388-391]. Non-human primates are a good animal model due to the similarities in the physiology, pharmacology, metabolism, and reproductive systems to those of humans. Exposure of fetal or neonatal monkeys to isoflurane, ketamine, or propofol for 3, 5, or >5 h causes

cortical neuronal cell death [390, 392-397]; these cellular changes are associated with long-lasting deficits in brain function following ketamine [398] and motor, social, and emotional deficits following isoflurane [399, 400].

Exposure to common anesthetic agents in young or adult rodents results in performance impairment in hippocampus-dependent [331, 401, 402] or motor cortex-dependent [403] learning tasks with differences based on type of anesthetic agent [404], the number of exposures [363], and sex [405, 406]. Possible molecular mechanisms include caspase activation [407, 408], suppression of ERK signaling [409-411], increased JNK signaling [412], and reduced PSD-95 expression [413-415] in young rodents, as well as reduced hippocampal acetylcholine levels [416-419] and nACh receptor signaling [420, 421], and elevated calcineurin-mediated neuroinflammation [422] in aged rodents. In contrast, evidence for cognitive changes following general anesthesia in adult rodents is inconclusive and studies have produced mixed results with some showing no persistent changes in memory function [369, 423-427], and others showing impaired hippocampus-dependent learning as assessed by Morris water maze and Barnes maze, weeks following isoflurane exposure [367, 428]. Sustained increases in $\alpha 5$ $GABA_A$ receptor activity in the adult mouse brain following a single exposure to isoflurane or etomidate is implicated in lasting impairments in hippocampal memory performance and synaptic plasticity [429-431]. Moreover, in adolescent rats, isoflurane-elicited affective and cognitive deficits are mitigated by blocking extrasynaptic $GABA_A$ receptor function [432], consistent with a wider range for the developmental window of susceptibility to enduring effects of general anesthesia. Reduction of BDNF expression, including *via* epigenetic mechanisms [433], has also been associated in learning and memory dysfunction in adult rats following isoflurane [433, 434], sevoflurane [435], and ketamine [436] administration.

4.1.3. Intersection with Alzheimer's Disease

Several studies have suggested that perioperative factors, including anesthetics, contribute to Alzheimer's disease pathogenesis. In various cell lines transfected with Alzheimer's disease mutant human amyloid precursor proteins (APP), clinically relevant concentrations of isoflurane can induce apoptosis *via* disruption of calcium homeostasis [437-439], alter APP processing, and increase amyloid beta (Aβ) levels [440, 441]. Accumulation of brain Aβ plaque burden was also recapitulated *in vivo* in Alzheimer's disease mice with halothane exposure [442]. Moreover, in wild-type rodents and in Alzheimer's disease model mice, sevoflurane, isoflurane, or enflurane induced Aβ oligomerization [443], tau hyperphosphorylation and cognitive decline [444-447] mediated by Akt and ERK activation [448, 449].

4.2. Clinical Assessment of Cognitive Function

As major pharmacological modulators of synaptic transmission, anesthetics impair memory and learning in animal studies, but translational relevance and extrapolation to clinical practice remain highly debated. Postoperative cognitive impairments recently termed perioperative neurocognitive disorders (PND; [450]), include delirium and postoperative cognitive dysfunction (POCD), manifested as an acute, confusional state occurring hours to days after surgery, to more durable deficits in memory, attention, concentration, and executive functions, respectively. Although the duration and onset of perioperative neurocognitive disorders are variable, longitudinal studies suggest that they are distinct manifestations of neurocognitive deficits, with variable incidence, triggered by the intersection between surgery, anesthesia, age, preexisting vulnerability, and individual cognitive trajectory [451-456].

4.2.1. Risk Factors for Elderly Populations

Many prospective and retrospective clinical studies have reported perioperative neurocognitive disorders affecting up to 41% of patients older than 60 years [457-459], while other reports did not detect a difference in objectively measured cognitive decline [460, 461]. The elderly are particularly affected but additional risk factors include pre-existing cognitive impairment or disease as well as education level [462, 463], type of surgery [464-468] and specific anesthetic agents and techniques [469]. For example, elderly patients undergoing desflurane or propofol anesthesia exhibit better cognitive function than those undergoing sevoflurane exposure based on better quality of emergence [470-474] and/or lower surgery-induced pro-inflammatory effects [475].

Several studies have explored the possible association between a specific genotype and perioperative neurocognitive disorders; polymorphisms of the human gene C-reactive protein [476], P-selectin [477], and platelet glycoprotein IIIa [478] suggest an additional vulnerability in genotype may increase susceptibility. Specific genetic variations in apolipoprotein E alleles are linked to increases in the risk of perioperative neurocognitive disorders and Alzheimer's disease [479, 480] as both general anesthesia and Alzheimer's disease are associated with deficits in cholinergic transmission [481-483] and synapse dysfunction [484]. Human biomarkers of Alzheimer's disease such as Aβ levels in the cerebrospinal fluid are increased 24 h following surgery under isoflurane anesthesia [485]. However, observational reports have been conflicting. In retrospective studies, no association between the risk of Alzheimer's disease and exposure to anesthesia in the 1- and 5-years preceding disease onset was found, nor between the risk of Alzheimer's disease and the number of surgical procedures [486-488]. Furthermore, no conclusive evidence from observational studies, including meta-analysis of case control studies or retrospective cohort studies, shows a link between anesthesia and surgery with the development of clinical dementia [489]. In contrast, a national case control study showed an associated risk between multiple surgeries with general anesthesia and a reduction in the onset of dementia [490]. Collectively, perioperative neurocognitive disorders are multifactorial with various biological and socioeconomic predisposing factors. Clinical observations may be confounded by temporal differences in onset of cognitive impairments, type of standardized testing, as well as inability to differentiate causation by anesthesia, surgery and/or inflammation.

4.2.2. Risk Factors for Juvenile Populations

Juvenile animals are highly susceptible to anesthetic-induced cognitive impairments. There is considerable preclinical evidence describing how general anesthetics alter brain and behavioral development in young animals [491]. Some

human studies have found an association between exposure to anesthesia in early childhood and increased risk of poor neurodevelopmental outcome [492-497], while some cohort studies have found no association [498-500].

In a randomized controlled trial comparing the neurodevelopmental outcome in children receiving general or spinal anesthesia (GAS study), exposure to sevoflurane for an average of just under one hour in infancy did not increase the risk of adverse neurodevelopmental outcomes at two or five years of age [501, 502]. The Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) study used a sibling-matched cohort design to test whether a single exposure to general anesthesia (intravenous or volatile) in healthy children younger than 36 months was associated with increased risk of impaired global cognitive function in early childhood (8 to 15 years), also showing no significant differences [503]. However, changes in primary or secondary measures may be dependent on the neuropsychological domain and specific patterns of vulnerability and insult. The Mayo Anesthesia Safely in Kids (MASK) study tested exposure to multiple procedures requiring anesthesia prior to age 3 years and found no associated deficits in general intelligence but did report modest impairments in processing speed and fine motor coordination [504]. These three studies provide strong evidence that a single short exposure to general anesthesia at a young age does not result in measurable alterations in neurodevelopmental outcome, but long-term effects of longer and multiple exposures on emotional, physical, or social development remain unknown.

CONCLUSION

Various presynaptic and postsynaptic signaling proteins involved in synaptic transmission and plasticity have been identified as major targets for the neurophysiological effects of general anesthesia. The differential effects between various anesthetics on these multiple targets likely contribute to their agent-specific pharmacological actions but may also mediate distinct undesirable toxic effects. Based on animal studies, understanding the mechanisms involved is essential for the development of more specific and safer anesthetic drugs, as well as for mechanism-based application of currently available agents. To date, the overwhelming translational plausibility of anesthetic neurotoxicity, even in vulnerable populations, has not been convincingly supported clinically, but the potential significance of an effect mandates further inquiry.

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CONFLICT OF INTEREST

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