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Mechanisms of action of general anesthetics

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TABLE OF CONTENTS

1. ABSTRACT

Since William Morton successfully demonstrated the use of inhaled ether for surgical anesthesia in 1846, the development of new anesthetics and safe general anesthesia techniques have contributed greatly to the advancement of surgery and other invasive procedures. However, the underlying neurocellular mechanisms by which the state of general anesthesia is achieved are only just beginning to be understood. The general anesthetic state comprises multiple components (amnesia, unconsciousness, analgesia, and immobility), each of which is mediated by effects on different neurotransmitter receptors and neuronal pathways. In this review, we focus on the mechanisms of action of inhaled and intravenous anesthetics, and we describe the neuronal systems thought to be involved in mediating the clinically relevant actions of general anesthetics. We then describe the neurotransmitter receptors that are the principal targets of many general anesthetics, in particular ã-aminobutyric acid type A receptor subtypes.

2. INTRODUCTION

General anesthesia is a complex pharmacological response induced by a chemically heterogeneous class of drugs, the so-called general anesthetics. Every year, tens of millions of patients are exposed to general anesthetics, drugs that remove the most precious human attribute—consciousness. By allowing for prolonged invasive procedures, general anesthesia is one of the foremost achievements of modern medical science. However, there is no objective or widely accepted definition of general anesthesia. The actions of general anesthetics depend on the concentrations reached, and include amnesia, excitation, analgesia, hypnosis, and hyperreflexia at low concentrations, and deep sedation, muscle relaxation, and reduced motor and autonomic responses to noxious stimuli at higher concentrations (1).

For more than a century, two concepts, the unitary hypothesis and the Meyer-Overton rule, have dominated

our understanding of the mechanisms underlying the actions of general anesthetics. Studies conducted over the past few decades have demonstrated that each of the behavioral responses to anesthetics is caused by selective actions on different parts of the brain and (or) specific molecular targets (1-4). In particular, the neurotransmitter-gated ion channels or ionotropic receptors are the major molecular targets of general anesthetics, and among these, the gamma-aminobutyric acid type A ($GABA_A$) receptor plays an important role. In the present review, we analyze the different theories on general anesthetic action and summarize the neuronal systems and molecular targets involved.

3. GENERAL ANESTHETICS

In 1846, William T. Morton at Massachusetts General Hospital successfully demonstrated that a patient who had inhaled ether did not experience pain during the removal of a tumor from his neck. Only a few years later, J. Simpson introduced chloroform into medical practice, while H. Wells reported the anesthetic properties of nitrous oxide. Over the ensuing decades, it became clear that general anesthesia is rarely achieved by a single agent but rather requires a combination of general anesthetics and other agents such as analgesics, muscle relaxants, and sedatives (1). Today, a variety of volatile and intravenous anesthetics are in clinical use, which demonstrated safety and efficacy. Structurally unrelated volatile compounds, such as ether (and safer derivatives such as isoflurane and halothane), chloroform, and nitrous oxide, possess analgesic and anesthetic properties, which led many to believe that these agents must act as non-specific neural depressants. Intravenous anesthetics, including pentobarbital, propofol, and thiopental, have been introduced over the last half-century for clinical surgery (2). The pharmacological studies reviewed here have shown that both types of anesthetics interact with specific molecular targets.

4. ACTIONS OF GENERAL ANESTHETICS

4.1. Sedation, hypnosis, amnesia, and immobility

The essential goals of the anesthetic state are unconsciousness, immobility, and amnesia.

4.1.1. Hypnosis and sedation

Hypnosis is commonly defined as a drug-induced impairment of the sensory and cognitive functions necessary to respond to environmental stimuli (2). In the clinical setting, patients are assumed to be unconscious if they fail to respond to verbal commands or mild shaking (1). Sedation refers to a decreased level of arousal, as indicated by longer response times to stimuli, decreased motor activity, and slurred speech. There are various definitions of sedation, which can be used as a synonym of hypnosis or to indicate incomplete hypnosis (1, 5). Sedation and hypnosis can be distinguished by the brain areas depressed. At sedative concentrations, propofol reduces neuronal activity prominently in neocortical networks. At higher (hypnotic) concentrations, activity in subcortical structures, including the thalamus, midbrain reticular formation, and possibly the hypothalamus, is also depressed (1).

During propofol-induced hypnosis, global cerebral blood flow and glucose metabolism are decreased significantly, and some brain regions, including specific areas of the cortex, thalamus and midbrain, show markedly higher levels of depression than others (6, 7). Similar to propofol, sevoflurane and the benzodiazepines midazolam and lorazepam cause a considerable decrease in thalamic cerebral blood flow during deep sedation (8, 9). Alkire proposed that thalamocortical cells, which have been identified as the main generators of the cortical delta rhythm, are involved in delta activity during the induction of anesthesia (10). Recent studies also revealed that the general anesthetic propofol gives rise to frontal and occipital á-rhythm at dose levels sufficient to induce loss of consciousness, which could be attributed to thalamocortical cells (11-14).

How does propofol affect the transmission of sensory information through the thalamus? At mildly sedating concentrations, propofol increased the rating of thermal pain in human subjects with a corresponding increase in evoked activity in the thalamus and somatosensory cortex (15). When subjects lost consciousness, noxious stimulus-evoked thalamic responses were abolished. At hypnotic concentrations of propofol, thalamic and cortical responses ceased. In addition, studies on auditory-evoked potentials demonstrated that propofol-induced loss of consciousness correlated with impaired transmission of auditory signs through the thalamus (16).

Although most general anesthetics strongly depress neuronal activity in the thalamocortical system at hypnotic concentrations, this is not necessarily the most important mechanism of anesthesia-induced loss of consciousness (17, 18). For example, ketamine produces anesthesia without reducing cortical metabolism, glutamate release, or sensory information flow through the thalamus (19-23). The potent antinociceptive effects of ketamine on NMDA receptors in the spinal cord and its inhibition of acetylcholine release from the pons also contribute to unconsciousness (19, 23). *In vitro* studies on isolated cortical networks also indicate that direct anesthetic actions on cortical neurons are involved in the hypnotic state. These investigations demonstrated that the slowing of oscillatory activity in the gamma (24) and theta/delta 4 ranges can be elicited by anesthetics in the absence of effects on subcortical structures, including the thalamus and midbrain.

4.1.2. Amnesia

Amnesia refers to a partial or complete loss of memory. Specific types of memories (e.g., episodic, conditioned, working, sensory, and motor) are formed within distinct brain structures, including the hippocampus, amygdala, prefrontal cortex, various sensory cortices (depending on stimulus modality) and motor cortices. An important goal of anesthesia is to block memory of the procedure. However, both implicit and explicit memory

formation is possible. Explicit memory refers to information that is consciously perceived and retained, and can subsequently be reported. Patients who accidentally awaken from anesthesia during surgery frequently have an unpleasant experience that is recalled for a long time thereafter. Implicit memory refers to information that is unconsciously perceived and cannot be reported (1).

Functional imaging studies in which human subjects were asked to memorize words during the administration of propofol identified that neuroanatomic regions subserving working memory were inhibited by general anesthetics (25). Because the concentration-dependence of propofol is similar for both depression of regional cerebral blood flow (rCBF) and oxidative metabolism, it is reasonable to assume that the propofol-induced depression of rCBF is directly associated with decreased neuronal activity (26). At mildly sedating concentrations, propofol decreased rCBF in right prefrontal and parietal regions close to those activated by a baseline working memory task. By contrast, even heavy propofol sedation did not affect the enhancement of rCBF in the primary auditory cortex induced by an increase in the word presentation rate. This differential sensitivity of cortical networks indicates that the sedative and amnesic effects of propofol do not result from nonspecific global depression of neuronal excitability. This conclusion was confirmed by recent studies demonstrating that higher cognitive functions of the frontal cortex are more sensitive to propofol sedation than event-related potentials generated in or around the primary auditory cortex (27). These results are compelling evidence that higher cognitive functions are selectively impaired during propofol sedation, whereas cortical sensory processing remains functional.

The aforementioned studies were conducted using an intravenous anesthetic (propofol). Do low concentrations of volatile anesthetics have a similar effect? Heinke and Schwarzbauer investigated the actions of isoflurane on human subjects performing a visual search task by functional magnetic resonance imaging of blood oxygenation level-dependent signal changes (28). At concentrations causing moderate sedation, subcortical areas and cortical regions involved in early visual information processing remained unaffected, whereas task-related activation of cortical areas involved in higher cognitive function was depressed. Studies investigating the effects of isoflurane on the visual system of monkeys produced similar results (29, 30); at sedative concentrations, isoflurane did not alter visual-evoked responses in neurons of the primary visual cortex, whereas the higher-order processing responsible for integrating visual input into a coherent visual representation was markedly disturbed.

4.1.3. Immobility

General anesthesia must also inhibit movement in response to noxious stimuli. Numerous studies indicate that anesthetic-induced ablation of movement in response to a noxious stimulus is mediated primarily by effects on the spinal cord (31). In rats, transection of the upper thoracic spinal cord or precollicular decerebration only minimally affected the capacity of volatile anesthetics to depress movement (32, 33), whereas delivery of anesthetic drugs specifically to the brain resulted in a three- to four-fold increase in the dose required to suppress noxious stimulus-induced movement compared to direct spinal administration (31, 34). Kungys *et al.* also found that propofol induces immobility by acting on the ventral horn of the spinal cord via a GABAergic mechanism (35).

4.2. Theories of anesthetic action

A detailed understanding of the physiological effects of general anesthetics is crucial for their safe application in patients. A wide range of structurally unrelated agents possess anesthetic activity, suggesting a common mechanism of action (36, 37). Around 1900, Meyer and Overton proposed the “lipid theory”, which states that volatile anesthetics act nonspecifically by affecting the structure of the nerve cell membrane, a postulate based on the strong correlation between anesthetic potency and solubility in olive oil. However, most researchers have abandoned this theory. Anesthetics do cause slight perturbations in lipid structure, but these changes can be reproduced by small, behaviorally insignificant changes in body temperature (38). Moreover, optical isomers of several anesthetic agents differ in potency, which is inconsistent with their nonspecific activity (39). Furthermore, seminal studies by Franks *et al.* showed that general anesthetics in fact interact directly with receptor proteins (40). Thus, it now appears unlikely that the different structural classes of inhaled anesthetics act through a single common mechanism.

In the past few decades, research on the neurocellular mechanisms of general anesthetic action has focused on membrane ligand-gated ion channels (ionotropic receptors). At clinically relevant concentrations, general anesthetics alter the discharge properties of central neurons, while leaving axonal action potentials (mediated by voltage-gated Na and K channels) largely unaffected. In the sections that follow, we will discuss the different types of ionotropic receptors modulated by general anesthetics within the clinical concentration range (2).

5. MECHANISM OF GENERAL ANESTHETIC ACTIONS

5.1. Anesthetic actions on the nervous system

The question of where anesthetic agents act in the central nervous system (CNS) to produce the specific effects required for general anesthesia has been addressed only recently. Approximately 20 years ago, Kendig *et al.* put forward the hypothesis that general anesthetic actions on specific regions of the CNS result in different components of general anesthesia (unconsciousness, immobility, and amnesia) (41, 42).

Anesthetic-induced ablation of movement in response to pain is mediated primarily by the spinal cord rather than higher brain centers, as this effect is still observed following spinal transection (37). However, experiments in animals have shown that ascending signals from the spinal cord affect the hypnotic action of anesthetics in the brain (43, 44) and descending signals

modify the immobilizing actions of anesthetics in the spinal cord (34, 45). Mildly hypnotic concentrations of isoflurane reduced task-evoked brain activation in several distinct regions of the association cortex, whereas activity in the visual cortex, motor cortex, and subcortical regions remained unchanged (28). Omographic assessment of regional uptake of glucose in deeply anesthetized volunteers also indicated that the thalamus and midbrain reticular formation were more depressed than other regions (10).

Many recent studies have revealed associations between depression in specific brain sites and the behavioral effects of general anesthetics. Nelson *et al.* implicated the tuberomammilary nucleus, an ã-aminobutyric acid (GABA)-modulated region of the hypothalamus linked to sleep states, in the sedative actions of some intravenously administered general anesthetics and perhaps inhaled agents (5). The amnesic effects of general anesthetics are closely related to suppression of activity in the hippocampus, a brain structure known to be essential for the formation of episodic memory in humans (46, 47). Sedation is related to depression of the neocortex (48) and thalamus (49), while the effects on the hypothalamus presumably contribute to the hypnotic action of these agents.

5.2. Molecular targets of general anesthetics

General anesthetics produce widespread depression in the CNS by enhancing inhibitory neurotransmission and reducing excitatory neurotransmission. Excitatory neurotransmitters, such as glutamate and acetylcholine, cause depolarization, whereas inhibitory neurotransmitters such as GABA and glycine reduce postsynaptic activity either by hyperpolarization or by shunting excitatory currents. The physiological actions of anesthetics and the various behavioral response patterns elicited are closely linked to actions on neuronal excitability mediated by effects on ionotropic transmitter receptors. Among these, $GABA_A$, glycine, nicotinic cholinergic, and N-methyl-D-aspartate (NMDA) subtype glutamate receptors are the major molecular targets of general anesthetics. Potassium channels and sodium channels are also sensitive to general anesthetics. Anesthetic actions at $GABA_A$ receptors have received by far the most attention.

5.2.1. $GABA_A$ receptors

The $GABA_A$ receptors are the most abundant inhibitory neurotransmitter receptors in the CNS (50), and their potential importance as an anesthetic target has been appreciated for many years (5, 51, 52). Each receptor is a heteromeric transmembrane protein complex that includes a chloride-permeable pore that opens in response to GABA binding, leading to hyperpolarization of the cell membrane, shunting of excitatory inputs, and reduced neuronal excitability (53). There are 18 known $GABA_A$ receptor subunit genes in the human genome, and although the vast majority of neuronal $GABA_A$ receptors are composed of á1â2ã2, á2â3ã2, or á3âã2 heteromultimers, a variety of other subunit combinations can form functional channels. Moreover, the neuroanatomical distribution of the various subunits is not homogeneous, suggesting a possible reason for the concentration-dependent effects of general anesthetics in different brain structures (3).

The functional effects of general anesthetics on $GABA_A$ receptors also depend on their subcellular distribution on the cell surface (3). $GABA_A$ receptors clustered at postsynaptic terminals are exposed to near-saturating concentrations of GABA, resulting in the generation of transient inhibitory postsynaptic currents (IPSCs) (54). Enhancement of fast synaptic inhibition is generally accepted as the primary mechanism underlying the actions of many GABAergic drugs, including sedatives, anxiolytics, and general anesthetics. Indeed, general anesthetics enhance the action of GABA on the $GABA_A$ receptor and potentiate $GABA_A$ receptor-mediated IPSCs (2, 55). In addition, several anesthetics have been shown to reduce the desensitization of $GABA_A$ receptors in the continued presence of GABA, increasing the duration of the inhibitory response (55, 56). Furthermore, anesthetics at higher concentrations directly activate $GABA_A$ receptors in the absence of GABA (57).

However, a large number of $GABA_A$ receptors are distributed outside the synapse, contributing to tonic inhibition (47, 57). This tonic inhibitory conductance is generated by higher-affinity, slowly desensitizing $GABA_A$ receptors that are activated by low concentrations of ambient GABA or GABA that "spills over" from synaptic sites. This tonic conductance regulates neuronal excitability and information processing (58, 59) and general anesthetics potentiate the tonic currents generated by extrasynaptic $GABA_A$ receptors (60). This potentiation may in fact have a much stronger inhibitory influence on neurons than potentiation of synaptic IPSCs because the total charge transfer mediated by these extrasynaptic currents is 2−3 times larger than that mediated by (synaptic) miniature inhibitory postsynaptic currents (mIPSCs), which is attributed to differences in desensitization rate, GABA affinity, total receptor number, or some combination of these factors. Indeed, postsynaptic and extrasynaptic $GABA_A$ receptors have distinct kinetic properties owing to differences in subunit composition. At synapses, the predominant receptor subtypes appear to be α1–3β2/3γ2, whereas receptors containing α4–6(α4βxδ, α5βxγ2, and α6βxδ) are predominantly or exclusively extrasynaptic (3). The α1, β1, and β3 subunits possess important functional sites for volatile anesthetics (61, 62). Particularly, two amino acids in the α1 subunit are critical for anesthetic action: serine 270 in the transmembrane 2 region and alanine 291 near the extracellular region of transmembrane 3 (61). Recently, two studies performed using knockout animals showed interesting and clear-cut results (41, 42) that strongly link specific anesthetics to extrasynaptic $GABA_A$ receptors. Chandra *et al.* showed that mice lacking α4 subunits lack the ataxic, sedative and analgesic responses to gaboxadol, a drug that selectively targets extrasynaptic $GABA_A$ receptors (63). Cheng *et al.* demonstrated that mice lacking the α5 subunit showed no sedative-hypnotic effects, although they did show some amnesic effects (46). In addition to their differential distribution in various brain regions, the functional effects of general anesthetics are dependent on their specific

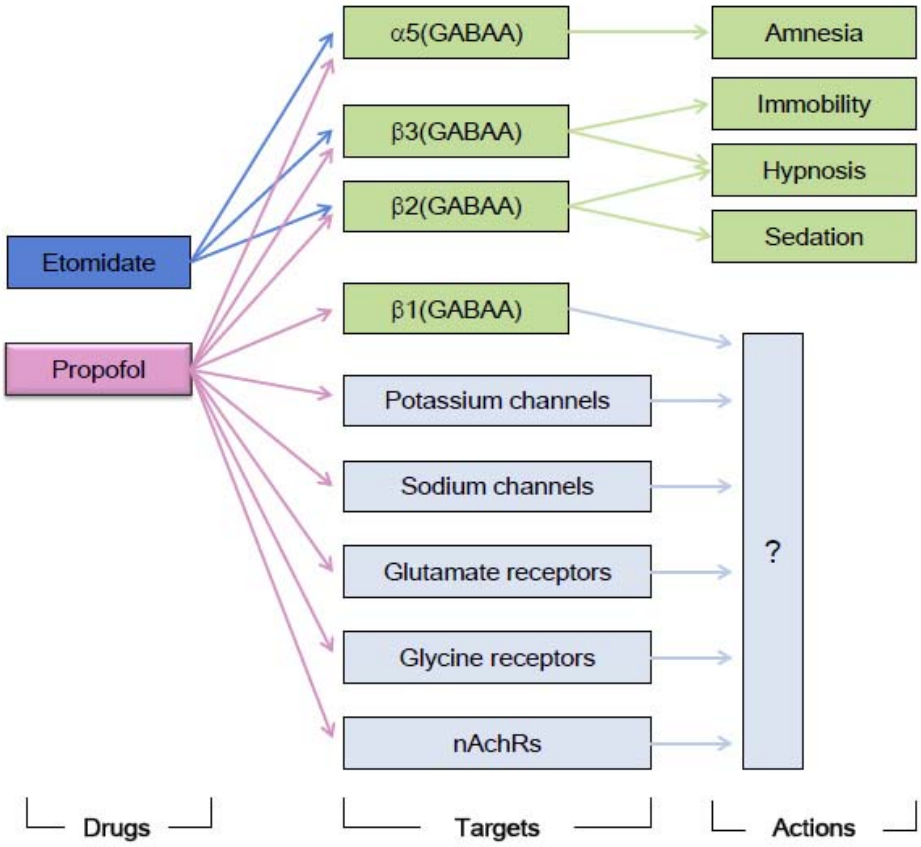

Figure 1. Roles of ionotropic receptor subtypes and other targets in the actions of the general anesthetics etomidate and propofol.

subunit composition. The proposed roles of $GABA_A$-receptor subtypes and other targets on etomidate and propofol action are summarized in Figure 1. Memory is particularly sensitive to general anesthetics because amnesia occurs at concentrations well below those causing sedation and analgesia (62). Receptors containing the GABA α5 subunit may be of particular importance to learning and memory, as mice with chromosomal deletion of α5 showed superior hippocampus-dependent learning over wild-type mice (64). Pharmacological studies suggest that this subunit combines with the β3 and γ subunits to form heteromeric complexes (65). Memory was also improved when the histidine 105 of the α5 subunit was substituted with arginine (α5His105Arg) (66). Furthermore, these α5His105Arg mice showed enhanced memory performance for trace fear conditioning. Inverse agonists that selectively inhibit the activity of $\alpha5GABA_A$ receptors improved memory performance in animal models and in humans with ethanol-induced memory impairment (67, 68). Thus, the amnesic effects of general anesthetics may stem from potentiation of IPSCs mediated by $GABA_A$ receptors containing α5, particularly receptors in the hippocampus.

Sedation refers to a decreased level of arousal as indicated by longer response times to external stimuli, decreased motor activity, and slurred speech. In animal models, indicators of sedation include reduced motor activity and arousal (1). Recent transgenic experiments revealed that $GABA_A$ receptors containing α1 and β2 subunits play a role in sedation. In β2 subunit (β2Asn265Ser) mutant mice, low doses of etomidate failed to reduce spontaneous locomotor activity, suggesting that the sedative effects of etomidate depend on $GABA_A$ receptors containing the β2 subunit (69). By contrast, the sedative effects of diazepam involve histidine 101 of the α1 subunit (70). In addition, the potentiation of neocortical IPSCs mediated by $GABA_A$ receptors containing α1 and β2 subunits contribute to the sedative actions of several inhaled anesthetics (71).

Hypnosis requires a higher concentration of anesthetic than sedation (1). Reynolds *et al.* showed that the duration of the loss of righting reflex induced by etomidate was reduced in β2 (Asn265Ser) mice (69). However, $GABA_A$ receptors containing the β2 subunit are only partially responsible for the hypnotic effect of etomidate. Two studies showed that etomidate-induced hypnosis also depends on the β3 subunit, as the duration of loss of righting reflex after intravenous injections of etomidate was reduced in β3 (Asn265Met) mice (72, 73). The induction of hypnosis by anesthetics, as opposed to sedation, is presumably mediated by additional effects on

the thalamus (74) and the tuberomammillary nucleus of the hypothalamus (5), suggesting that these areas may be enriched in $GABA_A$ subtypes containing β2 and (or) β3 subunits, although this remains to be proven.

5.2.2. Other ionotropic receptors and ion channels

5.2.2.1. Glycine receptors

Glycine is an inhibitory neurotransmitter with properties similar to those of GABA, but with particularly strong expression in the spinal cord. The spinal cord glycine receptor, composed of four á subunits and a single â subunit, is also a target of inhalation anesthetics (75). Indeed, the increased influx of chloride ions through glycine-gated channels mediates, at least in part, the immobility produced by inhaled anesthetics (76). Recently, Ye *et al.* (77) showed that the glycine receptor antagonist strychnine abolished the loss of righting reflex (LORR) induced by systemic administration of ethanol in rats. By contrast, strychnine had no effect on the LORR induced by ketamine (an NMDA-type glutamate receptor antagonist), suggesting that glycine receptors contribute to the hypnosis induced by ethanol. Nguyen *et al.* (78) showed that strychnine dose-dependently reduced propofol-induced LORR in rats and that propofol potentiated inhibitory currents in rat hypothalamic neurons, suggesting a role for central glycine receptors in propofol-induced hypnosis.

5.2.2.2. Nicotinic acetylcholine receptors (nAChRs)

Activation of nicotinic acetylcholine receptors causes excitatory postsynaptic currents (EPSCs) mediated by activation of a non-selective ACh-gated cation channel. General anesthetics at low concentrations decrease ACh-mediated EPSCs. Flood *et al.* demonstrated that □4□2 nAChRs were inhibited by isoflurane and propofol, and concluded that inhibition of specific nAChRs subtypes in the CNS, in addition to potentiation of $GABA_A$ and glycine receptors, may contribute to the effects and side effects of general anesthetics (79). Recently, Solt *et al.* showed that inhibition of human □4□2 neuronal nAChRs by volatile aromatic anesthetics depends on drug hydrophobicity (80).

5.2.2.3. Glutamate receptors

Glutamate is the predominant excitatory neurotransmitter in the CNS. Fast postsynaptic excitation is mediated by three classes of ionotropic glutamate receptors, each composed of distinct subunit combinations and named after selective agonists, NMDA, AMPA, and kainate. Two anesthetics, nitrous oxide and xenon (81), which have little or no effect on $GABA_A$ receptors, have some features in common with known NMDA receptor antagonists such as ketamine (82, 83). Both nitrous oxide and xenon potently reduce NMDA-receptor mediated synaptic transmission in the spinal cord and provide neuroprotection (84-86)

5.2.2.4. Potassium channels

Two-pore-domain potassium channels (the voltage-independent "leak" channels) are thought to provide 'background' modulation of neuronal excitability. Volatile anesthetics activate the two-pore-domain potassium channels that play an important role in setting the resting membrane potential (4).

Two-pore-domain potassium channels contain 15 different subunits, and five members of this channel family (TREK1, TREK2, TASK1, TASK3 and TRESK) can be directly activated by general anesthetics (87-92). Anesthetic sensitivity among these channels is not uniform. The effects of isoflurane and chloroform, for example, are variable, and TASK1 channels are barely affected by either, while all five channels are sensitive to halothane (89, 93, 94). The small anesthetics, such as xenon, nitrous oxide and cyclopropane, activate TREK1 channels but have no significant effect on TASK3 channels (95).

Activation of this channel inhibits neuronal activity by increasing the potassium conductance of the membrane, thereby hyperpolarizing the membrane and reducing the effects of excitatory currents (89). Two-pore-domain potassium channels are also found presynaptically, and their activation can be either excitatory (at inhibitory synapses) or inhibitory (at excitatory synapses) (96).

5.2.2.5. Sodium channels

Voltage-gated sodium channels propagate the regenerative axonal action potential and contribute to synaptic integration by selectively amplifying specific dendritic inputs (97). General anesthetics inhibit presynaptic voltage-gated sodium channels in glutamatergic neurons, thereby disrupting excitatory neurotransmission.

5.3. Intracellular signaling pathways

Binding of neurotransmitters and hormones to specific receptors activates a plethora of intracellular signaling cascades that can alter neuronal activity over multiple time scales by modulating ion channels (and other pre-existing proteins) and by influencing gene expression. Many of these signaling pathways are possible targets of general anesthetics. Agonists for G-protein-coupled receptors (GPCRs), such as μ opioid and α2 adrenergic receptors, can affect anesthetic sensitivity by reducing median alveolar concentration (MAC) (98). Inhaled anesthetics activate multiple rat olfactory GPCRs *in vivo* in a receptor- and agent-selective manner, suggesting direct effects on GPCRs (99, 100). However, similar effects on GPCRs relevant to critical anesthetic endpoints remain to be demonstrated.

Many anesthetic-sensitive receptors and ion channels, including those participating in synaptic plasticity, can be regulated by phosphorylation. Inhaled anesthetics enhance the activity of protein kinase C (PKC) isoforms and stimulate phosphorylation of specific PKC substrates (101). Structural studies have identified a potential binding site in the diacylgycerol binding domain of PKCδ, consistent with the ability of certain anesthetics to mimic this natural regulator by binding to the activating site (102). Moreover, isoflurane, propofol, and ketamine reduce phosphorylation of both NMDA S897 and AMPA S831, sites important for modulation of channel gating, and suppress downstream extracellular signal-regulated kinase ERK2 activation. These effects may explain the depressed glutamatergic transmission in the anesthetized mouse

cerebral cortex (103). Glutamatergic transmission is highly use-dependent, and this synaptic plasticity may be the neurocellular mechanism for at least some forms of learning and memory. Thus, suppression of glutamate receptors and downstream postsynaptic kinase cascades known to induce or sustain synaptic plasticity may account for the amnesic effects of general anesthetics (104).

6. CONCLUSIONS

General anesthesia is a collective term for several distinct behavioral endpoints, including amnesia, immobility, and unconsciousness, that are likely mediated by the concentration-dependent effects of anesthetics on distinct neural subsystems. For most of the past century, general anesthetics were thought to exert non-specific effects on neurons, possibly by altering membrane characteristics. In this review, we discussed evidence for the site-specific actions of general anesthetics in different brain regions and receptor populations. Most general anesthetics act on neurotransmitter-gated ion channels, of which the best studied is the $GABA_A$ receptor. Studies on the contributions of other anesthetic targets, such as glutamate receptors, dopamine receptors, leak potassium channels, and voltage-gated Na and K channels, to general anesthesia may facilitate the development of more efficacious and safer anesthetics.

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Abbreviations: $GABA_A$:γ gamma-aminobutyric acid type A; rCBF: regional cerebral blood flow; CNS: central nervous system; GABA: ã-aminobutyric acid; NMDA: N-methyl-D-aspartate; IPSCs: inhibitory postsynaptic currents; LORR: loss of the righting reflex; nAChRs: nicotinic acetylcholine receptors; EPSCs: excitatory postsynaptic currents; GPCRs: G-protein-coupled receptors; MAC: median alveolar concentration; PKC: protein kinase C.

Key Words: General Anesthetics, Ion Channels, $GABA_A$ Receptors, Amnesia, Immobility, Hypnosis, Sedation, Review

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