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Review articles

Mechanisms of anesthetic actions and the brain

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Abstract
The neural mechanisms behind anesthetic-induced behavioral changes such as loss of consciousness, amnesia, and analgesia, are insufficiently understood, though general anesthesia has been of tremendous importance for the development of medicine. In this review, I summarize what is currently known about general anesthetic actions at different organizational levels and discuss current and future research, using systems neuroscience approaches such as functional neuroimaging and quantitative electrophysiology to understand anesthesia actions at the integrated brain level.

Key words Anesthesia · General · Anesthetics · Volatile · Mechanisms of anesthetic action · Brain · Neurons · Functional imaging · Electroencephalography

Introduction

First introduced to clinical medicine more than 160 years ago, general anesthesia has been considered one of the most important advances in modern medicine and is now used for millions of patients who undergo surgical and other medical procedures each year. Despite the prevalence of their use, the fundamental question of how and where general anesthetics work remains unanswered [1]. The neural mechanisms behind anesthetic-induced behavioral changes such as loss of consciousness, amnesia, and analgesia, are particularly insufficiently understood [2,3].

General anesthesia can be addressed across the entire hierarchy of biological organization, from molecules to the behavior of organisms (Fig. 1). In past decades much research has been focused on molecular and cellular targets and actions of general anesthesia [4–6]. At these microscopic levels, accumulating evidence suggests that general anesthetics act on multiple neuronal membrane proteins that function as ion channels and neurotransmitter receptors [4,6]. These interactions may yield structural or dynamic consequences such as conformational changes in the target protein, stabilization or attenuation of subunit association, equilibrium shift, or competition with endogenous ligands [7]. However, which of these potential target molecules are critically affected is not known. At higher levels, we have little knowledge of the networks or structures most critical for general anesthesia or the essential neural processes that govern their action. Accordingly, we do not know how the actions at these different levels interplay to generate the anesthetic state.

In this review article I briefly summarize some aspects of what is currently known about general anesthetic actions at different organizational levels and discuss future prospects for research in this field, giving special consideration to emerging systems neuroscience approaches such as multimodal neuroimaging. I focus primarily on the general volatile anesthetics in common use: halothane, enflurane, isoflurane, sevoflurane, desflurane, and reference other agents (gaseous anesthetics, intravenous anesthetics) where appropriate.

Why do we search for anesthesia mechanisms?

General anesthesia is currently administered to approximately 40 million patients each year in the United States. Although mortality related solely to general anesthesia has been significantly reduced in recent decades to one death per 200 000 procedures [8], the improved safety of anesthesia is attributed mostly to the development of physiological monitors and establishment of anesthesiology as a medical specialty. Nevertheless, the toxicity and side effects of general anesthetics [9,10] and long-term cognitive problems after general anesthesia [11,12] still represent challenging issues, es-

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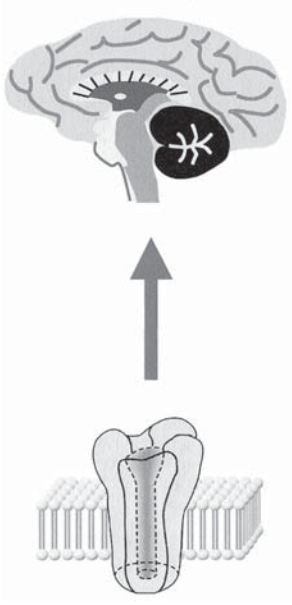

Behaviors	Amnesia, Unconsciousness, Antinociception, Immobility
Systems Neural structure Neural process	Cortex, Thalamus, Ascending reticular activating system, Spinal cord, Thalamocortical loops
Networks	Microcircuits
Cells	Neurons, Glial cells, Myocytes, Endocrine cells
Synapses	Inhibitory synaptic transmission Excitatory synaptic transmission
Molecules Submolecule	Ligand-gated ion channels Neurotransmitter receptors Second messenger systems Lipid bilayer

Fig. 1. Potential anesthetic targets at different biological organizational levels. How molecular-level interactions are translated into clinically observable behavioral effects is still unknown

pecially for patients with serious medical problems and for those of either very young or very old age. Most general anesthetics in current clinical use, including volatile and intravenous anesthetics, have significant side effects that may induce cardiovascular compromises in these patients [13]. Inhibition of ventilatory responses by general anesthetics is still one of the major reasons that patients require continuous monitoring and oxygen therapy in the post-anesthesia care unit. In light of the serious adverse side effects that can accompany anesthesia administration, it is essential that we more fully understand the mechanisms of general anesthetic actions, because doing so allows for the effective development of safer anesthesia alternatives.

Although it was not until recently considered a serious side effect, "awareness" during anesthesia has gained increasing public attention and is now considered a significant potential problem related to general anesthesia. Up to 54% of patients who had undergone anesthesia listed awareness, along with pain, as the issue that most worried them [14]. The incidence of awareness while under general anesthesia was reported as 0.1%–0.18% in the adult population [15,16]. Some who reported awareness during anesthesia also suffered delayed neurotic symptoms that required psychiatric treatment and long-term follow-up. Awareness during anesthesia has been reported in the pediatric population at a higher rate of incidence of 0.8% [17], suggesting the possibility of postoperative behavioral problems and potential long-term problems in children.

How can we better monitor "consciousness" during anesthesia? The popularity of the Bispectral Index (BIS) monitor, a processed electroencephalogram (EEG) parameter developed specifically to measure the hypnotic effects of anesthesia based on a large pool of human EEG data, appears to have contributed to reducing the incidence of awareness [18]. All anesthesia monitors recently developed—the BIS, the Patient State Index [19,20], Narcotrend [21], and entropy [22]—are based on surface EEG readings. The characteristic patterns of EEG changes under general anesthesia are well described [23,24], though little is known about the neurophysiological basis of the potential correlation between consciousness levels and EEG-based monitor values. Regional differences in general anesthetic effects on EEG are also known to be associated with loss of consciousness [25], but the neural correlates of these EEG changes remain to be elucidated. Accordingly, one of our most challenging tasks is to develop a new neurophysiological monitoring system based on our understanding of the neural processing behind anesthetic-induced behavioral changes, so that we anesthesiologists may assess patients' consciousness levels more precisely during general anesthesia. Understanding anesthetic actions upward in the hierarchy of biological organization will be key to the development of a future "consciousness" monitor.

Molecular mechanisms of general anesthesia: what do we kn ow?

Ligand-gated ion channels

Much research in past decades has focused on ligand-gated ion channels (LGICs) as targets of general anesthetics [4,6]. Since the 1980s, gamma-amino-butyric acid type A ($GABA_A$) chloride channels, particularly, have emerged as promising molecular targets of general

anesthetics. $GABA_A$ receptors are known to regulate anxiety, vigilance, memory, and muscle tension. GABAergic neurons and interneurons are ubiquitously expressed throughout the central nervous system (CNS) and are thought to play important neuromodulatory roles in numerous neuronal structures, including the hippocampus, thalamus, spinal cord, and cortex [26–28]. Many general anesthetics, intravenous as well as most of the volatile anesthetics, have been shown to allosterically modulate $GABA_A$ chloride channels, resulting in potentiation of inhibitory synaptic transmission. $GABA_A$ receptors are therefore likely to play an important role in the CNS depression associated with most general anesthetics [6,29,30]. Point mutation techniques have suggested that anesthetic binding sites for volatile anesthetics [31] and propofol [32] are located between the second and third transmembrane segments, and genetically engineered knock-in mice bearing specific mutations at these sites are found to be relatively insensitive to propofol and etomidate [33].

It is clear, however, that some clinical anesthetics, such as gaseous nitrous oxide and xenon, cyclopropane, and intravenous ketamine, have little effect on $GABA_A$ receptors [34]. Previous studies have demonstrated that these anesthetics inhibit excitatory synaptic transmission through N-methyl-D-aspartate (NMDA) glutamate receptors and/or neuronal nicotinic acetylcholine (nACh) receptors [35]. Most volatile anesthetics are also known to depress these excitatory synaptic transmissions [36]. A direct binding domain for halothane has been identified in the nACh receptors in Torpedo electric organ [37]. It appears that neuronal nACh receptors are not directly involved in the hypnotic effect of anesthesia, but do mediate modulatory effects on nociception and learning and memory, and likely contribute to general anesthetic effects [38]. NMDA receptors have also been suggested to play an important role in central and peripheral pain processing [39]. That each general anesthetic has shown a different effect profile on ion channels suggests that each also has a different behavioral effect profile [40].

G Protein-coupled receptors

A large family of G protein-coupled receptors (GPCRs) may be another important target of general anesthetics [41,42], and is well known to modulate most signaling in the CNS. Particularly, the rhodopsin family of GPCRs includes many neurotransmitter receptors, including muscarinic acetylcholine, noradrenaline, dopamine, adenosine, and opioid receptors [43]. Functionally, cholinergic neurotransmission is known to influence awareness, sleep, and learning and memory [44]. The α_2-adrenergic receptor appears to play a role in nociceptive responses, as well as in the state of arousal [45]. In fact, agonists and/or antagonists that work through these GPCRs have been reported to significantly alter anesthetic requirements in humans and animals [46–50]. Although this might include unrelated, parallel effects on the CNS, recent studies show that general anesthetics can interfere with GPCR signaling in vitro [51,52], suggesting that they have direct effects on GPCRs. The GPCR signaling pathways are also critical in other vital organ systems, such as the cardiovascular and respiratory systems, and general anesthetics have been shown to inhibit these pathways [53–56].

Direct binding of the volatile anesthetic halothane to the endogenous ligand binding site has been demonstrated in the interhelical core of a prototypical GPCR, rhodopsin [57,58]. Halothane competitively inhibits endogenous ligand binding to the GPCR in vitro, and the competition is consistent with the in vivo finding that rhodopsin regeneration, in which the retinal ligand binds to the receptor, was significantly inhibited under 1.5%–1.8% halothane anesthesia in mice and rats [59]. Given that the ligand-binding core is created with highly conserved residues in the GPCR family [43], and similar hydrophobic cavities exist in many membrane proteins, this halothane binding site may represent a common anesthetic binding motif for volatile anesthetics [57,60]. Evidence of direct binding, together with pharmacological findings, suggests that key features of general anesthesia, such as loss of consciousness and antinociception, can be attributed to a wide spectrum of roles of GPCR signaling in the CNS. However, anesthetic "side" effects that include a multitude of cardiovascular and autonomic features may also be involved.

"Background" potassium channels

A potentially important role of two-pore-domain K^+ (K_{2P}) channels in general anesthetic actions has recently emerged [61,62]. These channels are called "background" potassium channels. The channels provide neuronal background currents that establish resting membrane potential and input resistance, therefore regulating cellular excitability. General anesthetics have long been considered to reduce neuronal excitability by opening K^+ channels [63]. A novel family of mammalian K_{2P} channels is highly expressed in the human CNS. These channels are activated in various pathophysiological conditions, including cell volume expansion and intracellular acidosis, and by polysaturated fatty acids and lysophospholipids [64,65]. Volatile anesthetics have been shown to selectively open the K_{2P} channels known as TREK-1 and TREK-2, as well as other types (e.g., TASK-1, TASK-2), resulting in profound hyperpolarization at both presynaptic and postsynaptic membranes [62,66]. A new study shows that deletion of the *TREK-1* gene in mice induces heightened resistance to volatile

anesthetics when compared to other ion-channel knockout animals [67]. It is of interest that hyperpolarization by TREK-1 opening is suggested to play an important role in neuroprotection against ischemia and epileptic insults [61]. K^+ channels are expressed in other tissues as well and play an especially important role in the excitability of smooth muscle cells such as cardiomyocytes [68], suggesting potential involvement in eliciting anesthetic side effects.

Unique pharmacology of general anesthetics

The unique pharmacology of general anesthetics is important for understanding their actions and, in fact, suggests that general anesthetics have multiple molecular targets. General anesthesia is known to be produced by a remarkable number of structurally diverse molecules, ranging from a simple inert gas, xenon, to a complex molecule, alpha-chloralase. This range suggests that there is no single structurally specific receptor that mediates general anesthesia. Only a modest degree of stereoselectivity (~1.5 times) has been shown with isoflurane both in vivo and in vitro [69,70]. General anesthetics, and in particular volatiles, are unique in that a high aqueous EC_{50} is necessary to produce clinical effects in mammals (0.2–1.0 mM) [5]. Other agents known to act at specific receptors are effective at a much lower concentration range; for instance, neuromuscular blocking agents act at ~10 μM, and opioids at 10–100 nM. The high effective concentration of general anesthetics is consistent with their relatively featureless molecular structures and weak binding energetics [7]. In fact, widespread binding sites of volatile anesthetics are shown in rat brain slices [71] that may include membrane proteins as well as soluble proteins [72]. These findings, together, strongly support the notion that volatile anesthetics interact with multiple protein sites to exert clinical effects.

Integrated models for behavioral effects of anesthesia

General anesthesia has several distinct clinical endpoints determined by behavioral changes: loss of consciousness, amnesia, analgesia (antinociception), and immobility. Despite a substantial volume of literature on the potential molecular targets and actions discussed in the previous section, how these behavioral effects are achieved in central neural processing remains poorly understood [1,73]. Do general anesthetics affect discrete neuronal structures in the CNS or do they cause a global decrease in functional activation? What neuronal structures are critically involved in generating the anesthetic state if the effect is not global? Is the ascending reticular activating system, previously proposed based on classical electrophysiology [74,75], still the essential transmission for anesthesia? Are these anesthetic effects "neuron"-specific or "process" (coherent activity)-specific? All of these questions need to be answered in order to develop comprehensive explanations of the mechanisms by which general anesthetics cause behavioral changes.

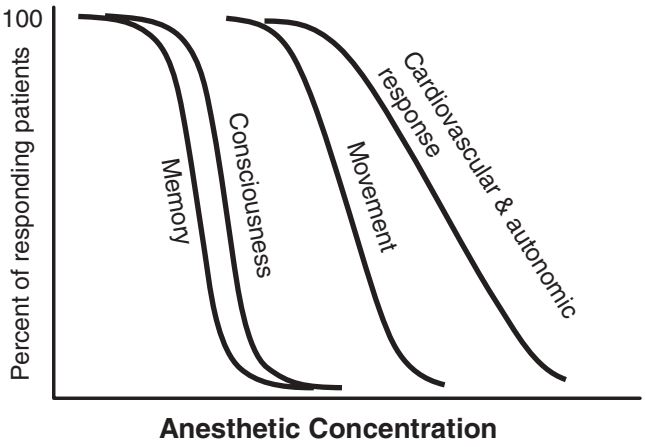

Fig. 2. The general relationship between anesthetic concentration and behavioral endpoints. The figure was developed from a number of previous studies. Memory (explicit memory) and consciousness (responsiveness) are inhibited at lower anesthetic concentrations than are necessary to prevent movement. The anesthetic concentration that blocks movement to noxious stimuli is known as the minimum alveolar concentration (MAC). Blockade of cardiovascular and autonomic responses to noxious stimuli requires much higher concentrations

In the 1990s, major progress was made in establishing that general anesthetics achieve immobilization largely by actions at the spinal cord level [76–78]. Literature also suggests that the concentrations required for many general anesthetics to suppress consciousness exceed the amnestic concentrations, but surgical immobility during noxious stimuli requires anesthetic concentrations substantially higher than those needed to suppress consciousness or induce amnesia [73] (Fig. 2). This finding indicates that different neuronal regions or processes may mediate behavioral effects. In fact, recent studies using functional neuroimaging have demonstrated interesting insights into the modulation of human brain activity by general anesthetics, and suggest that general anesthetics may affect specific neural structures during visual tasks [79] and auditory language-processing tasks in humans [80,81].

Loss of consciousness

The neural correlate of consciousness is still poorly understood. Since the pioneering work of Moruzzi and

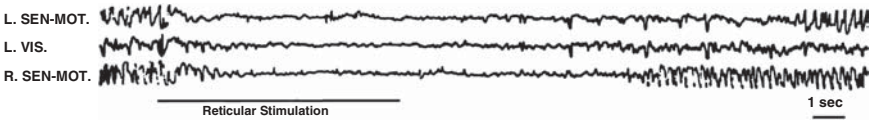

Fig. 3. Effect of stimulation of the brainstem reticular formation on electrocortical activity in a cat anesthetized with chloralosane. Left bulbo-reticular stimulation (3 V; 300 s^{-1}) induces low-voltage fast activity bilaterally. *L. SEN-MOT*, left sensory-motor cortex; *L. VIS.*, left visual area; *R. SEN-MOT.*, right sensory-motor cortex. Reprinted with permission from the *Journal of Neuropsychiatry and Clinical Neurosciences* [83](see reference for further details)

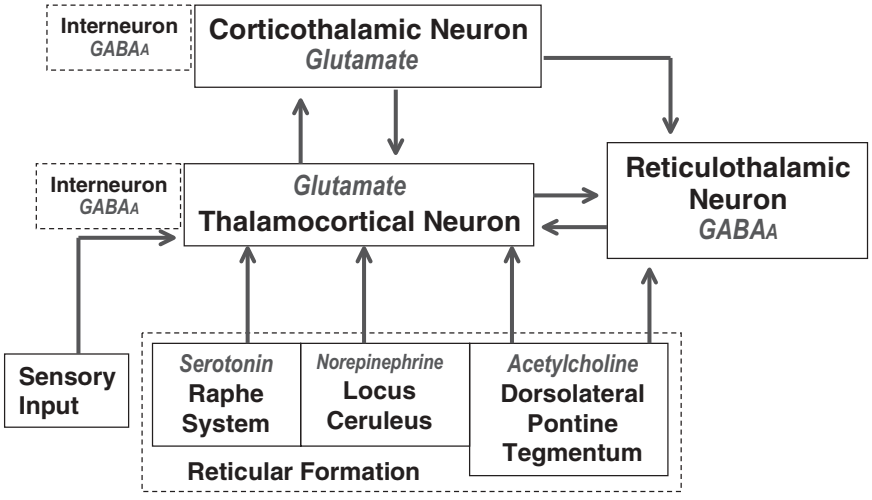

Fig. 4. Schematic depiction of mesenphalic, thalamic, and cortical neurons and pathways that are assumed to be involved in anesthetic-induced loss of consciousness. Major neurotransmitter systems are indicated in *gray italics*. The figure was developed from previous studies [25,85,86]. $GABA_A$, gamma-aminobutyric acid type A

Magoun [82,83] that established the involvement of the midbrain reticular formation in arousal, wakefulness, and sleep (Fig. 3), experimental work in animals has suggested that multiple structures, including the brainstem, basal forebrain, hypothalamus, thalamus, and cortices play key roles in the control of conscious states [84] (Fig. 4). All of these structures are affected by general anesthetics, and no single structure has been identified as most critical to anesthetic-induced unconsciousness.

However, recent studies with functional imaging and quantitative EEG suggest that thalamocortical loops may be a key component for anesthetic-induced unconsciousness [85] (Fig. 4). Positron emission tomography (PET) data have shown specific suppression of thalamic and midbrain reticular formation activity by halothane and isoflurane in humans [86], and, with connectivity analysis of PET data, disruption of functional interactions within thalamocortical networks has been shown to be associated with unconsciousness induced by these general anesthetics [87]. Advanced quantitative EEG analyses also suggest the important role of the thalamus in general anesthetic effects; particularly, inhibition of the nucleus reticularis and blockade of corticothalamocortical gamma loops [25] (Fig. 4). Propofol, an intravenous anesthetic, has been shown to decrease regional activity in the medial thalamus, cuneus, and posterior cingulate and orbitofrontal cortices in humans on PET; significant covariation between thalamic and midbrain blood-flow changes was observed [88], suggesting the potential of a common pathway for unconsciousness induced by different types of general anesthetics.

Amnesia

Understanding how general anesthetics affect memory and learning is crucial to preventing awareness during anesthesia—a potentially catastrophic complication. Memory appears to be composed of multiple separate systems supported by the hippocampus and related structures, including the amygdala, neostriatum, and cerebellum [89]. Memory process is also thought to require information processing in the cortical areas associated with higher cognitive functions. Whether memory formation occurs during general anesthesia is still controversial. Several studies have demonstrated that learning can occur in humans during general anesthesia [90–92]. A recent study shows that implicit memory persists in adequate hypnotic states with isoflurane [93], though other studies show no memory function during propofol or isoflurane anesthesia [94,95]. Nevertheless, most general anesthetics are known to cause anterograde amnesia at lower anesthetic concentrations than

are required to induce unconsciousness or immobility [96,97] (Fig. 2).

It appears that the memory-impairing effect of sevoflurane in rats is associated with the basolateral amygdala [98]—a finding that is consistent with an in vitro slice study showing that isoflurane reduces glutamatergic transmission and enhances $GABA_A$ receptor-mediated responses in this structure [99]. Lesion of the basolateral amygdala has also been demonstrated to block propofol- and benzodiazepine-induced amnesia in animals [100,101]. Although the amygdala may be one of the key structures in anesthetic-induced amnesia, general anesthetics have also been suggested to interact with other neuronal structures involved in the memory process, and a number of studies have shown that general anesthetics decrease synaptic transmission in hippocampal neurons [102–104]. Learning and memory involve a large population of neurons and interplay between complex information-processing mechanisms in the CNS. Future experiments involving these potential target systems are needed to elucidate the mechanisms of anesthesia-induced amnesia.

Analgesia and antinociception

"Analgesia" is defined as the absence of the sensation of pain without loss of consciousness. The term "antinociception" (-nociperception) is used to describe the effect of suppressing painful or injurious stimuli in general. Nevertheless, suppression of nociceptive responses has been considered one of the most important clinical endpoints for general anesthetics. Painful surgical stimuli can evoke hormonal and metabolic responses that are thought to contribute to postoperative morbidity and mortality [105,106]. These stress responses can be significantly reduced during general anesthesia, and in fact, higher concentrations of general anesthetics or combinations of general anesthetic and regional block may completely attenuate surgical stress responses [107]. Although attenuation of stress responses is thought to be beneficial to patient outcome, cardiovascular compromises may occur at deeper anesthetic states. It is thus important to develop an understanding of the mechanisms of how general anesthetics reduce somatosensory and visceral stimuli, so that we can develop safer targeted alternatives.

General anesthetics reduce neuronal activities in the somatosensory systems. In vivo electrophysiological recordings have shown that many anesthetics, including volatile and intravenous anesthetics, modify the responses of thalamic sensory relay neurons [75]. Anesthetic effects on sensory evoked potentials (SEP) have been extensively studied [24,108]. All volatile agents produce a dose-related increase in latency and a reduction in the amplitude of cortically recorded SEP responses (somatosensory [SSEP], and visual and auditory evoked potentials). Lesser effects are noted on the SSEP response recorded over the cervical spine, and the auditory brainstem response (ABR) is known to be less affected by anesthetics, suggesting subcortical potentials are less affected by general anesthetics [109]. These observations clearly indicate that a certain degree of sensory information is conveyed to the higher regions in the brain under clinical anesthesia.

Antognini and colleagues [110] performed a pioneering imaging study to investigate general anesthetic suppression of somatosensory pathways, using functional magnetic resonance imaging (fMRI) in humans. Isoflurane completely inhibited activation by tactile stimuli at 0.7%. Activation by noxious (electrical) stimulation was abolished in the primary and secondary cortices at 0.7%, and in subcortical regions (thalamus and caudate nucleus) at 1.3%. Likewise, cortical activation to noxious stimuli was abolished at 0.7% isoflurane in macaque monkeys at 1.5-Tesla fMRI [111]. A low concentration of propofol ($\sim 0.5\,\mu g \cdot ml^{-1}$) has also been shown to suppress somatosensory cortices during tactile stimulation in humans [112]. These findings may indicate that clinical concentrations of general anesthetics significantly reduce activation in ascending somatosensory pathways. However, a recent study using 9.4-Tesla fMRI suggests that isoflurane may reduce central tactile processing only in the areas of higher functions (secondary and higher cortices) and that the primary cortex and subcortical areas are activated by tactile stimuli at 1.4% isoflurane in squirrel monkeys (Fig. 5) [113]. Furthermore, literature suggests that a significant amount of visual processing still takes place under clinical anesthesia in macaque monkeys [114]. Further studies are needed to precisely characterize general anesthetic concentration-response relationships in central sensory processing, using high-field functional neuroimaging and advanced electrophysiology.

Immobility

Several studies demonstrate that the spinal cord mediates most of the ability of general anesthetics to produce immobility [73,115,116]. A preferentially anesthetized goat brain model was used to determine the importance of subcortical structures for the generation of purposeful movement in response to a painful stimulus under general anesthesia [76]. Immobility has also been shown to correlate little with EEG activity during noxious stimulation under anesthesia, suggesting that cortical electrical activity does not control motor responses to noxious stimulation [117]. The putative spinal cord sites include dorsal horn cells and motor neurons, and glycine and NMDA receptors seem more likely candidates for molecular targets [116].

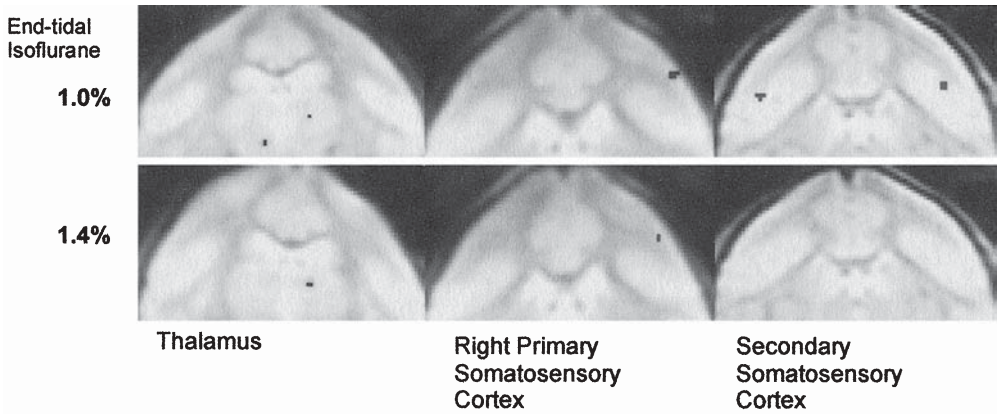

Fig. 5. Functional activation induced by vibrotactile stimulation delivered to the left finger in nonhuman primates (squirrel monkeys) shown in coronal slices. Activation was observed in the thalamus and the primary somatosensory cortex at endtidal isoflurane 0.5% (not shown), 1.0%, and 1.4%. Activation in the bilateral secondary somatosensory cortex was robust at 1.0%, but was not observed at 1.4%, suggesting that isoflurane anesthesia reduces central tactile processing only in the areas of higher functions. *Activated areas are shown in dark gray.* Blood oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) was obtained in two animals on a 9.4-Tesla scanner (Ishizawa et al. [113])

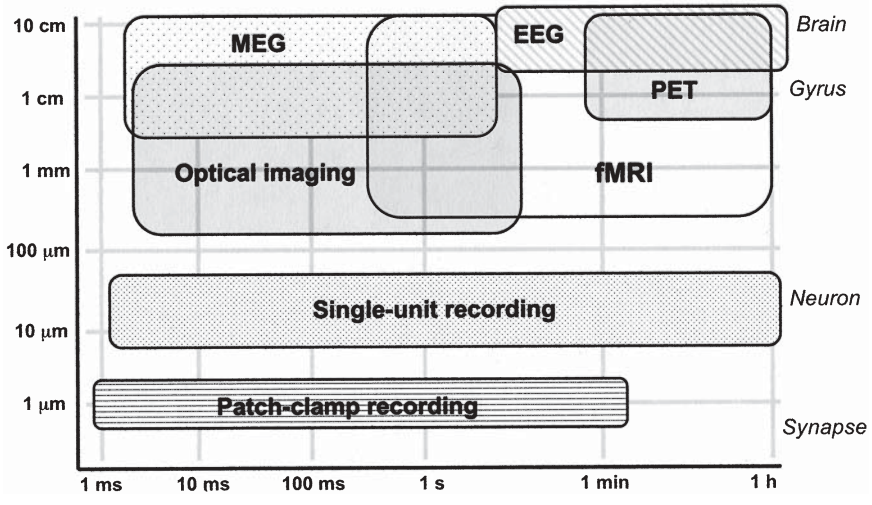

Fig. 6. Spatial and temporal resolution of various neuroscience techniques. Functional magnetic resonance imaging (*fMRI*) provides a good balance of spatial and temporal resolution. Combining approaches with complementary strengths is important for comprehensive explanations of anesthetic actions. Electroencephalography (*EEG*), fMRI, magnetoencephalography (*MEG*), and human optical imaging (from outside the skull) are considered noninvasive techniques. Positron emission tomography (*PET*) requires an injection of positron-labeled ligands

A systems neuroscience approach to anesthetic mechanisms

Neuronal circuits are composed of a complex network of numerous types of neurons that are intricately intertwined in the CNS. How do distinct neural circuits contribute to brain function? Systems neuroscience aims to understand how complex interactions between networks of neurons give rise to perception and behavior. Researchers focus on the vast divide that exists between molecular and cellular approaches to studying the brain and higher-level mental functions. Anesthesia mechanism research will thus greatly benefit from the integrated approach of systems neuroscience. In addition, general anesthetics may potentially be an important tool for understanding fundamental brain functions.

Functional neuroimaging

Functional magnetic resonance imaging (fMRI) is a powerful approach for defining activity in the brain and can be used to detect anesthetic-induced changes in the neural activity of various regions of the brain. The technique most commonly used, the blood oxygenation-level-dependent (BOLD) signal, is an indirect measure of neural activity based on the detection of local hemodynamic changes [118,119]. The BOLD signal increases in parallel with local increases in relative blood oxygenation, most probably as a direct consequence of an over-

supply of oxygenated blood by neurotransmitter action reflecting an increase in local neuronal signaling. fMRI provides a remarkable field of view (Fig. 6), and functional activation can be measured simultaneously and repeatedly across the entire brain. The BOLD technique is ideally suited for studying sensory pathways where simultaneous estimation of multiple areas can be crucial. Several studies suggest that the BOLD signal is correlated with electrophysiological activity, and that this hemodynamic measure may reflect more subtle, subthreshold potential changes [120–123]. There are, however, technical and analytical aspects that need to be developed. One inherent limitation is that BOLD fMRI derives from the uncertainties regarding the neurovascular coupling mechanism that generates the BOLD signal. At present, the reason for the mismatch between blood-flow supply and the consumption of blood oxygen is unclear. In addition, general anesthetics, and volatile anesthetics in particular, are known to cause cerebral vasodilatation and an increase in cerebral blood flow, suggesting potential effects on BOLD fMRI. It appears that awake animals show a higher BOLD signal than anesthetized animals, but confounding effects of general anesthetics on the BOLD signal are complex and need to be further elucidated [124,125].

Now more than 50 years old, positron emission tomography (PET) is an imaging method used to obtain quantitative molecular and biochemical information on physiological processes in the body. Although the temporal and spatial resolutions of PET are limited relative to those of fMRI (Fig. 6), the advantage of PET is its ability to image pathophysiological processes such as changes in metabolism, receptor function, molecular mechanisms, and hemodynamics. The limited availability of suitable positron-labeled ligands has been a major reason for a delay in translating PET technology to clinical applications. A number of studies have been performed using PET to investigate the effects of general anesthetics on regional cerebral blood flow and metabolism [112,126–128]. Although these studies only used $^{15}O_2$-labeled H_2O to measure change of cerebral blood flow, PET holds great potential for studying anesthetic mechanisms by the application of specific radioligands that allow the in vivo characterization of anesthetic effects on various neurotransmitter systems [129].

Quantitative electrophysiology and EEG

A central goal of anesthesia mechanism research is to understand how general anesthetics change neural activities that subsequently evoke behavioral changes. To this end, single-neuron electrophysiological techniques, including single-electrode, multi-electrode, and intracellular recording approaches are invaluable. These techniques can be used to directly record neuronal activity on a timescale of milliseconds (Fig. 6), providing temporal resolution that functional imaging techniques are not able to achieve at present. Electrophysiological approaches are, however, limited in several ways in in vivo experimental settings. Each electrode has a small field of view and can sample the activity of, at most, only several neurons. Despite many recent advances in implant technology, only up to 200 electrodes can be maintained in a single animal, and therefore sampling coverage is limited. Perhaps the most profound limitation of electrophysiology is that an investigator must rely on previous research findings and assumptions when choosing the optimal brain site for electrode placement. In addition, the invasiveness of these techniques precludes human studies. In limited cases, however, intracerebral electroencephalographic recordings, using indwelling electrodes in epileptic patients, have revealed progressive suppression of activity in the hippocampus with increased concentrations of sevoflurane [130]—a finding supported by subsequent neurophysiological animal studies that showed septal-hippocampal inactivation by both volatile and nonvolatile anesthetics [131]. Classic electrophysiology and functional imaging can therefore provide complementary strengths for understanding neural activity.

EEG is a phenomenon of the rostral structures of the brain, particularly the cerebral cortex, in large-scale neuronal circuits [132]. EEG thus appears to be correlated more reliably with neural functions linked mainly to the cortex (such as awareness or memory) than those linked to the spinal cord (e.g., immobility) [117]. Changes in EEG have long been established as providing reliable, empirical characterization of anesthetic-induced loss of consciousness [133,134] and characteristic patterns of the EEG changes are well documented (Fig. 7). Although it appears that EEG-based monitors contribute to a reduced incidence of awareness during anesthesia, the role of EEG in understanding anesthetic mechanisms is still limited, mainly by uncertainties surrounding the location of active sources in the brain. Recent progress has been made toward developing modern EEG source imaging with spatial and temporal dimensions [135], making it an important tool for investigating the action of general anesthetics. Human EEG is also known to demonstrate that distant areas of the brain exhibit increased global coherence during cognitive tasks, suggesting that oscillating neural activities work to generate global neuronal assemblies for cognitive functions [136,137]. Of emerging interest are oscillations in the gamma frequency range and observations that gamma activity appears to be closely correlated with cognitive functions [138]. Hence, advanced quan-

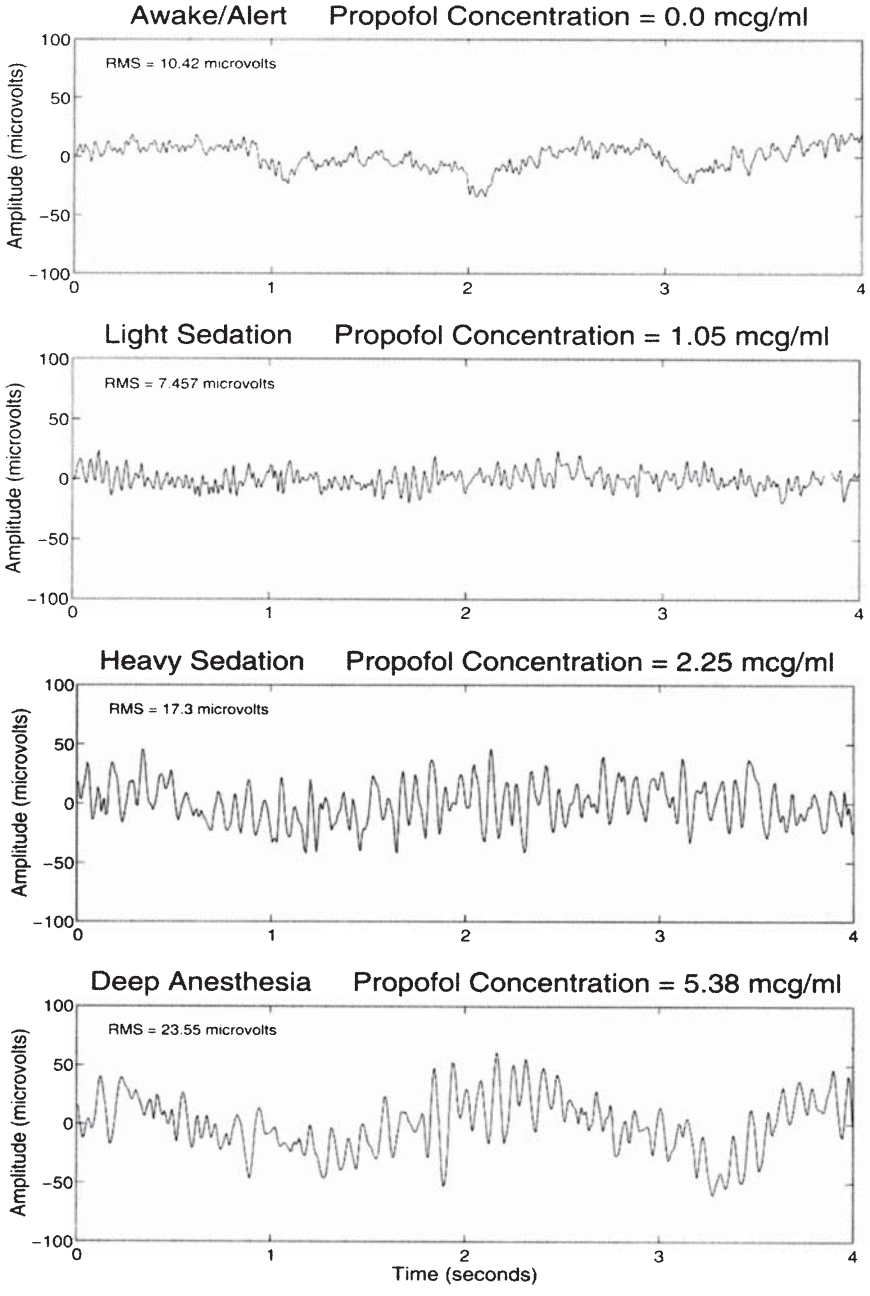

Fig. 7. Representative EEG changes with increasing serum concentrations of propofol in a single human volunteer. At each of the four concentrations, 4 s of raw EEG is shown with a representative time domain parameter (root mean square amplitude-RMS). No burst suppression activity was seen in this subject. Reprinted with permission from *Anesthesiology* [132] (see reference for further details)

titative EEG measures offer vast opportunities to study dynamic changes in anesthetic-induced unconsciousness and other behavioral effects.

Other new technologies

Magnetoencephalography (MEG) is a noninvasive technique to measure magnetic fields generated by small electrical currents in neurons of the brain. MEG provides direct information on the dynamics of neural activity and the location of their sources in the brain [139,140]. Although MEG and EEG are closely related, inferring the source of brain activation appears more straightforward with MEG than with EEG, reflecting the fact that MEG is selectively sensitive to currents flowing tangential to the scalp. Major advantages of MEG are high temporal resolution (on the level of milliseconds) and whole-cortex coverage (Fig. 6). The silent environment of MEG is also particularly well-suited for auditory studies. MEG does not, however, provide structural or anatomical information, and the data often need to be combined with imaging data such as those generated by MRI. Clinical experience with general anesthesia for MEG recording is limited [141], and the application of MEG to studies of anesthetic actions has not yet been reported.

Diffuse optical imaging (DOI), a technology made possible by recent advances in the understanding of light migration through tissue, measures changes in blood volume, oxygenated hemoglobin, and deoxygenated hemoglobin using near-infrared wavelengths [142]. DOI can be performed noninvasively from outside the skull, or invasively with open or thinned skulls. Advantages of DOI over other hemodynamic imaging techniques such as fMRI and PET include portability and rapid data acquisition (~1000-Hz sampling rates). Recent studies using optical imaging in awake, behaving small animals suggest great potential for investigating the hemodynamic correlates of a broad range of neurological processes, including anesthetic-induced behavioral changes [143,144].

Computational simulation for studying anesthetic actions in an integrated model has rather recently emerged [145]. Using computational approaches, Gottschalk and Haney [146] have shown modulation of the behavior of hippocampal neurons by increasing concentrations of general anesthetics. They have demonstrated how anesthetic modulation of ion channel activity could lead to more complex systems level behavior. With this technique, the interactions of the potential target molecules at neuronal and network levels can also be simulated. Computational simulation is therefore a useful tool for bridging anesthetic actions at different organizational levels.

Summary

Understanding anesthetic action at different biological organizational levels—from molecules to behavior—is essential for comprehensive explanations of anesthetic mechanisms and for future therapeutic implications, such as the development of safer drugs. What neural correlates in the brain are associated with anesthetic-induced behavioral changes? What neural changes represent anesthetic-induced adverse effects, or unrelated, parallel effects? We have endeavored to find answers to these fundamental questions, and we now appreciate the great opportunities to use recent technological innovations in systems neuroscience, such as multimodal neuroimaging and quantitative electrophysiology. Multidisciplinary approaches combining systems neuroscience with molecular/cellular physiology and pharmacology will allow us to relate anesthesia actions at the integrated brain level to the underlying molecular mechanisms at the single neuronal level.

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