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ANESTHETIC MECHANISMS (MB KELZ, SECTION EDITOR)

Mechanisms of Anesthetic Emergence: Evidence for Active Reanimation

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Abstract Historically, emergence from anesthesia was believed to progress only through the passive elimination of pharmacologic agents from the brain. However, recent studies indicate that anesthetic emergence may not simply be a process mirroring the induction of anesthesia. Several substances reduce the duration of anesthesia but not its induction time. Their action is not the result of a passive process, because they actively affect the kinetics of neurotransmitters or the endogenous sleep circuit to shorten anesthesia. The latest notable substance among this group of agents is methylphenidate, an inhibitor of dopamine and norepinephrine transporters. Studies on emergence from anesthesia aim not only to stimulate scientific interest but also to improve the clinical course following general anesthesia, when patients sometimes experience life-threatening complications such as myocardial infarction, bronchial asthma, and cerebral hemorrhage. This review discusses recent advances in this field, focusing mainly on the role of neurotransmitters and neuromodulators in anesthetic emergence.

Keywords Anesthetic emergence · Sleep · Brain network · Neurotransmitter · Neuromodulator

Introduction

Although more than 150 years have passed since the discovery of anesthesia, details regarding the mechanism of general anesthesia remain unclear. Historically, it was thought that the process of anesthetic emergence progressed only through the passive elimination of pharmacologic agents from the brain. However, a recent study indicated that anesthetic emergence may not be simply a process mirroring anesthetic induction [1•]. For example, the γ-aminobutyric acid (GABA) uptake inhibitors NO-711 and SKF89976A shortened the onset of the loss-of-righting reflex (LORR), but did not affect the duration of LORR induced by 1.5 % halothane and 2 % isoflurane. LORR is widely accepted as a sign of anesthetic unconsciousness in rodents.. Several studies reported that activation of orexin, an endogenous wakefulness-promoting substance, decreased LORR induced by barbiturate [2], propofol [3, 4], ketamine [5], and isoflurane [6] and sevoflurane [7•]. Orexin delayed anesthetic emergence but did not affect anesthetic induction. These results suggested that anesthetic emergence is a process that differs from anesthetic induction.

No unified theory exists that can explain every mechanism of anesthesia. Anesthesia acts on the brain network multimodally to alter network connectivity [7•]; therefore, anesthetic emergence might be a varied process. Nevertheless, the sequence of activation of consciousness, connectedness to the environment, and responsiveness is an important process for the smooth and uneventful emergence from anesthesia [8•]. Here, we discuss recent progress on the anesthetic emergence process, focusing on neuronal networks and neurotransmitters. First, we review current concepts regarding the mechanism of anesthetic induction.

Induction of Anesthesia: Overview

It is widely accepted that general anesthesia works at the molecular and cellular levels to enhance inhibitory components

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such as GABAergic neuronal activity to produce loss of consciousness (LOC). Despite our understanding of the molecular actions of anesthesia, it is not clear how these effects on molecular targets affect larger-scale neural circuits to produce unconsciousness. Various network parameters of brain connectivity might be altered by propofol-induced LOC [7•]. Currently, the leading hypothesis suggests that anesthetics disrupt cortical integration [9••, 10, 11••]. In the case of propofol, simultaneous recordings of multiscale neural activity from the human cortex showed that unconsciousness develops in seconds, accompanied by slow (<1 Hz) oscillation. This oscillation indicates that cortical neurons maintain a small-scale (<4 mm) functional connectivity similar to that of the conscious state, and that neuronal spike rates can recover to baseline levels after LOC despite continued unresponsiveness. Slow oscillations occur asynchronously across the cortex, disrupting functional connectivity between cortical areas. This diverse neuronal activity during propofol-induced LOC across the brain suggests that information transfer among distant (>2 cm) cortical networks is impaired [12•]. Therefore, cortical networks are fragmented both temporally and spatially, disrupting both local and long-range communication. The changes in neuronal dynamics induce functional isolation in time and space, whereas local neuronal networks remain intact. Subcortico-cortical and cortico-cortical connectivity breaks down during propofol-induced LOC. The degrees of these breakdowns are non-uniform and depend on anatomic structure. Thalamocortical connections were most affected, whereas no changes in connectivity were found within the primary sensory cortices. Furthermore, there was a profound decline in long-range connections and a reduction in whole-brain spatiotemporal integration [13•]. This de-orchestration of neuronal ensembles may indicate an essential aspect of the mechanism of general anesthesia-induced LOC (Fig. 1). Anesthesiologists thus need to become familiar with the language of networks. For example, in the case of propofol anesthesia, the normal alpha rhythm (8–13 Hz) shifted from the occipital cortex to the frontal cortex [14]. A recent study analyzing changes in electroencephalography (EEG) patterns before, during, and after anesthesia showed that general anesthesia with propofol and sevoflurane simplified the complex temporal pattern of brain networks. It also reduces the population of network backbones, transforming diverse brain connectivity into a more restricted and consistent pattern [11••].

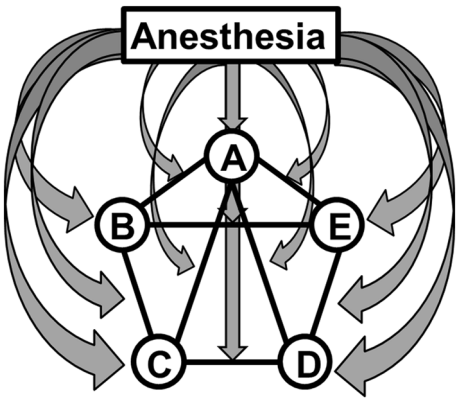

Fig. 1 Brain structure and neuronal connections responsible for maintaining wakefulness. Each *letter* denotes an anatomic structure, and *solid lines* indicate the neuronal connections among them. The structures include the cerebral cortex (*A*), hypothalamus (*B*), basal forebrain (*C*), thalamus (*D*), and brainstem (*E*). Wake-promoting systems are interconnected mainly in a mutually excitatory network. The cholinergic basal forebrain, orexinergic lateral hypothalamus, serotonergic raphe, noradrenergic locus coeruleus, and histaminergic tuberomammillary neurons all interact to promote wakefulness. Anesthesia alters this connectivity in different ways, depending on the type of anesthetic. If the connectivity strength falls below threshold, one loses consciousness. When strength returns to above threshold, consciousness emerges. The condition of emergence is not unitary.

Emergence from Anesthesia: Overview

A human study with positron emission tomography indicated several brain regions are activated in the consciousness state. The regions are the anterior cingulate cortex (ACC) in the medial frontal lobe, the midline thalamus, hypothalamus, the locus coeruleus/parabrachial area in the brainstem, the cerebellum, and portions of the lateral orbital frontal and parietal lobes. When the subjects are conscious, functional connectivity exists between the frontal and parietal brain areas, but that connectivity fades in conjunction with LOC by anesthetics. The return to consciousness was not associated with a significant restoration of cortical activation. Arousal-induced activations were mostly localized in deep, phylogenetically old brain structures rather than in the neocortex. These results suggested that the anesthetic recovery process may not be a simple mirror of induction [15••].

Historically, anesthesia emergence has been considered a passive process based on pharmacokinetics: redistribution or elimination of the anesthetic drugs from their central effect sites. However, other recent studies indicate this may not be the case. The process of emergence from general anesthesia is not just the inverse process of induction [16]. LOC consistently has been associated with a topologic disruption of brain neuronal network connectivity. However, the process of recovering consciousness from anesthesia has been associated with complex patterns of altered connection strength after the initial topologic structure gradually recovered. General anesthesia significantly alters brain network connectivity. An analysis of the regional effects on brain networks demonstrated that the parietal network was significantly disrupted, whereas the frontal network was minimally affected [7•].

One study recorded human EEG activity during the gradual induction of and emergence from unconsciousness

with propofol. LOC was marked simultaneously by an increase in low-frequency EEG power (<1 Hz) and a loss of spatially coherent occipital alpha oscillations (8–12 Hz). During emergence from unconsciousness, alpha amplitudes (8–12 Hz) were maximal at low-frequency nadirs (<1 Hz). This phase–amplitude relationship predicted the recovery of consciousness after the administration of commonly used anesthetic drugs [17••]. During emergence, frontal power shifted from the alpha and beta bands (12–20 Hz) to span the beta and gamma bands (>20 Hz) with increasing median frequency. These analyses showed that changes in broadband gamma/beta power coincide with the behavioral changes before LOC and after recovery of consciousness (ROC) [17••].

Next, we review important concepts of anesthetic emergence and describe how several neurotransmitters and modulators act on it.

Brain Anatomic Structures in Emergence from Anesthesia

General anesthesia consists of amnesia, analgesia, areflexia, and atonia. Based on neuroimaging findings, several studies reported that the thalamus appears to be a common site of modulation for several anesthetics. The brain's response to external stimuli is preserved in the primary sensory areas, suggesting that unconsciousness cannot be explained by cortical deafferentation or a diminution of cortical sensory reactivity.

Although functional connectivity in the frontoparietal association cortex is often reduced, a defining role for this change in LOC has yet to be elucidated. The functional connectivity of the nonspecific (intralaminar) thalamic nuclei is preferentially decreased by propofol. Higher-order thalamocortical connectivity is also reduced by certain anesthetics. Anesthetic LOC is not a blockage of corticofugal information transfer, but a disruption of higher-order cortical information integration. The prime candidates are those based on the posterior parietal–cingulate–precuneus region and the nonspecific thalamus [1••]. Overall, the brain structures targeted by anesthetics include the brainstem, thalamus, hypothalamus, basal forebrain, and cerebral cortex. Wake-promoting systems are interconnected, mainly in a mutually excitatory network. If their connectivity strength goes below the threshold, one will lose consciousness. When the strength returns to above the threshold, consciousness will emerge (Fig. 1). Among these, the so-called ascending reticular activating system (ARAS) is the most notable concept. ARAS is considered a network (reticulum) of nerve fibers arising from the brainstem that, through multiple intermediary sites, activates the forebrain during waking and rapid eye movement (REM) sleep. Electrical stimulation of the midbrain reticular formation in anesthetized cats produced an "activated" EEG similar to that seen during waking [18]. This result is probably one of the earliest findings indicating a relationship between sleep and anesthesia.

The ARAS consists of dorsal and ventral pathways that transfer brainstem activity to the cerebral cortex through the thalamus [19]. The dorsal pathway originates in the pontine and midbrain reticular formations, most prominently in the cholinergic in the lateral dorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) and glutamatergic neurons, which project to the "nonspecific" intralaminar and midline thalamic nuclei that diffusely innervate various areas of the cerebral cortex.

The ventral pathway also originates from the pontine/midbrain regions and projects to the lateral hypothalamic area (LHA) and tuberomammillary nuclei (TMN) of the hypothalamus, and to the basal forebrain. Neuronal fibers arising from the LHA and TMN also ascend to the basal forebrain, which in turn projects to the cortex. Noradrenergic neurons of the locus coeruleus and serotonergic neurons in the dorsal raphe contribute to both pathways and send direct projections to the cortex, as do histaminergic neurons of the TMN and orexinergic neurons of the lateral hypothalamus.

Sleep and Anesthesia

Since Nelson et al. [20] reported that general anesthesia shares an endogenous sleep circuit to induce hypnosis, the process of general anesthesia-induced unconsciousness has often been compared with sleep [21•, 22•, 23•, 24, 25]. For example, in the case of propofol, there are similarities as well as important differences in EEG dynamics [26]. Sleep spindles occur with a frequency range and spatial distribution [27] similar to propofol-induced frontal alpha/beta rhythms. The difference between EEG in sleep and EEG in propofol anesthesia lies in time-domain morphology. Both sleep and propofol produce EEG slow oscillations; however, less neuronal firing was observed in the propofol-induced slow oscillation compared with the sleep-induced slow oscillation. This finding suggests that a more profound degree of cortical depression occurred with propofol than with sleep [12•].

Recent studies suggest there are similarities between sleep and anesthesia-induced hypnotic effects [25, 28]. However, there are still many unsolved mysteries surrounding the hypnotic mechanisms of anesthesia and sleep [22•]. Clarifying these similarities may contribute not only to the discovery of the mechanism of anesthesia but also to a decrease in sleep disturbances following general anesthesia, which may cause several life-threatening complications such

as myocardial infarction, bronchial asthma, and cerebral hemorrhage [29, 30].

Neurotransmitters and Neuromodulators in Anesthetic Emergence: Overview

Multiple neurotransmitter systems contribute to the promotion of wakefulness; however, none functions as an absolutely essential player. Functional interactions exist among wake-promoting neuromodulatory systems that project to the cortex. Wake-promoting neuromodulatory systems are interconnected to form an excitatory network. The cholinergic (acetylcholine) basal forebrain, orexinergic lateral hypothalamic, serotonergic raphe, noradrenergic locus coeruleus, and histaminergic tuberomammillary neurons all interact to promote wakefulness. Thus, if one region is lesioned experimentally, the other systems should compensate and maintain cortical activation and wakefulness [31•]. No agent was discovered that depressed all neurotransmitter systems contributing to the promotion of wakefulness. This may be one reason no single agent can reverse anesthesia completely. Numerous studies showed that these neurotransmitters are involved in the mechanism of anesthesia [32•, 33••].

Noradrenaline

The central noradrenergic neuron system is divided into two groups: ventral and dorsal. The former arises from ventral caudal medulla that innervate the hypothalamus that is responsible for cardiovascular control. The amount of norepinephrine in dialysates from the posterior hypothalamus increased significantly only after the cessation of isoflurane. Noradrenergic neurons from the ventral region are involved in cardiovascular regulation during emergence from anesthetics [34]. The latter arises from the locus coeruleus. The locus coeruleus, and likely other noradrenergic nuclei, exerts potent wake-promoting actions by activating noradrenergic receptors located within multiple subcortical structures [35•]. Norepinephrine infusion into the nucleus basalis of Meynert of the basal forebrain, which is implicated in the regulation of the state of consciousness across normal sleep–wake cycles, resulted in a decrease in EEG delta power, and patients displayed purposeful behavior consisting of limb and head movements and sporadic crawling or walking. This result indicates the shallow depth of a desflurane infusion for anesthesia. [36•].

Following early studies of noradrenaline's effect on anesthesia status [37, 38], others have indicated that this substance shortens general anesthesia time. A recent study, for example, found that locus coeruleus noradrenergic neurons were destroyed by DSP-4, a selective neurotoxin of noradrenergic neurons, affecting ketamine and thiopental anesthesia time. DSP-4 increased the anesthesia duration of the GABA-mediated agent thiopental and decreased the anesthesia time and analgesic effect of ketamine, an *N*-methyl-D-aspartate (NMDA)-mediated anesthetic. The induction time of both anesthetics was not affected by the locus coeruleus treatment. Locus coeruleus noradrenergic neurons seem to be involved in the recovery process of both GABA- and NMDA-mediated anesthesia [39]. Chemical lesion of the noradrenergic neurons of the locus coeruleus decreased the duration of ketamine anesthesia, whereas it increased the duration of thiopental anesthesia. The noradrenergic content of the cortex and hippocampus was correlated with the duration of anesthesia for ketamine and inversely correlated with the duration of anesthesia for thiopental [39]. This study suggests that the locus coeruleus dampens thiopental anesthesia but facilitates ketamine anesthesia and argues for a role of the locus coeruleus in mediating the action of anesthetics.

Dopamine

Dopaminergic agents decrease anesthesia time. Methylphenidate (5 mg/kg intravenously), an inhibitor of dopamine and norepinephrine transporters, shortened propofol anesthesia (8 mg/kg intravenously) time by nearly half based on LORR duration in rats [40••]. Methylphenidate also induced emergence from isoflurane general anesthesia [41••]. The action was likely via D1 dopamine receptor [42]. These results indicate that methylphenidate may be useful in reversing general anesthetic–induced unconsciousness and respiratory depression at the end of surgery, and potentially may be used in day-surgery patients. However, there is some controversy regarding the use of methylphenidate for this indication [43]. It is believed that methylphenidate given before emergence from anesthesia interrupts the natural course of consciousness, connectedness, and responsiveness that is thought to be an important process for smooth recovery from anesthesia. Methylphenidate administered to rats caused hyperlocomotion depending on various genetic properties and age [44]; therefore, methylphenidate might cause cognitive dysfunction or delirium. Another concern regarding methylphenidate is rebound hypersomnolence [45]. Although these reports indicate potential risk with the routine use of methylphenidate for emergence from anesthesia, further study is needed to clarify the appropriate indication for this agent.

Acetylcholine

Central cholinergic neurons are involved in the mechanism of anesthesia. Several studies reported that cholinergic

neuronal activity is reversed during anesthesia. For example, Positron emission tomography studies in human subjects showed that a centrally acting anticholinesterase inhibitor, physostigmine, antagonizes propofol-induced unconsciousness accompanied with changes in regional blood flow in the thalamus [46]. Physostigmine also partially reverses sevoflurane in humans; subjects given physostigmine regained responsiveness to commands or spontaneously opened their eyes [47]. Moreover, physostigmine decreased recovery time of ketamine anesthesia [48]. In rats, intrathalamic microinjections of nicotine temporarily restored righting and mobility in animals; the righting occurred despite continued sevoflurane administration [49]. Systemic administration of propofol decreased acetylcholine release from the rat cortex. Microinjection of propofol into the perifornical area also decreased the acetylcholine release accompanying deep sedation [50]. Interestingly, cholinergic neurons are responsible for parasympathetic tone, whereas noradrenergic neurons are responsible for sympathetic tone. Cholinergic neurons and noradrenergic neurons have a counteracting effect on anesthesia time.

Histamine

Controversy exists regarding the role of histaminergic neurons in the anesthesia mechanism. Lesions of histaminergic cells in the tuberomammillary nucleus, the main source of histaminergic neurons, had diverse effects on emergence from anesthesia. Emergence from isoflurane anesthesia was prolonged, but emergence from propofol, pentobarbital, or ketamine anesthesia was not [51]. Histaminergic neurons are considered a key in endogenous arousal of the neuronal circuitry; thus, anesthetics produce their hypnotic effects through the neuronal circuitry. One study reported that the lower sensitivity to propofol in genetically mutated mice was mirrored by a reactivity to GABAergic inhibitory postsynaptic currents (IPSCs) in the tuberomammillary nucleus of the hypothalamus [52]. These results indicate that central histaminergic neurons play a crucial role in emergence from general anesthesia via the endogenous arousal neuronal circuitry. Later, the same group showed that histamine genetic manipulation did not affect propofol anesthesia in vivo. Histaminergic neurons deficient in synaptic $GABA_A$ receptors were significantly more excitable and were insensitive to the anesthetic propofol. Propofol-induced LORR was identical in HDC-2 mice and their littermate controls when propofol was administered intravenously [53••]. The in vivo result suggests that histaminergic neurons do not seem to be principal cell types in propofol-induced LOC. Further study is needed to define the role of histaminergic neurons in the mechanism of anesthesia.

GABA and NMDA

A notable hypothesis, the "flip-flop" model, predicts that increased and sustained GABAergic action on the cells of the thalamus, the cerebral cortex, and the hypothalamus promotes sleep [54]. $GABA_A$ receptors are widely distributed throughout the brain [55–57]. GABA receptors, especially $GABA_A$ receptors, are considered the most prominent target for various anesthetics [58•, 59]. Anesthetics bind the $GABA_A$ receptor and enhance the inward chloride current; then, the neurons are hyperpolarized. The GABAergic neuron system, like other classical neurotransmitter systems, has a unique anatomic structure in which a small number of inhibitory interneurons control many excitatory neurons, and anesthetic-induced enhancement of $GABA_A$ inhibition can inactivate large brain regions [60]. The preoptic area of the hypothalamus provides GABAergic inhibition to the principal arousal centers in the hypothalamus, midbrain, and pons [54]. These GABAergic synapses overlapping with pyramidal cells in the arousal centers may be sites of action for the GABAergic hypnotics. Although several papers of EEG study reported that GABAergic anesthetics act on the cerebral cortex [61–63], EEG cannot exclude the subcortical region as a possible action site of GABAergic anesthetics. Therefore it remains unknown whether the proximate cause of anesthetic-induced unconsciousness resides in the cortex or subcortically.

Ketamine has a high affinity for NMDA receptors on GABAergic inhibitory interneurons [64, 65]. Ketamine inhibits NMDA receptors, which are considered the primary target site, but it also inhibits GABAergic-enhanced conductance arising from α_6-containing $GABA_A$ receptors [66]. Therefore, the hypnotic mechanism of ketamine may be the same as that of the GABAergic anesthetics.

Orexin and Neuropeptide S

In addition to numerous neurotransmitter-related studies of anesthesia mechanisms, several studies report that wakefulness-promoting endogenous substances also facilitate emergence from anesthesia.

Orexin is one of the most important endogenous substances in sleep regulation [67–69]. Lack of its activity causes narcolepsy, which is characterized by severe, irresistible daytime sleepiness, abnormal sleep–wake patterns, and cataplexy, a specific sudden loss of muscle tone occurring with strong emotions, such as laughter [70]. Orexin promotes wakefulness [68, 69] and reduces the anesthesia duration of several agents, including barbiturate [2], ketamine [5], propofol [3, 4], isoflurane [6, 71], and sevoflurane [6]. Time to induction of anesthesia would be affected by many factors such as cardiac output, drug solubility, and driving gradients. However, none of these

studies reported orexin affected induction time of anesthesia compared to variable-matched control animals. These results suggest that induction and emergence are different processes.

Similar results were obtained in studies of another wakefulness-promoting endogenous substance, neuropeptide S (NPS). NPS enhanced wakefulness [72] and decreased both ketamine and thiopental anesthesia duration, but not their induction time [73]. Receptor antagonists of both orexin and NPS prolonged anesthesia duration [2, 4, 69, 73]. These results suggest that an endogenous sleep–wake-related neuronal architecture might be involved in the anesthetic mechanism, especially emergence.

Conclusions

The process of recovery from some anesthetics, such as propofol or dexmedetomidine, in anesthetic-induced LOC involves activation of the brainstem, thalamus, and anterior cingulate cortex arousal networks involved in ARAS. In addition to ARAS activation, restoration of functional connectivity within the frontoparietal network also develops [74].

Recent studies suggest that human cognition consists of interactions among distributed, functionally specialized brain networks [75]. Anesthetics modulate the network connections globally rather than locally [12•]. For example, one study using EEG in rats reported that fundamental "local" topologic properties of the neural network were maintained even during an isoflurane-anesthetized state; however, the strength of the network connections among different brain regions was considerably diverse. In fact, any single agent, such as methylphenidate, or natural arousal-promoting, neuromodulator substances (e.g., amines, acetylcholine, orexin, or glutamate) will accelerate anesthetic emergence partially but not completely. These results suggest that there is no single factor solely responsible for emergence from anesthesia, and that many factors might be involved in the process. They may work with one another to reintegrate the disrupted information channels among central nervous system neurons. If only one factor controlling all the integration were found, it would be the core element of the mechanism of anesthetic emergence. However, no such factor has been found; thus, there currently is no single theoretic framework explaining all the features of the transitions in the anesthetic state. Presently, from a practical perspective, we may conclude the anesthetic mechanism is as follows.

The mechanism of anesthesia is partially the same as that of sleep; thus, endogenous sleep–wakefulness-related substances or agents affecting sleep status also affect anesthetic status. Studies of the relationship between these factors and brain structure temporally and spatially will provide new horizons for anesthetic induction and emergence.

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Compliance with Ethics Guidelines

Conflict of Interest Tetsuya Kushikata and Kazuyoshi Hirota declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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