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Distinct Neural Mechanisms Between Anesthesia Induction and Emergence: A Narrative Review

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Anesthesia induction and emergence are critical periods for perioperative safety in the clinic. Traditionally, the emergence from general anesthesia has been recognized as a simple inverse process of induction resulting from the elimination of general anesthetics from the central nervous system. However, accumulated evidence has indicated that anesthesia induction and emergence are not mirror-image processes because of the occurrence of hysteresis/neural inertia in both animals and humans. An increasing number of studies have highlighted the critical role of orexinergic neurons and their involved circuits in the selective regulation of emergence but not the induction of general anesthesia. Moreover, additional brain regions have also been implicated in distinct neural mechanisms for anesthesia induction and emergence, which extends the concept that anesthetic induction and emergence are not antiparallel processes. Here, we reviewed the current literature and summarized the evidence regarding the differential mechanism of neural modulation in anesthesia induction and emergence, which will facilitate the understanding of the underlying neural mechanism for emergence from general anesthesia. (Anesth Analg 2025;141:162–71)

The emergence of general anesthesia has once been thought to be a simple inverse process of induction resulting from the elimination of general anesthetics. However, the existence of hysteresis/neural inertia, an intrinsic tendency of the central nervous system to resist transitions between unconscious and conscious states, provides evidence that anesthesia induction and emergence are not mirror-image processes.[1] Notably, hysteresis/neural inertia cannot be solely explained by pharmacokinetics but can be affected by genetic and pharmacologic manipulation in flies and mice.[1,2] This phenomenon is also observed in humans when comparing dose responses of slow-wave activity or functional magnetic resonance imaging (fMRI) signals between anesthesia induction and emergence,[3,4] indicating that asymmetric neural dynamics exist between induction and emergence and cannot solely result from pharmacokinetic effects. These findings provide important evidence that the induction and emergence of general anesthesia are not simple antiparallel processes, but the underlying neural mechanism is not well understood.

General anesthesia shares the common feature of reversible loss of consciousness with natural sleep.[5–7] Current evidence has shown that many brain nuclei and circuits that regulate sleep-wake behaviors are also associated with the actions of general anesthetics,[6–9] suggesting that a shared neural mechanism exists between sleep-wake cycles and general anesthesia. Orexinergic neurons play a critical role in maintaining wakefulness,[10] and earlier data showed that exogenous administration of orexin facilitated the emergence of general anesthesia in rats.[11,12] Kelz et al[13] reported that orexinergic neurons selectively regulate emergence but not the induction of volatile anesthesia, which provided the earliest evidence that anesthesia induction and emergence are not mirror-image processes. Since then, many orexinergic neuron-involving circuits have been found to selectively modulate emergence from general anesthesia. On the other hand, several brain regions were reported to be solely associated with anesthetic induction. For example, the gamma-aminobutyric acid (GABA) levels in the pontine reticular formation (PnO) were related to propofol induction but not to the emergence period. [13] In recent years, an increasing number of studies have revealed that more brain nuclei and circuits, as well as neuron types, play different roles in anesthesia induction and emergence, which supports the concept that distinct neurobiology underlies

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anesthesia induction and emergence. Interestingly, there is divergence in the selective modulation of emergence among diverse groups of general anesthetics, even among subclasses of the same type. In this review, we summarize the evidence of the distinct neural mechanisms involved in anesthesia induction and emergence (Table and Figure), which may provide new insights into the emergence of anesthesia from general anesthesia.

The original studies that reported differential effects of general anesthetics on the EC50 (the concentration or dose at which 50% of the animals lost or recovered their righting reflex) between loss of righting reflex (LORR) and recovery of righting reflex (RORR) were included. Considering that only a limited number of studies[14,15,31] have reported the EC50 of LORR or RORR, we also included studies with outcomes of induction and emergence time.

ROLE OF OREXINERGIC NEURONS IN THE LATERAL HYPOTHALAMUS (LH) UNDER GENERAL ANESTHESIA

Orexinergic neurons, located exclusively in the lateral hypothalamus (LH), mainly help to maintain wakefulness, while the loss of orexinergic neurons causes narcolepsy.[10,36] In 2008, Kelz and colleagues first provided evidence that orexinergic neurons in the perifornical hypothalamus selectively regulate emergence from volatile anesthesia.[14] Isoflurane and sevoflurane inhibited the activity of orexinergic neurons in the perifornical hypothalamus.[14] Notably, genetic ablation of orexinergic neurons or systemic administration of a selective orexin-1 receptor antagonist delayed emergence time without affecting the induction time or EC50 of the LORR.[14] This study proposed the notion that the neural circuits governing anesthetic induction and emergence might be distinct. Zhao et al[15] also reported the differential modulatory role of orexinergic neurons in the perifornical lateral hypothalamic area (PeFLH) in isoflurane induction and emergence in rats. The activation of PeFLH orexinergic neurons decreased the recovery time from isoflurane and increased the EC50 of the RORR, whereas the inhibition of PeFLH orexinergic neurons prolonged emergence without affecting the induction time or EC50 of the LORR.[15] Taken together, the current evidence indicates that orexinergic neurons play an important role in the selective modulation of emergence from volatile anesthesia. However, the activity of orexinergic neurons remains unchanged during halothane anesthesia, and the induction and emergence from halothane anesthesia do not change in orexin-deficient mice,[37] suggesting that other wake-promoting regions or circuits but not the orexin system regulate the emergence from halothane anesthesia.

ROLE OF PROJECTIONS INVOLVING OREXINERGIC NEURONS UNDER GENERAL ANESTHESIA

Many regions, including the dorsal raphe nucleus (DRN), ventral tegmental area (VTA), basal forebrain (BF), locus coeruleus (LC), paraventricular thalamic nucleus (PVT), lateral habenula (LHb), and prefrontal cortex (PFC), have been found to mediate the selective modulation of orexinergic neurons during emergence from general anesthesia.

The DRN, located in the brainstem, mainly sends serotonergic inputs to the forebrain and regulates diverse functions or diseases, such as stress, anxiety, sociability, temperature, sensory and motor functions, and sleep-wakefulness.[38–40] Yang et al[16] reported that serotonergic neurons in the DRN mediate the emergence-promoting effects of orexinergic neurons. Injecting orexin-A into the DRN promoted emergence from isoflurane anesthesia in rats, whereas injection of an orexin receptor type 1 antagonist prolonged emergence. However, neither orexin-A nor an orexin receptor type 1 antagonist influenced isoflurane induction.[16] Additionally, they showed that isoflurane inhibited the activities of serotonergic neurons in the DRN, which could be partially reversed by orexin-A injection.[16] However, this study did not directly manipulate the activities of serotonergic neurons in the DRN to observe the responses to isoflurane anesthesia. Moreover, the activity of serotonergic neurons was detected via c-Fos staining but not via real-time imaging. Two studies[17,18] also revealed the differential role of DRN serotonergic neurons in the induction and emergence of volatile anesthesia. Li et al[17] used both c-Fos staining and fiber photometry to show that the activity of DRN serotonergic neurons gradually decreased under isoflurane exposure but recovered before emergence occurred, suggesting a close relationship between the activity of DRN serotonergic neurons and consciousness levels under isoflurane anesthesia. Activation of DRN serotonergic neurons facilitates emergence from isoflurane anesthesia, whereas inhibition prolongs emergence without affecting induction time.[17] Similar findings were observed under sevoflurane anesthesia.[18] These 3 studies[16–18] suggested that DRN serotonergic neurons selectively regulate emergence from volatile anesthesia, which is at least partially modulated by serotonergic inputs. However, whether this phenomenon occurs for other types of general anesthetics, such as propofol, needs to be determined in future studies.

The VTA, a midbrain region that contains a large proportion of dopaminergic neurons, is well known for modulating reward,[41] addictions,[42] negative emotions,[41] and sleep-wakefulness cycles.[43] Similar to previous findings in the DRN,[16] injecting orexin-A into the VTA[19] also promoted emergence from isoflurane anesthesia in rats, whereas injection of an antagonist

Table. Study Characteristics

Study	Animals	Sex	Anesthetics	Brain region	Behavioral indicators	Effects on induction period	Effects on emergence period
Kelz et al[14]	Mice	Both	Isoflurane and sevoflurane	$PeFLH^{Orx}$	Induction time; emergence time; EC50	No change	Inhibition of $PeFLH^{Orx}$ delays emergence
Zhao et al[15]	Rats	Male	Isoflurane	$PeFLH^{Orx}$-PVT	Induction time; emergence time; EC50	No change	Activation of $PeFLH^{Orx}$-PVT accelerates emergence
Yang et al[16]	Rats	Male	Isoflurane	DRN^{Ser}	Induction time; emergence time	No change	Activation of DRN^{Ser} accelerates emergence
Li et al[17]	Rats and mice	Male	Isoflurane	DRN^{Ser}	Induction time; emergence time	No change	Activation of DRN^{Ser} accelerates emergence
Ma et al[18]	Mice	Male	Sevoflurane	DRN^{Ser}	Induction time; emergence time	No change	Activation of DRN^{Ser} accelerates emergence
Li et al[19]	Rats	Male	Isoflurane	$PeFLH^{Orx}$-VTA^{DA}	Induction time; emergence time	No change	Activation of $PeFLH^{Orx}$-VTA^{DA} accelerates emergence
Zhang et al[20]	Rats	Male	Isoflurane	BF^{Orx}	Induction time; emergence time	No change	Activation of BF^{Orx} accelerates emergence
Dong et al[21]	Rats	Male	Sevoflurane	BF^{Orx}	Induction time; emergence time	No change	Activation of BF^{Orx} accelerates emergence
Wang et al[22]	Rats	Male	Isoflurane	$PeFLH^{Orx}$-BF, $PeFLH^{Orx}$-LC	Induction time; emergence time	No change	Activation of $PeFLH^{Orx}$-BF^{Orx} or $PeFLH^{Orx}$-LC accelerates emergence
Cai et al[23]	Mice	Male	Isoflurane	BF^{PV}	Induction time; emergence time	Activation of BF^{PV} delays induction	No change
Ao et al[24]	Mice	Male	Isoflurane	LC^{TH}-PVT	Induction time; emergence time	No change	Activation of LC^{TH}-PVT accelerates emergence
Bu et al[25]	Mice	Male	Isoflurane	PVT^{Glu}	Induction time; emergence time	No change	Activation of PVT^{Glu} accelerates emergence
Zhou et al[26]	Mice	Male	Sevoflurane	LH^{Orx}-LHb^{GABA}	Induction time; emergence time	No change	Activation of LH^{Orx}-LHb^{GABA} accelerates emergence
Shirasaka et al[27]	Rats	Male	Propofol	PFC^{Orx}	Induction time; emergence time	No change	Activation of PFC^{Orx} accelerates emergence
Liu et al[28]	Mice	Male	Propofol	TRN^{GABA}	Induction time; emergence time	No change	Activation of TRN^{GABA} accelerates emergence
Lu et al[29]	Mice	Male	Isoflurane	PBN-LH, PBN-BF	Induction time; emergence time	No change	Activation of PBN-LH or PBN-BF accelerates emergence
Luo et al[30]	Rats	Male	Propofol and isoflurane	PBN	Induction time; emergence time	No change	Activation of PBN accelerates emergence
Fu et al[31]	Rats	Male	Propofol	CMT^{GABA}	Induction time; emergence time; ED_{50}	No change	Activation of CMT^{GABA} accelerates emergence
Yang et al[32]	Mice	Male	Isoflurane	OT^{DA}	Induction time; emergence time	No change	Activation of OT^{DA} accelerates emergence
Zhang et al[33]	Mice	Male	Sevoflurane	NAc^{D1R}-VP	Induction time; emergence time	No change	Activation of NAc^{D1R}-VP accelerates emergence
Niu et al[34]	Mice	Male	Sevoflurane	NAc^{D2R}-VP	Induction time; emergence time	Activation of NAc^{D2R}-VP accelerates induction	No change
Liu et al[35]	Mice	Male	Sevoflurane	SCN	Induction time; emergence time	No change	Activation of SCN accelerates emergence
Vanini et al[13]	Rats	Male	Propofol or isoflurane	PnO^{GABA}	Induction time; emergence time	Activation of PnO^{GABA} delays induction	No change

Abbreviations: BF^{Orx}, orexinergic terminals in basal forebrain; CMT^{GABA}, GABAergic neurons of central medial thalamic nucleus; DRN^{Ser}, serotonergic neurons of dorsal raphe nucleus; EC50, the concentration or dose at which 50% of the animals lost or recoverd their righting reflex; LC^{Orx}, orexinergic terminals in locus coeruleus; LH^{Orx}, orexinergic neurons of lateral hypothalamus; LHb^{GABA}, GABAergic neurons of lateral habenula; NAc^{D1R}, dopamine D1-receptor neurons of nucleus accumbens; NAc^{D2R}, dopamine D2-receptor neurons of nucleus accumbens; OT^{DA}, dopaminergic terminals of olfactory tubercle; PBN, parabrachial nucleus; $PeFLH^{Orx}$, orexinergic neurons of perifornical lateral hypothalamic area; PFC^{Orx}, orexinergic terminals in prefrontal cortex; PnO, pontine reticular formation; PV, parvalbumin neurons; PVT^{Glu}, glutamatergic neurons of paraventricular thalamic nucleus; SCN, suprachiasmatic nucleus; TH, tyrosine hydroxylase; TRN^{GABA}, GABAergic neurons of thalamic reticular nucleus; VP, ventral pallidum; VTA^{DA}, dopaminergic neurons of ventral tegmental area.

of the orexin-1 receptor delayed emergence. However, neither orexin-A nor antagonists of the orexin-1 receptor altered the induction time of isoflurane anesthesia. The authors also showed that orexin-A enhanced the firing frequency of dopaminergic neurons in the VTA,[19] suggesting that dopaminergic neurons in the

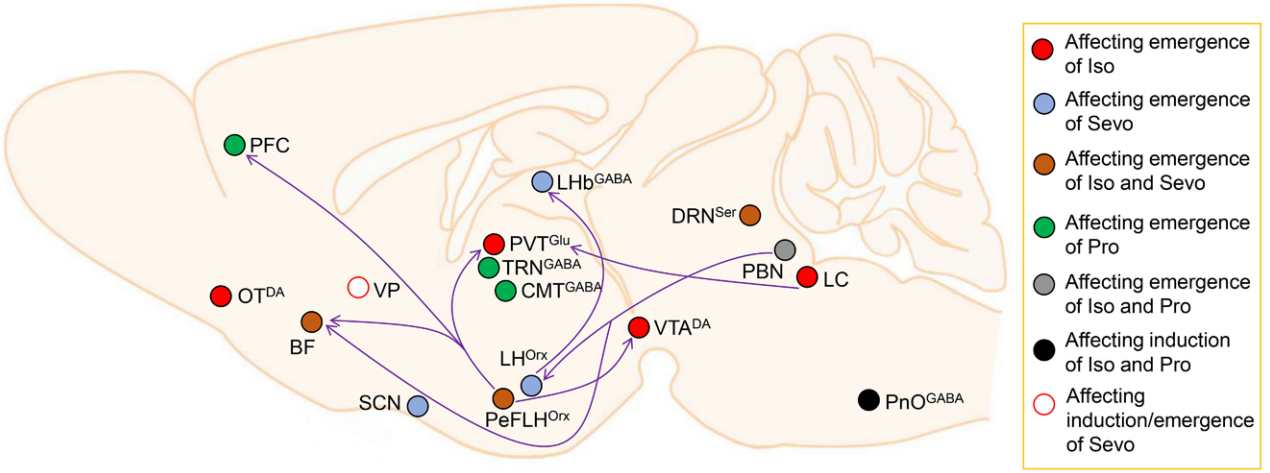

Figure. Sagittal section of the rodent brain showing the nuclei and circuits with selective modulation during anesthesia induction and emergence from general anesthesia. BF, basal forebrain; CMT^{GABA}, GABAergic neurons of the central medial thalamic nucleus; DRN^{Ser}, serotonergic neurons of the dorsal raphe nucleus; Iso, isoflurane; LC, locus coeruleus; LH^{Orx}, orexinergic neurons of the lateral hypothalamus; LHb^{GABA}, GABAergic neurons of the lateral habenula; OT^{DA}, dopaminergic terminals of the olfactory tubercle; PBN, parabrachial nucleus; $PeFLH^{Orx}$, orexinergic neurons of the perifornical lateral hypothalamic area; PFC, prefrontal cortex; PnO, pontine reticular formation; Pro, propofol; PVT^{Glu}, glutamatergic neurons of the paraventricular thalamic nucleus; SCN, suprachiasmatic nucleus; Sevo, sevoflurane; TRN^{GABA}, GABAergic neurons of the thalamic reticular nucleus; VP, ventral pallidum; VTA^{DA}, dopaminergic neurons of the ventral tegmental area.

VTA partially mediate the emergence-promoting effects of the orexin system.[19]

The BF mainly sends cholinergic projections and is implicated in sleep-wakefulness, cognition, learning, sensory signaling, and Alzheimer's and Parkinson's diseases.[44–48] Previous studies have shown that injecting orexin-A into the BF selectively accelerated emergence from isoflurane[20] and sevoflurane anesthesia.[21] Consistently, activation of orexinergic terminals in the BF promoted the emergence of isoflurane anesthesia without affecting induction.[22] In addition to orexin-A, the administration of histamine to the nucleus basalis magnocellularis of the BF facilitated the emergence of isoflurane anesthesia in rats,[49] suggesting the contribution of the histaminergic pathway in the BF to the emergence from isoflurane anesthesia. However, they did not assess whether the induction process was changed.[49] Unlike orexinergic signaling, activation of GABAergic neurons in the BF influences both isoflurane induction and emergence processes, as evidenced by increased induction time and decreased emergence time in mice.[50] The role of 2 common subtypes of GABAergic neurons in the BF, namely, somatostatin (SOM)- and parvalbumin (PV)-expressing neurons, in general anesthesia was further studied.[23] Activation of SOM neurons shortened the induction time and prolonged the emergence time of isoflurane anesthesia. However, the activation of PV neurons prolonged the induction time but did not affect the emergence time of mice under isoflurane anesthesia, suggesting the selective modulation of isoflurane emergence by BF PV neurons. Nevertheless, the effects of PV neurons on the EC50 of RORR should be determined to confirm this conclusion.

The LC, which mainly contains norepinephrine (NE) neurons, projects noradrenergic outputs throughout the central nervous system and primarily regulates arousal.[51] As in the BF, activation of orexinergic terminals in the LC facilitated emergence from isoflurane anesthesia without affecting induction.[22] Interestingly, plasma concentrations of orexin-A were elevated during emergence from isoflurane anesthesia.[20] In the clinic, evidence has shown that plasma orexin-A levels increase in surgical patients during the emergence of sevoflurane[52,53] or propofol[53] anesthesia but do not change during induction. Therefore, plasma orexin-A levels might be a novel indicator of consciousness during the emergence period of general anesthesia. However, manipulation of the noradrenergic system of the LC affected both the induction and emergence of isoflurane anesthesia.[54] The activation of LC-NE neurons induced cortical activation on electroencephalography (EEG), delayed isoflurane induction, and facilitated emergence, which was prevented by treatment with α1 or β noradrenergic antagonists.[54] There is also a significant proportion of tyrosine hydroxylase (TH) neurons in the LC. Ao et al[24] investigated the role of TH neurons in the LC under isoflurane anesthesia. They showed that the activity of LC TH neurons increased during emergence from isoflurane anesthesia. Activation of LC TH neurons or their projections to the PVT facilitated emergence and induced cortical activation, whereas inhibition produced the opposite effects. However, the induction time was not affected by manipulating the LC TH-PVT projection.[24]

The PVT, a glutamatergic node, regulates many important behaviors, such as motivation and reward,[55] fear,[56] drug addiction,[57] and sleep-wakefulness.[58]

Activation of PVT neurons induces wakefulness from sleep, whereas inhibition of PVT neurons suppresses wakefulness.[58] The PVT is also an effective downstream signal that mediates the selective emergence-promoting effects of PeFLH orexinergic neurons under isoflurane anesthesia.[15] However, the PeFLH-PVT circuit regulates both the induction and emergence of desflurane anesthesia.[15] Bu et al[25] also reported that activation of PVT glutamatergic neurons accelerated the emergence of isoflurane anesthesia in mice without affecting the induction process. Using fiber photometry, they showed that the Ca^{2+} signals gradually decreased after isoflurane inhalation and began to increase before RORR occurred but merely recovered to the approximate level of that at LORR after emergence. These results provide direct evidence for the theory of anesthetic hysteresis/neural inertia. However, a longer recording time is necessary to determine whether the activity will return to the baseline level before anesthesia, which could exclude the possibility of signal decay. Similarly, Ren et al[58] demonstrated that activation of PVT glutamatergic neurons shortens the emergence time from isoflurane anesthesia in mice, but they did not test whether the induction process is affected. Notably, previous studies have indicated that PVT activity is associated with both the induction and emergence of sevoflurane[59,60] and propofol anesthesia,[61] indicating that the neuronal effectors of action of other types of general anesthetics are distinct from those of isoflurane.

The LHb, located at the posterior-dorsal-medial end of the thalamus, serves as a key region in the pathophysiology of several psychiatric disorders, especially major depression.[62] The LHb receives LH orexinergic inputs, and activation of the projection from LH orexinergic neurons to LHb glutamate decarboxylase (GAD2)-expressing neurons shortens the emergence time of sevoflurane anesthesia, whereas inhibition of this pathway prolongs emergence time without affecting induction time.[26]

The PFC is considered to serve as the highest center for neural integration and is related to numerous important functions or disorders, such as emotions, reward, decision-making, cognition, motor functions, psychopathology, sleep, and wakefulness.[63–65] In addition to volatile anesthetics, the orexin system also regulates the general anesthesia induced by propofol. Shirasaka et al[27] reported that the injection of orexin-A in the PFC promoted the emergence of propofol, whereas the administration of an orexin-1 receptor antagonist prolonged the emergence time without affecting the induction time. Therefore, orexinergic neurons serve as common targets of both volatile and intravenous anesthetics to regulate emergence. They further showed that the orexin system may facilitate the emergence of propofol by inducing the release of NE and dopamine (DA) to enhance the noradrenergic and dopaminergic activity of the PFC.[27]

OTHER BRAIN REGIONS THAT DIFFERENTIALLY REGULATE ANESTHESIA INDUCTION AND EMERGENCE

Many brain regions have been found to differentially regulate anesthesia induction and emergence, although whether these differences are mediated by orexinergic inputs remains unclear. These regions included the thalamic reticular nucleus (TRN), parabrachial nucleus (PBN), central medial thalamic nucleus (CMT), olfactory tubercle (OT), ventral pallidum (VP), suprachiasmatic nucleus (SCN), and PnO.

The TRN is primarily composed of GABAergic neurons and is associated with the regulation of sensory processing,[66] emotions,[67] attention,[68] learning and memory,[68] neurodevelopmental disorders,[69] and sleep-wakefulness behaviors.[70,71] Liu et al[28] explored the role of the anterior TRN in propofol anesthesia in mice. They found that the activities of GABAergic neurons in the anterior TRN were inhibited after propofol infusion but gradually increased before RORR occurred. However, it remains unclear whether the activity at the RORR exhibited a full return to its preanesthetic baseline. Activation of GABAergic neurons in the anterior TRN promoted emergence from propofol anesthesia, whereas inhibition of these neurons delayed emergence. However, manipulation of TRN GABAergic neurons did not affect induction time. Interestingly, 1 study[50] showed that activation of GABAergic terminals in the TRN prolonged isoflurane induction and accelerated emergence in mice. However, activation of noradrenergic terminals in the TRN delays the emergence of propofol anesthesia and promotes the induction process.[72] Therefore, the distinct modulatory effects on induction and emergence in the TRN might depend on the type of neuronal population and the diverse groups of general anesthetics used. Notably, the circuits involved in TRN GABAergic neurons under propofol anesthesia have not been elucidated. Moreover, the role of other subregions of the TRN[73] in general anesthesia also needs to be addressed in future studies.

The PBN, located in the pons, plays a role in regulating many behaviors, such as sensory transmission,[74,75] defensive behaviors,[76] feeding,[77] and emotions.[78] The PBN is also a well-known wake-promoting brain region.[79] However, evidence regarding the differential effects of PBN on anesthesia induction and emergence is mixed. Lu et al[29] investigated the role of PBN-related projections under isoflurane anesthesia in mice. Optogenetic activation of the PBN-LH or PBN-BF pathway shortened the emergence time from isoflurane anesthesia without affecting the induction time. An increase in the number of PBN projections

might be associated with the distinct modulatory effects of isoflurane anesthesia on induction and emergence. Similarly, Luo et al[30] reported that activation of the PBN promoted the emergence of both propofol and isoflurane anesthesia without affecting the induction time. Muindi et al[80] also reported that electrical stimulation of the PBN could induce reanimation from isoflurane anesthesia in mice. However, the neuronal populations in the PBN that regulate emergence should be determined because a previous study showed that activation of PBN glutamatergic neurons accelerated the emergence of sevoflurane and prolonged the induction time.[81]

The CMT, a member of the limbic thalamus, participates in processing nociceptive signals as well as their related negative emotions.[82] Consistent with the results in the PFC,[27] Fu et al[31] reported that microinjection of NE into the CMT facilitated the emergence of propofol anesthesia but did not affect the induction time or EC50 of the LORR. Propofol enhances GABAergic transmission in CMT slices, which is partially reversed by the application of NE.[31] Hence, the noradrenergic system was suggested to play a role in the selective regulation of propofol emergence.

In addition to olfaction, the OT also regulates learning, motivated behaviors, and drug seeking.[83] The OT receives dense inputs from dopaminergic neurons via several nuclei, such as the VTA.[84] Yang et al[32] reported that local injection of D1 receptor (D1R) and D2R agonists into the OT accelerated the emergence from isoflurane anesthesia, while injection of antagonists of D1R and D2R prolonged the recovery time. Optogenetic activation of dopaminergic terminals in the OT also promoted the emergence of isoflurane anesthesia. However, D1R/D2R agonists, D1R/D2R antagonists, or optogenetic stimulation of dopaminergic terminals in the OT did not affect anesthesia induction. This study did not identify the source of dopaminergic inputs. Additionally, whether other neuronal types, such as dopamine D3 receptor-expressing granule cells in the OT,[33] selectively regulate the emergence from isoflurane anesthesia needs to be determined.

DA receptor-expressing neurons are the predominant type of neurons in the nucleus accumbens (NAc), which is well known for controlling reward and drug addictions.[85,86] Recent studies have demonstrated a role for the NAc in the regulation of general anesthesia. Zhang et al[87] showed that the activity of NAc^{D1R} neurons began to decrease after sevoflurane exposure and gradually recovered before RORR occurred. The Ca^{2+} signals at the LORR and RORR were comparable. Moreover, after RORR, the Ca^{2+} signals rapidly increased to an approximate level at preanesthesia, which was different from the slow recovery observed in the PVT.[25] Therefore, the recovery rate of neural activity after RORR might differ among nuclei, and it will be interesting to investigate the underlying molecular basis. Optical activation of NAc^{D1R} neurons prolonged induction time and shortened arousal time. These findings were consistent with those of another study.[88] They further showed that the activity of the NAc^{D1R}- VP pathway was inhibited under sevoflurane anesthesia.[87] Activation of the NAc^{D1R}-VP pathway reduces emergence time, whereas inhibition of the NAc^{D1R}-VP pathway prolongs emergence from sevoflurane anesthesia but does not change induction time.[87] Consistently, activation of the NAc^{D1R}-VP induced reanimation from sevoflurane anesthesia.[89] Conversely, activation of the NAc^{D2R}-VP shortened the induction time of sevoflurane anesthesia in mice without affecting emergence time.[34] These findings suggest that different types of dopamine receptor-expressing neurons in the NAc-VP might differentially regulate the induction and emergence of sevoflurane anesthesia.

The SCN, located in the anterior-ventral hypothalamus, contributes to regulating circadian rhythms,[90,91] such as sleep-wakefulness circuits.[92,93] A recent study reported that the activity of the SCN was associated with emergence from general anesthesia.[35] Liu et al[35] reported that monochromatic blue light (MBL) exposure enhanced the neuronal activity of the SCN under sevoflurane anesthesia in mice. MBL shortened the emergence time from sevoflurane anesthesia without influencing the induction time. These responses to MBL were abolished by SCN lesions. However, whether manipulation of the activity of the SCN directly influences the emergence of sevoflurane anesthesia should be determined.

The PnO is a region of the ascending reticular activating system and is implicated in sleep-wakefulness and general anesthesia.[94] Vanini et al[13] reported that PnO selectively regulates the induction process of general anesthesia. Decreasing GABA levels in the PnO shortened the induction of propofol or isoflurane in rats, whereas increasing GABA levels in the PnO prolonged the induction. However, the occurrence rate of emergence from propofol or isoflurane was not altered.[13] More regions that selectively regulate the induction of general anesthesia might be identified in future studies.

Using fMRI, Huang et al[4] provided human evidence regarding distinct neural mechanisms between anesthesia induction and emergence in large-scale brain networks. During the period from propofol delivery to unconsciousness, temporal autocorrelation of fMRI signals (an index of neural processing timescales) across the whole brain gradually increased, but functional connectivity gradually decreased. After consciousness recovery, rapid recovery of cortical but not subcortical neural processing and an abrupt

increase in subcorticocortical functional connectivity were observed. These findings indicate asymmetric neural dynamics between propofol induction and emergence, which cannot be solely explained by pharmacokinetic effects.

DISCUSSION

Current evidence consistently indicates that orexinergic neurons are critical for the selective regulation of emergence from general anesthesia induced by both volatile and intravenous anesthetics. Many brain regions have been found to mediate the emergence-promoting effects of orexinergic neurons. Moreover, plasma orexin-A levels might be a novel biomarker for the emergence of general anesthesia. Interestingly, the orexin system appears to not be associated with halothane anesthesia.[37] In recent years, emerging brain nuclei and circuits as well as neural types have been indicated to be associated with the distinct modulation between anesthesia induction and emergence, although their relationships with orexinergic neurons and the underlying molecular mechanism remain elusive. Notably, the distinct mechanisms underlying the differences between induction and emergence were not consistent among the different types of general anesthetics. For example, manipulation of PVT activity can selectively modulate the emergence of isoflurane anesthesia[15,25] but affects both the induction and emergence of sevoflurane,[59] desflurane,[15] and propofol[61] anesthesia. There is also divergence in the role of individual brain regions in the selective modulation of anesthesia induction and emergence. For example, activation of the NAc^{D1R}-VP circuit selectively accelerates the emergence of sevoflurane anesthesia,[87] whereas activation of the NAc^{D2R}-VP circuit selectively accelerates the induction of sevoflurane anesthesia.[34] Most recent studies reporting that induction is not a simple inverse process of emergence have focused on isoflurane anesthesia, and additional brain nuclei or circuits might differentially regulate the different periods of general anesthesia induced by other general anesthetics.

In addition to induction time, more reliable indicators, such as the EC50, should be used to assess the exact effects on anesthesia induction because it might be difficult to observe significant differences in induction time during the rapid induction period. For example, one study reported that the activation of PBN astrocytes did not affect the induction time of isoflurane anesthesia in mice but did significantly affect the EC50 of the LORR.[95] Importantly, poor study methods or designs might influence the results in the following cases: (1) extremely high doses of the anesthetic will cause a rapid LORR that cannot detect a difference in the induction time even if the nucleus in question does modulate induction; (2) assessment of the LORR that is too infrequent to detect a difference between groups; (3) lack of temperature maintenance or measurement in experimental mice to exclude the influence of hypothermia; and (4) use of pharmacologic antagonists or knockouts that enable the investigators to determine what happens in the naturalistic processes of induction or emergence that avoid the potential confounds of exogenous excitation/inhibition of neurons in ways that may never occur during the normal induction or emergence process. In this review, although all included studies reported changes in induction and emergence times, only 3 studies[14,15,31] reported EC50 values. Future studies are suggested to calculate the EC50 to determine the effects on anesthetic induction and emergence processes.

It should be determined whether sex differences exist in the distinct modulatory mechanism between anesthesia induction and emergence, as most of the current evidence on this topic was obtained from male rodents. Generally, females are more resistant to volatile anesthetics, which might be modulated by testosterone, and the underlying neuronal circuits are thought to be related to ventral hypothalamic sleep-promoting regions.[96] This might explain why women showed a greater incidence of awareness during general anesthesia. In addition to neuronal populations in the central nervous system, glial cells might also be associated with selective regulation under general anesthesia. One study[97] reported that mice lacking the mitochondrial complex I gene (Ndufs4) in astrocytes exhibited delayed emergence from isoflurane or halothane anesthesia, but the induction process did not change, suggesting that the normal mitochondrial function of astrocytes is selectively associated with emergence from volatile anesthesia.

In summary, this study comprehensively summarized the current evidence regarding the distinct neural mechanisms involved in the induction and emergence of general anesthesia, which will improve the understanding of the mechanisms underlying the emergence of general anesthesia.

DISCLOSURES

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