Understanding the neural mechanisms of general anesthesia from interaction with sleep-wake state: a decade of discovery [S]

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Abbreviations: A2AR, adenosine 2A receptor; AANs, anesthesia-activated neurons; ACh, cholinergic; AgRP, agouti-related protein; Amb, nucleus ambiguus; ARC, arcuate nucleus; BF, basal forebrain; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; BSR, burst-suppression ratio; CB1R, cannabinoid 1 receptor; CCK, cholecystokinin; CGRP, calcitonin gene-related peptide; CI, claustrum; CLT, central lateral thalamus; CMT, centromedial thalamic nucleus; CNO, clozapine-N-oxide; CR, calretinin; CRH, corticotropin releasing hormone; CVLM, caudal ventrolateral medulla; D1R, dopamine 1 receptor; D2R, dopamine 2 receptor; DA, dopaminergic; diLS, dorsal-intermediate lateral septum; DMH, dorsomedial hypothalamic nucleus; DMT, dorsal medial thalamus; DPGi, dorsal paragigantocellular nucleus; dDpMe, dorsal part of the deep mesencephalic nucleus; DRN, dorsal raphe nucleus; dStr, dorsal striatum; EC50-LORR, 50%

effective concentration for loss of righting reflex; EC50-RORR, 50% effective concentration for recovery of righting reflex; ED50, 50% effective dose; ED50-arousal score, 50% effective dose for achieving a arousal score; ED50-LORR, 50% effective dose for loss of righting reflex; EEG, electroencephalogram; EMG, electromyogram; fMRI, functional magnetic resonance imaging; GA, general anesthesia; GABA, γ-aminobutyric acid; Gal, galaninergic; $GABA_A$, gamma-aminobutyric acid subtype A; $GABA_B$, gamma-aminobutyric acid subtype B; Glu, glutamatergic; His, histaminergic; LC, locus coeruleus; LDT, laterodorsal tegmentum; LFP, local field potential; LH, lateral hypothalamus; LHb, lateral habenula; Lhx6, LIM homeodomain factor; LOC, loss of consciousness; LORR, loss of righting reflex; LPGi, lateral paragigantocellular nucleus; LPT, lateral pontine tegmentum; MCH, melanin-concentrating hormone; MnPO, median preoptic nucleus; MPTA, mesopontine tegmental anesthesia area; MS, medial septum; mSTN, medial subthalamic nucleus; NAc, nucleus accumbens; NB, nucleus basalis; NE, norepinephrine; NREM, non-rapid eye movement; NST, nucleus of the solitary tract; NTS, neurotensin; OB, olfactory bulb; OT, olfactory tubercle; OXT, oxytocin; Orx, orexinergic; PB, parabrachial nucleus; PDYN, prodynorphin; Pef, perifornical; PefLH, perifornical lateral hypothalamic area; PFC, prefrontal cortex; PnO, pontine reticular formation; POA, preoptic area; POMC, pro-opiomelanocortin; PPT, pedunculopontine tegmentum; preBötC, preBötzinger complex; PrL, prelimbic cortex; PT, pontine tegmentum; PV, parvalbumin; PVH, paraventricular nucleus of the hypothalamus; PVT, paraventricular thalamus; PZ, parafacial zone; REM, rapid eye movement; RMTg, rostromedial tegmental nucleus; RORR, recovery of righting reflex; RPa, raphe pallidus area; SLD, sublateral dorsal nucleus; SN, substantia nigra; SNr, substantia nigra pars reticulata; SOM, somatostatin; SON, supraoptic nucleus; SUM, supramammillary nucleus; TAC1, tachykinin 1; TMN, tuberomammillary nucleus; TRN, thalamic

reticular nucleus; VLPO, ventrolateral preoptic area; VMT, ventromedial thalamus; vPAG, ventral periaqueductal gray; vlPAG, ventrolateral periaqueductal gray; VLPO, ventrolateral preoptic area; VTA, ventral tegmental area; VP, ventral pallidum; ZI, zona incerta; 5HT, serotonergic.

Abstract

The development of cutting-edge techniques to study specific brain regions and neural circuits that regulate sleep-wake brain states and general anesthesia (GA), has increased our understanding of these states that exhibit similar neurophysiologic traits. This review summarizes current knowledge focusing on cell subtypes and neural circuits that control wakefulness, rapid eye movement (REM) sleep, non-REM sleep, and GA. We also review novel insights into their interactions and raise unresolved questions and challenges in this field. Comparisons of the overlapping neural substrates of sleep-wake and GA regulation will help us to understand sleep-wake transitions and how anesthetics cause reversible loss of consciousness.

Significance Statement

General anesthesia (GA), sharing numerous neurophysiologic traits with the process of natural sleep, is administered to millions of surgical patients annually. In the past decade, studies exploring the neural mechanisms underlying sleep-wake and GA have advanced our understanding of their interactions and how anesthetics cause reversible loss of consciousness. Pharmacotherapies targeting the neural substrates associated with sleep-wake and GA regulation have significance for clinical practice in GA and sleep medicine.

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I. Introduction

General anesthesia (GA) is a drug-induced reversible unconsciousness state during surgery. Physiological sleep is a spontaneous and rhythmical process that shifts between non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep in 90–120-min cycles. These two events have many differences: (1) generations: GA is an artificially altered state of consciousness, whereas sleep is a naturally occurring state; and (2) global electroencephalogram (EEG) signatures: neural oscillation dynamics induced by principal general anesthetics are globally different from sleep and exhibit drug-specific characteristics (Akeju and Brown, 2017). However, upon closer observations, there still exist substantial neurophysiologic similarities: (1) consciousness: the level of consciousness is reduced; (2) behaviors: both recovery from sleep and GA show similar behavior transitions from a decreased brain state to wakefulness, with increased body movement; (3) local EEG signatures (Fig. 1a–i): both conditions exhibit slow-wave activity and delta oscillation (Adamantidis et al., 2019; Akeju and Brown, 2017); and (4) autonomic functions: both conditions exhibit a state involving decreased body temperature, respiratory rate, blood pressure, and heart rate. With their similarities, there has been growing interest in understanding the neural mechanisms underlying these two states and their interactions.

Previous studies exploring the mechanism of GA actions have mainly focused on molecular targets such as $GABA_A$ (γ-aminobutyric acid, type A) receptors, N-Methyl-D-Aspartate receptors, two-pore-domain potassium channels, and hyperpolarization-activated cyclic nucleotide-gated channels (Hemmings et al., 2005; Rudolph and Antkowiak, 2004). However, the most confusing aspect is why different types of general anesthetics acting on distinctive molecular targets all finally induce a sleep-like behavior state without consciousness. With substantial evidence revealing that

GA influences the function of discrete networks rather than producing global suppression (Laitio et al., 2007; Palanca et al., 2017; White and Alkire, 2003), there is more research supporting the importance of neural networks in GA state transition modulation. Given the similarities between sleep and GA processing, the shared circuits hypothesis that different types of GA drugs possibly exert hypnotic effects through an overlapping neural network has become a hot research topic. Recently, with the development of cutting-edge techniques, including optogenetic/chemogenetic manipulation, electrophysiologic recording, calcium activity recording, anterograde or retrograde transsynaptic circuit tracing, neuroimaging, and behavioral tests in neuroscience, studies using the above technologies have provided further support to the overlapping neural circuits hypothesis.

In this review, we focus on techniques that enable specific targeting of neuronal populations and first review the nuclei involved in sleep-wake and GA regulations. We mainly reviewed studies about inhaled and intravenous general anesthetics that are most widely used in the clinic and also reviewed the anesthetic adjunct dexmedetomidine due to its specific pharmacological properties. Finally, we discuss the major findings and possible neural mechanisms of GA, as well as the implications of the interaction between sleep-wake and GA regulations.

II. Wake-sleep circuitry

According to EEG and electromyogram (EMG) profiles, sleep and wake states are typically determined as two discrete states. The transitions between NREM sleep and wakefulness typically occur over just a few seconds (Takahashi et al., 2010). Over the sleep period, NREM and REM sleep may switch back and forth, with occasional transitions to wakefulness (Saper et al., 2010). Neuroscientists began mapping the brain circuitry that controls sleep and wakefulness over 50 years ago (C. von Economo, 1930; Scammell et al., 2017), and in the last 10–20 years,

considerable advances have improved our understanding of the specific systems that regulate these states.

A. Wake-promoting nuclei

Historically, monoaminergic and cholinergic neurons were considered to be the key wake-promoting neurons (Jouvet, 1972). However, recent studies have highlighted the crucial roles of fast neurotransmitters (e.g., glutamate and GABA) and neuropeptides in regulating wakefulness (Fig. 2).

Several nuclei located in the forebrain are involved in wakefulness regulation. The basal forebrain (BF), a large heterogeneous structure, mainly contains three types of neuronal populations: cholinergic, glutamatergic, and GABAergic neurons. Cholinergic, glutamatergic, GABAergic, and parvalbumin (PV)-positive GABAergic ($GABA^{PV}$) neurons of the BF have been identified to be wake-promoting (Anaclet et al., 2015; Chen et al., 2016; Xu et al., 2015). Activation of purinergic P2 receptors in the BF also promotes wakefulness (Yang et al., 2018a). Moreover, glutamatergic neurons of the medial septum (MS) and GABAergic neurons of the dorsal-intermediate lateral septum (diLS) and the bed nucleus of the stria terminalis (BNST) are newly identified to be wake-promoting (An et al., 2021; Kodani et al., 2017; Wang et al., 2021a).

The basal ganglia (BG) system consists of four major nuclei in the forebrain and midbrain, that is, the striatum, globus pallidus, subthalamic nucleus, and substantia nigra (Lazarus et al., 2013; Lazarus et al., 2012). The striatum consists of the dorsal striatum, nucleus accumbens (NAc), and olfactory tubercle. We have uncovered that GABAergic dopamine 1 receptor (D1R)-expressing neurons of the dorsal striatum and NAc and GABAergic neurons of the ventral pallium are important for wakefulness regulations (Dong et al., 2022; Lazarus et al., 2013; Lazarus et al., 2012; Li et al.,

2021b; Luo et al., 2018b). A recent study also reported that corticotropin-releasing hormone (CRH)-expressing neurons in the medial subthalamic nucleus control arousal across wakefulness and REM sleep (Tseng et al., 2022).

The thalamus, being vital for consciousness modulation, contains multiple substructures involved in wakefulness control, including glutamatergic and calretinin-expressing neurons in the paraventricular thalamic nucleus (PVT) (Hua et al., 2018; Ren et al., 2018), matrix cells of the ventromedial thalamus (Honjoh et al., 2018), calretinin-expressing neurons in the dorsal medial thalamus (Matyas et al., 2018), and excitatory neurons in the centromedial thalamic nucleus (CMT) (Gent et al., 2018). Additionally, central lateral thalamus (CLT) neurons show lower spike rates during NREM sleep than during wakefulness.

The hypothalamus has long been considered important for sleep-wake regulation. Histaminergic neurons in the tuberomammillary nucleus (TMN) (Huang et al., 2006; Huang et al., 2007; Valdés et al., 2010; Yin et al., 2019a) and glutamatergic neurons in the supramammillary nucleus (Pedersen et al., 2017), preoptic area (POA) (Mondino et al., 2021), ventrolateral POA (VLPO) (Vanini et al., 2020), paraventricular nucleus of the hypothalamus (PVH) (Chen et al., 2021a; Wang et al., 2022), and lateral hypothalamus (LH) all participate in wakefulness promotion (Sotelo et al., 2022; Wang et al., 2021c). Further, LH GABAergic neurons promote arousal by inhibiting the thalamic reticular nucleus (TRN) and galaninergic VLPO neurons (Venner et al., 2016), (Venner et al., 2019). Additionally, neuropeptide-producing neurons are also involved in the regulation of wakefulness, including the arcuate nucleus agouti-related protein-expressing neurons in the hypothalamus (Goldstein et al., 2018), and oxytocin-, prodynorphin-, and CRH-expressing neurons in the PVH (Chen et al., 2021a; Li et al., 2020b; Ono et al., 2020). Additionally,

orexin/hypocretin-expressing neurons of the LH, particularly in the perifornical lateral hypothalamic area (PefLH), promote wakefulness by targeting multiple wake-promoting structures in the whole brain (Adamantidis et al., 2007; Scammell et al., 2017). Hyperexcitable orexin/hypocretin-expressing neurons in the LH drive sleep fragmentation during aging (Li et al., 2022b). However, there are paradoxical conclusions of the modulatory role of POA tachykinin 1 (TAC1) neurons, with one study showing that they are sleep-promoting (Chung et al., 2017), and another showing that they have a wake-promoting role (Reitz et al., 2021).

The brainstem consists of three parts, including the midbrain, pons, and medulla. Numerous monoaminergic neurons located in the brainstem are identified to be wake-promoting, including noradrenergic neurons of the locus coeruleus (LC) (Liang et al., 2021), serotonergic and dopaminergic neurons of the dorsal raphe nucleus (DRN) (Cho et al., 2017; Ito et al., 2013), and dopaminergic neurons of the ventral tegmental area (VTA) and ventral periaqueductal gray (vPAG) (Eban-Rothschild et al., 2016; Lu et al., 2006a). Although cholinergic laterodorsal tegmentum (LDT)/PPT has long been thought to be vital for cortical activation, activation of PPT cholinergic neurons only reduced slow EEG activity during NREM sleep (Kroeger et al., 2017). Glutamatergic neurons in the pedunculopontine tegmentum (PPT), VTA, parabrachial nucleus (PB), and TAC1 neurons in the nucleus of the solitary tract (NST) also drive wakefulness (Kaur et al., 2013; Kroeger et al., 2017; Qiu et al., 2016; Xu et al., 2021; Yao et al., 2022; Yu et al., 2019). Calcitonin gene-related peptide neurons in the external lateral PB drive the transitions from sleep to wakefulness during hypercapnia (Kaur et al., 2017). And the breathing control center (Cdh9/Dbx1 double-positive preBötzinger complex neurons) is also involved in wakefulness modulation (Yackle et al., 2017).

In addition to the above subcortical neural substrates, silencing a subset of neocortical layer 5 pyramidal and archicortical dentate gyrus granule cells in mice has been shown to markedly increase wakefulness, indicating the importance of the cortex in vigilance state control (Krone et al., 2021).

In summary, with the conventional monoaminergic and cholinergic signaling in wakefulness promotion, glutamatergic, GABAergic, and neuropeptides-expressing neurons also contribute to wakefulness regulation. These neural substrates are widely distributed in the whole brain and form a neural network for initiating and maintaining wakefulness.

B. NREM sleep-promoting nuclei

Compared to wake-promoting networks, the structures promoting NREM sleep are relatively limited (Fig. 3). For the BG system, activation of GABAergic adenosine A2A receptor (A2AR)-expressing neurons in the core region of the NAc, the dorsal striatum, and the olfactory tubercle has been shown to promote NREM sleep (Li et al., 2020a; Oishi et al., 2017; Yuan et al., 2017c). Glutamic acid decarboxylase 2-positive GABAergic neurons in the substantia nigra pars reticulata are also involved in sleep modulation (Liu et al., 2020c).

The hypothalamus has traditionally been regarded as a key region in sleep promotion. TMN-projecting GABAergic neurons in the POA are both sleep-active and sleep-promoting and co-express cholecystokinin, CRH, TAC1, and prodynorphin markers (Chung et al., 2017). Activation of hypothalamic arcuate nucleus pro-opiomelanocortin-expressing neurons promotes NREM sleep in a food-deprived condition (Goldstein et al., 2018). In addition, median preoptic nucleus GABAergic neurons (Vanini et al., 2020), VLPO galaninergic neurons (Kroeger et al., 2018), and supraoptic nucleus (SON)/paraSON anesthesia-activated neurons (AANs) all contribute to NREM

sleep promotion (Jiang-Xie et al., 2019).

The brainstem contains several NREM sleep-promoting nuclei. Excitatory glutamatergic neurons in the pontine tegmentum (PT) and neurotensin-expressing glutamatergic neurons in the ventrolateral periaqueductal gray (vlPAG) are known to promote NREM sleep (Hayashi et al., 2015; Zhong et al., 2019). GABAergic neurons in the VTA, rostromedial tegmental nucleus (RMTg), parafacial zone (PZ), caudal ventrolateral medulla, and cholinergic neurons in the nucleus ambiguus have been identified as NREM sleep-promoting (Yang et al., 2018b) (Anaclet et al., 2014; Yao et al., 2022; Yu et al., 2019). Additionally, components of NST barosensitive neurons also drive NREM sleep (Yao et al., 2022).

In addition, cortical neuronal nitric oxide synthase-expressing neurons and GABAergic LIM homeodomain factor Lhx6-expressing neurons of the zona incerta are involved in NREM sleep regulation (Liu et al., 2017a; Morairty et al., 2013). And the lateral habenula (LHb) is also associated with NREM sleep modulation (Gelegen et al., 2018). Blocking the output from the LHb was shown to cause highly fragmented NREM sleep, while the LHb lesion was also shown to decrease the amplitude of NREM sleep rebound in sleep-deprived animals (Zhang et al., 2016a). However, the role of BF somatostatin (SOM)-positive GABAergic ($GABA^{SOM}$) neurons has not yet been acknowledged. Xu et al. reported that activation of BF^{SOM} neurons increased the probability of transitions from wakefulness to NREM sleep (Xu et al., 2015), while Anaclet et al. found that BF $GABA^{SOM}$ neurons are neither NREM sleep-promoting nor wake-promoting per se due to their electrical heterogeneity (Anaclet et al., 2018). In addition, the TRN consists of a shell of GABAergic neurons that participate in sleep rhythm generation and sleep stability (Latchoumane et al., 2017).

In summary, most NREM sleep-promoting neurons are GABAergic and are distributed in the

BG system, hypothalamus, and brainstem; however, glutamatergic, cholinergic, and neuropeptide-expressing neurons are also involved in NREM sleep regulation.

C. REM sleep-regulating nuclei

As we summarized in our recently published review (Wang et al., 2021d), neurons involved in REM sleep can be generally divided into two types: REM-on and REM-off neurons (Fig. 4). Glutamatergic and GABAergic neurons of the sublaterodorsal nucleus (SLD) in the brainstem are essential for REM sleep regulation but their modulatory mechanisms are complex (Fuller et al., 2007). The SLD sends excitatory signals to GABAergic/glycinergic neurons in the ventromedial medulla and spinal cord to produce the muscle paralysis associated with REM sleep (Lu et al., 2006b; Sapin et al., 2009). Glutamatergic neurons in the SLD and caudal LDT are important for REM sleep generation (Krenzer et al., 2011). During wake and NREM sleep, the SLD is inhibited by GABAergic neurons of the vlPAG and adjacent lateral pontine tegmentum as well as monoaminergic neurons of the LC and raphe nuclei. During REM sleep, the vlPAG is likely inhibited by GABAergic neurons of the SLD and medulla (Kubin, 2001). Other brainstem structures involved in REM sleep generation and maintenance include cholinergic LDT/PPT and GABAergic lateral paragigantocellular nucleus/dorsal paragigantocellular nucleus (Sapin et al., 2009; Van Dort et al., 2015). Single-unit recordings have demonstrated that neurons in the ventromedial medulla fire fastest in REM sleep, while lesions of ventromedial medulla partially disrupt the atonia of REM sleep (Holmes and Jones, 1994). As for REM-off neurons, structures such as the DRN and LC are responsible for suppressing REM sleep (Monti, 2010; Saper et al., 2010; Wang et al., 2017; Weber et al., 2015).GABAergic neurons in the vlPAG, the adjacent dorsal part of the deep mesencephalic nucleus, and PPT also belong to REM-off neurons (Chen et al., 2022; Hayashi et al., 2015; Kroeger et al., 2017; Luppi et

al., 2013; Weber et al., 2018). The dorsomedial hypothalamic nucleus (DMH) consists of both REM-on and REM-off galaninergic neurons depending on distinct axon projections (Chen et al., 2018). The brain structures of the hypothalamus involved in REM sleep generation and maintenance include the extended VLPO and LH melanin-concentrating hormone-expressing neurons (Clément et al., 2012; Lu et al., 2002). Moreover, LH orexinergic terminals in the SLD also play a role in stabilizing REM sleep (Feng et al., 2020). Several other brain structures are also known to be related to REM sleep regulation. A2AR expressed in the olfactory bulb is responsible for suppressing REM sleep (Wang et al., 2017), while D2R localized in the basolateral amygdala and central cannabinoid 1 receptor localized in the MS is involved in REM sleep initiation (Hasegawa et al., 2022; Puskar et al., 2021). In summary, the neural substrates underlying REM sleep regulation are mainly located in the brainstem, and these structures overlap with wake-promoting nuclei such as the LC, PPT, and DRN.

II. Inhaled anesthetics

Inhaled GA, having been used for 180 years, is superior to intravenous GA in terms of avoiding intraoperative awareness, as well as its synergistic effects with analgesics and muscle relaxants. The neural substrates involved in inhaled GA modulation are listed in supplementary table 1–2 following the sequence of subcortical areas (telencephalon, diencephalon, and brainstem) and the cerebral cortex. As GA induction is not simply the opposite neurophysiological process of emergence but is subject to the regulation of distinct neural circuitry, we separately reviewed these two processes and classified neural substrates into three categories (i.e., GA-promoting, GA-antagonizing, and GA-promoting/antagonizing) (Fig. 5–6).

A. Neural substrates of inhaled induction

1. GA-promoting neural substrates for inhaled induction

Brain targets identified to be GA-promoting in inhaled GA induction are still rare. Fiber photometry experiments showed that NREM sleep-related LHb glutamatergic neurons were highly activated during isoflurane maintenance. Selective lesions or chemogenetic inhibition of LHb glutamatergic neurons accelerated isoflurane induction by acting on the LHb-RMTg pathway instead of the LHb-VTA pathway (Liu et al., 2021a). For the brainstem, chemogenetic activation of NREM sleep-promoting GABAergic neurons in the RMTg and nearby brainstem regions increased the sensitivity to sevoflurane-induced loss of righting reflex (LORR, regarded as a GA state in animals) (Vlasov et al., 2021). As LHb glutamatergic neurons promote inhaled induction through the LHb-RMTg pathway, one possible explanation is that RMTg GABAergic neurons are activated by the excitatory output of the LHb-RMTg pathway.

2. GA-antagonizing neural substrates for inhaled induction

Regarding the forebrain, mice with homozygous knockout of the vesicular acetylcholine transporter in the BF were found to be more sensitive to isoflurane GA (Leung et al., 2021). Chemogenetic/optogenetic activation of BF cholinergic neurons and $GABA^{PV}$ neurons delayed isoflurane induction, while lesions of these specific neurons enhanced isoflurane GA efficacy (Cai et al., 2021; Luo et al., 2020). These GA-antagonizing subpopulations may antagonize isoflurane-induced suppression of the whole brain and finally result in a delay of inhaled induction. Although chemogenetic experiments revealed that BF $GABA^{SOM}$ neurons are GA-promoting in isoflurane induction, selective lesions of these neurons delayed isoflurane induction (Cai et al., 2021). This may be due to the accumulation of sleep debt, similar to the increased sensitivity to isoflurane 24

days after the lesion of VLPO galaninergic neurons (Moore et al., 2012).

Regarding the septum, a lesion study showed that rats with MS lesions became more sensitive to isoflurane induction (Leung et al., 2013), indicating that the MS was GA-antagonizing.

Regarding the BG system, a resting-state functional magnetic resonance imaging (fMRI) study showed significantly reduced local clustering coefficients of the NAc in the isoflurane-anesthetized rat brain (Palanca et al., 2015). Chemogenetic activation of NAc D1R neurons delayed sevoflurane induction, while their inhibition exerted the opposite effect (Bao et al., 2021). As the NAc sends efferents to the LH (Luo et al., 2018b), we speculate that NAc D1R neuronal activation antagonizes inhaled induction by disinhibiting downstream GA-antagonizing neurons in the LH.

As one of the thalamic midline nuclei, PVT glutamatergic neurons have been proven to be GA-antagonizing in sevoflurane induction (Li et al., 2022a). C-fos (a marker of neuronal activity) staining and chemogenetic/optogenetic manipulations revealed that the neural activity of the PVT was suppressed by sevoflurane GA and PVT glutamatergic neurons delayed sevoflurane induction through projecting to the BNST. As there are AANs in the BNST during isoflurane exposure (Jiang-Xie et al., 2019), whether the glutaminergic PVT-BNST pathway delayed inhaled induction by inhibiting these AANs in the BNST remains to be determined.

Wake-promoting LH orexinergic and glutamatergic neurons are GA-antagonizing in inhaled induction. Although previous studies seemingly proved that LH orexinergic neurons were unrelated to GA induction, a recent study found that a GA-antagonizing effect of the orexinergic PefLH-PVT circuit in desflurane induction regulation, an effect which is likely mediated by orexin-2 receptors in the PVT (Zhao et al., 2021b). Another study found that activation of the wake-promoting glutamatergic LH-LHb pathway delayed isoflurane induction, whereas inhibition of this pathway had

the opposite effect (Zhao et al., 2021a). Apart from the LH, lesions of the TMN or cerebroventricular delivery of histamine 1 receptor antagonist increased the sensitivity to isoflurane GA induction but did not affect intravenous anesthetics (Luo and Leung, 2011). However, the neural circuits for the modulating effects of the TMN remain poorly understood.

In the brainstem, the wake-promoting vPAG dopaminergic neurons and PB glutamatergic neurons have been identified as GA-antagonizing. Lesioning vPAG DA neurons can prolong isoflurane induction (Liu et al., 2020b). *In vitro* electrophysiological recordings revealed that isoflurane probably suppresses the activity of vPAG DA neurons by activating $GABA_A$ receptors. Although nonspecific activation of PB neurons had no significant effect on isoflurane induction (Luo et al., 2018a), chemogenetic activation of PB glutamatergic neurons delayed sevoflurane induction (Wang et al., 2019). Electrophysiological recordings and behavioral tests showed that sevoflurane directly inhibited medial PB neurons through postsynaptic $GABA_A$ receptors and background potassium channels, while blocking medial PB $GABA_A$ receptors prolonged induction (Xu et al., 2020). We hypothesize that activation of these wake-promoting nuclei of the brainstem counteracts inhaled anesthetics' suppression on these brain targets and therefore delays the process of inhaled induction. Noteworthily, the role of LC noradrenergic neurons was not acknowledged. Vazey found that activation of LC noradrenergic neurons delayed isoflurane induction (Vazey and Aston-Jones, 2014), but Ao et al. found that LC noradrenergic neurons had no significant effect on isoflurane induction (Ao et al., 2021b), which may be due to the different animal species and virus used in their studies.

3. Dual GA-promoting and -antagonizing neural substrates for inhaled induction

The POA of the hypothalamus exhibits a dual role in inhaled induction. Chemogenetic activation of

POA TAC1-expressing neurons reduced the sensitivity to induction of isoflurane but not sevoflurane (Reitz et al., 2021). However, inhibition of these neurons did not alter the sensitivity to isoflurane induction, indicating that TAC1 neurons are only sufficient but not required for altering inhaled induction. For subregions of the POA, the amount of sleep loss induced by the VLPO-lesion was correlated with LORR time during isoflurane GA (Eikermann et al., 2011). Moreover, hypnotic doses of isoflurane/halothane can increase c-fos expression in the VLPO, and neurons depolarized by isoflurane belong to the subpopulation of VLPO sleep-active neurons (Moore et al., 2012). Lesioning VLPO galaninergic neurons reduced mice's sensitivity to isoflurane GA in the acute phase, but this effect was reversed in the long term. A possible explanation is that the VLPO lesion results in acute resistance to isoflurane GA due to sleep debt accumulation (Moore et al., 2012), indicating the interaction between sleep and GA.

The role of VTA subpopulations in the brainstem is complex. Chemogenetic/optogenetic experiments showed that VTA NREM sleep-promoting GABAergic neurons facilitated isoflurane induction via their projections to the LH (Yin et al., 2019b). Activation of VTA dopaminergic neurons delayed sevoflurane induction through the VTA-prelimbic cortex (PrL) pathway and the wake-promoting dopaminergic VTA-NAc pathway (Gui et al., 2021; Song et al., 2021). As VTA dopaminergic neurons were inhibited during inhaled induction, VTA GABAergic neurons may be disinhibited by VTA dopaminergic neurons through a local microcircuit, thereby exerting a GA-promoting effect. Rats with 6-hydroxydopamine-lesion in the VTA showed no significant difference in the sensitivity to isoflurane GA (Zhou et al., 2015), indicating that although VTA dopaminergic neurons are involved in GA induction, they are not necessary.

B. Neural substrates of inhaled emergence

1. GA-promoting neural substrates for inhaled emergence

Using capturing activated neuronal ensembles technology, a recent study found that NREM sleep-promoting AANs in the paraSON/SON can be activated by diverse GA drugs (isoflurane, ketamine, and dexmedetomidine) (Jiang-Xie et al., 2019). These AANs mainly comprised peptidergic neurons (e.g., expressing arginine vasopressin, oxytocin, and prodynorphin). Activation of SON AANs prolonged the duration of isoflurane GA and delayed emergence but did not affect the induction process. Noteworthily, the GA-promoting effect of AAN activation was long-lasting. This emphasizes the specific role of neuropeptides in GA modulation and provides an important direction for further research. It is important to clarify the similarities and differences between fast transmitters (GABA, glutamate) and neuropeptides in GA regulation.

Fiber photometry recordings showed that the Ca^{2+} signals of LHb glutamatergic neurons decreased during isoflurane emergence (Liu et al., 2021a). Optogenetic activation of the glutamatergic LHb-RMTg pathway delayed isoflurane emergence and deepened the depth of isoflurane GA. As RMTg GABAergic neurons are NREM sleep-promoting and GA-promoting in inhaled induction, it is possible that activation of LHb glutamatergic neurons delayed isoflurane emergence by activating RMTg GABAergic neurons.

2. GA-antagonizing neural substrates for inhaled emergence

Many researchers have identified the crucial role of the BF in inhaled emergence modulation. Fiber photometry recordings revealed that BF cholinergic neuronal activity peaked approximately at the moment of recovery of righting reflex (RORR) during isoflurane emergence (Luo et al., 2020). Activation of BF cholinergic neurons promoted isoflurane emergence, whereas lesions of these

neurons enhanced isoflurane GA efficacy. Although lesions of BF $GABA^{SOM}$ neurons delayed isoflurane emergence, chemogenetic inhibition of these neurons shortened the emergence time (Zhang et al., 2016c). However, the wake-promoting BF $GABA^{PV}$ neurons are not involved in isoflurane emergence modulation. Previous studies have found that activation of orexin signaling in the BF promoted isoflurane and sevoflurane emergence (Dong et al., 2009; Zhang et al., 2016c), and microinjection of norepinephrine (NE) into the nucleus basalis of Meynert of the BF accelerated desflurane emergence (Pillay et al., 2011). Histamine activation of H1 receptors but not H2 receptors in the basalis magnocellularis of the BF facilitated isoflurane emergence (Luo and Leung, 2009). Taken together, these studies implicate that the BF promotes GA emergence by integrating upstream orexinergic/noradrenergic/histaminergic signaling.

Both the MS and diLS are involved in inhaled emergence regulation. Optogenetic activation of the wake-promoting diLS GABAergic neurons facilitated isoflurane emergence through the VTA (Wang et al., 2021a). Lesions of the MS delayed recovery from isoflurane and halothane GA (Leung et al., 2013), indicating that the MS is GA-antagonizing. These studies provide us with a better understanding of the role of the limbic system in GA regulation.

Evidence from fMRI studies indicates a vital role of the BG system in GA regulation (Crone et al., 2017; Liang et al., 2012). Optogenetic activation of NAc D1R neurons promoted sevoflurane emergence by inducing both cortical activation and behavioral arousal (Bao et al., 2021). D1Rs located in the shell of NAc are found to be related to the delayed emergence after inhaled GA (Zhang et al., 2021). The emergence-promoting capacity of D1Rs in NAc shell declined in aged mice compared with young mice. Further research is needed to clarify the role of other sleep-wake-related nuclei of the BG system in GA regulation.

Accumulating evidence suggests that the thalamus is vital for regulating inhaled GA emergence. Compared to neighboring nuclei (i.e., dorsal medial thalamus and CMT), 50-Hz stimulation of the CLT effectively wakened macaques from isoflurane GA (Redinbaugh et al., 2020). The deep-layer activity of the cortex is sustained by interactions with the CLT, implying the existence of layer-specific thalamocortical correlates of consciousness during isoflurane GA. The wake-promoting ventromedial thalamus matrix cells and PVT glutamatergic neurons were identified to be GA-antagonizing. Optogenetic stimulation of mouse ventromedial thalamus cells during slow wave sevoflurane GA induced cortical EEG activation and behavioral emergence (Honjoh et al., 2018). Optogenetic activation of PVT glutamatergic neurons suppressed isoflurane-induced burst suppression and shortened the emergence time (Ren et al., 2018). A recent study further revealed that the glutamatergic PVT-BNST pathway can promote sevoflurane emergence (Li et al., 2022a). Retrograde tracing from the PVT labeled DA neurons in the hypothalamus and periaqueductal gray (Li et al., 2014). Local delivery of the D2R agonist quinpirole into the PVT reduced the burst-suppression ratio during deep isoflurane GA and shortened the emergence time (Ao et al., 2021a). In addition, optogenetic activation of the LC tyrosine-hydroxylase neuronal terminals in the PVT promoted isoflurane emergence but did not affect the induction process (Ao et al., 2021b). These studies indicate that the PVT also integrates upstream dopaminergic and noradrenergic signaling to promote inhaled emergence.

Numerous studies have proven that the hypothalamus plays an important role in promoting inhaled emergence. Although the POA has been traditionally regarded as a sleep center (Liu and Dan, 2019), chemogenetic activation of POA TAC1 neurons facilitated both isoflurane and sevoflurane emergence (Reitz et al., 2021). Although hypnotic doses of isoflurane/halothane

increase c-fos expression in the VLPO (Moore et al., 2012), a previous study found that unselective lesions of the VLPO deepened isoflurane GA (Eikermann et al., 2011). Noteworthily, chemogenetic activation of GABAergic or glutamatergic neurons in the MnPO/VLPO modulated sleep-wake architecture but did not alter isoflurane emergence (Vanini et al., 2020). Identification of the diversity of POA subpopulations at the genetically defined level may improve our understanding of the POA in GA regulation. Genetic ablation and pharmacologic blockade experiments showed that damaging orexinergic signaling delayed isoflurane/sevoflurane GA emergence but did not affect its sensitivity to induction (Kelz et al., 2008; Yang et al., 2019). Chemogenetic/optogenetic activation of the wake-promoting LH orexinergic neurons or the orexinergic PefLH-VTA/BF/LC pathways has been shown to accelerate isoflurane emergence (Li et al., 2019; Wang et al., 2020a; Zhou et al., 2018). And the orexinergic PefLH-PVT pathway is involved in accelerating both isoflurane and desflurane emergence (Zhao et al., 2021b). The wake-promoting GABAergic LH-TRN pathway and glutamatergic LH-LHb pathway both were capable of promoting isoflurane emergence (Herrera et al., 2016; Zhao et al., 2021a). Additionally, the DMH is involved in GA emergence modulation. Chemogenetic activation of the prefrontal cortex (PFC)-DMH/DMH-VLPO/DMH-PefLH pathway promoted isoflurane emergence and blockade of central cannabinoid 1 receptor at DMH glutamatergic synapses shortened isoflurane emergence through the VLPO and PefLH (Zhong et al., 2017). This study revealed that both top-down and bottom-up neural mechanisms are involved in the regulation of GA emergence (Mashour and Hudetz, 2017). Lesions of the TMN can prolong recovery from isoflurane GA (but not from propofol, pentobarbital, and ketamine GA) (Luo and Leung, 2011). However, specific manipulation targeting TMN subpopulations is still lacking. Given the cellular, structural, and functional diversity of the hypothalamus, exploring the neural

mechanisms of the hypothalamus in GA regulation remains an important topic for future research.

For the brainstem, several brain targets involved in the modulation of inhaled induction are also capable of promoting GA emergence. Lesions of the wake-promoting vPAG dopaminergic neurons delayed isoflurane emergence (Liu et al., 2020b). This highlights that apart from the VTA, dopaminergic neurons located in other brain areas are also involved in regulating inhaled emergence. Additionally, activation of the wake-promoting DRN serotonergic neurons accelerated isoflurane emergence partly through serotonergic 1A and 2C receptors (Li et al., 2021a). Using orexin A/B and their corresponding antagonists, DRN neurons were shown to be involved in the isoflurane emergence-promoting effect of orexin signaling (Li et al., 2021a; Yang et al., 2019). In addition to integrating upstream orexinergic signaling, the downstream neural circuits necessary for DRN serotonergic neurons to promote isoflurane emergence are unknown. Chemogenetic/optogenetic experiments revealed that LC noradrenergic neurons and their projections to the PVT are capable of promoting isoflurane emergence (Ao et al., 2021b; Vazey and Aston-Jones, 2014). Studies have found that LC neurons are subject to $GABA_B$ receptor-mediated tonic inhibition, while the infusion of $GABA_B$ receptor antagonists into the LC has been shown to promote emergence from deep isoflurane GA (Hung et al., 2020; Wang et al., 2015). A previous study reported that mice required more time to recover from isoflurane/sevoflurane anesthesia during the dark time but this effect was abolished in mice treated with the noradrenergic toxin (Wang et al., 2020b). As LC noradrenergic neurons widely project to the cerebral cortex and subcortical wake-promoting brain regions, the precise neural circuit mechanisms of the LC-NE system in inhaled emergence regulation remain to be elucidated. Chemogenetic experiments have shown that PB activation facilitated isoflurane emergence (Luo et al., 2018a; Qiu et al., 2016).

Using specific chemogenetic/optogenetic manipulations, PB glutamatergic neurons were shown to promote sevoflurane emergence (Wang et al., 2019). C-fos staining revealed that PB activation induced excitation of the cortical and subcortical (LH and BF) regions during sevoflurane GA. And blocking the medial PB $GABA_A$ receptors was shown to facilitate sevoflurane emergence (Xu et al., 2020). These studies clarify how the PB regulates sevoflurane emergence at the molecular, cellular, and neural circuit levels.

The role of the cerebral cortex has also been studied in recent years. Delivering cholinergic/noradrenergic agonists into the prefrontal PrL or the parietal region (posterior parietal cortex and medial parietal association cortex) of sevoflurane-anesthetic rats induced cortical activation and cholinergic stimulation of the prefrontal PrL can further produce wake-like behaviors (Pal et al., 2018). In addition, both the glutamatergic PFC-DMH pathway and the dopaminergic VTA-PrL pathway are capable of promoting inhaled emergence (Song et al., 2021; Zhong et al., 2017). These results indicate that the prefrontal PrL regulates inhaled emergence through both top-down and bottom-up influences.

3. Dual GA-promoting and -antagonizing neural substrates for inhaled emergence

In addition to inhaled induction, the VTA also plays a dual role in inhaled emergence regulation. Optogenetic activation of the wake-promoting VTA dopaminergic neurons promoted reanimation from isoflurane GA, and this effect could be reversed by the D1R antagonist (Taylor et al., 2016), indicating that the downstream mechanism involves D1Rs. However, rats with 6-hydroxydopamine-lesion of the VTA had no significant difference in emergence time (Zhou et al., 2015). Studies also have found that both the dopaminergic VTA-NAc and VTA-PrL pathways were capable of promoting sevoflurane emergence (Gui et al., 2021; Song et al., 2021). Conversely,

chemogenetic/optogenetic experiments revealed that activation of NREM sleep-promoting VTA GABAergic neurons deepened isoflurane GA through the LH (Yin et al., 2019b). Exploration of the interactions of different subpopulations in local microcircuits of the VTA is an interesting topic for future studies.

C. Other substrates related to inhaled GA

Several other subcortical structures have also been studied. The claustrum is a forebrain structure thought to be involved in consciousness (Chau et al., 2015). Electrical stimulation of the claustrum area during isoflurane GA shifted the EEG from a slow wave mode to a burst-suppression pattern (Pavel et al., 2019), but whether the claustrum is activated or inhibited by electrical stimulation is unknown. In addition, using the capturing activated neuronal ensembles method, Hua et al. discovered a distinct population of GABAergic neurons in the central amygdala (CeA_{GA} neurons), which are activated by diverse general anesthetics (isoflurane, ketamine, and dexmedetomidine) (Hua et al., 2020). These CeA_{GA} neurons were identified to be involved in GA-induced analgesia regulation.

Regarding the cerebral cortex, previous studies have shown that isoflurane decoupled dendro-somatic signaling in cortical layer 5 pyramidal neurons. Blocking metabotropic glutamatergic and cholinergic receptors mimics the effects of anesthetics on apical dendrite decoupling (Suzuki and Larkum, 2020). During the transition to and from GA, changes in synchrony in layer 5 pyramidal neurons coincide with loss of consciousness (LOC) and recovery of consciousness, respectively (Bharioke et al., 2022). Unraveling dynamic changes in neurotransmission during GA is another important aspect of understanding the fundamental mechanism of GA. Guo et al. found a global reduction in cortical GABA transmission during the isoflurane GA state, whereas glutamate

transmission varied among different cortical cell types (Guo et al., 2021). In contrast to the neural circuits of sleep-wake regulation, these studies emphasize the importance of the cerebral cortex in inhaled GA regulation.

III. Intravenous anesthetic propofol

Propofol is a widely used intravenous general anesthetic, with the $GABA_A$ receptor as its primary molecular target (Franks, 2008). Accumulating evidence suggests that propofol-induced LOC is associated with a global inhibition in the brain, particularly in the thalamocortical and frontoparietal networks. In 1999, Fiset et al. found that propofol preferentially decreased the regional cerebral blood flow in brain regions involved in arousal and performance of associative functions (Fiset et al., 1999). Ten years later, based on existing positron emission tomography technology, Mhuircheartaigh et al. identified a significant bilateral reduction in signals of both cortical and subcortical regions during propofol GA (Mhuircheartaigh et al., 2010). These data show that neurons in the cortex, thalamus, and reticular formation are similarly depressed by propofol (Andrada et al., 2012). Furthermore, Crone et al. showed that propofol-induced LOC is marked by a breakdown of pallido-cortical connectivity within the cortico-BG-thalamo-cortical loop (Crone et al., 2017). In addition, directional connectivity in frontal-parietal networks has also been shown to be inhibited by propofol (Lee et al., 2013). However, propofol was shown to have no significant effect on cortical sensory reactivity during deep sedation, because the nonspecific thalamocortical network was sharply depressed but the specific thalamocortical network was moderately influenced during propofol GA (Song and Yu, 2015). Alternatively, other than directly acting on either the cortical or subcortical regions, propofol may inhibit excitatory arousal pathways and/or potentiate sleep pathways. During propofol-induced mild sedation, several studies have observed a decrease

in the connectivity of the thalamus and an increase in connectivity within the pons of the brainstem using fMRI (Tang and Ramani, 2016). More specifically, propofol significantly increased c-fos expression in the VLPO sleep center versus a decrease in the number of c-fos-positive neurons in wake-related systems, including the TMN, LH, PeF, vlPAG, and supramammillary nucleus (Lu et al., 2008; Yue et al., 2021).

Next, we review the role that different brain areas play in the induction and emergence period of propofol GA (Fig. 7–8). The neural substrates that participate in propofol GA modulation are listed in supplementary table 3–4 following the same sequence of inhaled anesthetics.

A. Neural substrates of propofol induction

1. GA-promoting neural substrates for propofol induction

The LHb is a glutamatergic hub that projects to multiple GABAergic and aminergic nuclei that control arousal (Zhao et al., 2015). Gelegen et al. reported that sedative doses of propofol increased c-fos expression in the LHb and blocking LHb glutamatergic output greatly diminished propofol-induced LORR (Gelegen et al., 2018). It is commonly assumed that anesthetic-induced sedation results from the activation or potentiation of inhibitory circuits. This finding provides a novel view that activation of an excitatory pathway is also mechanistically essential for propofol-induced sedation.

The VLPO seems to be closely associated with propofol induction. Approximately 70% of neurons in the VLPO are inhibited by the wake-promoting neurotransmitter NE (NE− neurons, putative sleep-promoting neurons), and the remaining 30% of GABAergic neurons in the VLPO could be activated by the NE (NE+ neurons) (Gallopin et al., 2000). Patch-clamp experiments showed that propofol excited NE- neurons by reducing the GABAergic transmission and inhibited

NE+ neurons via histaminergic H1 and H2 receptors (Liu et al., 2017b; Liu et al., 2013). Another *in vitro* study found that propofol inhibited GABAergic transmission into VLPO neurons by M1 receptors of GABAergic nerve terminals projecting to VLPO neurons (Zhang et al., 2015a). More recently, an *in vivo* study showed that microinjection of $GABA_A$ receptor agonists into VLPO neurons shortened propofol-induced LORR and prolonged RORR (Yuan et al., 2017a; b), suggesting that potentiated GABAergic transmission in the VLPO represents a mechanism for propofol-induced GA. These findings suggest a possible mechanism whereby propofol inhibits GABAergic transmission into VLPO neurons and therefore disinhibits VLPO neurons to induce LOC. Furthermore, VLPO lesions yielded a negative effect on the sensitivity to propofol, and mostly reversed the propofol-induced decrease in neural activity of the LC (Zhang et al., 2015b), demonstrating the GA-promoting role of the VLPO in propofol GA induction.

Regarding the brainstem, chemogenetic activation of LC noradrenergic nerve terminals in the TRN decreased the 50% effective dose (ED50) of propofol GA (Zhang et al., 2019), indicating the increased sensitivity to propofol GA. Given the excitatory inputs from the LC to the TRN, it is deducible that there is a group of GA-promoting ensembles in the TRN. Minert et al. also discovered a small nucleus in an upper brainstem region, the mesopontine tegmental anesthesia area (MPTA), lesioning of which rendered resistance to systemically delivered anesthetics. Therefore, the MPTA appears to be a key node responsible for anesthetic induction and maintenance (Minert et al., 2017). On-target MPTA lesions have been shown to reduce sensitivity to propofol GA (Minert et al., 2020), suggesting its vital role in propofol induction.

2. GA-antagonizing neural substrates for propofol induction

The BF is one of the most pivotal GA-antagonizing brain regions in propofol induction. An *in vitro*

study revealed that propofol decreased the inherent excitability of BF cholinergic neurons via $GABA_A$ receptors (Chen et al., 2019). Cholinergic dysfunctions in the BF potentiated the propofol anesthetic effects (Laalou et al., 2008). Genetic lesions of BF cholinergic neurons markedly increased the potency of propofol GA (Luo et al., 2020). And optogenetic activation of the BF cholinergic neurons delayed propofol induction (Wang et al., 2021b). Apart from cholinergic neurons, BF glutamatergic neurons also take an active role in resisting propofol-induced LOC. Propofol was shown to inhibit the excitability of BF glutamatergic neurons by influencing the membrane's intrinsic properties and the inhibitory synaptic transmission, instead of affecting the glutamatergic transmissions (Li et al., 2020c). And optogenetic activation of BF glutamatergic neurons has been shown to reverse propofol-induced LOC (Wang et al., 2021b).

Additionally, lesions of the MS increased the sensitivity to propofol GA (Leung et al., 2013), indicating its GA-antagonizing effect in propofol induction.

As a key arousal node in the brainstem, a previous study using a zebrafish larval model found that propofol suppressed the excitability of LC neurons by inhibiting presynaptic excitatory inputs and inducing membrane hyperpolarization. Furthermore, local lesions of LC neurons via two-photon laser-based ablation or genetic impairment of NE synthesis accelerated propofol induction (Du et al., 2018). These findings indicate that the LC-NE system counteracts propofol induction.

In summary, there are only limited brain regions identified as GA-antagonizing substrates in propofol induction: cholinergic and glutamatergic neurons in the BF, NE-releasing neurons in the LC and the MS.

B. Neural substrates of propofol emergence

1. GA-promoting neural substrates for propofol emergence

Only the VLPO and LHb have been proven to be GA-promoting in the modulation of propofol emergence. Lesions of the VLPO accelerated propofol emergence (Zhang et al., 2015b). And microinjection of $GABA_A$ receptor agonists into VLPO neurons prolonged the emergence from propofol GA, suggesting that decreased GABAergic transmission in the VLPO may represent a mechanism for propofol emergence. As for the LHb, silencing glutamatergic neurons in the LHb induced a shorter LORR duration, indicating its GA-antagonizing effect in propofol emergence (Gelegen et al., 2018).

Additionally, chemogenetic activation of LC noradrenergic nerve terminals in the TRN prolonged the emergence of propofol GA (Zhang et al., 2019). Considering that the TRN receives the excitatory outputs from the LC, it is deducible that there is a group of GA-promoting ensembles in the TRN.

2. GA-antagonizing neural substrates for propofol emergence

Lesion experiments showed that the BF accelerated propofol emergence (Liu et al., 2020a). And pharmacological study further revealed that the $GABA_A$ receptors located in the BF were involved in the regulation of propofol emergence. Two main neuronal populations in the BF (i.e., cholinergic and glutamatergic neurons) are identified to be GA-antagonizing. Activation of BF cholinergic neurons shortened LORR durations (Luo et al., 2020). And optogenetic activation of BF cholinergic or glutamatergic neurons both significantly facilitated the emergence from propofol GA (Wang et al., 2021b). Interestingly, compared to the change in cholinergic activation-induced EEG oscillation bands, the glutamatergic activation showed broader band changes during propofol GA, indicating

the distinctive underlying neural mechanism. For the BF GABAergic neurons, the duration of propofol GA was prolonged in $GABA^{SOM}$ neuron-activated mice but was unaltered in the $GABA^{PV}$ neuron-activated group. Although inhibition of BF $GABA^{SOM}$ neurons but not $GABA^{PV}$ neurons shortened the duration of propofol GA, lesions of these two subtypes of neurons both increased the propofol GA duration (Cai et al., 2021). This contradictory but interesting phenomenon is possibly due to the accumulation of sleep debt and requires further study. The BF receives projections from orexin neurons and the orexin signals in the BF are shown to be involved in promoting propofol emergence. Microinjections of orexin-A in the BF facilitated propofol emergence, while orexin-1 receptor antagonist delayed recovery from propofol GA (Zhang et al., 2012). Moreover, as a substructure of the BF, the nucleus basalis (NB) is also propofol GA-antagonizing. Molecular mechanisms of the NB in propofol emergence regulation have also been studied. Microinjection of $GABA_A$ receptor agonist into the NB or nonspecific lesions of the NB both inhibited brain electrical activity and prolonged propofol emergence (Xing et al., 2020). Considering the heterogeneity and complexity of the BF's structure and components, its role in propofol emergence regulation differs with distinctive anatomical locations and neuron types.

Regarding the septum, electrolytic lesions of the MS prolonged propofol emergence. And septal lesioned rats displayed a larger increase in the low-frequency power of hippocampal EEG (Leung et al., 2013). However, whether the MS modulates propofol emergence through its wake-promoting glutamatergic neurons and the MS-LH pathway remains unknown.

Neuronal activities in the thalamus and deep cortical layers are most sensitive to changes in the consciousness level. 180-Hz stimulation of the central thalamus induced behavioral and neurophysiological arousal from propofol-anesthetized non-human primates (Bastos et al., 2021).

Redinbaugh et al. also found that deep-layer cortical activity was sustained because of interactions with the CLT (Redinbaugh et al., 2020). They observed that gamma-frequency CLT stimulation in anesthetized macaques restored arousal and wake-like neural processing, which provides empirical evidence for a circuit-level mechanism of consciousness: the reciprocal interaction between the CLT and deep cortical layers.

In the brainstem, the LC, VTA, PB, MPTA, and substantia nigra are GA-antagonizing substrates in propofol emergence. Local lesions of LC neurons via two-photon laser-based ablation or genetic impairment of NE synthesis retarded emergence from propofol GA (Du et al., 2018), indicating that the LC-NE system contributes to the promotion of propofol emergence. Interestingly, another study found that activation of LC noradrenergic terminals in the TRN prolonged propofol emergence (Zhang et al., 2019), which contradicts the GA-antagonizing effect of LC neurons. These results suggest that different LC projections may exert distinctive functions on GA regulation, highlighting the need for further studies to clarify the function of other LC projections. Both lesions of VTA dopaminergic neurons or substantia nigra dopaminergic neurons prolonged propofol emergence but did not alter its induction time or ED50 value (Shi et al., 2017; Zhou et al., 2015). These results imply that dopaminergic neurons in the midbrain are only necessary for propofol emergence but not for induction. PB neurons were suppressed in the propofol anesthesia phase but were robustly activated during the recovery process. Chemogenetic activation of PB neurons delayed propofol emergence without affecting the induction time (Luo et al., 2018a). Moreover, specific MPTA lesions prolonged the time to recover from propofol GA (Minert et al., 2020). These studies also suggested a vital role of the PB and MPTA in promoting propofol emergence.

3. Dual GA-promoting and -antagonizing neural substrates for propofol emergence

In the thalamus, activation of TRN GABAergic neurons facilitated arousal from propofol GA but did not impact the process of induction, suggesting that TRN GABAergic neurons are only involved in modulating propofol emergence (Liu et al., 2021c). Further, previous anterograde mapping showed LC-noradrenergic circuits in the TRN. Intra-TRN injection of NE and activation of noradrenergic terminals in the TRN both delayed arousal from propofol GA (Zhang et al., 2019), indicating that the effect of TRN on propofol emergence may occur as a result of the altered noradrenergic afferents into the TRN. However, activation of LC-noradrenergic terminals in the TRN impeded the recovery process (Zhang et al., 2019), implying that there are other types of neurons in the TRN that are GA-promoting but not GABAergic.

C. Other substrates related to propofol GA

Numerous correlation studies have investigated the neural mechanisms of propofol GA. Some brain regions are involved in the induction period (e.g., the pontine reticular formation (PnO)) only, while others regulate the emergence process (e.g., the CMT and TMN). Here, we review these findings according to their anatomical locations.

Using local field potential recording, the effect of propofol on BG activity has been investigated in patients with Parkinson's disease and found that propofol but not dexmedetomidine can specifically induce a decline of neural activity of the subthalamic nucleus (Martinez-Simon et al., 2017). A2AR agonists prolonged the duration of propofol GA, increased the c-fos expression in the NAc, and suppressed the functional connectivity of the NAc-DRN and NAc-cingulate cortex. In contrast, A2AR antagonist exerted opposite effects (Chen et al., 2021b). These results demonstrate the important roles of A2AR in propofol-induced LOC and suggest that the NAc-DRN neural circuit

might be involved in propofol GA; however, more research is needed to elucidate the role of the BG in propofol GA modulation.

Given the importance of the PVT in controlling wakefulness, recent studies have revealed that propofol hyperpolarized the membrane potentials of PVT neurons and dose-dependently induced $GABA_A$ receptor-mediated tonic inhibitory currents (Liu et al., 2021b), but the role of the PVT in systemically administered propofol remains to be explored. The CMT is considered as a part of the nonspecific arousal system (Van der Werf et al., 2002). There are greatly similar changes in the CMT local field potentials at 20–40 Hz at sleep onset and anesthetic-induced LORR: frequency reductions and power increases. For propofol and natural sleep, these changes in the CMT occur significantly earlier than that in the neocortex, suggesting that the transition from wakefulness to LORR is initiated by subcortical mechanisms (Baker et al., 2014). Additionally, as the CMT receives noradrenergic afferents from the LC (Jones and Yang, 1985), Fu et al. injected NE into the CMT and found that it accelerated propofol emergence and caused EEG changes in the PFC and the anterior cingulate cortex but did not influence propofol induction. And propofol suppressed neuronal excitability and enhanced GABAergic transmission in the CMT slices, which can be partly reversed by NE (Fu et al., 2017b). These findings indicate that the CMT noradrenergic pathway plays an important role in modulating propofol emergence.

Studies have also paid attention to TMN histaminergic neurons. It was found that propofol reduced c-fos expression in the TMN (Nelson et al., 2002). Local injections of a potent H3 receptor inverse agonist into the TMN accelerated propofol emergence, while local administration of GABA delayed this process (Xia et al., 2021). The LORR duration of propofol GA was decreased after microinjections of $GABA_A$ receptor antagonist into the TMN, further providing support to the

hypothesis that $GABA_A$ receptors on TMN histaminergic neurons are causally involved in propofol-induced sedation (Nelson et al., 2002). However, lesions of TMN neurons did not affect the time to LORR or RORR (Luo and Leung, 2011). Therefore, the exact role of TMN histaminergic neurons in propofol GA remains elusive.

The suppression of respiratory and cardiovascular reflex responses was frequently observed during propofol GA, suggesting potential additional actions of propofol on the brainstem. It was found that propofol evoked glutamate release onto neurons of the NST (a newly identified nuclei in sleep-wake regulation) and facilitated the phasic inhibitory transmission in second-order NST neurons to inhibit autonomic reflex pathways during GA (Jin et al., 2012; McDougall et al., 2008). In addition, GABAergic transmission in the oral part of the PnO contributes to the regulation of sleep and wakefulness (Vanini and Baghdoyan, 2013). Microinjection of GABA synthesis inhibitor (3-MPA) into the rostral PnO only facilitated the induction of propofol GA but did not alter the time to emergence (Vanini et al., 2014), suggesting that GABA levels in the PnO regulate propofol GA and extending the concept that anesthetic induction and emergence are not inverse processes. Studies also demonstrated a direct effect of propofol on cortical dynamics by a decrease in backward connectivity from frontal to parietal cortices (Boly et al., 2012). The significantly modulated cortical regions were the anterior insula, anterior cingulate cortex, and superior temporal gyrus (Mhuircheartaigh et al., 2010). Similar to the insular cortex, propofol facilitated GABA-mediated inhibitory synaptic transmission and preferentially enhanced fast-spiking GABAergic interneuron connections to pyramidal neurons, thereby suppressing the neural activities of their projection neurons (Koyanagi et al., 2014). Interestingly, neural activity in the primary sensory cortex was relatively preserved during propofol GA (Du et al., 2022), but the projection of sensory

information to high-order processing networks was blocked; so, the information integration was eventually prevented (Liu et al., 2012). Human studies suggested that the PFC is associated with consciousness, particularly the medial PFC, which showed significant changes during propofol induction and emergence (Leon-Dominguez et al., 2014). Infusion of $GABA_A$ receptor antagonist into the medial PFC has been shown to prolong propofol induction and reduce the emergence time, with a decreased level of dopamine, suggesting that propofol directly inhibits dopamine release in the medial PFC to induce LOC (Wang et al., 2016). In the hippocampus, propofol also induced a long-term enhancement of inhibitory GABAergic transmission in hippocampal cornus ammonis 1 pyramidal neurons (Zhang et al., 2016b). These results suggest that propofol may induce unconsciousness by effectively suppressing the excitatory output from the cortex.

Thus, although propofol can induce tonic inhibitory currents in diverse nuclei, such as the hippocampal cornus ammonis 1, spinal cord, brainstem nucleus, and the PVT, it is also possible that substantial brain regions and related pathways are causally involved in the induction and/or emergence of propofol GA-induced LOC. These experiments all add weight to the concept that sleep and GA have some common mechanisms.

III. Intravenous anesthetic ketamine

Ketamine is a noncompetitive N-Methyl-D-Aspartate antagonist, which has proven to be a safe anesthetic drug with potent analgesic properties for more than 50 years (Sinner and Graf, 2008). Apart from dissociative anesthetic and analgesic effects, ketamine has many other advantages that are considered beneficial in the perioperative period, such as bronchodilatory, sympathomimetic, and sedating properties (Barrett et al., 2020). In contrast to common GABA-mediated anesthetics with typical slow oscillations, EEG studies have shown the distinguishable electrophysiologic

profiles of ketamine: an increase in high beta and gamma oscillations (Akeju et al., 2016). However, only a few studies have focused on the neural mechanisms underlying ketamine GA at present.

Glutamate is one of the main neurotransmitters responsible for arousal and may be involved in ketamine-induced LOC. A previous study showed that ketamine attenuated glutamatergic neurotransmission by blocking the postsynaptic N-Methyl-D-Aspartate receptors in the primary somatosensory cortex and ventral posteromedial nucleus (a critical component of thalamocortical system) (Fu et al., 2017a; Yuan et al., 2016). Acetylcholine is another important excitatory neurotransmitter in the brain, which is released in the neocortex and hippocampus during arousal and exhibits maximal levels during active waking and active sleep (Semba, 2000; Woolf and Butcher, 2011). Ketamine increased acetylcholine levels in the hippocampus and PFC (Sato et al., 1996). Mice with ablation of the vesicular acetylcholine transporter gene from the BF had a lower ED50 for ketamine (Leung et al., 2021), suggesting that cholinergic neurons in the BF provide resistance to ketamine GA.

Ketamine induces an unusual state known as “dissociative anesthesia”: unconsciousness while preserving wakefulness, which is a state close to the vegetative state (Wilkins et al., 2011). A critical brain dynamics study found that ketamine allowed more awake-like dynamics to persist (Varley et al., 2020). During the administration of ketamine, frontal-parietal communication and somatosensory processing were preserved (Lee et al., 2013), but multisensory processing appeared to be diminished (Ballesteros et al., 2020). Furthermore, ketamine generated a gradual change in the oscillatory dynamics, in contrast to the sharp neural changes induced by propofol GA (Ballesteros et al., 2020). Specifically, Rao et al. found that the left caudate nucleus and middle frontal gyrus exhibited significant alterations in both neuronal activity and functional synchronization

using resting-state fMRI in rhesus monkeys (Rao et al., 2017). These findings suggested that the change in local functional properties in these areas may be involved in ketamine-induced potential neurobiological changes, including sedation.

Some region-specific and neuron type-specific studies have also been conducted. Anesthetic doses of ketamine-induced wakefulness-like c-fos immunoreactivity in cholinergic, monoaminergic, and orexinergic systems (e.g., the BF, TMN, and LC) and completely suppressed c-fos expression in the VLPO (Lu et al., 2008). Specifically, chemogeneic excitation of putative glutamatergic neurons in the PB did not affect delta oscillations or the recovery time of low-dose ketamine GA but had minor effects on delta oscillations and prolonged recovery time with high-dose ketamine GA (Melonakos et al., 2021), demonstrating the limited effect of PB activation on the neurophysiologic and behavioral effects of ketamine. Similarly, TMN orexin-saporin lesions had no significant effect on the anesthetic sensitivity to ketamine (Luo and Leung, 2011), although intracerebroventricular orexin-A significantly decreased the ketamine anesthesia time (Tose et al., 2009). Additionally, Tai et al. explored the role of the septal cholinergic neurons in modulating the sensitivity to ketamine anesthesia but found no significant difference (Tai et al., 2014). It has also been suggested that ketamine reduced the GABAergic neuronal firing rate within the VTA (Lee et al., 2001), whereas lesions of VTA dopaminergic neurons did not affect the anesthetic response to ketamine (Zhou et al., 2015). Only animals with vlPAG lesions reduced tail-flick latencies after ketamine administration (Lu et al., 2008). Given the limited evidence on ketamine GA mechanisms, more research is still required to elucidate its unique anesthetic features.

IV. Anesthetic adjunct dexmedetomidine

Dexmedetomidine, a highly selective α2-adrenoceptor agonist, is widely used in clinical anesthesia

for its unique characteristics of sedation, hypnosis, and analgesia. The hypnotic action of dexmedetomidine is exerted by activating pre- and post-synaptic α2-receptors in the LC and thereby inhibiting NE release (Weerink et al., 2017). The sleep-wake system is involved in the hypnotic action of dexmedetomidine. First, the dexmedetomidine-induced EEG signature closely resembles stage 2 of NREM sleep (Akeju and Brown, 2017). It was found that dexmedetomidine decreased the c-fos expression of the cerebral cortex and subcortical arousal systems (the LH, TMN, LC, and PB) and increased c-fos expression of the conventional sleep-promoting center VLPO (Feng et al., 2018), which is consistent with another study showing that the dexmedetomidine-induced c-fos expression pattern mirrors endogenous NREM sleep (Nelson et al., 2003). Similar to other general anesthetics (sevoflurane, propofol, and ketamine), NREM sleep-promoting paraSON/SON AANs were also activated by dexmedetomidine (Jiang-Xie et al., 2019). Behavioral tests showed that dexmedetomidine altered sleep-wake architecture by increasing the amount of NREM sleep, increasing the depth of sleep, and reducing wakefulness (Feng et al., 2018). Another study observed two interesting phenomena (Nelson et al., 2003): (1) $GABA_A$ antagonist gabazine administered to the TMN but not the LC diminished dexmedetomidine-induced LORR state; (2) lesions of the VLPO reduced dexmedetomidine-induced slow wave EEG and changed the c-fos expression in the TMN but not the LC. These results imply that the LC-VLPO-TMN circuit may be involved in the dexmedetomidine-induced LORR state. Applying siRNA knockdown and TetTag-pharmacogenetics methods, Zhang et al. found that dexmedetomidine-induced LORR state but not the sedation state depended on α2-adrenoceptors in the LC (Zhang et al., 2015c). Notably, dexmedetomidine-induced sedation and recovery sleep state required activation of neuronal ensembles in the lateral POA. These results indicate that different states of

consciousness induced by dexmedetomidine may depend on different neuronal populations. Using *in vivo* Ca^{2+} and dopamine measurements, VTA dopaminergic neurons were found to be activated after dexmedetomidine delivery (Qiu et al., 2020). However, chemogenetic activation of VTA dopaminergic neurons was found to decrease the low-frequency waves of cortical EEG (Qiu et al., 2020). This study provides a possible explanation for the rapid arousability upon dexmedetomidine sedation from the perspective of neural circuits.

V. Conclusion comments

Novel circuit-based approaches with neuronal type-specific and projection-specific targeting of circuit elements have helped to advance our view of sleep-wake and GA regulation. Induction and emergence of GA, two seemly symmetric neurophysiologic processes, are regulated by incompletely overlapped, or even separate neural substrates. We propose two possible neural mechanisms for GA induction: 1) wide inhibition of multiple wake-promoting neural substrates and following selective disinhibition of efferent NREM sleep-promoting neural substrates, 2) direct activation of sleep-active neural substrates (e.g., VLPO neurons (Moore et al., 2012)). The neural basis of GA emergence mainly results from the activation of wake-promoting brain regions and inhibition of limited sleep-promoting ensembles, such as the paraSON/SON AANs (Jiang-Xie et al., 2019), VTA GABAergic neurons (Yin et al., 2019b), and LHb glutamatergic neurons (Gelegen et al., 2018).

Recent research mapping neural circuitry has further expanded our understanding of GA regulation, not only by acting on traditionally recognized neural substrates (e.g., the brainstem, cortex-thalamus loop), but the BG and limbic systems also play a key role (e.g., NAc, diLS). The top-down and bottom-up mechanisms are both involved in GA induction/emergence modulations.

Apart from GABA, glutamate, and monoamine neurotransmitters, neuropeptides also play a substantive role in GA regulation, such as arginine vasopressin, oxytocin, and prodynorphin in the paraSON/SON, TAC1 in the POA, and orexin in the LH.

Exploring the neural circuitry for sleep-wake and GA regulations improves our understanding of their interactions. First, sleep loss increases the sensitivity to GA, but long-term sleep debt accumulation caused by lesions of sleep-promoting neurons (e.g., VLPO galaninergic neurons; BF $GABA^{SOM}$ neurons) reverses this effect (Cai et al., 2021; Moore et al., 2012). Second, we speculated that only a few sleep-wake regulating neural substrates are key to GA regulation, although a large body of GA-regulating ensembles have been identified to be shared with wake-sleep circuitry. This is because: 1) the hypnotic effect of different anesthetics has been shown to be modulated by the same neural substrates (e.g., LC noradrenergic neurons, PB glutamatergic neurons); 2) some brain targets are simultaneously involved in the cortical and behavioral alterations during GA (e.g., VTA dopaminergic neurons, NAc D1R neurons) (Bao et al., 2021; Taylor et al., 2016). Additionally, we propose that different brain stages with similar neural signatures (e.g., EEG/EMG pattern) may be regulated by shared neural circuitry, because cortical EEG signatures and regulatory neural substrates of anesthetics more closely resemble those of NREM sleep than those of REM sleep.

Despite these advances, several important questions remain unanswered. For instance, how do general anesthetics influence sleep quality after surgery? How can we precisely modulate anesthesia based on the sleep-wake architecture? Moreover, both sleep and GA influence the immune system (e.g., preserving cell-mediated immunity, affecting adaptive responses, and mediating inflammatory bursts) (Ackerman et al., 2021; Besedovsky et al., 2019; Kurosawa and

Kato, 2008; McAlpine et al., 2022), thereby closely affecting patients' recovery. Neural substrates involved in both sleep-wake and GA regulations have also been shown to mediate immune responses (e.g., PVH, VMH, NAc) (Li et al., 2020b; Pacheco-Lopez et al., 2005; Saurer et al., 2009), therefore, exploring how these neural substrates mediate immunological process helps develop perioperative immunotherapies and finally optimize surgical outcomes. With a better understanding of their interactions, we will gain deeper insights into the neural basis of sleep-wake and GA regulations and drive the potential for future drug discovery.

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Wrote or contributed to the writing of the manuscript: Bao, Jiang, Qu, Li, Miao, Huang.

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Footnotes

- [1] W.W.B. and S.J. contributed equally to this work.
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- All authors declare no competing interests.
- [S] This article has supplemental materials.

Figure legends

Fig 1. Characteristic EEG/EMG tracings during the wake-sleep state and GA of sevoflurane and propofol. (a–c) Examples of mouse EEG and EMG recordings during wakefulness, NREM sleep, and REM sleep. (d–f) Examples of mouse EEG and EMG recordings during the states of sevoflurane GA (unconsciousness compatible with surgical levels of anesthesia), burst suppression (a state occurring at a deeper level of GA), and isoelectricity (a state occurring at the deepest level of GA). (g–i) Similar to (d–f) but for propofol GA. The corresponding EEG spectrogram (upper panel), EEG (middle panel), and EMG (lower panel).

Fig 2. Summary of wake-promoting neurons. Green circles indicate the wake-promoting neurons distributed in the brain and the gray abbreviations in the bracket indicate their corresponding neuronal types.

Fig 3. Summary of NREM sleep-promoting neurons. Blue circles indicate the NREM sleep-promoting neurons distributed in the brain and the gray abbreviations in the bracket indicate their corresponding neuronal types.

Fig 4. Summary of REM sleep-promoting and REM sleep-suppressive neurons. Yellow circles indicate the REM sleep-promoting (yellow circles with solid lines, gray abbreviations in the bracket), REM sleep-suppressive (yellow circles with dotted lines, brown abbreviations in the bracket), and both REM sleep-promoting and REM sleep-suppressive (yellow circles with both solid lines and dotted lines, black abbreviations in the bracket) neurons distributed in the brain and the gray/brown/black abbreviations in the bracket indicate their corresponding neuronal types.

Fig 5. Diagram summarizing the neural circuits that regulate inhaled GA induction. Orange circles/lines represent GA-antagonizing neurons/neural pathways and the orange abbreviations in

the bracket indicate their corresponding neuronal types. Purple circles/lines represent GA-promoting neurons/neural pathways and the purple abbreviations in the bracket indicate their corresponding neuronal types.

Fig 6. Diagram summarizing the neural circuits that regulate inhaled GA emergence. Orange circles/lines represent GA-antagonizing neurons/neural pathways and the orange abbreviations in the bracket indicate their corresponding neuronal types. Brown lines represent monoaminergic GA-antagonizing pathways. Purple circles/lines represent GA-promoting neurons/neural pathways and the purple abbreviations in the bracket indicate their corresponding neuronal types. To avoid confusion, projections from VTA to PFC/PrL, DMH to LH/PefLH, and DMH to POA/VLPO represent the VTA-PrL, DMH-PefLH, and DMH-VLPO pathways, respectively.

Fig 7. Diagram summarizing the neural circuits that regulate propofol GA induction. Orange circles represent GA-antagonizing neurons and the orange abbreviations in the bracket indicate their corresponding neuronal types. Purple circles/lines represent GA-promoting neurons/neural pathways and the purple abbreviations in the bracket indicate their corresponding neuronal types.

Fig 8. Diagram summarizing the neural circuits that regulate propofol GA emergence. Orange circles represent GA-antagonizing neurons and the orange abbreviations in the bracket indicate their corresponding neuronal types. Purple circles/lines represent GA-promoting neurons/neural pathways and the purple abbreviations in the bracket indicate their corresponding neuronal types.

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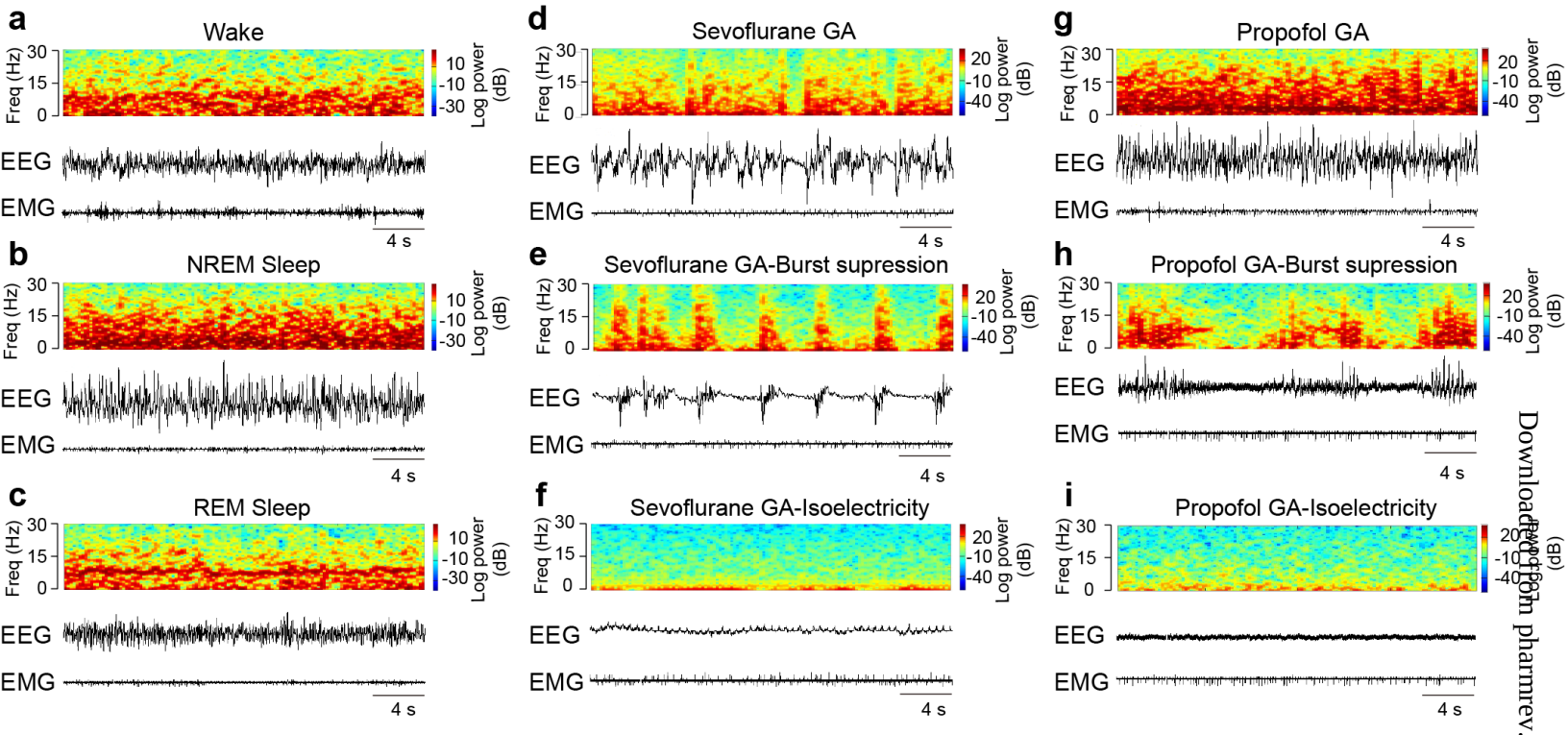

Figure 1

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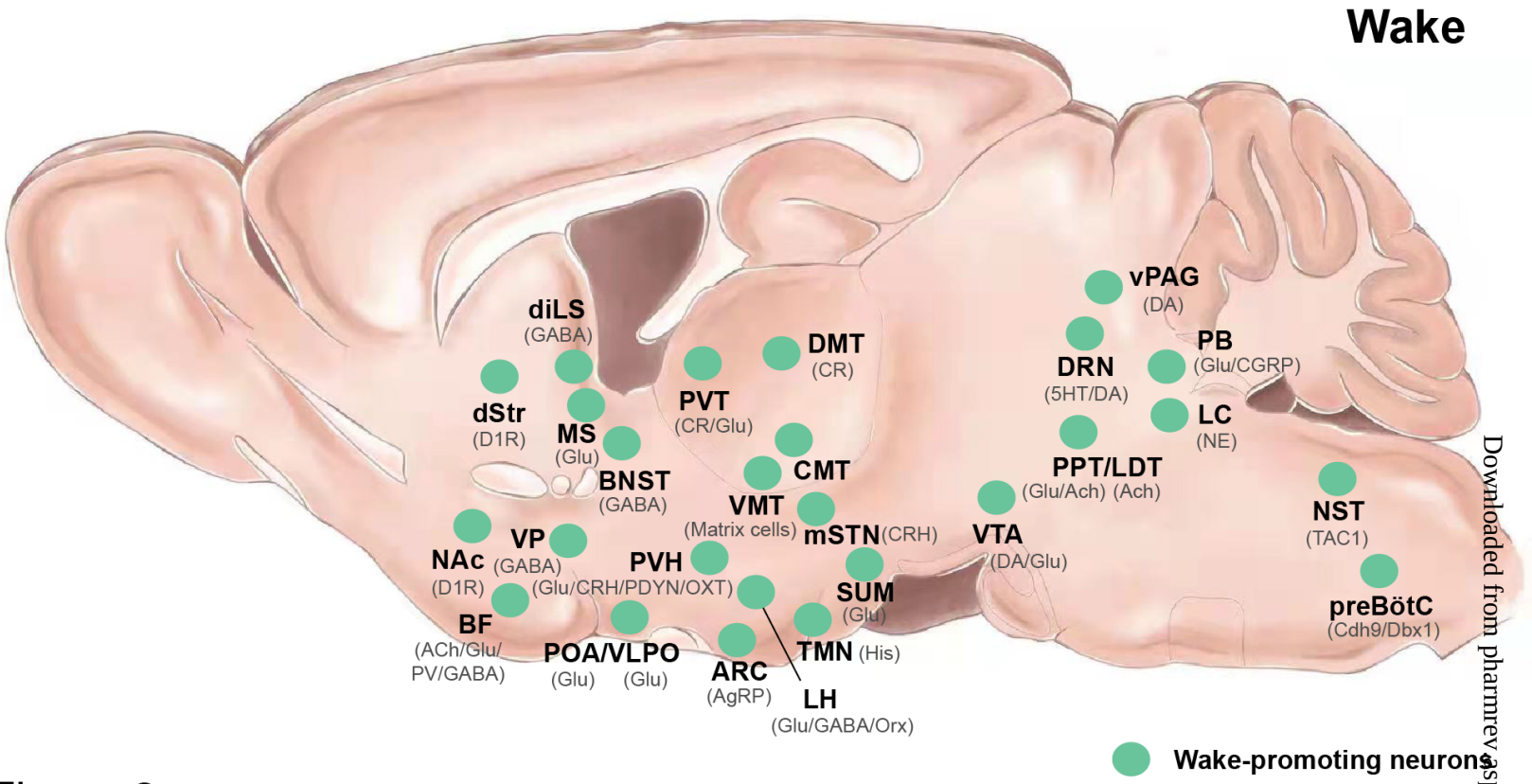

Figure 2

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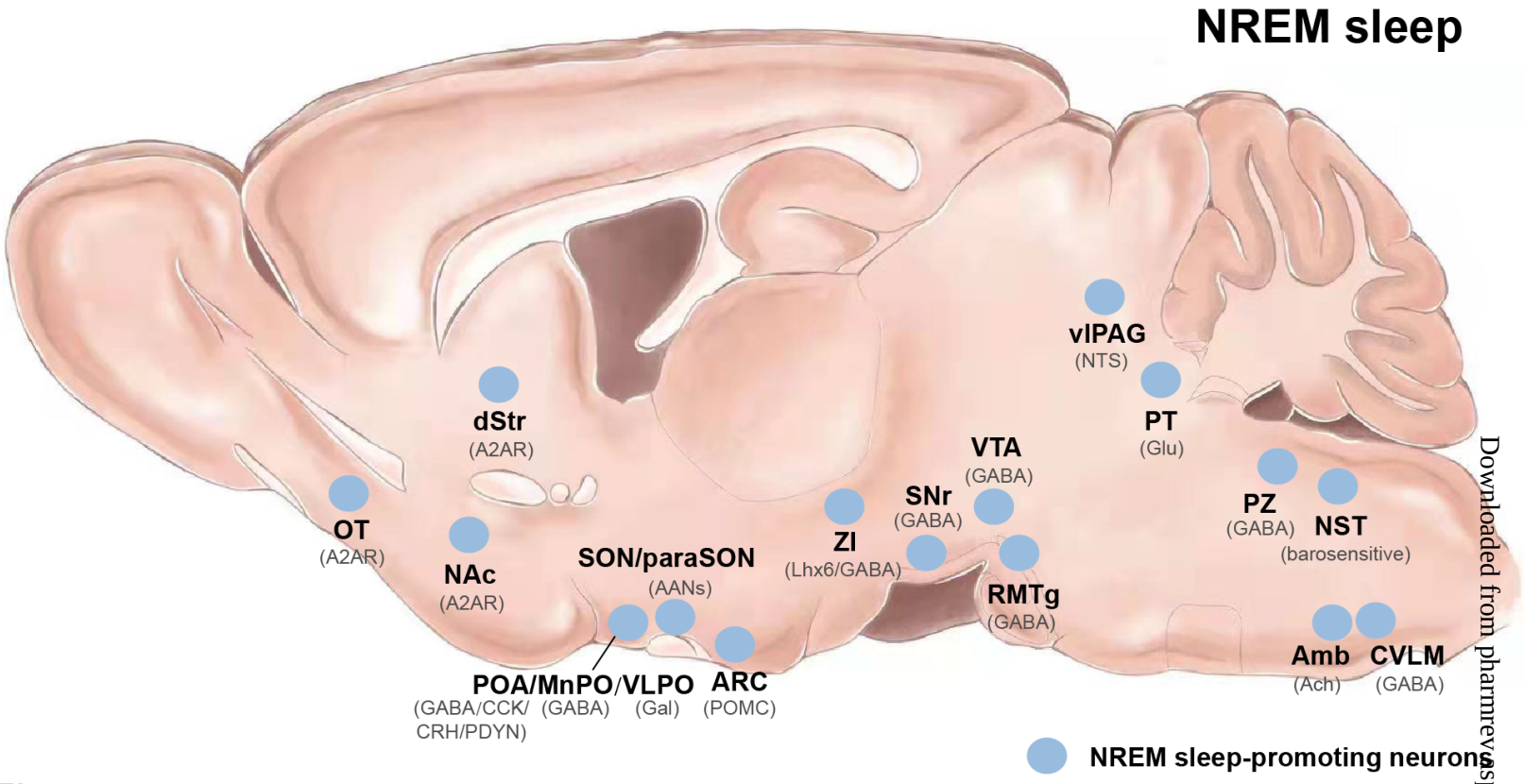

Figure 3

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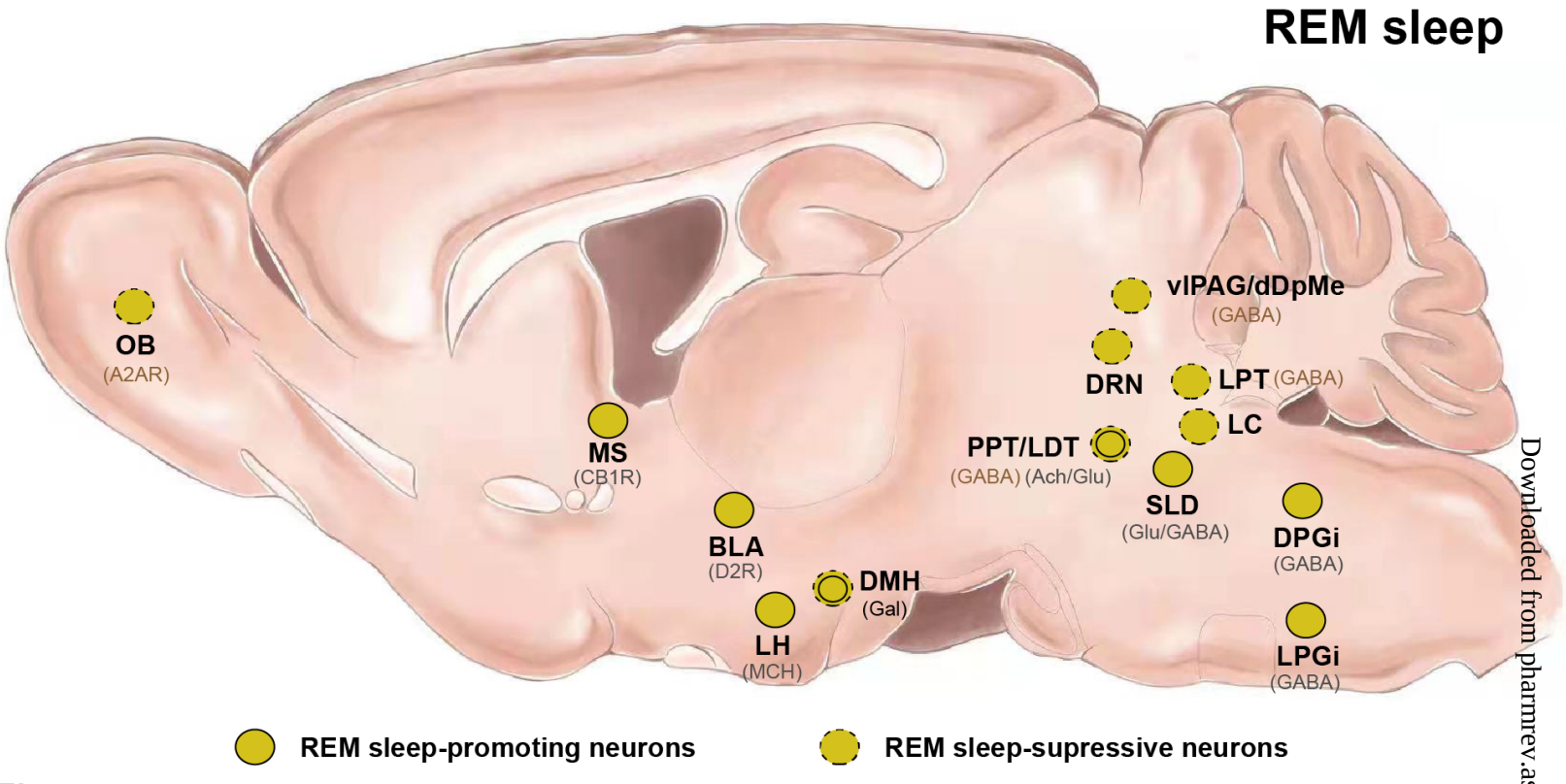

Figure 4

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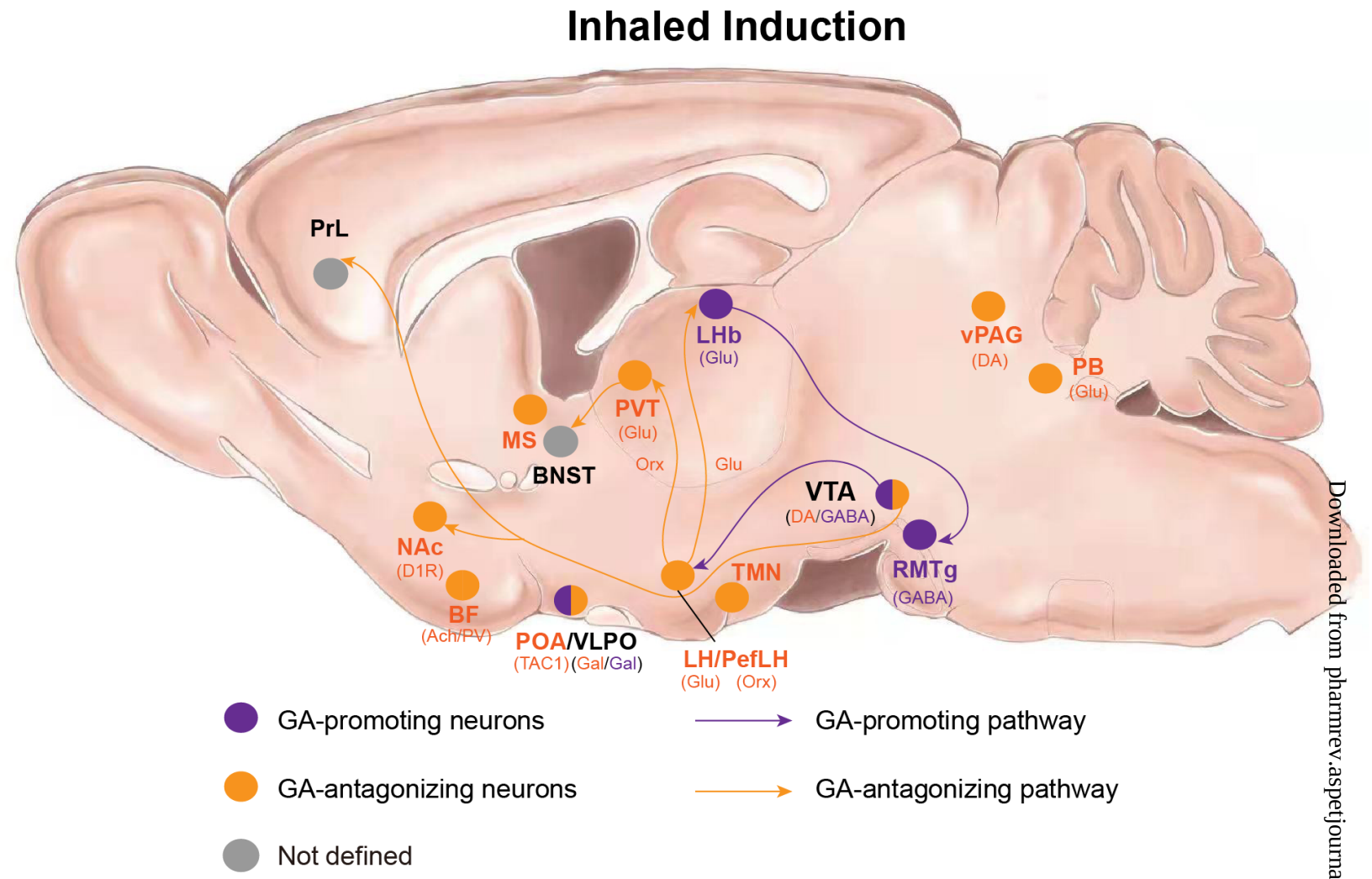

Figure 5

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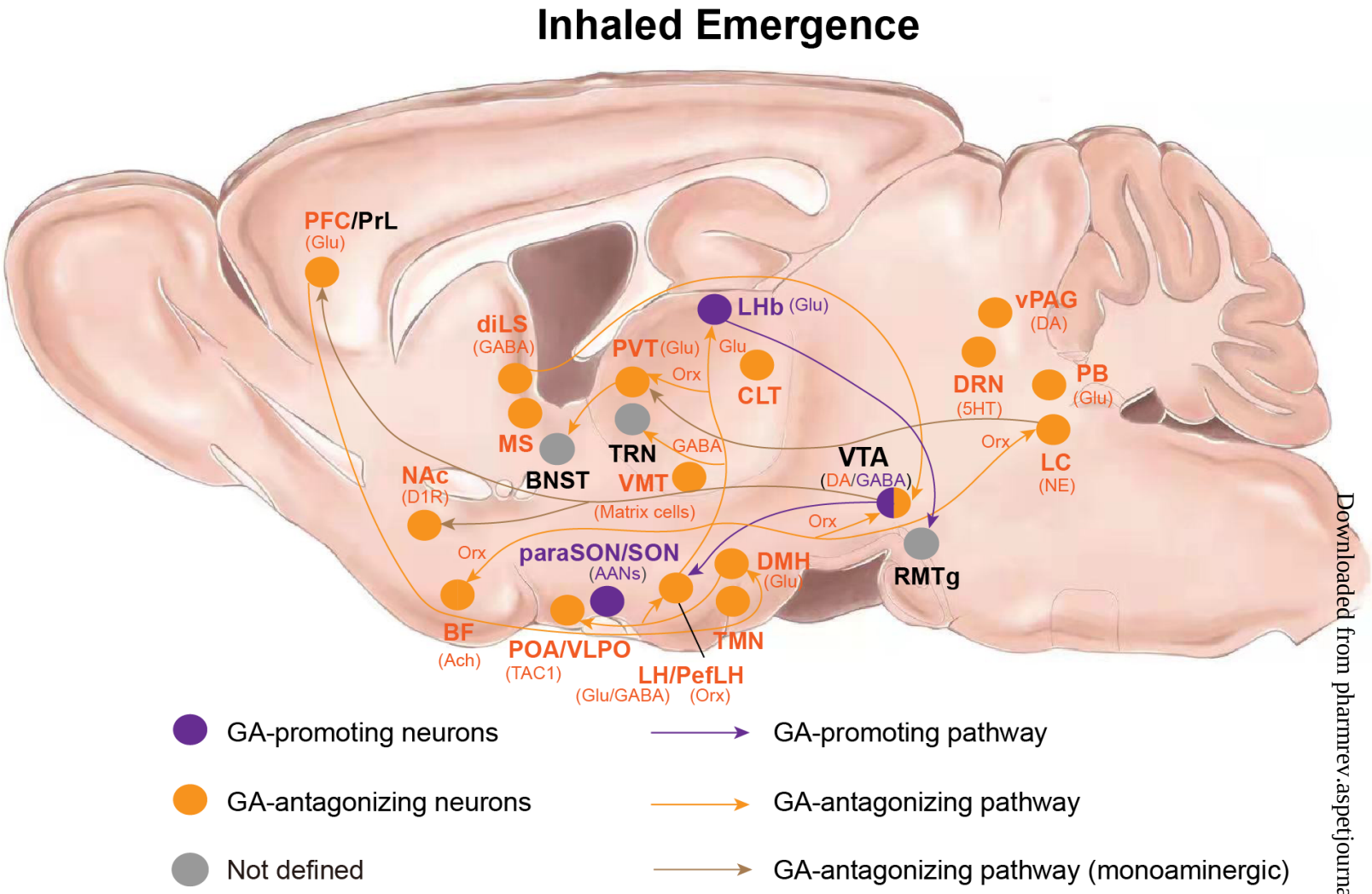

Figure 6

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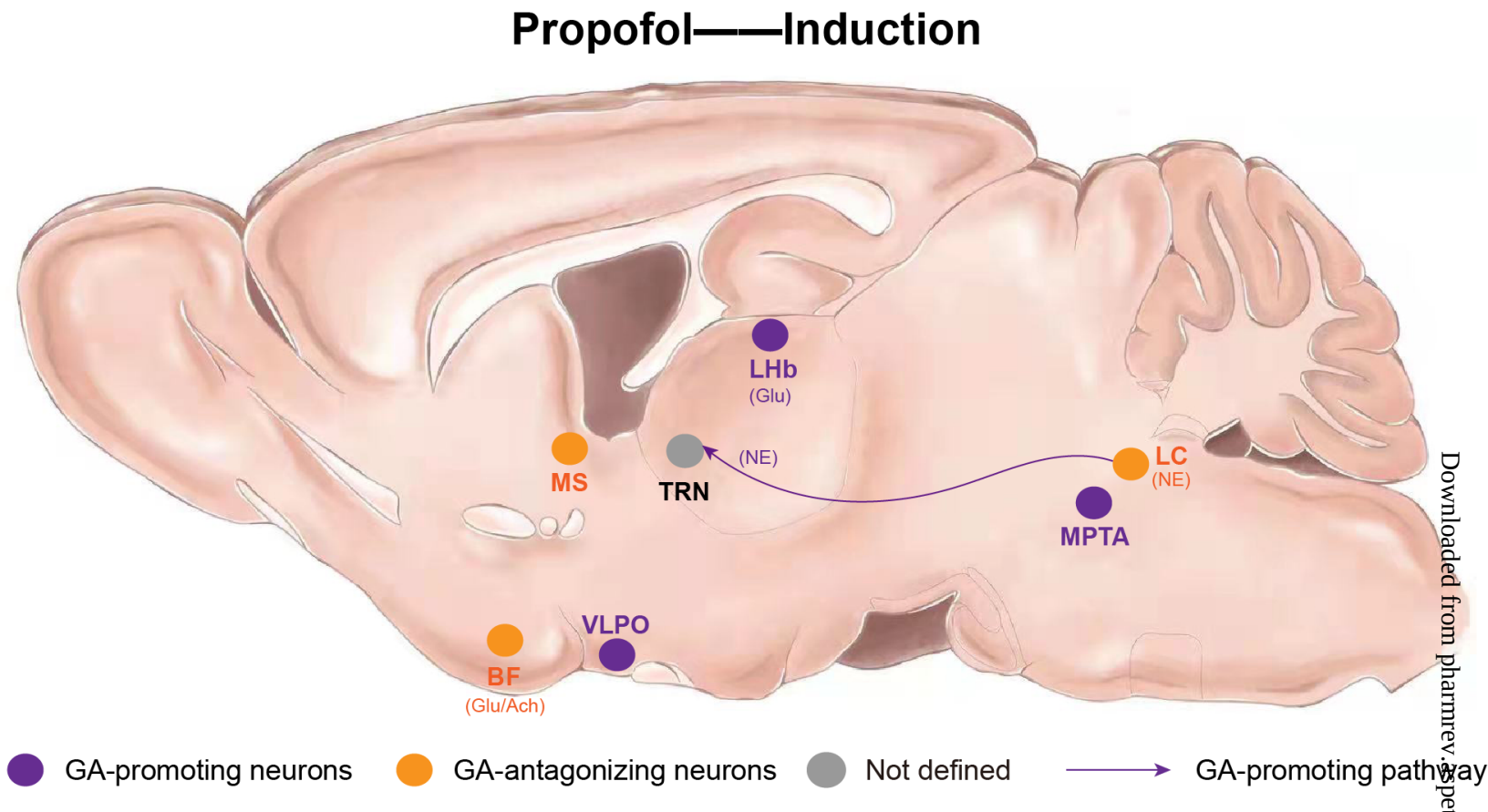

Figure 7

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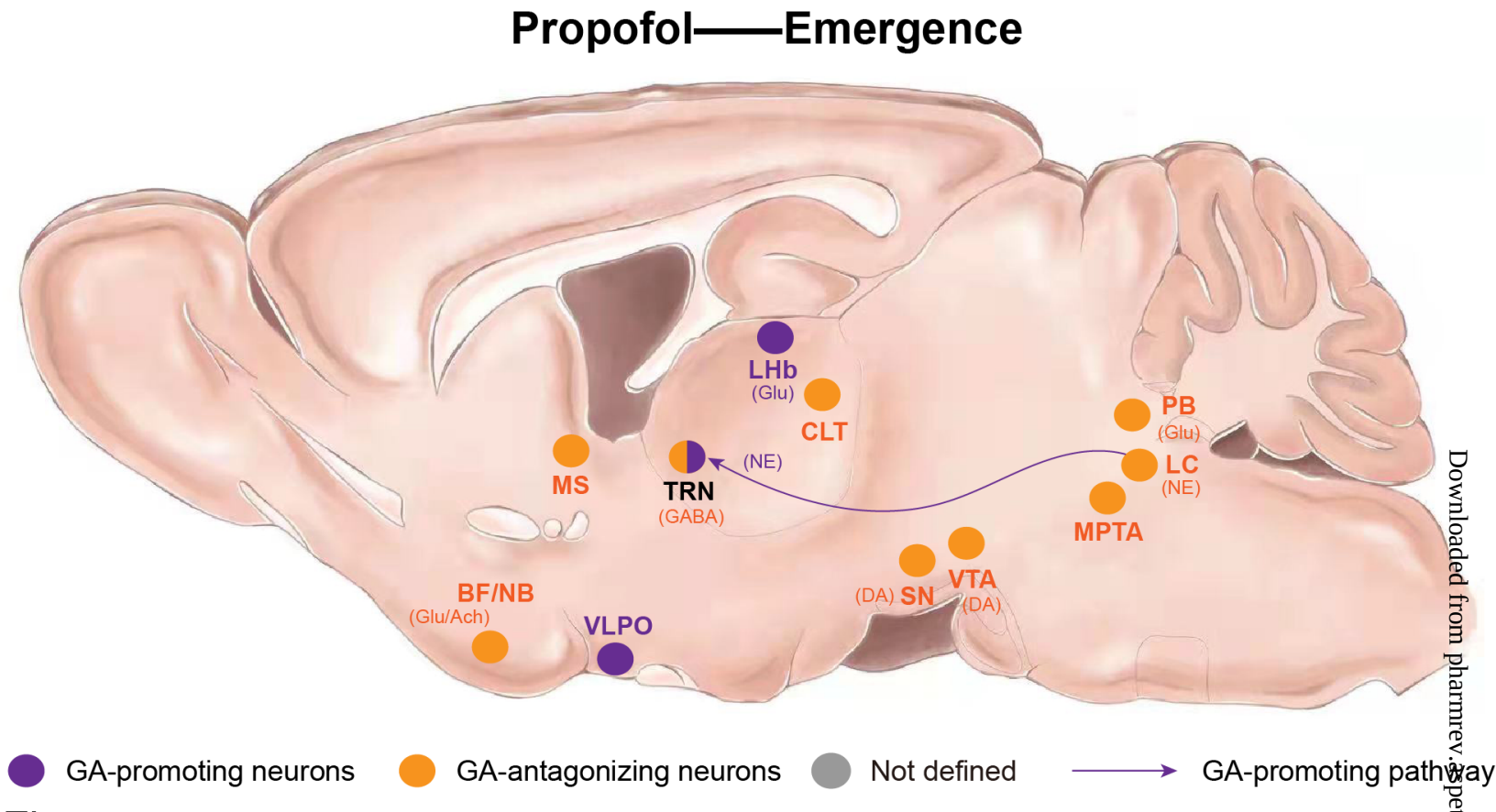

Figure 8

PHARMREV-AR-2022-000717

PHARMACOLOGICAL REVIEWS

Understanding the neural mechanisms of general anesthesia from interaction with sleep-wake state: a decade of discovery

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Supplementary Table 1. Effects of selective manipulation of the brain structures on inhaled anesthetic responses.

Structures	Neurons/ neural circuits	Anesthetics	Manipulation	Induction	Emergence	Reference
PFC	Glutamatergic terminals in the DMH	Isoflurane	Chemogenetic activation		RORR↓	(Zhong et al., 2017)
diLS	GABAergic neurons	Isoflurane	Optogenetic activation		EEG (Burst number↑ Burst duration↑ BSR↓); EMG (-); RORR↓	(Wang et al., 2021a)
		Isoflurane	Optogenetic inhibition		EEG (-); EMG (-); RORR↑	
NAc	D1R neurons	Sevoflurane	Chemogenetic activation	EC50-LORR↑; LORR↑	RORR↓	(Bao et al., 2021)
		Sevoflurane	Chemogenetic inhibition	EC50-LORR↓; LORR↓	RORR↑	
		Sevoflurane	Optogenetic activation		EEG (BSR↓ delta↓ beta↑); EMG↑; Arousal score↑	
BF	Cholinergic neurons	Isoflurane	Gene knockout	EC50-LORR↓	Hippocampal high-gamma power↓	(Leung et al., 2021)
		Isoflurane	Genetic lesions	LORR↓	EEG (delta↑ beta↓); RORR↑	(Luo et al., 2020)
		Isoflurane	Chemogenetic activation	LORR↑	EEG (delta↓ beta↑); RORR↓	
		Isoflurane	Optogenetic activation	LORR↑	RORR↓	
	GABAergic SOM-expressing neurons	Isoflurane	Genetic lesions	LORR↓	EEG (delta↓); RORR↑	(Cai et al., 2021)
	GABAergic PV-expressing neurons	Isoflurane	Genetic lesions	LORR↓	EEG (-); RORR (-)	
	GABAergic SOM-expressing neurons	Isoflurane	Chemogenetic activation	LORR↓	EEG (delta↑ gamma↓); RORR↑	

	GABAergic PV-expressing neurons	Isoflurane	Chemogenetic activation	LORR↑	EEG (delta↓); RORR (-)	
	GABAergic SOM-expressing neurons	Isoflurane	Chemogenetic inhibition	LORR↑	EEG (delta↓); RORR↓	
	GABAergic PV-expressing neurons	Isoflurane	Chemogenetic inhibition	LORR (-)	EEG (delta↑); RORR (-)	
PVT	Glutamatergic neurons	Isoflurane	Optogenetic activation		EEG (BSR↓ Burst duration↑ delta↑ theta↓); EMG (-); RORR↓	(Ren et al., 2018)
		Sevoflurane	Chemogenetic inhibition	EEG (delta↑); EC50-LORR↓; LORR↓	EEG (delta↑ theta↓); EC50-RORR↓; RORR↑	(Li et al., 2022)
		Sevoflurane	Optogenetic activation	LORR↑	EEG (BSR↓ delta↑ alpha↑ beta↑ gamma↑); Arousal score↑; RORR↓	
	Glutamatergic terminals in the BNST	Sevoflurane	Optogenetic activation	LORR↑	EEG (BSR↓ delta↑); Arousal score↑; RORR↓	
VMT	Matrix cells	Sevoflurane+ Dexmedetomidine	Optogenetic activation		EEG (slow wave activity↓ theta↓ gamma↑); Whisker EMG↑; Behavioral Arousal↑	(Honjoh et al., 2018)
SON and para-SON	AANs	Isoflurane	Optogenetic activation	Induction time (-)	Fully awake↑; Duration of unconsciousness↑	(Jiang-Xie et al., 2019)
		Isoflurane	Optogenetic inhibition	Induction time (-)	Fully awake↓; Duration of unconsciousness↓	
POA	TAC1 neurons	Isoflurane	Chemogenetic activation	EC50-LORR↑	EC50-RORR↑	(Reitz et al., 2020)
		Isoflurane	Chemogenetic inhibition	EC50-LORR (-)	EC50-RORR (-)	
		Sevoflurane	Chemogenetic activation	EC50-LORR (-)	EC50-RORR↑	
		Sevoflurane	Chemogenetic inhibition	EC50-LORR (-)	EC50-RORR (-)	

POA（VLPO）	Galaninergic neurons	Isoflurane	Galanin-saporin lesions 6 day	EC50-LORR↑		(Moore et al., 2012)
		Isoflurane	Galanin-saporin lesions 24 day	EC50-LORR↓		
	GABAergic neurons	Isoflurane	Chemogenetic activation	LORR (-)	RORR (-)	(Vanini et al., 2020)
	Glutamatergic neurons	Isoflurane	Chemogenetic activation	LORR (-)	LORR (-)	
POA（MnPO）	GABAergic neurons	Isoflurane	Chemogenetic activation	LORR (-)	RORR (-)	
	Glutamatergic neurons	Isoflurane	Chemogenetic activation	LORR (-)	0.5 mg/kg CNO: RORR (↑) 1.0 mg/kg CNO: RORR (-)	
LH	GABAergic terminals in the TRN	Isoflurane	Optogenetic activation		EEG (Burst duration↑ BSR↓); EMG↑	(Herrera et al., 2016)
	Glutamatergic neurons	Isoflurane	Genetic lesions	LORR↓	RORR↑	(Zhao et al., 2021a)
		Isoflurane	Chemogenetic activation	LORR↑	RORR↓	
		Isoflurane	Chemogenetic inhibition	LORR↓	RORR↑	
		Isoflurane	Optogenetic activation		EEG (BSR↓ delta↓ alpha↑ beta↑ gamma↑)	
		Isoflurane	Optogenetic inhibition		EEG (BSR (-) beta↓)	
	Glutamatergic terminals in the LHb	Isoflurane	Optogenetic activation	LORR↑	EEG (BSR↓ delta↓ beta↑ gamma↑); RORR↓	
		Isoflurane	Optogenetic inhibition	LORR↓	EEG (BSR (-) delta↑ beta↓ gamma↓); RORR↑	
LH (Pef)	Orexinergic neurons	Isoflurane	Chemogenetic activation		EEG (delta↓ alpha↑ beta↑); EMG↑; RORR↓	(Zhou et al., 2018)
		Isoflurane	Optogenetic activation	LORR (-)	EEG(BSR↓); RORR↓	(Wang et al., 2020)
		Isoflurane	Chemogenetic activation	EC50-LORR (-); LORR (-)	EC50-RORR↑; RORR↓	(Zhao et al., 2021b)

		Isoflurane	Chemogenetic inhibition	EC50-LORR↓; LORR (-)	EC50-RORR↓; RORR↑	
		Desflurane	Chemogenetic activation	EC50-LORR↑; LORR↑	EC50-RORR↑; RORR↓	
		Desflurane	Chemogenetic inhibition	EC50-LORR↓; LORR↓	EC50-RORR↓; RORR↑	
		Isoflurane	Optogenetic activation		EEG(BSR↓)	
		Desflurane	Optogenetic activation		EEG (BSR↓ delta↓ alpha↑ beta↑ gamma↑)	
	Orexinergic terminals in the PVT	Isoflurane	Chemogenetic activation	LORR (-)	RORR↓	
		Isoflurane	Chemogenetic inhibition	LORR (-)	RORR↑	
		Desflurane	Chemogenetic activation	LORR↑	RORR↓	
		Desflurane	Chemogenetic inhibition	LORR↓	RORR↑	
		Isoflurane	Optogenetic activation		EEG (BSR↓)	
		Desflurane	Optogenetic activation		EEG (BSR↓)	
	Orexinergic terminals in the BF	Isoflurane	Optogenetic activation		EEG (BSR↓ delta↓ theta↑ beta↑ gamma↑); Arousal score↑; RORR↓	(Wang et al., 2020)
	Orexinergic terminals in the LC	Isoflurane	Optogenetic activation		EEG (BSR↓ delta↓ beta↑ gamma↑); Arousal score↑; RORR↓	

	Orexinergic terminals in the VTA	Isoflurane	Optogenetic activation		EEG (BSR↓ delta↓ alpha↑ beta↑ gamma↑); Arousal score↑; RORR↓	(Li et al., 2019)
		Isoflurane	Optogenetic inhibition		EEG (BSR (-) theta↓ beta↓); Arousal score (-); RORR↑	
DMH	Glutamatergic terminals at LH (Pef)	Isoflurane	Chemogenetic activation		RORR↓	(Zhong et al., 2017)
LHb	Glutamatergic neurons	Isoflurane	Genetic lesions	LORR↑	EEG (Maintenance: delta↓ alpha↑ beta↑ BSR↓; Recovery: delta↓); RORR↓	(Liu et al., 2021a)
		Isoflurane	Chemogenetic activation	LORR↓	EEG (delta↑ gamma↓ BSR↑); RORR↑	
		Isoflurane	Chemogenetic inhibition	LORR↑	EEG (delta↓ theta↑ beta↑ BSR↓); RORR↓	
		Isoflurane	Optogenetic activation	EEG (delta↑ beta↓ gamma↓); LORR↓	EEG (delta↑ gamma↓); RORR↑	
	Glutamatergic terminals in the RMTg	Isoflurane	Optogenetic activation	EEG (delta↑ alpha↓ beta↓ gamma↓); LORR↓	EEG (delta↑ beta↓ gamma↓); RORR↑	
	Glutamatergic terminals in the VTA	Isoflurane	Optogenetic activation	LORR (-)	RORR (-)	
VTA	Dopaminergic neurons	Isoflurane	Lesions (infusion of 6-hydroxydopamine)	EC50-LORR (-); LORR (-)	RORR (-)	(Zhou et al., 2015)
		Isoflurane	Optogenetic activation		EEG (power < 5 Hz ↓ 6-17 Hz ↓); Arousal score↑	(Taylor et al., 2016)
		Sevoflurane	Chemogenetic activation	EEG (delta↓ beta↑); LORR↑	EEG (delta↓ theta↑ alpha↓ beta↑ gamma↑); RORR↓	(Song et al., 2021)
		Sevoflurane	Optogenetic activation	EEG (delta↓ beta↑ gamma↑); LORR↑	EEG (theta↓ beta↑ gamma↑); RORR↓	(Gui et al., 2021)
	Dopaminergic terminals in the	Sevoflurane	Optogenetic activation	EEG (delta↓ gamma↑); LORR↑	EEG (delta↓ gamma↑); RORR↓	

	NAc	Sevoflurane	Optogenetic inhibition	EEG (theta↑ alpha↑ gamma↓); LORR↓	EEG (delta↑ alpha↓ beta↓ gamma↓); RORR↑	
	Dopaminergic terminals in the PrL	Sevoflurane	Chemogenetic activation (retrograde label)	EEG (delta↓ theta↓ beta↑ gamma↑); LORR↑	EEG (delta↓ alpha↓ beta↑ gamma↑); RORR↓	(Song et al., 2021)
		Sevoflurane	Chemogenetic activation (anterograde label)	EEG (delta↓ gamma↑); LORR↑	EEG (alpha↓ gamma↑); RORR↓	
		Sevoflurane	Optogenetic activation	EEG (delta↓ alpha↓ gamma↑); LORR↑	EEG (delta↓ beta↑ gamma↑); RORR↓	
	GABAergic neurons	Isoflurane	Optogenetic activation		EEG (BSR↑ delta↑ beta↓ gamma↓)	(Yin et al., 2019)
		Isoflurane	Optogenetic inhibition		EEG (BSR↓ delta↓ theta↓ alpha↓ gamma↑)	
		Isoflurane	Chemogenetic activation	EC50-LORR↓; LORR↓	EC50-RORR↓; RORR↑	
		Isoflurane	Chemogenetic inhibition	EC50-LORR↑; LORR↑	EC50-RORR↑; RORR↓	
	GABAergic terminals in the LH	Isoflurane	Optogenetic activation	LORR↓	EEG (BSR↑ delta↑ gamma↓); RORR↑	
		Isoflurane	Optogenetic inhibition	LORR↑	EEG (BSR↓ delta ↓ alpha↓ gamma↑); RORR (-)	
RMTg	GABAergic neurons	Sevoflurane	Chemogenetic activation	EC50-LORR↓		(Vlasov et al., 2021)
vPAG	Dopaminergic neurons	Isoflurane	Lesions (infusion of 6-hydroxydopamine)	LORR↓	EEG (Maintenance: delta↑;Recovery：(-)); RORR↑	(Liu et al., 2020b)
DRN	Serotonergic neurons	Isoflurane	Optogenetic activation		EEG (BSR↓)	(Li et al., 2021)
		Isoflurane	Optogenetic inhibition		EEG (BSR↑)	
		Isoflurane	Chemogenetic activation	LORR (-)	RORR↓	
		Isoflurane	Chemogenetic inhibition	LORR (-)	RORR↑	

LC	Noradrenergic neurons	Isoflurane	Chemogenetic activation	LORR↑	EEG (BSR↓ delta↓ theta↑); RORR↓	(Vazey and Aston-Jones, 2014)
		Isoflurane	Chemogenetic activation	LORR (-)	EEG (BSR (-) delta↓ alpha↑); RORR↓	(Ao et al., 2021b)
	Noradrenergic terminals in the PVT	Isoflurane	Chemogenetic inhibition	LORR (-)	RORR↑	
		Isoflurane	Optogenetic activation	LORR (-)	EEG (BSR↓ delta↓ theta↑ alpha↑); RORR↓	
PB	Glutamatergic neurons	Sevoflurane	Chemogenetic activation	EC50-LORR↑; LORR↑	RORR↓	(Wang et al., 2019)
		Sevoflurane	Chemogenetic inhibition	EC50-LORR↓; LORR (-)	RORR↑	
		Sevoflurane	Optogenetic activation		EEG (delta↓ theta↑)	

↑↓ represent different indicators that increased or decreased compared to the control group, respectively; (-) represents no significant difference compared to the control group.

Supplementary Table 2. Effects of unselective manipulation of the brain structures on inhaled anesthetic responses.

Structure	Anesthetics	Subject	Manipulation	Induction	Emergence	Reference
PFC→DMH projection	Isoflurane	Rats	Chemogenetic activation		RORR↓	(Zhong et al., 2017)
PFC (PrL)	Sevoflurane	Rats	Dopamine receptor agonist	LORR↑	RORR↓	(Song et al., 2021)
	Sevoflurane	Rats	Dopamine receptor antagonist	LORR↓	RORR↑	
	Sevoflurane	Rats	Cholinergic agonist		EEG (theta/delta↑); wake-like behavior↑	(Pal et al., 2018)
	Sevoflurane	Rats	NE		EEG (theta/delta↑); wake-like behavior (-)	
Posterior parietal cortex	Sevoflurane	Rats	Cholinergic agonist		EEG (theta/delta↑); wake-like behavior (-)	
	Sevoflurane		NE		EEG (theta/delta↑); wake-like behavior (-)	
Medial parietal association cortex	Sevoflurane	Rats	Cholinergic agonist		EEG (theta/delta↑); wake-like behavior (-)	
CI	Isoflurane	Rats	Electrical stimulation		EEG(BSR↑)	(Pavel et al., 2019)
BF	Isoflurane	Rats	Orexin-A	LORR (-)	RORR↓	(Zhang et al., 2016)
	Isoflurane		Orexin-B	LORR (-)	RORR (-)	
	Isoflurane		Orexin-1 receptor antagonist	LORR (-)	RORR↑	
	Isoflurane		Orexin-2 receptor antagonist	LORR (-)	RORR (-)	
	Sevoflurane		Orexin-A	LORR (-)	EEG (30 or 100 pmol orexin-A: BSR↓); RORR↓	(Dong et al., 2009)
	Sevoflurane		Orexin-B	LORR (-)	EEG (30 pmol orexin-B: BSR (-), 100 pmol orexin-B: BSR (↓)); RORR (-)	
	Sevoflurane		Orexin-1 receptor antagonist	LORR (-)	RORR↑	

BF (nucleus basalis of Meynert)	Desflurane	Rats	NE		EEG (delta↓); Behavioral score↑	(Pillay et al., 2011)
BF (nucleus basalis magnocellularis)	Isoflurane	Rats	Histamine		EEG(BSR↓ delta↑ theta↑); RORR↓	(Luo and Leung, 2009)
	Isoflurane	Rats	Histamine receptor 1 antagonist		RORR↑	
	Isoflurane	Rats	Histamine receptor 2 antagonist		RORR (-)	
MS	Isoflurane	Rats	Electrolytic lesions	EC50-LORR↓	RORR↑	(Leung et al., 2013)
	Halothane	Rats	Electrolytic lesions		RORR↑	
CLT	Isoflurane	Monkeys	Electrical stimulation		Arousal score↑	(Redinbaugh et al., 2020)
PVT	Isoflurane	Mice	D2R agonist infusion	LORR (-)	EEG(BSR↓); RORR↓	(Ao et al., 2021a)
	Isoflurane		D2R antagonist infusion	LORR (-)	EEG (BSR (-)); RORR↑	
	Isoflurane	Rats	Orexin-A	LORR (-)	RORR↓	(Zhao et al., 2021b)
	Isoflurane	Rats	Orexin-B	LORR (-)	RORR↓	
	Desflurane	Rats	Orexin-A	LORR↑	RORR↓	
	Desflurane	Rats	Orexin-B	LORR↑	RORR↓	
	Isoflurane	Rats	Orexin-1 receptor antagonist	LORR (-)	RORR (-)	
	Isoflurane	Rats	Orexin-2 receptor antagonist	LORR (-)	RORR↑	
	Desflurane	Rats	Orexin-1 receptor antagonist	LORR (-)	RORR (-)	
	Desflurane	Rats	Orexin-2 receptor antagonist	LORR↓	RORR↑	
PVT-BNST projection	Sevoflurane	Mice	Chemogenetic inhibition	EC50-LORR↓; EEG (delta↑); LORR↓	EC50 (RORR)↓; EEG (delta↑); RORR↑	(Li et al., 2022)
POA(VLPO)	Isoflurane	Rats	Orexin-saporin lesions	LORR (-)	EEG (BSR↑); RORR↑	(Eikermann et al., 2011)
DMH-LH(Pef) projection	Isoflurane	Rats	Chemogenetic activation		RORR↓	(Zhong et al., 2017)

DMH-POA(VLPO) projection	Isoflurane	Rats	Chemogenetic activation		RORR↓	
TMN	Isoflurane	Rats	Orexin-saporin lesions	EC50-LORR↓; LORR (-)	RORR↑	(Luo and Leung, 2011)
VTA	Isoflurane	Rats	Orexin-A	LORR (-)	EEG (BSR↓); RORR↓	(Li et al., 2019)
	Isoflurane		Orexin-B	LORR (-)	EEG (-); RORR (-)	
	Isoflurane		Orexin-1 receptor antagonist	LORR (-)	EEG (-); RORR↑	
	Isoflurane		Orexin-2 receptor antagonist	LORR (-)	EEG (-); RORR (-)	
VTA-NAc	Sevoflurane	Mice	Chemogenetic activation	EEG (delta↓gamma↑); LORR↑	EEG (delta↓ gamma↑); RORR↓	(Gui et al., 2021)
	Sevoflurane	Mice	Chemogenetic inhibition	EEG (delta↑ beta↓ gamma↓); LORR↓	EEG (delta↑ alpha↓ beta↓ gamma↓); RORR↑	
DRN	Isoflurane	Rats	Orexin-A	LORR (-)	EEG(BSR↓delta↓); RORR↓	(Yang et al., 2019)
	Isoflurane		Orexin-B	LORR (-)	EEG (BSR (-)); RORR (-)	
	Isoflurane		Orexin-1 receptor antagonist	LORR (-)	RORR↑	
	Isoflurane		Orexin-2 receptor antagonist	LORR (-)	RORR (-)	
vPAG	Isoflurane	Rats	$GABA_A$ receptor agonist	LORR↓	EEG (delta↑ beta↓); RORR↑	(Liu et al., 2020b)
	Isoflurane		$GABA_A$ receptor antagonist	LORR↑	EEG (delta↓); RORR↓	
LC	Isoflurane	Rats	$GABA_B$ receptor antagonist		EEG (delta↓ theta↑); Behavioral emergence↑	(Hung et al., 2020)
PB	Isoflurane	Rats	Chemogenetic activation	LORR (-)	EEG (Maintenance: (-); Recovery: delta↓); RORR↓	(Luo et al., 2018)
medial PB	Sevoflurane	Mice	$GABA_A$ receptor antagonist	1.5% sevoflurane: LORR↑; 3.0% sevoflurane: LORR (-)	1.5% sevoflurane: RORR↓; 3.0% sevoflurane: RORR (-)	(Xu et al., 2020)

↑↓ represent different indicators that increased or decreased compared to the control group, respectively; (-) represents no significant difference compared to the control group.

Supplementary Table 3. Effects of selective manipulation of the brain structures on intravenous anesthetic responses.

Structures	Neurons/ Neural circuits	Anesthetics	Manipulation	Induction	Emergence	Reference
BF	GABAergic SOM-expressing neurons	Propofol	Genetic lesions		LORR Durations↑; EEG (delta↓ beta↑)	(Cai et al., 2021)
		Propofol	Chemogenetic activation		LORR Durations↑; EEG (delta↑)	
		Propofol	Chemogenetic inhibition		LORR Durations↓; EEG (delta↓)	
	GABAergic PV-expressing neurons	Propofol	Genetic lesions		LORR Durations↑; EEG (-)	
		Propofol	Chemogenetic activation		LORR Durations (-); EEG (-)	
		Propofol	Chemogenetic inhibition		LORR Durations (-); EEG (delta↑ theta ↓)	
	Cholinergic neurons	Propofol	Genetic lesions		LORR Durations↑; EEG (delta↑ beta↓)	(Luo et al., 2020)
		Propofol	Chemogenetic activation		LORR Durations↓; EEG (delta↓ beta↑ gamma↑)	
		Propofol	Optogenetic activation		LORR Durations↓	
		Propofol	Optogenetic activation	LORR↑; ED50-LORR↑	RORR↓; medial PFC LFP (delta↓ beta↑ low gamma↑)	(Wang et al., 2021b)
		Ketamine	Gene knockout	ED50-LORR↓		(Leung et al., 2021)
	Glutamatergic	Propofol	Optogenetic activation	LORR↑; ED50-LORR↑	RORR↓; medial PFC LFP (all band↑)	(Wang et al., 2021b)
TRN	GABAergic neurons	Propofol	Chemogenetic activation	LORR (-)	RORR↓	(Liu et al., 2021b)
		Propofol	Chemogenetic inhibition	LORR (-)	RORR↑	
		Propofol	Optogenetic activation	LORR (-)	RORR↓	
		Propofol	Optogenetic inhibition	LORR (-)	RORR↑	
LHb	Glutamatergic	Propofol	Genetic lesions	ED50-LORR↑	LORR Durations↓; EEG (delta↓)	(Gelegen et al., 2018)

SN	Dopaminergic	Propofol	Lesions (infusion of 6-hydroxydopamine)	LORR (-); ED50-LORR (-)	RORR↑; EEG (delta↑)	(Fu Shi, 2017)
VTA	Dopaminergic	Propofol	Lesions (infusion of 6-hydroxydopamine)	LORR (-); ED50-LORR (-)	RORR↑	(Zhou et al., 2015)
		Ketamine		LORR (-); ED50-LORR (-)	RORR (-)	
LC	Noradrenergic terminals in the TRN	Propofol	Chemogenetic activation	ED50-LORR↓	RORR↑; EEG (delta↑)	(Zhang et al., 2019)
PB	Glutamatergic	Ketamine	Chemogenetic activation		RORR (-)	(Melonakos et al., 2021)

↑↓ represent different indicators that increased or decreased compared to the control group, respectively; (-) represents no significant difference compared to the control group.

Supplementary Table 4. Effects of unselective manipulation of the brain structures on intravenous anesthetic responses.

Structures	Anesthetics	Subject	Manipulation	Induction	Emergence	Reference
medial PFC	Propofol	Rats	$GABA_A$ receptor antagonist	LORR↑	RORR↓	(Wang et al., 2016)
BF	Propofol	Rats	Ibotenic acid lesions	LORR (-)	RORR↑; EEG (delta↑)	(Liu et al., 2020a)
	Propofol		$GABA_A$ receptor agonist	LORR (-)	RORR↑; EEG (delta↑ gamma↓)	
	Propofol		$GABA_A$ receptor antagonist	LORR (-)	RORR↓; EEG (delta↓ gamma↑)	
	Propofol	Rats	Orexin-A	LORR (-)	RORR↓; EEG (BSR↓)	(Zhang et al., 2012)
	Propofol		Orexin-1 receptor antagonist	LORR (-)	RORR↑	
BF (NB)	Propofol	Rats	Ibotenic acid lesions	LORR (-)	RORR↑; EEG (delta↑)	(Xing et al., 2020)
	Propofol		$GABA_A$ receptor agonist	LORR (-)	RORR↑; EEG (delta↑ gamma↓)	
	Propofol		$GABA_A$ receptor antagonist	LORR (-)	RORR↓; EEG (delta↓)	
MS	Propofol	Rats	Electrolytic lesions	ED50-LORR↓	LORR Durations↑; Duration of loss of tail-pinch response ↑	(Leung et al., 2013)
CLT	Propofol	Monkeys	Electrical stimulation		Arousal score↑	(Redinbaugh et al., 2020)
CMT	Propofol	Rats	NE	LORR (-); ED50-LORR (-)	RORR↓; EEG (PFC: theta↑, anterior cingulate cortex: delta↓ theta↑ alpha↑)	(Fu et al., 2017)
TRN	Propofol	Mice	NE	LORR (-); ED50-LORR↓	RORR↑; EEG (delta↑)	(Zhang et al., 2019)
TMN	Ketamine	Rats	Orexin-saporin lesions	LORR (-); ED50-LORR (-)	RORR (-)	(Luo and Leung, 2011)

	Propofol		Orexin-saporin lesions	LORR (-); ED50-LORR (-)	RORR (-)	
			Histamine receptor 3 inverse agonist		RORR↓	(Xia et al., 2021)
			GABA		RORR↑	
			$GABA_A$ receptor antagonist		LORR Durations↓	(Nelson et al., 2002)
VLPO	Propofol	Rats	Ibotenic acid lesions	LORR↑	LORR Durations↓	(Zhang et al., 2015)
			$GABA_A$ agonist	LORR↓	RORR↑	(Yuan et al., 2017)
			$GABA_A$ antagonist	LORR↑	RORR↓	
vlPAG	Ketamine	Rats	Ibotenic acid lesions		Tail-flick latencies↓	(Lu et al., 2008)
LC	Propofol	Zebrafish	Two-photon laser lesions	LORR↓	RORR↑	(Du et al., 2018)
			Impair NE synthesis	LORR↓	RORR↑	
		Rats	$GABA_A$ receptor antagonist	LORR (-)		(Zhang et al., 2015)
MPTA	Propofol	Rats	Ibotenic acid lesions	ED50-arousal score↑	RORR↑	(Minert et al., 2020)
	Ketamine			ED50-arousal score (-)	RORR (-)	
PB	Propofol	Rats	Chemogenetic activation	LORR (-)	RORR↓; EEG (Maintenance: (-), recovery: delta↓ beta↑)	(Luo et al., 2018)
PnO			GABA synthesis inhibitor	LORR↓	RORR (-)	(Vanini et al., 2014)
	Propofol		GABA uptake inhibitor	LORR↑	RORR (-)	

↑↓ represent different indicators that increased or decreased compared to the control group, respectively; (-) represents no significant difference compared to the control group.

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