The Neural Circuits Underlying General Anesthesia and Sleep

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Abstract

General anesthesia is characterized by loss of consciousness, amnesia, analgesia, and immobility. Important molecular targets of general anesthetics have been identified, but the neural circuits underlying the discrete endpoints of general anesthesia remain incompletely understood. General anesthesia and natural sleep share the common feature of reversible unconsciousness, and recent developments in neuroscience have enabled elegant studies that investigate the brain nuclei and neural circuits underlying this important endpoint.

A common approach to measure cortical activity across the brain is electroencephalography (EEG), which can reflect local neuronal activity as well as connectivity among brain regions. The EEG oscillations observed during general anesthesia depend greatly on the anesthetic agent as well as dosing, and only some resemble those observed during sleep. For example, the EEG oscillations during dexmedetomidine sedation are similar to those of stage 2 non-rapid eye movement (NREM) sleep, but high doses of propofol and ether anesthetics produce burst suppression, a pattern that is never observed during natural sleep.

Sleep is primarily driven by withdrawal of subcortical excitation to the cortex, but anesthetics can directly act at both subcortical and cortical targets. While some anesthetics appear to activate specific sleep-active regions to induce unconsciousness, not all sleep-active regions play a significant role in anesthesia. Anesthetics also inhibit cortical neurons, and it is likely that each class of anesthetic drugs produces a distinct combination of subcortical and cortical effects that lead to unconsciousness. Conversely, arousal circuits that promote wakefulness are involved in

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anesthetic emergence and activating them can induce emergence and accelerate recovery of consciousness.

Modern neuroscience techniques that enable the manipulation of specific neural circuits have led to new insights into the neural circuitry underlying general anesthesia and sleep. In the coming years, we will continue to better understand the mechanisms that generate these distinct states of reversible unconsciousness.

Introduction:

General anesthetics produce a reversible state of unconsciousness, amnesia, analgesia, and immobility in response to pain. Since the introduction of general anesthesia into clinical practice, research in anesthetic mechanisms has been shaped by several influential theories. Claude Bernard proposed that anesthetics share a single, unified mechanism of action.[1] This hypothesis was strongly reinforced by the findings of Meyer and Overton, who independently discovered that anesthetic potency correlated strongly with lipophilicity.[2] Thus the lipid theory—stating that anesthetics act by disrupting the lipid bilayer of neuronal cell membranes—dominated thinking in the field for nearly a century.

In the 1980s, it was discovered that general anesthetics interact with hydrophobic sites on proteins,[3] commencing a new era of identifying relevant protein targets for anesthetics. It is now evident that anesthetics act at specific molecular sites on ionotropic receptors, voltage-gated ion channels, and metabotropic receptors to produce neuronal inhibition.[4] Substantial work has focused on anesthetic potentiation of γ-aminobutyric acid (GABA) receptors, which are responsible for the majority of inhibitory neurotransmission in the brain.[5]

Despite important advances in the molecular pharmacology of general anesthetics, the neuroanatomic sites of anesthetic action were largely unknown until it was reported that the spinal cord—not the brain—is the predominant site where anesthetics act to block motor responses to painful stimuli.[6,7] Another seminal finding was that the microinjection of barbiturates into the upper brainstem of rodents produces general anesthesia.[8] These important findings demonstrated that discrete neuroanatomic sites underlie different endpoints of anesthesia such as immobility and unconsciousness.

In recent years, there has been growing interest in studying how anesthetic drugs converge onto neural pathways of natural sleep to produce unconsciousness.[9] Sleep serves as a useful metaphor for anesthesiologists to explain general anesthesia to patients, as the two share the behavioral trait of reversible unconsciousness.[10] However, the states are distinct and clarity of terminology should be a goal in clinical and scientific discourse. In this review, the states of general anesthesia and sleep will be compared, highlighting important similarities and differences in neurophysiology and the neural circuit mechanisms underlying unconsciousness.

Comparison of Anesthesia and Sleep States

Important characteristics of general anesthesia and natural sleep are summarized in Table 1. Reversible loss of consciousness is a common feature, but the depth of unconsciousness

differs markedly. During natural sleep, responsiveness to loud verbal or strong tactile stimulation remains intact, as well as the ability to maintain or restore a patent airway with adequate spontaneous ventilation. Based on the degree of unresponsiveness and airway patency, natural sleep is akin to the American Society of Anesthesiologists' definition of "moderate sedation."[11] This is in contrast to general anesthesia, which is defined by behavioral unresponsiveness, even to painful stimuli. It is worth noting, however, that individuals with anatomically compromised airways may be vulnerable to reduced muscle activation and ventilatory drive during unconsciousness, in the setting of both general anesthesia and sleep (for a comprehensive review of this topic, please see the review by Hillman and Chung[12]). Individuals with obstructive sleep apnea are particularly vulnerable to developing a compromised upper airway when administered sedatives, analgesics and muscle relaxants. Preoperative screening tools to identify individuals with obstructive sleep apnea can mitigate vulnerabilities and other comorbidities that normally increase perioperative risk of hypoventilation and asphyxia during general anesthesia.[13]

Sleep is a natural process that occurs rhythmically, alternating between non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep in 90–120 minute cycles throughout the night.[14–16] In humans, NREM sleep is classified into three stages (N1-N3) from lighter to deeper sleep.[16] In contrast, during REM sleep the cerebral cortex is active, more closely resembling the awake state.[15]

The two main mechanisms that affect the timing and duration of sleep are homeostatic mechanisms (i.e. the pressure to sleep that increases with prolonged wakefulness) and circadian rhythms.[17] In animals, prolonged propofol exposure does not result in sleep deprivation, suggesting that propofol sedation satisfies the homeostatic need for sleep.[18] However, in sleep-deprived animals sevoflurane exposure allows for selective recovery of NREM sleep,[19] while REM sleep debt continues to accumulate.[20] These studies suggest that different anesthetics may satisfy the homeostatic need for specific components of natural sleep. On the other hand, the NMDA receptor antagonist ketamine has been shown to inhibit light-entrainment to the suprachiasmatic nucleus clock (the process by which the circadian clock is synchronized to light cues), and extended exposure to GABAergic anesthetics is predicted to induce temporary phase-shifts in the sleep-wake cycle.[21] Phase-shift effects could alter the trajectory of post-operative recovery, and clinical research on this topic is ongoing.[21] Molecular studies have shown that exposure to sevoflurane, dexmedetomidine and propofol can each inhibit the expression of key circadian clock genes, though these effects were more notable when anesthetics were administered during the active phase (dark-phase for rodents) than during the inactive phase (light-phase for rodents).[21] Overall, the accrued sleep debt is usually not considered when clinicians administer anesthetics for surgery, but ongoing research has the potential to improve postoperative care by examining postoperative sleep disturbances.

The effects of sleep and anesthesia on memory reveal fundamental differences between the two states. People awaken from sleep with the sense that time has passed, and sleep plays an important role in memory processing and consolidation.[22,23] Upon emergence from general anesthesia, patients often describe feeling like no time had passed since induction, even after many hours of surgery. It has been reported that formation of new memories during

emergence does not occur until patients can maintain sustained wakefulness.[24] Anesthetics administered after a learning task impair memory consolidation and disrupt hippocampal activity.[25–28] It is evident that general anesthetics hamper learning and memory, whereas sleep has beneficial effects on memory formation and consolidation.

EEG Findings in Sleep and General Anesthesia

A comparison of the frontal electroencephalogram (EEG) during natural sleep and general anesthesia reveals some shared features, but also many state- and drug-specific differences. Upon sleep onset, there is an increase in frontal slow (<1 Hz) and delta (1–4 Hz) oscillations, with frontal areas synchronizing earlier than other cortical areas.[29] The three stages of human NREM sleep are further characterized based on unique EEG features such as high amplitude k-complexes, and sleep spindles in the 12–16 Hz range (Fig. 1A).[17,30] The most prominent EEG feature shared between natural sleep and general anesthesia is the presence of large amplitude slow and delta oscillations.[30,31] Slow-delta oscillations can be induced by dexmedetomidine, propofol, and ether anesthetics,[32–35] and partly originate from a loss of excitatory inputs from the brainstem arousal nuclei to the cortex.[30]

Dexmedetomidine, a selective α_2-adrenergic receptor agonist, produces EEG findings most closely resembling NREM sleep (Fig. 1B–C). Spindles, which are commonly observed in NREM Stage 2, are also present in the frontal EEG during dexmedetomidine sedation, with peak power around 13 Hz.[34,36,37] At higher doses that produce deeper sedation, spindles disappear and slow-delta oscillations dominate the EEG, similar to NREM Stage 3 sleep.[36,38]

Propofol enhances inhibitory neurotransmission by potentiating the activity of GABA at synaptic and extrasynaptic $GABA_A$ receptors.[9] Compared to dexmedetomidine, propofol produces larger amplitude slow oscillations representative of longer periods of neuronal silence and enhanced disconnection from the environment.[33,34] Upon loss of consciousness with propofol, there is an anteriorization of alpha power from the occipital cortex to the frontal cortex that is reversed upon return of consciousness.[39–41] Unlike sleep spindles that are intermittent and brief, propofol induces continuous alpha (8–12 Hz) oscillations.[39,42] Propofol also increases functional connectivity between the anterior and posterior cingulate cortices.[33] At very high doses, propofol produces burst suppression, a pattern of intermittent bursts of activity punctuated by electrical silence, a pattern that is not observed during natural sleep (Fig. 1D).

Ether anesthetics such as isoflurane and sevoflurane are known to modulate several important molecular targets to produce neuronal inhibition, including $GABA_A$ receptors, glutamate receptors, and two-pore domain potassium channels.[43] Like propofol, sevoflurane increases slow-delta and alpha oscillations. The latter are focused in the frontal cortex and have a peak around 10 Hz during unconsciousness.[35,44] However, at higher doses sevoflurane also increases theta (4–8 Hz) oscillations that are not observed during propofol anesthesia.[35] At very high doses, ether anesthetics also produce burst suppression like propofol.

Ketamine is a dissociative anesthetic that is thought to act primarily by blocking excitatory NMDA-type glutamate receptors.[4] At high doses that induce unconsciousness, ketamine produces a unique "gamma burst" pattern consisting of gamma (30–70 Hz) oscillations alternating with slow-delta oscillations.[45,46] Although gamma oscillations can be associated with wakeful consciousness, those observed during ketamine anesthesia are distinct and may be the result of ketamine preferentially inhibiting cortical interneurons, resulting in increased pyramidal neuronal activity.[45] In addition, ketamine-induced EEG patterns may originate from decreased brainstem inputs to the thalamus and cortex or from the direct inhibitory actions of ketamine on the thalamus.[45]

In summary, while many anesthetics produce slow, delta, and alpha oscillations that resemble certain EEG features of NREM sleep, each drug class produces a unique constellation of neurophysiological signatures that are dose- and state-specific. Compared to other anesthetics and sedatives, dexmedetomidine produces EEG patterns that are most similar to NREM sleep, suggesting that the states may share similar underlying mechanisms at the level of neural circuits. Whereas, high doses propofol and ether anesthetics produce burst suppression, and ketamine produces "gamma burst" activity, none of which are observed during natural sleep.

Cortical Effects of Anesthesia and Sleep

During sleep, unconsciousness is primarily driven by sleep-active, subcortical areas that inhibit ascending arousal nuclei.[47,48] This inhibition decreases the release of excitatory neurotransmitters—such as acetylcholine, histamine, and norepinephrine—and reduces cortical activation.[17] In contrast, anesthetic agents can act directly on a variety of cortical receptors, decreasing the spontaneous activity of cortical neurons[49] and the sensitivity of those neurons to subcortical inputs.[50]

Many recent studies have revealed that the direct actions of anesthetics on cortical neurons —or "top-down" mechanisms—are important for anesthetic-induced unconsciousness.[51] Anesthetics may induce unconsciousness by direct actions on cortical neurons, which have been demonstrated in cortical slice preparations. Isoflurane, enflurane, halothane, propofol, pentobarbital, and ketamine have all been shown to inhibit spontaneous action potentials in cortical neurons.[49,52] Isoflurane decreases the amplitude of excitatory synaptic potentials, [50,53] while ketamine preferentially inhibits NMDA receptors on GABAergic interneurons, leading to disinhibition of pyramidal neurons.[54–56]

Activity of genetically distinct neuronal types is also affected in ways that causally influence the cortical EEG. For instance, parvalbumin-positive and pyramidal neurons fire most actively during the peak of the slow oscillation during both sleep and chloral hydrate anesthesia.[57,58] Such parallels between sleep and anesthesia may underlie the similar slow and delta oscillations observed in both states that are traditionally thought to underlie loss of consciousness.[59] The cortical actions of anesthetics may point to a shared mechanism that produces anesthetic-induced unconsciousness: despite affecting diverse molecular targets, propofol, ketamine, and sevoflurane each reduce frontal-to-parietal brain communication.[60]

Anesthetics likely induce unconsciousness at both the subcortical and cortical levels, acting on subcortical areas to decrease arousal while simultaneously affecting the cortex to degrade the contents of consciousness.[61] In support of this hypothesis, the delivery of carbachol to the prefrontal cortex of rats mimics the stimulation of the subcortical ascending cholinergic inputs to the cortex and restores wakefulness during sevoflurane anesthesia.[62] However, carbachol delivery does not restore high gamma (85–155 Hz) connectivity between cortical areas, suggesting that the contents of consciousness remain disrupted.[63] Additionally, anesthetics modulate information exchanges between auditory stimuli and the primary auditory cortex action potentials that are not linked to the transition to loss of consciousness. [64] Together, these results suggest that direct actions on the cortex play a critical role in anesthetic-induced unconsciousness.

Subcortical Circuits Underlying Anesthesia and Sleep

Based on their profound inhibitory effects on the brain, systemically administered general anesthetics were historically thought to function by widespread neural suppression. This notion was challenged by a study that identified a focal zone in the rat midbrain that produced rapid and reversible loss of consciousness after microinjections of pentobarbital.[8] Referred to as the mesopontine tegmentum anesthetic locus (MPTA), this region (Fig. 2) has since been implicated in sleep[65] and described as a consciousness "switch" for anesthesia.[66] While not all anesthetics are equally impacted by MPTA lesions,[67] there is substantial evidence supporting the "shared circuits hypothesis" of anesthesia and sleep.

The role of the ventrolateral preoptic nucleus (VLPO, Fig. 2) in promoting sleep has long been supported by early investigations of neural activity across arousal states, and from lesion studies.[67,68] Advanced optogenetic, pharmacogenetic, and RNA sequencing techniques have further characterized the sleep-promoting neurons in the VLPO, which send inhibitory projections to arousal circuits to both induce and maintain sleep.[69–71] While GABAergic anesthetics have been shown to activate sleep-promoting VLPO neurons,[72,73] lesion studies have yielded conflicting results. Ablating the VLPO attenuates loss of righting induced by propofol,[74] but effects on isoflurane are inconsistent with reports showing both increased and decreased sensitivity, possibly due to the long-term sleep disruptions caused by VLPO lesions.[73,75] More recently, selective targeting of GABAergic and glutamatergic VLPO neurons using designer receptors has confirmed that isoflurane does not rely on the VLPO to induce loss of consciousness, in contrast to natural sleep.[71] Similarly, the median preoptic nucleus (MnPO), a region both functionally and structurally connected to the VLPO,[76] initiates and maintains NREM sleep but not isoflurane-induced unconsciousness.[71]

Another inhibitory brain region that may be involved in both general anesthesia and sleep is the thalamic reticular nucleus (TRN), which is involved in NREM sleep[68] and generates spindle oscillations.[77] TRN stimulation further suppresses cortical activity during isoflurane anesthesia,[68] and increases sensitivity to propofol through $GABA_B$ receptors.[78,79] A recent study found a novel group of GABAergic and glutamatergic neurons in the supraoptic nucleus (SON) of the hypothalamus that was activated by multiple anesthetics and that promoted NREM sleep.[80] Using modern genetic techniques, the group also identified neurons which serve as a common substrate for both anesthesia and analgesia in the central

amygdala,[81] illustrating the potential for new tools to advance our understanding of the neural circuitry underlying anesthesia and sleep.[82]

Investigations of the lateral habenula (LHb), a region that modulates midbrain dopaminergic neurotransmission, have demonstrated its involvement in facilitating NREM sleep,[100,101] as well as maintaining circadian rhythms,[83–85] homeostatic sleep regulation,[86] and NREM sleep stability.[87] A variety of general anesthetics activate LHb neurons, including propofol, ketamine, pentobarbital, and chloral hydrate,[72,88] and inhibiting LHb glutamate release reduces sensitivity to propofol. These findings implicate brain areas downstream from the LHb in anesthetic induction.[87] The LHb sends projections to multiple regions including the GABAergic rostromedial tegmental nucleus (RMTg), which in turn sends inhibitory projections to dopamine neurons in the ventral tegmental area (VTA).[89,90] Although studies of the RMTg have been limited in the context of sleep and anesthesia, it appears to play a role in NREM sleep.[90] Furthermore, inhibition of its downstream targets, the dopaminergic VTA and substantia nigra pars compacta, promotes sleep,[90–92] and selectively activating a subpopulation of GABAergic VTA projections to the lateral hypothalamus increases anesthetic depth.[93] Another target of the VTA implicated in sleep is the core of the nucleus accumbens (NAc),[94] which regulates NREM sleep.[94,95] Interestingly, although $GABA_A$ agonists infused into the NAc do not induce unconsciousness, they do increase sensitivity to halothane anesthesia.[96]

Additionally, general anesthetics directly inhibit wake-active nuclei, such as the tuberomammilary nucleus (TMN) and locus coeruleus (LC). The TMN is the only brain site containing histaminergic neurons,[97] which are active during waking periods and quiescent in sleep. Both $GABA_A$ receptor activation[98] and NMDA receptor antagonism[99] in the TMN promote NREM sleep. Likewise, GABAergic anesthetics inhibit TMN neural activity.[72] Although TMN lesions increase sensitivity to isoflurane, they do not affect pentobarbital or propofol anesthesia.[100]

The LC is comprised of arousal-promoting noradrenergic neurons, which are most active during wake, less active during NREM sleep, and silent during REM sleep.[101] Optogenetic studies have demonstrated that reduced LC firing promotes memory consolidation and decreases sensory-evoked awakenings during REM sleep.[102,103] Both propofol and isoflurane inhibit LC neural firing.[104] However, while stimulating LC neurons impairs isoflurane-induced unconsciousness,[105] LC inhibition is not required for propofol's effects.[74] Moreover, halothane has no impact on LC firing rate.[104]

Lastly, although cholinergic neurons in the laterodorsal and peduculopontine tegmentum (LDT, PPT) drive the transition from NREM to REM sleep,[106] they are not activated by a broad range of anesthetics, including isoflurane, pentobarbital, and ketamine.[72] Overall, while anesthesia and sleep share some overlapping subcortical mechanisms (Fig. 2), there are many differences that are often anesthetic-specific. For a comprehensive review of the putative sites of action of distinct anesthetics on the brain, please see the review by Brown, *et al.*[107]

Neural Circuits of Arousal and Anesthetic Emergence

Recently, there has been considerable interest in investigating the role of subcortical arousal circuits in anesthetic emergence.[108] The central medial thalamus, part of the ascending reticular activating system, has been studied widely in the context of arousal and anesthetic emergence. Neurons in the central medial thalamus are inhibited by anesthetics.[109–112] Microinjection studies of the central medial thalamus have shown that activating nicotinic acetylcholine receptors or blocking Kv1 potassium channels increases neural activity and reverses sevoflurane-induced unconsciousness.[110,113,114] Microinjections of norepinephrine into the central medial thalamus during propofol anesthesia lead to EEG signs of cortical arousal and accelerates time to emergence.[115] These findings suggest that activating neurons in the central medial thalamus during anesthesia can shorten time to emergence and, in some cases, reverse anesthetic-induced unconsciousness.

The arousal-promoting orexinergic system also has notable effects on emergence. Suppressing orexinergic signaling delays emergence from ether anesthetics, but not the alkane anesthetic halothane.[104,116–119] Plasma orexin-A levels increase in humans upon emergence from propofol and sevoflurane anesthesia, consistent with the notion that the orexinergic system is involved in emergence.[120,121]

The cholinergic system, which is critical for promoting arousal, also modulates emergence from anesthesia. Intracerebroventricular microinfusions of drugs promoting cholinergic neurotransmission during continuous isoflurane anesthesia lead to EEG and behavioral signs of arousal, although return of righting reflex was not observed.[122] Microinjecting the cholinergic agonist, carbachol, into the prefrontal cortex restores the righting reflex and other conscious behaviors in rats during sevoflurane anesthesia,[62] suggesting that cholinergic neurotransmission plays a critical role in emergence.

Enhancing arousal-promoting dopaminergic neurotransmission from the ventral tegmental area (VTA)—particularly via activation of dopamine type 1 (D_1) receptors—has been shown to restore consciousness in rodents anesthetized with propofol and ether anesthetics.[123–129] Of the multiple dopaminergic projections from the VTA, inputs to the nucleus accumbens provide the most potent arousal stimulus from natural sleep.[92]

The parabrachial nucleus is a glutamatergic brainstem arousal nucleus involved in wakefulness and anesthetic emergence, with projections to the basal forebrain, thalamus, and arousal-promoting orexinergic neurons of the lateral hypothalamus.[130] Parabrachial neurons are suppressed by anesthetics and activated during emergence.[130,131] Optogenetic, chemogenetic, and electrical stimulation of parabrachial neurons generates EEG and behavioral evidence of arousal during sleep and general anesthesia by propofol, isoflurane and sevoflurane.[130–132]

Neuromodulators have also been found to play a role in emergence. Studies have shown that adenosine antagonists, including caffeine, can facilitate emergence from isoflurane and propofol anesthesia in humans and rodents.[133–135] More recently, a study in humans found that intravenous caffeine accelerated time to emergence from isoflurane anesthesia.[136]

Finally, the benzodiazepine antagonist flumazenil has been shown to have modest effects on accelerating emergence time from general anesthesia in rodents and humans.[137–139]

Discussion

General anesthetics are a diverse class of drugs that appear to produce unconsciousness by targeting numerous neural circuits in cortical and subcortical regions. Each anesthetic produces distinct cortical EEG signatures that are dose-dependent, which suggests that multiple neural circuits contribute to producing unconsciousness. This is evident when comparing dissimilar agents such as the GABAergic anesthetic propofol and the NMDA receptor antagonist ketamine. However, the existence of similar neural oscillations during general anesthesia and sleep (e.g. slow-delta oscillations) suggests that some general anesthetics converge onto sleep-active neural circuits to induce unconsciousness. However, general anesthetics also directly inhibit cortical neurons, as well as subcortical arousal-promoting neurons. All these actions likely contribute to suppress wakefulness. In addition, activating arousal nuclei accelerates emergence and restores consciousness in anesthetized subjects.

Recent advances in neuroscience such as optogenetics and chemogenetics have enabled detailed studies of the neural circuit mechanisms underlying anesthesia and sleep.[82] Recently, a new genetic technique of tracking, targeting, and stimulating specific neural populations has allowed the targeting of specific behavior-associated brain loci, including "anesthesia-activated neurons" (AANs) located in the supraoptic nucleus of the hypothalamus.[140] These AAN neurons were not only activated by a range of anesthetics, but their activation also promoted slow-wave sleep, illustrating the potential of these emerging techniques to further advance our knowledge of the neural circuitry underlying complex phenomena. Gaining insights into the neural circuitry underlying general anesthesia and sleep will likely lead to improved methods for controlling arousal states in the perioperative setting.

Acknowledgements:

Glossary of Terms:

AANs
Anesthesia-activated neurons

D_1
Dopamine type 1

EEG

Electroencephalogram

Kv1 potassium channels
Voltage-gated potassium channel family 1

LHb
Lateral habenula

LH
Lateral hypothalamus

LDT, PPT
Laterodorsal and peduculopontine tegmentum

LC
Locus coeruleus

MPTA
Mesopontine tegmentum anesthetic locus

NMDA
N-methyl-D-aspartate

NREM
Non-rapid eye movement

NAc
Nucleus accumbens

PB
Parabrachial nucleus

REM
Rapid eye movement

RMTg
Rostromedial tegmental nucleus

SON
Supraoptic nucleus

TRN
Thalamic reticular nucleus

TMN
Tuberomammilary nucleus

VTA
Ventral tegmental area

VLPO

Ventrolateral preoptic nucleus

GABA$_A$ receptors

γ-aminobutyric acid type A receptors

GABA$_B$ receptors

γ-aminobutyric acid type B receptors

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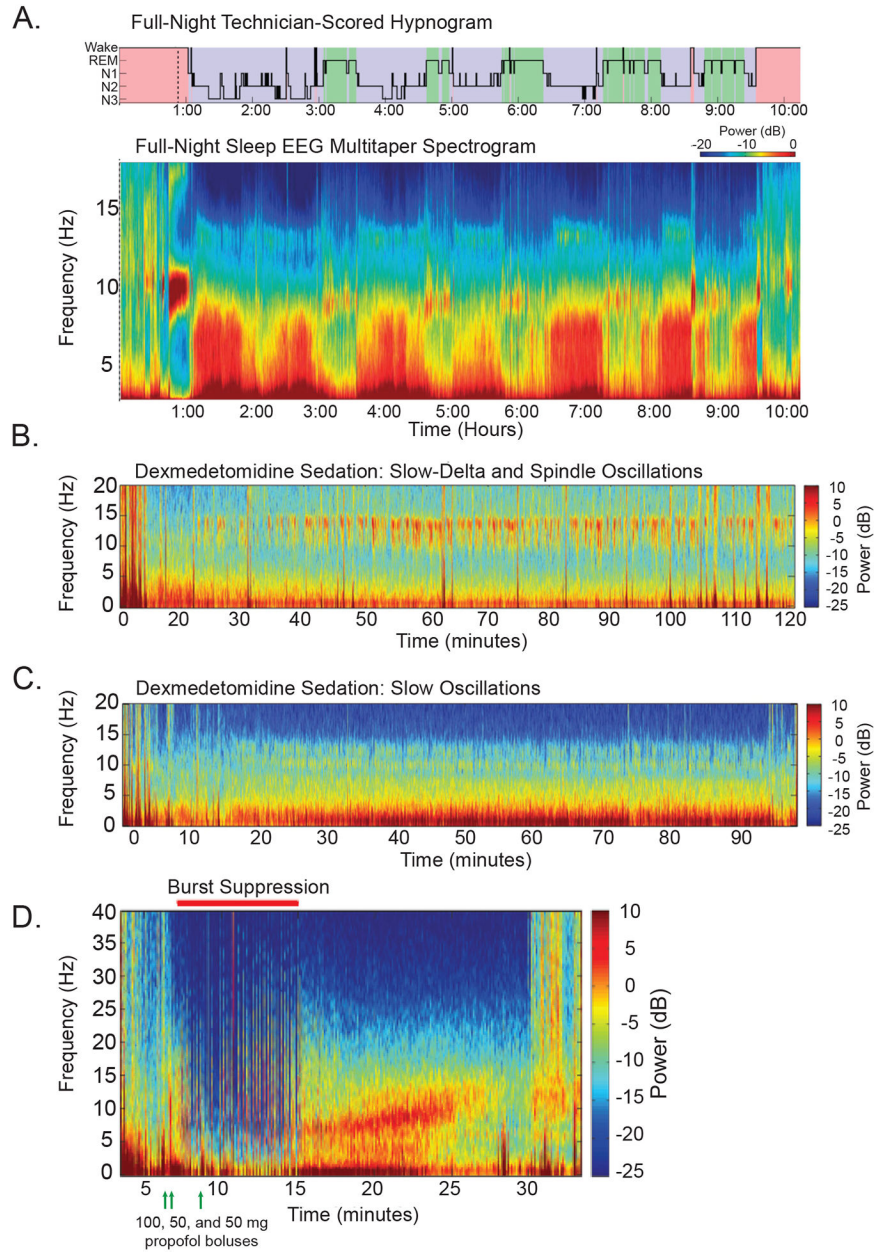
Figure 1.
Electroencephalographic features distinct to general anesthesia and sleep. A comparison of frontal EEG recordings from humans during general anesthesia and sleep reveal similarities and differences in the neural oscillations observed. A) A full night's natural sleep is shown as a spectrogram (lower panel) across hours of the night with the corresponding hypnogram (upper panel) identifying the stages of wake, rapid eye movement (REM) sleep, and non-rapid eye movement (NREM) stages 1–3 sleep (N1-3). The pattern of progressing sleep stages can be seen as cyclic increases in power (warmer red colors) for frequencies <10 Hz. Some sleep spindles can be seen at 12–15 Hz during the N1-N2 stages of sleep. B) An EEG of a patient receiving a continuous infusion of low dose dexmedetomidine (0.65 µh kg^{-1} h^{-1}) shows mild sedation in which spindles (9–15 Hz) and increased power of slow-delta

(0.1–4 Hz) oscillations can be seen. The presence of spindles and slow-delta activity is similar to those features seen during NREM stage 2 sleep. C) An EEG of a patient receiving a continuous infusion of higher dose dexmedetomidine (0.85 μg kg^{-1} h^{-1}) shows moderate to deep sedation in which slow-delta oscillations are primarily increased. D) A bolus dose of propofol (100 mg, first green arrow) at minute 3 causes the EEG to transition to increased slow oscillation power. Two additional propofol boluses (50 mg each, green arrows) cause the EEG to shift to a burst suppression pattern from minutes 8 to 17. Afterward, the EEG shifts again to increased slow-delta and alpha (9–12 Hz) oscillation power (minute 17–25), until the patient begins to emerge at 24 minutes and the slow-delta and alpha oscillation power begins to decrease. Part A is adapted with permission from Prerau MJ, Brown RE, Bianchi MT, Ellenbogen JM, Purdon PL. Sleep Neurophysiological Dynamics Through the Lens of Multitaper Spectral Analysis. *Physiology.* 2017;32(1):60–92. Parts B-D are adapted with permission from Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures. *Anesthesiology.* 2015;123(4):937–960. Abbreviations: Electroencephalogram (EEG), non-rapid eye movement (NREM), and rapid eye movement (REM).
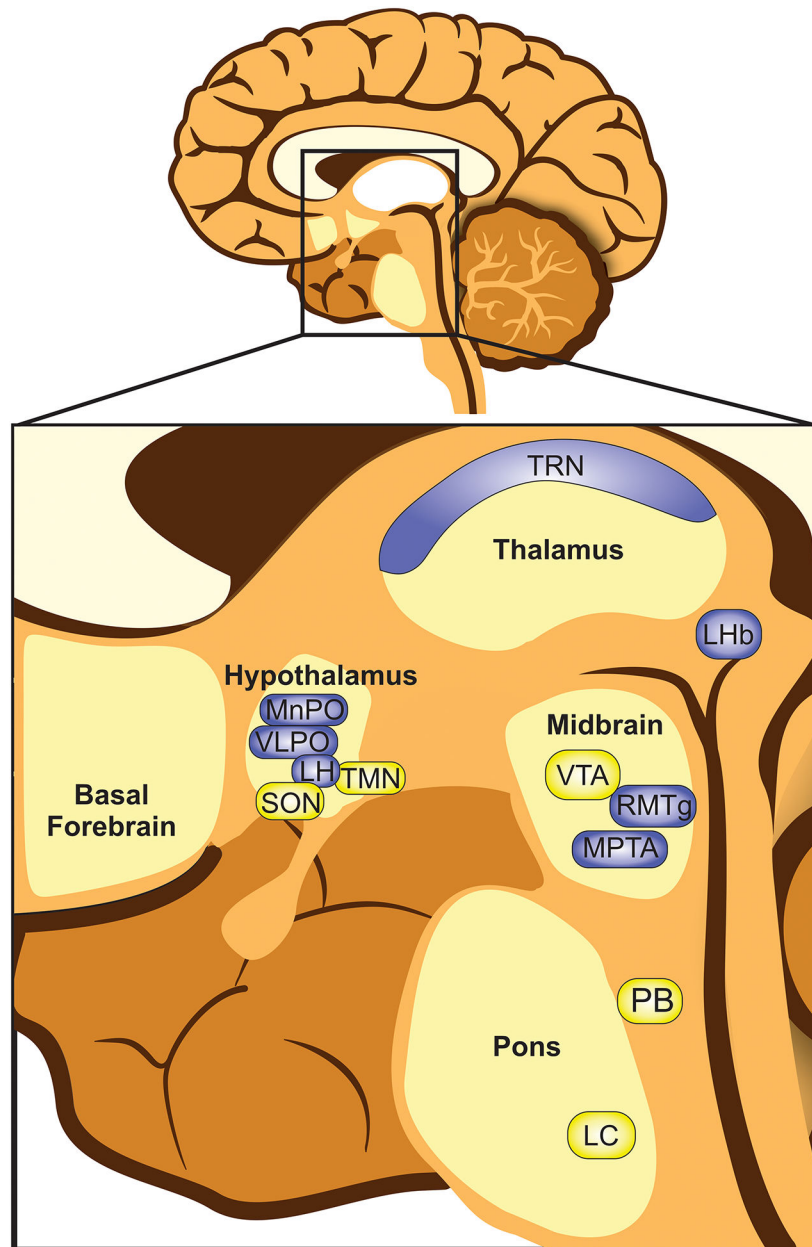
Figure 2.
Subcortical areas implicated in the regulation of sleep and anesthesia-induced loss of consciousness. Subcortical areas are shown in the magnified inset of a human brain. Loss of consciousness generally involves silencing wake-active nuclei (yellow) and stimulating sleep-active nuclei (blue). Hypothalamic nuclei: lateral hypothalamus (LH), ventrolateral preoptic area (VLPO), median preoptic area (MnPO), supraoptic nucleus (SON) and the tuberomammillary nucleus (TMN). Thalamic nuclei: thalamic reticular nucleus (TRN). Lateral habenula (LHb). Midbrain: ventral tegmental nucleus (VTA), rostromedial tegmental nucleus (RMTg), and mesopontine tegmental anesthesia area (MPTA). Pons: locus coeruleus (LC) and parabrachial nucleus (PB). Note: not all structures are located midline. For a

comprehensive review of the putative sites of action of distinct anesthetics on the brain, please see the review by Brown, *et al.*[107]

Table 1.

A comparison of general anesthesia and sleep:

	Natural Sleep	**General Anesthesia**
Loss of consciousness?	Yes	Yes
Reversible?	Yes	Yes
Arousable?	Yes- with sufficient external stimuli	No
Cyclical/Ultradian rhythm?	Yes	No
Susceptible to homeostatic pressures?	Yes	Maybe
Can relieve sleep pressure?	Yes	Maybe
Memory formation?	Important for memory processing and consolidation	No
Sense of time passing?	Yes	No