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Neural oscillations demonstrate that general anesthesia and sedative states are neurophysiologically distinct from sleep

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Abstract

General anesthesia is a man-made neurophysiological state comprised of unconsciousness, amnesia, analgesia, and immobility along with maintenance of physiological stability. Growing evidence suggests that anesthetic-induced neural oscillations are a primary mechanism of anesthetic action. Each anesthetic drug class produces distinct oscillatory dynamics that can be related to the circuit mechanisms of drug action. Sleep is a naturally occurring state of decreased arousal that is essential for normal health. Physiological measurements (electrooculogram, electromyogram) and neural oscillatory (electroencephalogram) dynamics are used to empirically characterize sleep into rapid eye movement sleep and the three stages of non-rapid eye movement sleep. In this review, we discuss the differences between anesthesia- and sleep-induced altered states from the perspective of neural oscillations.

Introduction

The first public demonstration of ether anesthesia took place at the Massachusetts General Hospital in 1846 [1]. Ever since, general anesthesia (GA) has been essential for the safe and humane conduct of surgical and invasive diagnostic procedures [2,3]. GA is a reversible drug-induced state comprised of unconsciousness, amnesia, analgesia, and immobility with maintenance of physiological stability [3]. In the United States, intravenous hypnotics (propofol) or modern day derivatives of ether (desflurane, isoflurane, sevoflurane) are typically administered to produce GA or sedative states [4-6]. These anesthetics modulate the gamma amino-butyric acid A ($GABA_A$) receptor, and other receptor targets [4-6]. Like sleep, GA and sedative states are associated with altered levels of arousal [3,4]. Thus, it not surprising that sleep is a common, albeit incorrect, metaphor for referring to anesthesia-induced states.

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Sleep is a natural occurring state of decreased arousal – crucial for normal cardiovascular, immune and cognitive function – that is actively generated by centers in the brainstem, hypothalamus, and basal forebrain [7-10**]. Physiological measurements (electrooculogram, electromyogram) and neural oscillatory dynamics that are readily visible in the electroencephalogram (EEG) are used to empirically characterize sleep into rapid eye movement (REM) sleep and the three stages of non-rapid eye movement (NREM) sleep, which we denote as N1, N2 and N3. This empirical characterization of sleep into different stages provides a framework that currently guides clinical and basic science research studies of sleep mechanisms [7-10**]. Non-REM sleep stages reflect brain inactivation, and are linked to synaptic plasticity and memory formation [7]. REM sleep, which is most commonly associated with dreaming, has been linked to memory consolidation and emotional regulation [7].

Anesthetic drug action in brainstem arousal nuclei suggests a partial mechanism to explain GA and sedative states [11-16]. Significant simultaneous modulation of activity at other targets in the central nervous systems, including the thalamus and cortex [17-24], helps explain why GA is a more profound behavioral state of decreased arousal compared to sleep. It also explains why anesthetics significantly affect sensory, memory encoding, and cognitive processing circuits [4]. The differences between the neural oscillatory dynamics of GA and sleep alone make clear that GA and sleep are neurophysiologically distinct brain states. In this review, we discuss the differences between anesthesia- and sleep-induced altered states from the perspective of neural oscillations.

1. Sleep stages and their associated Electroencephalogram Oscillations

During sleep, the human brain cycles between non-REM and REM sleep stages [7]. Sleep typically begins with stage N1, transitions to stage N2 followed by stage N3 and on to REM sleep. The cycle then begins again and is repeated approximately every 90 to 120 minutes. Each of these sleep stages, or a combination, may be important for specific health benefits [7]. N1 sleep is characterized by the loss of occipital alpha (8-12 Hz) oscillations that are associated with relaxed wakefulness, and decreased beta (13-25 Hz) oscillation power (Fig. 1A) [7]. N2 sleep is characterized by slow-delta oscillations, K-complexes, and sleep spindle oscillations (12-16 Hz) (Fig. 1B) [7,25]. K-complexes are transient low-frequency oscillations that reflect reduced cortical neuronal activity [7,25]. Spindle oscillations reflect rebound bursting in thalamocortical neurons [7,25]. Slow-delta oscillations, which are larger in amplitude than N2 sleep slow oscillations, dominate N3 sleep (Fig. 1C) [7,25]. Slow-delta oscillations are a result of profound cortical and thalamic hyperpolarization [7,25]. They likely result from decreased brainstem inputs to the thalamus and cortex due to GABAergic and galanergic inhibition of brainstem arousal nuclei [7-10]. REM sleep is associated with an activated EEG pattern that is comprised of mixed frequencies, and the absence of K-complexes or sleep spindles (Fig. 1D) [7,25].

2. EEG Oscillations During General Anesthesia

2.1. Slow-delta oscillations

Slow-delta oscillations are a shared feature of sleep and GA (Figs. 1,2). Recent studies suggest that slow-delta oscillations identical to those observed *in vivo* require an intact thalamocortical network [26]. This is consistent with the slow-delta oscillations that were first observed in cortical EEG by Frederic Bremer in the 1930s when he performed a surgical transection at the level of the mesencephalon in cats [27]. This brain preparation, which severed excitatory brainstem inputs to the thalamus and cortex, was termed cerveau isolé (isolated cerebrum) [27].

Slow-delta oscillations are also observed when GA is induced or maintained with anesthetics (propofol, ethers) that facilitate inhibitory post-synaptic currents (IPSCs) by enhancing $GABA_A$ receptor decay-time and conductance (Fig. 2A,B) [3,4,19,22**,28**-33]. Similar to sleep, a mechanism to explain these GABAergic slow-delta oscillations likely involves loss of excitatory inputs from brainstem arousal centers to the cortex [7,10**]. However, numerous lines of evidence suggest that inhibition of brainstem arousal nuclei that send excitatory inputs to the cortex is not sufficient to explain GA-induced slow-delta oscillations.

Sleep slow-delta oscillations are synchronous with relatively brief periods of inactivity in cortical neurons [34]. In contrast, slow-delta oscillations observed under propofol-induced slow-delta oscillations are asynchronous with prolonged periods of inactivity in cortical neurons [19]. A source localization study of propofol GA and sleep described more putative cortical sources for propofol GA slow-delta oscillations compared to sleep [31]. This suggests that significantly greater enhancement of IPSCs in cortical circuits could explain in part the functional differences between sleep and GA-induced slow-delta oscillations.

An empirical clinical observation supports the notion that GA slow-delta oscillations result from significant enhancement of IPSCs in cortical circuits. The amplitude of GA slow-delta oscillation increases in a dose dependent fashion until a plateau is reached [32], after which, increased drug administration results in burst suppression, which is characterized by brief bursts of spikes, sharp waves, or slow waves of relatively high amplitude alternating with periods of relatively flat EEG, termed isoelectricity (Fig. 2C) [3,20,22**]. Further drug increases results in a brain state that is characterized by only isoelectric periods [3,20,22**]. Notably, burst suppression and isoelectricity are brain states of relative cortical quiescence that are not observed during normal sleep or cerveau isole preparations [27]. Rather, they are closely associated with cortical pathologies such as diffuse anoxic brain injury, hypothermia and Ohtahara syndrome [3,35].

2.2. Alpha Oscillations

Alpha oscillations are not a characteristic feature of non-REM sleep [7]. This is highlighted by the fact that Hans Berger, the inventor of electroencephalogram, first distinguished an “awake restful with eyes closed” state from sleep by associating occipital alpha oscillations (8-12 Hz) with wakefulness [36]. Although not a part of the empirical characterization of sleep, short bursts of alpha power, which likely reflect micro-arousals or complete arousals, have been described during REM sleep [25**,37,38]. Anesthetics that enhance IPSCs

through $GABA_A$ receptor targeting induce and maintain strong alpha oscillations (Fig. 2A,B). However, in contrast to the occipital alpha oscillations that are associated with wakefulness, $GABA_A$ associated alpha oscillations are frontally dominant, larger in amplitude, and highly coherent [18,21,29,30,33,39,40].

A model to explain the generation of anesthesia-induced coherent alpha oscillations suggests that an increase in $GABA_A$ decay-time and conductance results in cortical alpha oscillatory dynamics [18]. At the same time, increased $GABA_A$ decay-time and conductance in the thalamus leads to enhanced rebound spiking of relay cells, strengthening the intrinsic alpha oscillatory dynamic of the thalamus [18]. The net result is reciprocal thalamic-cortical alpha oscillation coupling [18]. It is important to note that GA-induced alpha oscillations occur in a frequency range and spatial distribution that is similar to sleep spindles (12-16 Hz) [18,21,29,30,33,39,40]. However, sleep spindles have a transient envelope with a refractory period of several seconds [7,25], whereas GA-induced alpha oscillations do not exhibit such a refractory period [18,21,29,30,33,39,40]. Further, GA alpha oscillations have only been found to occur with slow-delta oscillations [21,22,28-30,32,33,40], and the amplitude of GA alpha oscillations is modulated significantly by the phase of the slow-delta oscillations [33].

2.3. Gamma Oscillations

Gamma oscillations (> 30Hz) or “active EEG” are a characteristic feature of REM sleep (Fig. 2D) [7,25]. Ketamine, which is an N-methyl-D-aspartate (NMDA) receptor antagonist commonly administered to produce GA, is also associated with gamma oscillations. However, REM sleep gamma oscillations are distinct from ketamine-GA gamma oscillations. Ketamine effectively blocks excitatory NMDA receptors on fast-spiking cortical interneurons to down regulate interneuron activity, and decrease GABA release at the interneuron-pyramidal neuron junction [43]. The net result of decreased cortical inhibitory tone is markedly excited pyramidal neuronal activity [43]. A prediction of the ketamine-induced “excited” cortical state is high-frequency neural oscillations.

Consistent with this prediction gamma oscillations, which are tightly constrained to a narrow frequency band (~30-45 Hz), are a characteristic feature of ketamine-GA is (Fig. 2D) [41*]. Ketamine-GA gamma oscillations alternate with slow-oscillations in a characteristic “gamma-burst” pattern (Fig. 2D) [41**,44]. With decreasing drug concentrations, the slow-delta oscillations are first to dissipate [41**]. It is possible that the ketamine slow-delta oscillations result in part from reduced activity of glutamatergic projections from the parabrachial nucleus to the basal forebrain and the thalamus [10**], or by direct drug action in the thalamus [45,46]. However, mechanisms to explain the dynamics of ketamine-induced slow and gamma oscillations are an area of active investigation.

3. EEG Oscillations during anesthesia-induced brain states of sedation

Compared to GA, sedation is a closer behavioral approximation to sleep because arousal to consciousness can be achieved from sedated states. However, sedatives do not produce physiological sleep.

3.1. Beta Oscillations

Beta oscillations are associated with sedative states induced by anesthetics that enhance IPSCs through $GABA_A$ receptor targeting (Fig. 3A) [33,47,48]. In contrast, non-REM sleep is associated with a decrease of beta oscillations (Fig. 1) [49]. A model to explain sedation-induced beta oscillations suggests that they originate similar to the mechanism proposed for anesthesia-induced alpha oscillations [17]. A modest increase in $GABA_A$ decay-time and conductance causes low threshold spiking (LTS) interneuron antisynchrony that patterns pyramidal cell spiking into a beta rhythm [17]. Potentiation of the GABA synaptic currents causes a reduction in a slow potassium membrane current (M-current) that causes an increase in LTS cell excitability and rebound spiking [17]. Thus, gradually increasing the dose of a GABAergic anesthetic results in a continuous oscillatory peak dynamic that begins in the beta frequency range during sedative states and travels to the alpha frequency range during GA [33]. Beta oscillations are also a conserved neurophysiological feature of sleep medications that enhance GABA IPSCs [50-53]. Therefore, it is not surprising that these medications are associated cognitive side effects that closely parallel those that are also associated with anesthetics [54*].

3.2. Dexmedetomidine-Induced Spindle Oscillations and Slow Oscillations

Spindle oscillations with transient-time domain morphology, similar to N2 sleep spindles, are observed during sedation with dexmedetomidine (Fig. 3B). Dexmedetomidine binds to pre-synaptic a2a adrenergic receptors on neurons projecting from the locus ceruleus (LC), causing hyperpolarization and decreased norepinephrine release [55-60]. A consequence of decreased adrenergic signaling through presynaptic mechanisms is the loss of adrenergic inhibition of neurons in the pre-optic area of the hypothalamus [3,4,7,10**]. Activation of these neurons, and their subsequent inhibition of midbrain and pontine arousal centers, along with decreased cortical excitation produce the dexmedetomidine sedation state [3,4]. Thus, the activity patterns of various arousal nuclei during dexmedetomidine-induced sedation are similar to sleep [55-60]. Therefore, with respect to amplitude and frequency characteristics, it is not surprising that dexmedetomidine slow-delta and spindle oscillations resemble N2 sleep features [29,61,62]. We note that dexmedetomidine-induced K-complexes have not been described [29,61,62]. Clinically, dexmedetomidine is the only sedative agent that has been demonstrated to reduce the incidence of delirium, [63-66] an acute brain dysfunction not explained by a preexisting neurocognitive disorder.

4. Conclusions and Future Directions

The principal sleep medications (i.e. Zolpidem, benzodiazepines), which are among the most widely sold pharmaceuticals, act by enhancing IPSPs at $GABA_A$ receptors. Although these drugs may act on the brainstem arousal nuclei (Fig. 4a), they also directly act on cortical circuits in a manner that is similar to GABAergic anesthetic drugs (Fig. 4b). At equisedative doses, the most prominent neural oscillatory dynamic that reflects GABAergic anesthetic-drug action on cortical circuits are beta oscillations [17,18,21]. Thus, beta oscillations and the neurocognitive side effects (i.e. amnesia, complex sleep related disorders) associated with the principal sleep medications are most likely due to undesired actions of these agents in cortical circuits [50-54*]. The NMDA receptor antagonist ketamine acts differently in

cortical circuits to produce gamma oscillations (Fig. 4c) [3,4]. Ketamine-induced hallucinations are also suggestive of direct drug action in cortical circuits [3,4]. Dexmedetomidine produces spindle and slow-delta oscillations that share features with N2 sleep oscillatory dynamics (Fig. 3b) [29,61,62]. This closer neurophysiological approximation to N2 sleep compared to other anesthetics may be due to the fact that dexmedetomidine alters cortical dynamics indirectly by decreasing ascending noradrenergic inputs to the thalamus and cortex (Fig. 4d) [3,4].

We conclude that the principal anesthetic drugs and sleep medications do not produce physiological sleep (Fig. 4e). Thus, it is unlikely that anesthetics may be administered to fully compensate for sleep need or to confer benefits that are attributable to sleep. Furthermore, the neural oscillations produced by these agents likely contribute to drug-induced brain dysfunction.

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Highlights

- Neural oscillations provide a framework for comparing general anesthesia and sleep
- Anesthetic drugs do not induce the physiological neural oscillations of sleep
- Non-physiological neural oscillations may explain drug-induced neurocognitive dysfunction

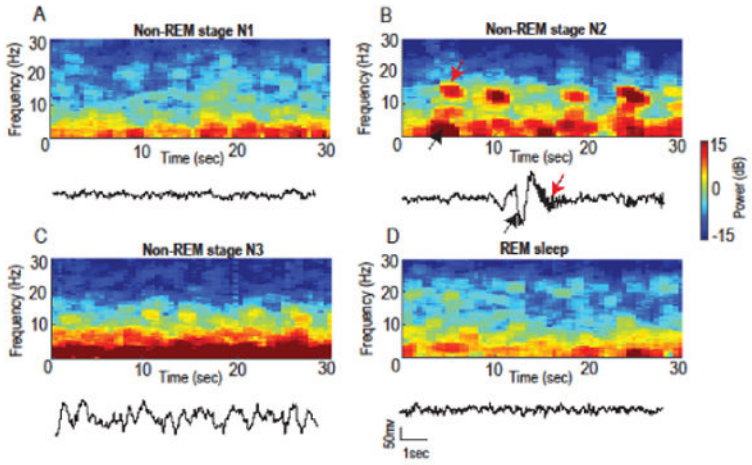

Figure 1.

Sleep stages have distinct EEG signatures that result from differences in the neural circuits that are involved in their generation and maintenance. The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. These signatures are also visible in the raw EEG signal (black traces represent first 10 seconds of data shown in spectrogram). A. EEG slowing and the loss of the awake state alpha oscillations are distinguishing features of N1 sleep. B. Slow-delta (0.1-4Hz) oscillations, K-complexes (black arrow on spectrogram and raw EEG), and spindle oscillations (12-16 Hz, red arrow on spectrogram and raw EEG) are distinguishing features of N2 sleep. C. The predominance of slow-delta oscillations is a distinguishing feature of N3 sleep. D. Activated “saw-tooth” EEG without the awake-state alpha oscillations are distinguishing features of REM sleep.

dB; decibels; EEG, electroencephalogram; Hz, Hertz; N1, non-rapid eye movement stage 1 sleep; N2, non-rapid eye movement stage 3 sleep; N3, non-rapid eye movement stage 3 sleep; REM, rapid eye movement.

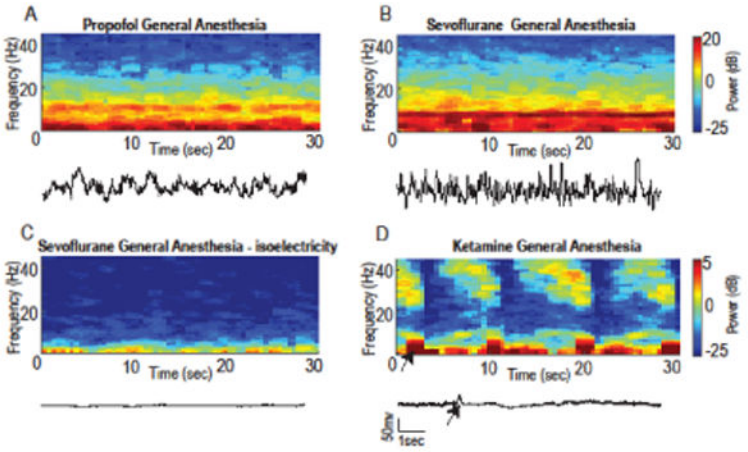

Figure 2.

General Anesthesia. Each anesthetic drug has a different EEG signature that results from differences in the neural circuits that are involved in state generation and maintenance. The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. These signatures are also visible in the raw EEG signal (black traces represent first 10 seconds of data shown in spectrogram). A. Slow-delta (0.1-4 Hz) and alpha (8-12 Hz) oscillations are the predominant EEG signatures of propofol-general. This finding is consistent with the EEG signatures of other intravenous $GABA_A$ receptor anesthetics (i.e. benzodiazepines, etomidate) during general anesthesia. B. Slow-delta oscillations, theta (4-8 Hz), and alpha oscillations are the predominant EEG signatures of sevoflurane-general anesthesia. This finding is consistent with the EEG signatures of other modern day derivatives of ether during general anesthesia (desflurane, isoflurane). The close similarities between the EEG signatures of propofol and modern day derivatives ether anesthesia has been suggested to result from enhancement of $GABA_A$ receptor IPSCs. C. Isoelectricity is observed when high doses of anesthetics such as sevoflurane and propofol are administered. Significantly enhancement of IPSCs in cortical circuits is a mechanism to explain isoelectricity. D. Gamma oscillations (-30-45 Hz) that are interspersed with slow-delta (black arrow on spectrogram and raw EEG) oscillations are the predominant EEG signatures of general anesthesia maintained with the NMDA receptor antagonist ketamine. dB; decibels; EEG, electroencephalogram; $GABA_A$, gamma amino butyric acid A; Hz, Hertz; IPSCs, inhibitory post synaptic currents; NMDA, N-methyl-D-aspartate.

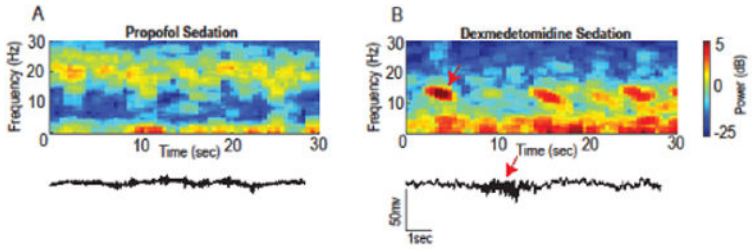

Figure 3.

Sedation States. Each anesthetic drug has a different EEG signature that results from differences in the neural circuits that are involved in state generation and maintenance. The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. These signatures are also visible in the raw EEG signal (black traces represent first 10 seconds of data shown in spectrogram). The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. A. Beta (-13-30 Hz) oscillations are the predominant EEG signature of sedation maintained by propofol and other medications that enhance $GABA_A$ receptor IPSCs (i.e. ether anesthetics, benzodiazepines, Zolpidem). B. Slow-delta and spindle (12-16 Hz; red arrow on spectrogram and raw EEG) oscillations are the predominant EEG signatures of dexmedetomidine-sedation. These dexmedetomidine-induced EEG signatures very closely approximate the EEG signatures of N2 sleep (Fig. 1B).

dB; decibels; EEG, electroencephalogram; $GABA_A$, gamma amino butyric acid A; Hz, Hertz; IPSCs, inhibitory post synaptic currents;

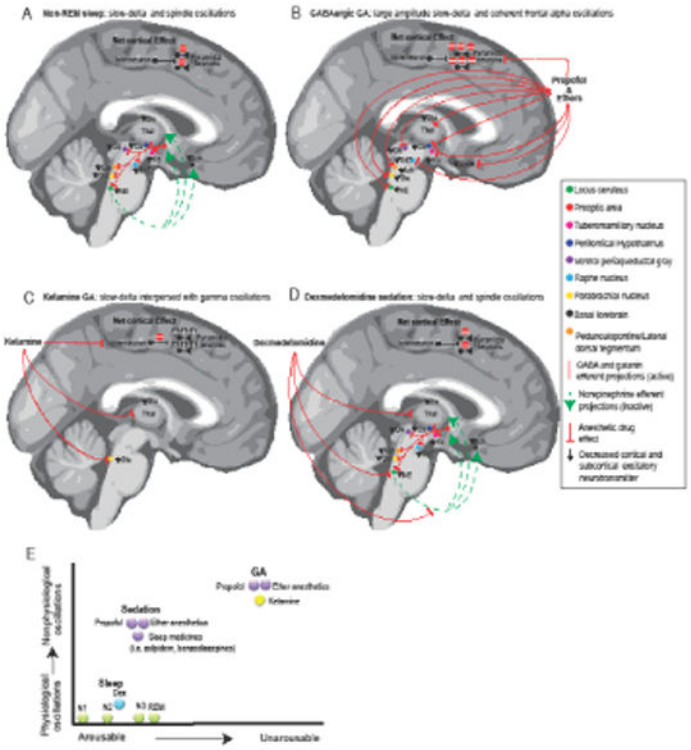

Figure 4.

Anesthetics produce unconsciousness by acting on subcortical and cortical circuits. A. A mechanism to explain non-REM sleep is GABA- and galanin- mediated inhibition of brainstem arousal nuclei from sleep active cells in the preoptic area of the hypothalamus. Decreased firing rate of locus ceruleus cells and norepinephrine release from efferent projections to the preoptic area is a putative mechanism to explain activation of sleep active cells and non-REM sleep initiation. Decreased norepinephrine to the cortex, thalamus, and basal forebrain also contribute to decreased arousal. Other sites that are not depicted (i.e. cells in the parafacial zone) may play important roles in non-REM sleep. B. Propofol, ether anesthetics, and other medications that significantly enhance $GABA_A$ receptor IPSCs decrease arousal by enhancing the inhibitory activity of GABAergic interneurons in the cortex and thalamus. They also inhibit the major excitatory brainstem nuclei that project directly and indirectly to the cortex. C. Ketamine likely decreases the level of arousal by directly targeting the thalamus and also by blocking glutamatergic projections from the parabrachial nucleus to the thalamus. In the cortex, ketamine decreases arousal by blocking inhibitory interneurons, leading to markedly excited pyramidal neurons. This markedly excited state is associated with increased blood flow, cerebral glucose metabolism, and hallucinations. D. Dexmedetomidine impairs the release of norepinephrine from projection neurons from the LC to the POA, basal forebrain, and thalamus. Similar to sleep, this activates the endogenous sleep promoting cells in the POA. These sleep active cells inhibit of brainstem arousal nuclei. Dexmedetomidine may also impair the level of arousal by targeting autoreceptors on the LC and adrenergic receptors in other brain regions such as the thalamus. E. The principal anesthetic and sedative agents do not produce physiological sleep.

$GABA_A$, gamma amino butyric acid A; IPSCs, inhibitory post synaptic currents; LC, locus ceruleus; non-REM, non-rapid eye movement; POA, preoptic area