Published in final edited form as:
Curr Anesthesiol Rep. 2013 March 1; 3(1): 1–9. doi:10.1007/s40140-012-0007-0.

Sleep and Anesthesia Interactions: A Pharmacological Appraisal

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Abstract

Anesthetics have been used in clinical practice for over a hundred years, yet their mechanisms of action remain poorly understood. One tempting hypothesis to explain their hypnotic properties posits that anesthetics exert a component of their effects by “hijacking” the endogenous arousal circuitry of the brain. Modulation of activity within sleep- and wake-related neuroanatomic systems could thus explain some of the varied effects produced by anesthetics. There has been a recent explosion of research into the neuroanatomic substrates affected by various anesthetics. In this review, we will highlight the relevant sleep architecture and systems and focus on studies over the past few years that implicate these sleep-related structures as targets of anesthetics. These studies highlight a promising area of investigation regarding the mechanisms of action of anesthetics and provide an important model for future study.

Keywords

sleep; anesthesia; NREM; REM; slow wave

Introduction

The anesthetic state is characterized by alteration in level of consciousness, decreased responsiveness to external stimuli, amnesia, decreased muscle tone, and altered autonomic responsiveness. The degree to which each of these effects is achieved depends both on the anesthetic agent and its dose. Individual anesthetics have variable efficacy in eliciting each of the components of the anesthetic state suggesting that subtle, yet important differences exist in their molecular mechanisms of action.

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Disclosure
M.T. Scharf: none; M.B. Kelz: compensation from Galleon Pharmaceuticals, Inc. for, serving as a consultant.

The precise way anesthetics work remains mysterious. In this review, we focus upon anesthetic actions in the neuronal systems known to modulate sleep and arousal. An obvious parallel is that in both sleep and the anesthetic state there is a decreased response to external stimuli and a decreased level of consciousness. This raises the intriguing possibility that the hypnotic component of general anesthesia may arise via specific interactions in the brain with networks that regulate sleep and wakefulness [1, 2]. Our aim is to highlight important studies published in the past several years.

Neuroimaging studies have proven to be a powerful tool in studying the minimal neuronal substrates required for conscious perception and the effects of anesthetic agents in disrupting consciousness [3–5]. A recent landmark study addressed the question of which brain regions are critical for reconstitution of consciousness following exposure to two distinct anesthetics, dexmedetomidine or propofol. Dexmedetomidine is uniquely analogous to sleep in that it has the property of permitting awakening during anesthesia merely by using environmental stimuli. By investigating these two anesthetics the authors were able to distinguish changes in regional brain activity underlying anesthetic emergence from epiphenomena caused by varying anesthetic drug levels. The authors demonstrated that the structures activated when consciousness returned were phylogenetically old and included the anterior cingulate cortex, thalamus, hypothalamus and locus coeruleus/parabrachial area in the brainstem [6]. Surprisingly, they did not discover a necessary widespread reactivation of neocortex. Rather, the anesthetic-induced recruitment of regions with a known role in modulation of sleep-wake suggests a commonality between the way sleep and hypnosis are achieved [7].

Sleep is a relatively quiescent state characterized by decreased behavioral activity and responsiveness to stimuli. Far from a monolithic process, sleep involves an interplay of numerous neuroanatomical regions and systems. The interaction of these systems produces distinct stages comprised of wake, the various stages of non-rapid eye movement sleep (NREM), and rapid eye movement sleep (REM). The deeper stages of NREM sleep are characterized by increased cortical synchronization, manifested as slow waves. In contrast, wake and REM display cortical desynchronization. The increased cortical synchronization seen during deeper stages of NREM, often expressed as the relative amount of slow wave activity, delta power, is of particular interest as the delta power has been shown to correlate with the homeostatic drive to sleep [8].

Given the similarities between anesthesia and sleep, an interesting question that arises is: can anesthetics substitute for sleep? If so, what elements of sleep are restored by anesthesia? One way to address these questions is to characterize how anesthetics affect subsequent sleep and how anesthetics alter the response to sleep deprivation [9].

Rodents exposed at the beginning of the rest phase to sevoflurane, isoflurane or halothane anesthesia for 6 hours all showed increased REM sleep time and decreased REM latency during the active period [10]. These results suggest that REM sleep debt accrues during sevoflurane, isoflurane or halothane anesthesia and consequently, that these volatile anesthetics do not substitute for REM sleep. Conversely, no NREM sleep debt accrued following the 6-hour exposure to isoflurane or sevoflurane suggesting that these two anesthetics (unlike halothane) may indeed substitute for NREM sleep. Similarly, when rats were exposed to isoflurane following 24 hours of selective REM sleep deprivation or to sevoflurane following 12 hours of total sleep deprivation, there was no dissipation of REM sleep debt during anesthesia. Rather, REM sleep rebound discharged over the typical time course but was delayed until cessation of anesthetic exposure [7, 9]. However, as seen in the aforementioned study, NREM sleep debt did dissipate during sevoflurane anesthesia and

post-anesthesia delta power was significantly reduced indicating a complete recovery of NREM sleep during sevoflurane [9].

In contrast to volatile anesthetics, rats exposed to intravenous propofol anesthesia following sleep deprivation had no differences in recovery sleep compared to non-anesthetized control rats [11] suggesting that propofol may discharge both NREM and REM sleep debt comparable to natural sleep. Moreover, sleep debt did not appear to accrue during prolonged propofol exposure, suggesting that propofol might satisfy both NREM and REM sleep requirements [12]. Taken together, these data show that different anesthetics have distinct interactions with the sleep, arousal, and homeostatic control systems.

Consistent with the role of anesthetics as fulfilling some of the homeostatic functions of sleep, the increase in slow wave activity following a 4-hour sleep deprivation was blunted after a 1-hour exposure to hypnotic doses of isoflurane or desflurane. As hypnotic doses of isoflurane and desflurane ordinarily produce an electroencephalogram (EEG) enriched in continuous slow wave activity, desflurane titrated to isoelectric EEG depth produced the same result arguing that the anesthetic itself, rather than specific anesthetic-evoked EEG features, altered the post-sleep deprivation course [13]. While anesthetic-induced slow waves can share a similar origin and propagation pattern as those of endogenous slow wave sleep, it should be noted that subtle, yet potentially critical differences do exist in these two types of slow waves [14].

Additional evidence supporting a relationship between anesthetics and the endogenous sleep machinery comes from experiments assessing anesthetic sensitivity following sleep deprivation. Sleep deprivation reduced the time required for sevoflurane-induced loss of righting reflex, a behavioral surrogate for loss of consciousness in animals [9]. Furthermore, sensitivity to isoflurane was increased following selective REM sleep deprivation [15], extending the known effects of sleep deprivation in enhancing the sensitivity to anesthetics [16]. These results demonstrate that increasing sleep drive increases sensitivity to anesthetics and support an interaction between endogenous sleep drive and anesthesia.

A detailed discussion of the neurobiology of sleep is beyond the scope of this review and the reader is referred to excellent recent reviews [17–19]. We will review the recent literature on anesthetic modulation of sleep areas by neuroanatomical system.

Brainstem

The brainstem contains numerous ascending neurotransmitter systems that play a vital role in mediating arousal. Two brainstem areas in particular, the pontine reticular formation (PRF) and the locus coeruleus (LC), are well studied as potential mediators of anesthetic action. The PRF is an important structure in promoting the cortical activation associated with wake and REM [1, 20, 21]. Neurotransmitters in the PRF such as adenosine, orexin/hypocretin, glutamate, GABA, and acetylcholine are each known to modulate arousal state [1, 22–27].

During REM sleep, GABA levels in the PRF decreased and acetylcholine levels increased [28]. These results show a relationship between GABA and acetylcholine in the PRF, and REM sleep, raising the possibility that modulation of these neurotransmitters may modulate sleep. Indeed, administration of the GABA agonist muscimol into the PRF increased wake and decreased NREM and REM sleep; administration of the $GABA_A$ antagonists bicuculline or gabazine, increased NREM and REM and decreased wake [29–32]. Interestingly, bicuculline also increased acetylcholine in the PRF [32], suggesting that GABA and acetylcholine are functionally related in modulating sleep. In fact, administration of the acetylcholinesterase inhibitor neostigmine into the contralateral PRF decreased GABA in

the PRF and altered EEG spectrum to resemble REM sleep [28]. These studies argue that acetylcholine release in the PRF causes a local decrease in GABA, which, in turn, leads to decreased binding of $GABA_A$ receptors and increased sleep, particularly REM sleep.

Studies with isoflurane support the notion that the PRF is also an important site of anesthetic action. Isoflurane decreased GABA levels in the PRF [33]. Behaviorally, the $GABA_A$ antagonist bicuculline injected into the PRF prolonged isoflurane-induced hypnosis [32]. Similarly, pharmacologic administration into the PRF of an agent that decreased GABA levels decreased the time needed for isoflurane to induce loss of righting reflex; the opposite effect was observed after administration of an agent that increased GABA levels in the PRF [33].

In summary, lower GABA and higher acetylcholine in the PRF promote hypnosis. These effects are mediated by the $GABA_A$ receptor. Isoflurane decreases GABA in the PRF, and agents that decrease GABAergic tone in the PRF potentiate the hypnotic effect of isoflurane. These observations are consistent with the hypothesis that isoflurane promotes hypnosis by decreasing GABA levels in the PRF.

The LC is the largest source of noradrenergic neurons in the brain, sends diffuse projections throughout the neuraxis, and has been implicated in regulating attention and arousal [34]. The LC exhibits state-specific firing patterns with the highest levels occurring during wakefulness [35]. Acute optogenetic activation of the LC is sufficient to immediately awaken sleeping animals, while inhibition of the LC prevents hypocretin/orexin-induced awakening [36, 37]. Pharmacologic, genetic, and lesion studies, have all implicated the LC in altering anesthetic responsiveness to a variety of distinct anesthetics [38–40]. Activity in the LC was inhibited during exposure to many anesthetics including isoflurane, propofol, and dexmedetomidine [41–43]. However, the causal relationship between inhibition of the LC by dexmedetomidine and the ensuing onset of hypnosis has recently been called into question [38, 44, 45]. Nevertheless, several studies point to altered emergence when adrenergic signaling is disrupted. Chemical lesion of the noradrenergic neurons of the LC decreased the duration of ketamine anesthesia whereas it increased the duration of thiopental anesthesia. The noradrenergic content in the cortex and hippocampus was correlated with the duration of anesthesia for ketamine and inversely correlated with duration of anesthesia for thiopental [40]. This study suggests that the LC dampens thiopental anesthesia whereas it facilitates ketamine anesthesia and argues for a role of the LC in mediating the action of anesthetics.

A role for the dopaminergic system in modulating anesthetic sensitivity has recently been proposed. While ventral tegmental area dopaminergic neurons do not exhibit state-dependent firing, electrical microstimulation of the ventral tegmental area, administration of dopamine D1 receptor agonists, or administration of methylphenidate, all actively induced emergence from anesthesia [46–49]. These studies argue for a role of the dopaminergic system in modulating hypnosis [50].

Hypothalamus

The preoptic area of the hypothalamus plays a prominent role in the regulation of sleep. The ventrolateral preoptic area (VLPO) has a distinct population of GABAergic neurons that are sleep-active [51, 52]. In contrast, the adjacent median preoptic nucleus contains a population of neurons that also have increased activity during sleep but, unlike sleep-active VLPO neurons, these neurons are also activated prior to sleep onset and have been implicated in tracking sleep debt [18]. The VLPO neurons send projections to numerous regions including prominent projections to the histaminergic neurons of the tuberomammillary nucleus [52, 53]. In turn, the histaminergic neurons of the tuberomammillary nucleus send diffuse

projections in the brain including the cortex [54] and are active during wake [55]. The VLPO-tuberomammillary nucleus circuit has been implicated as an important sleep regulatory system (see below).

Several types of anesthetics including volatiles, propofol, barbiturates, and dexmedetomidine activate the VLPO and inhibit the tuberomammillary nucleus [41, 56–59]. Behaviorally, the $GABA_A$ receptor antagonist gabazine administered into the tuberomammillary nucleus attenuated anesthetic-induced hypnosis [41, 56], but genetic deletion of $GABA_A$ receptors in TMN did not affect behavioral sensitivity to anesthetics [60]. Direct delivery of anesthetics into TMN, unlike anesthetic microinjection into the brainstem [61], is not sufficient to cause hypnosis [56] and suggests that the TMN may not be critical for hypnosis.

Bilateral VLPO lesions led to a decrease in the c-Fos expression in the tuberomammillary nucleus induced by dexmedetomidine and attenuated the dexmedetomidine-induced increase in slow wave sleep [41]. These results suggest that dexmedetomidine hypnosis is accomplished, at least in part, by activating the sleep-active VLPO, which subsequently inhibits the cortical-activating areas. In rats with longstanding orexin-saporin lesions of VLPO, surprisingly, VLPO cell loss was correlated with a higher EEG burst-suppression ratio, decreased time to loss of righting reflex and increased time to recovery of righting reflex following isoflurane anesthesia, suggesting that VLPO loss led to *increased* sensitivity to isoflurane. However, the VLPO-lesioned animals also had significantly decreased total sleep time. In fact, the degree of sleep loss was correlated to the higher burst suppression ratio, the decrease in the time to loss of righting reflex, and the increase in the time to recovery of righting reflex [62]. These findings suggest that the degree of sleep loss predicts the sensitivity to anesthetics. In a study from our laboratory, isoflurane increased the c-Fos expression in VLPO to a level similar to that observed during spontaneous sleep and depolarized electrophysiologically-identified putative sleep-active VLPO neurons via the closure of a background potassium conductance. To directly assess the necessity of the VLPO in mediating the effects of isoflurane, the VLPO was lesioned with galanin-saporin and sensitivity to isoflurane was assessed at different time points after the lesion. Interestingly, lesion of the VLPO decreased the sensitivity to isoflurane as assessed by loss of righting reflex at 6 days post-lesion. However, at 24 days post-lesion, the lesioned mice showed an increased sensitivity to isoflurane [59]. This disparity is likely due to the fact that the VLPO-lesioned mice developed an increased sleep debt over time and, as has been demonstrated, sleep debt can increase sensitivity to anesthetics.

Another prominent hypothalamic sleep regulatory system consists of lateral hypothalamic hypocretin/orexin neurons. The hypocretin/orexin neurons project diffusely throughout the brain [63] and are active during wake [64, 65]. Importantly, genetic deletion of the hypocretin/orexin gene causes narcolepsy [66, 67]. Activation of hypocretin/orexin neurons promotes wakefulness [37]. Inhibition of the hypocretin/orexin neurons might facilitate anesthetic induction, however it has actually been shown to markedly delay anesthetic emergence [68–71]. Indeed, isoflurane, sevoflurane, propofol, and pentobarbital, all decreased c-Fos expression in hypocretin/orexin neurons [42, 57, 68, 71]. Interestingly, this effect was not observed with dexmedetomidine or halothane [42, 43], thus confirming an agent-specific neuronal diversity of anesthetic action. Furthermore, propofol potentiated inhibitory GABA currents in hypocretin/orexin neurons. Behaviorally, the propofol-induced loss of righting reflex time was shortened after intracerebrovascular injection of hypocretin/orexin in rats [42], further supporting a role for hypocretin/orexin in facilitating emergence. A similar effect was observed with dexmedetomidine but not ketamine [42], suggesting that the arousing effect of administered hypocretin/orexin is specific to the encountered anesthetic mechanism (i.e, dexmedetomidine vs. ketamine).

Basal Forebrain

The basal forebrain is comprised of the magnocellular cholinergic system in the medial septum, nucleus basalis of Meynert, substantia innominata, and horizontal and vertical limbs of the diagonal band of Broca [72]. The basal forebrain sends diffuse projections, prominently cholinergic ones, that play a role in the cortical activation associated with wake and REM [72, 73]. Furthermore, the basal forebrain receives inputs from other sleep-related structures in the brain [18]. Therefore, the basal forebrain is also well-positioned to modulate the actions of anesthetics.

Indeed, rats with saporin lesion of basal forebrain cholinergic neurons had longer duration of loss of response to tail pinch and loss of righting after treatment with the anesthetics propofol or pentobarbital. Electrophysiologically, lesioned animals demonstrated increased delta power following propofol administration, an effect not observed in non-lesioned animals under these conditions. These observations suggest that the absence of basal forebrain cholinergic neurons promotes cortical synchronization and increased sensitivity to anesthetics. However, loss of these cholinergic neurons did not alter the duration of the response to tail pinch or righting after halothane [74]. These results implicate the cholinergic neurons of the basal forebrain in mediating sensitivity to propofol or pentobarbital, but not halothane. Furthermore, the lack of an effect of cholinergic lesion on sensitivity to halothane suggests that the activating influence of cholinergic neurons of the basal forebrain plays a role in mediating the effects of certain anesthetics, i.e. propofol and pentobarbital, and does not simply facilitate hypnosis in a non-specific manner.

The basal forebrain is one of the targets of histaminergic neurons of the tuberomammillary nucleus [54] and noradrenergic neurons of the LC [75]. Histamine in the basal forebrain would be expected to promote cortical activation. Indeed, in rats anesthetized with isoflurane, histamine injected into the nucleus basalis of Meynert decreased anesthetic-induced burst suppression. This effect was blocked by an H1 but not an H2, antagonist [76]. Similar results were obtained with norepinephrine. In rats under desflurane anesthesia, norepinephrine injection into the nucleus basalis of Meynert promoted transient behavioral arousal. Electrophysiologically, norepinephrine injection caused decreased delta power and increased cortical entropy, indicating increased cortical activation. In fact, the level of decreased delta activity in the frontal cortex predicted the level of behavioral arousal, which suggests that these phenomena were linked [77]. These studies show that injection of wake-promoting neurotransmitters in the basal forebrain can partially counteract the hypnotic actions of anesthetics.

In addition to the well-characterized circuitry of the basal forebrain, local adenosine has been implicated as an important regulator of the homeostatic drive to sleep [78]. Adenosine, a by-product of ATP degradation, increased in the basal forebrain following sleep deprivation [79, 80] and basal forebrain administration of adenosine increased NREM, REM, as well as delta power during NREM sleep [81, 82]. Similarly, administration of an agent that caused increased wake and decreased NREM and REM sleep was associated with decreased adenosine in the substantia innominata [83]. Therefore, modulation of adenosine in the basal forebrain is a potential mechanism for anesthetic-induced hypnosis.

Cumulatively, these studies highlight the relationship between the basal forebrain and anesthetics. Manipulation of the basal forebrain can alter the behavioral and electrophysiologic response to anesthetics. These studies suggest that the basal forebrain is part of the circuitry that can modulate anesthetic actions.

Thalamus

The thalamus acts as a relay station that gates sensory inputs to the cortex. The thalamus sends projections to, and receives projections from, the cortex. The interaction between the thalamus and cortex shapes the electrophysiologic characteristics of sleep [84]. Anesthetics can affect thalamocortical and reticular thalamic neurons that are important components of the sleep machinery. Specifically, both intravenous and volatile anesthetics including pentobarbital [85], propofol [86], halothane [87], and isoflurane [88, 89] inhibit thalamocortical neurons either directly or by interacting with reticular thalamic neurons. One of the most reproducible findings in human imaging studies is the anesthetic-induced deactivation of thalamus with loss of consciousness [90]. Loss of thalamocortical connectivity is considered a key event underlying loss of consciousness both during anesthesia and sleep [4, 91].

Modeling studies have addressed the thalamic role in anesthetic-induced hypnosis [92, 93]. In a study modeling human sleep, propofol-induced $GABA_A$ activation promoted thalamic involvement and cortical synchronization. Interestingly, the reticular nucleus of the thalamus, which sends prominent GABAergic projections to other thalamic nuclei, was able to synchronize disparate relay nuclei and thus, facilitate cortical synchronization over large areas of cortex [94]. This study suggests that propofol may induce hypnosis, at least in part, by acting on the thalamus.

As anesthetics can cause hyperpolarization of thalamocortical relay neurons, treatments which depolarize these neurons have been shown to reverse anesthetic hypnosis. Localized microinjection of the acetylcholine receptor agonist nicotine into the central medial thalamus antagonized sevoflurane anesthesia [95]. A similar transient behavioral arousal during sevoflurane or desflurane anesthesia was observed with central medial thalamic injection of an antibody to a potassium channel (Kv1.2), which would produce a depolarizing effect by impairing potassium efflux [96]. These studies show that direct activation of the thalamus can overcome the hypnosis of anesthesia and implicate the thalamus as another part of the circuitry that can mediate anesthetic action.

Cortex

From an evolutionary standpoint, the cerebral cortex is the most modern part of the brain and one that distinguishes phylogenetically advanced organisms from more primitive ones. Sleep is present in simple organisms, emphasizing that a highly specialized cerebral cortex is not required for sleep [97, 98]. However, the cortex is clearly modulated during sleep-wake as evidenced in the EEG. While maintaining the sleep-wake function is mostly accomplished by ascending neurotransmitter systems, anesthetics exert some of their effects by acting directly on cortical in addition to subcortical sites.

During sleep, there is a breakdown in effective connectivity with a loss of both spatial and temporal propagation of information across the cerebral cortex [99]. A similar breakdown in connectivity occurs with anesthetic-induced loss of consciousness [100]. However, whether disrupted connectivity is a direct effect of anesthetics upon the cortex or it arises as an indirect consequence of their action on subcortical sites, remains controversial. Nonetheless, breakdown in effective cortical connectivity is a feature common to both sleep and anesthetic-induced loss of consciousness, highlighting another similarity between these two states.

In the past few years, tremendous progress has been made in linking brain activity with altered states of consciousness. Imaging studies have revealed that a substantial level of activity persists in the posterior cingulate/precuneus, medial prefrontal, and temporoparietal

cortices in the absence of overt goal-directed tasks. These regions comprise what is called the default-mode network (DMN), as its activity is thought to reflect inwardly-directed conscious processing. During waking, activity in DMN is anti-correlated with activity in the lateral frontoparietal network that focus attention upon the external world [101]. In deep sleep, there is a weakening and partial decoupling of frontal and posterior areas of the DMN [102] as well as significant changes in the DMN-to-frontoparietal network integrity [103]. Anesthetic-induced unconsciousness is also associated with connectivity changes in intrinsic and extrinsic networks [4, 5, 104, 105]. However, it seems that persistent oscillations in the DMN across different states likely reflects an invariant, intrinsic organization of the brain [106, 107], and the manner sleep and anesthetics interact with this system remains an active area of investigation.

An emerging theme is that asymmetries arise in the direction of information transfer within the brain with loss of consciousness. A sentinel study in rodents assessing flow of information to and from the visual cortex found that feedback information in the gamma frequency band was preferentially inhibited during halothane or isoflurane anesthesia [108]. Importantly, congruent results were found in humans: feedback and feedforward connectivity were reduced by propofol or sevoflurane, but there was a greater reduction in the feedback of information [109, 110, 111]. As stated by Hudetz, in the anesthetized brain information is received, but not perceived. Although sleep and anesthesia share many parallels, these studies shed light on one key difference: the ability of environmental stimuli to cause arousal during sleep, but not anesthetic-induced hypnosis.

Conclusion

We are now only on the cusp of understanding how anesthetics exert their effects. Sleep and anesthesia share a number of important properties and the investigation of anesthetic action on the sleep regulatory structures in the brain provides a context by which to understand anesthetic action. There has been an explosion of research over the past few years implicating the structures in the brain that regulate sleep as being important targets of anesthetics. The fact that certain anesthetics can substitute for aspects of sleep and that sleep deprivation can alter anesthetic sensitivity highlights the intimate relationship between sleep and anesthesia. Further understanding of the interplay between sleep and anesthesia, including the similarities and differences, may have important implications in the treatment of sleep disorders and optimization of novel anesthetic agents.

Acknowledgments

The authors are supported by grant R01 088156 from the National Institute of General Medical Sciences (NIGMS).

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