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Neurochemical Modulators of Sleep and Anesthetic States

Christa J. Van Dort[1,2], **Helen A. Baghdoyan**[1], and **Ralph Lydic**[1,2]

[1]Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan, USA

[2]Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan, USA

The regulation of consciousness is a fundamental question that has a long and storied association with philosophy. Today, consciousness studies command a central position in contemporary neuroscience[1-3]. The complexities of consciousness studies and the pressing demands of clinical care have led most anesthesiologists to focus on research problems with pragmatic outcomes. Yet the ability to accurately assess and manipulate states of consciousness with anesthetic drugs is the ultimate concern for every surgical patient and anesthesia provider. This volume recognizes consciousness studies as a legitimate and accessible concern for anesthesiology. This chapter considers the relationship between molecules known to regulate the loss of consciousness during anesthesia and molecules that regulate the loss of consciousness during physiological sleep. Sleep neurobiology has been shown to provide unique insights into the study of consciousness[4-6]. The proposal[7,8] that neuronal networks that evolved to generate states of sleep and wakefulness also contribute to the generation of anesthetic states has been supported by many laboratories[9-19]. There is evidence that the loss of consciousness during sleep is caused, in part, by the loss of functional connectivity and information processing[20]. Functional connectivity is critically dependent on neurochemical transmission. Therefore, this chapter focuses on intravenous and volatile anesthetics that have been shown to alter endogenous neurotransmitters known to regulate states of consciousness. Reviews on sleep from an anesthesiology perspective are available elsewhere[8,21-24].

The present overview is derived from a September 2007 PubMed title search of peer-reviewed papers linking 10 commonly used anesthetics with 11 endogenous molecules known to regulate states of consciousness. The list of intravenous anesthetics includes propofol, pentobarbital, ketamine, etomidate, and midazolam. The list of volatile anesthetics includes isoflurane, sevoflurane, nitrous oxide, xenon, and desflurane. The 11 endogenous molecules known to regulate sleep/wake states[25] include acetylcholine (ACh), gamma-aminobutyric acid (GABA), glutamate, adenosine, dopamine, histamine, serotonin, norepinephrine, hypocretin/orexin, glycine, and galanin. This 10 by 11 matrix was searched from 1950 to 2007 and identified 660 references. A search of the last 10 years (1997 to 2007) revealed a total of 192 references (Tables 1 and 2).

I. Intravenous Anesthetics Alter Neurotransmitters that Regulate Sleep and Wakefulness

The endogenous neurotransmitters and neuromodulators ACh, GABA, glutamate, the monoamines (dopamine, histamine, serotonin, and norepinephrine), and adenosine contribute to generating and maintaining states of sleep and wakefulness. The following section

Correspondence and Proofs to: Ralph Lydic, Ph.D., Department of Anesthesiology, University of Michigan, 7433 Medical Sciences Bldg. I, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-5615, Voice: (734) 647-7831, Fax: (734) 764-9332, E-Mail: rlydic@umich.edu.

selectively highlights studies investigating the effects of the most cited agents (Table 1), propofol and ketamine, on these neurotransmitter systems.

1. Propofol

Propofol was successfully introduced into clinical practice during the late 1980s. Propofol is a small hydrophobic alkylphenol derivative and its anesthetic actions are mediated primarily via the $GABA_A$ receptor[26]. Propofol also alters the actions of other sleep-related neuromodulators. As reviewed below, the anesthetic effects of propofol also may be mediated by its effects on monoaminergic, GABAergic, glutamatergic, cholinergic, and adenosinergic neurotransmission in brain regions known to regulate sleep and wakefulness.

1.1 Monoamines—A consistent finding from studies of sleep neurobiology is that monoamines promote wakefulness (reviewed in[25]). Serotonin containing neurons in the dorsal raphe, norepinephrine containing neurons in the locus coeruleus, and histaminergic neurons in the tuberomammillary nucleus discharge at their fastest rates during wakefulness, slow their discharge rates during non-rapid eye movement (NREM) sleep, and are silent during rapid eye movement (REM) sleep. This wake-on/sleep-off discharge pattern is consistent with a role for these monoaminergic neurotransmitters in promoting wakefulness. Interestingly, although dopaminergic neurons in the ventral tegmental area do not change their discharge rates across the sleep-wake cycle, a large body of evidence demonstrates that dopamine also promotes wakefulness (reviewed in[12]).

The cell groups described above provide monoaminergic input to the prefrontal cortex, which contributes to the regulation of behavioral arousal[27]. Serotonin levels in rat frontal cortex decrease during sleep compared to wakefulness[28], as would be predicted by the wake-on/sleep-off discharge pattern of serotonergic neurons. Similarly, norepinephrine levels decrease during REM sleep compared to wakefulness in rat medial prefrontal cortex[29]. Dopamine levels in rat medial prefrontal cortex also vary across the sleep wake cycle such that dopamine levels are greater during the electroencephalographically (EEG) activated states of wakefulness and REM sleep compared to the EEG deactivated state of NREM sleep[29]. In the locus coeruleus and amygdala the release of norepinephrine and serotonin decreases with sleep whereas dopamine release does not change, demonstrating that neurochemical changes during sleep are neurotransmitter and brain region dependent[30].

The elimination of waking consciousness by propofol may be due, in part, to suppression of monoaminergic transmission in multiple arousal promoting brain regions. Dopamine levels in the nucleus accumbens are greater during wakefulness and REM sleep[29] than during NREM sleep, and propofol decreases dopamine release in the nucleus accumbens[31,32]. However, propofol increases dopamine and serotonin metabolites in rat somatosensory cortex[33]. This finding suggests that propofol increases the release of these transmitters in rat somatosensory cortex. Dopamine and serotonin each can cause excitation or inhibition, depending upon the type of receptor they activate. Thus, it will be important to combine electrophysiological and neurochemical studies to provide a complete understanding of the effects of anesthetics on monoaminergic neurotransmission in specific brain regions.

Systemic administration of epinephrine, norepinephrine, and dopamine decreases arterial blood propofol concentrations and increase cardiac output in sheep under continuous propofol infusion, suggesting that monoamines can reverse propofol anesthesia by altering circulation[34]. Systemic administration of the alpha2 receptor agonist clonidine to rats increases the duration of anesthesia produced by propofol and decreases prefrontal cortex norepinephrine release[35]. This same study also found that systemic administration of the alpha2 receptor antagonist yohimbine decreases the duration of propofol anesthesia and increases cortical norepinephrine release. Given the important role of monoamines in promoting wakefulness, a

productive area for future studies will be to determine whether propofol inhibits monoaminergic neurotransmission in the prefrontal cortex and the locus coeruleus. The mechanisms of anesthetic action, similar to the neurobiology of sleep, will be better understood as the effects of anesthetics on neurotransmission are elucidated on a brain region-by-region basis.

1.2 GABA—GABA is an inhibitory amino acid involved in actively generating sleep[25] and anesthesia[36]. The $GABA_A$ receptor is made up of 5 subunits. The alpha, beta, and gamma subunits all have been shown to be involved in the regulation of sleep and anesthesia. Most $GABA_A$ receptors are composed of 2 alpha, 2 beta, and 1 gamma subunit[37]. The combination of receptor subtypes that comprise the $GABA_A$ receptor varies in different brain regions and may account for differential effects of drugs in each region (reviewed in[38]). For example, the ability of propofol to activate $GABA_A$ receptors varies with the type of alpha subunit (alpha1 versus alpha6)[39]. The endogenous molecule GABA and the anesthetic propofol act at different subtypes of the $GABA_A$ receptor beta2 subunit (MW 54 versus 56 kDa) to produce differential effects on naturally occurring sleep versus anesthesia[40].

Administration of $GABA_A$ receptor agonists or antagonists to brain regions regulating states of consciousness can either increase or decrease wakefulness, depending on the brain region into which the drugs are administered. For example, enhancing GABAergic inhibition in brain regions that promote arousal, such as the posterior hypothalamus, locus coeruleus, and dorsal raphe nucleus, produces sleep (reviewed in[12]). In contrast, administering GABAmimetics into the pontine reticular formation increases wakefulness and decreases sleep[41-43]. Anesthetics enhance GABAergic neurotransmission by increasing chloride ion conductance and causing neuronal hyperpolarization (reviewed in[38]). In the brain stem locus coeruleus and dorsal raphe nucleus, GABA levels are highest during REM sleep[44] and, as noted above, electrophysiological data show that locus coeruleus and dorsal raphe neurons cease firing during REM sleep (reviewed in[25]). Propofol acting at $GABA_A$ receptors inhibits the firing of locus coeruleus neurons[45]. The time to propofol-induced loss of righting, used as a measure of sedation, is reduced by microinjecting a $GABA_A$ receptor antagonist into the tuberomammillary nucleus of the hypothalamus, a wakefulness promoting brain region[14]. This finding suggests that propofol causes its sedative effects, in part, by potentiating GABAergic inhibition of hypothalamic neurons that promote wakefulness. Similarly, intravenous administration of gabazine and picrotoxin, which block transmission at $GABA_A$ receptors, causes large increases in the ED_{50} for propofol induced immobility in rat[46]. These findings support the interpretation that immobility caused by propofol is mediated by $GABA_A$ receptors.

Propofol decreases regional cerebral glucose metabolism in rat[47] and human[48], and the extent of this depression varies by brain region. In humans, regional cerebral glucose metabolism in the cortex showed greater depression than in subcortical areas and the greatest depression within the cortex occurred in the left anterior cingulate and inferior colliculus[48]. Propofol enhances GABAergic neurotransmission[49] and the glucose metabolism data correlate with the high benzodiazepine receptor density in human cerebral cortex[50]. The brain regions in which propofol selectively alters cerebral metabolism provide targets for further localization of function studies aiming to identify the mechanisms by which propofol produces anesthesia.

1.3 Glutamate—There is considerable evidence that excitatory amino acids contribute to the regulation of both sleep- and anesthesia-induced losses of waking consciousness. Glutamatergic transmission in many brain regions is important for sleep and anesthesia. In the brainstem, the laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) nuclei contain neurons that contribute to REM sleep generation (reviewed in[12]). Microinjection of glutamate into the PPT induces waking and/or REM sleep depending on the concentration of injected glutamate[51]. Glutamate levels in the PPT are greater during wakefulness than during

NREM sleep or REM sleep[52], consistent with the interpretation that glutamate in the LDT and PPT promotes arousal. Further evidence that glutamate promotes wakefulness is shown by systemic administration of the glutamate receptor antagonist riluzole which increases NREM sleep and REM sleep in rats[53]. However, intracerebroventricular administration of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonists MK-801 and AP5 decreases REM sleep but does not change NREM sleep or wakefulness[54]. The present search of the literature identified no studies that quantified the effect of propofol on brainstem levels of glutamate.

Available data demonstrate that the role of glutamate in the regulation of consciousness also varies as a function of brain region. In one study, glutamate levels in the orbitofrontal cortex of rat were highest during REM sleep, decreased during wakefulness, and lowest during NREM sleep[55]. These data are consistent with the interpretation that glutamate promotes an activated cortical EEG. Glutamate levels did not change in the prefrontal cortex during NREM sleep and REM sleep compared to levels during wakefulness[29], suggesting that cortical glutamate is not involved in sleep regulation. REM sleep deprivation in the rat increased cortical glutamate levels[56] alternatively implying that glutamate in the cortex is somehow involved in the regulation of sleep. In the basal forebrain, microinjection of the glutamate receptor agonists NMDA or alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) increased wakefulness and gamma (30-60 Hz) EEG activity and decreased delta (1-4 Hz) EEG activity[57]. Microinjection of NMDA and AMPA into the cholinergic cell area of the basal forebrain also caused C-fos activation, a widely used marker of neuronal activity[57]. These results are consistent with the interpretation that glutamate in the basal forebrain promotes waking consciousness.

Data from many species and brain regions demonstrate that propofol decreases presynaptic, sodium channel-dependent, glutamate release in cortical, striatal, and hippocampal synaptosomes isolated from rats, mice, and guinea pigs[58,59]. Only one study showed that propofol did not change presynaptic glutamate uptake, binding, or transport in rat cortical isolated nerve terminal preparations[60]. Another study by the same group demonstrated that propofol did inhibit calcium dependent evoked glutamate release in rat cortical synaptosomes[61]. Considered together, these data suggest that propofol depresses glutamate neurotransmission but the exact mechanism has yet to be elucidated.

Both NMDA and AMPA receptors are important for the regulation of sleep, but only NMDA receptors contribute to the inhibition of currents in cultured mouse hippocampal neurons by propofol[62]. This inhibition occurs by allosteric modulation of the channel versus blockade of the channel. The literature search did not reveal any studies that have characterized the effect of propofol on metabotropic glutamate receptors. An exciting opportunity for future studies is to elucidate the role of glutamate in the neurochemical regulation of consciousness.

1.4 ACh—There is a long-standing appreciation that cholinergic neurotransmission contributes to the loss of consciousness associated with sleep and anesthesia[8,63]. Pontine ACh contributes to the generation of REM sleep and ACh release within the pontine reticular formation is greater during REM sleep than during NREM sleep and wakefulness[64]. The clinical finding that the acetylcholinesterase inhibitor physostigmine reverses propofol sedation suggests that propofol produces unconsciousness, in part, by disrupting cholinergic neurotransmission[13]. REM sleep, like wakefulness, is a brain activated state that is characterized by increases in cholinergic neurotransmission. Brain activated states of consciousness, such as wakefulness and REM sleep, are promoted by drugs that enhance cholinergic neurotransmission. Thus, the finding that physostigmine causes arousal from propofol sedation in humans[13] is consistent with data showing that administering neostigmine

or carbachol into the pontine reticular formation causes a REM sleep-like state in mouse[65], rat[66], and cat[67].

The foregoing gain-of-function data illustrated by manipulations that increase ACh are complimented by loss-of-function studies that chemically eliminate cholinergic neurons. For example, the immunotoxin 192 IgG-Saporin selectively destroys basal forebrain cholinergic neurons. In rat, intracerebroventricular administration of 192 IgG-Saporin caused a reduction in ACh levels in frontoparietal cortex and hippocampus and a decrease in propofol-induced locomotor inhibition[16]. These findings suggest that inhibition of basal forebrain cholinergic neurons contributes to the hypnotic effect of propofol[16]. Results from this study are also consistent with the notion that anesthetics act in a brain site specific manner, because acetylcholine levels in the striatum and cerebellum were not reduced by treatment with 192 IgG-Saporin. The cerebellum and striatum are not brain regions with primary arousal state regulating functions.

Both muscarinic and nicotinic ACh receptors are important for the regulation of sleep and wakefulness. In vitro studies show that propofol blocks ACh-induced muscarinic M1 receptor currents[68]. Propofol also inhibits nicotinic ACh receptor mediated currents when the nicotinic receptor is composed of the alpha4 beta2 subunit but not the alpha7 homomeric subunit[69,70]. ACh release within the cerebral cortex and dorsal hippocampus is greater during wakefulness and REM sleep than during NREM sleep[71]. Propofol decreased ACh release in rat frontal cortex and hippocampus[72], providing additional support for the conclusion that propofol causes sedation, in part, by inhibiting cholinergic neurotransmission in brain regions that regulate arousal.

1.5 Adenosine—Consistent with the idea that the neuronal circuits controlling sleep are preferentially modulated by anesthetics[7], local administration of propofol to the medial preoptic area, a region known to promote sleep[25], decreased latency to sleep onset, increased NREM sleep, and increased total sleep time[73]. The idea that neuronal networks that generate sleep also regulate anesthesia suggests the possibility that prior sleep history may affect anesthetic action. However, no clinical studies have demonstrated any difference in anesthetic requirement that is dependent on sleep deprivation. Preclinical studies have shown that sleep deprivation can enhance the sedative effects of propofol. Rats were sleep deprived for 24 h and then administered propofol anesthesia. Although loss of righting response is not identical to sleep, sleep deprivation decreased the latency for and prolonged the duration of loss of righting response caused by propofol[74]. These results also support the view that propofol acts at circuits involved in sleep regulation.

Adenosine is a sleep promoting neuromodulator that acts through 4 G protein coupled receptor subtypes, A_1, A_{2A}, A_{2B}, and A_3. During prolonged wakefulness brain adenosine levels increase within the basal forebrain and cortex[75]. The ability of sleep deprivation to decrease loss of righting response in rat was partially reversed by administration of adenosine A_1 and A_{2A} receptor antagonists[17]. Adenosine is known to inhibit excitatory neurotransmission through adenosine A_1 receptors[76]. In another study, rats were sleep deprived for 24 h and then allowed to have 6 h of ad libitum sleep or 6 h of propofol anesthesia. Rats that experienced ad libitum sleep and propofol anesthesia had similar amounts of NREM sleep and REM sleep[77]. The authors interpreted these results to suggest that propofol anesthesia provides some of the restorative processes that take place during naturally occurring sleep.

2. Ketamine

Ketamine was first tested clinically in the mid 1960s[78,79]. The term dissociative anesthetic was introduced at that time, and referred to the findings that during treatment with ketamine, sensory information appeared to reach the sensory cortex but was not accurately perceived due to

depression of cortical association areas[78]. Thus, ketamine caused a dissociation between nociceptive input and the subjective experience of nociception. Ketamine is a phencyclidine derivative that produces analgesia and amnesia without causing a complete loss of consciousness[26,80,81]. The primary mechanism of ketamine anesthesia is by antagonism of NMDA receptors[82]. Through NMDA receptor blockade, ketamine alters the actions of several arousal state related neurotransmitters, as outlined below.

2.1 Monoamines—Emergence from ketamine anesthesia is often characterized by confusion, agitation, visual hallucinations, and delirium[82]. This psychomimetic response has been well-investigated in the context of schizophrenia research[83-86]. Psychotic-like symptoms occurring during ketamine emergence may result from ketamine induced increases in dopamine release, particularly in the cerebral cortex. Subanesthetic doses of ketamine increase the release of dopamine and serotonin in rat prefrontal cortex[87,88] and increase dopamine release in rat nucleus accumbens[89]. Increased dopamine release in the nucleus accumbens may contribute to the addictive properties of ketamine[89]. Brain imaging of healthy human volunteers showed that subanesthetic doses of ketamine decreased the binding of a dopamine D2/D3 receptor agonist in the posterior cingulate and retrosplenial cortices[83]. This decrease in agonist binding was most likely due to a ketamine induced increase in dopamine release, as ketamine increases cortical dopamine release in rat[83,85].

Dopamine receptor subtypes contribute to the emergence responses to ketamine. Subanesthetic doses of ketamine in rodents cause hyperlocomotor activity characterized by staggering and stereotypic head-wagging. These behavioral responses to ketamine are reduced in dopamine D1A receptor knockout mice, suggesting a role for the dopamine D1 receptor in mediating emergence responses to ketamine[90]. Studies using in vitro expression systems for dopamine D2 receptors or rat membrane preparations have found conflicting results. One study showed that ketamine has high affinity for dopamine D2 receptors[91], whereas another study found that ketamine does not cause functional responses via the dopamine D2 receptor[92]. In vivo binding studies in humans using PET imaging have suggested that subanesthetic doses of ketamine increase dopamine D2 receptor binding in the striatum but not the cerebellum[86], whereas similar studies using a different ligand in monkeys showed no ketamine induced change in D2 receptor binding in the basal ganglia or cerebellum[93]. As noted repeatedly throughout this chapter, the brain region where anesthetic induced changes in neurotransmission occur is key to determining the response and the relevance to anesthetic mechanisms of action. Changes in dopamine levels in the cerebral cortex are much more likely to alter mental state than are changes in dopamine levels within the striatum or cerebellum.

Studies using in vitro expression systems of monoamine transmitters indicated that ketamine causes a direct inhibition of monoamine transporters, which would enhance monoaminergic effects and provide an additional mechanism underlying the ketamine emergence reaction[94]. Dopamine transporters, but not norepinephrine or serotonin transporters, are selectively inhibited by the S(+)-isomer of ketamine[94]. In vivo studies have shown that ketamine increases norepinephrine release in rat medial prefrontal cortex[95]. Norepinephrine release is normally greater during wakefulness than during physiological sleep, thus the ketamine-induced increase in norepinephrine may account for some of the dissociative properties of ketamine.

2.2 GABA—Ketamine has been shown to have some effects on GABAergic neurotransmission, but as of yet it is unclear if ketamine-induced alterations in GABAergic transmission are related to the mechanism of ketamine anesthesia. In vivo studies report that systemic administration of the $GABA_A$ receptor agonist muscimol potentiates ketamine-induced loss of righting response, and coadministration of the $GABA_A$ receptor antagonist bicuculline with ketamine antagonizes ketamine-induced loss of righting[96]. Data from other studies suggest that these responses are mediated indirectly. For example, studies using in vitro

expression systems have shown that at clinically relevant concentrations, ketamine does not modulate recombinant $GABA_A$ receptor activity[97]. Furthermore, the $GABA_A$ receptor antagonists picrotoxin and gabazine cause only a small increase in the ED_{50} for ketamine induced inhibition of mobility in response to a noxious stimulus, suggesting an indirect role of $GABA_A$ receptors[46]. Finally, acute and chronic systemic administration of ketamine does not change GABA levels in rat medial prefrontal cortex[87].

2.3 Glutamate—Ketamine is a noncompetitive NMDA receptor antagonist and the anesthetic effects of ketamine are thought to result primarily from NMDA receptor blockade. For example, the ketamine induced increase in dopamine release (discussed above in the section on monoamines[83,85,87,88] is mediated by NMDA receptors. Studies measuring glutamate show that chronic treatment with ketamine decreases cerebrospinal fluid glutamate levels in rats[98]. During cerebral ischemia glutamate transporters reverse and release glutamate into the extracellular space causing neuronal damage[99]. Intravenous anesthetics are thought to be neuroprotective by decreasing this glutamate release into the extracellular space[99]. In Chinese hamster ovary cells transfected with a cloned human glial glutamate transporter, ketamine decreased glutamate-induced outward currents suggesting that ketamine modulates glutamate transporters in vitro[99]. Many studies have investigated the role of glutamatergic signaling and the dissociative state that is produced by ketamine anesthesia. Ketamine increases glutamate release in the nucleus accumbens[100] and prefrontal cortex of rat[88]. Ketamine also increases anterior cingulate glutamate activity in humans[101]. These region-specific increases in glutamate likely account for some of the dissociative properties produced by ketamine anesthesia.

2.4 ACh—Ketamine modulates cholinergic neurotransmission in multiple brain regions and at both muscarinic and nicotinic cholinergic receptors. Many studies have demonstrated that ketamine is a noncompetitive inhibitor at nicotinic ACh receptors[70,102]. The inhibition of neuronal nicotinic ACh receptors by ketamine is subunit dependent, and nicotinic receptors that contain the beta1 versus beta2 subunit are more sensitive to ketamine[103]. Additionally, the presence of a single amino acid in the extracellular transmembrane region of the alpha7 subunit of nicotinic receptors determines whether ketamine can inhibit nicotinic receptor currents[104]. These data are consistent with the interpretation that ketamine produces anesthesia, in part, by modulating nicotinic ACh receptors. The story is complicated, however, because the S enantiomer of ketamine is three times more potent than the R enantiomer, yet in vitro the two enantiomers inhibit neuronal nicotinic ACh receptor currents equally[105]. In contrast to the prior study, these data suggest that the anesthetic effects of ketamine are unlikely to be mediated primarily through nicotinic receptor signaling[105]. Another mechanism by which ketamine might modulate cholinergic neurotransmission is through muscarinic ACh receptors. Fewer studies have investigated the effects of ketamine on the five subtypes of muscarinic cholinergic receptors. Ketamine has been shown to inhibit M1 muscarinic ACh receptor currents in vitro[106]. Consistent with the idea that ketamine anesthesia modulates cholinergic neurotransmission, repeated administration of ketamine causes up regulation of muscarinic cholinergic receptors in the forebrain[107].

Several studies have determined the effect of ketamine on brain ACh release in vivo. Two studies demonstrated that systemically administered ketamine increased frontal[108] and prefrontal[109] ACh release in rat. These data are difficult to interpret relative to the present chapter because cortical ACh promotes waking consciousness. As noted above, ketamine is a dissociative anesthetic and the increase in cortical ACh release may contribute to the ability of ketamine to activate the bispectral index[110]. Intravenous delivery of ketamine as well as local ketamine administration to cat pontine reticular formation decreases ACh release and inhibits REM sleep[80]. The finding that ketamine increases ACh release in cortex[108,109] and decreases ACh release in the reticular formation[80] again emphasizes that efforts to elucidate

the neurochemical regulation of sleep and anesthesia can anticipate results to vary as a function of brain region. Thus, we consider the postulate of a single “anesthesia center” in the brain to be an unhelpful throwback to the hope for a single, unifying mechanism.

2.5 Adenosine—Only one study was identified that investigated the role of adenosine in the mechanism of action of ketamine. That study found that an adenosine A_{2A} receptor agonist blocked ketamine induced hyperactivity, suggesting that adenosine or adenosine receptors may somehow contribute to ketamine induced locomotor activation[111]. Adenosine is an important modulator of physiological sleep and alertness during wakefulness, and future studies examining the effects of ketamine on the actions of adenosine in the basal forebrain and prefrontal cortex are likely to contribute to a mechanistic understanding of ketamine induced alterations in arousal state.

II. Volatile Anesthetics Alter Neurotransmitters that Regulate Sleep and Wakefulness

This section selectively highlights the effects of isoflurane and sevoflurane, the most studied and widely used inhaled anesthetics (Table 2), on endogenous sleep-related molecules that include monoamines, ACh, GABA, glutamate, and adenosine.

3. Isoflurane

Ether, nitrous oxide, and chloroform were among the first molecules recognized for their anesthetic properties during the 1840s. Isoflurane, a halogenated ether, was developed in 1965 and entered clinical practice in the late 1970s[112]. Isoflurane binds to a specific site on the $GABA_A$ receptor to enhance neuronal inhibition. Additionally, isoflurane alters neurotransmission by varying the effects of many other sleep-regulating neuromodulators. Whether the effects of isoflurane on the transmitter systems discussed below are direct or indirect remains to be determined.

3.1 Monoamines—Few studies have investigated the role of serotonergic neurotransmission in isoflurane anesthesia. The medullary hypoglossal nucleus innervates the genioglossal muscles of the tongue and genioglossal muscles can obstruct patency of the airway. Endogenous serotonin excites hypoglossal neurons[113] and isoflurane depresses the excitatory effect of serotonin on hypoglossal motoneurons in dogs[114]. Isoflurane also decreases hippocampal serotonin levels in wild type and serotonin transporter knockout mice[115]. These results indicate that the mechanism by which isoflurane decreases hippocampal serotonin levels is independent of the serotonin transporter. Decreases in serotonin levels persisted for several hours after cessation of isoflurane[115]. Hippocampal serotonin contributes to cognition and affect, and these data encourage additional studies to determine if isoflurane-induced decreases in hippocampal serotonin cause subsequent behavioral consequences.

Nitrous oxide and isoflurane are commonly coadministered and nitrous oxide produces analgesia, in part, by altering norepinephrine release in the spinal cord. Electrophysiological data show that isoflurane and norepinephrine each enhanced inhibitory postsynaptic currents in rat substantia gelatinosa neurons[116]. Coadministration of isoflurane and norepinephrine produced a greater increase in inhibitory postsynaptic currents than either drug alone, suggesting that isoflurane may produce analgesia, in part, by modulating norepinephrine neurotransmission at the level of the spinal cord dorsal horn[116].

The preoptic area of the hypothalamus contains NREM sleep promoting neurons and is important for thermoregulation (reviewed in[117]). General anesthetics disrupt thermoregulatory control by neural mechanisms that remain unclear. Isoflurane increases preoptic area

norepinephrine release in rat brain slices, suggesting that enhanced norepinephrine signaling in the hypothalamus may contribute to hypothermia during isoflurane anesthesia[118].

Histaminergic neurons in the tuberomammillary nucleus of the posterior hypothalamus are an important component of wakefulness promoting neuronal systems (reviewed in[119]). However, few studies have investigated the effects of volatile anesthetics on histaminergic neurotransmission. One study investigated histamine metabolism in rat hypothalamus and found that isoflurane altered histamine turnover differentially in the anterior versus the posterior hypothalamus[120]. Isoflurane was shown to increase histamine levels by inhibiting histamine degradation in both the anterior and posterior hypothalamus. However, histamine degradation was increased during the post-isoflurane recovery period only in the posterior hypothalamus[120]. The post-anesthesia increase in histamine turnover within the posterior hypothalamus is consistent with the wakefulness promoting role of both histamine and the posterior hypothalamus. In contrast, the anterior hypothalamus contains sleep promoting GABAergic neurons that do not respond to histamine[121]. These data showing brain region specific effects of isoflurane on histamine metabolism[120] encourage future studies examining the effects of isoflurane on synaptic transmission within the anterior and posterior hypothalamus. Such studies can be expected to yield mechanistic insights into how anesthetics alter states of consciousness.

Dopamine is wakefulness promoting in animals and in humans[12]. For example, intracerebroventricular administration of dopamine D1 and D2 receptor agonists during physiological sleep in rats causes an increase in wakefulness, an increase in motor activity, and a decrease in sleep[122]. Isoflurane increases basal dopamine release and dopamine metabolites in rat striatum in vivo[123,124,125] and in rat striatal slices ex vivo[125]. Dopamine transporter knock out mice show an increase in wakefulness and a decrease in NREM sleep[126]. Positron emission tomography studies in rhesus monkey[127] and in human[128] demonstrated that dopamine transporter binding in the striatum decreases during isoflurane anesthesia. These studies suggest that isoflurane increases dopamine levels by inhibiting dopamine reuptake. In vitro experiments confirm that isoflurane causes internalization of the dopamine transporter[129].

Emergence from anesthesia can be associated with an excitatory agitation phase, particularly in preschool children[130]. Striatal dopamine may contribute to this emergence reaction. In mice, recovery from isoflurane anesthesia is characterized by increased locomotor activity and increased dopamine turnover in the nucleus accumbens and striatum[131]. The importance of investigating these mechanisms in multiple brain regions is demonstrated by the fact that dopamine levels within the cortex and nucleus accumbens are greater during the activated states of wakefulness and REM sleep[29], whereas dopamine levels in the locus coeruleus and amygdala do not change across the sleep wake cycle[30].

3.2 GABA—$GABA_A$ receptors are an important target for inhalation anesthetics and contain a binding site for isoflurane[132]. Clinically relevant concentrations of isoflurane reduce the amplitude and extend the decay of GABA evoked currents by slowing the rate of GABA unbinding from recombinant $GABA_A$ receptors[133]. Isoflurane enhances $GABA_A$ receptor mediated currents in cultured rat cerebral cortical neurons[134] and, at clinically relevant concentrations, inhibits both the release and reuptake of GABA in mouse cortical brain slices[135]. Isoflurane also increases the binding of the benzodiazepine receptor antagonist ^{11}C-flumazenil to $GABA_A$ receptors in human cortex and cerebellum, as demonstrated by positron emission tomography[136]. Further evidence that isoflurane modulates GABAergic neurotransmission is demonstrated by the ability of an intrathecally administered $GABA_A$ receptor antagonist to increase the minimum alveolar concentration (MAC) value of isoflurane by 47% in rats[137].

There have been few studies characterizing changes in endogenous GABA levels during states of sleep, wakefulness, or general anesthesia. GABA levels during sleep are increased above waking levels in cat dorsal raphe nucleus[44], locus coeruleus[138], and posterior hypothalamus[139]. These findings support the interpretation that GABAergic inhibition of these wakefulness promoting monoaminergic nuclei contributes to the generation of physiological sleep. Compared to waking levels, isoflurane has been shown to decrease GABA levels in rat basal forebrain and somatosensory cortex[140]. Preliminary data from cat also show that GABA levels in the substantia innominata region of the basal forebrain are lower during isoflurane anesthesia than during wakefulness[141]. GABAergic input to the cortex from the basal forebrain can cause excitation by inhibiting cortical inhibitory interneurons[142-144]. Thus, the isoflurane induced decrease in cortical GABA[140] is consistent with the fact that isoflurane decreases cortical activation and slows the cortical EEG. Interestingly, isoflurane caused no change in posterior hypothalamic GABA levels[140]. Thus, even during states of general anesthesia there are brain site specific changes in GABAergic transmission.

The capability of isoflurane to produce anesthesia is dependent on the composition of $GABA_A$ receptor subunits. For example, a mutation in the alpha1 subunit of the $GABA_A$ receptor makes the receptor insensitive to isoflurane[145]. The ability of isoflurane to enhance GABA evoked $GABA_A$ receptor currents in cultured Sf9 cells is dependent on the presence of the gamma2s subunit[146]. GABA-mediated currents have been studied using an in vitro expression system transfected with recombinant $GABA_A$ receptors, and dual effects were reported[147]. At clinically relevant concentrations isoflurane was shown to potentiate GABA-mediated currents, and at higher concentrations isoflurane inhibited GABA currents[147]. The potentiating effects that predominate at lower concentrations are thought to be relevant for the mechanism of isoflurane action. Studies in rat indicate that spinal $GABA_A$ receptors can contribute to immobility caused by isoflurane[148]. The role of $GABA_A$ receptors in mediating immobility is not straight forward. For example, pharmacological blocking studies from this same group conclude that the immobilizing effect of isoflurane is not mediated by $GABA_A$ receptors[46]. Transgenic mice have been used in an effort to clarify which components of the $GABA_A$ receptor mediate immobility caused by isoflurane. Mice with a knock-in mutation in the beta3 subunit of the $GABA_A$ receptor are less sensitive to the immobilizing action of isoflurane[149].

3.3 Glutamate—One mechanism by which isoflurane has been proposed to cause anesthesia is by inhibiting excitatory neurotransmission. Glutamate is the major excitatory amino acid transmitter in the brain, and the effects of glutamate can be reduced by decreasing its release, increasing its uptake, or blocking its receptors. Glutamate transporters are located on neurons and glia, and take up extracellular glutamate to regulate synaptic glutamate levels. Uptake is the major inactivation mechanism for glutamate, as it is not enzymatically degraded.

Isoflurane has been shown to reduce glutamate release in isolated nerve terminals derived from rat cortex, hippocampus, and striatum[58,150]. Isoflurane decreases glutamate release in rat hippocampal[151] and cerebral cortex slices[135]. At greater concentrations, however, isoflurane also inhibits glutamate uptake[135]. The authors suggest that the effects of isoflurane depend upon a balance between inhibition of release and inhibition of reuptake[135]. Several other studies have shown that isoflurane increases glutamate uptake. In cultured rat glial cells, isoflurane increases glutamate uptake via glutamate transporters[152] and in vivo inhibitors of glutamate transporters increase MAC for isoflurane in rat[153]. Isoflurane also increases glutamate uptake in rat cerebral cortex synaptosomes[154]. Five types of glutamate transporters have been identified, and isoflurane increases the expression and activity of glutamate type 3 transporters in cultured rat glioma cells[155]. Isoflurane causes phosphorylation of a serine residue to activate the glutamate type 3 transporter and redistribute it to the plasma membrane[156].

Glutamate causes excitation by activating NMDA receptors, and NMDA receptor activation requires the binding of both glutamate and glycine. Isoflurane has recently been shown to inhibit NMDA receptors by binding to the glycine site[157]. This finding suggests that blocking the excitatory effects of glutamate at NMDA receptors may be one mechanism underlying the anesthetic and neuroprotective effects of isoflurane.

The above studies were performed using reduced preparations such as cell cultures, synaptosomes, or brain slices. Few in vivo studies using intact animals have determined the effects of isoflurane on glutamatergic transmission. In vivo microdialysis work using rat demonstrated that isoflurane differentially alters glutamate levels depending on brain region[140]. Compared to wakefulness, isoflurane causes a concentration dependent increase in glutamate levels in the basal forebrain, an increase in somatosensory cortex glutamate levels at one concentration only, and no effect on glutamate levels in the posterior hypothalamus[140]. The mechanistic implications of the surprising finding that isoflurane increases basal forebrain glutamate levels are not yet clear.

3.4 ACh—Isoflurane modulates nicotinic and muscarinic cholinergic receptors, and the release of ACh. Nicotinic receptors are comprised of five subunits, and several studies have investigated the role of various nicotinic ACh receptor subunits in the mechanism of action of volatile anesthetics[158]. Isoflurane at clinically relevant concentrations inhibits neuronal nicotinic ACh receptor currents expressed in vitro when the receptors contain the alpha4-beta2 subunit combination[159]. Isoflurane does not block the response of homomeric alpha7 nicotinic receptors to ACh when the anesthetic and the agonist are coadministered[69]. However, clinically relevant concentrations of isoflurane do inhibit homomeric alpha7 nicotinic receptors when the anesthetic is applied prior to ACh, or when ACh is applied in high concentrations[160]. These findings may be relevant in vivo, because alpha7 nicotinic receptors do occur in brain[160], and synaptic levels of neurotransmitters have been estimated to reach concentrations in the micromolar to millimolar range. The effects of isoflurane on native (i.e., non-recombinant) nicotinic receptors also have been investigated[161]. Interestingly, both isoflurane and a structurally similar halogenated molecule that does not cause immobility but does have amnestic properties inhibits native neuronal nicotinic ACh receptors in rat medial habenula neurons[161]. Another structurally similar agent with neither immobilizing nor amnestic properties does not block nicotinic receptor-mediated currents[161]. These data suggest that the amnestic effects of isoflurane may be mediated, in part, by nicotinic receptors in the medial habenula. More in vivo studies are needed to determine if nicotinic ACh receptors are relevant for the production of anesthesia by isoflurane.

There are five muscarinic cholinergic receptor subtypes, and isoflurane has been shown to inhibit M3 but not M1 muscarinic receptors[162]. M1 and M3 receptors are structurally quite similar, thus different effects of the same anesthetic on these two subtypes implies that the site of action is quite specific. More recently, the same investigators showed that isoflurane-induced inhibition of M3 receptor signaling is mediated by an increase in protein kinase C activity, but the site of action on the M3 receptor has not yet been localized[163]. Another study found that intracerebroventricular administration of the acetylcholinesterase inhibitor neostigmine or the muscarinic agonist oxotremorine to isoflurane anesthetized rats increases spontaneous limb and orofacial exploratory movements, indicating increased arousal[10]. Cholinergic activation during isoflurane anesthesia also activates the cortex, as indicated by an increase in cross-approximate entropy of the bihemispheric frontal EEG[10]. These data are consistent with the interpretation that activation of central cholinergic neurotransmission can reverse some aspects of isoflurane anesthesia.

Studies of intact brain using in vivo microdialysis report that isoflurane causes a dose dependent decrease in ACh release in rat cerebral cortex[140,164], rat striatum[164], and cat pontine reticular

formation[165]. The effect of isoflurane on ACh release varies with age. Isoflurane causes a significantly larger decrease in prefrontal cortex ACh release in old versus young rats[166]. Future studies are needed to determine whether aged rats show performance or memory deficits following isoflurane anesthesia. Such a finding would support the interpretation that isoflurane-induced decreases in prefrontal cortex ACh release may contribute to increased post-operative delirium in the elderly.

3.5 Adenosine—Peroperative adenosine infusion in humans undergoing breast surgery decreases isoflurane requirement and decreases postoperative analgesic requirement[167]. A similar study of patients undergoing shoulder surgery showed that adenosine reduces the requirement for isoflurane but has no effect on postoperative analgesic requirement[168]. Although adenosine is well recognized to have antinociceptive effects[169], few studies have examined the possible role of adenosine in mediating the anesthetic effects of isoflurane. In rat, isoflurane-induced reductions in focal cerebral ischemia are blocked by an adenosine A_1 receptor antagonist, indicating that this neuroprotective effect of isoflurane may be mediated by adenosine A_1 receptors[170]. Isoflurane-induced activation of adenosine A_1 receptors in primary cultures of rat hippocampal neurons also suppresses spontaneous calcium oscillations[171]. This study suggests that another mechanism by which isoflurane may be neuroprotective is by increasing adenosine levels[171].

4. Sevoflurane

Sevoflurane is a nonflammable halogenated ether. Sevoflurane is the newest inhalation anesthetic to be used in humans, and was introduced into clinical practice in the late 1980s. The effects of sevoflurane on sleep-related neurotransmitters and neuromodulators are discussed below.

4.1 Monoamines—Few studies have investigated the role of monoaminergic neurotransmission in sevoflurane anesthesia. Sevoflurane produces a higher incidence of agitation during emergence from anesthesia in children than other general anesthetics [130,172]. Alpha2 adrenergic agonists, such as dexmedetomidine, decrease the frequency of emergence agitation by sevoflurane[172], and alpha2 agonists inhibit the firing of noradrenergic locus coeruleus neurons[173]. Noradrenergic neurons in the locus coeruleus promote wakefulness (reviewed in[25]), and sevoflurane directly excites noradrenergic locus coeruleus neurons in rat[174]. Sevoflurane increases norepinephrine release in rat preoptic area [175]. Taken together, these data support the interpretation that noradrenergic neurotransmission contributes to emergence agitation produced by sevoflurane. The monoamines dopamine and histamine also promote wakefulness (reviewed in[25]), and sevoflurane increases cortical dopamine release in rat brain slices by modulating dopamine transporters[176]. Sevoflurane also increases hypothalamic histamine levels in rat by inhibiting histamine metabolism[120].

4.2 GABA—Sevoflurane, similar to many anesthetic molecules, enhances transmission at $GABA_A$ receptors. Using recombinant alpha1, beta2, gamma2 $GABA_A$ receptors, isoflurane has been shown to increase the affinity of GABA and cause an open-channel block at the $GABA_A$ receptor[177]. These data suggest sevoflurane increases GABAergic transmission by binding to at least two different sites on $GABA_A$ receptors[177]. Sevoflurane also promotes GABA evoked $GABA_A$ receptor chloride currents in isolated rat hippocampal neurons and modulates the GABA response by altering activation and decay phases of the current[178]. The modulation of hippocampal GABA receptors by sevoflurane is dependent on norepinephrine signaling, as coadministration of sevoflurane and norepinephrine have a large additive effect on inhibitory post synaptic currents and prolong the decay of the current[179]. These results suggest that sevoflurane anesthesia is mediated, in part, by enhanced GABAergic neurotransmission. This interpretation awaits confirmation from in vivo studies.

4.3 Glutamate—General anesthetics are thought to produce their effects by the dual actions of increasing inhibitory GABAergic neurotransmission and inhibiting excitatory glutamatergic neurotransmission. Sevoflurane has been shown to decrease calcium dependent glutamate release using synaptosomes isolated from human cerebral cortex[180]. Another study using rat cortical neurons also demonstrated that sevoflurane decreases glutamate release[181]. These data encourage additional experiments designed to determine whether the sevoflurane-induced decrease in glutamate release contributes to the anesthetic effects of sevoflurane in vivo.

4.4 ACh—Cholinergic neurotransmission is important for the regulation of sleep and waking consciousness, as well as anesthesia[8,12]. Nicotinic receptors are inhibited by several anesthetics[69,158], including sevoflurane[182]. In humans, thalamocortical connectivity is suppressed when anesthetics induce loss of consciousness[183]. Nicotinic receptors are densely expressed throughout the human thalamus[184], and microinjection of nicotine into rat central medial thalamus reverses the sevoflurane induced loss of righting response[185]. These data suggest that suppression of midline thalamic cholinergic neurons contribute to sevoflurane induced unconsciousness.

4.5 Adenosine—The PubMed review revealed no studies examining the role of adenosinergic neurotransmission in sevoflurane anesthesia.

III. Conclusions

A recurring theme that emerges from any consideration of anesthetic alterations in brain neurochemistry is that the direction and magnitude of chemical change varies as a function of brain region and anesthetic agent. There is no evidence that any single mechanism or brain region regulates the loss of waking consciousness during sleep or anesthesia. Even within seemingly homogenous states of consciousness, the brain reveals widely disparate levels of activation (reviewed in[186-188]). Such data make clear that understanding anesthetic alterations in consciousness will be limited unless the cellular and molecular mechanisms are elucidated on a brain region-by-region basis. Progress can be made if future studies include local delivery of anesthetic molecules along with measurement of endogenous neurotransmitters in specific brain regions. Another limitation concerns the lack of rigor regarding how anesthetic states of consciousness are classified. The terms loss of righting reflex, sleep, sedation, hypnosis, and sleep-time are often used casually to reach desired conclusions regarding anesthesia-induced alterations in consciousness. This lack of terminological rigor is particularly problematic for speculative extrapolations seeking to establish a link between pre-clinical studies and clinical implications. A formal and consistent classification of states based on physiological and behavioral traits[189,190] is essential and clinically relevant[191]. Drugs which selectively suspend consciousness are a logical path to understanding the neurological substrate of consciousness[192] and anesthesiology has unique potential to contribute to the clinical neuroscience of consciousness studies[132,186,193]. Finally, judgments concerning the status of consciousness studies for anesthesiology should be tempered by expectations that incorporate an evolutionary perspective. Neurochemical networks that evolved to generate the loss of waking consciousness during sleep are the most logical substrates through which anesthetic molecules eliminate waking consciousness. Continuing efforts by anesthesiologists to understand consciousness will be promoted by research paradigms that incorporate the specific brain regions and neurochemical modulators of sleep.

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Table 1

Intravenous Anesthetic Agents and Sleep-Related Neurotransmitters

The matrix summarizes the total number of peer reviewed publications obtained from a PubMed search spanning from 1997 to 2007, in which the title listed both the intravenous (I.V.) agent (rows) and the endogenous neurotransmitter molecule (columns). The first column lists the five I.V. agents and columns 2 through 6 list the neurotransmitters studied. Monoamines include serotonin, norepinephrine, dopamine, and histamine. Column 7 summarizes the total number of citations for each I.V. agent.

I.V. Anesthetics	Monoamines	GABA	Glutamate	Acetylcholine	Adenosine	Total
Propofol	12	7	6	4	6	35
Ketamine	13	4	5	11	1	34
Pentobarbital	4	8	2	1	2	17
Midazolam	2	4	4	1	2	13
Etomidate	1	6	1	1	0	9
Total	32	29	18	18	11	108

Table 2

Volatile Anesthetic Agents and Sleep-Related Neurotransmitters

The number of peer reviewed publications derived from a PubMed search ranging from 1997 to 2007 in which the title listed both the volatile anesthetic (first column) and the endogenous neurotransmitter molecule (columns 2 through 6) is presented in this table. The right-most column summarizes the total number of citations for each agent. The bottom right cell gives the total number of studies found that investigated the effects of volatile anesthetics on neurotransmitters.

Volatile Anesthetics	Monoamines	GABA	Glutamate	Acetylcholine	Adenosine	Total
Isoflurane	14	13	12	8	7	54
Sevoflurane	3	3	2	3	0	11
Nitrous	3	2	3	2	0	10
Xenon	3	1	1	2	1	8
Desflurane	0	0	0	0	1	1
Total	23	19	18	15	9	84