11

Sleep, Memory, and Consciousness

Key Points

1. Sleep is an active process generated in the brain.
2. Structures in the brainstem, diencephalon, and basal forebrain control the sleep-wake cycle and are directly modulated by general anesthetics.
3. Sleep and anesthesia are similar states with distinct traits, with each satisfying neurobiologic features of the other.
4. Distinct memory functions are subserved by distinct neural structures.
5. Limbic system structures such as the hippocampus and amygdala are critical for memory and play a role in anesthetic-induced amnesia.

Within 10 years of Morton's public demonstration of general anesthesia, ether, nitrous oxide, and chloroform were all in widespread use. The existence of three agents with diverse chemical structures led Claude Bernard in 1875 to speculate that the state of general anesthesia must arise through a common mechanism of action. Although decades of research have demonstrated multiple, nonoverlapping molecular targets for individual anesthetics (see Chapters 20 and 26) and appear to refute Bernard's hypothesis, a unitary network theory of anesthetic action remains possible from a systems perspective.

Traditionally, the state of general anesthesia is divided into various behavioral end points, including amnesia, hypnosis (defined as a lack of perceptive awareness to non-noxious stimuli), analgesia, immobility, and blunting of autonomic reflexes. These end points are produced by specific interactions of general anesthetics on discrete neuronal loci. Although volatile anesthetics come closest to being complete and thus capable of producing each of the components of the anesthetized state, the majority of anesthetic drugs fail to satisfy all criteria.

Nonetheless, diverse anesthetics acting at distinct receptor targets might produce common neurophysiologic adaptations in relevant circuits culminating in the behavioral end points that are recognizable as general anesthesia. This chapter considers two distinct anesthetic end points, hypnosis and amnesia. Using sleep as a paradigm to understand the system's neuroscience of control of the arousal state, the first section explores behavioral state transitions, as well as the effects of anesthetics on these circuits.

The second section describes the neurophysiology and neurobiology of memory formation and concludes with a discussion of their modulation by anesthetics. Finally, in the last section we address the emerging science of consciousness and discuss how anesthetics reversibly alter its expression.

Neuronal Systems That Regulate Arousal States

Exquisite regulation of the arousal state confers a survival advantage. Predators who fall asleep during the chase may starve, whereas prey caught napping at inopportune times suffer an equally dire fate. Thus, the need to regulate the arousal state seems obvious for all. However, the requirement for sleep in the first place remains mysterious. Prolonged loss of sleep leads to impaired thermoregulation, metabolism, and immune function and, ultimately, to death.

Given the tremendous cost of sleep in terms of opportunity—time that might otherwise be spent seeking food or shelter or procreating—one might presume that it offers some as yet unclear selective advantage in an evolutionary sense.

Recent hypotheses about the beneficial effects of sleep include restoration of the neuronal homeostasis essential for...
synaptic function, consolidation of memories, and initiation and expression of neuronal plasticity (reviewed elsewhere). Whatever its true role, evolution has exerted a selective pressure on organisms to sleep (Table 11-1). Molecular, neuronal, and behavioral conservation of sleep implies that it also carried a survival advantage in ancestral mammals. Hence, it should not be surprising that the neuronal underpinnings for control of arousal lie in subcortical structures deep within the brainstem, thalamus, and hypothalamus in regions where they are conserved across the animal kingdom.

### Passive versus Active Theories of Sleep

The discovery on which the neurobiology of control of the arousal state is built belonged to Frederic Bremer (1892-1982). In 1935, Bremer demonstrated that transection of the caudal medulla, although producing paralysis requiring mechanical ventilation, also produced an animal that remained alert, with normal sleep-wake cycles. Conversely, transection through the mesencephalon, immediately caudal to the nucleus of the third cranial nerve, yielded an animal that breathed spontaneously but was unresponsive and displayed a continuous sleep pattern in its electroencephalogram (EEG) (Fig. 11-1). Bremer's discovery formed the foundation for the passive theory of sleep. However, passive notions of sleep predate Bremer. The roots for this idea exist in the surviving sixth century BC writings of the Greek philosopher Alcmaeon and were known to Aristotle, who expounded on them in his treatise De Somno et Vigilia (“On Sleep and Waking”). Bremer's experimental evidence lent credence to the ancient Greek idea that sleep is caused by isolation of the brain from the rest of the body. Bremer hypothesized that sleep results anytime that the brain is deprived of its tonic sensory input. Under this passive view, sleep was nothing more than a default state produced by cessation of the active state—waking. A student of Bremer's, Giuseppe Moruzzi (1910-1986), fortified his mentor's hypothesis in collaboration with the physiologist Horace Magoun (1907-1991). Using electrical stimulation of the brainstem reticular formation (which falls in between Bremer's mesencephalic and caudal medullary lesion sites), Moruzzi and Magoun stimulated wakefulness while suppressing sleep and in so doing made the first description of the ascending reticular activating system. Together, they also narrowed the window for inducing a persist-

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**Figure 11-1** Brainstem transections may radically alter the state of arousal. **A**, Bremer's cerveau isole cat in which transection at the collicular level prevents brainstem and hypothalamic arousal-promoting signals from reaching the forebrain, thereby producing a state of deep coma. **B**, This contrasts with the enephale isole cat, in which transection through the caudal medulla disrupts spontaneous ventilation but leaves control of the arousal state intact. (Modified from Steriade M, Constantinescu E, Apostol V: Correlations between alterations of the cortical transaminase activity and EEG patterns of sleep and wakefulness induced by brain-stem transections. Brain Res 13:177-180, 1969.)
An alternative theory accounting for sleep requires its active genesis. According to the active sleep hypothesis, sleep is generated when specific neuronal systems increase their firing rates and thus inhibit the output of other neuronal structures required for wakefulness. Evidence for an active genesis of sleep has accumulated. During World War I, an outbreak of viral encephalitis reached pandemic proportions. Although many survivors experienced symptoms of profound and prolonged sleepiness (hypersomnolence), a smaller subset of survivors exhibited profound and prolonged insomnia. Based on postmortem neuropathologic observations and correlations with the premortem clinical condition, Baron Constantine von Economo (1876-1931) astutely noticed that the insomnia had sustained damage within the anterior hypothalamus around the preoptic area, as well as damage to the basal forebrain. Those exhibiting hypersomnolence had sustained posterior hypotalamic damage. Von Economo correctly predicted the existence of a sleep-promoting region of brain within the anterior hypothalamus near the optic chiasm, in addition to a wake-promoting region in the posterior hypothalamus. His predictions made more than three quarters of a century ago have withstood the scrutiny of time. Experimental evidence for a hypnogenic center in the preoptic area of the hypothalamus was confirmed in rats and cats inasmuch as insomnia also resulted after lesions to the preoptic area,9 as well as after bilateral micro-injection of muscimol, a γ-aminobutyric acid (GABA) agonist, into the preoptic area.10 Finally, the discovery of a population of inhibitory GABAergic neuronal whose activity displays state-dependent firing patterns,12 with the highest discharge rates occurring during sleep13 and whose efferent projections inhibit wake-promoting centers (reviewed by Saper and colleagues14), fulfills all the criteria for the active generation of sleep.

Although controversy between active and passive mechanisms of the genesis of sleep still remains, these modes need not be mutually exclusive. As we discuss later, the hypnogenic neural substrates that promote sleep antagonize the wake-promoting regions in brain. In the absence of neuropathology, synchronized communication between these sleep- and wake-active neural populations ensures smooth and appropriately timed transitions between arousal states.15

### Physiologic Patterns of Wakefulness and Sleep

The states of sleep and wakefulness may be characterized physiologically by recording the EEG and electromyogram (EMG). Wakefulness is identified by a fast-frequency, low-amplitude rhythm on the EEG that is “desynchronized,” together with the presence of maximal motor activity on the EMG (Fig. 11-3). Broadly speaking, sleep may be subdivided into two distinct patterns, REM sleep and NREM sleep, which is also known as slow-wave sleep. During NREM sleep, the EEG displays large-amplitude, slow frequencies in the δ range of 0.5 to 4 Hz that dominate the power spectrum. Motor tone is lower during NREM sleep than during wakefulness (Fig. 11-3). NREM sleep patterns contrast dramatically with wakefulness, in which the EEG is desynchronized and exhibits low-amplitude, fast frequencies. During REM sleep, the EEG is also desynchronized and is virtually indistinguishable from wakefulness. However, as opposed to wakefulness, EMG activity during REM sleep is minimal to
absent. The presence of θ activity (4 to 8 Hz) is also an abundant feature of REM sleep, as is eye movement, which may be recorded with an electro-oculogram (EOG) (for review see Harris 16).

**Wakefulness**

Protecting the neural systems responsible for generating wakefulness is so fundamental to survival that evolution has distributed its expression across multiple and partially redundant systems, each contributing in a unique, but nonessential, way to promotion and maintenance of wakefulness. Specific centers in the brain alter their electrical output in proportion to the organism’s arousal state. Among these regions, noradrenergic neurons of the locus ceruleus (LC), histaminergic neurons of the tuberomammillary nucleus (TMN), serotonergic neurons of the dorsal and median raphe nuclei (RN), and the newly recognized population of dopaminergic neurons in the ventral periaqueductal gray (vPAG) matter are all monoaminergic centers that display arousal state-dependent firing patterns (Fig. 11-4) (for review see Jones 19). Their highest discharge rates occur during wakefulness, decrease during NREM sleep, and become virtually quiescent during REM sleep. This pattern contrasts with that of brainstem and basal forebrain cholinergic neurons, which are most active during both wakefulness and REM sleep but decrease their output during NREM sleep, as discussed later. Neurons containing the wake-promoting and wake-sustaining neuropeptide orexin (also known as hypocretin) share similarities with other monoaminergic systems. Although confined to the posterior, lateral, and dorsomedial hypothalamus, orexinergic neurons also innervate the entire neuroaxis of the central nervous system (CNS) from forebrain through the spinal cord. These neurons exhibit maximal activity during wakefulness, reduce their firing during NREM sleep, and become quiescent during REM.19,20 The orexinergic population positively reinforces wakefulness by stimulating activity in the monoaminergic centers just mentioned. In all mammals studied to date, including humans, impaired orexin signaling causes narcolepsy, a primary disorder affecting the organization of sleep and wakefulness. Although narcoleptics show behavioral state instability and transition to and from sleep at inopportune times, the total amount of sleep and wakefulness remains unchanged. Consistent with this notion, isolated lesion studies in animal models along with pharmacologic and gene knockout experiments have demonstrated that no single monoaminergic, cholinergic, glutamatergic, or orexinergic wake-active center is absolutely required for wakefulness.21

Nonetheless, Bremer, Moruzzi, and Magoun demonstrated that complete disruption of the brainstem reticular core, including the laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT), precludes wakefulness. The cholinergic LDT and PPT, the noradrenergic LC, the dopaminergic vPAG, and the serotonergic RN are stimulated byafferent sensory input. Together, these systems ascend through two pathways to stimulate cortical activity and expression of wakefulness (Fig. 11-5). Dorsal fibers synapse in the thalamus, where their input is relayed indirectly to the cortex via glutamatergic thalamocortical afferents. Ventral fibers synapse in the posterior hypothalamus and basal forebrain while communicating with the histaminergic TMN and cholinergic basal forebrain centers on their way to the cortex. Finally, noradrenergic LC and serotonergic RN neurons send afferent input directly to the cortex. Although brainstem and hypothalamic activity modulates wakefulness, the cerebral cortex itself
contributes to self-awakening through its efferent projections to the thalamus and reticular formation.  

**NREM Sleep**

With a notable exception of the ventrolateral preoptic (VLPO) nucleus, overall electrical activity in most regions of brain is decreased during NREM sleep. This observation correlates with passive notions of sleep in which tonic wake-promoting input dissipates. During NREM sleep, monoaminergic, orexinergic, and cholinergic groups are inhibited by efficent signals emanating from the preoptic anterior hypothalamus, specifically, a cluster of neurons localized to the VLPO nucleus that use the inhibitory neurotransmitters GABA and galanin (see Fig. 11-4). VLPO neurons are sleep active and display increased firing rates and c-Fos immediate early gene expression during sleep.  

Sleep-active VLPO neurons have an antagonistic relationship with wake-active centers such that VLPO activation inhibits firing in wake-active centers. Conversely, rapid firing of wake-active regions inhibits the VLPO nucleus. This network design leads to a bistable behavioral state of arousal favoring either sleep or wakefulness but not rapid transitions between the two. Not surprisingly, destruction of the VLPO nucleus with an excitatory amino acid lesion that destroys cell bodies while leaving fibers of passage intact causes insomnia.  

Although preoptic anterior hypothalamic VLPO neurons actively generate NREM sleep, neurons in the thalamus also alter their electrical activity patterns in critical ways during NREM sleep. Thalamic reticular and thalamocortical neurons begin to fire in bursts. This process generates slow spindles evident on the EEG. Burst firing of thalamocortical neurons transiently causes deactivation of the cortex by reversibly disconnecting it from sensory stimuli normally conveyed to the cortex from the...
Deafferentation of the cortex by intrinsic thalamic activity is reminiscent of Bremer’s lesion studies in which permanent deafferentation of the cortex formed the experimental basis of the passive nature of sleep. Together, VLPO and thalamic activity patterns provide mechanistic neuronal network explanations for the active and passive theories of sleep.

**REM Sleep**

Control of REM sleep is also regulated in the brain. Although several neuroanatomic centers participate in regulation and coordination of REM onset and offset, the main effector responsible for the generation of REM sleep resides in the pontine reticular formation. Transsection studies by Michel Jouvet (1925-) in the cat further localized brainstem REM control within thepons to the nucleus pontis oralis (PnO), which appears to be necessary for REM expression. Direct injection of cholinergic agonists into the thalamus.

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of the eVLPO nucleus reduce the amount of REM sleep, the eVLPO nucleus appears to play a special role in generation of REM sleep.\(^{30}\)

The behavioral constellation of REM sleep is dissociable into various components, each with its own specific mechanisms and neuroanatomic controllers. The cardinal signs of REM sleep include rapid eye movement, atonia of all motor groups except for the diaphragm, and activation of a low-voltage, fast-frequency EEG rhythm. Subcortical recordings demonstrate ponto-geniculo-occipital (PGO) waves. This characteristic spiky EEG pattern of REM sleep originates in the pons, is transmitted to the thalamic lateral geniculate, and terminates in the occipital cortex. The REM- and wake-active population of LDT and PPT neurons with rostral projections is important for production of the desynchronized fast-frequency, low-amplitude EEG found in both wakefulness and REM sleep.\(^{35}\) REM atonia is initiated by a group of pontine reticular neurons that synapse in the bulbar reticular formation before terminating their signal on spinal cord motor neurons. The subset of pontine reticular formation neurons initiating atonia is a non-noradrenergic population of neurons adjacent to the LC, termed either the pericereus ceruleus alpha or subcereulens (SubC) in cats or the sublateral dorsal (SLD) nucleus in rodents.\(^{31,32}\)

Exit from REM sleep transitions into either NREM sleep or wakefulness and is triggered by “REM-off” groups. The observation that noradrenergic LC neurons decrease their firing rate during NREM sleep and become virtually quiescent during REM sleep, together with pharmacologic and lesion studies, had suggested that inhibition of the LC was a requirement for entry into REM sleep and that LC neurons might serve as REM-off cells. However, genetic studies in noradrenergic-deficient mice have conclusively demonstrated the continued existence of normal, or nearly normal, REM sleep despite the absence of norepinephrine.\(^{33,34}\) Thus, the adrenergic neurons of the LC cannot be an exclusive REM-off population. Neurons of the ventrolateral periaqueductal gray (vIPAG) matter also serve to terminate REM episodes, as proved by pharmacologic studies during which muscimol inhibition of this region increases REM sleep and also by elegant immunohistochemical mapping combined with vIPAG lesions.\(^{35-37}\) vIPAG neurons form a mutually antagonistic inhibitory loop with those of the SLD nucleus to efficiently generate or inhibit REM sleep.\(^{35}\)

**Somnogen-Induced Transitions Between Arousal States**

Even though cortical EEG and EMG patterns and activity in the sleep- or wake-active centers in the brainstem, hypothalamus, and thalamus are well known during states of sleep or wakefulness, the mechanisms responsible for entry into or exit from a given state remain mysterious. The humoral theory of sleep regulation was independently proposed nearly 100 years ago by French and Japanese neuroscientists. Intrathecal infusion of cerebrospinal fluid (CSF) harvested from sleep-deprived dogs into rested normal dogs caused the recipient dogs to promptly fall asleep.\(^{38,39}\) This result suggested the existence of an endogenous somnogen, a “hormone” circulating in the CSF whose accumulation could cause the onset of sleep. Over the past century, the list of potential somnogens has grown to include substances as diverse as proteins—\(\delta\) sleep–inducing peptide (DSIP)\(^{40}\); lipids—\(\alpha\)-octa-decenamide\(^1\); hormones—melatonin; cytokines—interleukin-1; eicosanoids—prostaglandin D\(_2\) (PGD\(_2\)); and a nucleoside—adenosine.\(^{41}\) We shall review data for the latter two putative somnogens, which have been studied most extensively.

Infusion of femtomolar concentrations of PGD\(_2\) into the third ventricle induces both NREM and REM sleep in rats that is indistinguishable from natural sleep.\(^{42}\) PGD\(_2\) levels fluctuate in the CSF with circadian frequency paralleling sleep-wake cycles. Sleep deprivation proportionally elevates CSF PGD\(_2\) levels, thus also supporting a role for PGD\(_2\) as an endogenous somnogen. PGD\(_2\) is synthesized by the enzyme prostaglandin D synthetase, which is localized in the arachnoid membrane and choroids plexus (Fig. 11-6), and is secreted directly into CSF, where it is the second most abundant protein. Microdialysis studies confirm a specific sleep-promoting activity of picomolar quantities of PGD\(_2\). However, this somnogenic activity is present only when PGD\(_2\) is infused in the vicinity of the preoptic area of the hypothalamus. The most pronounced activity of PGD\(_2\) is observed when it is

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**Figure 11-6** Molecular mechanisms of sleep promotion by the endogenous somnogen prostaglandin D\(_2\) (PGD\(_2\)). The prostaglandin D\(_2\) receptor (DPR) lines the ventral surface of the basal forebrain and preoptic area (purple area). The DPR is thought to transmit the somnogenic PGD\(_2\) signal from cerebrospinal fluid to the ventrolateral preoptic nucleus (VLPO, shown in red), with adenosine being used as a signaling molecule. This signal transduction event activates VLPO neurons via the adenosine A\(_{2A}\) receptor, which leads to inhibition of wake-active histaminergic groups such as the tuberomammillary nucleus (TMN, shown in blue). (Modified from Hoyashi O, Urade Y. Prostaglandin D\(_2\) in sleep-wake regulation: Recent progress and perspectives. Neuroscientist 8:12, 2002.)

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infused beneath the VLPO nucleus. Infusion of a PGD₂ antagonist into the third ventricle reversibly and dose-dependently inhibits both REM and NREM sleep (for review see Hayashi and Urade). On binding to the D-type prostanoid receptor (DPR), which is localized to the arachnoid membrane lining the ventral surface of the brain, the somnogenic signal of PGD₂ appears to be transduced indirectly by activation of the VLPO nucleus. The mechanism for VLPO activation after subarachnoid infusion of PGD₂ appears to require adenosine because coadministration of an adenosine receptor A₁ antagonist blocks the somnogenic activity of PGD₂. Conversely, administration of an adenosine A₁ agonist mimics the somnogenic activity of PGD₂. As adenosine levels accumulate, they activate A₁ receptor–expressing neurons to directly or indirectly activate the VLPO nucleus. Hence, it appears that adenosine may function as the neurotransmitter that couples the humoral to the neural mechanisms driving sleep-wake regulation. With this model the homeostatic drive to sleep accumulates proportionally to increases in the endogenous somnogens PGD₂ and adenosine. The existence of such somnogenic substances that accumulate with time argues for active rather than passive generation of sleep.

### Anesthesia and Sleep

Anesthesia is a state that shares phenotypic similarities with sleep, and hence the metaphor of “going to sleep” is commonly used to describe induction of general anesthesia in the clinical setting. Not only are anesthesia and sleep similar states, but they also share common neurobiologic traits; indeed, the hypnotic component of anesthesia may result from specific actions of anesthetics on the neural systems that regulate natural sleep. Support for this hypothesis comes from a variety of studies. During sleep and general anesthesia, there is reduced responsiveness to external stimuli. Functional brain imaging during anesthetic-induced unconsciousness has been shown to inhibit thalamic and midbrain reticular formation nuclei. Anesthetic blockade of thalamic information transfer, which disrupts somatosensory input from reaching higher cortical centers, has also been confirmed with more direct microelectrode recordings. In both instances, these anesthetic effects on the thalamus resemble the naturally occurring thalamocortical inhibition characteristic of NREM sleep.

### Sleep Deprivation

Sleep deprivation potentiates the hypnotic action of anesthetics, including propofol and isoflurane. Moreover, the sleep debt that would otherwise ensue after sleep deprivation dissipates during propofol anesthesia; however, it remains unknown whether other features of sleep deprivation (for example, on immune function) might also be ameliorated by hypnotic doses of propofol. The bispectral index monitor, designed to track the depth of anesthetic-induced hypnosis, also appears to be useful in recording the onset and depth of sleep.

### Endogenous Somnogens and Anesthetics

Infusion of adenosine in low doses potentiates the hypnotic actions of intravenous and volatile anesthetics, thereby reducing the amount of anesthetic required to achieve a given depth of anesthesia. This effect is reproduced by 2-chloroadenosine, a potent adenosine analog, and by dipyridamole, an adenosine uptake blocker and adenosine deaminase inhibitor. Conversely, administration of theophylline, an adenosinergic antagonist, produces partial resistance to anesthesia. Mechanistically, these data fit well with an effect of adenosine on activation of the hypothalamic sleep center, the VLPO nucleus (see later discussion). Meanwhile, exposure to anesthetics such as isoflurane affects the levels of endogenous somnogens, with isoflurane altering the balance between prostaglandin E₂, a wake-promoting prostaglandin, and PGD₂, a sleep-inducing prostaglandin, in the hypothalamus.

### Effects of Anesthetics on Sleep Circuits

Knowledge of the endogenous arousal systems is an essential prerequisite for any discussion of the mechanisms of action of psychostimulants, sedative-hypnotics, and general anesthetics. Predicted actions of anesthetics based on their known effects at individual cells expressing single recombinant neurotransmitter receptors, including GABAergic, glutamatergic, cholinergic, adrenergic, histaminergic, serotonergic, and orexinergic receptors or voltage-gated calcium, sodium, or potassium channels, allow the generation of testable hypotheses. However, anesthetics distribute throughout the entire brain (Fig. 11-7), and because the majority of sleep- and wake-active nuclei send bidirectional signals that may be either mutually inhibitory, excitatory, or one...

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inhibitory in one direction with an excitatory return, the actual effects of anesthetics on net circuit output must be empirically tested because existing models do not account for all the complexity in the circuits.38

**Thalamic Sites**

The passive theories of sleep set forth by Bremer are similar to many passive concepts of general anesthesia. A central tenet of NREM sleep and anesthesia is that the cortex is deprived of sensory input. Whether by exogenous lesions, as in Bremer’s cerebellar isole cat, or by endogenous closing of thalamic gates, anesthetics appear to act on NREM sleep circuits, thereby leading to shared mechanisms of action. Within the thalamus, there is a simple architecture of cell types consisting of reticular neurons and thalamocortical neurons that communicate with the cortex while also integrating peripheral input (Fig. 11-8). Activation of the reticular neurons during NREM sleep and anesthesia causes hyperpolarization of thalamocortical relay neurons, which in turn blocks propagation of the action potential through thalamocortical relay neurons. As a result, thalamocortical neurons are prevented from relaying peripheral input to higher cortical centers. This is the mechanism by which the thalamic gates close to transiently, yet reversibly, sever the cortex from the periphery.33,39,40 Midline thalamic nuclei are thought to play a critical role in generating conscious awareness and appropriately receiving afferent input from most reticular activating arousal-promoting centers.41 Imaging studies confirm a regionally selective reduction in midline thalamic blood flow, metabolism, and by extension, activity.42-45 Support for a thalamocortical consciousness switch has recently been strengthened by the finding that microinjection of nicotine into the centromedian nucleus of the thalamus reverses sevoflurane-induced hypnosis (discussed later). These conclusions are mitigated by the fact that administration of nicotine into the centromedial nucleus results in seizures. However, support for the central thalamus as an arousal center that is capable of reversing unconsciousness also comes from literature on the persistent vegetative state. High-frequency stimulation of the central thalamus in the rat has been associated with widespread cortical activation and enhanced cognitive function.46 Furthermore, deep brain stimulation of the central thalamus has been shown to reverse some of the behavioral deficits in a patient suffering traumatic brain injury.47

Because nicotinic acetylcholine receptors are heavily expressed in the thalamus and because many anesthetics inhibit signaling via nicotinic acetylcholine receptors, suppression of the cholinergic arousal system may be one mechanism through which many anesthetics produce unconsciousness.48 Processed EEG measures of anesthetic depth also reveal an important role for the cholinergic arousal system inasmuch as intracerebroventricular infusions of neostigmine or the muscarinic agonist oxotremorine arouse isoflurane-anesthetized rats.49

**Hypothalamic Sites**

Thalamic nuclei receive input from the ascending brainstem reticular activating system via a dorsal pathway and also receive hypothalamic input from wake-active centers such as histaminergic and orexinergic neurons (see Fig. 11-5). As discussed earlier, the thalamic gates close during NREM sleep and exposure to several anesthetics, and this closure is facilitated by decreased input of monoaminergic, cholinergic, and orexinergic signals during anesthesia. GABAergic anesthetics such as propofol and barbiturates exert their hypnotic effects by inactivating histaminergic neurons of the TMN46 (see Fig. 11-4). This action may be explained at the molecular level by potentiation of inhibitory GABAergic projection from the sleep center, the VLPO nucleus. Disinhibition of the VLPO nucleus, in turn, shuts down other wake-active groups and further reinforces VLPO activity. This feed-forward mechanism stabilizes the hypnotic state.48 Blockade of the wake-promoting histaminergic signal is also the mechanism by which the anti-histaminergic drug diphenhydramine precipitates sleep. Recovery or emergence from anesthetic hypnosis is facilitated by wake-promoting orexinergic neurons, which are inhibited by volatile anesthetics such as isoflurane and sevoflurane.49

**Brainstem Sites**

One finding that has emerged from studying the hypnotic properties of different anesthetic agents is that there is neither a unitary...
molecular target nor an invariant neuronal site of action common to all anesthetics. This point is illustrated by dexmedetomidine, an α₂-adrenergic agonist. The behavioral hypnosis of dexmedetomidine results from the drug’s ability to inactivate noradrenergic neurons of the LC (Fig. 11-4). This event disinhibits the VLPO nucleus, which subsequently inactivates other arousal centers via the VLPO’s GABAergic and galaninergic inhibitory signaling, as discussed earlier.70 As with propofol and barbiturates acting on the TMN, the common consequence of VLPO disinhibition is stabilization of the hypnotic state. Pharmacologic and lesion experiments that alter both monoaminergic reticular activating function and anesthetic sensitivity can now be reinterpreted in the framework of integrated arousal network activity. Depletion of CNS catecholamines, including norepinephrine, serotonin, dopamine, and histamine, produces hypersensitivity to anesthetics.49 Conversely, pretreatment with a monoamine oxidase inhibitor or acute exposure to amphetamine, both of which increase catecholamine levels in the brain, produces partial resistance to anesthetics.70 Focusing once again on noradrenergic neurons of the LC, chemical depletion of norepinephrine with 6-hydroxydopamine71 and electrolytic destruction of LC neurons72 both produce hypersensitivity to anesthetics, probably by removing an inhibitory signal to the VLPO nucleus.

These pharmacologic treatments affect other monoaminergic systems in addition to the noradrenergic neurons. Moreover, the action of amphetamines or monoamine oxidase inhibitors on serotonergic or dopaminergic systems might also account for a portion of the anesthetic effects. In support of this concept, destruction of serotonergic RN neurons with the toxin 5,6-dihydroxytryptamine or direct electrolytic lesions of serotonergic RN neurons also cause hypersensitivity to anesthetics.7374 Once again, as with lesions of the LC, these actions may be interpreted in the light of partial VLPO disinhibition (see Fig. 11-4).

The discovery that pentobarbital and muscimol, a GABA A agonist, cause behavioral and EEG signs of hypnosis when microinjected into a discrete upper brainstem site, termed the mesopontine tegmentum (MPTA) in rats, has revealed yet another important anesthetic locus.75 Neuroanatomic tracing studies have shown that MPTA neurons project to thalamic, hypothalamic, and brainstem sites traditionally recognized as part of the ascending reticular activating system. Like other known wake-active systems, MPTA neurons are spontaneously active during wakefulness and are thought to decrease their firing rates during NREM sleep and under anesthesia.7576 MPTA neurons also project to the septohippocampal system, thus providing a link to yet another anesthetic locus (see later).

**Limbic System**

Strong emotions such as fear, rage, and joy are accompanied by a heightened state of arousal. Hence, it should not be surprising that the limbic system, which responds to emotional content, connects to arousal circuits. Specifically, within the limbic system the medial septum and hippocampus also participate in modulating awareness. This knowledge of neuroanatomy helps explain how inhibition of the medial septum or hippocampus by local injection of muscimol decreases the doses of propofol and pentobarbital needed for hypnosis.75 The role of limbic system structures such as the hippocampus and amygdala in memory function and anesthetic-mediated amnesia is discussed later.

**Summary**

Although once considered a passive process in which the cortex loses afferent input, sleep is now recognized as an actively generated state whose genesis depends on the integrated contribution of multiple neuronal input. Increased understanding of the relevant neuronal circuits controlling sleep and wakefulness has opened a series of investigations into anesthetic-induced hypnosis. These studies suggest that anesthetic-induced unconsciousness may arise in part from selective actions of our drugs on these critical nuclei. One basic principle that appears to tie all the neuroanatomic studies together is that inactivation of structures mediating normal arousal appears to enhance the effects of general anesthetic–induced hypnosis. Conversely, activation of these regions appears to produce partial resistance to anesthetic-induced hypnosis.

**Memory**

In this portion of the chapter we provide a discussion of the major themes in our understanding of memory as it has developed over the past 100 years. Three major themes are clear.76 First, there are multiple memory systems that are subserved by specific brain regions and neural circuits. Second, there are multiple stages of memory that are mediated by distinct molecular mechanisms. Third, alterations in the strength of connections between neurons—termed *synaptic plasticity*—is a critical component of the way in which memories are stored in neural circuits. After investigating these three major themes of memory research, we describe the molecular mechanisms by which memories are stored and define potential mechanisms by which anesthetics might induce amnesia. Because the hippocampus and amygdala have been the focus of many studies of memory storage and because modulation of their function may underlie anesthetic-induced amnesia, our discussion will focus on these memory systems.

Over the centuries, memory has fascinated poets, philosophers, and scientists. Memory represents an experience-dependent change in behavior, and it is critical to our sense of self, as well as the development of human society and culture. Thus, it is not surprising that memory remained for centuries the domain of philosophers, many of whom speculated on what memory was and how it might be maintained over a lifetime. In *Theaetetus*, Plato proposed that thoughts might be stamped into memory the way a signet ring makes an impression in wax. When he discussed a theory of cognition in *Timaeus*, Plato was among the first to suggest that the brain contains the higher, rational soul that controls our actions, but his idea was that this rational soul interacted with a lower, appetitive soul in the gut to form images on the surface of the liver.77 Experimental work by scientists on memory had its origins in the 19th century when neurologists and psychiatrists such as Jackson, Ribot, and Alzheimer began to identify patients with memory deficits and psychologists such as Hémbinghaus, Müller, and Pileecker began to define different types and stages of memory.78 Importantly, the early clinical work on brain-lesioned patients placed memory into the hands of neuroscientists, who defined the importance of the brain in memory, in contrast to earlier proposals by philosophers, in which it was
suggested that memory was subserved by other organ systems. As this experimental and clinical work was being carried out on memory, anatomists such as Santiago Ramón y Cajal (1852-1934) were identifying the critical cellular components of the nervous system by using histologic stains to identify distinct classes of neurons and glia within the brain. Cajal’s “Neuron Doctrine” led him to postulate that it would be these connections between neurons (later called synapses) that might mediate memory storage. With the work of Ivan Pavlov (1849-1936) on the conditioned reflex, the field of memory began to be a central component of the growing field of psychology.

### Distinct Memory Systems Subserve Distinct Types of Memory

The field of memory research was revolutionized in the middle part of the 20th century by the patient H.M. by Wilder Graves Penfield (1891-1976), Brenda Milner (1918-), and others. Work in the first half of the 20th century that followed on the work of Pavlov had failed to define specific memory systems, as was suggested by the work of Jackson, Ribot, and Alzheimer and popularized by the phrenologist Joseph Gall. Karl Lashley, working at Harvard, suggested that memories might not be localized to specific brain regions inasmuch as his lesion studies in rodents failed to identify such specific circuits. Rather, Lashley proposed his laws of mass action and “equipotentiality,” both based on the ideas that the entire cerebral cortex contributes to memory and that other brain regions can compensate for damage to a certain region of the brain. The study of H.M. thus came in striking contrast to these conclusions of Lashley. At 27 years of age, H.M. underwent surgery to remove portions of his temporal lobe in an effort to treat intractable epilepsy that had developed after a childhood accident. As became clear 40 years later when H.M.’s brain was studied by magnetic resonance imaging techniques, his neurosurgeon Wilder Penfield had removed the bulk of his hippocampus bilaterally and portions of his amygdala (Fig. 11-9). Thus, it is no surprise that H.M. had severe anterograde memory deficits in the ability to acquire new memories.

Neuropsychological evaluation by Brenda Milner and others revealed two surprising aspects of the amnesia that followed H.M.’s surgery. First, he also exhibited retrograde amnesia—that is, certain memories of events before his surgery were lost. As this retrograde amnesia was probed in more detail,

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*Figure 11-9* There are distinct types of memory (A) that are mediated by distinct brain systems (B).
it was found that H.M.’s memory of temporally distinct events was intact, and a "gradient" of retrograde amnesia was revealed that decreased with time. This observation of time-limited retrograde amnesia is in keeping with the "law of regression" proposed by Jackson and Ribot that recent memories are the first to be affected by amnesia.84,85 This observation also suggests that retrieval and storage of very long-term memories (so-called remote memory) are mediated by neural circuits that were not altered by H.M.’s surgery. We now know that these very long-term memories require the cortex—particularly the anterior cingulate cortex, for storage and retrieval.86 Second and perhaps most important, H.M. exhibited normal learning and memory for certain tasks, a finding that was first shown for a mirror drawing task. This second aspect of H.M.’s amnesia gave rise to the idea of multiple memory systems, each of which mediate particular types of memory. There appears to be at least two reasons why Lashley did not observe the existence of multiple memory systems. H.M.’s lesions were not precisely focused on specific neural circuits, and his behavioral tasks, which were complex maze tasks, were not configured to probe selectively specific memory systems.

The conclusions from the study of H.M. have been confirmed and extended over the past 50 years, and similar memory deficits have been observed in patients with damage limited to specific subregions of the hippocampus.83,87,88 A variety of memory systems have been defined by both lesion experiments and functional magnetic resonance imaging studies (Fig. 11-9).

### Types of Memory

Memory is divided into two large classes termed declarative or nondeclarative memories, depending on whether the memory can be consciously recalled or not.89 Nondeclarative memory includes procedural memory, of which bike riding and mirror drawing represent clear examples. Declarative memory, which is consciously recalled, consists of semantic and episodic memory. The hippocampal formation, lesioned in patient H.M., is a major component of the episodic memory system (see Fig. 11-9). Indeed, H.M. had specific deficits in his ability to store and recall episodic memories—the memory of facts and events that provide most of our conscious recollection of life’s experiences. Although much work has focused on the role of the hippocampus in the recollection of episodic memories, recent work has extended the study of the hippocampus to investigate whether patients with hippocampal damage are able to imagine new experiences.90 Patients with hippocampal damage are impaired at imaging new experience, in
part because their imagined experiences lack spatial coherence and consist of fragmented images in the absence of configural representation of an environmental setting. Beyond its role in our conscious recollection of our past, the hippocampus also makes a critical contribution to our ability to imagine new experiences.

The existence of multiple memory systems provides a critical analytic tool for the analysis of memory deficits observed in patients. A particularly striking example of such a “double dissociation” between types of memory comes from the work of Damasio and colleagues.92 They examined a patient with bilateral damage to the amygdala and a patient with bilateral hippocampal damage in classic conditioning tasks. The patient with amygdala damage was unable to acquire conditioning of autonomic responses but did acquire declarative knowledge about the conditioning trials. In contrast, the patient with hippocampal damage learned the conditioned autonomic responses but not the facts. One clinical implication of the existence of multiple memory systems is that appropriate neuropsychological testing combined with structural and functional magnetic resonance imaging can be used to identify the basis of memory deficits in patients.

**Memory Consolidation and Different Stages of Memory**

In 1900, Georg Elias Müller (1850-1934) and his student Alfonso Pilzecker (1865-1949), working at the University of Göttingen, Germany, published a seminal 300-page paper describing 40 experiments on the nature of memory.92 In this work, Müller and Pilzecker presented clear evidence that memory does not immediately develop after learning but instead takes time to be consolidated and stored. Their primary evidence came from two classes of observations termed perseveration and retroactive inhibition. Using lists of nonsense syllables presented as paired associates, Müller and Pilzecker found a strong tendency for syllable pairs to be maintained in a subject's mind for some minutes after learning. Such “perseveration” was interpreted to reflect the persistence of a memory trace that was necessary to encode the memory. In a set of experiments designed to test this idea, they presented subjects with a second list of words at some time interval after the first list. If this second list followed the first list by 30 seconds, “retroactive interference” was observed—subjects showed less retention of the first word list. If learning of the second list was delayed by 6 minutes, such interference was not seen. Müller and Pilzecker concluded: “After all this, there is no alternative but to assume that after reading a list of syllables, certain physiological processes, which serve to strengthen the associations induced during reading of that list, continue with decreasing intensity for a period of time” (quoted by Lechner and colleagues92).

With these pioneering experiments, Müller and Pilzecker laid the groundwork for what today is termed memory consolidation—the idea that memories initially persist in a fragile state and are stabilized over time as they are consolidated into long-term memory.93 Although it was immediately realized that the work on perseveration and retroactive interference provided an explanation for the temporally graded retrograde amnesia observed in patients by Ribot and Jackson, it took some time for this idea to have an impact on animal studies. It was not until 1949 that two papers reported retroactive interference in rodents with the use of electroconvulsive shock to induce retrograde amnesia.94,95 In theoretical work at the same time, Hebb and Gerard96,97 proposed that memory consisted of two “traces” of reverberating neural activity that first gives rise to short-term memory and then to long-term memory (Fig. 11-10). An interesting question that is still actively being explored is whether these short-term and long-term memory traces occur in series or in parallel. Although much work assumes that they are serial, some intriguing experiments suggest that they may form independently in parallel. Despite the fact that much work on memory consolidation has focused on impairing memory after training, memory can also be enhanced during the period of consolidation, as revealed by the work of McGaugh.97 Thus, the existence of periods of memory consolidation provides an evolutionarily important mechanism to modulate our responses to learned experiences.

The concepts of memory consolidation were critically important for the development of biologically based approaches to memory storage. In particular, postulates that structural

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**Figure 11-10** Memory consists of distinct phases, including short-term memory, long-term memory, and long-lasting memory. Distinct molecular mechanisms underlie each of these phases. Although these memory phases are shown schematically as though they exist in series, evidence suggests that they may also partially exist in parallel, thus implying that they are mediated by distinct molecular mechanisms acting independently. (From McGaugh JL: Memory—a century of consolidation. Science 287:248, 2000.)
changes might underlie memory traces led to development of the idea that proteins might mediate memory storage and then that RNA synthesis was required. With the development of molecular biology, the finding that translation and transcription were critical for memory storage put study of the molecular mechanisms of memory firmly in the realm of the central dogma of molecular biology and led to the use of molecular techniques by many researchers to probe how information is stored in neural circuits. Furthermore, it became clear that it was molecular cascades of signaling molecules, transcription factors, and waves of RNA and protein synthesis that explained the perseveration and retroactive interference observed by experimental psychologists.

Cellular and Molecular Mechanisms of Memory Storage

At the cellular level, the most striking finding about the potential biologic basis of memory came in 1973 when Bliss and Lomo discovered that repeated high-frequency stimulation of input to the hippocampus in vivo resulted in a long-term potentiation (LTP) of synaptic transmission. LTP provides a cellular model of memory. Evidence has suggested that processes similar to LTP may mediate memory because induction of LTP impairs ("occludes") subsequent memory formation. LTP is induced after learning. Furthermore, genetic and biochemical manipulations that impair LTP also lead to memory impairment. The development of in vitro slice preparations to study hippocampal LTP and manipulate hippocampal slices pharmacologically and electrophysiologically has been critical for identification of the molecular mechanisms underlying synaptic plasticity and memory.

Like behavioral memory, hippocampal LTP is an experience-dependent process, and extensive evidence suggests that these processes are mediated by similar molecular mechanisms. Repeated synaptic stimulation in hippocampal slices, as well as behavioral training, activates the N-methyl-D-aspartate (NMDA)-type glutamate receptor, a molecular coincidence detector activated by glutamate and postsynaptic depolarization. When activated, the NMDA receptor becomes permeant to calcium. The resultant influx of calcium into the postsynaptic neuron activates a number of second messenger signaling pathways, including calmodulin kinases (CaMKs), adenylyl cyclase, and mitogen-activated protein kinases (MAPKs). Synaptic plasticity and behavioral memory are also modulated by neurotransmitters that activate G protein–coupled receptors, such as dopamine and norepinephrine, which in turn also modulate intracellular signaling pathways.

This local synaptic activation mediates plasticity for the first hour or so after induction of LTP. Long-term plasticity, called L-LTP, lasts for many hours and involves the induction of new gene transcription and the synthesis of new proteins. Thus, long-lasting forms of LTP, like long-term memory, are selectively sensitive to inhibition of protein and RNA synthesis. Study of the molecular mechanisms of translational and transcriptional regulation has led to two surprises in recent years. First, the synthesis of new proteins can occur, in part, within the dendrite locally at the synapse, thereby providing a potentially long-lasting synaptic tag to mark synapses that are potentiated. Second, regulation of transcription involves epigenetic mechanisms of chromatin modification, DNA methylation, and chromatin remodeling—mechanisms that were thought to function primarily in a developmental context. It is interesting to suggest that memory may, in part, be stored as epigenetic modifications that alter the expression of select genes.

One important question is how activation of these various signal transduction pathways, changes in gene expression, and epigenetic marks give rise to long-lasting increases in synaptic transmission and memory. The α-amino-3-hydroxy-5-methyl-4-isoazopropionic acid (AMPA)-type glutamate receptor provides one potential target of these molecular mechanisms. Kinas activated by influx of calcium, such as CaMKII, phosphorylate the GluR1 subunit of the AMPA receptor, which increases its open time and the amount of receptor available on the cell surface at the synapse. Increased levels and activity of the AMPA receptor would increase the depolarization resulting from release of glutamate at the synapse, thereby increasing synaptic strength. Long-lasting forms of LTP activate gene expression and increase transcription of the gene encoding GluR1. Thus, although there are clearly a variety of molecular targets by which synaptic strength can be stably enhanced, the AMPA receptor provides an attractive effector mechanism.

Anesthetic-Induced Amnesia

At larger doses, administration of virtually any anesthetic drug produces loss of consciousness, which in turn results in episodic amnesia. Because monitors capable of assessing memory formation, storage, and retrieval are lacking, one common clinical strategy relies on delivery of hypnotic doses of anesthetics to ensure amnesia. However, anesthetic drugs have the capacity to produce amnesia at subhypnotic doses. The engrams (physical alterations in neural tissue thought to be the substrate for memory) most readily impaired by anesthetic drugs involve episodic memories. Although multiple mechanisms might account for anesthetic-induced amnesia, at subhypnotic doses, benzodiazepines such as midazolam and intravenous anesthetics such as propofol primarily affect either long-term memory storage or its retrieval. At plasma concentrations of 40 ng/mL of midazolam or 0.9 μg/mL of propofol, humans are able to encode and retain memories over a period of 15 to 30 minutes. However, these memories are lost before consolidation.

Even though the circuit-level, neuronal, and molecular mechanisms of anesthetic-induced amnesia remain incompletely understood, animal studies suggest that amnestic doses of anesthetics have the capacity to interfere with memory formation at multiple points. For the volatile anesthetics, memory formation is impaired at drug concentrations between a 25% and 50% of the minimum alveolar concentration (MAC) in humans and rodents, with individual agents differing slightly in their amnestic potency relative to their MAC (immobilizing dose). LTP is a form of synaptic plasticity thought to contribute to memory and it represents a cellular model of memory as discussed earlier. In addition to impairing memory at the behavioral level, anesthetics such as isoflurane may also impair or completely abolish LTP in hippocampal slice preparations. Other anesthetics such as barbiturates, benzodiazepines, and propofol likewise alter the expression of LTP and long-term depression in hippocampal slice preparations, thereby providing cellular correlates of their amnestic properties. In these instances, anesthetics are
thought to impair LTP via GABAergic mechanisms. Subunit-containing GABA, receptors are highly sensitive to amnestic concentrations of isoflurane. However, other receptor signaling systems are certainly involved in mediating anesthetic-induced amnesia.

Hippocampal θ rhythms (or θ oscillations) are the largest-amplitude synchronous EEG signals that can be recorded from mammalian brain. θ Oscillations have a characteristic frequency in the 5- to 12-Hz range in the behaving rat and dominate the EEG spectrum during NREM sleep (as discussed earlier), as well as during waking behavior essential for survival, such as exploration. Hippocampal θ oscillations are thought to facilitate mnemonic processes in vitro and in vivo. At the circuit level, anesthetics have recently been shown to alter hippocampal θ oscillations, a finding that may underlie anesthetic-induced amnesia.

At the molecular level, propofol inhibits NMDA receptor-mediated activation of one subclass of the MAPK superfamily, extracellular signal-regulated protein kinase 1/2 (ERK1/2), in hippocampal neurons. This results in concurrent inhibition of transcriptional activity inasmuch as interference with MAPKs can uncouple synaptic events from nuclear responses. This finding might provide a molecular mechanism through which an anesthetic impairs transcription-dependent encoding of memory. However, whether this mechanism represents a common action of anesthetic-induced amnesia awaits further elucidation.

The hippocampus is not the only limbic system structure thought to be involved in anesthetic-induced amnesia. It has now been established in animal models that the basolateral nucleus of the amygdala is critical for the amnestic effects of general anesthetics. Propofol, benzodiazepines, and sevoflurane lose their amnestic power if the basal nucleus of the amygdala is lesioned. These data suggest that the amnesic doses of general anesthetics modulate output of the amygdala in such a way that memory formation is diminished. The role of the amygdala in anesthetic-mediated amnesia may be related to the hippocampus because the two structures are strongly interconnected. Furthermore, the inability of an anesthetic agent to suppress
memory has clinical implications for patients who are experiencing intraoperative awareness, a topic to which we turn in the next section.

## Consciousness

### Historical Background

It has been known since antiquity that inhalation of certain gases may alter consciousness. As Strabo (64 BC–AD 25) wrote of the Delphic oracles: "They say that the seat of the oracle is a cavern hallowed deep down in the earth, with a rather narrow mouth, from which rises a vapor that produces divine possession. A tripod is set above this cleft, mounting which, the Pythia inhales the vapor and prophesies." Only recently did evidence emerge that the general anesthetic ethylene may have been the vapor in the Temple of Apollo that induced these mystical states.123

In the modern era, renowned psychologist William James’ experiments with nitrous oxide influenced one of his greatest works, *The Varieties of Religious Experience*, and yielded an 1898 article titled “Consciousness under Nitrous Oxide.”124 By the end of the 19th century, James and others regarded consciousness as a fundamental scientific question. In the 20th century, however, the dominating psychological paradigms of behaviorism and psychoanalysis disregarded or actively discouraged consciousness as a subject of serious inquiry. This antipathy toward the scientific study of consciousness persisted until the 1980s. Although Harvard anesthesiologist Henry Beecher promoted general anesthetics as a tool to study consciousness in the mid-20th century,125 it was not until the 21st century that a true renaissance of interest in consciousness and anesthesia emerged. The current focus on consciousness within the field of anesthesiology is related primarily to anesthetic mechanisms or intraoperative awareness.

### Neural Correlates of Consciousness

Whereas philosophers at the time of the Delphic oracles were concerned with the nature of being (ontology), the focus of 18th century thinkers such as Immanuel Kant was the nature and mechanism of knowing (epistemology). In his *Critique of Pure Reason*, Kant argued that our minds affect the ideas that we have about nature. Human experience of reality has two nonintersecting parts: (1) the part accessed by our senses (the phenomenal realm) and (2) the part outside cognition (the noumenal realm). The mind must posses, according to Kant, innate categories to be able to take the information in the phenomenal realm and make inferences about what lies in the noumenal one. Stated another way, he posited that the mind was modular, with discrete faculties that subserved specific cognitive functions. He recognized, however, that for these specific functions to be translated into a unified perceptual experience, there must be a process of integration that is essential.

Consistent with the philosophy of Kant, neuroscientist Giulio Tononi has proposed a 21st-century “information integration” theory of consciousness, as well as a theoretical model that expresses the capacity of neural systems to synthesize information.126,127 Tononi suggests that consciousness reflects a higher capacity to integrate information processed in functionally specialized modules, which is why, for example, thalamocortical circuits seem to be more relevant to conscious processes than cerebellar circuits do.

In more concrete terms, the neural correlates of particular sensory modalities (e.g., the visual) must ultimately be combined with other sensory modalities (e.g., the tactile) to generate a unified perception. This is also true of the various submodalities of sensory perception (such as color, form, and motion in visual processing). For example, we do not perceive the sun as sequentially spherical, yellow, and warm, but instead experience all these distinct traits at one time. Thus, there is a unity to our conscious experience. Because, however, the brain processes these traits in a number of discrete neuronal subpopulations (e.g., visual and somatosensory cortices), there must be a higher-order process that synthesizes the information. This process is often referred to as “cognitive binding.”126,129

Cognitive binding is thought to be necessary, though perhaps not sufficient, for consciousness itself. Several mechanisms for integration of neural information have been proposed, including convergence, assembly, and synchrony.130,131 Binding by convergence is a hierarchic processing strategy characterized by transmission of information from primary to higher-order brain regions for integration.132-134 Binding by assembly refers to information synthesized in a Hebbian cell assembly, that is, a group of interrelated neurons whose connections grow stronger with repeated firing together.150 Finally, binding by synchrony introduces a temporal dimension to synthesis and is thought to be associated with neural events at the frequency of 40 Hz.156-158

Many of the neural regions or processes that are considered correlates of consciousness are linked to integration of information. Neural correlates may be identified through a number of methods, including clinicopathologic correlation, functional neuromaging, and neurophysiologic recording. A number of candidates for the neural substrate of consciousness emerged in the 1980s and 1990s, including

- Extended reticular-thalamic activation system
- Intralaminar nucleus in the thalamus
- Reentrant loops in thalamocortical systems
- 40-Hz rhythmic activity in thalamocortical systems
- Neurons in the superior temporal sulcus
- Neural activity in visual area V5/MT
- Neurons in the extrastriate visual cortex projecting to prefrontal areas
- Anterior cingulate system
- Recurrent processing from higher to lower cortical areas

Rees and colleagues discussed the evidence for many of these neural correlates of human consciousness.147 As we discuss in the following sections, these correlates may serve as the anatomic or neurophysiologic substrates on which general anesthetics act to suppress consciousness.

### Effects of Anesthetics on Neural Correlates

General anesthetics may generate unconsciousness by suppressing the activity of the neural correlates at various levels of neural organization, as well as by disrupting processes of information...
integration. It has become clear that many of the proposed neural correlates of consciousness are modulated by general anesthetics.

Subcortical and Thalamocortical Effects

Functional neuroimaging by positron-emission tomography (PET) during isoflurane or halothane anesthesia demonstrated reduced cerebral glucose metabolism in subcortical structures associated with arousal, including the thalamus and midbrain reticular formation.\(^4\) PET has also revealed suppression of thalamic activity in association with propofol-induced unconsciousness.\(^5\) Other subcortical structures affected include the arousal-promoting TMN in the hypothalamus, which has been associated with anesthetic-induced hypnosis.\(^6\)

Recent data acquired by electrophysiologic techniques in humans have brought into question the role of subcortical structures such as the thalamus. Because PET has poor temporal resolution,\(^1\) Velly and associates compared cortical EEG tracings with recordings from subcortical deep brain electrodes in the human subthalamic nucleus. The authors were able to deduce that their field recordings were actually detecting thalamic rather than subthalamic activity. Loss of consciousness with propofol or sevoflurane was correlated with the cortical EEG, whereas minimal changes in the subcortical recording were identified. As discussed earlier, Alkire and colleagues demonstrated that nicotinic cholinergic agonism in the central medial thalamic nucleus could reverse sevoflurane-induced unconsciousness.\(^7\) Although it would appear that these data contradict the findings of Velly and coworkers, administration of the nicotinic antagonist mecamylamine in the central medial nucleus did not induce anesthesia or even reduce anesthetic requirements. Alkire and associates concluded that the central medial nucleus may be an "on" switch for arousal but not an "off" switch for anesthesia.

The thalamocortical system is thought to be critical for consciousness. The resonance of thalamocortical circuits has been proposed as the "dynamic core" of consciousness\(^8\) and is consistent with cognitive binding by 40-Hz oscillations.\(^9\) Alkire and associates described a "unified theory of narcosis" based on the finding that thalamocortical circuits were disrupted under general anesthesia.\(^10\) It has been demonstrated that isoflurane and halothane disrupt functional connectivity between the thalamus and cortex.\(^11\) Functional connectivity is the causal influence of one brain region on another that occurs beyond a mere anatomic connection.\(^12\) Propofol has also been shown to induce a hyperpolarization block of thalamocortical neurons.\(^13\)

Cortical and Corticocortical Effects

General anesthetics have been demonstrated to affect a number of cortical brain regions. Variable electromagnetic tomographic analysis has demonstrated that multiple general anesthetics induce reversible inhibition of the medial orbital and dorsolateral prefrontal and frontal cortex, anterior cingulate cortex, and paracentral gyrus.\(^14\) The finding of frontal and cingulate cortex inhibition was consistent with previous PET findings of propofol-induced anesthesia.\(^15\) As noted earlier, both the prefrontal and anterior cingulate cortices have been proposed as neural correlates of conscious processing.

It has been demonstrated that general anesthetics of distinct pharmacologic properties affect EEG coherence in a similar way during unconsciousness, an effect that is reversed on the return of consciousness.\(^16\) In 176 cases of human surgical anesthesia using a variety of both inhaled and intravenous anesthetics, there were invariant changes in the electrical uncoupling of brain regions. Multivariate analysis of quantitative EEG recordings showed that \(\gamma\) oscillations (35 to 50 Hz) of the rostral and caudal regions of the brain became uncoupled from one another. These changes were associated with the onset of anesthesia, intensified with increasing depth of anesthesia, and reversed with the termination of anesthesia.

Rostrocaudal dissociation is of particular relevance given the proposed scans of 40-Hz oscillations that sweep from the frontal to the occipital cortex and back again.\(^17\) In addition to this functional rostrocaudal disconnection, the hemispheres themselves became functionally disconnected. The effects of anesthesia on rostrocaudal processing have been studied in animal models as well. It has been demonstrated that processing of visual stimuli during anesthesia can be transmitted from the occipital to the frontal cortex, whereas recurrent processing from the frontal back to the occipital cortex is interrupted.\(^18\)

This finding is consistent with the proposed neural correlate of recurrent processing of neural information,\(^19\) that is, transmission of signals from higher-order areas back to primary processing areas.

Other studies in humans have shown functional uncoupling of neural regions in association with general anesthesia. Peltier and colleagues demonstrated loss of functional connectivity in the cerebral cortex during sevoflurane anesthesia.\(^20\) This provides further evidence that anesthetics uncouple the activity of cortical regions that would otherwise influence one another in the waking state.

Information Dissociation and Unconscious States

Based on the effect of anesthetic-mediated interruption of neural information synthesis, a "cognitive unbinding" paradigm of general anesthesia was postulated.\(^21\) This framework explicitly stated that anesthetics may function by interrupting various cognitive binding processes from the cellular to the global brain level. This was based, in part, on findings by John and associates who demonstrated functional uncoupling of the hemispheric and rostrocaudal axes of the brain (interruption of synchronous binding). The cognitive unbinding paradigm was also based on interruption of synthetic processes in cortical area MT under isoflurane (interruption of convergent binding).\(^22\)

John and Prichard's "anesthetic cascade" supported the concept of cognitive unbinding while at the same time postulated a specific stepwise process by which anesthetics suppress consciousness.\(^23\) The proposed "cascade" is as follows:

- Depression of the brainstem reduces the influence of the ascending reticular activating system on the thalamus and cortex.
- Depression of mesolimbic-dorsolateral prefrontal cortex interactions leads to blockade of memory storage.
- Further depression of the ascending reticular activating system leads to hyperpolarization of GABAergic neurons in the nucleus reticularis of the thalamus, which results in blockade of thalamocortical reverberations and the associated \(\gamma\) oscillations underlying perception.
Functional uncoupling of parietal-frontal cortical activity, thereby interrupting cognition, and finally Reduced awareness of and increase in frontal δ- and θ-band activity.

Recent data on the temporal relationship of subcortical anesthetic effects bring into question the first step of the cascade. Furthermore, it is unclear how agents such as ketamine or nitrous oxide, which can lead to EEG activation rather than depression, fit within the proposed anesthetic cascade. Nonetheless, the anesthetic cascade is one of the most specific and data-driven theories of anesthetic-induced unconsciousness.

Wall and Hicks supported both cognitive unbinding and the anesthetic cascade based on EEG phase-space analysis of emergence from sevoflurane anesthesia in humans. Return of consciousness was characterized by a higher-dimensional phase space, reflecting a complexity of brain dynamics that could sustain consciousness. The fractal “strange attractors” that were identified on emergence were posited to be the coherence of &dgr; frequencies associated with unconsciousness, in what the authors referred to as “cognitive rebinding.”

These frameworks of anesthetic-induced unconsciousness as information dissociation are supported by recent studies of other unconscious states. Studies of brain-injured patients in vegetative states have revealed fragmented cerebral activity and loss of effective cortical connectivity. It has therefore been suggested that vegetative states are “disconnection” syndromes. The neural regions affected in vegetative states include the frontal cortex, cingulate cortex, association cortices, and thalamus, which are also targets for general anesthetics. Like anesthesia, recovery from vegetative states is associated with return of thalamocortical connectivity.

As discussed earlier, sleep is a state with a number of traits similar to general anesthesia. Using transcranial magnetic stimulation and EEG recordings of subjects either asleep or awake, Massimini and coworkers demonstrated that NREM sleep is also characterized by loss of effective cortical connectivity. The loss of cortical connectivity associated with sleep suggests a common feature with anesthetic-induced unconsciousness and vegetative states.

### Consciousness in the Operating Room

Although consciousness is emerging as an important scientific problem that is intimately linked to the mechanism of general anesthesia, it can also pose a clinical problem intraoperatively. Awareness during general anesthesia—which denotes both awareness and subsequent explicit recall of intraoperative events—is a complication receiving increased attention by both patients and clinicians. Dreaming is another subjective state that can occur during anesthesia, with an incidence of 22% in patients undergoing elective cases. Although some cases represented “near-miss” experiences of awareness, others were thought to occur during recovery from anesthesia.

Despite recent attention by the medical community and the lay press, the incidence of intraoperative awareness—and hence the magnitude of the problem—remains uncertain. A multicenter study in the United States by Sebel and colleagues estimated an incidence of awareness with explicit recall of approximately 0.13%, a rate consistent with large European studies demonstrating awareness in 1 to 2 per 1000 cases. In contrast, a recent study of awareness in a regional medical system reported a much lower incidence of 1 episode of awareness per 14,560 cases, or 0.0069%. The timing and content of postoperative interviews probably play a role in this discrepancy.

A proportion of patients experiencing awareness may subsequently exhibit serious psychological sequelae, including post-traumatic stress disorder. Earlier studies reported a greater than 50% incidence of post-traumatic stress disorder, whereas more recent studies suggest a much lower rate of occurrence. Because of the profound distress that it can induce in patients, a reliable and practical method of detecting intraoperative consciousness would be an important clinical advance.

### Assessing Consciousness Intraoperatively

As early as 1937, Gibbs and coauthors reported that EEG measurements were sensitive to the effects of general anesthetics. However, the use of unprocessed EEG data to assess anesthetic depth in the operating room is impractical for a number of reasons: (1) there is no unique electrical “signature” of an unprocessed EEG that is invariant, (2) the use of standard multiple-channel diagnostic EEG devices is cumbersome in the intraoperative setting, and (3) the use of such diagnostic devices—capable of localizing the source of abnormal signal patterns—generally requires a dedicated interpreter. Because of these limitations, EEG monitors with a minimal number of channels that use processing algorithms have been developed in an attempt to monitor anesthetic depth and detect intraoperative awareness (see Chapter 39).

Fourier transformation of raw EEG data enables the derivation of median power and spectral edge frequencies, and a number of devices available for intraoperative use are based on Fourier-transformed EEG data. The bispectral index (BIS; Aspect Medical Systems, Natick MA) analyzes burst suppression, β-band power, and bispectral coherence of δ and θ waves. The Narcotrend Monitor (MonitorTechnik, Bad Bramstedt, Germany) analyzes stages and substages of anesthesia and was based on a similar developmental process as the BIS (with a distinct algorithm). The Patient State Index (PSI; Physiometrix, Inc., N. Billerica, MA) is derived from quantitative EEG techniques and is based on signal relationships between the frontal and occipital brain regions. Entropy monitors (e.g., S/5, Instrumentarium Corp. [Datex-Ohmeda], Helsinki, Finland) are based on the concept of information entropy posited by Shannon and analyze randomness in frequency and phase relationships with the use of both EEG and frontal EMG. Entropy monitors measure state entropy (response over the range of 0.8 to 32 Hz, reflecting the EEG-dominant spectrum) and response entropy (response over the range of 0.8 to 47 Hz, reflecting both EEG and EMG spectra). Whereas the aforementioned monitors record spontaneous EEG, the stimulus-response technique of auditory evoked potentials has also been used to assess anesthetic depth and can be analyzed in conjunction with other EEG signaling parameters. Because the BIS has been extensively studied and is the most frequently used monitor to assess depth of anesthesia, it will be the focus of the remaining sections.

### Development and Validation of the BIS Monitor

The BIS monitor was developed empirically by analyzing a high-fidelity database of EEG recordings from approximately 2000 patients who received a variety of commonly used general
anesthetics, sedative-hypnotics, and opioids (see Chapter 39). Segments of the EEG were compared with clinical findings of hypnosis; candidate spectral and bispectral features of these segments were computed and tested for their ability to distinguish the clinically described hypnotic states. The best of these features were then combined by multivariate statistical modeling to form a composite index (dimensionless number between 0 and 100, where 0 is isoelectric and 100 is awake), which underwent further prospective testing in a larger database.

In the mid-1990s, a number of studies demonstrated that changes in BIS values were associated with movement in response to noxious stimuli, as well as hemodynamic responses to interventions such as laryngoscopy. A multicentered study using movement as the measured outcome found that BIS values had better response with hypnotic drugs such as isoflurane and propofol than with opiates. Whereas some studies focused on the relationship of BIS to movement in an attempt to validate the BIS in terms of MAC, other studies investigated the relationship of BIS to hypnosis, or MAC-mind. Flashman and associates used propofol or thiopental to induce anesthesia while continuously monitoring the BIS. BIS values above 60 were highly correlated with the ability of subjects to respond to verbal command. Another multicentered investigation focused on validation of the BIS monitor by comparing BIS values with anesthetic drug concentrations and level of sedation. Other studies confirmed the value of the BIS in measuring hypnotic response to both inhalable and intravenous general anesthetics. The BIS has also been validated for assessing the depth of anesthesia in children.

One study in a high-risk population showed a significantly decreased incidence of confirmed awareness. When combining both “possible” and “confirmed” awareness events, however, there was no difference between the BIS and control groups. Furthermore, the high number needed to treat (138) and the associated cost ($2200 U.S. dollars) in the high-risk group bring into question the use of the BIS to prevent awareness in the general population.

Comparison of the BIS with Other EEG-Based Monitors

Because of validation of the BIS in a number of clinical studies, other emerging technologies have been compared with the BIS and control groups. Further, the high number needed to treat (138) and the associated cost ($2200 U.S. dollars) in the high-risk group bring into question the use of the BIS to prevent awareness in the general population.

The Narcotrend monitor has been shown to correlate well with predicted propofol concentrations in addition to the BIS. The Narcotrend index correlated with the BIS during propofol and remifentanil anesthesia in a small number of patients ($n = 26$). The BIS and Narcotrend indices were also shown to be comparable in monitoring the depth of propofol anesthesia. State entropy and response entropy show close correlation with the BIS in assessing sevoflurane anesthesia, as well as propofol-remifentanil anesthesia. In a small study evaluating loss of response to verbal command and loss of consciousness during propofol anesthesia, it was suggested that state entropy may be more useful than the BIS. One study also demonstrated comparable performance of the BIS and entropy modules during both intravenous and inhaled anesthesia, with less electrocautery interference by the entropy monitor.

Limitations of the BIS

There are numerous limitations associated with BIS monitoring. One such limitation is that BIS values remain unchanged or even elevated during nitrous oxide anesthesia. The intravenous anesthetic ketamine may also elevate BIS levels, perhaps reflecting its ability to increase the beta power of the EEG spectrum. It is of interest that both ketamine and nitrous oxide are thought to act primarily through NMDA glutamate receptors. The anesthetic effect of xenon, which also acts on this receptor system, is similarly not reflected with BIS technology. It is of further interest that although spectral entropy values are increased by ketamine in a similar manner to the BIS, the addition of nitrous oxide has been shown to decrease state and response entropy values. Conversely, BIS values are sensitive to nonanesthetic agents routinely administered in the operating room, and have been shown to decrease in patients receiving neuromuscular blockers, while fully conscious and while anesthetized. BIS values derived from multiple sensors on the same patient have also been shown to be discordant, suggesting intrapatient variability and poor reproducibility of the index. These and other limitations indicate the need for more sophisticated monitors of anesthetic depth that are linked to the neurophysiologic mechanisms of consciousness.

Conclusion

The oscillating states of sleep and wakefulness are fundamental features of our existence; as such, they have been pondered philosophically since antiquity and explored scientifically in modern times. The field of anesthesiology has much to gain from these investigations and, just as importantly, much to offer in return. Our further understanding of the neuroscientific mechanisms of general anesthesia may provide fundamental insight into the nature of consciousness, unconsciousness, and the memories that bind them together to form a stable sense of self.

References


http://www.us elsevierhealth.com/Medicine/Anesthesiology/book/9781416066248/Millers-Anesthesia/


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