CHAPTER

42

Sleep, Dreaming, and Wakefulness

Sleep is a behavioral state that alternates with waking. It is characterized by a recumbent posture, a raised threshold to sensory stimulation, a low level of motor output, and a unique behavior—dreaming. The complex neurobiology of these behavioral features of sleep has been explored at the systemic, cellular, and molecular levels since the mid-1960s. Although these studies have provided substantial insight into the physiology and pathology of sleep, only recently have we begun to obtain definitive answers to the adaptive significance of sleep, the behavioral state that takes up one-third of our lives.

In contrast to sleep, the conscious behavior of waking is characterized by an active and deliberate sensorimotor discourse with the environment. For maintenance of waking behavior, neural gates must remain open for sensory input and motor output, the brain must be tuned and activated, and the chemical microclimate must be appropriate for processing and recording of information. Wakefulness is accompanied by conscious experience that reaches its highest level of complexity in adult humans. Waking behavior includes a number of cognitive aspects, such as sensation, perception, attention, memory, instinct, emotion, volition, cognition, and language, that make up our awareness of the world and self and form the basis of an adaptive interaction with our environment. This chapter focuses on the mechanisms of behavioral state control that make such interactions possible, with an emphasis on sleep as a component of adaptive behavior.

THE TWO STATES OF SLEEP: RAPID EYE MOVEMENT AND NONRAPID EYE MOVEMENT

The behavioral signs of sleep vary regularly during every period of sleep; posture, arousal, threshold, and motor output change in a stereotyped, cyclic manner. Although these changes can be observed directly, their study is facilitated by placing electrodes on the scalp to measure the electrical activity of the brain. From these electroencephalograms (EEGs) (Fig. 42.1), two distinct substates of sleep—rapid eye movement (REM) and non-REM (NREM)—can be discerned. Both show interesting contrasts with waking, and these contrasts improve our understanding of states of consciousness.

At the onset of sleep, the brain begins to deactivate, and awareness of the outside world is lost. A well-described sequence of thalamocortical events causes the progressive slowing of brain waves, seen on EEG during this phase of NREM sleep. The threshold for arousal rises in proportion to the degree of EEG slowing, and at the greatest depth of sleep, awakenings are often difficult, incomplete, and brief. This sleep state is designated the slow wave or delta phase of NREM sleep. People have little or no recall of conscious experience in deep NREM sleep. Many autonomic and regulatory functions, such as heart rate, blood pressure, and respiration rate, diminish in NREM sleep, but some neuroendocrine activity

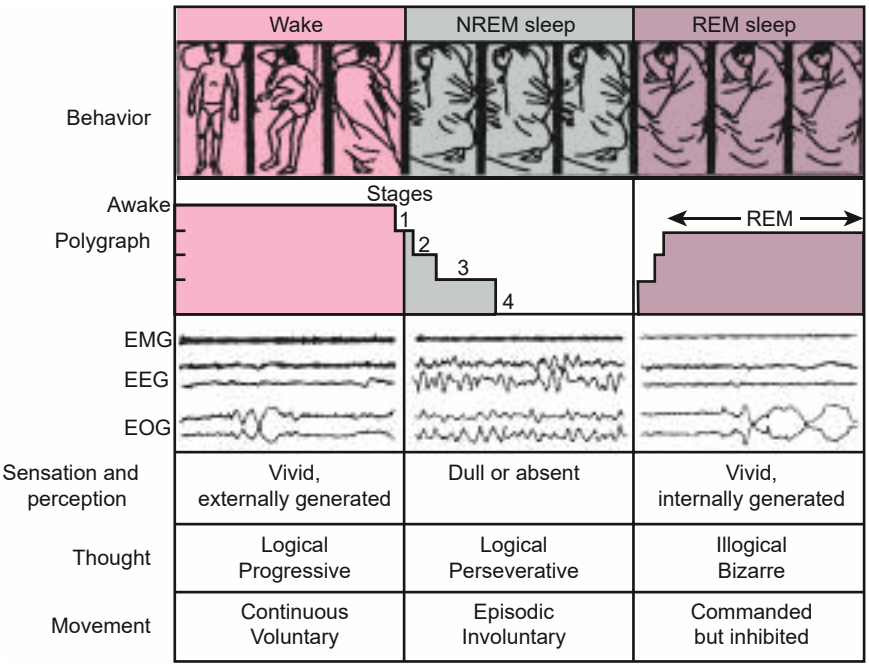

FIGURE 42.1 Behavioral states in humans. Body position changes during waking and at the time of phase changes in the sleep cycle. Removal of facilitation (during stages 1–4 of NREM sleep) and addition of inhibition (during REM sleep) account for immobility during sleep. In dreams, we imagine that we move, but no movement occurs. Tracings of electrical activity are shown in ~20-s sample records. The amplitude of the electromyogram (EMG) is highest in waking, intermediate in NREM sleep, and lowest in REM sleep. The electroencephalogram (EEG) and electrooculogram (EOG) are activated in waking and REM sleep and inactivated in NREM sleep. Reprinted with permission from Hobson and Steriade (1986).

increases. The pulsatile release of growth hormone and sexual maturation hormones from the pituitary is maximal during sleep, with over 95% of the daily output occurring in NREM sleep.

At regular intervals during sleep, the brain reactivates into a state characterized by fast, low-voltage activity in the EEG, along with muscle atonia and rapid eye movements. This sleep state, termed rapid eye movement sleep because of prominent eye movements, differs from waking in several ways, but most notably by an inhibition of sensory input and motor output. Postural shifts precede and follow REM sleep; eye movements, intermittent small muscle twitching, and penile erection occur during REM sleep. The presence (or absence) of REM sleep erection is used clinically to distinguish between psychological and physiological male impotence. In REM sleep, many autonomic functions change; the fine control of temperature and cardiopulmonary function is lost.

People aroused from NREM sleep, especially early in the night, are confused, have difficulty reporting conscious experience, and return to sleep rapidly. Subjects aroused from REM sleep, especially during periods with frequent eye movements, often give detailed reports of dreams characterized by vivid hallucinations, bizarre thinking, and intense emotion. Although dreaming also occurs during NREM sleep, it is much more strongly associated with the activated brain of REM sleep.

NREM and REM Phases Alternate throughout Sleep

REM and NREM sleep states alternate, with a cycle of about 90 min in adult humans. NREM phases are deeper and longer early in the night (Fig. 42.2A). Together with the regularity of the periods (Fig. 42.2B), this property has suggested that a damped oscillator is the underlying neural mechanism for NREM–REM cycles. The portion of the 24-h day devoted to NREM and REM sleep varies across the lifespan and across species (Fig. 42.3; Table 42.1).

Sleep Appears to Have Multiple Functions

As a quiescent and ecologically protected behavior, sleep fosters conservation of energy, defense from predation, and an opportunity for repair of injury. The anabolic character of NREM sleep (e.g., brain and body inactivity and hormone release) suggests a rest and restoration function. In contrast, the high proportion of REM sleep in the developing brain, the high level

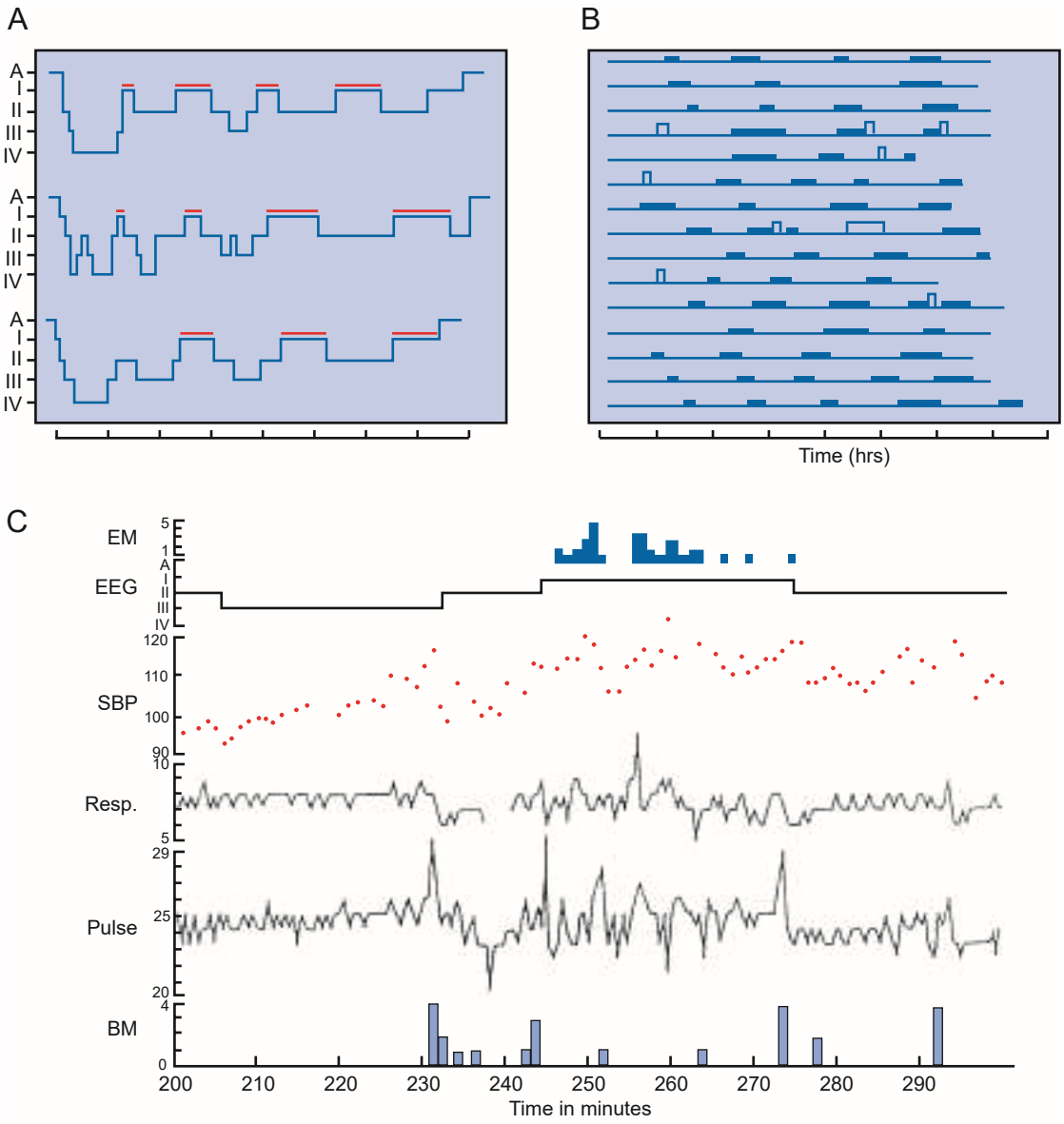

FIGURE 42.2 Periodic activation in sleep cycles. (A) The sleep stages of three people are graphed. The first two or three cycles of the night are dominated by deep stages (3 and 4) of NREM sleep, and REM sleep (indicated by red bars) is brief or nonexistent. During the last two cycles of the night, NREM sleep is lighter (stage 2), and REM episodes are longer, sometimes more than an hour. (B) Fifteen nights of sleep. Each line represents one night of sleep, with REM periods shown as solid bars and periods of wake as taller, open bars. Each record began at the onset of sleep. The amount of time before the first episode of REM varies, but once REM has begun, the interval between episodes is fairly constant. (C) Eye movements (EM), EEG, systolic blood pressure (SBP), respiration (Resp.), pulse, and body movement (BM) over 100 min of uninterrupted sleep. The interval from 242 to 273 min is considered the REM period, although eye movements are not continuous during that interval.

of forebrain activity, and the stereotyped movements in REM sleep suggest a role of REM sleep in brain development and plasticity. Sleep is now known to be important for immune and hormone regulations and memory consolidation. Restriction of sleep to even four hours per night is sufficient to produce impairment of these functions. The crucial role of sleep is illustrated by studies showing that prolonged sleep deprivation results in the disruption of metabolic and caloric homeostasis and eventually death.

Summary

Sleep and waking are distinct, alternate behavioral states that are mutually exclusive, but interrelated. Within sleep, two substates of behavior are readily

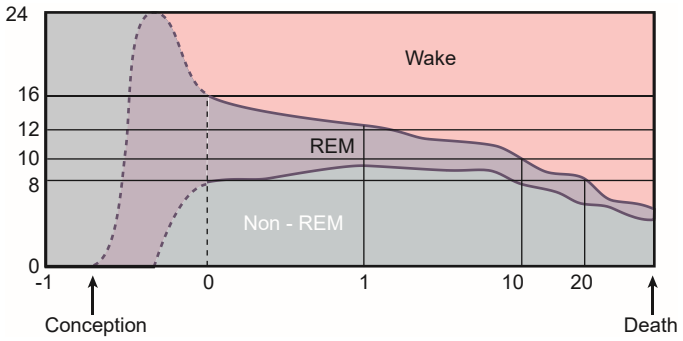

FIGURE 42.3 Portions of a 24-h day that are devoted to waking, REM sleep, and non-REM (NREM) sleep change over a lifetime. Although the timing of these changes *in utero* is not known with certainty (dotted lines), data from premature infants are consistent with REM sleep occupying most of life at a gestational age of 26 weeks. After 26 weeks, the time spent in waking increases until death.

TABLE 42.1 Phylogeny of Rest and Sleep

Organism	Rest	Sleep	REM Sleep
Mammals			
Adults	+	+	+
Neonates	+	+	+
Birds			
Adults	+	+	+, –
Neonates	+	+	+, –
Reptiles	+	+	–
Amphibians	+	+, –	–
Fish	+	+, –	–

REM, rapid eye movement; +, present; +, –, ambiguously or inconsistently present; –, absent.

distinguishable by electroencephalographic recordings, termed rapid eye movement (REM) and non-REM (NREM) sleep. NREM sleep in humans is subdivided further into four levels of increasingly deep sleep (stages I–IV). The characteristic behaviors of sleep include relaxed posture, elevated thresholds for sensory arousal, and diminished motor activity. The NREM and REM sleep phases alternate throughout the sleep period in cycles. Although all the functions of sleep are not yet known, much scientific evidence favors roles for sleep in the restoration, maintenance, and development of a range of physiological and cognitive functions.

SLEEP IN THE MODERN ERA OF NEUROSCIENCE

Philosophical speculation about the nature of sleep and conscious behavior is as old as recorded history, and many philosophers, including the Ionian Greeks, anticipated the physicalistic models that only recently have been articulated in modern neuroscience (for details of the following historical material, refer to Hobson, 1988). A signal event of the modern era of neuroscience was the discovery of the electrical nature of brain activity and, more specifically, the 1928 discovery of the human electroencephalogram (EEG) by the German psychiatrist Adolf Berger.

The state-dependent nature of the EEG helped Berger convince his skeptical critics that the rhythmic oscillations he recorded across the human scalp with his galvanometer originated in the brain and were not artifacts of movement or of scalp muscle activity. When his subjects relaxed, closed their eyes, or dozed off, the low-voltage brain waves associated with alertness gave way to higher voltage, lower frequency patterns (Fig. 42.4). These patterns stopped immediately when the subjects were aroused.

Waking and Sleep Initially Were Viewed as Activated and Nonactivated States

Following Berger's discovery, a flurry of descriptive and experimental studies aimed at understanding the EEG itself, the full range of its state-dependent variability, and the control of that variability by the brain, were performed. Loomis and Harvey were the first to describe the tendency of the EEG to show systematic changes in activity as subjects fell asleep at night (tracings 3–5 of Fig. 42.4).

Because other mammals shared these correlations between arousal level and EEG, the Belgian physiologist Frederick Bremer made experimental transections of the mammalian brain to determine the nature and source of EEG activation (the low-voltage, fast pattern of waking) and deactivation (the high-voltage, slow pattern of sleep). Thinking the activity level probably depended on sensory input, Bremer transected the brain of the cat at the level of the first cervical spinal cord segment, producing a condition called *encephale isole*. He was surprised to find that the isolated forebrain was activated and alert despite this transection of a major portion of its sensory input. When he then transected the midbrain at the intercollicular level, creating the *cerveau isole* condition, he observed a sleep-like state with persistent EEG slowing and unresponsiveness. Bremer incorrectly inferred that removal of the trigeminal nerve afferents (which entered the brain stem between the level of the two cuts) accounted for the sleep-like state of the *cerveau isole*.

Sleep Can Be Induced Electrically

That sleep might be an active brain process—and not simply the absence of waking as Bremer sup-

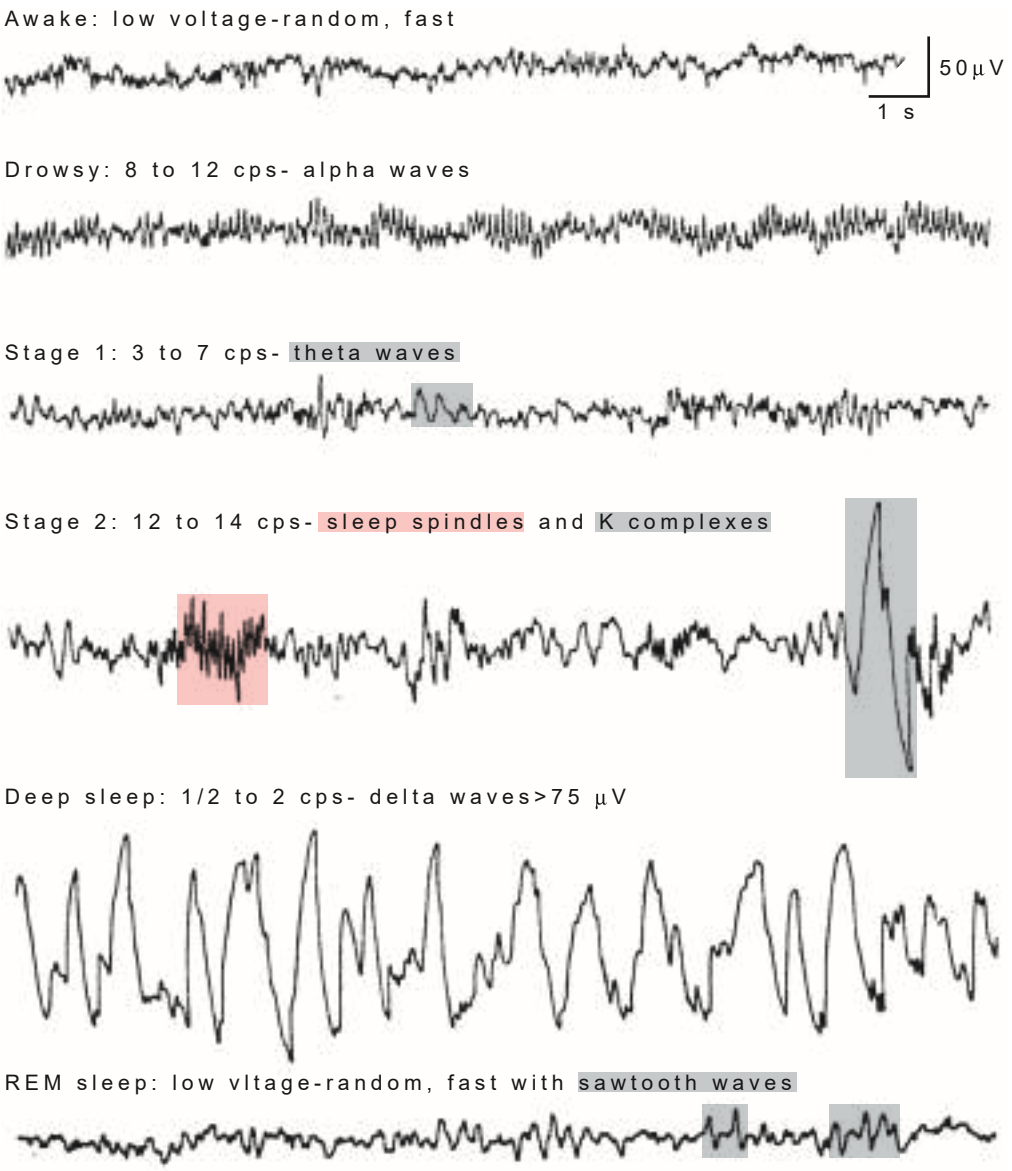

FIGURE 42.4 Electroencephalograms showing electrical activity of the human brain during different stages of sleep.

posed—was first experimentally suggested by the work of the Swiss Nobel laureate W. R. Hess. Hess was involved in a broad program investigating the effects of electrical stimulation of the subcortical regions mediating autonomic control (especially the hypothalamus). He discovered that by stimulating the thalamocortical system at the frequencies of intrinsic EEG spindles (short series of waves) and slow waves, he could induce the behavioral and electrographic signs of sleeping in unanesthetized cats. This discovery opened the door to the idea that sleep and waking might be active processes, each with its own specific cellular and metabolic mechanisms and functional consequences. This paradigm has since born abundant scientific fruit. For example, the precise details of spindle and slow wave elaboration have been worked out (Steriade, 2000). In addition, the paradigm correctly anticipated the finding that central homologues of sympathetic neurons mediate waking, whereas central cholinergic neurons mediate REM sleep (Hobson and Steriade, 1986; Steriade and McCarley, 1990).

The intrinsic nature of brain activation was clearly demonstrated in 1949 when Giuseppe Moruzzi and Horace Magoun discovered that EEG desynchronization and behavioral arousal could be produced by high-frequency electrical stimulation of the midbrain. To explain their observation, Moruzzi and Magoun proposed that the nonspecific (i.e., nonsensory) reticu-

lar activating system operates both in series and in parallel with the ascending sensory pathways. This concept allowed for the translation of afferent stimuli into central activation (Bremer's idea) and opened the door to the more radical idea that not only waking but also adaptive behavior during sleep could be activated by brain stem mechanisms without a need for sensory stimulation.

Now that we accept the idea that the spontaneous activity of neurons determines the substages of sleep, it is difficult for us to appreciate the strength and persistence of its predecessor, the reflex concept of sleep. Scientific giants such as Ivan Pavlov and Charles Sherrington were so inspired by the reflex doctrine that they were convinced that brain activity simply ceased in the absence of sensory input (Box 42.1).

The Brain–Mind Is Activated during REM Sleep

In 1953, Eugene Aserinsky and Nathaniel Kleitman, working in Chicago, discovered that the brain–mind did indeed self-activate during sleep. They observed regularly timed, spontaneous desynchronization of the EEG, accompanied by clusters of rapid, saccadic eye movements and acute accelerations of heart and respiration rates (see Figs. 42.1 and 42.2C). Working with Kleitman, William Dement then showed that these periods of spontaneous autoactivation of the brain–mind, namely REM sleep, were associated with dreaming and that this autoactivation process was also found in another mammal, the cat.

In adult humans, the intrinsic cycle of inactivation (NREM sleep) and activation (REM sleep) recurs with a period length of 90–100 min (Fig. 42.2). REM sleep occupies 20 to 25% of the recording time and NREM the remainder (75–80%) (Hobson, 1989). The NREM phases of the first two cycles are deep and long, whereas REM phases, during which sleep lightens, occupy more of the last two or three cycles.

Input–Output Gating Occurs during Sleep

The paradoxical preservation of sleep in the face of dreaming in REM sleep began to be explained when Francois Michel and Michel Jouvet, working in Lyon in 1959, demonstrated that inhibition of muscle activity was a component of REM sleep in cats. Using transection, lesion, and stimulation techniques, the Jouvet team also discovered that the control system for REM sleep was located in the pontine brain stem. The pons is the source of EEG activation and REMs. Muscle inhibition is also mediated by pontine signals, but these are relayed via the inhibitory bulbar reticular formation to the spinal cord. Synchronous with each flurry of REMs, periodic activation signals, or pontogeniculo-occipital (PGO) waves, are sent from the pons up to the forebrain (and down to the spinal cord). The PGO waves trigger bursts of firing by geniculate and cortical neurons which, during waking, process sensory inputs and motor outputs, whereas other signals originating in the brain stem damp sensory input (via presynaptic inhibition) and motor output (via postsynaptic inhibition) (Calloway *et al*., 1987).

BOX 42.1

DEAFFERENTATION VERSUS INTERNAL MODULATION: A PARADIGM SHIFT FOR SLEEP NEUROBIOLOGY

Before the discovery of the neuromodulatory systems of the brain by the Swedish team led by Kjell Fuxe in the early 1960s, scientists who studied sleep could not understand that the brain could control its own state and that the stages of sleep were actively generated. Thus such neurobiological giants as Charles Sherrington were convinced that because sleep occurred *when* environmental stimulus levels were low (which is normally true), it also occurred *because* stimulus levels were low (which is false). In light of the discovery of the reticular activating system by Giuseppe Moruzzi and Horace Magoun in 1949 and REM sleep in 1953 by Eugene Aserinsky and Nathaniel Kleitman, this theory of deafferentation gradually was replaced by a model of active internal control of the brain by the regular variations in balance between different brain regions and neuromodulators, especially NE, 5-HT, and ACh. This paradigm shift has not only led to the specification of increasingly detailed mechanisms for regulation of the brain state, but has opened the door to an appreciation of sleep as functionally significant in ways that are actively complementary to waking. This understanding of brain activity in sleep inevitably makes the emerging panoply of sleep disorders explicable and potentially treatable via a deeper understanding of sleep neurobiology.

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Thus, in REM sleep the brain–mind is effectively offline with respect to external inputs and outputs and receives internally generated signals. Sensory input is also blocked during NREM sleep, but neither PGO waves nor the active inhibition of motor output is seen outside of REM sleep.

The cellular and molecular bases of these dramatic changes in input–output gating have been detailed using Sherrington's reflex paradigm together with extracellular and intracellular recording techniques (Hobson and Steriade, 1986). For example, such techniques revealed that during REM sleep, each motor neuron was subject to a 10-mV hyperpolarization, which blocked all but a few of the activation signals generated by the REM–PGO system. Furthermore, studies showed that this inhibition was mediated by glycine (Chase *et al*., 1989). When this motor inhibition was disrupted experimentally by lesions in the pons, the cats, still in a REM-like sleep state but without the atonia, showed stereotyped behaviors (such as defense and attack postures). These behaviors reflected the activation, in REM, of the generators that produce the motor patterns for these instinctual, fixed acts (see Jouvet, 1999). In humans with REM sleep behavior disorder (see later), a similar acting out of dreams is observed.

These studies indicated that in normal REM sleep, motor inhibition prevents the motor commands of the generators of instinctual behavior patterns from being acted out. As a result, during REM these patterns are unexpressed in the outside world but occur in a fictive manner within the internal world of the brain–mind. One strong significance of these findings for a theory of dream consciousness lies in their ability to explain the ubiquity of imagined movement in dreams (Hobson *et al*., 2000).

Summary

The scientific history of sleep began with the application of electroencephalography in 1928, demonstrating that the electrical activity of the brain changed but did not cease during sleep. Subsequent refinements revealed the necessary role of the reticular formation for cortical arousal during sleep and the association of this arousal with desynchronized cortical activity. In addition, emulating the oscillatory EEG spindles of thalamic projections to cortex allowed sleep to be induced by direct thalamic electrical stimulation in experimental animals. Sleep studies in the 1950s showed REM sleep to be a "paradoxical" state in which sleep was at its deepest, yet accompanied by rapid eye movements and sympathetic signs of arousal, interpreted as dreaming, and accompanied by still further reductions of postural muscle tone. During REM sleep, pontine waves of activity arise with each flurry of eye movements, during which motor activity is deeply depressed.

ANATOMY AND PHYSIOLOGY OF BRAIN STEM REGULATORY SYSTEMS

Brain Stem Reticular Formation Contains Specific Neuronal Groups Involved in Behavioral State Regulation

Moruzzi and Magoun's original concept of a nonspecific reticular activating system has been elaborated and greatly modified by subsequent anatomical and physiological studies. Two general principles have emerged. One is that most of the classic reticular core neurons have very specific afferent inputs and highly organized outputs. The other is that the reticular formation contains small groups of neurons that send widely branching axons to distant parts of the brain, where their neurotransmitters modulate brain function.

The input–output characteristics of each of the reticular formation's multiple subsystems reflect specific sensorimotor function, modulatory function, or both. For example, many neurons of the reticular formation are involved in the integration of eye, head, and trunk positions as these change to accommodate specific behavioral challenges and tasks. These reticular neurons receive inputs from skin, muscle, bone, and joint receptors in the periphery, which they integrate and link to the vestibular and cerebellar circuits that determine posture and movement. This information must also be integrated by higher brain structures in the visual, somatosensory, and motor systems to develop the complex motor patterns of adaptive behavior.

Several chemically specified neuronal groups also lie in the reticular formation. They have patterns of connections that differ from those of the previously discussed neurons of the reticular formation. Dahlstrom and Fuxe (1964) were the first to identify neuronal populations in the brain that produced norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT). (For additional discussion of these and other neurotransmitter systems discussed in this chapter, see Chapter 7 and Fig. 43.2.)

The groups of NE neurons (designated A1–A7 by Dahlstrom and Fuxe) are located in the pons and medulla in two major groups. One group consists of scattered neurons largely located in the ventral and lateral reticular formation. The most caudal neurons (A1–A3) project rostrally to the brain stem, hypothalamus, and basal forebrain, whereas the rostral groups (A5 and A7) project caudally to the brain stem and

spinal cord. These neuronal groups, together called the lateral tegmental neuron group (Moore and Card, 1984) appear to be involved in hypothalamic regulation and motor control.

The major NE cell group is the locus coeruleus (A4 and A6). This compact cell group is located in the rostral pontine reticular formation and central gray matter. The neurons of the locus coeruleus project widely but in a highly specific pattern. One group of locus coeruleus neurons appears to project largely caudally to sensory regions of the brain stem and spinal cord. Other neurons of the locus coeruleus project widely to the cerebellar cortex, dorsal thalamus, and cerebral cortex (Moore and Card, 1984). Thus, the projection patterns of the locus coeruleus appear to be primarily to sensory structures and to cortical structures involved in integration. From this we could expect the locus coeruleus to be involved in regulating sensory input and cortical activation. As we shall see, this expectation is in accord with the available information on function.

Two additional subsets of chemically identified neurons appear critically involved in behavioral state regulation. The first subset to be discovered contained the 5-HT neurons of the brain stem raphé (Dahlstrom and Fuxe, 1964) (B1–B9 in their nomenclature). These neurons extend from caudal medulla to midbrain and are located predominantly in the raphé nuclei, a set of neuronal groups located in the midline of the brain stem reticular formation. The largest numbers of 5-HT neurons are found in the midbrain nuclei, the dorsal raphé nuclei, and the median raphé nuclei (B8 and B9). These groups project rostrally, innervating nearly the entire forebrain in a pattern that also suggests a role in regulation of behavioral state.

The other important set of reticular formation nuclei involved in behavioral state control produces acetylcholine (ACh) as its neurotransmitter. ACh was well known as the transmitter of motor neurons, but early work indicated that ACh is found in nonmotor brain areas. Two sets of cholinergic neurons are involved in control of the behavioral state. The first set is two pontine nuclei: the laterodorsal tegmental nucleus and the pedunculopontine nucleus. Cholinergic neurons in these nuclei project to the brain stem reticular formation, hypothalamus, thalamus, and basal forebrain. The projection to the forebrain involves the second set of cholinergic neurons, those in the medial septum, the nucleus of the diagonal band, and the substantia innominata–nucleus basalis complex. This set projects to limbic forebrain, including the hippocampus, and to the neocortex.

In contrast to the modulatory neurons, which are characterized by their production of norepinephrine, 5-HT, and ACh, neurons in reticular formation nuclei that are involved in sensorimotor integration typically produce either the excitatory transmitter glutamate or the inhibitory transmitter GABA.

Sensorimotor and Modulatory Reticular Neurons Differ Functionally

Sensorimotor and modulatory neurons of the reticular formation differ markedly in their firing properties. Sensorimotor neurons, approximately 50 to 75 μm in diameter, can fire continuously at high rates of up to 50 Hz and can generate bursts of up to 500 Hz. Their larger axons, especially those projecting to the spinal cord, have conduction velocities in excess of 100 m/s (Hobson and Steriade, 1986), making these neurons well suited to rapid posture adjustment and motor control.

Modulatory neurons are smaller (10–25 μm in diameter) than sensorimotor neurons, and even those with long axons conduct their signals very slowly (1 m/s). They fire wider spikes (2 ms in duration) at much slower tonic frequencies (1–10 Hz) than sensorimotor neurons. In addition, they often show a very regular, metronome-like firing pattern, a reflection of the pacemaker properties they share with the Purkinje cells of the heart. As their leaky membranes spontaneously and slowly depolarize, they reach threshold, fire, and then self-inhibit, becoming refractory even to exogenous excitatory inputs. Modulatory neurons are much less likely than sensorimotor neurons to fire in clusters or bursts unless powerfully excited; even then, they adapt rapidly. Thus, modulatory neurons are well suited to detect novel input. Because of their vast postsynaptic domain, they can also help set behavioral and mental states.

The contrasting features of sensorimotor and modulatory neurons confer functionally important distinctions on their neuronal populations. The high rate of discharge of the sensorimotor neurons, acting through extensive interconnections that tie together sensorimotor neurons, causes exponential recruitment. This amplification occurs in response to novel stimuli requiring analysis and directed action (in the wake state) and in the generation of REM sleep, a state of sustained activation (when the system is offline with respect to its inputs and outputs).

In contrast, the feedback inhibition and pacemaker potentials of modulatory neurons allow the production of highly synchronized output during waking and sleeping. These features also somehow cause an exponential decline in the firing rate of these neurons during REM sleep, until firing stops. Studies suggest that this REM sleep inhibition may involve a GABAergic action that arises in the hypothalamus at sleep onset and

spreads through the brain stem as NREM sleep progresses to REM (Fig. 42.5). These contrasting properties of sensorimotor and modulatory neurons of the reticular formation are the physical basis for the reciprocal interaction that causes NREM–REM sleep cycles.

Waking Requires Active Maintenance

Moruzzi and Magoun (1949) demonstrated that reticular formation is necessary to maintain the waking conscious state. Lesions in the midbrain reticular formation, sparing the lemniscal sensory pathways, result in a state that resembles NREM sleep. Although maintenance of the waking state often seems effortless, it requires brain mechanisms that compete with other active mechanisms that promote and mediate sleep.

Later, Dann *et al*. (1984) proposed that two mechanisms interact to regulate sleep–wake cycles. One of these, outlined in detail in Chapter 41, is a circadian rhythm in the propensity to fall asleep (curve C, Fig. 42.5). The tendency to fall asleep is normally lowest early in the day, peaks at about late afternoon, and then declines in the evening. Thus sleepiness cycles independent of sleeping and waking. That is, if a subject is deprived of sleep, sleepiness will continue to follow a circadian rhythm. The second mechanism is a homeostatic property, designated S in Fig. 42.5. It increases as a function of the amount of time since the last sleep episode. S can be conceptualized as a sleep-promoting substance that accumulates during waking and dissipates during sleep. Although a large amount of work has been devoted to identifying a "sleep substance," whether one or more such substances normally is involved in sleep regulation remains unclear (Strecker *et al*., 2000; Krueger and Fang, in Lydic and Baghdoyan, 1999). Many factors likely contribute to the homeostatic regulation of sleep.

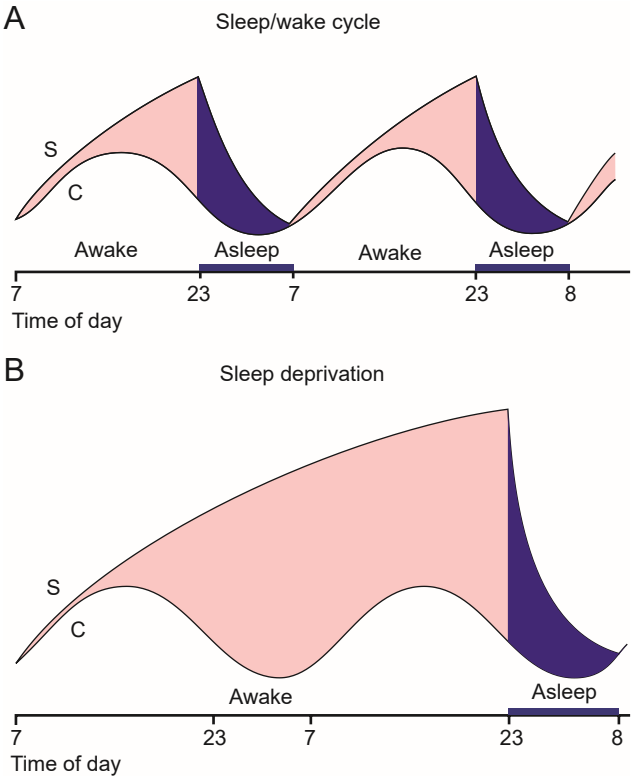

FIGURE 42.5 The Borbely and Daan model of sleep regulation. Sleep is assumed to result from the actions of process C and process S. Process C follows a circadian rhythm and is independent of sleeping and waking. Process S, on the other hand, depends on sleep–wake behavior; S declines during sleep and rises continuously during sleep deprivation. The period of recovery sleep that follows sleep deprivation is more intensive but only slightly longer than normal. If curve C represents the threshold for waking up, then at any time, "sleep pressure" is the (vertical) distance between the S and C curves. The greater the distance, the greater the pressure to fall asleep. Reprinted with permission from Daan *et al*. (1984).

Waking is a complex state. Its fundamental features are the maintenance of sensory input from multiple receptors, the capacity for directing attention and accessing memory, the constant readjustments of posture, the maintenance of forebrain activation, and an array of motor output. It is worth noting here, however, that reticular formation plays a crucial role in the initiation and maintenance of both wakefulness and sleep. We now focus on the active control of sleep.

The onset of sleep occurs when the combined S and C factors near their peak and the environmental milieu is conducive to sleep. At this point, the brain stem and cortical mechanisms of waking are relaxed: vigilance lapses, muscle tone declines, eyelids close, and the EEG slows. Because the cortex is still active, removal of ascending influences often results in sudden unresponsiveness, which may be associated with dream-like imagery. This sleep onset mentation usually is abolished quickly by the thalamocortical oscillation of deeper NREM sleep. As NREM sleep begins, the incomplete relaxation of the mechanisms maintaining muscle tone may result in paroxysmal twitching, a form of myoclonus often affecting the legs.

Hypothalamic Control of Sleep–Wake Transitions

Clinical and experimental findings have shown that lesions to anterior portions of the hypothalamus cause insomnia, and stimulation of this area promotes sleep, whereas lesions of the posterior hypothalamus cause hypersomnolence and neurons in this region decrease firing during sleep (Saper *et al*. 2001, 2005a). During NREM sleep, neurons in the ventrolateral preoptic area (VLPO) of the anterior hypothalamus show an increase in metabolic activity (Saper *et al*., 2001, 2005). These VLPO neurons produce both the inhibi-

tory amino acid gamma-aminobutyric acid (GABA) and the inhibitory neuropeptide galanin and project to histaminergic neurons in the tuberomammillary nucleus (TMN) of the posterior hypothalamus as well as to brain stem noradrenaline (NE) and serotonin (5-HT) producing neurons of the locus coeruleus (LC) and dorsal raphé (DR) nuclei, respectively, all of which project widely to the thalamus and cortex where they promote waking (Saper et al. 2001, 2005, Fig. 42.6). The LC, DRN and TMN, in turn, innervate and inhibit the GABA and galaninergic neurons of the VLPO (Saper *et al*. 2001).

Saper and colleagues (2001, 2005) have suggested that this mutually inhibitory arrangement constitutes a biological analog of a bistable electrical "flip-flop" switch in which either the sleep (VLPO dominant) or wake (LC, DRN, TMN dominant) conditions are self-reinforcing stable states whereas intermediate states are highly transient (Fig. 42.7). The neuropeptide orexin (also called hypocretin) produced by cells in the lateral hypothalamus plays a key modulatory role in this flip-flop mechanism by providing excitatory drive on aminergic neurons, thereby further stabilizing the waking end of the bipolar sleep–wake switch (Borbely, 1982; Borbely and Achermann, 2005; Daan et al. 1984, Fig. 42.5). In the sleep disorder narcolepsy, these orexin-producing neurons are lost, most likely due to an autoimmune mechanism (Black, 2005), and wake to sleep transitions can occur at inappropriate times.

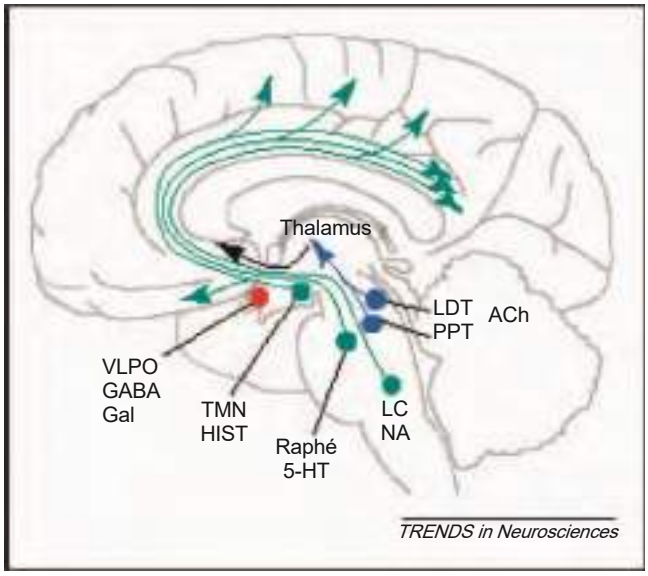

FIGURE 42.6 Integrated model of sleep onset and REM–NREM oscillation proposed by Shiromani *et al*. I. During prolonged wakefulness, accumulating adenosine inhibits specific GABAergic anterior hypothalamic and basal forebrain neurons, which have been inhibiting the sleep–active VLPO neurons during waking. II. Disinhibited sleep–active GABAergic neurons of the VLPO and adjacent structures then inhibit the wake–active histaminergic neurons of the TMN, as well as those of the pontine aminergic (DR and LC) and cholinergic (LDT/PPT) ascending arousal systems, thereby initiating NREM sleep. III. Forebrain activation by ascending aminergic and orexinergic arousal systems is disfacilitated. IV. Once NREM sleep is thus established, the executive networks of the pons initiate and maintain the ultradian REM/NREM cycle. ACh, acetylcholine; DRN, dorsal raphe nucleus; GABA, γ-amino butyric acid; LC, locus coeruleus; 5-HT, serotonin; LDT, laterodorsal tegmental nucleus; NE, norepinephrine; PRF, pontine reticular formation; TMN, tuberomammillary nucleus. From Pace-Schott and Hobson (2001).

Homeostatic and Circadian Control of Sleep Onset

The two-process model of sleep propensity suggests that homeostatic mechanisms (Process S) interact with circadian factors (Process C) to regulate behaviorally expressed sleep and waking (Borbely, 1982; Borbely and Achermann, 2005 Daan *et al.* 1984, Fig. 42.5). The purine nucleoside adenosine is currently the most widely suggested endogenous somnogen—a substance whose accumulation in the brain over prolonged wakefulness constitutes the physiological basis of Process S (Basheer, *et al*. 2004). Although adenosine may directly inhibit basal forebrain cholinergic neurons that project to the cortex and promote waking (Basheer *et al*., 2004) recent findings suggest that adenosine's effects may occur elsewhere (Blanco-Centurion *et al*., 2006) such as at A2A adenosine receptors in ventral striatal areas (Satoh *et al*., 1999) or on GABAergic anterior hypothalamic and basal forebrain neurons projecting to the VLPO (Shiromani *et al*., 1999). Evidence also exists for endogenous somnogenic actions of interleukin-1, prostaglandin D1, growth hormone releasing hormone (McGinty and Szymusiak, 2005) and the fatty acid oleomide (Mendelson and Basile, 2001).

Details of the molecular biological and cellular basis of Process C are in Chapter 41 (Lowrey and Takahashi, 2004). Briefly, molecular clocks in cells of the suprachiasmatic nucleus (SCN) of the anterior hypothalamus maintain a near-perfect 24-hour periodicity (Czeisler *et al*., 1999) via interlocking positive and negative feedback control of transcription and translation of circadian genes (Lowrey and Takahashi, 2004). This endogenous clock is entrained to the ambient photoperiod via photoreceptive pigments like melanopsin in retinal ganglion cells (Peirson and Foster, 2006) that send glutamatergic signals to the SCN via the retinohypothalamic tract (Antle and Silver, 2005). The SCN conveys circadian information via the subparaventricular and dorsomedial nuclei of the hypothalamus to the VLPO to influence sleep–wake transitions (Saper *et al*., 2005). Secretion of the pineal sleep hormone melatonin is also controlled by the SCN and provides an internal indicator of circadian time as well as feedback influence on the SCN via its melatonin receptors (Arendt, 2006).

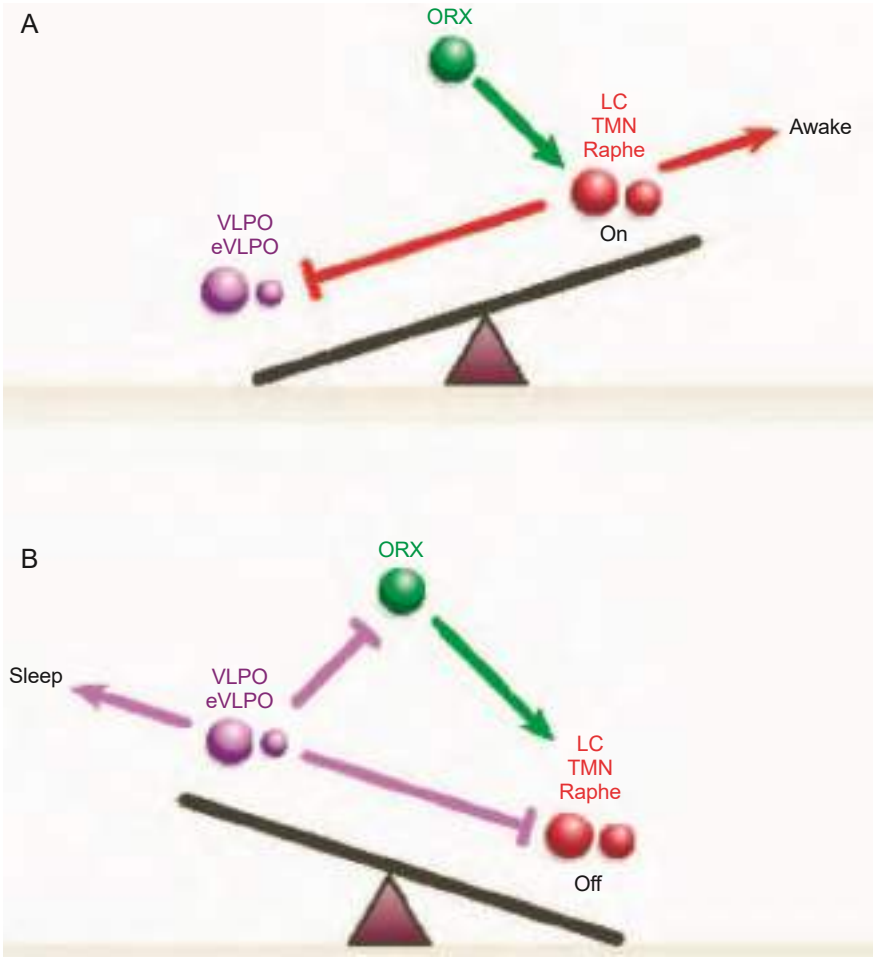

FIGURE 42.7 Thalamocortical oscillations in vivo. Sleep spindle oscillations are generated by synapses in the thalamus. (A, left) Potentials recorded through a microelectrode inserted in the deafferented reticular thalamic nucleus of a cat. The arrow points to one spindle sequence. (A, right) Spindle oscillations recorded from the thalamus of a cat with an upper brainstem transection that created an isolated forebrain preparation. The figure shows two spindle sequences (the second marked by an arrow) and, between them, lower frequency (delta) waves. (B) Neuronal connections involved in the generation of spindle oscillations. (C) Intracellular recordings of one spindle sequence (see A) in three types of neurons (cortical, reticular thalamic, and thalamocortical). Ca2+, calcium ions; IPSP, inhibitory postsynaptic potential.

NREM Sleep Rhythms Require Thalamo-cortical Interaction

Reciprocally interconnected thalamic and cortical neurons form the circuits that are the physiological basis of the NREM oscillations including delta and slow (<1 Hz) oscillatory rhythms and the spindle and K-complex wave forms ((Steriade, 2000, 2006, see Fig. 42.4). In NREM, thalamic and cortical neurons shift into this oscillatory mode when the influence of ascending arousal systems of the brain stem, hypothalamus, and basal forebrain decrease. During waking, these ascending systems modulate thalamocortical circuits with the arousal-promoting neuromodulators acetylcholine (Ach), NE, 5-HT, and histamine. Similarly, during REM sleep, thalamocortical rhythms are prevented by cholinergic thalamic activation originating from brain stem cholinergic nuclei (Steriade, 2000, 2006).

Intrinsic oscillations of NREM represent the combined influence of two neuronal mechanisms: (1) inhibitory influence by neurons of the thalamic reticular nucleus—a thin sheet of GABAergic neurons surrounding the thalamic periphery—on thalamic neurons projecting to the cortex; and (2) an oscillation within cortical neurons involving alternation between a prolonged hyperpolarization phase and a shorter, rapidly spiking, depolarized phase (Steriade, 2000, 2006, Fig. 42.8). This latter rhythm is generated entirely within cortical networks, is the neuronal basis of the <1 Hz slow EEG oscillation, and exerts an organizing or grouping influence on other intrinsic NREM sleep rhythms (Steriade, 2000, 2006).

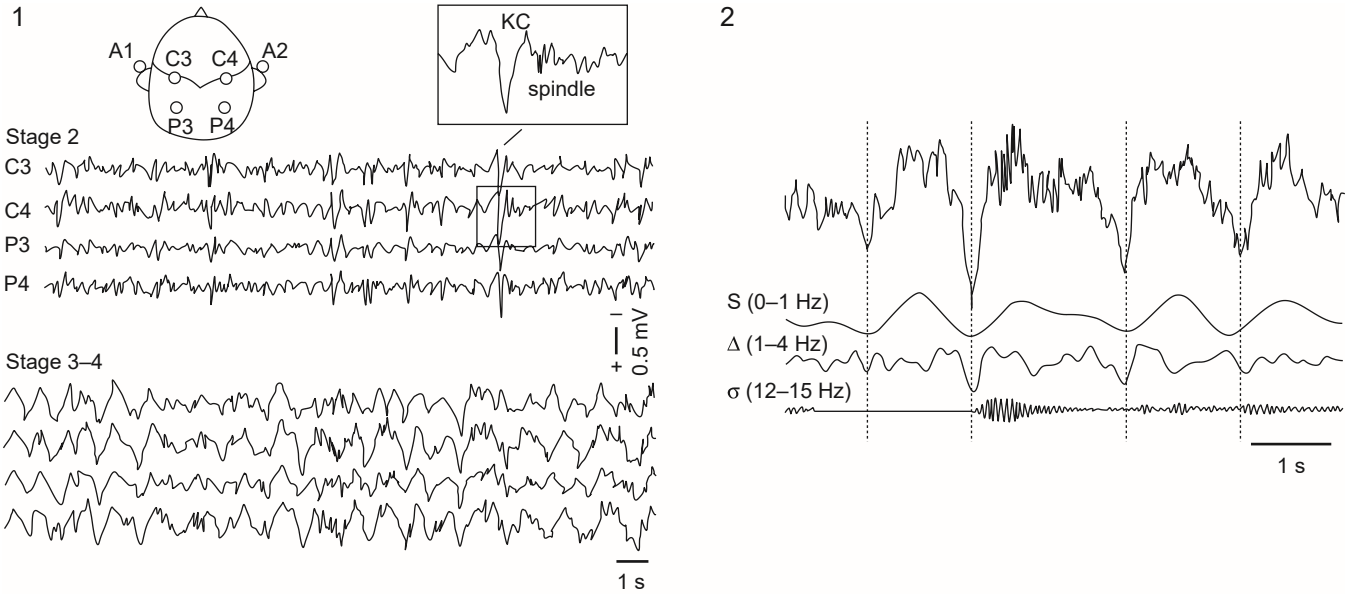

FIGURE 42.8 `Schematic representation of the REM sleep generation process. A distributed network involves cells at many brain levels (left). The network is represented as comprising 3 neuronal systems (center) that mediate REM sleep electrographic phenomena (right). Postulated inhibitory connections are shown as red circles; postulated excitatory connections as green circles; and cholinergic pontine nuclei are shown as blue circles. It should be noted that the actual synaptic signs of many of the aminergic and reticular pathways remain to be demonstrated and, in many cases, the neuronal architecture is known to be far more complex than indicated here (e.g., the thalamus and cortex). During REM, additive facilitatory effects on pontine REM-on cells are postulated to occur via disinhibition (resulting from the marked reduction in firing rate by aminergic neurons at REM sleep onset) and through excitation (resulting from mutually excitatory cholinergic–noncholinergic cell interactions within the pontine tegmentum). The net result is strong tonic and phasic activation of reticular and sensorimotor neurons in REM sleep. REM sleep phenomena are postulated to be mediated as follows: EEG desynchronization results from a net tonic increase in reticular, thalamocortical, and cortical neuronal firing rates. PGO waves are the result of tonic disinhibition and phasic excitation of burst cells in the lateral pontomesencephalic tegmentum. Rapid eye movements are the consequence of phasic firing by reticular and vestibular cells; the latter (not shown) excite oculomotor neurons directly. Muscular atonia is the consequence of tonic postsynaptic inhibition of spinal anterior horn cells by the pontomedullary reticular formation. Muscle twitches occur when excitation by reticular and pyramidal tract motorneurons phasically overcomes the tonic inhibition of the anterior horn cells. RN, raphé nuclei; LC, locus coeruleus; P, peribrachial region; PPT, pedunculopontine tegmental nucleus; LDT, laterodorsal tegmental nucleus; mPRF, meso- and mediopontine tegmentum (e.g., gigantocellular tegmental field, parvocellular tegmental field); RAS, midbrain reticular activating system; BIRF, bulbospinal inhibitory reticular formation (e.g., gigantocellular tegmental field, parvocellular tegmental field, magnocellular tegmental field); TC, thalamocortical; CT, cortical; PT cell, pyramidal cell; III, oculomotor; IV, trochlear; V, trigmenial motor nuclei; AHC, anterior horn cell. From Hobson et al. (2000).

The cortical slow oscillation initiates sleep spindles during its depolarized phase when cortico-thalamic neurons excite thalamic reticular neurons (Steriade, 2000, 2006). The resulting periodic inhibition by thalamic reticular neurons on thalamo-cortical neurons changes their firing from a transmission mode in which firing frequency is proportional to the strength of a sensory input to a bursting mode in which transmission of sensory information to the cortex is blocked (McCormick and Bal, 1997). This bursting mode is initiated when thalamo-cortical neurons are sufficiently hyperpolarized by thalamic reticular inhibition to activate a unique ion channel that opens only when their membrane potential falls well below its normal resting potential (McCormick and Bal, 1997). Opening of this channel begins a series of membrane events ("H" currents followed by "T" or "low-threshold calcium spike" currents) that culminates in thalamo-cortical neurons emitting a series of spikes that impinge on the cortex at spindle frequency (Steriade, 2000, 2006, Fig. 42.9).

Delta frequency EEG oscillations may have both thalamic and cortico-thalamic origins (Steriade, 2000, 2006). Delta-frequency oscillations can arise via thalamic neurons' intrinsic delta-frequency pacemaker property or, alternatively, when cortico-thalamic neurons excite thalamic reticular neurons that, in turn, hyperpolarize the thalamo-cortical neurons causing them to stimulate the cortex at delta frequency (Steriade, 2000, 2006).

In the transition from NREM to REM, activation of the thalamus by brain stem cholinergic neurons blocks the intrinsic oscillations resulting in a cortical "desynchronization." This appears as a speeding and diversification of EEG frequencies along with a decrease in the amplitude of oscillations in the EEG (Steriade,

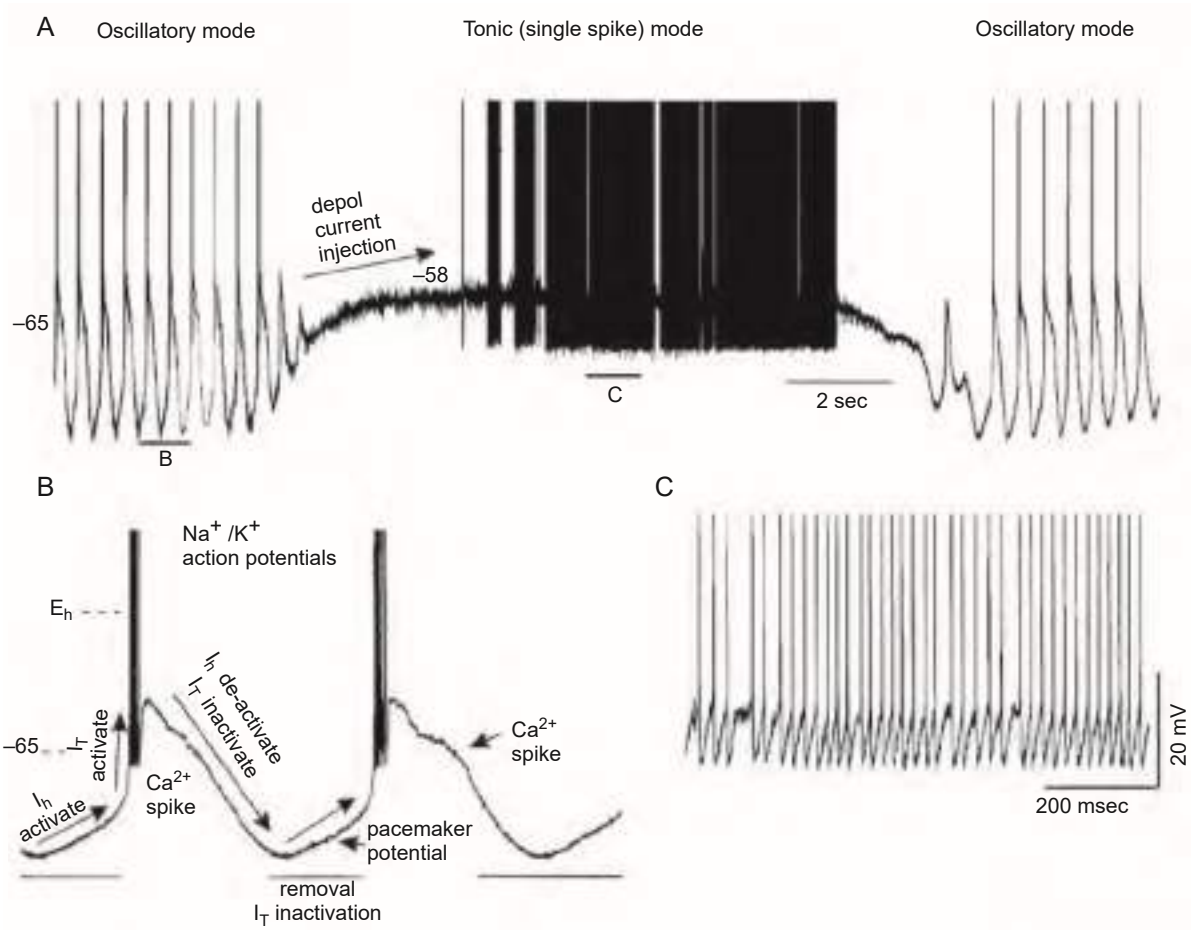

FIGURE 42.9 Sites of REM induction. (A, left) Filled circle indicates site of injection of carbachol into peribrachial pons. Small dots indicate location of cholinergic cells and crosses location of PGO burst cells. (A, right) Injection of carbachol, an acetylcholine agonist, in the perimedian pons (magenta dot) causes short-term induction of REM sleep. Injection of the peribrachial pons (yellow dot) causes long-term induction of REM sleep. After injection of a cholinergic agonist into the peribrachial pons, ponto-geniculo-occipital (PGO) burst cell activity and PGO waves can be measured immediately in the lateral geniculate body (LGB) on the same side (ipsilateral) of the brain as the injections (B, left). Hypothesized connections among the PGO trigger zone (PB), modulatory aminergic raphé (R), locus coeruleus (LC), and paramedian pontine reticular cells (FTC) are shown. (C, left) Injections of carbachol at the PB site shown in A produce immediate PGO waves in the ipsilateral LGB. After 24 h, REM sleep intensifies (C, middle) and remains so for 6 days (C, right). FTC, FTG, and FTP are reticular tegmented nuclei. ACh are cholinergic nuclei. RN, red nucleus; IC, inferior colliculus; SC, superior colliculus; BC, brachium conjunctiuum.

2000, 2006). Cholinergic desynchronization of EEG in REM and waking occurs via (1) an inhibitory effect on GABAergic thalamic reticular neurons that disinhibits their thalamo-cortical targets, and (2) by cholinergic excitatory influence on thalamo-cortical neurons that facilitates their glutamatergic excitation of the cortex (Steriade, 2000, 2006).

REM Sleep Is Initiated in the Brain Stem

The cellular and molecular events that produce the regular alternation of REM and NREM sleep emerge under brain stem control once sleep has been achieved (Hobson *et al*., 2000; Jones, 2005). As described in the previous section, activation of the cortex in REM sleep occurs when the intrinsic oscillations of NREM sleep are blocked by the brain stem ascending reticular activating system's (ARAS) cholinergic reactivation of the thalamus (Steriade, 2000, 2006). A second, more ventral ascending activation pathway by which the ARAS can produce cortical activation and desynchrony involves excitation of the cholinergic neurons of the basal forebrain that project widely to the cortex and promote arousal in waking (Jones, 2005; Lu *et al*., 2006a). The cardinal physiological features of REM include:

- EEG desynchronization
- Phasic potentials recorded sequentially in the pons, thalamic lateral geniculate body and the occipital cortex of the cat, termed ponto-geniculo-occipital (PGO) waves or P-waves in the rat (Datta, 1998)

- Rapid eye movements
- A change in hippocampal EEG from irregular rhythms to a regular theta rhythm
- Skeletal muscle atonia

The earliest cellular model of the brain stem REM sleep generator, the reciprocal interaction (RI) model, suggested that regular alternation of REM and NREM sleep results from the interaction of aminergic REM-off and cholinergic REM-on neuronal populations in the pontine brain stem (Hobson et al., 1975; McCarley and Hobson, 1975, Figs. 42.10 and 42.11).

The aminergic and cholinergic neurons described in the RI hypothesis are components of the brain stem ARAS, a system that also includes large and varied populations of glutamatergic and GABAergic neurons (Hobson *et al.*, 2000; Lydic and Baghdoyan, 2005; Jones, 2005). The key cholinergic neurons supporting thalamic activation in REM reside in the laterodorsal tegmental (LDT) and pedunculopontine (PPT) nuclei of the pons-midbrain junction (mesopontine tegmentum). Aminergic REM-off neurons of the LC and DR also occur in the mesopontine region. Many glutamatergic and GABAergic ARAS neurons are located ventral to the mesopontine tegmentum in the medial pontine reticular formation (mPRF). Many of these neurons bear Ach receptors (are "cholinoceptive").

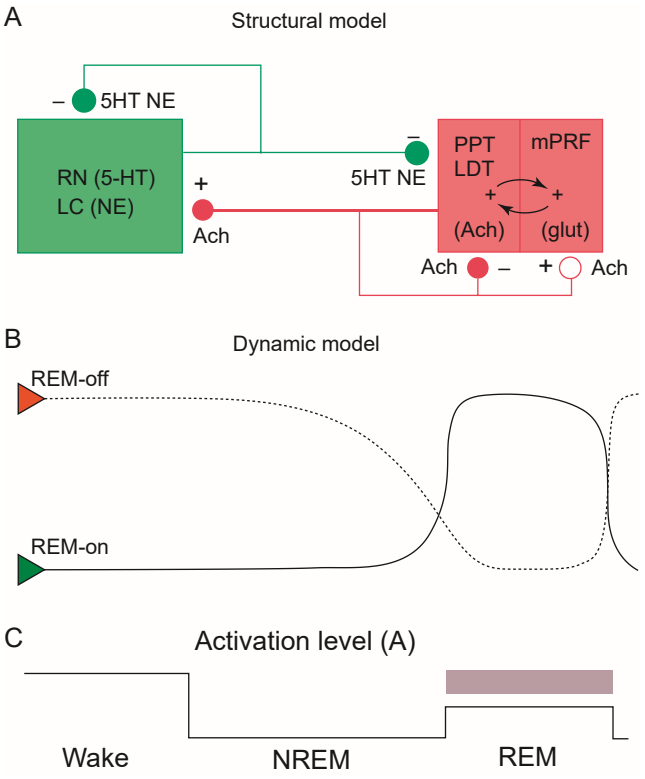

FIGURE 42.10 Structural and dynamic models of activation in REM sleep. (A) In the structural model, REM-on cells of the pontine reticular formation are excited by acetylcholine (ACh) or they produce excitatory signals using ACh in their synaptic terminals (or they do both). REM-off cells respond to or use NE or 5-HT as inhibitory neurotransmitters (or they do both). (B) In the dynamic model, during waking the pontine aminergic system (dashed line) is active continuously and inhibits the pontine cholinergic system (solid line). During NREM sleep, aminergic activity decreases, allowing cholinergic activity to rise. By the time REM sleep begins, the aminergic system is off and cholinergic excitation has peaked.

The RI hypothesis is supported by extensive experimental and clinical findings showing powerful effects of Ach and the monoamines NE and 5-HT on the REM-NREM oscillator. For example, in many regions of the pontine reticular activating system of cats, microinjection of either drugs like carbachol that mimic the action of acetylcholine (cholinergic agonists) or drugs like neostigmine that block the enzymatic degradation of naturally produced acetylcholine (acetylcholinesterase inhibitors) produces a state indistinguishable from naturally occurring REM sleep (Hobson *et al.*, 2000; Lydic and Baghdoyan, 2005). Moreover, REM sleep is reduced or blocked by microinjection of noradrenergic or serotonergic agonists into the pontine brain stem of animals as well as by systemic administration, in humans, of drugs that block the synaptic reuptake or enzymatic degradation of naturally produced monoamines such as many antidepressants (Hobson *et al.*, 2000). PGO waves result from tonic disinhibition and phasic excitation of bursting cells in the peribrachial region of the mesopontine tegmentum and, like REM sleep, they can be triggered and augmented by cholinergic stimulation (Datta, 1997).

Major roles for acetylcholine and the monoamines in REM-NREM control continue to be reported (reviewed in Lydic and Baghdoyan, 2005; Pace-Schott and Hobson, 2002), and many intermediate synaptic steps for both the activation of REM-on neurons in the mesopontine tegmentum and the suppression of REM-off aminergic nuclei also have been described. For example, mutually excitatory interactions between cholinergic and glutamatergic neurons may underlie the rapidly escalating firing of pontine reticular REM-on neurons during REM sleep (see Pace-Schott and Hobson, 2002). Similarly, during REM, inhibition of REM-off aminergic neurons in the LC and DR by brain stem GABAergic neurons may remove their inhibitory influence on REM-on cell populations (see Pace-Schott and Hobson, 2002). GABAergic inhibition by neurons of periaqueductal gray area (PAG), substantia nigra pars reticulata, dorsal paragigantocellular nucleus, or local pontine interneurons may be responsible for shutting down REM-off serotonergic and noradrenergic cells (Gervasoni *et al.*, 2000; reviewed in Jones, 2005).

Other models on the control of REM onset and offset have emphasized interactions between brain

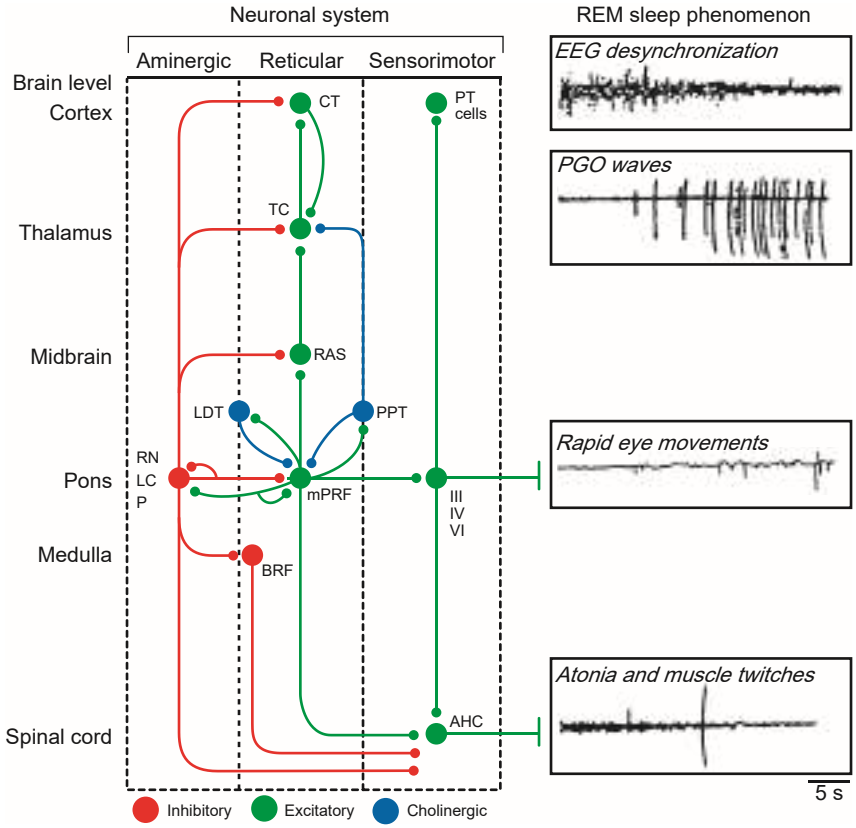

FIGURE 42.11 Convergent findings on relative regional brain activation and deactivation in REM compared to waking. A schematic sagittal view of the human brain showing those areas of relative activation and deactivation in REM sleep compared to waking and/or NREM sleep, which were reported in two or more of the three PET studies published to date (Braun et al., 1997; Maquet et al., 1996; Nofzinger et al., 1997; see Hobson et al., 2000 for citations). Only those areas that could be matched easily between two or more studies are illustrated here and a realistic morphology of the depicted areas is not implied. Note that considerably more extensive areas of activation and deactivation are reported in the individual studies; these more detailed findings are reviewed in Hobson et al. (2000). The depicted areas are thus viewed most realistically as representative portions of larger CNS areas subserving similar functions (e.g., limbic-related cortex, ascending activation pathways, and multimodal association cortex).

stem GABAergic cell populations in which GABAergic inhibition plays both REM facilitory and REM inhibitory roles. For example, Boissard *et al*. (2002) have suggested that the onset of REM in the rat is triggered by the release of neurons of the pontine sublaterodorsal (SLD) nucleus from tonic GABAergic inhibition. In addition, a GABAergic "switch" between waking and REM has been reported in the nucleus pontine oralis (within the mPRF) of cats (Xi *et al*., 2001). Most recently, Lu *et al*. (2006b) have proposed that a GABAergic flip-flop switch, analogous to the earlier hypothalamic flip-flop switch, controls the alternation of REM and NREM sleep states in the rat via REM-off regions in the ventrolateral periaqueductal gray and lateral pontine tegmentum that project to REM-on regions in the SLD, precoeruleus, and periventricular grey mesopontine areas. Discrepancies between models proposing that REM results from brain stem GABAergic interactions and those suggesting release of mesopontine cholinergic neurons from inhibition by aminergic nuclei may result from: (1) GABAergic models being derived mainly from work in the rat whereas aminergic-cholinergic models were derived in cats, and (2) hierarchical, horizontal, or redundant control by overlapping GABAergic and aminergic/cholinergic brain stem circuits paralleling the multiple overlapping ascending arousal circuits whose cholinergic, aminergic, and orexinergic components promote waking (Saper *et al*., 2005).

Other Brain Stem and Diencephalic Neurotransmitter Systems Participating in Behavioral State Control

Despite the prominence of cholinergic, aminergic, and amino acid (GABAergic and glutamatergic) neuronal populations in the control of the sleep–wake and REM–NREM cycles, many additional neurotransmit-

ter systems participate in the modulation sleep states. Such neurochemicals may exert their effects on behavioral state by interacting with aminergic, cholinergic, and amino acid neurons that exert a more direct "executive" control on sleep and waking states. In addition, such neurochemicals may have roles in mediating specific physiological signs of REM and NREM sleep.

Other Monoamines

In addition to the prominent roles of norepinephrine, serotonin, and histamine, recent findings have begun to identify roles for a fourth monoamine, dopamine, in sleep wake regulation. Until just recently, little attention was paid to potential roles of dopamine in sleep–wake control because, unlike the other monoamines, firing rate of dopaminergic cells in the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA) did not appear to vary with behavioral state (see Hobson et al., 2000). However, Lu *et al*. (2006b) have identified wake–active dopaminergic neurons in the ventral PAG that project to many of the traditional neuronal components of sleep–wake regulation. These investigators hypothesize that these neurons constitute a dopaminergic component of monoaminergic ascending wake–promoting arousal systems analogous to serotonergic, noradrenergic, and histaminergic systems in the DR, LC, and TMN, respectively (Saper *et al*., 2005). Additional emerging evidence for a dopaminergic component to behavioral state control includes the findings that (1) dopamine concentrations in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) are greater during REM and waking than during NREM sleep (Lena *et al*., 2005), (2) VTA dopaminergic neurons switch to a burst firing mode in REM (Dahan *et al*., 2007), (3) metabolism increases in the dopaminergic ventral tegmental area during REM rebound (Maloney *et al*., 2002), and (4) mice with abnormally high brain dopamine levels display an abnormal REM-like waking that is reversible with a D2 antagonist (Dzirasa *et al*., 2006).

Histaminergic projections of the TMN diffusely innervate the entire forebrain and brain stem (Shiromani *et al*., 1999). Histaminergic TMN neurons show a behavioral state-dependent pattern of firing similar to LC and DR neurons (Saper *et al*., 2001). In addition, like serotonergic and noradrenergic neurons, histaminergic neurons are tonically inhibited during sleep by GABAergic and galaninergic projections from the VLPO (Saper *et al*., 2001).

Amino Acid Neurotransmitters

The brain's most ubiquitous inhibitory neurotransmitter, GABA, is involved at many stages in the control of the sleep–wake and the REM–NREM cycle (Jones, 2005). In addition to its roles in sleep onset and maintenance, thalamo-cortical oscillations and REM facilitation/inhibition described earlier, GABAergic inhibition also controls the neurons that generate PGO waves (Datta, 1997). Another inhibitory neurotransmitter, glycine, is responsible for the postsynaptic inhibition of somatic motoneurons that results in REM atonia (Chase and Morales, 2005). In addition to its important roles in ascending reticular activation and thalamo-cortical oscillations described earlier, the brain's most ubiquitous excitatory neurotransmitter, glutamate, transmits signals from pontine REM-control regions to inhibitory glycinergic and GABAergic cells of the medulla that, in turn, suppress somatic motoneurons to produce REM atonia (Boissard *et al*., 2002; Jones, 2005).

Intercellularly Diffusible Gaseous Neurotransmitter: Nitric Oxide (NO)

NO has recently been widely implicated in sleep cycle modulation and functions primarily as an intercellular messenger, which can enhance the synaptic release of neurotransmitters such as ACh and enhance capillary vasodilation (Leonard and Lydic, 1999). NO is coproduced by cholinergic mesopontine neurons and may play a role in maintaining the cholinergically mediated REM sleep state in both the pons and the thalamus (Leonard and Lydic, 1999).

Neuropeptides

Neuropeptides are increasingly seen to play diverse roles in regulation of the sleep–wake and REM–NREM cycles. As described earlier, the hypothalamic peptide galanin participates in the inhibition of wake-promoting centers during sleep onset, the hypothalamic peptide orexin promotes waking (Saper *et al*., 2001) and cytokine peptides may play roles as endogenous somnogens (McGinty and Szmusiak, 2005). Other peptides implicated in the REM–NREM and sleep–wake cycles include vasoactive intestinal polypeptide (Steiger and Holsboer, 1997), as well as numerous hormones (Obal and Krueger, 1999) such as corticotropin releasing hormone (Chang and Opp, 2001).

Second Messengers and Intranuclear Events

As in other areas of neuroscience, research on behavioral state control is now beginning to extend its inquiry beyond the neurotransmitter and its receptors to the roles of intracellular second messengers and gene transcription. For example, Bandyopadhya *et al*. (2006) have shown variation with prior amount of REM sleep in the intracellular concentrations of the catalytic subunit of protein kinase A (PKA), the component of PKA that enters the nucleus to phosphorylate CRE-binding protein. Similarly, manipulation of

the cAMP-PKA pathway has been shown to modify the REM sleep effects of cholinergic activation of muscarinic receptors in the mPRF (Capece *et al*., 1997). The specific profile of genes selectively activated in different sleep–wake states is also a current area of intense investigation (Wisor and Kilduff, 2005; Tononi and Cirelli, 2001).

Summary

Circadian and homeostatic factors together regulate sleep–wake propensity. Circadian information is provided by reliable molecular clocks in cells of the SCN of the anterior hypothalamus. SCN neurons transmit circadian information via several hypothalamic nuclei to sites where its influence is combined with information on homeostatic sleep pressure indexed by endogenous somnogenic substances such as adenosine that accumulate during waking.

A key structure in the initiation of NREM sleep is the VLPO in the anterior hypothalamus whose inhibitory GABA and galaninergic neurons inhibit wake-promoting arousal systems originating in cholinergic, noradrenergic, serotonergic, and dopaminergic brain stem nuclei, the histaminergic TMN in the posterior hypothalamus, and cholinergic arousal systems of the basal forebrain and brain stem. During waking, the peptide neuromodulator orexin from cells in the lateral hypothalamus further excites these aminergic and cholinergic arousal systems and stabilizes the waking pole of a bistable sleep–wake mechanism analogous to an electrical flip-flop circuit.

The ascending arousal systems of waking and REM suppress the endogenous oscillatory rhythms generated in thalamo-cortical circuits that manifest as the slow oscillation, spindle, and delta brain waves of the EEG in NREM sleep. The slow oscillatory rhythm is generated by cortical neurons and reflects a pattern of prolonged hyperpolarization followed by burst firing that controls the timing of spindles, delta waves, and K-complexes in the NREM sleep EEG.

Aminergic, cholinergic, and orexinergic neuromodulation promotes the activated brain states of waking but cholinergic and perhaps dopaminergic arousal systems promote the activated state of REM sleep. After sleep is initiated, an ultradian oscillator located near the junction of the pons and midbrain controls the regular alternation of NREM and REM sleep stages. This alternation of states involves a reciprocal interaction between aminergic REM-on and cholinergic REM-off cell groups, the interactions of which are mediated by interposed excitatory, inhibitory, and autoregulatory circuits that utilize the amino acid neurotransmitters GABA and glutamate. Substantial species differences may exist in mechanisms of REM-NREM control and mutually inhibitory GABAergic circuits may exert the most proximal control of sleep state alternation in rodents.

Additional neurochemicals such as the amino acid glycine and neuropeptide hormones contribute to the regulation of sleep–wake and REM–NREM cycles as well as to specific physiological signs of particular behavioral states. Contemporary neurophysiological research is elucidating the intracellular events taking place in second messenger systems and the cell nucleus. Emerging details on the molecular expression of specific sleep-related genes will undoubtedly provide an increasingly detailed understanding of causal mechanisms underlying the control of behavioral state.

MODELING THE CONTROL OF BEHAVIORAL STATE

Two linked models—one neurobiological (McCarley and Hobson, 1975) and the other psychophysiological (Hobson and McCarley, 1977; Hobson *et al*., 2000)—have been advanced to organize experimental findings and their implications for a theory of consciousness. According to the neurobiological model (Fig. 42.10), in waking, brain activation and open input–output gates result from a combination of continual aminergic activity and phasic (waxing and waning) aminergic and cholinergic activities. In contrast, in REM sleep the continually low level of aminergic activity and the periodic increases in cholinergic activity close input–output gates, activate the brain, and periodically stimulate the brain.

The subjective experience of waking, NREM sleep, and REM sleep can tentatively be linked to the accompanying changes in physiology (Table 42.2). Sensation and perception decline progressively during the cortical deactivation that occurs at the onset of sleep; responsiveness declines further as NREM sleep deepens. During REM sleep the brain reactivates, but presynaptic inhibition blocks sensory signals. REMs and their associated PGO waves act as internal stimuli, which take the place of stimuli from external sources. The brain stem sends information about eye movements to the thalamocortical visual system, possibly contributing to the intense visual hallucinations of dreams. Furthermore, these PGO signals also drive the amygdala, perhaps accounting for such emotions as anxiety and surprise in dreams. Interestingly, PET studies show an increase of regional cerebral blood flow in limbic structures, including the amygdala during REM sleep.

In the early days of the EEG, brain waves with frequencies greater than 25 Hz were either ignored or

TABLE 42.2 Physiological Basis of Changes That Occur during Dreaming

Function	Change (compared with waking)	Hypothesized Cause
Sensory input	Blocked	Presynaptic inhibition
Perception (external)	Diminished	Blockade of sensory input
Perception (internal)	Enhanced	Removal of inhibition from networks that store sensory representations
Attention	Lost	Aminergic modulation decreases, causing a decrease in the ratio of signal to noise
Memory (recent)	Diminished	Because of a decrease in aminergic activity, activated representations are not stored in memory
Memory (remote)	Enhanced	Removal of inhibition from networks that store memory representations
Orientation	Unstable	Internally inconsistent signals are generated by cholinergic systems
Thought	Poor reasoning, processing hyper-associative	Loss of attention, memory, and volition leads to failure of sequencing and rule inconstancy; analogy replaces analysis
Insight	Self-reflection lost	Failures of attention, logic, and memory weaken second- (and third-) order representations
Language (internal)	Confabulatory	Aminergic demodulation frees the use of language from the restraint of logic
Emotion	Episodically strong	Cholinergic hyperstimulation of the amygdala and related structures of the temporal lobe trigger emotional storms, which are not modulated by aminergic activity
Instinct	Episodically strong	Cholinergic hyperstimulation of the hypothalamus and limbic forebrain triggers fixed motor programs, which are experienced fictively but not enacted
Volition	Weak	Cortical motor control cannot compete with disinhibited subcortical networks
Output	Blocked	Postsynaptic inhibition

filtered out because of the problem of interference by 50- or 60-Hz artifacts from electrical power sources. Later, researchers were able to focus on the possibility that 40-Hz EEG activity synchronizes processing in cortical areas.

Rodolfo Llinás proposed that as the cortex is scanned by the thalamus, 40-Hz waves propagate from the frontal to the occipital poles (Kahn *et al*., 1997). Noting that 40-Hz activity is observed in REM sleep as well as in waking, he suggested that intrinsic neuronal oscillations are important in the genesis of both states of consciousness and that the main difference between waking and dreaming arises from differences in input–output gating (Llinás and Pare, 1991). In addition to being without temporal or spatial input, in REM sleep the brain has little background aminergic activity; this lack may contribute to the declines in attention, orientation, memory, and logic that characterize dreaming and make dreams difficult to remember (Hobson *et al*., 2000).

Neuroimaging and Lesion Studies of Sleep and Dreaming

Functional neuroimaging studies have revealed distinctive differences in regional brain activation between the cardinal behavioral states of waking, NREM sleep and REM sleep (for a review and original citations, see Hobson *et al*., 2000). In brief, widespread deactivation of the forebrain and brain stem is seen following sleep onset, and activation further decreases with the increasing depth of NREM sleep from NREM stage 1 to 2 to slow-wave sleep (SWS). Subsequently in REM sleep, however, there is selective reactivation to waking or above-waking levels in brain stem, diencephalic, subcortical limbic, cortico-limbic, and selected cortical association areas. Notably however, during REM, significant deactivation of the dorsolateral prefrontal cortex relative to waking persists. Figure 42.12 illustrates the structures found to be activated or deactivated in two or more of these recent neuroimaging studies.

These findings have led to an updating of the original activation synthesis hypothesis of dreaming (Hobson and McCarley, 1977), which now emphasizes that the distinctive cognitive features of dreams result from simultaneous autoactivation of the limbic brain (with consequent dream emotionality and salience) combined with the deactivation of executive structures subserving logic and working memory (with consequent dream bizarreness and disorientation) (Hobson *et al*., 2000).

Complementing these findings have been neuropsychological findings on brain-damaged patients by

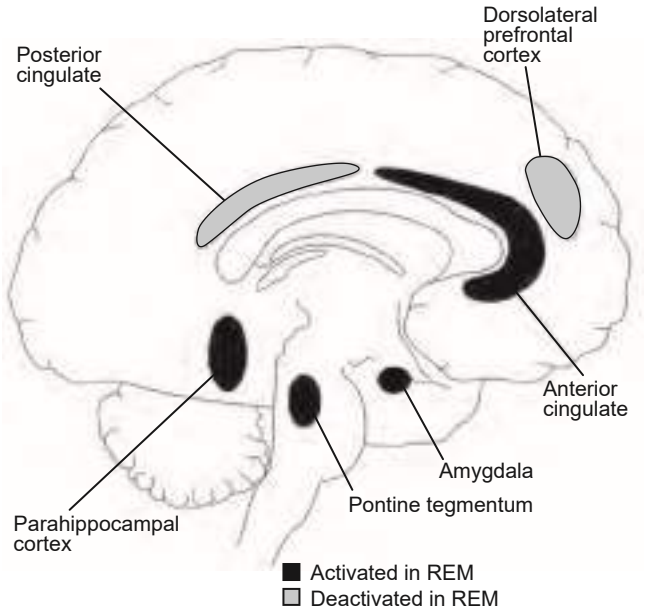

FIGURE 42.12 Central and obstructive sleep apnea. During waking, the respiratory oscillator of the medulla receives tonic drive from other neural structures and can respond to voluntary and metabolic signals to change breathing pattern. Muscle tone keeps the oropharynx open to the flow of air. In NREM sleep, central drive decreases, and the rate and depth of ventilation fall. If the decrease is excessive, central sleep apnea results, including a complete, albeit temporary, cessation of breathing. If the airway collapses, obstructive sleep apnea may result, with a similar cessation of breathing. During REM sleep, activation of pontine generator neurons drives the respiratory oscillator, and desynchronization may lead to breathing efforts that are too frequent or strong (hyperpnea) or that stop. During REM sleep the oscillator also becomes unresponsive to metabolic signals.

Solms (1997). In these studies, dorsolateral prefrontal damage was found to have little effect on dreaming. This is in keeping with its relative inactivity during REM and the apparent diminution of its mnemonic, orientational, and logical functioning in dreaming. In contrast, destructive lesions of multimodal parietal areas resulted in global cessation of dreaming, and lesions of the visual association cortex led to nonvisual dreaming. This is in keeping with the activation, in REM, of the supramarginal gyrus and inferotemporal cortex in some PET studies and the highly visuospatial nature of dreaming. Similarly, disconnective lesions in upper brain stem-limbic-prefrontal areas led to global cessation of dreaming in keeping with their activation in REM and the highly emotional and personally salient quality of dreaming (Box 42.2).

Central Autonomic Control Systems Are State Dependent

Alterations in cognitive and vegetative functions are linked to changes in central modulatory systems during sleep. For example, active hypothalamic temperature control is diminished or abandoned in REM sleep (Hobson, 1989), and the sensitivity of the respiratory control system is likewise diminished. As a result, a neuron that is sensitive to temperature or pO_2 during waking loses that responsiveness during REM sleep. Sleep, then, involves significant changes in the reflex

BOX 42.2

REGIONAL ACTIVATION AND DEACTIVATION: IMAGING THE HUMAN BRAIN AWAKE AND ASLEEP

Not only is the brain surprisingly and strongly activated during REM sleep, but its various subregions are activated and deactivated in a pattern quite different from that of waking. The mechanism of this differential activation pattern, revealed in PET, SPECT, and fMRI functional neuroimaging studies, is unknown, but it seems quite likely that the underlying shifts in regional metabolism and blood flow are orchestrated by the neuromodulators, which play this role in the rest of the body.

Compared to waking, deep NREM sleep shows a rather global deactivation pattern in keeping with the observed EEG slowing and synchronization. However, in REM, some areas are hyperactivated (among which the pontine brain stem, the limbic system, and the paralimbic cortex are most notable), whereas others are deactivated (among which the posterior cingulate and the dorsolateral prefrontal cortex are most notable).

These shifts in regional blood flow, and by inference regional neuronal activity, map nicely onto the observed changes in consciousness. Thus activation of the amygdala and other sub-cortical and cortical limbic structures is relevant to the domination of dream consciousness by emotion, the selective activation of only certain of the multimodal cortices is relevant to the hyper-associative quality of dreaming, whereas the inactivation of the dorsolateral prefrontal cortex seems relevant to the defects in cognition and memory. At last, the human brain and its wondrous array of conscious states is amenable to neurobiological analysis, in real time, in real people, and in patients as well as in healthy individuals.

Edward F. Pace-Schott, J. Allan Hobson and Robert Stickgold

control of autonomic function. Our understanding of changes in the control of vegetative and sensorimotor functions during waking and sleep can be applied to understand sleep-related dysfunctions such as insomnia (inability to sleep), hypersomnia (excessive sleepiness), and parasomnia (sleep with reflex responses to stimuli) (Hobson, 1989).

Sleep Disorders Result from Disrupted Control of Behavioral State

When central nervous system (CNS) aminergic activity increases, the brain is shifted in the direction of hyperarousal, and stress and insomnia can result. If stress and insomnia are prolonged, the chronic sympathetic overdrive can harm cardiovascular, cognitive, and behavioral functions of an animal. Behavioral and pharmacologic interventions that decrease sympathetic output can be used to reduce this hyperarousal, allowing the restoration of more normal sleep. But pharmacologic interventions invariably additionally modify the structure of sleep itself, reducing its quality. (For reviews of sleep disorders discussed later, see Kryger *et al*., 2005, and Hobson, 1989.)

The decrease in CNS aminergic activity (as in depression or narcolepsy) has opposite effects on cardiovascular, cognitive, and behavioral systems. As sleepiness appears, attention and cognition decline, and motor activity is impaired. Under these conditions, the cholinergic system is disinhibited, and the REM generator is triggered abnormally easily. The result is unwanted sleepiness or frank REM sleep attacks. These symptoms are decreased by aminergic agonists, such as blockers of amine reuptake, and psychostimulants, both of which boost sympathetic activity. Notably, many such drugs have both proaminergic and anticholinergic actions.

Respiratory Dysfunction Is Common in Sleep

One of the more dramatic problems associated with sleep is an exaggeration, at sleep onset, of the normal decline in respiratory drive (Chapter 37). Also, respiratory irregularity may be provoked by the altered brain stem activity of REM sleep. This sleep-dependent disruption of respiratory function, known as central sleep apnea, involves a decrease in respiratory drive during sleep (Fig. 42.13). More commonly, especially in obese people, mechanical collapse or compression of the airway can result in peripheral (or obstructive) sleep apnea, in which ventilation decreases because of a mechanical problem in the oropharynx. In peripheral sleep apnea, central respiratory drive causes continued respiratory effort. Eventually, the increase in CO_2 in the brain leads to an arousal which in turn produces increased muscle tone in the oropharynx, and the airway opens. As the person falls into deeper sleep again, the oropharynx relaxes and the airway can become obstructed again until arousal recurs. In severe cases, arousals every one to two minutes all night are common.

People with sleep apnea usually feel excessively sleepy during daytime because frequent arousal prevents deep, sustained sleep. They are often unaware of their sleep-dependent breathing pattern because they are never fully aroused from sleep. Instead, observant friends or family often describe seeing these signs of respiratory dysfunction. In a sleep laboratory, EEG, respiratory effort, and cardiovascular parameters (e.g., heart rate, blood pressure, and oxygen saturation) are measured to quantify the problem. Sleep apnea can be treated by having the person wear a mask through which air is forced gently, helping to keep the airways open. The pressure of the air fluctuates to allow regular exhalation. People with sleep apnea are treated not only to alleviate their constant drowsiness, but to prevent long-term effects of sleep apnea, such as cardiopulmonary complications.

Motor Disturbances Can Occur during Sleep

Parasomnias that affect the skeletal motor system can occur in either REM or NREM sleep. In NREM sleep these parasomnias (e.g., sleep walking, sleep talking, tooth grinding, and night terrors) are seen mainly in young people, and reflect motor responses to the outputs of central motor pattern generators. Normally, responses to these generators are disinhibited at sleep onset and inhibited during REM sleep, when no motor commands normally are enacted. Extensive motor output in REM sleep requires the overpowering of the normal muscle atonia of REM sleep, and REM sleep behavior disorder can be a sign of degenerative brain disease in the elderly. Because of a failure to inhibit the expression of motor acts in REM, people with this disorder may literally enact their dream scenarios in their bedrooms. Given the normal lack of this active motor suppression during NREM sleep, it remains a mystery why dreams arising during NREM sleep fail to produce robust motor output.

A syndrome strikingly similar to REM sleep behavior disorder can be induced experimentally by bilateral lesions of the pontine tegmentum in cats. When in REM sleep, these animals perform stereotyped behavior sequences, such as hissing, piloerection, pouncing, and jumping. Jouvet called these "hallucinatory behaviors," and Morrison called the phenomenon "REM sleep without atonia" (Jouvet, 1999). Because the ability of a cat to inhibit motor pattern commands during

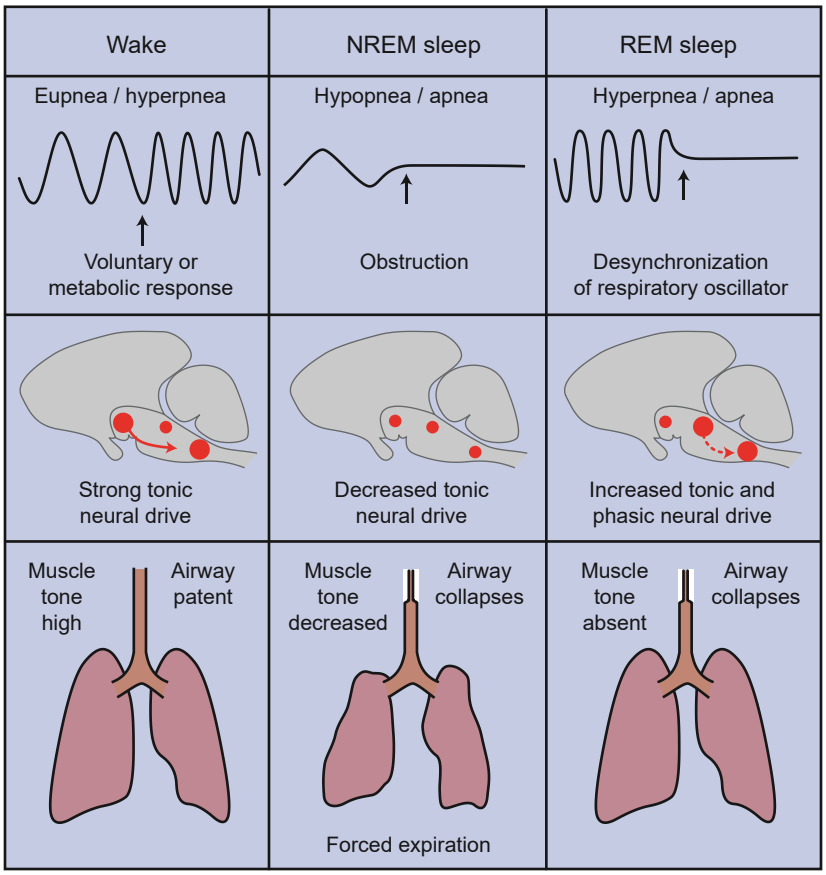

FIGURE 42.13 Central and obstructive sleep apnea. During waking, the respiratory oscillator of the medulla receives tonic drive from other neural structures and can respond to voluntary and metabolic signals to change breathing pattern. Muscle tone keeps the oropharynx open to the flow of air. In NREM sleep, central drive decreases, and the rate and depth of ventilation fall. If the decrease is excessive, central sleep apnea results, including a complete, albeit temporary, cessation of breathing. If the airway collapses, obstructive sleep apnea may result, with a similar cessation of breathing. During REM sleep, activation of pontine generator neurons drives the respiratory oscillator, and desynchronization may lead to breathing efforts that are too frequent or strong (hyperpnea) or that stop. During REM sleep the oscillator also becomes unresponsive to metabolic signals.

REM sleep is impaired by the lesions, they act out commands that are normally initiated during REM sleep. The instinctual aspect of these released behaviors is relevant to the psychophysiology of dreaming and has important implications for the hypothesis that REM sleep serves an active maintenance function.

Summary

Two models attempt to explain sleep and wakefulness. In the neurobiological model, sleep and waking are the result of a hypothalamic sleep-wake switch followed by reciprocal, phasic interactions between aminergic and cholinergic neurons and related circuitry. In the psychophysiological model, the influences of external and internal sensations are emphasized. During slow-wave sleep, thalamocortical synchronous activity diminishes responsiveness to the external world. During REM sleep, under the influence of cholinergic projections to the forebrain, internal representations of visual information predominate. In addition to changes in levels of sensory arousal and cognitive performance during sleeping, vegetative functions such as circadian rhythm recognition, body temperature, and autonomic activity also are regulated coordinately. Disorders of sleep influence emotional and cognitive functions adversely. Prolonged sleep deprivation is lethal, ending in a septic state of immunodeficiency, strongly suggesting that sleep serves important but uncertainly mediated maintenance functions.

The brain undergoes daily, complex, systematic changes in state that profoundly alter the nature of our consciousness, behavior, autonomic control, and physiologic homeostasis. At the root of these changes is the circadian clock. Located in the hypothalamus, this clock programs rest–activity and body temperature cycles. It also gates the NREM–REM sleep cycle control system in the pons.

BOX 42.3

CONSCIOUSNESS IN WAKING, SLEEPING, AND DREAMING: A MODEL FOR MENTAL ILLNESS

Since the brain is continuously active across states of sleep, so is the mind. Every modality of conscious experience can be shown to be state dependent, and particularly strong contrasts are evident between waking and dreaming, the two conscious states associated with higher levels of brain activation.

These alterations in consciousness are particularly informative to neurologists and psychiatrists because they provide new ways of thinking about the brain basis of mental illness. When brain activation declines in NREM sleep, most aspects of waking consciousness also decline. But when the brain is activated again during REM sleep, it does not reinstate waking consciousness. Instead, consciousness changes in an almost qualitative manner: Perception, instead of being shaped by external forms, becomes hallucinatory. Cognition is similarly deranged. Instead of being oriented, the dreaming mind loses track of time place and person. Instead of thinking actively and critically, the dreaming mind indulges in nonsequiturs, ad-hoc explanations, and other illogical whims. Memory, during dreams, instead of being declaratively faithful to recent history, is fragmented in its disconnection from current events and globally deficient in recalling them. Emotion, instead of being restrained and focused in response to percepts and thoughts, comes to dominate and organize dreaming consciousness often in strikingly salient ways. All these features of dream consciousness are normal and all are closely related to the changes in brain modulation. Because they are formally similar to the symptoms of the major psychoses, they suggest that mental illness may reflect genetic and environmental dysfunction of brain modulatory systems.

Edward F. Pace-Schott, J. Allan Hobson and Robert Stickgold

Some cellular and molecular details of the brain stem diencephalic behavioral state control system are clear: For the awake state, the noradrenergic locus coeruleus and the serotonergic raphé neurons of the pons, histaminergic and orexinergic neurons of the hypothalamus and, possibly, midbrain dopaminergic neurons must fire regularly to support alertness, attentiveness, memory, orientation, logical thought, and emotional stability. When the output of these chemical systems diminishes, drowsiness occurs. When sleep begins, the output of these systems declines further, and the brain–mind enters NREM sleep, a phase of lowered consciousness which, at times, might lapse into true unconsciousness. As NREM sleep continues, cholinergic activity increases gradually. At the NREM–REM transition, the activity of the serotonergic and nonadrenergic systems is at its nadir, and the output of the cholinergic system is increasing exponentially. This chemical switch results in the cholinergic activation and autostimulation of REM sleep. Combined with the lack of aminergic stimulation, this cholinergic overdrive contributes to the characteristic hallucination, delusion, disorientation, memory loss, and emotional intensity of REM sleep dreaming. What replaces these influences during NREM dreaming remains unknown.

Although the details of these daily changes in brain chemistry remain to be specified, consequences of their dysfunction are becoming more clearly understood through the study of insomnias, hypersomnias, and parasomnias. Integration of data from basic neurobiology, cognitive psychology, and clinical science enables the construction of specific, testable models of how waking and sleep affect our conscious experience. These models, in turn, constitute the building blocks of a scientific theory of consciousness.

SLEEP HAS MULTIPLE FUNCTIONS

Although it is easy to conceptualize the function of waking and to understand the adaptive value of consciousness, it has been difficult to move beyond the subjectively compelling but scientifically unsatisfactory notion of sleep as rest. But recent evidence indicates that sleep plays important roles in many physiological and cognitive systems. Evidence strongly suggests that sleep has an anabolic and actively conservative function that is related to the complexity of the mammalian brain (Table 42.1). In fact, Bennington and Heller (1995) propose that an important function of NREM sleep is to restore brain glycogen stores.

The most dramatic evidence of this homeostatic function comes from sleep deprivation studies in rats in which sleep deprivation was fatal when it persisted for four to six weeks. Early in the deprivation period,

the rats began to eat more but could not maintain their body weight. Later, they lost their ability to maintain body temperature and developed strong heat-seeking behavior, and, finally, they died. Although the cause of this death remains uncertain, it is suspected to result from overwhelming sepsis because of immunodeficiency. The study implied that the maintenance of metabolic caloric balance, thermal equilibrium, and immune competence require sleep (Rechtschaffen and Bergman, 2002).

Additional evidence links immune function and sleep. Pappenheimer found that NREM sleep in rabbits was enhanced by dimuramyl peptides of bacterial cell wall origin. NREM sleep is also enhanced by the cytokines interleukin-1 and interleukin-2, both of which are released during NREM sleep (Krueger *et al*., 1999). But perhaps more to the point, immunizing subjects with an anti-influenza vaccine during a period when sleep was restricted to 4 hours per night reduced the normal production of anti-influenza antibodies by 57% (Spiegel *et al*., 2002).

Contributing to the notion that sleep has an anabolic function is the abundance of sleep in early life. REM sleep predominates *in utero*, where its stereotypic pattern of motor activation and its chemical microenvironment could promote CNS development (Hobson, 1989). Sleep also plays a role in hormonal regulation. Growth and development are most likely enhanced by the release of growth hormone and gonadotropins in slow wave sleep. Such hormone release declines, along with slow wave sleep, after growth and sexual maturation are complete, around 30 years of age. Recent studies have demonstrated the importance of sleep for normal regulation of glucose and prevention of diabetes (Knutson *et al*., 2006).

Sleep and Memory Are Interdependent

Perhaps the clearest evidence of a function for sleep is for its role in consolidating recently formed memories (Stickgold, 2005). One of the most notable examples is the discovery, in rats, by Carlyle Smith, of "REM windows" (Smith, 1995), which are time periods after an animal is trained on specific tasks when the animal shows enhanced quantities of REM sleep and when retention of learning could be decreased by selective REM sleep deprivation. Thus, not only does REM sleep appear to be critical for the maintenance of this learning, but animals also increase their REM sleep after training, presumably by a homeostatic mechanism that regulates the amounts of different sleep stages based on the needs of the organism. Subsequent studies in humans have led to the theory that REM sleep is especially important for the consolidation of procedural memories, which are defined as memories of how to do things in the absence of explicit rules, such as how to ride a bicycle or read a map. In contrast, SWS has been implicated in the consolidation of explicit or declarative memory, which includes autobiographical memories as well as general knowledge of facts. However, studies on a procedural visual discrimination task have shown a requirement for both REM and SWS on the night following training in order for next day improvement on the task to be observed (Stickgold *et al*., 2000b). This finding supports an earlier theory based on animal studies in which a two-step process involving both REM and SWS was hypothesized. In humans, the requirement for sleep immediately following learning was shown when subjects who were sleep deprived the night following training, but who then were allowed two nights of unrestricted recovery sleep before testing, showed no significant task improvement (Stickgold *et al*., 2000a). In addition to procedural learning tasks, REM effects have been reported in humans on learning of complex logic games, foreign language acquisition, intensive studying in general, and both REM and SWS effects have been reported for the consolidation and processing of emotional memories. In contrast, sleep-dependent consolidation of simple motor skill learning, such as for a sequential finger-tapping task, correlates with Stage II NREM sleep (Walker *et al*., 2002).

There is also evidence that normal sleep-dependent memory consolidation is altered in patients with psychiatric disorders. Patients with schizophrenia show normal learning of the finger-tapping task during training, but no overnight improvement (Fig. 42.14; Manoach *et al*., 2004).

No Function for Dreaming Has Been Identified

Does dreaming also serve a function? Answering this question is not yet possible, because we do not know how to separate possible functions of the experience of dreaming from functions of the neurobiological processes that produce it. But REM sleep dream content can predict who will become clinically depressed following marital divorce or separation (Cartwright *et al*., 1998), suggesting that dreaming may serve to modulate emotional states during waking.

Dreaming may also play a role in modifying associative memory networks. Subjects awakened from REM sleep show preferential activation of more distantly related associated than seen either during waking or during NREM sleep (Stickgold *et al*., 1999). Such preferential activation of weak associations might explain the bizarre content of dreams during REM

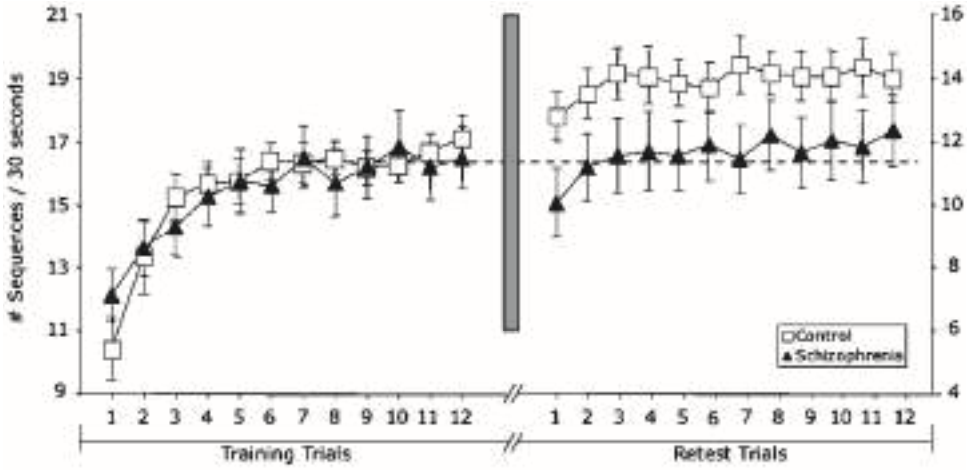

FIGURE 42.14 Sleep-dependent memory consolidation. Subjects were asked to type the sequence "41324" as quickly and accurately as they could for 30 sec and then reset for 30 sec before doing it again. Twelve trials were performed on each of two successive days. The control subjects showed a 16% increase in speed overnight, whereas the schizophrenia patients showed none.

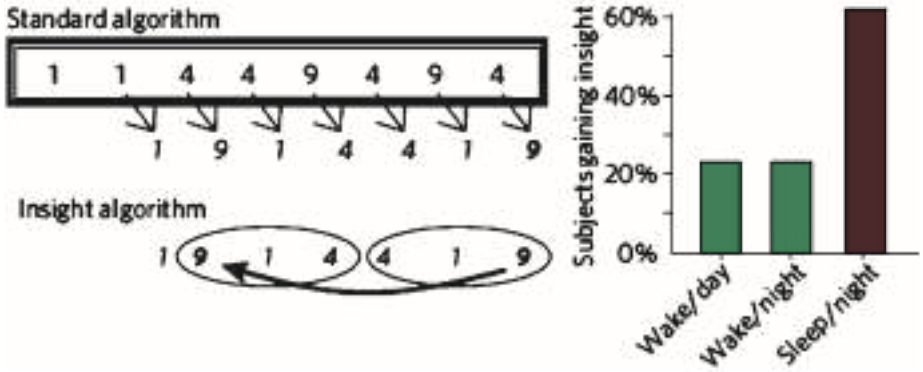

FIGURE 42.15 Sleep facilitates mathematical insight. Subjects are taught to reduce an eight-digit sequence to a single digit (*9* at the right), through six intermediate calculations (in italics) with a standard algorithm. Unknown to the subjects, the task is designed so that the last three calculations form a mirror image of the preceding three, and thus the second intermediate calculation matches the final answer. Right: subjects who slept between training and testing were more than twice as likely to discover the insight algorithm than those not allowed sleep.

sleep, and may permit the brain to discover creative solutions to problems during sleep. Indeed, sleep has been shown to increase the likelihood of such discoveries (Fig. 42.15; Wagner *et al.*, 2004). But whether the conscious experience of dreaming is crucial for any of these sleep-dependent processes remains unknown.

Summary

Sleep represents a complex behavioral and neurobiological process that is conserved across much of the animal kingdom. REM sleep is similarly conserved across the class Mammalia. The complex, REM–NREM cycle suggests that these distinct neurophysiological and neurochemical brain states have evolved to subserve specific functions. One hypothesis is that the types of sleep stages and their timing across the night evolved to meet the demands of varying memory systems for effective offline processing during sleep. Whether dreaming also evolved to permit offline cognitive and affective processing remains an open question.

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