lesions in the anterior hypothalamus. He proposed that neurons in this area are important for inhibiting the brain stem arousal system to allow sleep. Modern studies have shown a system of wake–sleep circuitry in the brain that is remarkably close to von Economo's model.

The Ascending Arousal System in the Brain Stem and Hypothalamus Innervates the Forebrain

The composition of the ascending arousal system has been debated since von Economo's time. In the late 1940s and early 1950s, lesion studies confirmed that damage to the upper midbrain reticular formation could cause coma, whereas electrical stimulation of this region could arouse animals. The location and nature of the wake-promoting neurons were unknown.

In the succeeding decades, it became clear that these lesions damaged the axons of neurons in the upper brain stem that project to the forebrain, including noradrenergic neurons in the locus ceruleus, serotonergic neurons in the dorsal and median raphe, and midbrain dopaminergic neurons (Chapter 40). The axons of other neurons in the posterior hypothalamus, including those producing histamine and orexin, also join this pathway, which splits into two bundles, with some projections innervating the thalamus and others the hypothalamus, basal forebrain, and cerebral cortex (Figure 44–3).

Neurons contributing to all of these ascending pathways fire fastest during the awake state but much slower during sleep, suggesting that they are wake-promoting. However, although many monoamine antagonists cause sleepiness, and lesions of the

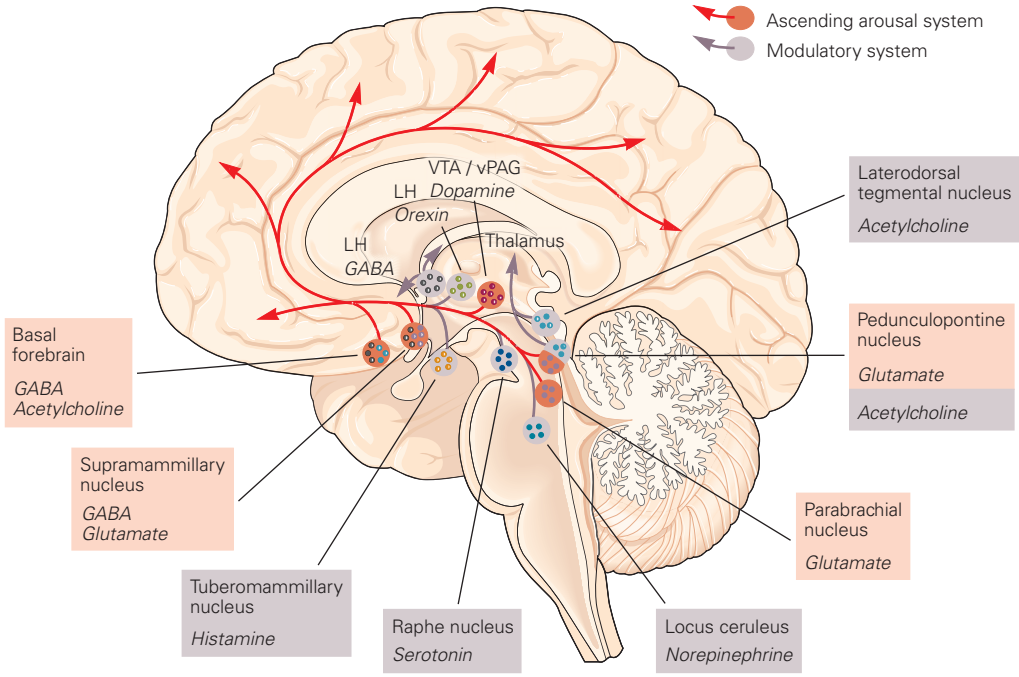


Figure 44–3 The ascending arousal system. The ascending arousal system comprises primarily axons from glutamatergic neurons in the parabrachial and pedunculopontine tegmental nuclei and cholinergic and GABAergic (**dark gray**) neurons in the basal forebrain. Lesions of either the parabrachial and pedunculopontine nuclei or the basal forebrain cause coma. Of somewhat lesser importance are dopaminergic neurons in the ventral tegmental area (**VTA**) and ventral periaqueductal gray (**vPAG**) matter and glutamatergic and GABAergic neurons in the supramammillary nucleus, where lesions can increase sleep by about 20%. In addition, populations of modulatory neurons can strongly promote wakefulness when stimulated, but when damaged cause minimal changes in wake–sleep amounts. These include the monoaminergic neurons in the noradrenergic locus ceruleus, the serotonergic dorsal and median raphe nuclei, and the histaminergic tuberomammillary nucleus; the cholinergic neurons in the pedunculopontine and lateral dorsal tegmental nuclei; and the orexinergic neurons in the lateral hypothalamus (**LH**). All of these neurons send their axons through the hypothalamus and basal forebrain directly to the cerebral cortex, where their net effect is to increase cortical arousal. Many of the modulatory pathways also activate the thalamus, enabling thalamic transmission of sensory information to the cerebral cortex. GABAergic neurons in the lateral hypothalamus also promote wakefulness by inhibiting neurons in the ventrolateral preoptic area and reticular nucleus of the thalamus that oppose wakefulness.

monoaminergic cell groups impair the ability to stay awake under adverse conditions, such lesions have little lasting effect on the amount or timing of wake or sleep.

Lesions of the orexinergic neurons in the lateral hypothalamus cause narcolepsy, a condition in which sleep–wake states are present in normal amounts but are unstable, as discussed later. In fact, of all of the monoaminergic cell groups that are thought to contribute to arousal, only lesions of the dopaminergic neurons near the dorsal raphe nucleus cause small but long-lasting reductions in arousal, resulting in about a 20% increase in total sleep time. Interestingly, the ability of drugs such as amphetamine or modafinil to promote wakefulness appears to depend upon their ability to block dopamine reuptake, as mice with deletions of the dopamine transporter do not respond to these drugs.

Because lesions of the ascending monoaminergic and orexinergic pathways have little if any effect on the total amount of wakefulness, recent work has emphasized the role of glutamatergic, cholinergic, and GABAergic neurons in maintaining wakefulness. Lesions of glutamatergic neurons in the dorsolateral rostral pons, including the parabrachial nucleus and adjacent pedunculopontine tegmental nucleus, cause a comatose state from which the animals cannot be awakened. Lesions confined to the thalamus impair the content of consciousness but have relatively little effect on wake–sleep cycles. On the other hand, lesions of the posterior lateral hypothalamus cause profound sleepiness, which cannot be accounted for by damage to the orexinergic or histaminergic neurons in this region. Glutamatergic neurons in the supramammillary region, which activate the cortex, and GABAergic neurons in the lateral hypothalamus that inhibit sleep-promoting circuits, may account for this arousal effect. Finally, large bilateral lesions of the basal forebrain also can produce coma, similar to lesions of the dorsolateral pons. Optogenetic or chemogenetic activation of cholinergic, GABAergic, or glutamatergic neurons in the basal forebrain indicates that neurons of all three types may produce arousal.

Thus, the current view of the ascending arousal system is that the crucial components are glutamatergic neurons in the dorsolateral pons, supramammillary hypothalamus, and basal forebrain; cholinergic neurons in the dorsolateral pons and basal forebrain; and GABAergic neurons in the lateral hypothalamus and basal forebrain. These are likely to be augmented by modulatory pathways containing orexin and monoamines, needed to allow full and sustained wakefulness particularly under adverse conditions (Figure 44–3).

Damage to the Ascending Arousal System Causes Coma

Consciousness depends upon the activity of the cerebral hemispheres during the awake state. Hence, loss of consciousness occurs when there is injury to the ascending arousal system or to both cerebral hemispheres, or there is a severe metabolic derangement (eg, low blood sugar, inadequate oxygenation, various forms of drug intoxication) that affects both the arousal system and its cortical targets. A patient who cannot be awakened, even by vigorous stimulation, is said to be in a coma. Those who can be partially awakened by such stimuli are said to be stuporous or obtunded.

The clinical approach to a comatose or obtunded patient is first to determine if there is injury to the ascending arousal system. Because of the proximity of the arousal pathways to those that control eye movement and pupillary responses, as well as respiration and some motor responses (Chapter 40), clinicians examine these brain stem functions carefully. If these functions are intact, it is likely that the problem is due to a metabolic condition, which can be assessed by various blood and spinal fluid tests. In addition, a computed tomographic (CT) scan of the brain is needed to look for pathology affecting both cerebral hemispheres (eg, a large tumor or blood clot).

Circuits Composed of Mutually Inhibitory Neurons Control Transitions From Wake to Sleep and From Non-REM to REM Sleep

In contrast to coma, sleep is a temporary, reversible loss of consciousness produced by specific brain circuitry that inhibits the ascending arousal system. Neurons in the ventrolateral preoptic nucleus contain the inhibitory neurotransmitters GABA and galanin and project extensively to most parts of the ascending arousal system. These preoptic neurons fire slowest during wakefulness, increase their firing as animals fall asleep, and fire fastest during deep sleep after a period of sleep deprivation.

Similarly, GABAergic neurons in the nearby median preoptic nucleus also promote sleep and project to some components of the arousal system. Lesions of these preoptic neurons result in fragmented sleep and cause animals to lose as much as half of their total sleep. Of clinical relevance, elderly people often have fragmented sleep, and those with the most fragmented sleep show the greatest loss of the sleep-promoting ventrolateral preoptic galanin neurons in postmortem examination. In addition, a population of GABAergic neurons in the parafacial zone, a region near the facial

nerve as it courses through the brain stem, inhibits the parabrachial nucleus. Lesions of the parafacial zone also result in loss of up to half of total sleep time.

Interestingly, the ventrolateral preoptic neurons receive inhibitory inputs from neurons throughout the arousal system. Mutually inhibitory connections between the ventrolateral preoptic neurons and the arousal system result in a neural circuit with properties similar to an electrical flip-flop switch, in which each side of the circuit turns the other off. Such a circuit produces rapid and full transitions between two states. Although it may sometimes appear that it takes a long time to fall asleep, the actual transitions from wake to sleep, or vice versa, are generally quick, taking only a few seconds to a few minutes. In fact, most animals spend nearly their entire day clearly awake or asleep, with very little time spent in transitions. These rapid transitions are behaviorally adaptive as an animal would be vulnerable in an intermediate, drowsy state. A neural flip-flop switch prevents this situation because when either side of the switch gains advantage over the other, the circuit produces a rapid and complete transition in state (Figure 44–4).

REM sleep is generated by a network of brain stem neurons centered in the pons. The fast EEG rhythms and dream activity of REM sleep are thought to be driven by coordinated activity of glutamatergic neurons in the subceruleus region (ventral to the locus ceruleus in the pons) plus cholinergic and glutamatergic neurons in the parabrachial and pedunculopontine tegmental nucleus that innervate the basal forebrain and thalamus. Other glutamatergic subceruleus neurons produce the paralysis of REM sleep via projections to the ventromedial medulla and spinal cord, where they activate GABAergic and glycinergic neurons that deeply hyperpolarize motor neurons.

The subceruleus area in turn receives input from a population of GABAergic neurons in and just lateral to the periaqueductal gray matter, where the cerebral aqueduct opens into the fourth ventricle. These neurons are most active during wake and non-REM sleep, and they inhibit the subceruleus neurons, preventing entry into REM sleep. Conversely, GABAergic neurons in the subceruleus area also project back to the ventrolateral periaqueductal gray region. The mutual inhibition between the two populations of neurons may form another flip-flop switch that promotes rapid and complete transitions into and out of REM sleep.

Interestingly, the noradrenergic locus ceruleus and serotonergic dorsal raphe nucleus innervate and inhibit the subceruleus region. Thus, REM sleep is often reduced when people take antidepressants that increase brain levels of serotonin or norepinephrine. In addition, as these monoaminergic neurons are active during wakefulness, they prevent direct transitions from wake into REM sleep (Figure 44–5).

Sleep Is Regulated by Homeostatic and Circadian Drives

The circadian regulation of sleep obeys a 24-hour biological clock (described later), whereas the homeostatic drive for sleep gradually accumulates during the awake state. After a period of sleep deprivation, much of the lost sleep is recovered over the next few nights, which in younger people may involve deeper and longer periods of stage N3 non-REM sleep.

REM sleep is also recovered after REM deprivation; rebound REM sleep can include especially intense dreams, long periods of REM sleep, and occasional breakthrough of REM sleep phenomena into wakefulness, such as dream-like hallucinations or brief paralysis when falling asleep or waking up. Rebound sleep on a weekend is commonly enriched in REM sleep in people who wake up early to an alarm clock on workdays and miss out on the last portion of sleep, which is mainly REM sleep.

The Homeostatic Pressure for Sleep Depends on Humoral Factors

Humoral factors circulating in the brain signal the homeostatic pressure for non-REM sleep. The brain is metabolically quite active during wakefulness and uses ATP, but with sustained periods of wakefulness, ATP is dephosphorylated to adenosine, which acts as a local neuromodulator in the extracellular environment. Adenosine type 1 receptors are inhibitory receptors that are expressed on wake-promoting neurons and in many other parts of the brain, so higher adenosine levels may produce sleepiness by inhibiting these neurons. In addition, adenosine can excite neurons via adenosine type 2a receptors; these receptors are common in the shell of the nucleus accumbens and may cause sleepiness by means of projections to the hypothalamus that activate the ventrolateral preoptic neurons.

The pressure for sleep can be measured by the time it takes an individual to fall asleep if given the opportunity in a comfortable environment. This approach is used by sleep clinicians in the Multiple Sleep Latency Test, in which an individual is given 20-minute intervals to try to fall asleep in a comfortable, quiet bed every 2 hours beginning at 9 am, for five sleep opportunities. An individual who is well rested generally

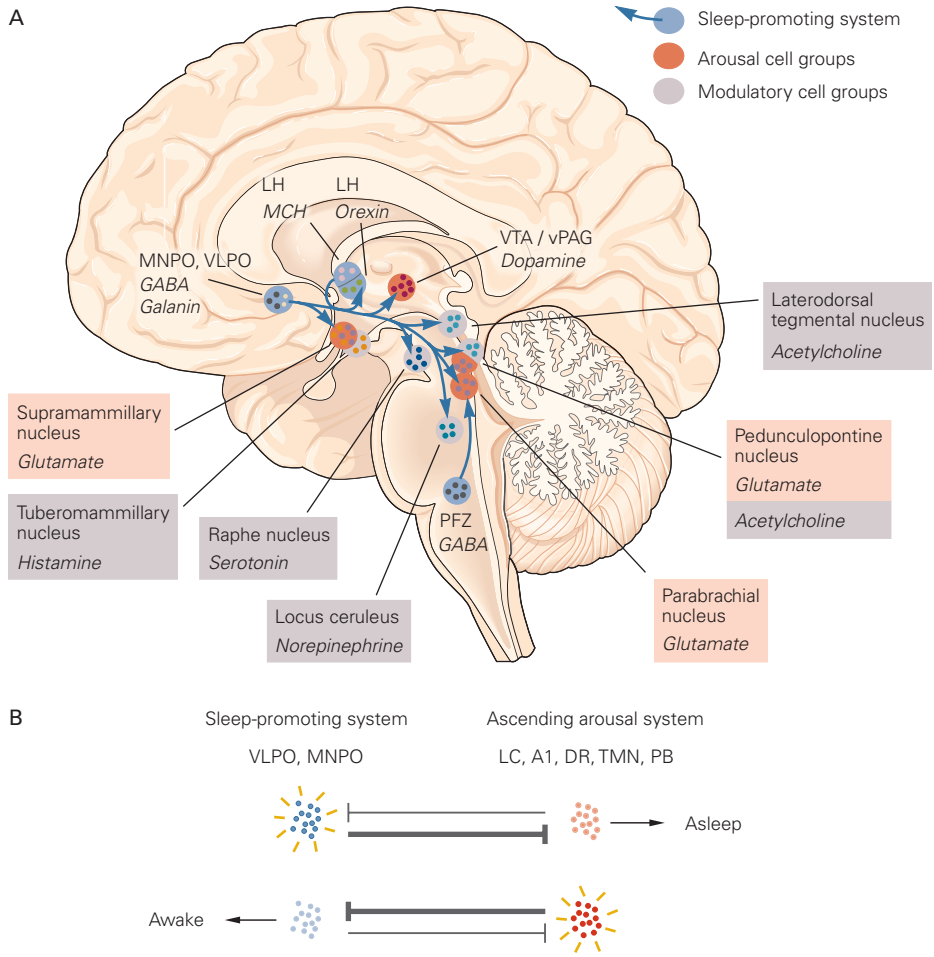


Figure 44–4 Sleep-promoting pathways.

A. The components of the ascending arousal system (Figure 44–3) receive inhibitory, largely GABAergic inputs from sleep-promoting neurons. Neurons in the ventrolateral and median preoptic nuclei (**VLPO, MNPO**) innervate the entire arousal-promoting system, while those in the parafacial zone (**PFZ**) innervate mainly the parabrachial area. Many of the VLPO neurons also contain galanin (GAL), an inhibitory peptide. Neurons in the lateral hypothalamus (**LH**) that release melanin-concentrating hormone (**MCH**) may promote REM sleep by inhibiting both nearby orexinergic neurons as well as neurons in the periaqueductal gray matter that prevent REM sleep (see Figure 44–5). (Abbreviations: **vPAG**, ventral periaqueductal gray; **VTA**, ventral tegmental area.)

B. The flip-flop switch relationship of the ventrolateral and median preoptic nuclei and the mutually inhibitory components of the ascending arousal system (**LC**, locus ceruleus; **A1**, noradrenergic neurons; **DR**, dorsal raphe; **TMN**, tuberomammillary nucleus; **PB**, parabrachial nucleus). When activated, the sleep-promoting neurons inhibit the components of the ascending arousal system. However, the sleep-promoting cell groups are also inhibited by the arousal system. The net effect is that the individual spends most time fully awake or asleep while minimizing time in transitional states.

takes at least 15 to 20 minutes to fall asleep, but a very sleepy person can easily fall asleep within a few minutes in each nap. Another test of sleep pressure is the Psychomotor Vigilance Task. The subject is told to watch a small lamp and press a button as soon as they see the light turned on. The light then turns on at random times over a 5- to 10-minute test period; sleepy subjects are inattentive and intermittently are slow or completely fail to respond to the light stimulus.

Circadian Rhythms Are Controlled by a Biological Clock in the Suprachiasmatic Nucleus

Circadian rhythms are roughly 24-hour physiological rhythms that synchronize the internal state of an animal with the external daily environment and anticipate various physiologic demands that occur on a daily basis. In humans, circadian wake-promoting signals during the day counterbalance the rising homeostatic

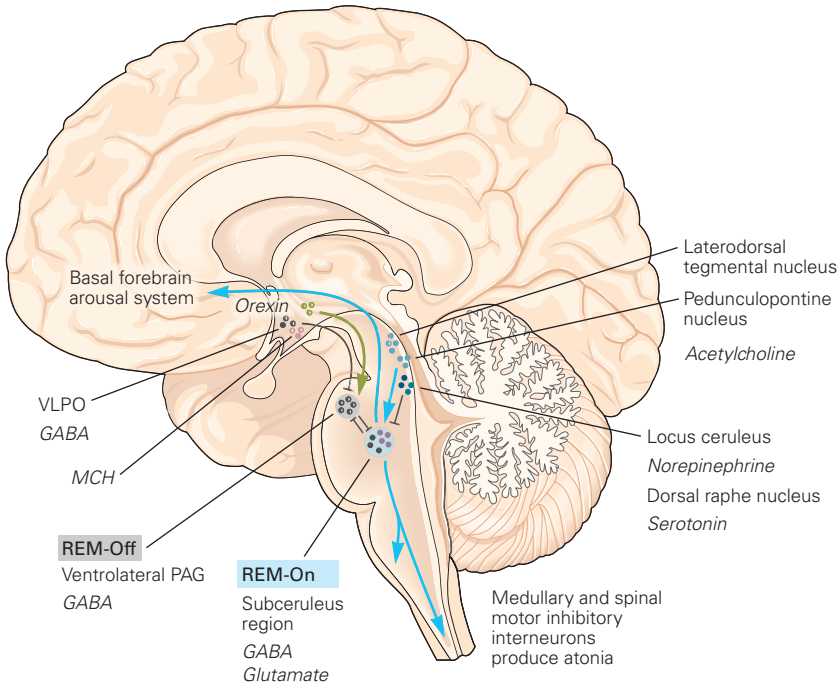
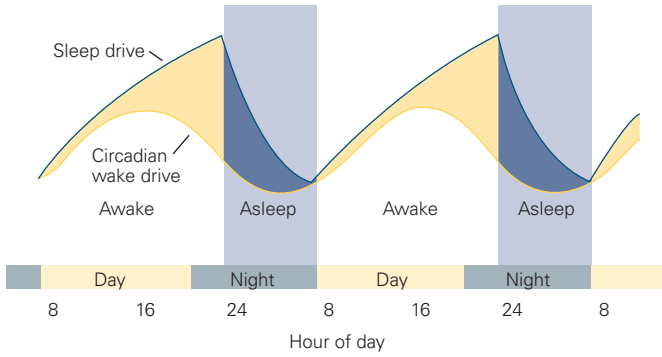


Figure 44–5 The REM sleep switch. Brain stem neurons are essential for controlling the transitions between non–rapid eye movement (**REM**) and REM sleep. REM sleep is generated by a population of neurons in the rostral pons, just ventral to the laterodorsal tegmental nucleus and locus ceruleus, in what is called the sublaterodorsal area in rodents and the subceruleus region in humans. These glutamatergic neurons project to other parts of the brain stem, where they initiate the motor and autonomic manifestations of REM sleep, and to the forebrain, where they mediate behavioral and electroencephalographic components of REM sleep. The descending projection activates inhibitory interneurons in the medulla and spinal cord that profoundly hyperpolarize motor neurons and prevent the individual from acting out his or her dreams. These REM-on neurons are inhibited by GABAergic neurons in the ventrolateral periaqueductal gray matter and adjacent pontine reticular formation, while the latter are themselves inhibited by neurons in the REM-on region, thus forming a flip-flop switch (see Figure 44–4B). These REM-off neurons are under the control of forebrain neurons, including neurons that release the excitatory orexin neuropeptides, neurons in the ventrolateral preoptic nucleus (**VLPO**) that release the inhibitory signaling molecules γ-aminobutyric acid (**GABA**) and galanin, and hypothalamic neurons that release the inhibitory neuropeptide melanin-concentrating hormone (**MCH**). In addition, modulatory neurons in the locus ceruleus and dorsal raphe inhibit the REM generator, whereas cholinergic neurons in the pedunculopontine and laterodorsal tegmental nuclei promote REM sleep. This model explains many clinical observations, such as the fact that cholinergic agonist drugs promote REM sleep, whereas drugs such as antidepressants that increase monoamine levels suppress REM sleep. Loss of orexinergic neurons can cause abrupt onset of REM sleep, whereas loss of REM-on neurons in the sublaterodorsal area abolishes atonia during REM sleep. Thus, individuals with this condition act out their dreams (*REM sleep behavior disorder*).

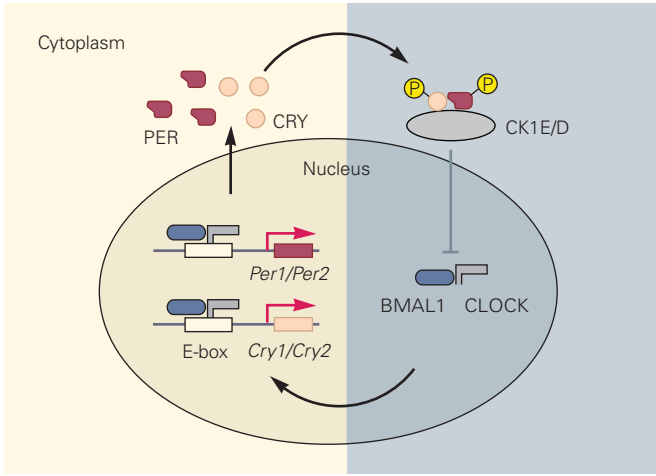
sleep pressure. The circadian wake-promoting signal dips slightly in the mid-afternoon, when many people take a nap or siesta. Around the habitual bedtime, this circadian waking influence rapidly collapses, the homeostatic drive for sleep is unopposed, and sleep ensues. In the hour or two before the customary waking time, circadian promotion of sleep occurs to ensure an adequate amount of sleep, since homeostatic sleep pressure is low late in the sleep period (Figure 44–6A).

Circadian rhythms are driven by a small group of GABAergic neurons in the suprachiasmatic nucleus located in the hypothalamus just above the optic chiasm. The 24-hour rhythm of activity in this biological clock is driven by a set of "clock genes," which undergo a transcriptional-translational cycle with an approximately 24-hour period. The positive limb of the loop consists of two proteins, BMAL1 and CLOCK, which dimerize and form a transcription factor that binds to the E-box motif, which is found in the promoter region of hundreds of genes that undergo daily cycles in their expression. Among those genes whose expression is increased by BMAL1 and CLOCK are the *Period* and *Cryptochrome* genes. Their protein products also dimerize, form a complex with casein kinase 1 delta or epsilon, and are translocated to the nucleus of the cell, where they cause BMAL1 and CLOCK to dissociate

A Wake–sleep cycle with light cues



B Genetic clock of the wake–sleep cycle



C Wake–sleep cycle without light cues

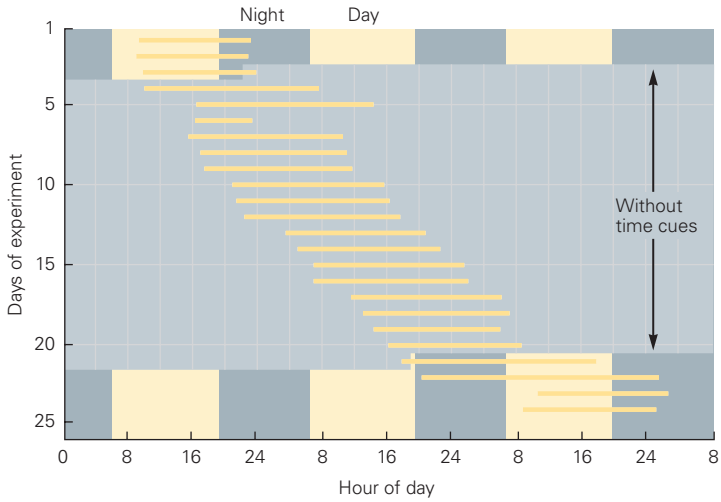


Figure 44–6 The circadian drive for wakefulness interacts with the homeostatic drive for sleep to shape wake–sleep cycles.

A. Sleep drive builds up gradually over the course of a long period of wakefulness, whereas the circadian drive for wakefulness varies on a 24-hour cycle, regardless of previous sleep. The peak of this circadian wake cycle occurs in the hours before bed, as the homeostatic sleep drive is rising, whereas the low point occurs in the hours just before the habitual time of awakening, when the homeostatic drive for sleep is ebbing.

B. The 24-hour rhythm in mammalian cells is regulated by a set of proteins that form a transcriptional-translational loop. BMAL1 and CLOCK form a dimer that binds to the E-box motif found on many genes that have circadian rhythms of transcription. Among these are the *Period 1* and *2* genes (*Per1, Per2*) and the *Cryptochrome 1* and *2* genes (*Cry1, Cry2*). Their products dimerize and form a complex with casein-1 kinase epsilon or delta (**CK1E/D**). The complex translocates to the nucleus, where it inhibits the dimerization of BMAL1 and CLOCK, causing it to fall off the E-box. This reduces the transcription of *Period* and *Cryptochrome* genes; as PER and CRY proteins are degraded, BMAL1 and CLOCK dimerize once more, and the cycle repeats.

C. Circadian rhythms regulate the timing of sleep and wake. The plot shows the wake cycles (**yellow bars**) of an individual who initially lives under regular lighting conditions for 3 days and then lives in a dimly lit environment with no time cues for 18 days. The individual maintains daily cycles of about 25.2 hours, drifting an entire day over this period. Blind people who cannot relay light signals to the suprachiasmatic nucleus (see Figure 44–7) often live continuously like this, a condition called non–24-hour wake–sleep disorder.

from the E-box, reducing transcription of many genes, including themselves. This results in a fall in Period and Cryptochrome proteins until BMAL1 and CLOCK can once more dimerize, restarting the cycle. In addition to this core loop, additional genetic side loops modulate the period of the circadian clock (Figure 44–6B).

This daily gene cycle functions in almost all cells in the body, including those in the brain, and it is essential for driving a wide range of circadian rhythms, from secretion of hormones and digestive enzymes to readying the liver for metabolic processing of food and the cardiovascular system for the active period of the day. When removed from the body and placed in a culture dish, most cells in the body rapidly fall out of synchrony, as the individual cellular clock cycles vary between cells by as much as an hour or two from the 24-hour mean. However, when neurons of the suprachiasmatic nucleus are cultured they continue to communicate with one another and thereby synchronize their cellular rhythms. This coordinated activity by suprachiasmatic neurons results in a close to 24-hour rhythm; the average period in humans who are placed in a continuous dim light environment is 24.1 hours, resulting in a slow drift in circadian rhythms (Figure 44–6C).

The suprachiasmatic nucleus exerts control over all of the other body clocks by regulating body temperature as well as autonomic, endocrine, and behavioral functions. Interestingly, although the daily rhythm in body temperature can adjust the timing of rhythms in many organs, the rhythm of the suprachiasmatic nucleus itself is highly resistant to changes in temperature, so its fundamental pacemaking is unaltered. In the end, the circadian timing of the brain and body runs on suprachiasmatic time.

Still, the suprachiasmatic clock must be entrained to the external world. If it were not, each person with a 24.1-hour cycle would progressively wake up six minutes later each day than the day before and would be unable to adjust to seasonal variations in sunrise and sunset. To avoid this situation, the suprachiasmatic nucleus receives direct inputs from a special class of retinal ganglion cells that signal light levels, rather than participating in image formation. Like all retinal ganglion cells, these neurons receive inputs from rods and cones, but they also contain melanopsin, a photopigment that makes them intrinsically photosensitive and hence they function as luminance detectors. In addition to entraining internal circadian rhythms to the ambient light cycle, these cells also regulate other non–image-forming visual functions such as the pupillary light reflex and the feeling of pain that can occur when one looks into bright lights.

Some individuals have unusually short circadian periods due to mutations in clock genes or their regulatory elements. For example, individuals with *familial advanced sleep-phase syndrome* prefer to go to bed early in the evening and cannot sleep past 3 or 4 am. In families with this disorder, mutations in the genes coding for Period or Casein kinase-1 delta result in more rapid cycling of the clock.

Blind people in whom the melanopsin-containing neurons are damaged lack visual input to their suprachiasmatic nucleus, often resulting in *non–24-hour sleep–wake rhythm disorder*. Because most people have an intrinsic cycle longer than 24 hours, circadian rhythms in these individuals drift, becoming a few minutes later each day, so that most of the time they are out of synch with the rest of the world. They lack the ability to entrain to external light–dark conditions because the suprachiasmatic nucleus lacks the crucial resetting signal from the retina. This problem is most common in people who have lost their eyes (eg, due to trauma or infection), but it is not seen in blind people in whom the melanopsin-containing neurons are intact (eg, blindness due to degeneration of rods and cones, or problems with the cornea or lens) and who also retain their pupillary light reflexes.

In contrast to light, which is signaled by the melanopsin neurons, the hormone melatonin signals darkness. Melatonin is made by the pineal gland, and the suprachiasmatic neurons time its release through communication with neurons in the paraventricular nucleus of the hypothalamus that activate sympathetic innervation of the pineal gland. Neurons in the suprachiasmatic nucleus contain melatonin receptors, which reinforce circadian rhythms. Similarly, exogenous melatonin or melatonin agonists can entrain circadian rhythms, promoting sleep by regularizing sleep onset. This treatment approach is particularly useful in entraining circadian rhythms in individuals with non–24-hour sleep–wake rhythm disorder.

Circadian Control of Sleep Depends on Hypothalamic Relays

The suprachiasmatic nucleus is most active during the daily light period in all mammalian species. While humans are diurnal (awake during the day and asleep during the night), nocturnal mammals have the opposite activity cycle. How can such opposite behavioral patterns be set by the suprachiasmatic nucleus if it is most active during the light period?

The answer appears to lie in a series of relays interposed between the suprachiasmatic nucleus and the wake–sleep control circuitry, which give the circadian

timing system flexibility in meeting the needs of the individual. The suprachiasmatic neurons are GABAergic, and they send the bulk of their output to an adjacent region called the subparaventricular zone. This area in the anterior hypothalamus contains mostly GABAergic neurons that fire in antiphase to the suprachiasmatic nucleus, ie, are most active at night. The targets of the subparaventricular zone largely overlap those of the suprachiasmatic nucleus, including parts of the paraventricular, dorsomedial, ventromedial, and lateral hypothalamus that regulate various physiological and behavioral systems. Presumably, then, the timing of a particular physiological or behavioral function would depend upon the relationships of these two antiphase circadian inputs to their target neurons.

One crucial target of the subparaventricular zone is the dorsomedial nucleus of the hypothalamus, which regulates a number of circadian behaviors, including the wake–sleep cycle. Lesions of the dorsomedial nucleus severely disrupt circadian rhythms of sleep, feeding, locomotor activity, and corticosteroid secretion. The dorsomedial nucleus is thought to promote wakefulness via GABAergic projections to the ventrolateral preoptic nucleus and glutamatergic projections to the lateral hypothalamus (Figure 44–7).

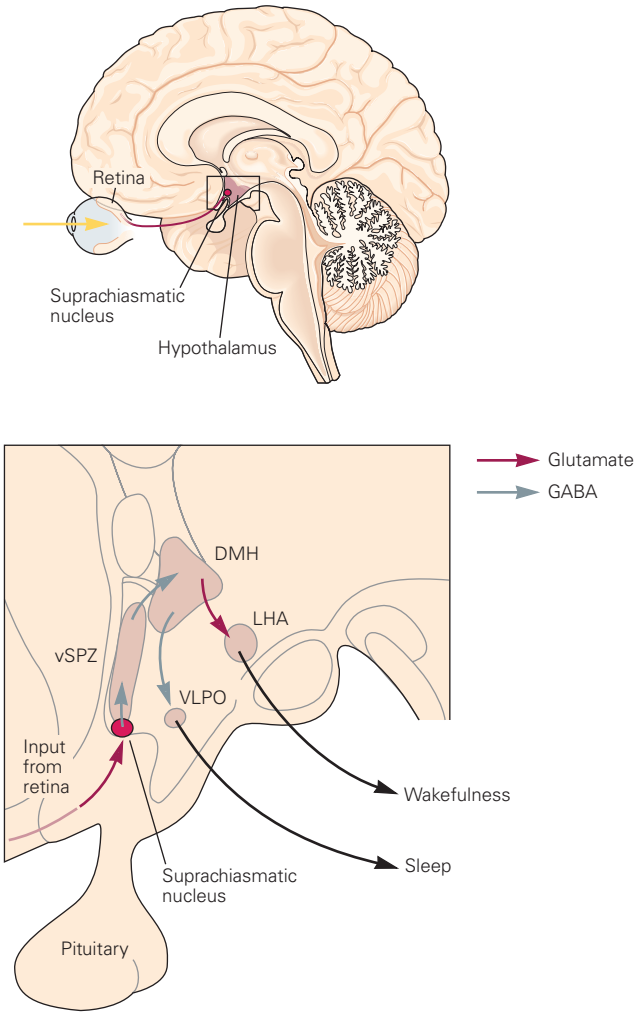


Figure 44–7 **Neurons in the suprachiasmatic nucleus provide a master clock for wake–sleep.** Retinal inputs signaling light activate the suprachiasmatic nucleus (**upper figure**), which then drives the wake–sleep cycle through a series of relays in the hypothalamus (**lower figure**). The sagittal section through the hypothalamus shows the suprachiasmatic nucleus projecting to neurons in the ventral subparaventricular zone (**vSPZ**), which in turn project to the dorsomedial nucleus of the hypothalamus (**DMH**). The DMH contains glutamatergic neurons that excite orexinergic and glutamatergic neurons in the lateral hypothalamic area (**LHA**), causing wakefulness. GABAergic neurons in the DMH inhibit the ventrolateral preoptic nucleus (**VLPO**), turning off the sleep-promoting system. Animals with DMH lesions fail to show circadian rhythms of wake–sleep and sleep about an hour more per day.

Sleep Loss Impairs Cognition and Memory

When people are sleepy, they often have impaired vigilance, working memory, judgement, and insight. Some of the attentional problems may be caused by *microsleeps*, brief periods of slower cortical activity. For example, subjects who rarely miss stimuli on the Psychomotor Vigilance Task when well rested may miss over 20% of the visual stimuli when sleepy. In addition to these global lapses in cortical function, sleepiness can also produce *local sleep* with slow EEG waves in focal cortical areas. Executive function is often the first thing to fail with sleepiness, and sleep-deprived people show reduced metabolism and focal slowing in the frontal cortex in EEGs.

While sleepiness impairs cognition, sleep itself helps consolidate memories. When subjects are taught a simple motor task, such as pressing buttons in a predetermined sequence, they become more efficient with practice. Robert Stickgold and colleagues found that if the training is in the morning, and the subjects are tested 12 hours later in the evening (without intervening sleep), they perform at about the same level as when they stopped their training. However, if they are tested the next morning after a night of sleep, they usually perform better than on the day of training. Subjects who are trained in the evening still perform better 12 hours later if they have had a chance to sleep overnight but not if they remained awake. Improvement of certain types of memory consolidation (eg, memory for a visual perception task) is correlated with the amount of REM sleep, while other types (eg, memory for a finger-tapping sequence task) correlate with stage N2 non-REM sleep.

These studies suggest that in each stage of sleep the cerebral cortex undergoes synaptic reorganization to consolidate the memory of specific types of salient information. Conversely, this memory consolidation is lost when subjects are deprived of sleep or have fragmented sleep. A related theory, proposed by Giulio Tononi and Chiara Cirelli, is that rebalancing of synaptic strengths based on recent experience (synaptic homeostasis) occurs during sleep. The size of many excitatory synapses is increased during learning, requiring that some excitatory inputs be reduced to avoid overexciting the target neuron. Tononi and Cirelli found that the size of smaller synapses in motor and sensory cortex is reduced during sleep, resulting in strong inputs being strengthened while competing weaker ones are removed.

Diseases that cause sleep loss or that wake people from sleep can impair cognition. For example, *obstructive sleep apnea* can severely fragment sleep, resulting in daytime sleepiness, inattention, and other cognitive impairments. Fragmented sleep is also common in Alzheimer disease. Alzheimer patients tend to have fewer neurons in the ventrolateral preoptic nucleus, and the extent of neuronal loss correlates with their degree of sleep fragmentation. Whether treating sleep fragmentation can improve cognition in Alzheimer patients remains to be determined.

Sleep Changes With Age

Sleep changes with age in striking and characteristic ways. As every new parent quickly learns, the lengthy sleep time of a newborn is distributed almost randomly throughout the day. Although the EEG rhythms in newborns are not as well formed as those of older children or adults, more than 50% (8–9 hours per day) of that sleep is spent in a state much like REM sleep.

Sleep recordings from a premature infant exhibit an even higher percentage of REM-like sleep, indicating that in utero the fetus spends a large fraction of the day in a brain-activated but movement-inhibited state. As neuronal activity influences the development of functional circuits in the brain (Chapters 48 and 49), it is reasonable to think that the spontaneous activity of the immature brain during sleep facilitates the development of neural circuits.

By approximately 4 months of age, the average baby begins to show diurnal rhythms that are synchronized with day and night, much to the relief of weary parents. The total duration of sleep gradually declines, and by 5 years of age, the child may sleep 11 hours each night plus a nap, and 10 hours of sleep is typical around age 10. At these early ages, sleep is deep; stage N3 is prominent, with an abundance of delta waves in the EEG. As a result, children are not easily wakened by environmental stimuli.

With age, sleep becomes lighter and more fragmented. The percentage of time spent in stage N3 sleep drops across adulthood, and by the age of 50 to 60, it is not unusual for N3 to fade entirely, especially in men. This shift toward lighter stages of non-REM sleep results in two to three times as many spontaneous awakenings and more easily disrupted sleep. Many sleep disorders, including insomnia and sleep apnea, become more prevalent with age, and insomnia is common, often due to waking in response to neural signals to empty the bladder or due to discomfort from menopausal symptoms or from arthritis and other diseases. Why this change occurs with age is unclear; homeostatic sleep pressure appears normal, but the neural mechanisms for producing deep non-REM sleep may be less effective.

Disruptions in Sleep Circuitry Contribute to Many Sleep Disorders

Insomnia May Be Caused by Incomplete Inhibition of the Arousal System

Insomnia is one of the most common problems in all of medicine, yet the underlying neurobiology remains a mystery. Insomnia is defined as difficulty falling asleep or trouble staying asleep, so that function the next day is impaired. Positron emission tomography studies in patients with chronic insomnia demonstrate unusual activation of brain arousal systems during sleep, and the EEG often shows persistence of high-frequency activity (15–30 Hz) that is usually seen only during wake.

In addition, rats exposed to acute stress show high-frequency EEG activity during sleep, as well as simultaneous activity in neurons of the ventrolateral preoptic nucleus and components of the arousal system, such as the locus ceruleus and histamine neurons. This simultaneous activation can produce a unique state in which the EEG shows slow waves consistent with sleep along with high-frequency activity consistent with the awake state; this may explain why some patients appear asleep on the polysomnogram recording but they may feel awake.

Clinically, insomnia is often treated with cognitive behavioral therapy that is aimed at reducing the hyperarousal and improving sleep habits. Some patients may be treated with benzodiazepines and