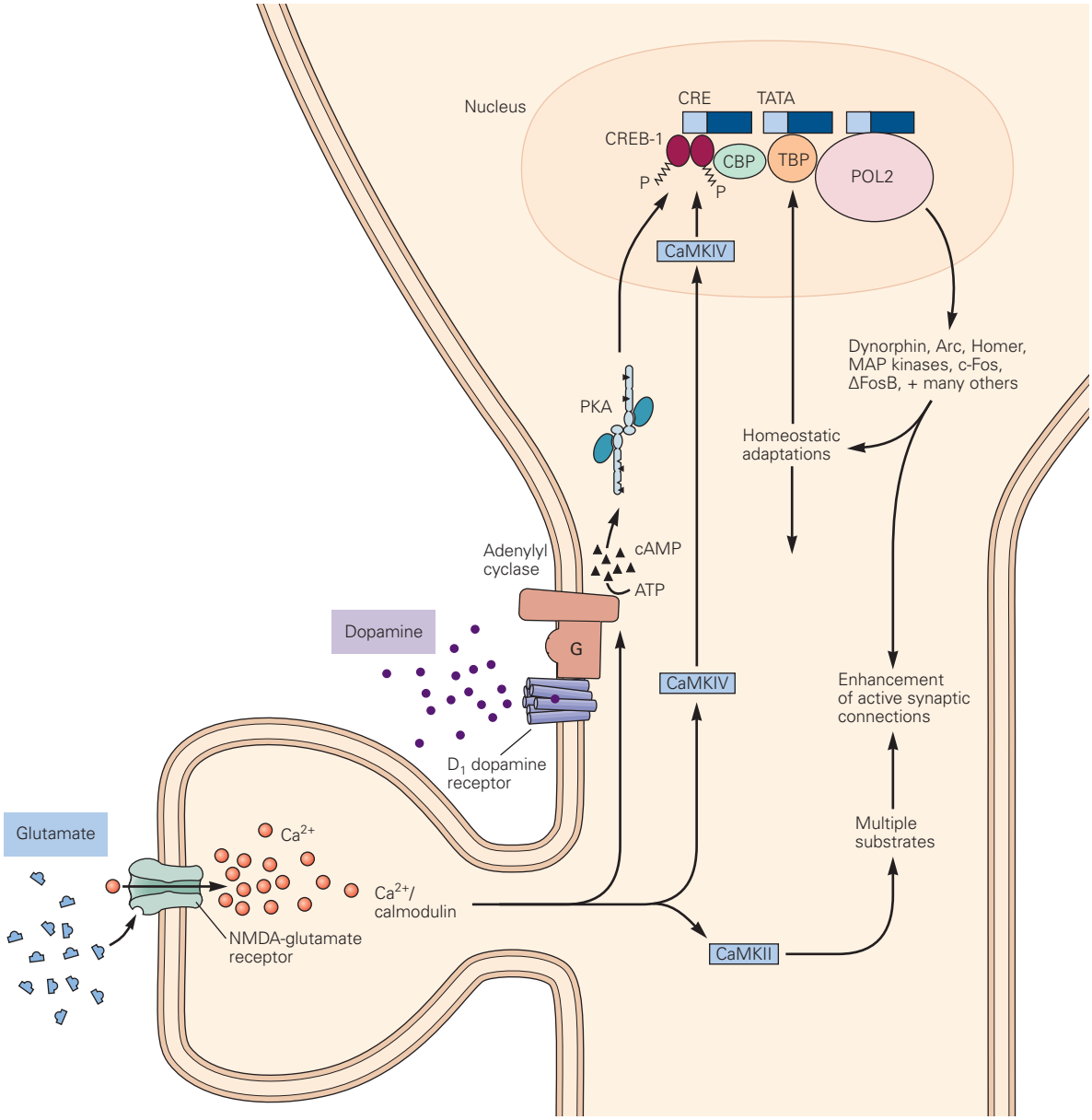

Figure 43–6 Dopamine- and glutamate-activated intracellular signaling pathways implicated in drug addiction. NMDA-type glutamate receptors permit Ca^{2+} entry, which binds calmodulin. The Ca^{2+}/calmodulin complex activates two types of Ca^{2+}/calmodulin-dependent protein kinases, CaMKII in the cytoplasm and CaMKIV in the cell nucleus. Certain dopamine receptors activate a stimulatory G protein that in turn activates adenylyl cyclase to produce cyclic adenosine monophosphate (**cAMP**). The cAMP-dependent protein kinase A (**PKA**) catalytic subunit can enter the nucleus. Once activated in the nucleus, both PKA and CaMKIV phosphorylate and thus activate cAMP response element binding protein (**CREB**). CREB recruits CREB-binding protein (**CBP**) and many other chromatin regulatory proteins and thereby activates the RNA polymerase II–dependent transcription of many genes, giving rise to proteins that can alter cellular function. Arc and Homer are localized in synaptic regions; mitogen-activated protein (**MAP**) kinases are protein kinases that control numerous cellular processes; Fos and ΔFosB are transcription factors; and dynorphin is a type of endogenous opioid peptide. These proteins are thought to contribute both to homeostatic responses to excessive dopamine stimulation and to the morphological and functional changes in synapses associated with memory formation. (Abbreviations: **ATP**, adenosine triphosphate; **NMDA**, *N*-methyl-D-aspartate; **POL 2**, RNA polymerase 2; **TBP**, TATA binding protein.)

immature, thin dendritic spines, whereas during later withdrawal, LTP-like responses occur coincidently with increased numbers of mature, mushroom-shaped spines. These findings suggest that repeated drug use weakens certain glutamatergic synapses with nucleus accumbens neurons via the induction of so-called *silent synapses* (Chapter 54), with a subset of these synapses strengthening during prolonged withdrawal.

These advances now define several ongoing lines of investigation. We need to understand which particular glutamatergic connections are affected and how those changes contribute to behavioral features of addiction. We need to define the molecular basis of this time-dependent synaptic plasticity, which is mediated in part through transcriptional mechanisms and altered expression levels of a host of proteins, including glutamate receptors, postsynaptic density proteins, proteins that regulate the actin cytoskeleton, and so on (Figure 43–6). In addition, we need to examine drug-induced glutamatergic synaptic plasticity at the several other reward-related brain regions that become corrupted in an addicted state, beyond the ventral tegmental area and nucleus accumbens. Finally, we need to understand how repeated exposure to drugs of abuse also corrupts inhibitory GABAergic synaptic transmission throughout this circuitry.

Whole-Cell Plasticity

As with synaptic plasticity, most examples of drug-induced whole-cell plasticity involve the ventral tegmental area and nucleus accumbens. For example, repeated cocaine exposure increases the intrinsic excitability of nucleus accumbens neurons, which contributes to reward tolerance. This adaptation is due in part to a decrease in expression of specific types of K^+ channels mediated by CREB, thus linking molecular-transcriptional adaptations to altered neural activity and an addiction-related behavioral abnormality. Repeated opiate exposure also increases the intrinsic excitability of dopaminergic neurons in the ventral tegmental area, but in a manner that impedes dopaminergic transmission to the nucleus accumbens. As with repeated cocaine exposure, this adaptation too is mediated by suppression of certain K^+ channels and contributes to reward tolerance.

Circuit Plasticity

Advanced tools are making it possible for the first time to track the activity of specific nerve cell types in the brain in awake, active animals and to experimentally manipulate the activity of those cells and study the behavioral consequences (Chapter 5). This is enabling scientists to define the precise ensembles of neurons within a given brain region that are affected by drug exposure over the life cycle of addiction—from initial drug exposure to compulsive drug consumption to withdrawal and relapse—and to provide causal evidence for the involvement of those neurons and the microcircuits within which they function. This work is beginning to define the distinct roles that various glutamatergic projections to the nucleus accumbens—from the prefrontal cortex, hippocampus, amygdala, and thalamus—play in controlling different cell types in the nucleus accumbens and the broader reward circuitry and in producing distinct addiction-related behavioral abnormalities.

While we have focused exclusively in this chapter on the effects of acute and chronic actions of drugs of abuse on the neural control of behavior, we realize that this is an oversimplification. As discussed in Chapter 7, neuronal function is intricately controlled by a host of nonneural cells in the brain, including astroglia, microglia, oligodendrocytes, and endothelial cells. There is growing evidence that each of these cell types is affected both directly and indirectly by drugs of abuse and that these nonneuronal actions also affect the long-term behavioral consequences of drug exposure. Integrating such actions with the neuronal effects of drugs of abuse will be required to achieve a comprehensive understanding of addiction.

Natural Addictions Share Biological Mechanisms With Drug Addictions

As previously indicated, the brain's reward circuitry evolved to motivate individuals to pursue natural rewards such as food, sex, and social interactions. Just as drug-addicted individuals display compulsive consumption of drugs of abuse, some people exhibit compulsive consumption of nondrug rewards (eg, compulsive overeating, shopping, gambling, video gaming, and sex), with behavioral consequences very similar to those observed in drug addiction. An interesting question for the field is whether these so-called "natural addictions" are mediated by some of the same molecular, cellular, and circuit adaptations that underlie drug addiction.

It is possible that these normal pleasurable behaviors excessively activate reward mechanisms in certain individuals who are particularly susceptible due to genetic or nongenetic factors. As with drugs, such activation may result in profound alterations in motivation that promote the repetition of initially rewarding behavior, despite the impact of negative consequences

associated with the resulting compulsive behavior. It is far more difficult to study the neurobiological basis of natural addictions because of limitations in animal models (imagine a mouse model of compulsive shopping!), although progress is being made in developing such paradigms. In any event, brain imaging studies in humans support the notion that addictions to both drugs and behavioral rewards are associated with similar dysregulation of the brain's reward circuitry (Figure 43–3).

Highlights

1. Motivational states drive behaviors that either seek rewards or defend against or avoid aversive stimuli. Motivational states themselves are determined by a variety of internal and external variables. Internal variables include both physiological states and cognitive states. External variables include stimuli that possess innately rewarding or aversive properties, although the motivational significance of these properties may be modified by internal variables.
2. Rewards are desirable objects, stimuli, or actions. Rewards tend to elicit motivational states that drive approach behaviors. Rewards can meet regulatory needs on a short timescale, but can also result from complex sequences of behavior that achieve a long-term goal.
3. Key components of reward-related circuitry in the brain include dopaminergic neurons and brain areas targeted by dopaminergic neurons, such as the nucleus accumbens, ventral pallidum, amygdala, hippocampus, and parts of the prefrontal cortex. However, dopamine itself does not account for hedonic experiences.
4. Many dopaminergic neurons exhibit physiological response properties that suggest they communicate a prediction-error signal, with enhanced activity occurring when something better than expected occurs. This type of signal could play a critical role in different forms of reinforcement learning, learning that links stimuli or actions to rewards. However, recent studies have revealed more response heterogeneity in dopaminergic neurons than previously appreciated, including responses to aversive stimuli. This heterogeneity and its complex effects on neural circuit function remain active areas of investigation.
5. Drug addiction can be defined as the compulsive seeking and taking of a drug despite negative consequences to one's physical health or occupational and social functioning. The risk for addiction is roughly 50% genetic, with many hundreds of genes, each of which contributes a very small effect to this heritability. Important nongenetic risk factors include a history of adverse life events.
6. Drugs of abuse compose only a very small fraction of known chemical compounds. These drugs are chemically diverse, with each type acting initially on a distinct protein target. Nevertheless, the drugs can induce a common behavioral syndrome because their actions at these targets converge in producing similar functional effects on midbrain dopaminergic neurons or their projection regions such as the nucleus accumbens.
7. Addiction requires repeated exposure to a drug of abuse. Such repeated exposure is often accompanied by tolerance, sensitization, and dependence/withdrawal. While many nonabused drugs can produce tolerance and dependence/withdrawal, drugs of abuse are unique in their ability to produce these adaptations as well as sensitization in motivational and reward states.
8. The adaptations underlying drug addiction are mediated in part through lasting changes in gene expression, which result in altered intrinsic activity of neurons as well as structural and functional alterations in their synaptic contacts within the brain's reward circuitry.
9. An important goal of current research is to understand how a myriad of molecular changes summate to underlie specific changes in neural and synaptic function. Likewise, it will be important to understand how these neural and synaptic changes combine to alter the functioning of the brain's larger reward-related circuitry, so as to mediate specific behavioral abnormalities that define an addicted state.
10. This delineation of molecular, cellular, and circuit mechanisms of addiction will require increased attention to the specific cell types (neuronal and nonneuronal) in which certain drug-induced adaptations occur and to the specific microcircuits within the reward pathways affected by those adaptations.
11. A subset of individuals show addiction-like behavioral abnormalities to nondrug rewards, such as food, gambling, and sex. Evidence suggests that such so-called natural addictions are mediated by the same brain circuitry involved in drug addiction, with some common molecular and cellular abnormalities implicated as well.
12. These considerations highlight the need to learn more about the precise molecular, cellular, and

circuit bases of drug addiction. Nonetheless, our evolving understanding of the brain's reward circuitry and how individual synapses and cells in that circuitry are altered by drug exposure in a way that corrupts circuit function and usurps normal systems of reward and associative memory provides a compelling notion of what happens in the addicted brain.

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C. Daniel Salzman

Selected Reading

Berridge KC, Robinson TE. 2016. Liking, wanting, incentive-sensitization theory of addiction. Am Psychologist 71: 670–679.

Di Chiara G. 1998. A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. J Psychopharmacol 12:54–67.

Hyman SE, Malenka RC, Nestler EJ. 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci 29:565–598.

Olds J, Milner PM. 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psych 47:419–427.

Schultz W. 2015. Neuronal reward and decision signals: from theories to data. Physiol Rev 95:853–951.

Wise RA, Koob GF. 2014. The development and maintenance of drug addiction. Neuropsychopharmacology 39:254–262.

References

Bevilacqua L, Goldman D. 2013. Genetics of impulsive behavior. Philos Trans R Soc Lond B Biol Sci 368:20120380.

Calipari ES, Bagot RC, Purushothaman I, et al. 2016. In vivo imaging identifies temporal signature of D1 and D2 medium spiny neurons in cocaine reward. Proc Natl Acad Sci U S A 113:2726–2731.

Carlezon WA Jr, Chartoff EH. 2007. Intracranial self-stimulation (ICSS) in rodents to study the neurobiology of motivation. Nat Protoc 2:2987–2995.

Dong Y. 2016. Silent synapse-based circuitry remodeling in drug addiction. Int J Neuropsychopharmacol 19:pyv136.

Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW. 2008. Review. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philos Trans R Soc Lond B Biol Sci 363:3125–3135.

Gipson CD, Kupchik YM, Kalivas PW. 2014. Rapid, transient synaptic plasticity in addiction. Neuropharmacology 76 Pt B:276–286.

Goldstein RZ, Volkow ND. 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci 12:652–669.

Grant S, London ED, Newlin DB, et al. 1996. Activation of memory circuits during cue-elicited cocaine cravings. Proc Natl Acad Sci U S A 93:12040–12045.

Loweth JA, Tseng KY, Wolf ME. 2014. Adaptations in AMPA receptor transmission in the nucleus accumbens contributing to incubation of cocaine craving. Neuropharmacology 76 Pt B:287–300.

Lüscher C, Malenka RC. 2011. Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. Neuron 69:650–663.

Matsumoto M, Hikosaka O. 2009. Two types of dopamine neuron distinctly convey positive and negative motivational signals. Nature 459:837–841.

Nestler EJ, Kenny PJ, Russo SJ, Schaefer A. 2020. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*, 4th ed. New York: McGraw-Hill.

Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. 2006. Dopamine-dependent prediction errors underpin reward-seeking behavior in humans. Nature 442: 1042–1045.

Polter AM, Kauer JA. 2014. Stress and VTA synapses: implications for addiction and depression. Eur J Neurosci 39:1179–1188.

Robbins TW, Clark L. 2015. Behavioral addictions. Curr Opin Neurobiol 30:66–72.

Robinson TE, Kolb B. 2004. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology 47(Suppl 1):33–46.

Robison AJ, Nestler EJ. 2011. Transcriptional and epigenetic mechanisms of addiction. Nat Rev Neurosci 12:623–637.

Russo SJ, Nestler EJ. 2013. The brain reward circuitry in mood disorders. Nat Rev Neurosci 14:609–625.

Schmidt HD, McGinty JF, West AE, Sadri-Vakili G. 2013. Epigenetics and psychostimulant addiction. Cold Spring Harb Perspect Med 3:a012047.

Schultz W, Dayan P, Montague PR. 1997. A neural substrate of prediction and reward. Science 275:1593–1599.

Scofield MD, Kalivas PW. 2014. Astrocytic dysfunction and addiction: consequences of impaired glutamate homeostasis. Neuroscientist 20:610–622.

Stuber GD, Britt JP, Bonci A. 2012. Optogenetic modulation of neural circuits that underlie reward seeking. Biol Psychiatry 71:1061–1067.

Volkow ND, Morales M. 2015. The brain on drugs: from reward to addiction. Cell 162:712–725.

44

Sleep and Wakefulness

Sleep Consists of Alternating Periods of REM Sleep and Non-REM Sleep

The Ascending Arousal System Promotes Wakefulness

- The Ascending Arousal System in the Brain Stem and Hypothalamus Innervates the Forebrain
- Damage to the Ascending Arousal System Causes Coma
- Circuits Composed of Mutually Inhibitory Neurons Control Transitions From Wake to Sleep and From Non-REM to REM Sleep

Sleep Is Regulated by Homeostatic and Circadian Drives

- The Homeostatic Pressure for Sleep Depends on Humoral Factors
- Circadian Rhythms Are Controlled by a Biological Clock in the Suprachiasmatic Nucleus
- Circadian Control of Sleep Depends on Hypothalamic Relays
- Sleep Loss Impairs Cognition and Memory

Sleep Changes With Age

Disruptions in Sleep Circuitry Contribute to Many Sleep Disorders

- Insomnia May Be Caused by Incomplete Inhibition of the Arousal System
- Sleep Apnea Fragments Sleep and Impairs Cognition
- Narcolepsy Is Caused by a Loss of Orexinergic Neurons
- REM Sleep Behavior Disorder Is Caused by Failure of REM Sleep Paralysis Circuits
- Restless Legs Syndrome and Periodic Limb Movement Disorder Disrupt Sleep
- Non-REM Parasomnias Include Sleepwalking, Sleep Talking, and Night Terrors

Sleep Has Many Functions

Highlights

Sleep is a remarkable state. It consumes fully a third of our lives—approximately 25 years in the average lifetime—yet we know little about what happens in the brain during this daily excursion. Perhaps even more surprising, the exact functions of sleep and of dreaming, one of the more noteworthy components of sleep, are still unknown.

Although the psychological content of dreams has been a rich subject of speculation from Plato and Aristotle to Sigmund Freud, we still do not understand whether dreams carry deep personal meaning, as Freud hypothesized, or represent the brain "throwing out its trash," the bits and pieces of daily experience that are not worth retaining, as Francis Crick speculated. One function of sleep may be to allow synaptic remodeling and consolidation of memory traces reflecting the day's experiences, but the role of dreaming in this process remains a subject of intense debate.

When studying sleep and wakefulness, researchers typically use a polysomnogram, which consists of three physiological measures: brain activity measured by an electroencephalogram (EEG) (see Figure 58–1), eye movements recorded by an electro-oculogram (EOG), and muscle tone measured by an electromyogram (EMG) (Figure 44–1B). In clinical polysomnograms, respiration is also measured, as breathing during sleep is disrupted in many patients with sleep disorders.

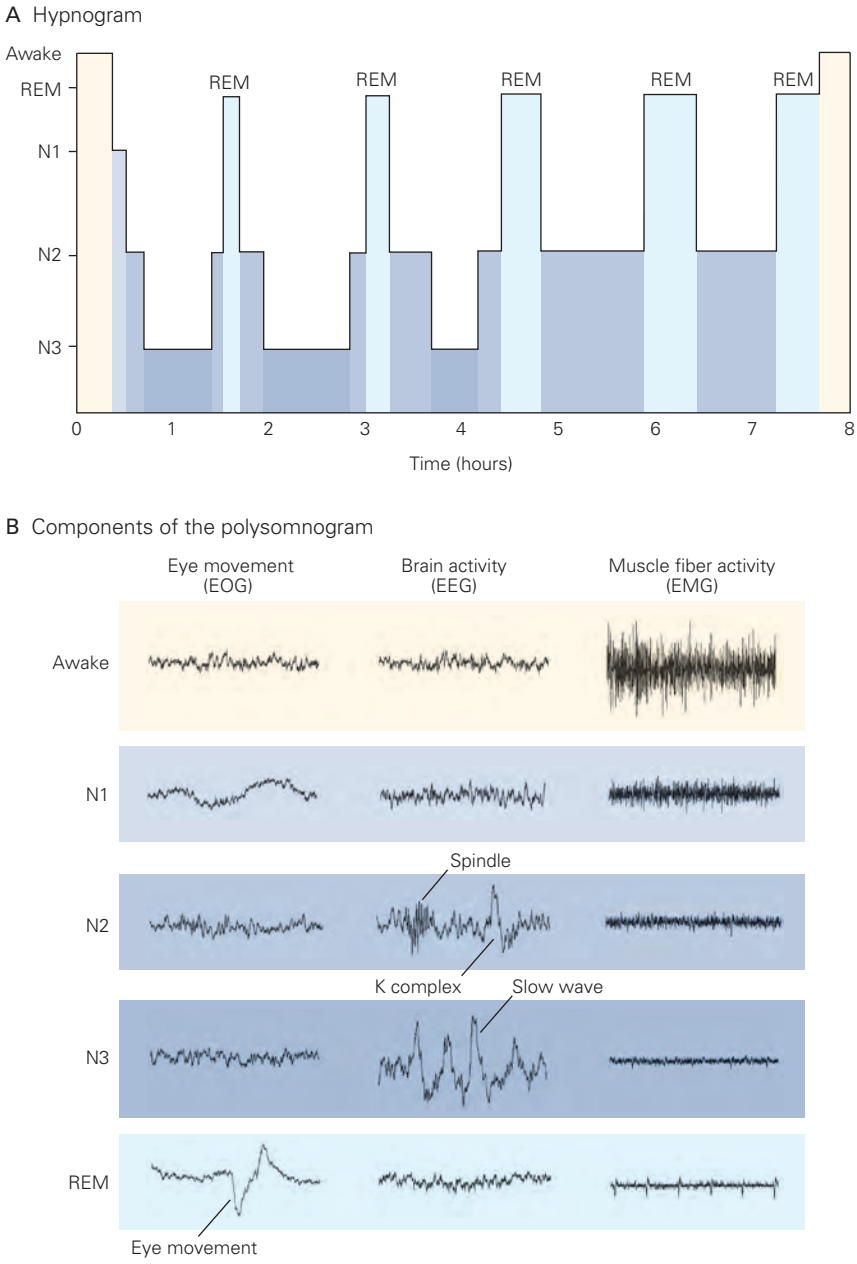

Figure 44–1 Electrophysiological patterns of wakefulness and sleep.

A. A hypnogram or graph showing the progression of sleep stages over a typical night in a healthy young person. Periods of rapid eye movement (**REM**) sleep alternate with non-REM sleep about every 90 minutes. An individual typically progresses from the awake state into light non-REM sleep (N1) then progressively deeper non-REM sleep (N2, N3), then back to lighter non-REM sleep before the first period of REM sleep occurs (**light blue bars**). As the night progresses, the individual spends less time in the deepest stage of non-REM sleep, and the duration of REM sleep periods increases.

B. The records show the components of the polysomnogram used to distinguish sleep stages. The electro-oculogram (**EOG**) records eye movements from electrodes on either side of the eyes. The electroencephalogram (**EEG**) records cortical field potentials from the scalp; the electromyogram (**EMG**) records muscle fiber firing through the skin. During the awake state, the EOG shows voluntary eye movements, the EEG shows fast low-amplitude activity, and the EMG shows variable muscle tone. Stage N1 sleep is characterized by a slight slowing of EEG frequencies and slow roving eye movements, with less EMG activity; stage N2 is characterized by bursts of 12- to 14-Hz activity called sleep spindles and high-voltage slow waves called K-complexes; stage N3 is dominated by high-voltage slow waves. During REM sleep, the EEG is similar to that of the awake state. Rapid eye movements can be seen on the EOG, but the EMG is so silent that contamination by tiny electrocardiogram signals can sometimes be seen (as in the illustrated case).

During wakefulness, the EEG is characterized by mainly high-frequency, low-voltage activity, indicative of the unique activity of individual cortical neurons; the EOG shows frequent eye movements; and the EMG shows moderate and variable muscle tone. During quiet wakefulness, with eyes closed, rhythmic EEG waves in the alpha range (8–13 Hz) are common, particularly over the occipital region. For most of the sleep period, the EEG shows slower activity, but periodically during the night, there are shifts into a sleep state with a faster, lower-voltage EEG, loss of muscle tone, and rapid eye movements called rapid eye movement (REM) sleep. The entire period of slow EEG activity, from light drowsiness to deep sleep, is referred to as non-REM sleep and is divided into three stages, N1 to N3 (Figure 44–1).

Sleep Consists of Alternating Periods of REM Sleep and Non-REM Sleep

As an individual becomes drowsy and transitions into light non-REM sleep (stage N1), the EEG slows and shows waves in the theta range (4–7 Hz) (Figure 44–1B).

Consciousness begins to fade during stage N1, but the individual may still be awakened by minimal stimulation. Stage N2 often contains some slow EEG activity in the theta and delta range (0.5–4 Hz) as well as *sleep spindles*, 10- to 16-Hz waxing and waning EEG oscillations lasting 1 to 2 seconds, typically with a gradual onset and offset so the EEG waves resemble an old-fashioned spindle tapered at both ends. The EEG also may show large, single slow waves called *K-complexes* (Figure 44–1B). During stage N3, the EEG shows abundant, very slow EEG delta activity. During stages N2 and N3, people are generally unconscious of the world around them as the slow cortical activity disrupts information processing. Across all stages of non-REM sleep, eye movements are absent, muscle tone is low, breathing is slow and regular, and body temperature falls.

Slow EEG activity and sleep spindles arise, respectively, from cortico-cortical and cortico-thalamic electrophysiological interactions. During non-REM sleep, the membrane potential of cortical pyramidal neurons fluctuates between *Up states* (when they are depolarized and fire) and *Down states* (when they are hyperpolarized and silent). These slow oscillations in membrane potential, which occur even in an isolated cortical slab, correlate with slow waves in the EEG. During stage N2 sleep, spindles arise from an interaction of neurons in the reticular nucleus of the thalamus and thalamocortical relay neurons. Thalamocortical neurons are generally hyperpolarized and inactive during non-REM sleep, but inhibition from the reticular thalamic neurons can result in the opening of low-threshold Ca^{2+} channels, which drive a burst of Na^{+} spikes in the thalamocortical neurons. The thalamocortical neurons then excite and recruit more reticular neurons, initiating the next cycle of the sleep spindle. This pattern of inhibition and excitation repeats about every 100 ms, and after several cycles, the spindle activity wanes as the reticular neurons become less responsive (Figure 44–2).

After about 90 minutes of sleep, people usually enter the stage known as REM sleep, a period in which dreams are often vivid and sometimes bizarre. REM sleep was discovered in 1953 when Eugene Aserinsky and Nathaniel Kleitman observed that across a night of sleep, adults have several episodes of jerky conjugate eye movements, and when awakened from this state, about three-fourths of subjects reported dreams with visual imagery.

Muscle tone is extremely low during REM sleep, owing to inhibition of motor neurons by descending pathways from the brain stem. This paralysis affects nearly all motor neurons except those that support respiration, eye movements, and a few other functions such as sphincter control. As discussed later in this chapter, this inhibition of motor neurons is crucial as it prevents the physical enactment of dreams.

During REM sleep, the body undergoes many additional physiological changes. Body temperature falls during non-REM sleep, and it can fall further during REM sleep as the generation and retention of heat are minimal. Autonomic regulation is altered such that heart rate and blood pressure can vary wildly. In addition, men experience penile erections and women experience physiological signs of sexual arousal during REM sleep.

Across the night, episodes of non-REM sleep alternate with REM sleep, and each of these sleep cycles takes about 90 minutes. Sleep in a healthy young adult usually begins with a rapid descent into stage N3 non-REM sleep, followed by lighter non-REM sleep and then some REM sleep, and with each cycle, non-REM sleep becomes lighter and the periods of REM sleep become longer (Figure 44–1A). At the end of the sleep period, people often wake spontaneously from an episode of REM sleep.

The Ascending Arousal System Promotes Wakefulness

Modern perspectives of the neural basis of sleep and wakefulness go back about 100 years to the concepts derived by the neurologist and neuropathologist Baron Constantin von Economo. Around World War I, he observed an unusual type of encephalitis, believed to be a viral infection of the brain that specifically attacked the sleep–wake control circuitry. In most cases, patients had "encephalitis lethargica," sleeping 20 or more hours per day. When they awoke, they were generally cogent, but they would stay awake only long enough to eat and then go right back to sleep. This intense sleepiness would persist for many months before improving. But in patients who died during this interval, von Economo found focal damage to the brain, at the junction of the midbrain and diencephalon, leading him to hypothesize that the upper brain stem and posterior hypothalamus contain critical circuitry that activates the forebrain, producing a normal wakeful state.

Other patients afflicted in the same epidemic had just the opposite problem: unrelenting severe insomnia. They would be restless and, despite feeling sleepy, unable to fall asleep. Eventually, they would fall into a fitful sleep for only a few hours each day, but would waken without feeling refreshed. In post mortem examinations of these patients, von Economo found

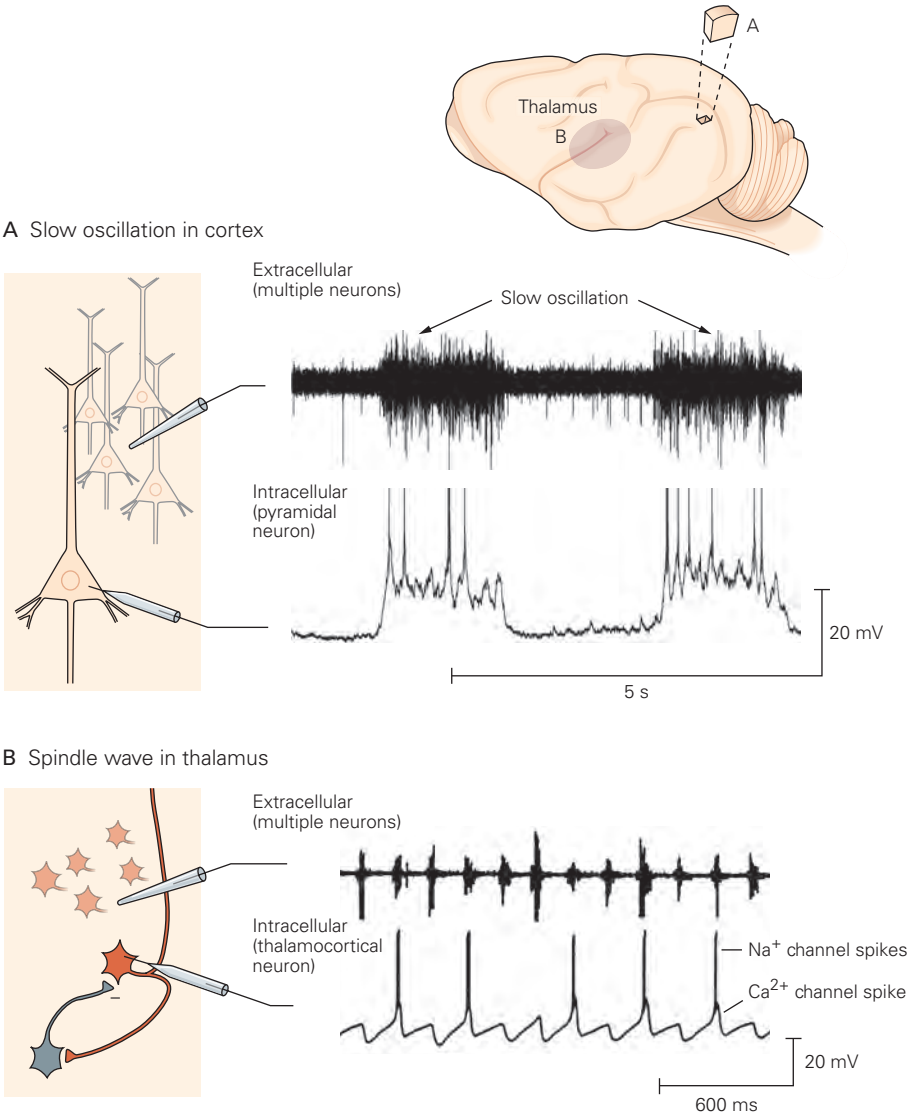

Figure 44–2 Cellular mechanisms of electroencephalogram rhythms during sleep.

A. The slow oscillation that underlies the slow waves of the EEG during non-REM sleep is generated within the cerebral cortex by intrinsic massively recurrent excitatory and inhibitory connections. Slow waves will continue even in an isolated cortical slab. Intracellular recordings from such neurons during slow oscillations show rhythmic down states when the individual neurons are hyperpolarized and do not fire, alternating with up states when the membrane potential is more depolarized and the neurons fire multiple action potentials. This synchronous firing produces waves of dendritic potentials, which appear as slow waves in the EEG. (Data from Dr. David McCormick.)

B. Similarly, in a thalamic slice, recurrent circuitry generates spindle waves. A burst of spikes in reticular nucleus neurons (**gray**) hyperpolarizes thalamocortical relay neurons (**red**) sufficiently to de-inactivate low-threshold (T-type) Ca^{2+} channels. As the hyperpolarization wanes, these Ca^{2+} channels open and the resultant Ca^{2+} current depolarizes the relay neuron, producing a brief burst of Na^+ channel spikes on top of a Ca^{2+} channel spike plateau. Meanwhile, as the burst in the relay cell continues, its excitatory output generates a T-type Ca^{2+} channel spike in the reticular neuron, which drives another burst of Na^+ spikes. The resultant volley of feedback inhibition to the relay cells initiates a new burst cycle. This firing pattern recurs 12 to 14 times per second, and the resulting waves of thalamocortical action potentials reaching the cortex produce sleep spindles in the EEG. The upper trace shows action potentials from a local population of relay cells. The lower trace shows inhibitory postsynaptic potentials and spike bursts from an individual relay cell; on this slow time base, each upstroke in the intracellular record represents a burst of up to six action potentials. As the trace shows, individual relay neurons do not reach spike threshold during every cycle of the spindle wave. As a result, the amplitude of the extracellular spike activity varies from cycle to cycle, depending on which neurons happen to fire and their distances from the extracellular electrode tip. However, each burst of thalamic firing would produce a volley of excitatory postsynaptic potentials in the cortex, resulting in an electroencephalogram wave, time-locked to the thalamic firing. (Reproduced, with permission, from Bal, von Krosigk, and McCormick 1995. Copyright © 1995 The Physiological Society.)

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

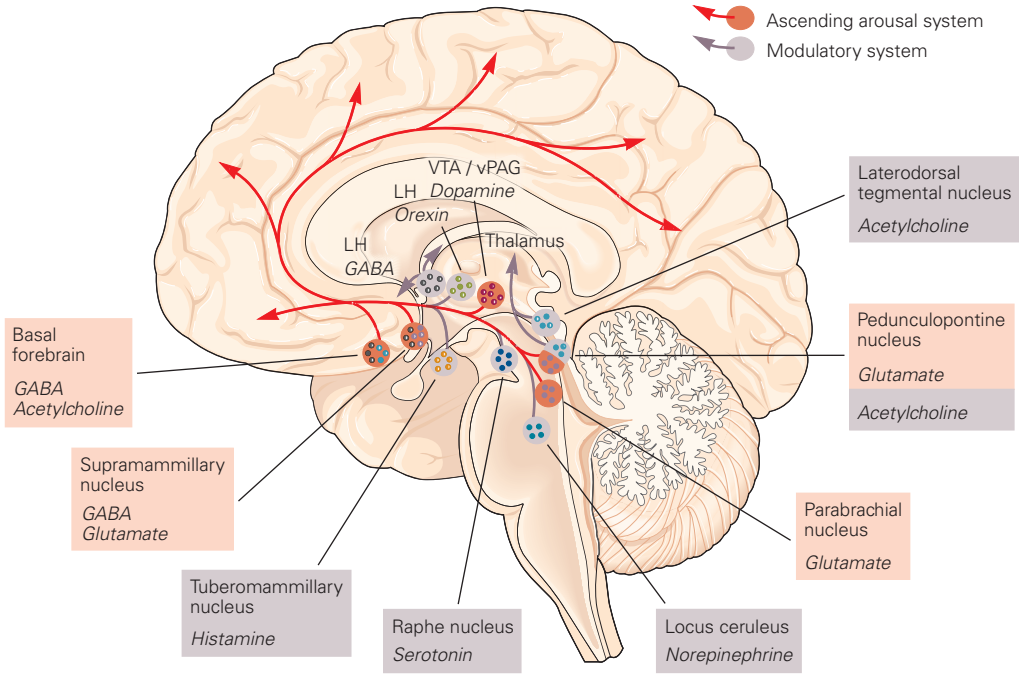

Figure 44–3 The ascending arousal system. The ascending arousal system comprises primarily axons from glutamatergic neurons in the parabrachial and pedunculopontine tegmental nuclei and cholinergic and GABAergic (**dark gray**) neurons in the basal forebrain. Lesions of either the parabrachial and pedunculopontine 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.