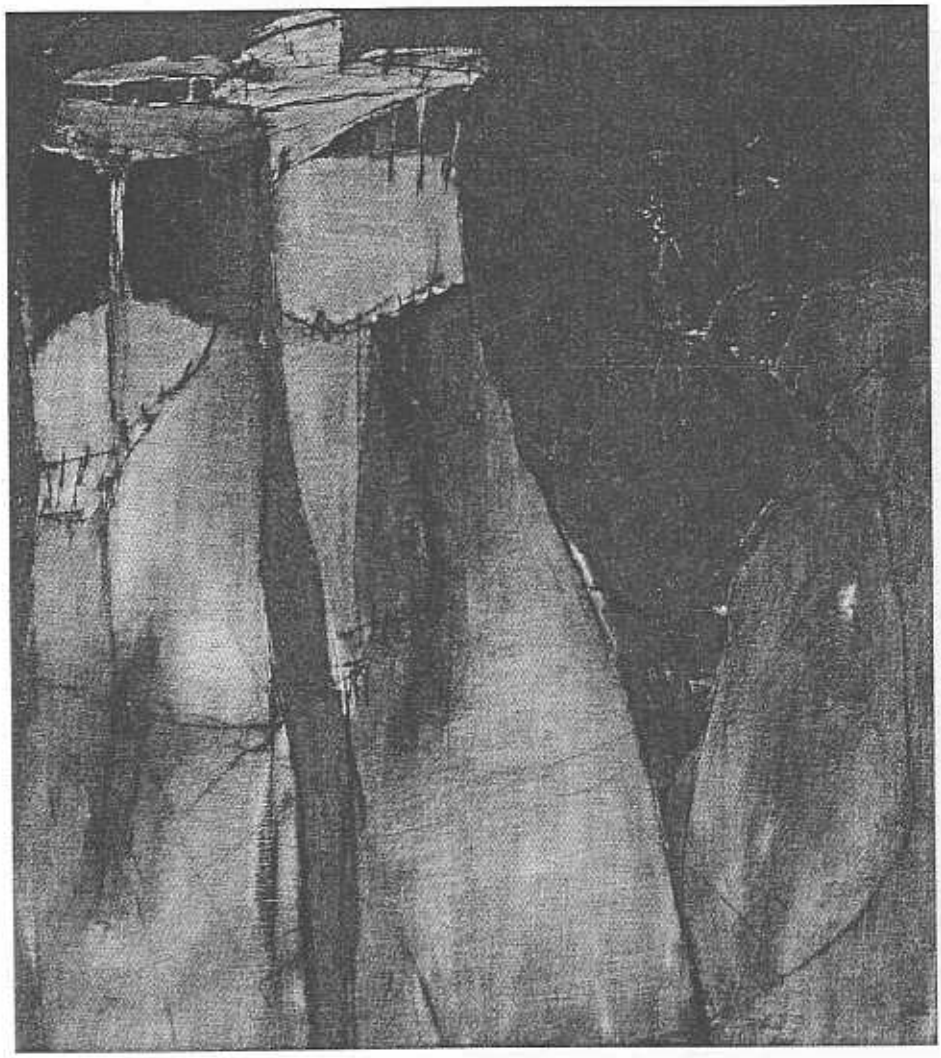
CHAPTER 9

Sleep and Biological Rhythms



Untitled by Sandra Guloff.

CHAPTER

OUTLINE

Why do we sleep? Why do we spend at least one-third of our lives doing something that provides most of us with only a few fleeting memories? I will attempt to answer this question in several ways. In the first two parts of this chapter I will describe what is known about the phenomenon of sleep: How much do we sleep? What do we do while asleep? What happens if we do not get enough sleep? Does sleep perform a restorative function? In the third part of the chapter I will describe the search for the chemicals and the neural circuits that control sleep and wakefulness. In the fourth section I will explore whether sleeping medications are effective and what we know about sleepwalking and other sleep-related disorders. In the final part of the chapter I will discuss the brain's biological clock—the mechanism that controls daily rhythms of sleep and activity.

A Physiological and Behavioral Description

Sleep is a behavior. That statement may seem peculiar, because we usually think of behaviors as activities that involve movements, such as walking or talking. Except for the rapid eye movements that accompany a particular stage, sleep is not distinguished by movement. What characterizes sleep is that the insistent urge of sleepiness forces us to seek out a quiet, comfortable place, lie down, and remain there for several hours. Because we remember very little about what happens while we sleep, we tend to think of sleep more as a state of consciousness than as a behavior. The change in consciousness is undeniable, but it should not prevent us from noticing the behavioral changes.

Stages of Sleep

The best research on human sleep is conducted in a sleep laboratory. A sleep laboratory, usually located at a university or medical center, consists of one or several small bedrooms adjacent to an observation room, where the experimenter spends the night (trying to stay awake). The experimenter prepares the sleeper for electrophysiological measurements by attaching electrodes to the scalp to monitor the electroencephalogram (EEG) and to the chin to monitor muscle activity, recorded as the **electromyogram** (EMG). Electrodes attached around the eyes monitor eye movements, recorded as the **electro-oculogram** (EOG). In addition, other electrodes and transducing devices can be used to monitor autonomic measures such as heart rate, respiration, and skin conductance. Wires from the electrodes are bundled together in a "ponytail," which is then plugged into a junction box at the head of the bed. (See *Figure 9.1.*)

During wakefulness the EEG of a normal person shows two basic patterns of activity: *alpha activity* and *beta activity.* **Alpha activity** consists of regular, medium-frequency waves of 8–12 Hz. The brain produces this activity when a person is resting quietly, not particularly aroused or excited and not engaged in strenuous mental activity (such as problem solving). Although alpha waves sometimes occur

electromyogram (EMG) (*my oh gram*) An electrical potential recorded from an electrode placed on or in a muscle.

electro-oculogram (EOG) (*ah kew loh gram*) An electrical potential from the eyes, recorded by means of electrodes placed on the skin around them; detects eye movements.

alpha activity Smooth electrical activity of 8–12 Hz recorded from the brain; generally associated with a state of relaxation.

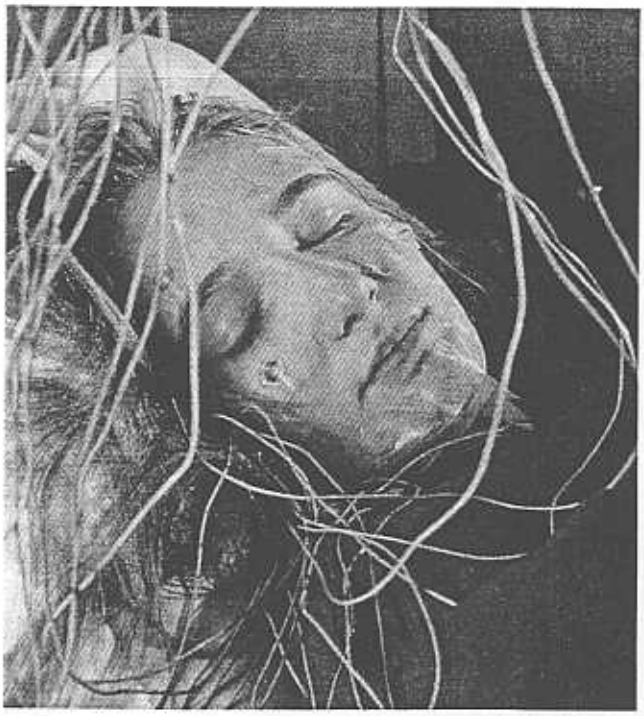


Figure 9.1

A subject prepared for a night's sleep in a sleep laboratory. (Philippe Plailly/Science Photo Library/Photo Researchers Inc.)

when a person's eyes are open, they are much more prevalent when the eyes are closed. The other type of waking EEG pattern, **beta activity**, consists of irregular, mostly low-amplitude waves of 13–30 Hz. This activity occurs when a person is alert and attentive to events in the environment or is thinking actively. (See *Figure 9.2.*)

What is the significance of these two types of waveforms? As we saw in Chapter 5, the EEG is a recording of the summed postsynaptic activity of cerebral neurons (mostly, neurons in the cerebral cortex). Therefore, a low-frequency, high-voltage EEG (alpha activity, as opposed to beta activity) reflects neural **synchrony.** These waves are produced by a regular, synchronized pattern of activity in a large number of neurons. The activity of the individual neurons is analogous to a large number of people chanting the same words together (speaking *synchronously*). Similarly, beta activity is referred to as **desynchrony**; it is like a large number of people broken into many small groups, each carrying on an individual conversation.

The analogy helps to explain why desynchrony is generally assumed to represent activation, whereas synchrony reflects a resting or depressed state. A group of people who are all chanting the same message will process very little information; only one message is being produced. On the other hand, a desynchronized group will process and transmit many different messages. The alert, waking state of the brain is more like the desynchronized group of people, with much information processing going on. During synchrony the neurons of the resting brain (especially the cortex) quietly murmur the same message in unison.

Let us look at a typical night's sleep of a female college student on her third night in the laboratory. (Of course, we would obtain similar results from a male, with one exception, which is noted later.) The experimenter attaches the electrodes, turns the lights off, and closes the door. Our subject becomes drowsy and soon enters stage 1 sleep, marked by the presence of some **theta activity** (3.5–7.5 Hz). This stage is actually a transition between sleep and wakefulness; if we watch our volunteer's eyelids, we will see that from time to time they slowly open and close and that her eyes roll upward and downward. (See *Figure 9.2.*) About 10 minutes later she enters stage 2 sleep. The EEG during this stage is generally irregular but contains periods of theta activity, *sleep spindles,* and *K complexes.* Sleep spindles are short bursts of waves of 12–14 Hz that occur between two and five times a minute during stages 1–4 of sleep. Some investigators believe that sleep spindles represent the activity of a mechanism that decreases the brain's sensitivity to sensory input—disconnects the brain from the outside world, so to speak—and thus permits the person to enter deeper stages of sleep (Bowersox, Kaitin, and Dement, 1985; Steriade, 1992). The sleep of older people contains fewer sleep spindles and is generally accompanied by more awakenings during the night. K complexes are sudden, sharp waveforms, which, unlike sleep spindles, are usually found only during stage 2 sleep. They spontaneously occur at the rate of approximately one per minute but often can be triggered by noises—especially unexpected noises (Niiyama et al., 1995, 1996). Some investigators believe that they, too, represent mechanisms involved in keeping the person asleep (Wauquier, Aloe, and Declerck, 1995). (See *Figure 9.2.*)

The subject is sleeping soundly now; but if awakened, she might report that she has not been asleep. This phenomenon often is reported by nurses who awaken loudly snoring patients early in the night (probably to give them a sleeping pill) and find that the patients insist they were

beta activity Irregular electrical activity of 13–30 Hz recorded from the brain; generally associated with a state of arousal.

synchrony High-voltage, low-frequency EEG activity, characteristic of slow-wave sleep or coma, during which neurons fire together in a regular fashion.

desynchrony Irregular electrical activity recorded from the brain, generally associated with periods of arousal.

theta activity EEG activity of 3.5–7.5 Hz that occurs intermittently during early stages of slow-wave sleep and REM sleep.

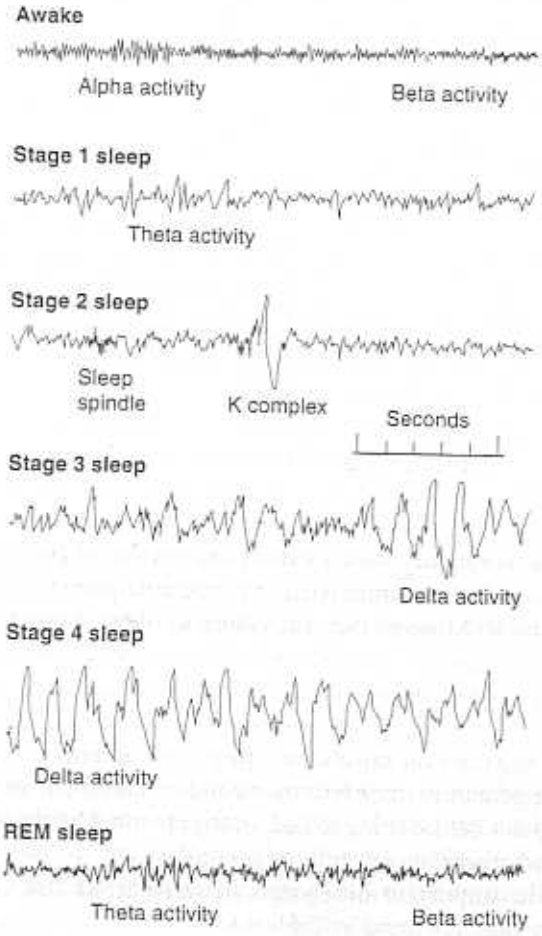


Figure 9.2

An EEG recording of the stages of sleep.
(From Horne, J. A. *Why We Sleep: The Functions of Sleep in Humans and Other Mammals.* Oxford, England: Oxford University Press, 1988.)

lying there awake all the time. About 15 minutes later the subject enters stage 3 sleep, signaled by the occurrence of high-amplitude **delta activity** (less than 3.5 Hz). (See *Figure 9.2.*) The distinction between stage 3 and stage 4 is not clear-cut; stage 3 contains 20–50 percent delta activity, and stage 4 contains more than 50 percent. (See *Figure 9.2.*)

About 90 minutes after the beginning of sleep (and about 45 minutes after the onset of stage 4 sleep), we notice an abrupt change in a number of physiological measures recorded from our subject. The EEG suddenly becomes mostly desynchronized, with a sprinkling of theta waves, very similar to the record obtained during stage 1 sleep. (See *Figure 9.2.*) We also note that her eyes are rapidly darting back and forth beneath her closed eyelids. We can see this activity in the EOG, recorded from electrodes attached to the skin around her eyes, or we can observe the eye movements directly—the cornea produces a bulge in the closed eyelids that can be seen to move about. We also see that the EMG becomes silent; there is a profound loss of muscle tonus. In fact, physiological studies have shown that, aside from occasional twitching, a person actually becomes paralyzed during REM sleep.

This peculiar stage of sleep is quite distinct from the quiet sleep we saw earlier. It is usually referred to as **REM sleep** (for the rapid eye movements that characterize it). It has also been called *paradoxical sleep,* because of the presence of beta activity, which is usually seen during wakefulness or stage 1 sleep. The term *paradoxical* merely reflects people's surprise at observing an unexpected phenomenon, but the years since its first discovery (reported by Aserinsky and Kleitman in 1953) have blunted the surprise value.

At this point I should introduce some terminology. Stages 1–4 are usually referred to as **non-REM sleep.** Stages 3 and 4 are referred to as **slow-wave sleep,** because of the presence of delta activity. As we will see, research has focused on the role of REM sleep and of slow-wave sleep; most investigators believe that the other stages of non-REM sleep, stages 1 and 2, are less important than the others. (As we shall see, when people are sleep deprived, they make up most of their slow-wave sleep and REM sleep, but not their stage 1 and stage 2 sleep.) By some criteria stage 4 is the deepest stage of sleep; only loud noises will cause a person to awaken, and when awakened, the person acts groggy and confused. During REM sleep a person might not react to noises, but he or she is easily aroused by meaningful stimuli, such as the sound of his or her name. Also, when awakened from REM sleep, a person appears alert and attentive.

If we arouse our volunteer during REM sleep and ask her what was going on, she will almost certainly report that she had been dreaming. The dreams of REM sleep tend to be narrative in form; there is a storylike progression of events. If we wake her during slow-wave sleep and ask, "Were you dreaming?" she will most likely say, "No." However, if we question her more carefully, she might report the presence of a thought, an image, or some emotion. I will return to this issue later.

During the rest of the night our subject's sleep alternates between periods of REM and non-REM sleep. Each cycle is

delta activity Regular, synchronous electrical activity of less than 4 Hz recorded from the brain; occurs during the deepest stages of slow-wave sleep.

REM sleep A period of desynchronized EEG activity during sleep, at which time dreaming, rapid eye movements, and muscular paralysis occur; also called *paradoxical sleep.*

non-REM sleep All stages of sleep except REM sleep.

slow-wave sleep Non-REM sleep, characterized by synchronized EEG activity during its deeper stages.

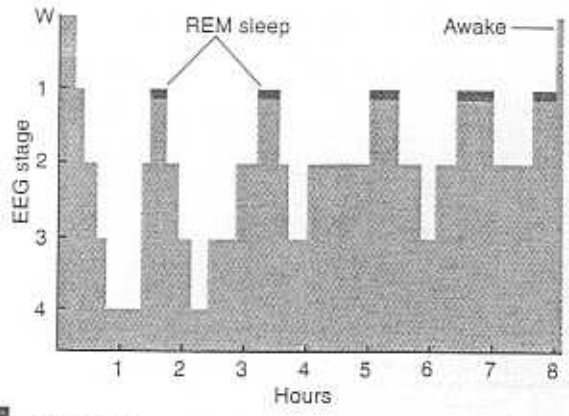


Figure 9.3

A typical pattern of the stages of sleep during a single night. The dark blue shading indicates REM sleep.

approximately 90 minutes long, containing a 20- to 30-minute bout of REM sleep. Thus, an 8-hour sleep will contain four or five periods of REM sleep. Figure 9.3 shows a graph of a typical night's sleep. The *x*-axis indicates the EEG activity that is being recorded; thus, REM sleep and stage 1 sleep are placed on the same line because similar patterns of EEG activity occur at these times. Note that most slow-wave sleep (stages 3 and 4) occurs during the first half of night. Subsequent bouts of non-REM sleep contain more and more stage 2 sleep, and bouts of REM sleep (indicated by the horizontal bars) become more prolonged. (See *Figure 9.3.*)

The fact that REM sleep occurs at regular 90-minute intervals suggests that a brain mechanism alternately causes REM and slow-wave sleep. Normally, a period of slow-wave sleep must precede REM sleep. In addition, there seems to be a refractory period after each occurrence of REM sleep, during which time REM sleep cannot take place again. In fact, the cyclical nature of REM sleep appears to be controlled by a "clock" in the brain that also controls an activity cycle that continues through waking. The first suggestion that a 90-minute activity cycle occurs throughout the day came from the observation that infants who are fed on demand show regular feeding patterns (Kleitman, 1961). Later studies found 90-minute cycles of rest and activity, including such activities as eating, drinking, smoking, heart rate, oxygen consumption, stomach motility, urine production, and performance on various tasks that make demands upon a person's ability to pay attention. Kleitman termed this phenomenon the **basic rest–activity cycle.** (See Kleitman, 1982, for a review.) As we will see later in this chapter, an internal "clock," probably located in the medulla, causes regular changes in activity and alertness during the day and controls periods of slow-wave and REM sleep at night.

As we saw, during REM sleep we become paralyzed; most of our spinal and cranial motor neurons are strongly inhibited. (Obviously, the ones that control respiration and eye movements are spared.) At the same time the brain is very active. Cerebral blood flow and oxygen consumption are accelerated. In addition, a male's penis will become at least partially erect, and a female's vaginal secretions will increase. However, Fisher, Gross, and Zuch (1965) found that in males, genital changes do not signify that the person is experiencing a dream with sexual content. (Of course, people can have dreams with frank sexual content. In males some dreams culminate in ejaculation—the so-called nocturnal emissions, or "wet dreams." Females, too, sometimes experience orgasm during sleep.)

The fact that penile erections occur during REM sleep, independent of sexual arousal, has been used clinically to assess the causes of impotence (Karacan, Salis, and Williams, 1978; Singer and Weiner, 1996). A subject sleeps in the laboratory with a device attached to his penis that measures its circumference. If penile enlargement occurs during REM sleep, then his failure to obtain an erection during attempts at intercourse is not caused by physiological problems such as nerve damage or a circulatory disorder. (A neurologist told me that there is a less expensive way to gather the same data. The patient obtains a strip of postage stamps, moistens them, and applies them around his penis before going to bed. In the morning he checks to see whether the perforations are broken.)

The important differences between REM and slow-wave sleep are listed in *Table 9.1.*

Mental Activity During Sleep

Although sleep is a period during which we do not respond very much to the environment, it is incorrect to refer to sleep as a state of unconsciousness. Consciousness during sleep certainly differs from waking consciousness, but we *are* conscious then. In the morning we usually for-

Table 9.1
Principal characteristics of REM and slow-wave sleep

REM Sleep	Slow-Wave Sleep
EEG desynchrony (rapid, irregular waves)	EEG synchrony (slow waves)
Lack of muscle tonus	Moderate muscle tonus
Rapid eye movements	Slow or absent eye movements
Penile erection or vaginal secretion	Lack of genital activity
Dreams	

get what we experienced while asleep, so in retrospect we conclude that we were unconscious. However, when experimenters wake sleeping subjects, the reports that the subjects give make it clear that they were conscious.

Some people insist that they never dream. They are wrong; everyone dreams. What does happen, however, is that most dreams are subsequently forgotten. Unless a person awakens during or immediately after a dream, the dream will not be remembered. Many people who thought they had not had a dream for years have been startled by the vivid narrations they were able to supply when roused during REM sleep in the laboratory. Even the most vivid experiences can be completely erased from consciousness. I am sure that many of you have had the experience of waking during a particularly interesting dream. You decide to tell your friends about it, and you start to review what you will say. As you do so, the memory just slips away. You can't remember the slightest detail of the dream, which was so vivid and real just a few seconds ago. You may feel that if you could remember just one detail about it, everything would come back. Understanding this phenomenon would probably tell us much about the more general issue of learning and forgetting.

Madsen et al. (1991) found that the rate of cerebral blood flow in the human brain during REM sleep was high in the visual association cortex but low in the inferior frontal cortex. As we shall see in Chapter 14, the inferior frontal cortex is involved in making plans and keeping track of the organization of events in time. As Madsen and his colleagues noted, dreams are characterized by good visual images (undoubtedly involving the visual association cortex), but they are poorly organized with respect to time; for example, past, present, and future are often interchanged (Hobson, 1988). And as Melges (1982) put it, "the dreamer often has no feeling of striving for long-term goals but rather is carried along by the flow of time by circumstances that crop up in an unpredictable way." This quote could just as well be describing the daily life of a person whose inferior frontal cortex has been damaged.

Several investigators have suggested that the eye movements made during REM sleep are related to the visual imagery that occurs while we dream. Roffwarg et al. (1962) recorded the eye movements of subjects during REM sleep and then awakened them and asked them to describe what had been happening in their dreams. They found that the eye movements were similar to what would have been expected if the subjects had actually been watching these events. Miyauchi, Takino, and Azakami (1990) recorded the EEG of sleeping subjects and found that a particular wave accompanied eye movements during REM sleep. This wave was also seen when waking subjects scanned a scene—but it was *not* seen when they simply made eye movements in a dark room. Therefore, the EEG wave is not produced by eye movements themselves but may actually indicate that the subjects had been scanning a visual image during a dream.

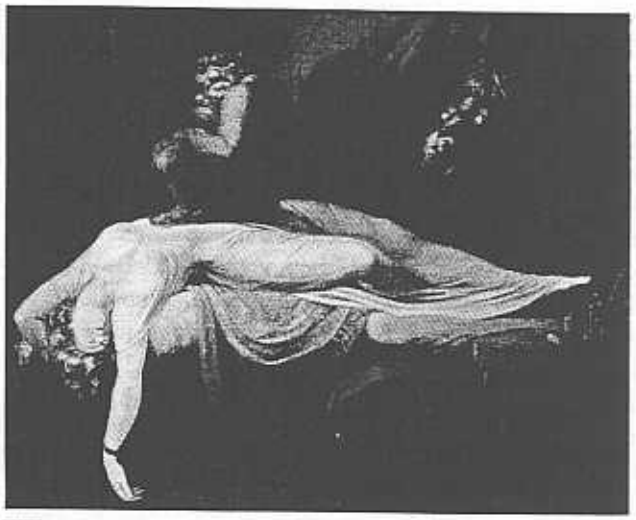


Figure 9.4

The Nightmare, 1781, by Henry Fuseli, Swiss, 1741–1825. (Gift of Mr. and Mrs. Bert L. Smokler and Mr. and Mrs. Lawrence A. Fleischman, Acc. No. 55.5. Courtesy of The Detroit Institute of Arts.)

Evidence indicates that the particular brain mechanisms that become active during a dream are those that would become active if the events in the dream were actually occurring. For example, cortical and subcortical motor mechanisms become active during a dream that contains movement—as if the person were actually moving (McCarley and Hobson, 1979). In addition, if a dream involves talking and listening, regions of the dreamer's brain that are involved in speaking and listening become especially active (Hong et al., 1996). (Brain mechanisms of verbal communication are discussed in Chapter 16.)

Although narrative, storylike dreaming occurs during REM sleep, mental activity can also accompany slow-wave sleep. Some of the most terrifying nightmares occur during slow-wave sleep, especially stage 4 sleep (Fisher et al., 1970). If people are awakened from slow-wave sleep, they are unlikely to report a storylike dream. Instead, they often report a situation, such as being crushed or suffocated or simply a feeling of fear or dread. This common sensation is reflected in the terms that some languages use for describing what we call a *nightmare*. For example, in French the word is *cauchemar*, or "pressing devil." Figure 9.4 shows a victim of a nightmare (undoubtedly in the throes of stage 4 slow-wave sleep) being squashed by an *incubus* (from the Latin *incubare*, "to lie upon"). (See *Figure 9.4.*)

basic rest–activity cycle A 90-min cycle (in humans) of waxing and waning alertness, controlled by a biological clock in the caudal brain stem; controls cycles of REM sleep and slow-wave sleep.

Interim Summary

Sleep is generally regarded as a state, but it is, nevertheless, a behavior. The stages of non-REM sleep, stages 1 through 4, are defined by EEG activity. Slow-wave sleep (stages 3 and 4) includes the two deepest stages. Alertness consists of desynchronized beta activity (13–30 Hz); relaxation and drowsiness consist of alpha activity (8–12 Hz); stage 1 sleep consists of alternating periods of alpha activity, irregular fast activity, and theta activity (3.5–7.5 Hz); the EEG of stage 2 sleep lacks alpha activity but contains sleep spindles (short periods of 12–14 Hz activity) and occasional K complexes; stage 3 sleep consists of 20–50 percent delta activity (less than 3.5 Hz); and stage 4 sleep consists of more than 50 percent delta activity. About 90 minutes after the beginning of sleep, people enter REM sleep. Cycles of REM and slow-wave sleep alternate in periods of approximately 90 minutes.

REM sleep consists of rapid eye movements, a desynchronized EEG, sensitivity to external stimulation, muscular paralysis, genital activity, and dreaming. Mental activity can accompany slow-wave sleep, too, but it is usually static rather than narrative, like dreams during REM sleep.

Why Do We Sleep?

We all know how insistent the urge to sleep can be and how uncomfortable we feel when we have to resist it and stay awake. With the exception of the effects of severe pain and the need to breathe, sleepiness is probably the most insistent drive. People can commit suicide by refusing to eat or drink, but even the most stoical person cannot indefinitely defy the urge to sleep. Sleep will come, sooner or later, no matter how hard a person tries to stay awake. Although the issue is not yet settled, most researchers believe that the primary function of slow-wave sleep is to permit the brain to rest. REM sleep appears to promote brain development and learning, but how it might do so is not yet understood.

Functions of Slow-Wave Sleep

Sleep is a universal phenomenon among vertebrates. As far as we know, all mammals and birds sleep (Durie, 1981). Reptiles also sleep, and fish and amphibians enter periods of quiescence that probably can be called sleep. However, only warm-blooded vertebrates (mammals and birds) exhibit unequivocal REM sleep, with muscular paralysis, EEG signs of desynchrony, and rapid eye movements. Obviously, birds such as flamingos, which sleep while perched on one leg, do not lose tone in the muscles they use to remain standing. Also, animals such as moles, which move their eyes very little while awake, show few signs of eye movement while asleep. The functions of REM sleep will be discussed separately, in a later section.

Sleep appears to be essential to survival. Evidence for this assertion comes from the fact that sleep is found in some species of mammals that would seem to be better off without it. For example, the Indus dolphin *(Platanista indi)* lives in the muddy waters of the Indus estuary in Pakistan (Pilleri, 1979). Over the years it has become blind, presumably because vision is not useful in the animal's environment. (It has an excellent sonar system, which it uses to navigate and find prey.) However, despite the dangers caused by sleeping, sleep has not disappeared. The Indus dolphin never stops swimming; doing so would result in injury, because of the dangerous currents and the vast quantities of debris carried by the river during the monsoon season. Pilleri captured two dolphins and studied their habits. He found that they slept a total of 7 hours a day, in brief naps of 4–60 seconds each. If sleep were simply an adaptive response, why was it not eliminated (as vision was) through the process of natural selection?

Some other species of marine mammals have developed an extraordinary pattern of sleep: The cerebral hemispheres take turns sleeping, presumably because that strategy always permits at least one hemisphere to be alert. The bottlenose dolphin *(Tursiops truncatus)* and the porpoise *(Phocoena phocoena)* both sleep this way (Mukhametov, 1984). Figure 9.5 shows the EEG recordings from the two hemispheres; note that slow-wave sleep occurs independently in the left and right hemispheres. (See *Figure 9.5.*)

Sleep does not seem to be related to physical exercise; thus, its most important role is probably not rest and re-

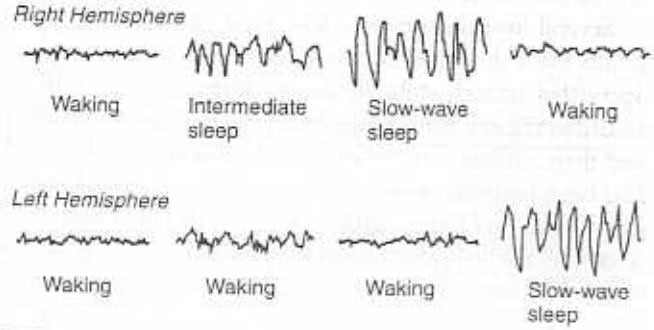


Figure 9.5

Sleep in a dolphin. The two hemispheres sleep independently, presumably so that the animal remains behaviorally alert. (Adapted from Mukhametov, L. M., in *Sleep Mechanisms*, edited by A. A. Barbély and J. L. Valatx. Munich: Springer-Verlag, 1984.)

cuperation of the body. However, it *does* appear to be needed to keep the brain functioning normally. (For convenience I will talk about the "body" and the "brain" in the following section, even though we both know that the brain is a part of the body.)

Effects of Sleep Deprivation

When we are forced to miss a night's sleep, we become very sleepy. The fact that sleepiness is so motivating suggests that sleep is a necessity of life. If so, it should be possible to deprive people or laboratory animals of sleep and see what functions are disrupted. We should then be able to infer the role that sleep plays. However, the results of sleep deprivation studies have not revealed as much as investigators had originally hoped.

■ **Studies with Humans** Deprivation studies with human subjects have not obtained persuasive evidence that sleep is needed to keep the body functioning normally. Horne (1978) reviewed over fifty experiments in which people had been deprived of sleep. He reported that most of them found that sleep deprivation did not interfere with people's ability to perform physical exercise. In addition, the studies found no evidence of a physiological stress response to sleep deprivation. However, people's cognitive abilities were affected; some people reported perceptual distortions or even hallucinations and had trouble concentrating on mental tasks.

What happens to sleep-deprived subjects after they are permitted to sleep again? Most of them sleep longer the next night or two, but they never regain all of the sleep they lost. In one remarkable case a seventeen-year-old boy stayed awake for 264 hours so that he could obtain a place in the *Guinness Book of World Records* (Gulevich, Dement, and Johnson, 1966). After his ordeal the boy slept for a little less than 15 hours and awoke feeling fine. He slept slightly more than 10 hours the second night and just under 9 hours the third. Almost 67 hours were never made up. However, percentages of recovery were not equal for all stages of sleep. Only 7 percent of stages 1 and 2 were made up, but 68 percent of stage 4 slow-wave sleep and 53 percent of REM sleep were made up. Other studies (for example, Kales et al., 1970) have found similar results, suggesting that stage 4 sleep and REM sleep are more important than the other stages.

As I mentioned earlier, REM sleep will be discussed later. But what do we know about the possible functions of slow-wave sleep? What happens then that is so important? Both cerebral metabolic rate and cerebral blood flow decline during slow-wave sleep, falling to about 75 percent of the waking level during stage 4 sleep (Sakai et al., 1979; Buchsbaum et al., 1989; Maquet, 1995). In particular, the regions that have the highest levels of activity during waking show the highest levels of delta waves—and the lowest levels of activity—during slow-wave sleep. Thus, the presence of delta activity in a particular region of the brain appears to indicate that that region is resting. As we know from behavioral observation, people are unreactive to all but intense stimuli during slow-wave sleep and, if awakened, act groggy and confused—as if their cerebral cortex has been shut down and has not yet resumed its functioning. In addition, several studies have shown that missing a single night's sleep impairs people's cognitive abilities; presumably, the brain needs sleep to function at peak efficiency (Harrison and Horne, 1998; 1999) These observations suggest that during stage 4 sleep the brain is, indeed, resting.

An inherited neurological disorder called **fatal familial insomnia** results in damage to portions of the thalamus (Sforza et al., 1995; Gallassi et al., 1996). The symptoms of this disease include deficits in attention and memory, followed by a dreamlike, confused state; loss of control of the autonomic nervous system and the endocrine system; and insomnia. The first signs of sleep disturbances are reductions in sleep spindles and K complexes. As the disease progresses, slow-wave sleep completely disappears and only brief episodes of REM sleep (without the accompanying paralysis) remain. As the name indicates, the disease is fatal. Whether the insomnia, caused by the brain damage, contributes to the other symptoms and to the patient's death is not known. In any case, as we shall see in the next section, when laboratory animals are kept awake indefinitely, they too will die.

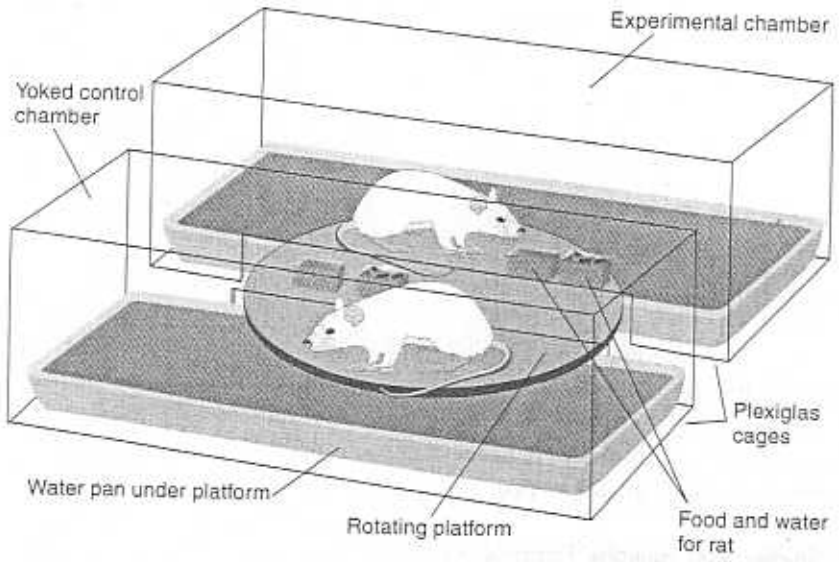
■ **Studies with Laboratory Animals** Until recently, sleep deprivation studies with animals have provided us with little insight into the role of sleep. Because animals cannot be "persuaded" to stay awake, it is especially difficult to separate the effects of sleep deprivation from those caused by the method used to keep the animals awake. We can ask a human volunteer to try to stay awake and can expect some cooperation. He or she will say, "I'm getting sleepy—help me to stay awake." However, animals are interested only in getting to sleep and must constantly be stimulated—and hence stressed. Rechtschaffen and his colleagues (Rechtschaffen et al., 1983, 1989; Rechtschaffen and Bergmann, 1995) devised a procedure to control for the effects of forced exercise that are necessary to keep an animal from sleeping. They constructed a circular platform on which two rats lived, each restrained in a plastic cage. When the platform was rotated by an electrical motor, the rats were forced to walk to avoid falling into a pool of water. (See *Figure 9.6.*)

fatal familial insomnia A fatal inherited disorder characterized by progressive insomnia.

Figure 9.6

The apparatus used to deprive rats of sleep. Whenever one of the pair of rats in the experimental chambers fell asleep, the turntable was rotated until the animal was awake for 6 seconds.

(Redrawn from Rechtschaffen, A., Gilliland, M. A., Bergmann, B. M., and Winter, J. B. *Science*, 1983, *221*, 182–184.)



The investigators employed a *yoked-control* procedure to deprive one rat of sleep but force both members of the pair to exercise an equal amount of time. (The term is used for any experiment in which two animals receive the same treatment at the same time, like two oxen fastened together with a yoke.) A computer recorded the EEGs and EMGs of both rats and detected both slow-wave and REM sleep. One rat served as the experimental (sleep-deprived) animal, and the other served as the yoked control. As soon as the EEG recording indicated that the experimental animal was falling asleep, the computer turned on the motor that rotated the disk, forcing both animals to exercise. Because the platform rotated whenever the experimental animal started to sleep, the procedure reduced the experimental animal's total sleep time by 87 percent. However, the sleep time of the yoked-control rat was reduced by only 31 percent.

Sleep deprivation had serious effects. The control animals remained in perfect health. However, the experimental animals looked sick and stopped grooming their fur. They became weak and uncoordinated and lost their ability to regulate their body temperature. (As we will see later, neurons involved in sleep also appear to be involved in thermoregulation.) Although they began eating much more food than normal, their metabolic rates became so high that they continued to lose weight. Eventually, the rats died. The cause of death is still not certain. The rats' brains appeared to be normal, and there were no obvious signs of inflammation or damage to other internal organs. The animals' levels of stress hormones were not unusually high, so the deaths could not be attributed to simple stress. If they were given a high-calorie diet to compensate for their increased metabolic rate, the rats lived longer, but eventually they succumbed (Everson and Wehr, 1993). Everson (1995) suggested that the sleep deprivation may disrupt the immune system and, as a consequence, the animals develop toxic infections of the blood.

As we saw, the effects of sleep deprivation are less drastic in humans than in rats. Perhaps human sleep deprivation studies have just not continued long enough to cause serious harm. The human body is much larger than that of a rat, and changes in metabolic rate would take much longer to affect body weight—and prolonged sleep deprivation of human subjects would clearly be unethical.

Effects of Exercise on Sleep

Sleep deprivation studies with humans suggest that the brain may need slow-wave sleep to recover from the day's activities but that the rest of the body does not. Another way to determine whether sleep is needed for restoration of physiological functioning is to look at the effects of daytime activity on nighttime sleep. If the function of sleep is to repair the effects of activity during waking hours, then we should expect that sleep and exercise are related. That is, we should sleep more after a day of vigorous exercise than after a day spent quietly at an office desk.

However, the relation between sleep and exercise is not very compelling. For example, Ryback and Lewis (1971) found no changes in slow-wave or REM sleep of healthy subjects who spent six weeks resting in bed. If sleep repairs wear and tear, we would expect these people to sleep less. Adey, Bors, and Porter (1968) studied the sleep of *completely* immobile quadriplegics and paraplegics and found only a small decrease in slow-wave sleep as compared with uninjured people.

Horne (1981, 1988) reported that some studies have found that exercise increases slow-wave sleep but others have

not. He noted that an important factor seems to be the climate in which the exercise occurs. If the temperature and the humidity are high, the exercise is likely to increase slow-wave sleep. Horne suggested that the important variable might be whether the exercise succeeded in heating the body.

To test this hypothesis, Horne and Moore (1985) had subjects exercise on a treadmill. Some subjects were cooled by electric fans, and their skin was periodically sprayed with water. Their body temperature rose only 1°C. That night, the slow-wave sleep of the "hot exercised" subjects rose by 25 percent, whereas that of the "cool exercised" subjects was unchanged. Horne (1988) now believes that the increased body temperature itself is not the significant factor but that an increase in brain temperature is. Perhaps, he said, an increase in brain temperature raises its metabolic rate and hence its demand for more slow-wave sleep. A preliminary study suggests that this hypothesis may have some merit. Horne and Harley (1989) warmed subjects' heads and faces with a hair dryer, which raised their brain temperature by an estimated 1°C. Four of the six subjects showed an increase in slow-wave sleep the next night. Clearly, further research is needed.

Effects of Mental Activity on Sleep

If the primary function of slow-wave sleep is to permit the brain to rest and recover from its daily activity, then we might expect that a person would spend more time in slow-wave sleep after a day of intense cerebral activity. Indeed, as we just saw, that is precisely the way that Horne interpreted the effects of increased body temperature. First of all, tasks that demand alertness and mental activity *do* increase glucose metabolism in the brain, as measured by a PET scanner (Roland, 1984). The most significant increases are seen in the frontal lobes, where delta activity is most intense during slow-wave sleep. In an experiment that supports this interpretation, Kattler, Dijk, and Borbély (1994) stimulated a person's hand with a vibrator, which activated the contralateral somatosensory cortex. The next night, a recording of the subject's EEG showed more delta activity in that region of the brain. Presumably, the increased activity of the cortical neurons called for more rest during the following night's sleep.

In an ingenious study Horne and Minard (1985) found a way to increase mental activity without affecting physical activity and without causing stress. The investigators told subjects to show up for an experiment in which they were supposed to take some tests designed to measure reading skills. When the subjects turned up, however, they were told that the plans had been changed. They were invited for a day out, at the expense of the experimenters. (Not surprisingly, the subjects willingly accepted.) They spent the day visiting an art exhibition, a shopping center, a museum, an amusement park, a zoo, and an interesting mansion. After a scenic drive through the countryside they watched a movie in a local theater. They were driven from place to place and certainly did not become overheated by exercise. After the movie they returned to the sleep laboratory. They said they were tired, and they readily fell asleep. Their sleep duration was normal, and they awoke feeling refreshed. However, their slow-wave sleep—particularly stage 4 sleep—was increased.

Functions of REM Sleep

Clearly, REM sleep is a time of intense physiological activity. The eyes dart about rapidly, the heart rate shows sudden accelerations and decelerations, breathing becomes irregular, and the brain becomes more active. It would be unreasonable to expect that REM sleep has the same functions as slow-wave sleep. An early report on the effects of REM sleep deprivation (Dement, 1960) observed that as the deprivation progressed, subjects had to be awakened from REM sleep more frequently; the "pressure" to enter REM sleep built up. Furthermore, after several days of REM sleep deprivation, subjects would show a **rebound phenomenon** when permitted to sleep normally; they spent a much greater-than-normal percentage of the recovery night in REM sleep. This rebound suggests that there is a need for a certain amount of REM sleep—that REM sleep is controlled by a regulatory mechanism. If selective deprivation causes a deficiency in REM sleep, the deficiency is made up later, when uninterrupted sleep is permitted.

How have investigators explained the occurrence of REM sleep? Many investigators have suggested that it somehow promotes learning. Some have suggested that memories of events of the previous day—especially those dealing with emotionally related information—are consolidated and integrated with existing memories (Greenberg and Pearlman, 1974); others have suggested that this time is utilized to accomplish the opposite function: to flush useless information from memory, to prevent the storage of useless clutter (Crick and Mitchison, 1983, 1995).

The fact that the sleep of infants consists mainly of REM sleep has suggested to others that this stage is associated with brain development (Roffwarg, Muzio, and Dement, 1966). The association could go either way; brain

rebound phenomenon The increased frequency or intensity of a phenomenon after it has been temporarily suppressed; for example, the increase in REM sleep seen after a period of REM sleep deprivation.

development could cause REM sleep (perhaps to tidy up after spurts of neural growth), or REM sleep could be setting the stage for brain growth to occur.

The developmental hypothesis is supported by the fact that infant animals born with well-developed brains (such as guinea pigs) spend proportionally less time in REM sleep than infant animals born with less-developed brains (such as rats, cats, or humans). Researchers have long been struck by the fact that the highest proportion of REM sleep is seen during the most active phase of brain development. Perhaps, then, REM sleep plays a role in this process. Studies of human fetuses and infants born prematurely indicate that REM sleep begins to appear 30 weeks after conception and peaks at around 40 weeks (Roffwarg, Muzio, and Dement, 1966; Petre-Quadens and De Lee, 1974; Inoue et al., 1986). Approximately 70 percent of a newborn infant's sleep is REM sleep. By six months of age this proportion has declined to approximately 30 percent. By eight years of age it has fallen to approximately 22 percent, and by late adulthood it is less than 15 percent.

Mirmiran (1995) described a series of studies he and his colleagues performed with infant rats. They injected the rats with drugs that suppressed REM sleep during the second and third weeks of life and found that the animals showed behavioral abnormalities as adults. In addition, their cerebral cortexes and brain stems were smaller than those of control subjects. Marks et al. (1995) found that brain lesions that disrupted one of the phenomena of REM sleep (PGO waves, described later) also disrupted development of the animals' visual systems. Of course, we cannot be sure that the effects of the drugs or the brain lesions on brain development were caused by the REM sleep deprivation; the treatments may have had additional effects.

But if the function of REM sleep is to promote brain development, why do adults have REM sleep? One possibility is that REM sleep facilitates the massive changes in the brain that occur during development but also the more modest changes responsible for learning that occur later in life. Studies with laboratory animals suggest that REM sleep performs functions that facilitate learning. Investigators have carried out two types of experiments. In the first they train animals in a learning task and then deprive them of REM sleep for a period of time. If REM sleep facilitates learning—perhaps by promoting changes in the brain that store the information just acquired—then animals deprived of the opportunity to engage in REM sleep after the training session should not learn as well as control subjects. In the second type of experiment, investigators train animals in a learning task and then monitor their sleep for several hours. An increase in REM sleep suggests that learning increases the need for this stage of sleep.

Experiments of both types have obtained positive results. For example, when animals are deprived of REM sleep after participating in a training session, they learn the task more slowly; thus, REM sleep deprivation retards memory formation. Most investigators believe that a learning experience starts a process that results in structural and biochemical changes in the brain. Perhaps some part of this process requires REM sleep to operate most effectively. In fact, if animals are deprived of sleep at the appropriate time after a training session (for a rat this usually occurs around 8 hours later), their performance will be poorer than that of animals permitted to obtain REM sleep (Smith, 1996).

In an example of the second type of experiment, Bloch, Hennevin, and Leconte (1977) gave rats daily training trials in a complex maze. They found that the experience enhanced subsequent REM sleep. Moreover, daily performance was related to subsequent REM sleep. The lower curve in Figure 9.7 shows REM sleep as a percentage of total sleep. The upper curve illustrates the animals' performance in the maze. You can see that the largest increase in running speed (possibly representing the largest increase in learning) was accompanied by the largest amount of REM sleep. Also note that once the task was well learned (after day 6), REM sleep declined to baseline levels. (See *Figure 9.7.*)

In contrast to the studies with laboratory animals, studies with human subjects show that REM sleep deprivation has only a small effect on a person's ability to learn or to remember what was previously learned. But several studies have found that learning can affect the amount of REM sleep a person obtains. For example, several studies found that retarded children engaged in less REM sleep than normal chil-

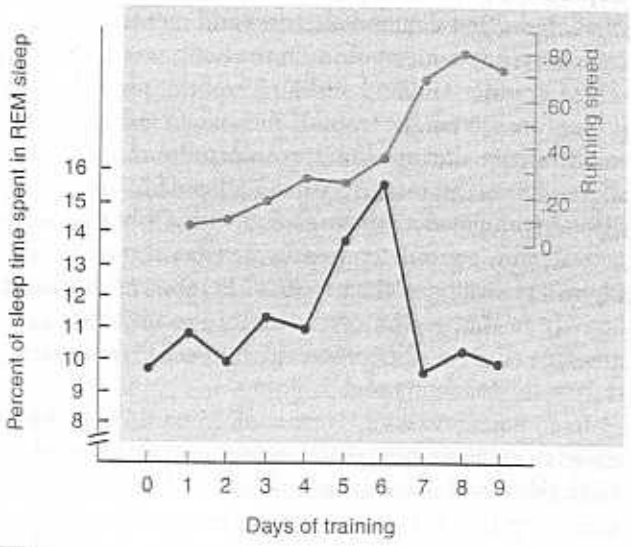


Figure 9.7

Percentage of sleep time spent in REM sleep (*lower curve*) as a function of maze-learning performance (*upper curve*).

(From Bloch, V., Hennevin, E., and Leconte, P., in *Neurobiology of Sleep and Memory*, edited by R. R. Drucker-Colin and J. L. McGaugh. New York: Academic Press, 1978.)

dren and that intellectually gifted children engaged in more (Dujardin, Guerrien, and Leconte, 1990). In addition, Smith and Lapp (1991) found that REM sleep of college students increased during exam time, when they presumably were spending more time learning new information.

As we saw, REM sleep seems to be regulated. If a person (or a laboratory animal) is deprived of REM sleep, he or she will show a rebound effect later when permitted to sleep undisturbed. In other words, going without REM sleep causes a REM deficit to accumulate, just as staying awake causes a general sleep deficit to accumulate. But what contributes to the REM deficit? It is possible that REM sleep and slow-wave sleep both help the brain to rest and recuperate from the wear and tear caused by wakefulness. On the other hand, it is possible that only slow-wave sleep provides rest and recuperation but has some deleterious side effects—and that REM sleep provides an antidote for these side effects. In other words, it is possible that slow-wave sleep repairs the effects of waking and that REM sleep repairs the effects of slow-wave sleep. Benington and Heller (1994) suggested that, indeed, REM sleep serves slow-wave sleep, not waking. They noted that in healthy individuals REM sleep does not occur until after a period of slow-wave sleep. In addition, the amount of REM sleep during a given night is related to the total time the person sleeps, not how long the person was awake the previous day. (See *Figure 9.8.*)

A particularly interesting case of brain damage suggests that whatever the functions of REM sleep may be, they do not appear to be necessary for survival. Lavie et al. (1984) reported that a 33-year-old man whose head was injured by shrapnel at age 20 engaged in almost no REM sleep. In the sleep laboratory the man slept an average of 4.5 hours. On three of eight nights he engaged in no REM sleep; the average on the other five nights was approximately 6 minutes. The pieces of metal damaged the pons, left temporal lobe, and left thalamus. As we shall see later in this chapter, the pons seems to be the part of the brain that controls REM sleep. The almost complete lack of REM sleep did not appear to cause serious side effects. After receiving his injury, the man completed high school, attended law school, and began practicing law. (I have a feeling that I could work in a lawyer joke here, but I think I'll refrain.)

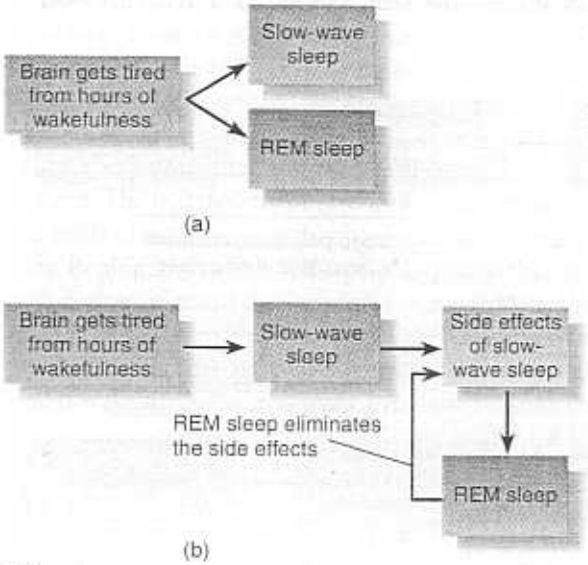


Figure 9.8

Two possible explanations for the relation between waking, slow-wave sleep, and REM sleep. (a) The wear and tear on the brain produced by wakefulness produces a need for both slow-wave sleep and REM sleep. (b) Wakefulness produces a need for slow-wave sleep, which, as it repairs this need, produces side effects that can be repaired only by REM sleep.

interim summary

The two principal explanations for sleep are that sleep serves as an adaptive response or that it provides a period of restoration. The fact that all vertebrates sleep, including some that would seem to be better off without it, suggests that sleep is more than an adaptive response.

In humans the effects of several days of sleep deprivation include perceptual distortions and (sometimes) mild hallucinations and difficulty performing tasks that require prolonged concentration. These effects suggest that sleep deprivation impairs cerebral functioning. Deep slow-wave sleep appears to be the most important stage, and perhaps its function is to permit the brain to recuperate. Animals that are sleep-deprived eventually die. Their symptoms include increased body temperature and metabolic rate, voracious eating, weight loss, but no obvious signs of a stress response. Fatal familial insomnia is an inherited disease that results in degeneration of parts of the thalamus, deficits in attention and memory, a dreamlike state, loss of control of the autonomic nervous system and the endocrine system, insomnia, and death.

Exercise can increase the amount of slow-wave sleep a person receives, but only if the brain temperature rises; the effect can be abolished by cooling the person's head and face. Perhaps, then, the most important function of slow-wave sleep is to lower the brain's metabolism and permit it to rest. In support of this hypothesis research has shown that slow-wave sleep does indeed reduce the brain's metabolic rate and that increased mental activity can cause an increase in slow-wave sleep the next night.

The functions of REM sleep are even less understood than those of slow-wave sleep. REM sleep may promote brain development and learning. So far, the evidence is inconclusive, although several studies have shown a moderate

relation between REM sleep and learning. It appears that REM sleep is a response to slow-wave sleep.

Physiological Mechanisms of Sleep and Waking

So far, I have discussed the nature of sleep, its functions, problems associated with it, and the control of biological rhythms. Now it is time to examine what researchers have discovered about the physiological mechanisms that are responsible for the behavior of sleep and for its counterpart, alert wakefulness. But before doing so, I must emphasize that sleep does not occur simply because neurons get tired and begin to fire more slowly. Like other behaviors, sleep occurs when certain neural circuits become *active.*

Chemical Control of Sleep

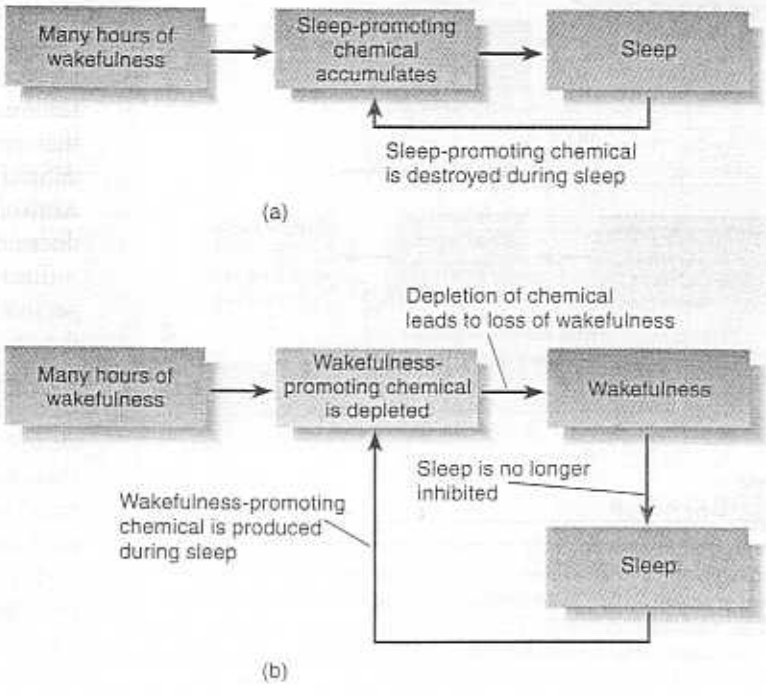
As we have seen, sleep is *regulated;* that is, if an organism is deprived of slow-wave sleep or REM sleep, the organism will make up at least part of the missed sleep when permitted to do so. In addition, the amount of slow-wave sleep that a person obtains during a daytime nap is deducted from the amount of slow-wave sleep he or she obtains the next night (Karacan et al., 1970). These facts suggest that some physiological mechanism monitors the amount of sleep that an organism receives. What might this mechanism be?

The most obvious explanation would be that the body produces either *sleep-promoting substances* during wakefulness or *wakefulness-promoting* substances during sleep. For example, a sleep-promoting substance might accumulate during wakefulness and be destroyed during sleep. The longer someone is awake, the longer he or she has to sleep to deactivate this substance. Obviously, because slow-wave sleep and REM sleep are mostly independent of each other, there would have to be two substances, one for each stage of sleep. As we saw earlier, Benington and Heller (1994) suggested that although slow-wave sleep may provide an opportunity for the brain to rest, it creates its own need for REM sleep. Of course, the opposite could be true; sleep could be regulated by a *wakefulness-promoting* substance. This substance would be used up during wakefulness and be manufactured only during sleep. A *decline* in the level of this substance would cause sleepiness. (See *Figure 9.9.*)

Where might these substances be located? They do not appear to be found in the general circulation of the body. As we saw earlier, the cerebral hemispheres of the bottlenose dolphin sleep at different times (Mukhametov, 1984). If sleep were controlled by *blood-borne* chemicals, the hemispheres should sleep at the same time. This observation suggests that if sleep is controlled by chemicals, these chemicals are produced within the brain and act there. Oleksenko et al. (1992) obtained evidence that indicates that each hemisphere of the brain incurs its own sleep debt. The researchers deprived a bottlenose dolphin of sleep in only one hemisphere. When they allowed the animal to sleep normally, they saw a rebound of slow-wave sleep only in the deprived hemisphere.

Figure 9.9

Hypothetical roles of chemicals in sleep. (a) A sleep-promoting chemical accumulates during wakefulness and is destroyed during sleep. (b) A wakefulness-promoting chemical is depleted during waking and is produced during sleep.



What chemical (or chemicals) might be involved in the control of sleep? An important category of drugs, the benzodiazepines, promotes sleep. In fact, they are widely used to treat insomnia. As we saw in Chapter 4, these drugs act on the benzodiazepine binding site located at the $GABA_A$ receptor. The existence of a special receptor suggests the existence of at least one endogenous ligand for this receptor, and this ligand could be involved in the control of sleep. However, no one has yet discovered a benzodiazepine-like substance whose concentration in the brain varies as a function of sleepiness.

A second category of drugs affects both sleep and body temperature. For example, anti-inflammatory drugs such as aspirin and ibuprofen reduce body temperature and interfere with sleep (Murphy et al., 1994), and a class of chemicals known as the *cytokines* increases body temperature and produces drowsiness (Knefati et al., 1995; Krueger and Majde, 1995). As we will see later in this chapter, increases in brain temperature activate a region of the brain necessary for the induction of sleep. Thus, it is possible that the anti-inflammatory drugs and the cytokines affect sleep indirectly, through their effects on temperature of the brain.

Benington, Kodali, and Heller (1995) suggested that a nucleoside neurotransmitter, *adenosine,* may play a primary role in the control of sleep. They noted that the primary nutrient of the brain is glucose, carried to it by the blood. The blood supply usually delivers an adequate amount of glucose, but if some regions of the brain become especially active, the cells located there consume the glucose faster than it can be supplied. In such cases extra nutrients are supplied by astrocytes (Swanson, 1992; Swanson and Choi, 1993). As we saw in Chapter 2, astrocytes maintain a small stock of nutrients in the form of glycogen, an insoluble carbohydrate that is also stocked by the liver and the muscles. The metabolism of glycogen causes an increase in the levels of adenosine, a chemical that has inhibitory effects. Benington and his colleagues suggested that this accumulation of adenosine produces increased amounts of delta activity during the next night's sleep. The cells in that region rest, and the astrocytes renew their stock of glycogen. If wakefulness is prolonged, even more adenosine accumulates, producing the cognitive and emotional effects seen during sleep deprivation. In support of this hypothesis the investigators found that when they administered a drug that stimulates adenosine receptors, they saw increases in delta activity during the animals' slow-wave sleep.

More recent evidence supports the hypothesis that adenosine plays a role in regulating sleep but suggests that it acts primarily in a specific region of the brain: the ventrolateral preoptic area. The adenosine hypothesis is discussed later in this chapter, in a section on the neural control of sleep.

Neural Control of Arousal

As we have seen, sleep is not a unitary condition but consists of several different stages with very different characteristics. Wakefulness, too, is nonuniform; sometimes we are alert and attentive, and sometimes we fail to notice much about what is happening around us. Of course, sleepiness has an effect on wakefulness; if we are fighting to stay awake, the struggle might impair our ability to concentrate on other things. But everyday observations suggest that even when we are not sleepy, our alertness can vary. For example, when we observe something very interesting (or frightening, or simply surprising), we feel ourselves become more activated and aware of our surroundings.

Experimental evidence suggests that the brain stem contains circuits of neurons that can increase an animal's level of alertness and activation—what is commonly referred to as *arousal.* In 1949 Moruzzi and Magoun found that electrical stimulation of the brain stem reticular formation produced arousal. The reticular formation, which occupies the central core of the brain stem, receives collateral axons from ascending sensory pathways. Presumably, sensory input, the event that normally produces arousal, activates the reticular formation by means of these collateral axons. The activated reticular formation then arouses the cerebral cortex by means of two pathways (Jones, 1990). The dorsal pathway projects to the medial and intralaminar nuclei of the thalamus, which in turn projects to the cerebral cortex; and the ventral pathway projects to the lateral hypothalamus, basal ganglia, and basal forebrain region. One part of the basal forebrain region projects extensively to the cerebral cortex, and another part projects to the hippocampus. (See *Figure 9.10.*)

At least four different systems of neurons play a role in some aspect of arousal and wakefulness: acetylcholinergic,

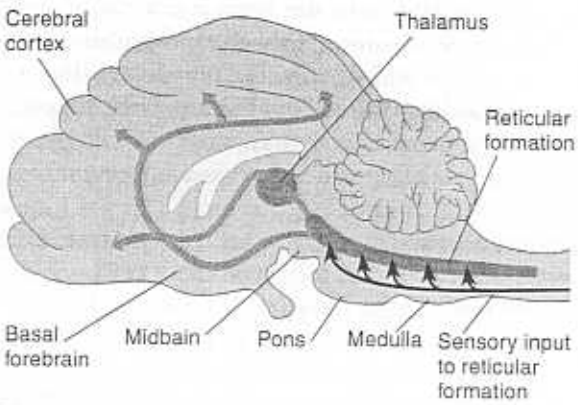


Figure 9.10

A midsagittal view of a cat brain, showing the reticular formation and its hypothesized role in arousal.

noradrenergic, serotonergic, and histaminergic (Wada et al., 1991; McCormick, 1992; Marrocco, Witte, and Davidson, 1994).

Acetylcholine

One of the most important neurotransmitters involved in arousal is acetylcholine. Two groups of acetylcholinergic neurons, one in the pons and one located in the basal forebrain, produce activation and cortical desynchrony when they are stimulated (Jones, 1990; Steriade, 1996). (A third group of neurons, located in the medial septum, controls the activity of the hippocampus. Because of the importance of the hippocampus in learning, this structure is described later, in Chapter 15.) Researchers have long known that acetylcholinergic antagonists decrease EEG signs of cortical arousal and that acetylcholinergic agonists increase them (Vanderwolf, 1992). Day, Damsma, and Fibiger (1991) used microdialysis probes to measure the release of acetylcholine in the striatum, hippocampus, and frontal cortex—three regions whose activity is closely related to an animal's alertness and behavioral arousal. They found that the levels of ACh in these regions were closely related to the animals' level of activity. In addition, Rasmusson, Clow, and Szerb (1994) electrically stimulated a region of the dorsal pons and found that the stimulation activated the cerebral cortex and increased the release of acetylcholine there by 350 percent (as measured by microdialysis probes). A group of acetylcholinergic neurons located in the basal forebrain forms an essential part of the pathway responsible for this effect. If these neurons were deactivated by infusing a local anesthetic or drugs that blocked synaptic transmission, the activating effects of the pontine stimulation were abolished.

Norepinephrine

Investigators have long known that catecholamine agonists such as amphetamine produce arousal and sleeplessness. These effects appear to be primarily mediated by the noradrenergic system of the **locus coeruleus**, located in the dorsal pons. Neurons of the locus coeruleus send axons that branch widely, releasing norepinephrine (from axonal varicosities) throughout the neocortex, hippocampus, thalamus, cerebellar cortex, pons, and medulla; thus, they potentially affect widespread and important regions of the brain. (See *Figure 9.11.*)

Aston-Jones and Bloom (1981a) recorded from noradrenergic neurons of the locus coeruleus (LC) across the sleep-waking cycle in unrestrained rats. As Figure 9.12 shows, these neurons exhibited a close relation to behavioral arousal. Note the decline in firing rate before and during sleep and the abrupt increase when the animal wakes. The rate of firing of neurons in the locus coeruleus falls almost to zero during REM sleep and increases dramatically when the animal wakes. As we shall see later in this chapter, these facts suggest that these neurons (along with serotonergic neurons) play a role in controlling REM sleep. (See *Figure 9.12.*)

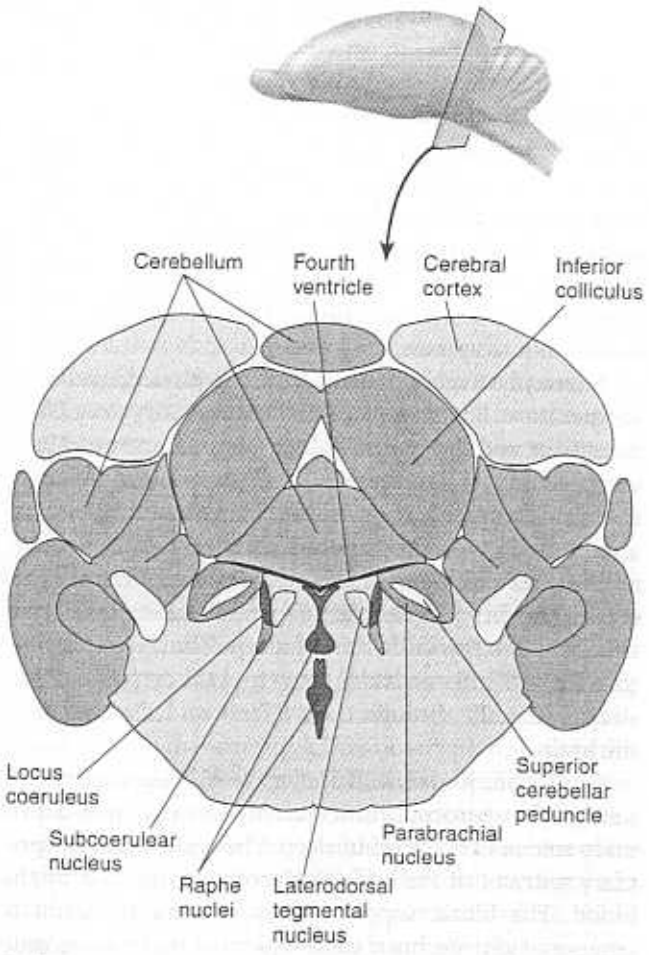


Figure 9.11

A section through the pons of a rat, showing the location of the locus coeruleus, which contains the cell bodies of most of the brain's noradrenergic neurons. Also shown are some structures that play a role in REM sleep, which is discussed later.

(Adapted from Paxinos, G., and Watson, C. *The Rat Brain in Stereotaxic Coordinates.* Sydney: Academic Press, 1982. Redrawn with permission.)

Aston-Jones and Bloom (1981a, 1981b) found that although sudden environmental stimuli presented during sleep or quiet wakefulness increased the activity of noradrenergic LC neurons, the firing rate of these neurons was

locus coeruleus (*sa roo lee us*) A dark-colored group of noradrenergic cell bodies located in the pons near the rostral end of the floor of the fourth ventricle; involved in arousal and vigilance.

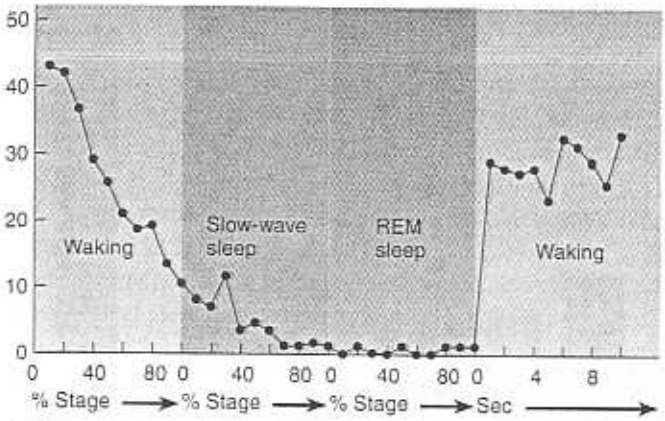


Figure 9.12

Activity of noradrenergic neurons in the locus coeruleus of freely moving rats during various stages of sleep and waking.

(From Aston-Jones, G., and Bloom, F. E. *The Journal of Neuroscience*, 1981, *1*, 876–886. Copyright 1981, The Society for Neuroscience.)

very low while the animals were performing activities that are normally accompanied by a high level of arousal, such as grooming or drinking sweetened water. In particular, the neurons became active when the experimenters presented stimuli that disrupted the animals' ongoing behavior. Stimuli that did not produce a behavioral change had little or no effect. The researchers suggested that these neurons showed the highest level of activity when the animals were *vigilant*—paying attention to stimuli in their environment.

In a subsequent study, Aston-Jones et al. (1994) recorded the electrical activity of noradrenergic LC neurons in monkeys performing a task that required them to watch for a particular stimulus that would appear on a video display. The investigators observed that the monkeys performed best when the rate of firing of the LC neurons was high. After the monkeys worked for a long time at the task, the neurons' rate of firing fell—and so did the monkeys' performance. These results support the conclusion that the activation of LC neurons (and their release of norepinephrine) increases vigilance.

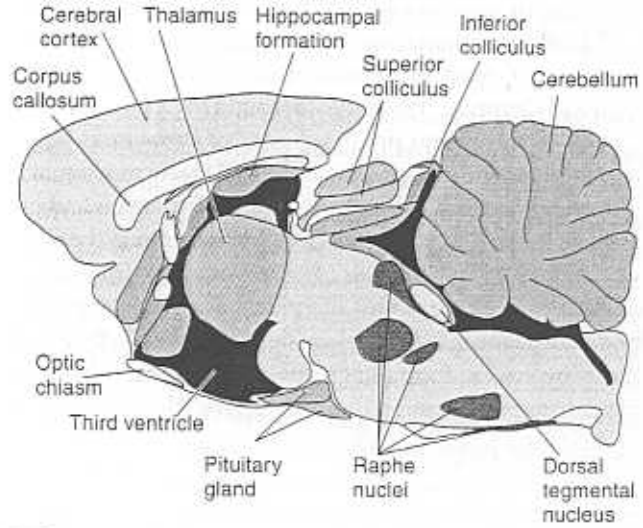


Figure 9.13

The raphe nuclei, the location of the cell bodies of most of the brain's serotonergic neurons.

(Adapted from Paxinos, G., and Watson, C. *The Rat Brain in Stereotaxic Coordinates*. Sydney: Academic Press, 1982. Redrawn with permission.)

Serotonin

A third neurotransmitter, serotonin (5-HT) also appears to play a role in activating behavior. Almost all of the brain's serotonergic neurons are found in the **raphe nuclei**, which are located in the medullary and pontine regions of the reticular formation. (See *Figure 9.13.*) The axons of these neurons project to many parts of the brain, including the thalamus, hypothalamus, basal ganglia, hippocampus, and neocortex. Stimulation of the raphe nuclei causes locomotion and cortical arousal (as measured by the EEG), whereas PCPA, a drug that prevents the synthesis of serotonin, reduces cortical arousal (Peck and Vanderwolf, 1991). Unlike noradrenergic neurons, which increase their rate of firing during stressful situations, serotonergic neurons do *not* respond to external stimuli that produce pain or induce a stress response (Jacobs, Wilkinson, and Fornal, 1990).

Jacobs and Fornal (1993, 1997) suggested that one specific contribution of serotonergic neurons to activation is facilitation of continuous, automatic movements, such as pacing, chewing, and grooming. On the other hand, when animals engage in orienting responses to novel stimuli, the activity of serotonergic neurons decreases. Perhaps serotonergic neurons are involved in facilitating ongoing activities and suppressing the processing of sensory information, preventing reactions that might disrupt the ongoing activities.

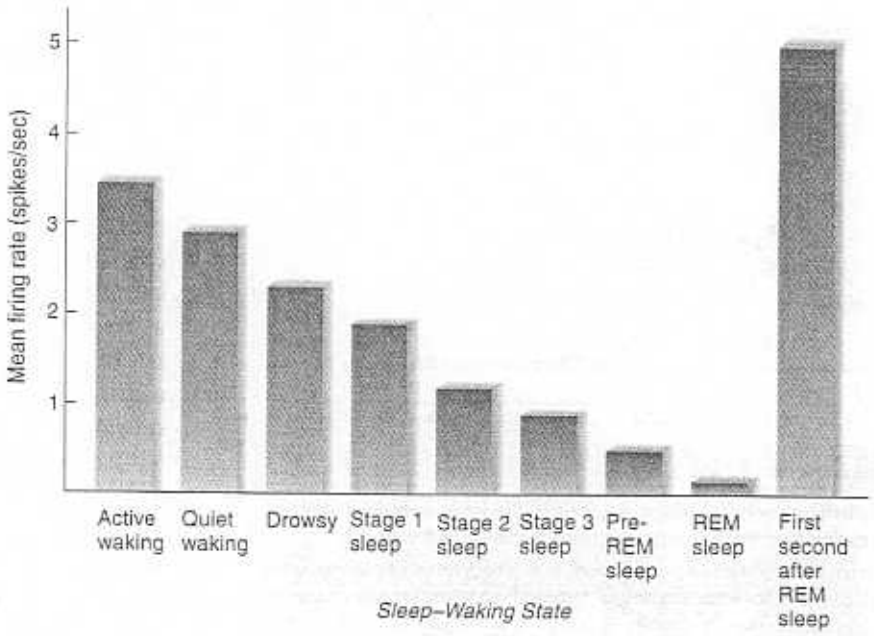
Figure 9.14 shows the activity of serotonergic neurons, recorded by Trulson and Jacobs (1979). As you can see, these neurons, like the noradrenergic neurons studied by Aston-Jones and Bloom (1981a), were most active during waking. Their firing rate declined during slow-wave sleep and became virtually zero during REM sleep. However, once the period of REM sleep ended, the neurons temporarily became very active again. (See *Figure 9.14.*)

raphe nuclei (*ruh fay*) A group of nuclei located in the reticular formation of the medulla, pons, and midbrain, situated along the midline; contain serotonergic neurons.

Figure 9.14

Activity of serotonergic (5-HT-secreting) neurons in the dorsal raphe nuclei of freely moving cats during various stages of sleep and waking.

(Adapted from Trulson, M. E., and Jacobs, B. L. *Brain Research, 1979, 163,* 135–150. Redrawn with permission.)



Histamine

The fourth neurotransmitter implicated in the control of wakefulness and arousal is histamine, a compound synthesized from histidine, an amino acid. The cell bodies of histaminergic neurons are located in the **tuberomammillary nucleus** of the hypothalamus, located at the base of the brain just rostral to the mammillary bodies. The axons of these neurons project primarily to the cerebral cortex, thalamus, basal ganglia, basal forebrain, and hypothalamus. The projections to the cerebral cortex directly increase cortical activation and arousal, and projections to the basal forebrain do so indirectly, by exciting the acetylcholinergic neurons located there (Khateb et al., 1995). Injections of drugs that prevent the synthesis of histamine or block histamine H_1 receptors decrease waking and increase sleep (Lin, Sakai, and Jouvet, 1988). Also, the activity of histaminergic neurons is high during waking but low during slow-wave and REM sleep (Steininger et al., 1996).

You are undoubtedly aware that antihistamines, used to treat allergies, can cause drowsiness. They do so by blocking histamine H_1 receptors. More modern antihistamines cannot cross the blood–brain barrier, so they do not cause drowsiness.

Neural Control of Slow-Wave Sleep

Although sleep is a behavior that involves most of the brain, one region seems to be particularly important: the **ventrolateral preoptic area** (VLPA). The preoptic area is a part of the basal forebrain, located just rostral to the hypothalamus. Nauta (1946) found that destruction of this area produced total insomnia in rats. The animals subsequently fell into a coma and died; the average survival time was only three days. McGinty and Sterman (1968) found that cats reacted somewhat differently; the animals did not become sleepless until several days after the lesion was made. Two of the cats, whose sleep was totally suppressed, died within ten days. Infusions of kainic acid into the preoptic area, which destroys cell bodies without damaging axons passing through the region, also suppresses sleep (Szymusiak and McGinty, 1986b; John et al., 1994).

The effects of these lesion experiments are corroborated by the effects of electrical stimulation of the preoptic area. Sterman and Clemente (1962a, 1962b) found that electrical stimulation of this region produced signs of drowsiness in the behavior and the EEG of unanesthetized, freely moving cats. The average latency period between the stimulation and the changes in the EEG was 30 seconds, but sometimes the effect was immediate. The animals often subsequently fell asleep.

A considerable amount of evidence suggests that forebrain mechanisms involved in sleep are closely linked to those involved in thermoregulation—an animal's ability to regulate its body temperature. One region of the basal fore-

tuberomammillary nucleus A nucleus in the ventral posterior hypothalamus, just rostral to the mammillary bodies; contains histaminergic neurons involved in cortical activation and behavioral arousal.

ventrolateral preoptic area (VLPA) A group of GABAergic neurons in the preoptic area whose activity suppresses alertness and behavioral arousal and promotes sleep.

brain contains neurons involved in thermoregulation. Some of these neurons are directly sensitive to changes in brain temperature, and some receive information from thermosensors located in the skin. Warming of this region decreases the activity of acetylcholinergic neurons of the basal forebrain and posterior hypothalamus (including neurons of the tuberomammillary nucleus) and induces slow-wave sleep (McGinty, Szymusiak, and Thomson, 1994; Alam, Szymusiak, and McGinty, 1995; Steininger et al., 1999). The excessive sleepiness that accompanies a fever may be produced by this mechanism. And perhaps the connections between the thermosensors in the skin and the preoptic area account for the drowsiness and lassitude we feel on a hot day.

Several recording studies confirm the effects of lesions and stimulation. For example, Sherin et al. (1996) found increased levels of Fos protein during sleep in a cluster of neurons in the ventrolateral preoptic area. (As we saw in Chapter 5, when neurons are stimulated, their levels of Fos protein increase.) Szymusiak et al. (1998) found that the activity of single neurons in the VLPA increased during both slow-wave and REM sleep. When the animals were deprived of sleep for 12–14 hours and were then allowed to sleep, neurons in the VLPA showed an especially high rate of firing—as if the drive to sleep were particularly intense.

Anatomical and histochemical studies indicate that the VLPA contains inhibitory GABA-secreting neurons and that these neurons send their axons to the tuberomammillary nucleus, raphe nuclei, and locus coeruleus (Sherin et al., 1998). As we saw in the previous subsection, stimulation of these three regions causes cortical activation and behavioral arousal. The fact that stimulation of the VLPA inhibits these regions is consistent with other evidence indicating that activation of the VLPA induces sleep.

As we saw earlier in this chapter, adenosine is produced when neurons become especially active, and accumulation of adenosine may be at least one of the chemicals that stimulate drowsiness and sleep. Indeed, evidence suggests that this is the case; adenosine exerts an antiwaking effect in the basal forebrain. Porkka-Heiskanen et al. (1997) used microdialysis to measure adenosine levels in the region of the basal forebrain rich in acetylcholine-secreting neurons. They found that the level of adenosine increased during wakefulness and decreased during sleep. In addition, infusion of an adenosine agonist into this region inhibited the acetylcholinergic neurons and increased sleep.

Figure 9.15 summarizes the results described in this section.

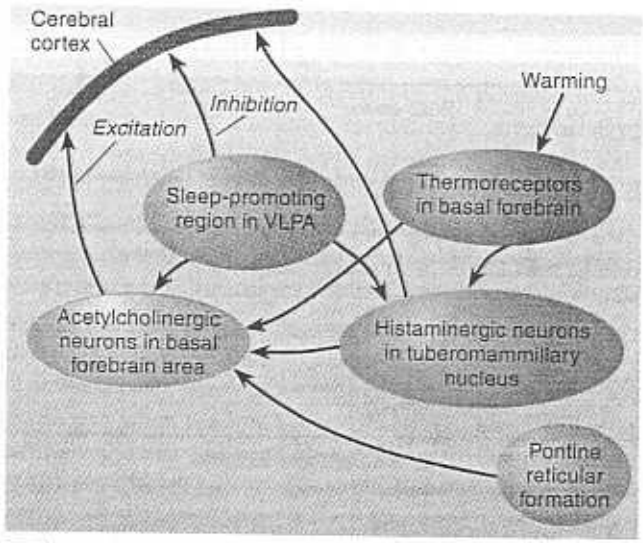


Figure 9.15

A schematic diagram of the role of the ventrolateral preoptic area (VLPA) in sleep and the wakefulness-promoting effects of the tuberomammillary nucleus and the pontine reticular formation. Black arrows indicate excitation; red arrows indicate inhibition. The role of the thalamus is omitted for simplicity.

Neural Control of REM Sleep

As we saw earlier in this chapter, REM sleep consists of desynchronized EEG activity, muscular paralysis, rapid eye movements, and (in humans, at least) increased genital activity. The rate of cerebral metabolism is as high as it is during waking (Maquet et al., 1990), and were it not for the state of paralysis, the level of *physical* activity would also be high. In laboratory animals REM sleep also includes *PGO waves*. PGO waves (for pons, geniculate, and occipital) are the first manifestation of REM sleep. They consist of brief, phasic bursts of electrical activity that originate in the pons and are propagated to the lateral geniculate nuclei and then to the primary visual (occipital) cortex. They can be seen only when electrodes are placed directly into the brain, so they have not been recorded in humans. It seems likely, however, that they occur in our species, too. Figure 9.16 shows the typical onset of REM sleep, recorded in a cat. The first sign of an impending bout of REM sleep is the presence of PGO waves—in this case recorded from electrodes implanted in the lateral geniculate nucleus. Next, the EEG becomes desynchronized, and then muscular activity ceases and rapid eye movements commence. (See *Figure 9.16.*)

As we shall see, REM sleep is controlled by mechanisms located within the pons. The executive mechanism (that is, the one whose activity turns on the various components of REM sleep) consists of a group of neurons in the dorsal

PGO wave Bursts of phasic electrical activity originating in the pons, followed by activity in the lateral geniculate nucleus and visual cortex; a characteristic of REM sleep.

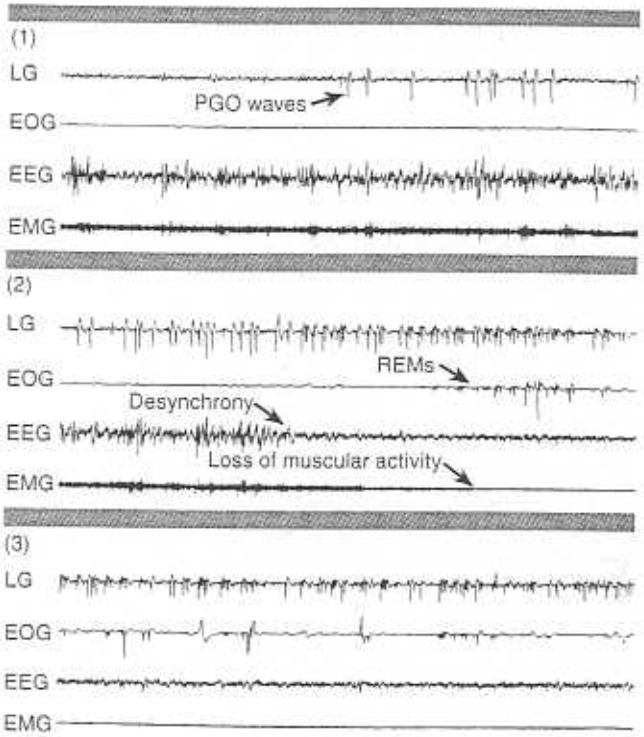


Figure 9.16

Onset of REM sleep in a cat. The arrows indicate the onset of PGO waves, EEG desynchrony, loss of muscular activity, and rapid eye movements. LG = lateral geniculate nucleus; EOG = electro-oculogram (eye movements).

(Adapted from Steriade, M., Paré, D., Bouhassira, D., Deschênes, M., and Oakson, G. *Journal of Neuroscience*, 1989, 9, 2215–2229. Reprinted with permission.)

pons that secrete acetylcholine. During waking and slow-wave sleep, REM sleep is inhibited by the serotonergic neurons of the raphe nuclei and the noradrenergic neurons of the locus coeruleus.

The Executive Mechanism

Researchers have long known that acetylcholinergic agonists facilitate REM sleep. Stoyva and Metcalf (1968) found that people who have been exposed to organophosphate insecticides, which act as acetylcholine agonists, spend an increased time in REM sleep. In a controlled experiment with human subjects, Sitaram, Moore, and Gillin (1978) found that an ACh agonist (arecoline) shortened the interval between periods of REM sleep and that an acetylcholinergic antagonist (scopolamine) lengthened it.

Jasper and Tessier (1969) analyzed the levels of acetylcholine that had been released by terminal buttons in the cat cerebral cortex. They found that the levels of ACh were highest during waking and REM sleep and were lowest during slow-wave sleep. Using 2-DG autoradiography in cats, Lydic et al. (1991) found that the rate of glucose metabolism was elevated in the regions of the brain that contain ACh-secreting neurons or that receive input from the axons of these neurons. As we saw earlier in this chapter, acetylcholinergic neurons play an important role in cerebral activation during alert wakefulness. The findings I just cited suggest that these neurons are also responsible for the cerebral activation seen during REM sleep.

The brain contains several groups of acetylcholinergic neurons. The ones that play the most central role in triggering the onset of REM sleep are found in the dorsolateral pons, primarily in the *pedunculopontine tegmental nucleus* (PPT) and *laterodorsal tegmental nucleus* (LDT) (Jones and Beaudet, 1987). Most investigators now refer to this region as the **peribrachial area**, because it is located in the region of the brachium conjunctivum. Figure 9.17 contains two drawings through the brain stem of a cat, prepared by Jones and Beaudet (1987). The locations of acetylcholinergic cell bodies (identified by a stain for choline acetyltransferase) are shown by colored circles. As you can see, these neurons surround the brachium conjunctivum (bc). (See *Figure 9.17.*)

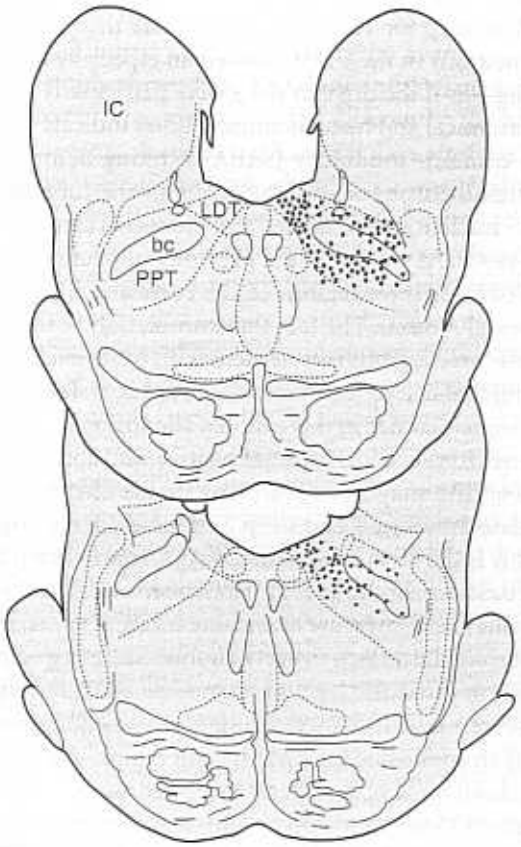


Figure 9.17

Acetylcholinergic neurons (colored circles) in the peribrachial area of the cat, as revealed by a stain for choline acetyltransferase. LDT = lateral tegmental nucleus; PPT = pedunculopontine tegmental nucleus; bc = brachium conjunctivum; IC = inferior colliculus.

(Adapted from Jones, B. E., and Beaudet, A. *Journal of Comparative Neurology*, 1987, 261, 15–32. Reprinted with permission.)

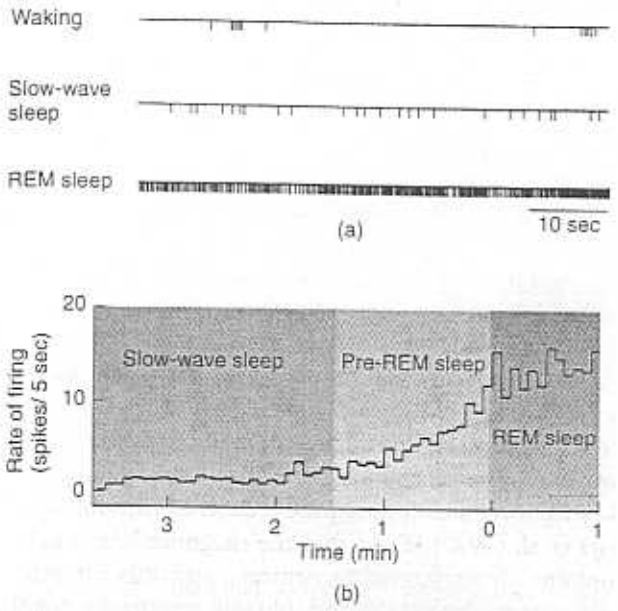


Figure 9.18

Firing pattern of an acetylcholinergic REM-ON cell in the peribrachial area of the pons. (a) Action potentials during 60-min intervals during waking, slow-wave sleep, and REM sleep. (b) Rate of firing just before and after the transition from slow-wave sleep to REM sleep. The increase in activity begins approximately 80 sec before the onset of REM sleep.

(Adapted from El Mansari, M., Sakai, K., and Jouvet, M. *Experimental Brain Research*, 1989, *76*, 519–529.)

Several studies (for example, El Mansari, Sakai, and Jouvet, 1989; Steriade et al., 1990; Kayama, Ohta, and Jodo, 1992) have shown that the activity of single neurons in the peribrachial area is related to the sleep cycle. Most of these neurons fire at a high rate during REM sleep or during both REM sleep and active wakefulness. Figure 9.18 shows the activity of a so-called *REM-ON* cell, which fires at a high rate only during REM sleep. As you can see, this neuron increased its activity approximately 80 sec before the onset of REM sleep. The increase in the activity of these acetylcholinergic cells may be the event that initiates a bout of REM sleep. (See *Figure 9.18.*)

Webster and Jones (1988) made lesions of the peribrachial area by infusing kainic acid into this region. They found that REM sleep was drastically reduced. The amount of REM sleep that remained was directly related to the number of cholinergic neurons that were spared.

Where do the acetylcholinergic neurons of the peribrachial area exert their effects? The axons of these neurons project to the medial pontine reticular formation; to several regions of the forebrain, including the thalamus, basal ganglia, preoptic area, hippocampus, hypothalamus, and cingulate cortex; and to several brain stem regions involved with the control of eye movements (Cornwall, Cooper, and Phillipson, 1990; Bolton, Cornwall, and Phillipson, 1993).

Let us examine the role of these connections. If a small amount of **carbachol**, a drug that stimulates acetylcholine receptors, is infused into the region of the pons ventral to the locus coeruleus, the animal will display some or all of the components of REM sleep (Katayama et al., 1986; Callaway et al., 1987). Some investigators refer to the general region of these infusions as the *mesopontine* (or *medial pontine*) *reticular formation*, others call it the *nucleus reticularis pontis oralis (RPO)*, and yet others call it the *gigantocellular tegmental field (FTG)* (Siegel, 1989). Unfortunately, although the regions referred to by these names overlap, the terms are not completely synonymous, which makes for confusion when reading the research literature. I will refer to the region as the **medial pontine reticular formation** (MPRF). Carbachol is effective when infused into the MPRF because it stimulates postsynaptic acetylcholine receptors of neurons that receive projections from the ACh cells of the peribrachial area (Quattrochi et al., 1989). For this reason this region is often referred to as the *cholinoceptive* region of the MPRF because it is *receptive* to ACh. As you might expect, microdialysis studies have found increased levels of acetylcholine in this region during REM sleep (Kodama, Takahashi, and Honda, 1990).

The critical cholinoceptive region—the region where infusions of carbachol produce all of the components of REM sleep—appears to be the ventral portion of the MPRF in cats (Garzón, De Andrés, and Reinoso-Suárez, 1998). As you might expect, lesions of the MPRF, like those of the peribrachial area, reduce or abolish REM sleep (Siegel, 1989). (See *Figure 9.19.*)

If the acetylcholinergic neurons in the peribrachial area of the pons are responsible for the onset of REM sleep, how do they control each of its components, cortical arousal, PGO waves, rapid eye movements, and muscular paralysis? As we saw, the acetylcholinergic neurons of the pons comprise an integral part of the reticular activating system. They send axons directly to regions of the thalamus that are involved in the control of cortical arousal. In addition, these neurons send axons to glutamatergic neurons in the mesopontine reticular formation, which, in turn, send axons to the acetylcholinergic neurons of the basal forebrain. Activation of these forebrain neurons produces arousal and cortical desynchrony. PGO waves appear to be

peribrachial area (*pair ee* ***bray*** *kee ul*) The region around the brachium conjunctivum, located in the dorsolateral pons; contains acetylcholinergic neurons involved in the initiation of REM sleep.

carbachol (*car ba call*) A drug that stimulates acetylcholine receptors.

medial pontine reticular formation (MPRF) A region that contains neurons involved in the initiation of REM sleep; activated by acetylcholinergic neurons of the peribrachial area.

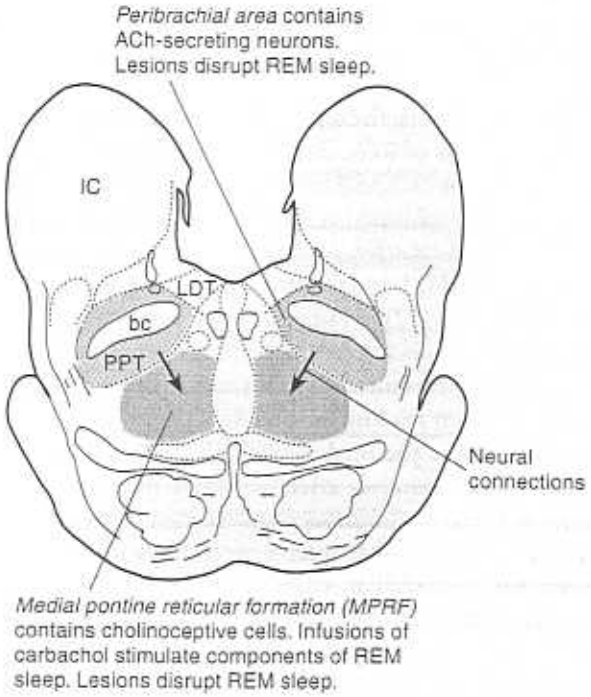


Figure 9.19

A cross section through the pons of a cat, showing the locations of the peribrachial area and the medial pontine reticular formation (MPRF), regions involved in the control of REM sleep.

controlled by direct connections between the peribrachial area and the lateral geniculate nucleus (Sakai and Jouvet, 1980; Steriade et al., 1990). The control of rapid eye movements appears to be achieved by projections from the peribrachial area to the tectum (Webster and Jones, 1988).

The last of the REM-related phenomena, muscular paralysis, is particularly interesting. As we will see, some patients with lesions in the brain stem fail to become paralyzed during REM sleep and thus act out their dreams. (This phenomenon is called *REM without atonia.*) The same thing happens—that is, assuming that cats dream—when a lesion is placed just caudal to the peribrachial area of the pons. Jouvet (1972) described this phenomenon:

> To a naive observer, the cat, which is standing, looks awake since it may attack unknown enemies, play with an absent mouse, or display flight behavior. There are orienting movements of the head or eyes toward imaginary stimuli, although the animal does not respond to visual or auditory stimuli. These extraordinary episodes . . . are a good argument that "dreaming" occurs during [REM sleep] in the cat. (Jouvet, 1972, pp. 236–237)

Jouvet's lesions destroyed a set of neurons responsible for the muscular paralysis that occurs during REM sleep. These neurons are located just ventral to the locus coeruleus—in the subcoerulear region. Their axons travel caudally to the **magnocellular nucleus,** located in the medial medulla (Sakai, 1980). Neurons in the magnocellular nucleus send axons to the spinal cord, where they form inhibitory synapses with motor neurons (Morales, Boxer, and Chase, 1987).

There is good evidence that this pathway is responsible for the atonia that accompanies REM sleep. Shouse and Siegel (1992) found that lesions of the subcoerulear region had no effect on REM sleep itself but abolished the atonia that accompanies it. Kanamori, Sakai, and Jouvet (1980) recorded from single neurons in the magnocellular nucleus in unrestrained cats and found that they became active during REM sleep. Sakai (1980) found that electrical stimulation of this nucleus caused paralysis in awake cats, and Schenkel and Siegel (1989) found that lesions of the magnocellular nucleus produced REM without atonia. Fort et al. (1990) found that the magnocellular nucleus contains glycine-secreting neurons, and this inhibitory transmitter substance is undoubtedly responsible for the inhibition of the motor neurons located in the spinal cord.

The fact that our brains contain an elaborate mechanism whose sole function is to keep us paralyzed while we dream—that is, to prevent us from acting out our dreams—suggests that the motor components of dreams are as important as the sensory components. Perhaps the practice our motor system gets during REM sleep helps us to improve our performance of behaviors we have learned that day. The inhibition of the motor neurons in the spinal cord prevents the movements being practiced from actually occurring, with the exception of a few harmless twitches of the hands and feet.

As you will certainly appreciate, the neural circuitry controlling REM sleep is rather complicated. Figure 9.20 summarizes the evidence I have just reviewed. The first event preceding a bout of REM sleep appears to be activation of acetylcholinergic neurons in the peribrachial area of the dorsolateral pons. These neurons directly activate brain stem mechanisms responsible for rapid eye movements and trigger PGO waves through their connections with the lateral geniculate nucleus of the thalamus. They also activate neurons in the subcoerulear area that, through their connections with the nucleus magnocellularis of the medulla, produce atonia. Finally, these neurons activate neurons in the MPRF that, in turn, activate acetylcholinergic neurons of the basal forebrain responsible for the cortical activation that accompanies REM sleep. (See *Figure 9.20.*)

magnocellular nucleus A nucleus in the medulla; involved in the atonia (muscular paralysis) that accompanies REM sleep.

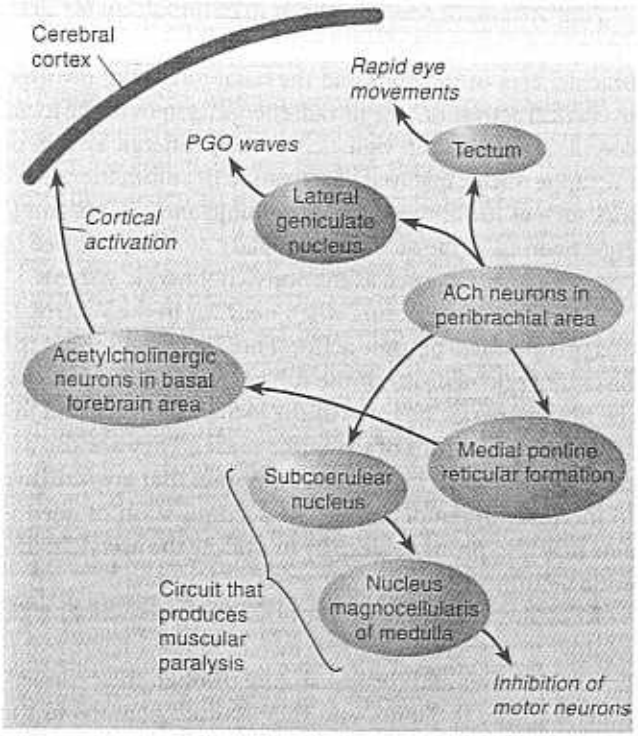


Figure 9.20

A summary of the neural circuitry thought to be responsible for REM sleep. The dashed arrow represents a connection from the MPRF to the peribrachial area that appears to be responsible for some of the phenomena of REM sleep produced by infusion of carbachol into the MPRF.

Why, you might ask, does an infusion of an ACh agonist such as carbachol into the MPRF induce REM sleep? After all, neurons in the MPRF seem to be directly involved in producing just one component of REM sleep: cortical activation. The other components of REM sleep are produced directly by neurons in the peribrachial area or the subcoerulear region. The answer seems to lie in the fact that neurons in the MPRF send axons to the peribrachial area (Reinoso-Suárez et al., 1994). Presumably, the activation of neurons in the MPRF with carbachol causes the neurons in the peribrachial region to be activated as well, triggering the rest of the components of REM sleep.

As we saw earlier, when an animal (including a member of our own species) is deprived of REM sleep, it shows a rebound effect when the period of deprivation ends. Mallick, Siegel, and Fahringer (1989) placed recording electrodes next to REM-ON neurons in the peribrachial area of the pons—that is, near those neurons that become active during REM sleep. They found that short-term REM sleep deprivation increased the activity of these neurons, even while the cats were awake. They suggested that this activity might represent the "REM pressure" that is responsible for the rebound effect. Of course, the experiment does not reveal *why* REM sleep deprivation makes these neurons become more active. When we find the answer to that question, we will learn more about the functions of REM sleep.

One of the factors (but certainly not the only one) that stimulates REM sleep is temperature. As we saw, brain temperature falls during slow-wave sleep; in fact, this fall in temperature (reflecting a decrease in metabolic activity of the brain) may even be one of the major functions of this phase of sleep. The fall in temperature appears to stimulate neurons responsible for REM sleep (Jouvet, 1975). The increased brain activity that occurs during REM sleep causes a rise in brain temperature, which then falls again during the subsequent period of slow-wave sleep.

Serotonin and Norepinephrine

As you will learn in a discussion of sleep disorders later in this chapter, serotonergic and noradrenergic agonists have inhibitory effects on REM sleep. In addition, the rate of activity in the serotonergic neurons of the raphe nuclei and the noradrenergic neurons of the locus coeruleus are at their very lowest levels during sleep. The patterns of firing of noradrenergic neurons of the locus coeruleus and the serotonergic neurons of the raphe nuclei were presented in Figures 9.12 and 9.14, respectively.

Evidence suggests that the activity of neurons in the locus coeruleus and the dorsal raphe nucleus normally inhibits REM sleep and that a reduction in the rate of firing of these neurons is the event that triggers a bout of REM sleep. For example, Figure 9.21 shows the very close linkage between the activity of a single unit in the dorsal raphe nucleus and the occurrence of PGO waves, the first manifestation of REM sleep (Lydic, McCarley, and Hobson, 1983). Note that the PGO waves occur only when the serotonergic neuron is silent. (See *Figure 9.21.*)

Anatomical and pharmacological studies provide further evidence. Acetylcholinergic neurons in the peribrachial area receive both serotonergic and noradrenergic inputs (Honda and Semba, 1994; Leonard et al., 1995). In addition, the

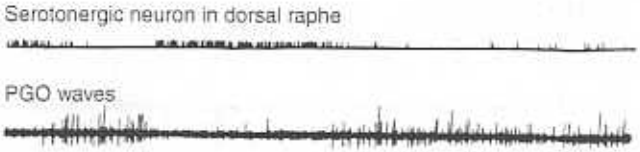


Figure 9.21

Activity of a single unit in the dorsal raphe nucleus. Note that the activity is *inversely* related to the occurrence of PGO waves, the first sign of REM sleep.

(Adapted from Lydic, R., McCarley, R. W., and Hobson, J. A. *Brain Research*, 1983, *274*, 365–370. Redrawn with permission.)

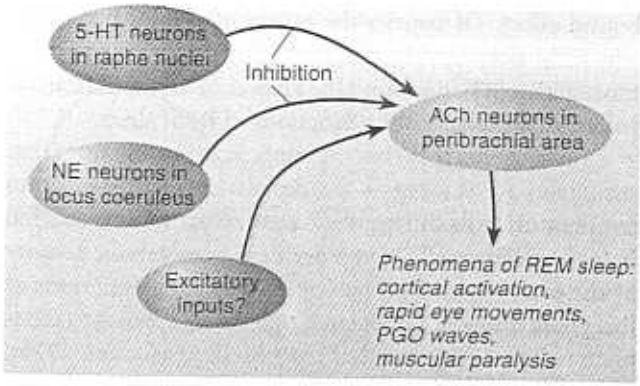


Figure 9.22

Interactions between serotonergic, noradrenergic, and acetylcholinergic neurons in the control of REM sleep.

cholinoceptive region of the MPRF also receives both serotonergic and noradrenergic inputs (Semba, 1993). Portas et al. (1996) infused a drug into the dorsal raphe nucleus that inhibits the release of serotonin. As a result, the animals exhibited a three-fold increase in REM sleep. Bier and McCarley (1994) found that infusions of a noradrenergic antagonist into the MPRF also causes an increase in REM sleep.

Several unanswered questions await further research. As we saw in an earlier section, neurons in the sleep-promoting region of the VLPA inhibit both the locus coeruleus and the raphe nuclei, which explains why the activity of noradrenergic and serotonergic neurons decreases during sleep. But what is responsible for the further inhibition of these neurons during REM sleep? Is there an excitatory input to the peribrachial area as well as the inhibitory ones whose activity *increases* at the beginning of REM sleep? Where is the pacemaker that controls the regular cycles of REM and slow-wave sleep, and how is this pacemaker connected to the REM sleep mechanisms in the pons? And finally, are rises and falls in brain temperature partly responsible for these cycles? (See *Figure 9.22.*)

interim summary

The fact that the amount of sleep is regulated suggests that sleep-promoting substances (produced during wakefulness) or wakefulness-promoting substances (produced during sleep) may exist. The sleeping pattern of the dolphin brain suggests that such substances do not accumulate in the blood. Evidence suggests that adenosine, released when neurons are obliged to utilize the supply of glycogen stored in astrocytes, serves as the link between increased brain metabolism and the necessity of sleep.

Four systems of neurons appear to be important for alert, active wakefulness: the acetylcholinergic system of the peribrachial area of the pons and the basal forebrain, involved in cortical activation; the noradrenergic system of the locus coeruleus, involved in vigilance; the serotonergic system of the raphe nuclei, involved in activation of automatic behaviors such as locomotion and grooming; and the histaminergic neurons of the tuberomammillary nucleus, involved in cortical activation, such as the acetylcholinergic systems.

Slow-wave sleep occurs when neurons in the ventrolateral preoptic area become active. These neurons inhibit the histaminergic neurons of the tuberomammillary nucleus, the noradrenergic neurons of the locus coeruleus, and the serotonergic neurons of the raphe nuclei. They are also activated by neurons in the basal forebrain that are sensitive to increases in temperature. The accumulation of adenosine may also promote sleep by inhibiting the acetylcholinergic neurons in the preoptic area.

REM sleep occurs when the activity of acetylcholinergic neurons in the peribrachial area increases. These neurons initiate PGO waves and cortical arousal through their connections with the thalamus, and they activate neurons in the MPRF that in turn activate the acetylcholinergic neurons of the basal forebrain. The peribrachial neurons also produce rapid eye movements through their connections with motor neurons in the tectum. Atonia (muscular paralysis that prevents our acting out our dreams) is produced by a group of acetylcholinergic neurons located in the subcoerulear nucleus that activate other neurons located in the magnocellular nucleus of the medulla, which in turn produce inhibition of motor neurons in the spinal cord. REM sleep, too, is related to temperature; it normally occurs only after the brain temperature has been lowered by a period of slow-wave sleep.

The noradrenergic neurons of the locus coeruleus and the serotonergic neurons of the raphe nuclei have inhibitory effects on pontine neurons responsible for REM sleep. Bouts of REM sleep begin only after the activity of the noradrenergic and serotonergic neurons ceases; whether this event is the only one to trigger REM sleep or whether direct excitation of acetylcholinergic neurons also occurs is not yet known.

Disorders of Sleep

Insomnia

Insomnia is a problem said to affect approximately 25 percent of the population occasionally, and 9 percent regularly (Ancoli-Israel and Roth, 1999). At the outset I must emphasize that there is no single definition of insomnia that

can apply to all people. The amount of sleep that individuals require is quite variable. A short sleeper may feel fine with 5 hours; a long sleeper may still feel unrefreshed after 10 hours of sleep. Insomnia must be defined in relation to a person's particular sleep needs. Some short sleepers have sought medical assistance because they thought that they were supposed to get more sleep, even though they felt fine. These people should be reassured that whatever amount of sleep seems to be enough *is* enough. Meddis, Pearson, and Langford (1973) reported the case of a 70-year-old woman who slept approximately 1 hour each day (documented by sessions in a sleep laboratory). She felt fine and was of the opinion that most people "wasted much time" in bed.

Ironically, one of the most important causes of insomnia seems to be sleeping medication. Insomnia is not a disease that can be corrected with a medicine, in the way that diabetes can be treated with insulin. Insomnia is a symptom. If it is caused by pain or discomfort, the physical ailment that leads to the sleeplessness should be treated. If it is secondary to personal problems or psychological disorders, these problems should be dealt with directly. Patients who receive a sleeping medication develop a tolerance to the drug and suffer rebound symptoms if it is withdrawn (Weitzman, 1981). That is, the drug loses its effectiveness, so the patient requests larger doses from the physician. If the patient attempts to sleep without the accustomed medication or even takes a smaller dose one night, he or she is likely to experience a withdrawal effect: a severe disturbance of sleep. The patient becomes convinced that the insomnia is even worse than before and turns to more medication for relief. This common syndrome is called **drug dependency insomnia**. Kales et al. (1979) found that withdrawal of some sleeping medications produced a rebound insomnia after the drugs were used for as few as three nights.

Most patients who receive a prescription for a sleeping medication are given one on the basis of their own description of their symptoms. That is, they tell their physician that they sleep very little at night, and the drug is prescribed on the basis of this testimony. Very few patients are observed during a night's sleep in a sleep laboratory; thus, insomnia is one of the few medical problems that physicians treat without having direct clinical evidence for its existence. But studies on the sleep of people who complain of insomnia show that most of them grossly underestimate the amount of time they actually sleep. The U.S. Institute of Medicine (1979) found that most insomniacs, even without sleeping medication, fall asleep in less than 30 minutes and sleep for at least 6 hours. *With* sleeping medication they obtained less than a 15-minute reduction in falling asleep, and their sleep length was increased by only about 30 minutes. Given the unfortunate side effects, sleeping medication does not seem to be worthwhile, except perhaps on a short-term basis.

For many years the goal of sleeping medication was to help people fall asleep, and when drug companies evaluated potential medications, they concentrated on that property. However, if we think about the ultimate goal of sleeping medication, it is to make the person feel more refreshed the next day. If a medication puts people to sleep right away but produces a hangover of grogginess and difficulty concentrating the next day, it is worse than useless. In fact, many drugs that are traditionally used to treat insomnia had just this effect. More recently, researchers have recognized that the true evaluation of a sleeping medication must be made during wakefulness the following day (American Psychiatric Association, 1994), and "hangover-free" drugs are finally being developed (Hajak et al., 1995).

A particular form of insomnia is caused by an inability to sleep and breathe at the same time. Patients with this disorder, called **sleep apnea**, fall asleep and then cease to breathe. (Nearly all people, especially people who snore, have occasional episodes of sleep apnea, but not to the extent that it interferes with sleep.) During a period of sleep apnea the level of carbon dioxide in the blood stimulates chemoreceptors (neurons that detect the presence of certain chemicals), and the person wakes up, gasping for air. The oxygen level of the blood returns to normal, the person falls asleep, and the whole cycle begins again. Fortunately, many cases of sleep apnea are caused by an obstruction of the airway that can be corrected surgically or relieved by a device that attaches to the sleeper's face and provides pressurized air that keeps the airway open (Sher, 1990; Westbrook, 1990).

Problems Associated with REM Sleep

Narcolepsy (*narke* means "numbness," and *lepsis* means "seizure") is a neurological disorder characterized by sleep (or some of its components) at inappropriate times. The symptoms can be described in terms of what we know about the phenomena of sleep. The primary symptom of narcolepsy is the sleep attack. The narcoleptic sleep attack is an overwhelming urge to sleep that can happen at any time but occurs most often under monotonous, boring conditions. Sleep (which appears to be entirely normal)

drug dependency insomnia An insomnia caused by the side effects of ever-increasing doses of sleeping medications.

sleep apnea (*app nee a*) Cessation of breathing while sleeping.

narcolepsy (*nahr ko lep see*) A sleep disorder characterized by periods of irresistible sleep, attacks of cataplexy, sleep paralysis, and hypnagogic hallucinations.

sleep attack A symptom of narcolepsy; an irresistible urge to sleep during the day, after which the person awakes feeling refreshed.

generally lasts for 2 to 5 minutes. The person usually wakes up feeling refreshed.

Another symptom of narcolepsy—in fact, the most striking one—is **cataplexy** (from *kata,* "down," and *plexis,* "stroke"). During a cataplectic attack a person will suddenly wilt and fall like a sack of flour. The person will lie there, *fully conscious,* for a few seconds to several minutes. What apparently happens is that one of the phenomena of REM sleep—muscular paralysis—occurs at an inappropriate time. As we saw, this loss of tonus is caused by massive inhibition of motor neurons in the spinal cord. When this happens during waking, the victim of a cataplectic attack falls as suddenly as if a switch had been thrown.

Cataplexy is quite different from a narcoleptic sleep attack; cataplexy is usually precipitated by strong emotion or by sudden physical effort, especially if the patient is caught unawares. Laughter, anger, or an effort to catch a suddenly thrown object can trigger a cataplectic attack. In fact, as Guilleminault, Wilson, and Dement (1974) noted, even people who do not have cataplexy sometimes lose muscle strength after a bout of intense laughter. (Perhaps that is why we say a person can become "weak from laughter.") Common situations that bring on cataplexy are attempting to discipline one's children or making love (an awkward time to become paralyzed!).

REM sleep paralysis sometimes intrudes into waking, but at a time that does not present any physical danger—just before or just after normal sleep, when a person is already lying down. This symptom of narcolepsy is referred to as **sleep paralysis,** an inability to move just before the onset of sleep or upon waking in the morning. A person can be snapped out of sleep paralysis by being touched or by hearing someone call his or her name. Sometimes, the mental components of REM sleep intrude into sleep paralysis; that is, the person dreams while lying awake, paralyzed. These episodes, called **hypnagogic hallucinations,** are often alarming or even terrifying. (The term *hypnagogic* comes from the Greek words *hupnos,* "sleep," and *agogos,* "leading.")

Almost certainly, narcolepsy is produced by a brain abnormality that causes the neural mechanisms responsible for various aspects of REM sleep to become active at inappropriate times. Indeed, Rechtschaffen et al. (1963) found that narcoleptic patients generally skip the slow-wave sleep that normally begins a night's sleep; instead, they go directly into REM sleep from waking. This finding suggests that in the brains of narcoleptics, the neural mechanisms that produce REM sleep are poorly controlled.

Narcolepsy is primarily a genetic disorder (Aldrich, 1992). One report (Plazzi et al, 1996) found evidence for a lesion in the pontine reticular formation in 3 narcoleptic patients; another study of 12 narcoleptic patients (Frey and Heiserman, 1997) found no evidence for pontine lesions. Researchers have bred dogs afflicted with narcolepsy, with the hopes that discovery of the causes of canine narcolepsy may further research on human narcolepsy. (See *Figure 9.23.*)

Research with narcoleptic dogs has finally paid off. Lin et al. (1999) discovered that a mutation of a specific gene is responsible for canine narcolepsy. The product of this gene is a receptor for a neuropeptide called *orexin* (also known as *hypocretin*). There are two orexin receptors: orexin A and orexin B. As we will see in Chapter 13, the orexin A receptor is involved in stimulation of hunger. Lin and his colleagues discovered that the mutation responsible for canine narcolepsy involves the orexin B receptor.

Chemelli et al. (1999) prepared a targeted mutation in mice against the orexin gene and found that the animals showed symptoms of narcolepsy. Like human patients with narcolepsy, they went directly into REM sleep from waking. Nishino et al. (2000) performed an analysis of the cerebrospinal fluid of normal subjects and patients with narcolepsy. They found a complete absence of orexin in seven of the nine narcoleptic patients. On the basis of previous genetic studies, the investigators suggested that most cases of human narcolepsy are unlikely to be caused by a mutation in a gene responsible for production of orexin. Instead, they hypothesized, most cases are the result of a disorder in genetically susceptible individuals that causes the immune system to attack and destroy orexin-secreting neurons. The narcolepsy seen in two patients with high levels of orexin may have been caused by a mutation of a gene responsible for production of the orexin B receptor.

The symptoms of narcolepsy can be successfully treated with drugs. As we saw, both noradrenergic and serotonergic neurons exert inhibitory control over the acetylcholinergic neurons in the peribrachial area. Sleep attacks are diminished by stimulants such a methylphenidate (Ritalin), a catecholamine agonist (Vgontzas and Kales, 1999). The REM sleep phenomena (cataplexy, sleep paralysis, and hypnagogic hallucinations) can be alleviated by antidepressant drugs, which facilitate both serotonergic and noradrenergic activity (Mitler, 1994; Hublin, 1996). Often, the drugs are given together.

Several years ago, Schenck et al. (1986) reported the existence of an interesting disorder. The formal name is *REM*

cataplexy (*kat* a plex ee) A symptom of narcolepsy; complete paralysis that occurs during waking.

sleep paralysis A symptom of narcolepsy; paralysis occurring just before a person falls asleep.

hypnagogic hallucination (*hip* na *gah jik*) A symptom of narcolepsy; vivid dreams that occur just before a person falls asleep; accompanied by sleep paralysis.

REM without atonia (*ay tone* ee a) A neurological disorder in which the person does not become paralyzed during REM sleep and thus acts out dreams.

(a) (b) (c)

Figure 9.23

A dog undergoing a cataplectic attack triggered by its excitement at finding some food on the floor. (a) Sniffing the food. (b) Muscles beginning to relax. (c) The dog is temporarily paralyzed, as it would be during REM sleep.

(Photos courtesy of the Sleep Disorders Foundation, Stanford University.)

sleep behavior disorder, but a better name is REM without atonia. (*Atonia* refers to the lack of muscular activity seen during paralysis.) As you now know, REM sleep is accompanied by paralysis. Although the motor cortex and subcortical motor systems are extremely active (McCarley and Hobson, 1979), people are unable to move at this time. The fact that they are dreaming suggests the possibility that but for the paralysis, they would act out their dreams. Indeed, they would. The behavior of people who exhibit REM without atonia corresponds with the contents of their dreams. Consider the following case:

> I was a halfback playing football, and after the quarterback received the ball from the center he lateraled it sideways to me and I'm supposed to go around end and cut back over tackle and—this is very vivid—as I cut back over tackle there is this big 280-pound tackle waiting, so I, according to football rules, was to give him my shoulder and bounce him out of the way . . . when I came to I was standing in front of our dresser and I had [gotten up out of bed and run and] knocked lamps, mirrors and everything off the dresser, hit my head against the wall and my knee against the dresser. (Schenck et al., 1986, p. 294)

Like narcolepsy, REM without atonia appears to be an inherited disorder (Schenck et al., 1996). In addition, it can be caused by brain damage—possibly, to the pathway between the subcoerulear region to the magnocellular nucleus (Culebras and Moore, 1989). The symptoms of REM without atonia are the opposite of those of cataplexy; that is, rather than exhibit paralysis outside REM sleep, patients with REM without atonia *fail* to exhibit paralysis *during* REM sleep. As you might expect, the drugs used to treat the symptoms of cataplexy will aggravate the symptoms of REM without atonia (Schenck and Mahowald, 1992). REM without atonia is usually treated by clonazepam, a benzodiazepine (Schenck, Hurwitz, and Mahowald, 1996).

Problems Associated with Slow-Wave Sleep

Some maladaptive behaviors occur during slow-wave sleep, especially during its deepest phase, stage 4. These behaviors include bedwetting *(nocturnal enuresis)*, sleepwalking *(somnambulism)*, and night terrors *(pavor nocturnus)*. All three events occur most frequently in children. Often bedwetting can be cured by training methods, such as having a special electronic circuit ring a bell when the first few drops of urine are detected in the bedsheet (a few drops usually precede the ensuing flood). Night terrors consist of anguished screams, trembling, a rapid pulse, and usually no memory of what caused the terror. Night terrors and somnambulism usually cure themselves as the child gets older. Neither of these phenomena is related to REM sleep; a sleepwalking person is *not* acting out a dream. Most authorities firmly advise that the best treatment for these two disorders is no treatment at all. There is no evidence that they are associated (at least in childhood) with mental disorders or personality variables.

interim summary

Although many people believe that they have insomnia—that they do not obtain as much sleep as they would like—insomnia is not a disease. Insomnia can be caused by depression, pain, illness, or even excited anticipation of a pleasurable event. Far too many people receive sleeping medications, which often lead to a condition called drug dependency insomnia. Sometimes, insomnia is caused

by sleep apnea, which can often be corrected surgically or treated by wearing a mask that delivers pressurized air.

Narcolepsy is characterized by four symptoms. *Sleep attacks* consist of overwhelming urges to sleep for a few minutes. *Cataplexy* is sudden paralysis, during which the person remains conscious. *Sleep paralysis* is similar to cataplexy, but it occurs just before sleep or on waking. *Hypnagogic hallucinations* are dreams that occur during periods of sleep paralysis, just before a night's sleep. Sleep attacks are treated with stimulants such as amphetamine, and the other symptoms are treated with serotonin agonists. Studies with narcoleptic dogs indicate that this disorder can be caused by pathologies in a system of neurons that secrete a nueropeptide known as orexin (or hypocretin). Another disorder associated with REM sleep, REM without atonia, is a genetic disorder that can also be produced by damage to brain stem mechanisms that produce paralysis during REM sleep.

During slow-wave sleep, especially during stage 4, some people are afflicted by bedwetting (nocturnal enuresis), sleepwalking (somnambulism), or night terrors (pavor nocturnus). These problems are most common in children, who usually outgrow them. Only if they occur in adults do they suggest the existence of a physical or psychological disorder.

Biological Clocks

Much of our behavior follows regular rhythms. For example, we saw that the stages of sleep are organized around a 90-minute cycle of REM and slow-wave sleep. The same rhythm continues during the day as the basic rest–activity cycle. And, of course, our daily pattern of sleep and waking follows a 24-hour cycle. Finally, many animals display seasonal breeding rhythms in which reproductive behaviors and hormone levels show yearly fluctuations. In recent years investigators have learned much about the neural mechanisms responsible for these rhythms.

Circadian Rhythms and Zeitgebers

Daily rhythms in behavior and physiological processes are found throughout the plant and animal world. These cycles are generally called **circadian rhythms.** (*Circa* means "about," and *dies* means "day"; therefore, a circadian rhythm is one that varies on a cycle of approximately 24 hours.) Some of these rhythms are passive responses to changes in illumination. However, other rhythms are controlled by mechanisms within the organism—by "internal clocks." For example, Figure 9.24 shows the activity of a rat during various conditions of illumination. Each horizontal line represents 24 hours. Vertical tick marks represent the animal's activity in a running wheel. The upper portion of the figure shows the activity of the rat during a normal day–night cycle, with alternating 12-hour periods of light and dark. Notice that the animal is active during the night, which is normal for a rat. (See *Figure 9.24.*)

Next, the dark–light cycle was shifted by 6 hours; the animal's activity cycle quickly followed the change. (See *Figure 9.24.*) Finally, dim lights were left on continuously. The cyclical pattern in the rat's activity remained. Because there were no cycles of light and dark in the rat's environment, the source of rhythmicity must be located within the animal; that is, the animal must possess an internal, biological clock. You can see that the rat's clock was not set precisely to 24 hours; when the illumination was held constant, the clock ran a bit slow. The animal began its bout of activity almost one hour later each day. (See *Figure 9.24.*)

The phenomenon illustrated in Figure 9.24 is typical of the circadian rhythms shown by many species. A free-running clock, with a cycle a little longer than 24 hours, controls some biological functions—in this case, motor activity. Regular daily variation in the level of illumination (that is, sunlight and darkness) normally keeps the clock adjusted to 24 hours. Light serves as a **zeitgeber** (German

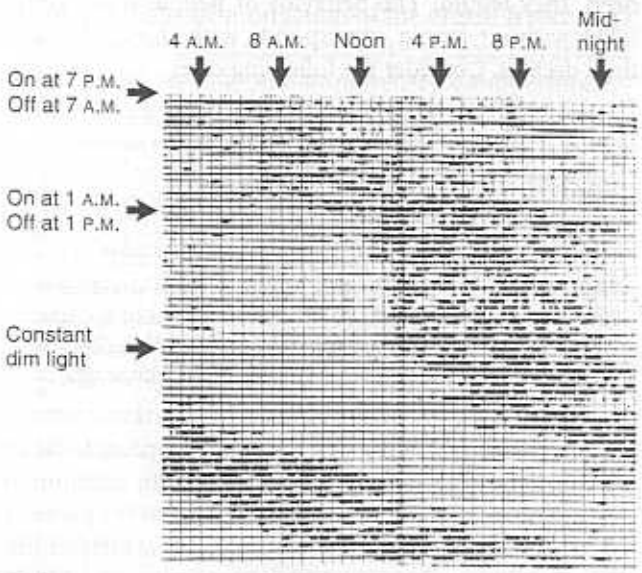


Figure 9.24

Wheel-running activity of a rat. Note that the animal's activity occurs at "night" (that is, during the 12 hours the light is off) and that the active period is reset when the light period is changed. When the animal is maintained in constant dim illumination, it displays a free-running activity cycle of approximately 25 hours. (From Groblewski, T. A., Nuñez, A., and Gold, R. M. Paper presented at the meeting of the Eastern Psychological Association, April 1980.)

for "time giver"); it synchronizes the endogenous rhythm. Studies with many species of animals have shown that if they are maintained in constant darkness (or constant dim light), a brief period of bright light will reset their internal clock, advancing or retarding it, depending upon when the light flash occurs (Aschoff, 1979). For example, if an animal is exposed to bright light soon after dusk, the biological clock is set back to an earlier time—as if dusk had not yet arrived. On the other hand, if the light occurs late at night, the biological clock is set ahead to a later time—as if dawn had already come.

Like other animals, humans exhibit circadian rhythms. Our normal period of inactivity begins several hours after the start of the dark portion of the day–night cycle and persists for a variable amount of time into the light portion. Without the benefits of modern civilization we would probably go to sleep earlier and get up earlier than we do; we use artificial lights to delay our bedtime and window shades to extend our time for sleep. Under constant illumination our biological clocks will run free, gaining or losing time like a watch that runs too slow or too fast. Different people have different cycle lengths, but most people in that situation will begin to live a "day" that is approximately 25 hours long. This works out quite well, because the morning light, acting as a zeitgeber, simply resets the clock.

The Suprachiasmatic Nucleus

Role of the SCN

Researchers working independently in two laboratories (Moore and Eichler, 1972; Stephan and Zucker, 1972) discovered that the primary biological clock of the rat is located in the **suprachiasmatic nucleus** (SCN) of the hypothalamus; they found that lesions disrupted circadian rhythms of wheel running, drinking, and hormonal secretion. The SCN also provides the primary control over the timing of sleep cycles. Rats are nocturnal animals; they sleep during the day and forage and feed at night. Lesions of the SCN abolish this pattern; sleep occurs in bouts randomly dispersed throughout both day and night (Ibuka and Kawamura, 1975; Stephan and Nuñez, 1977). However, rats with SCN lesions still obtain the same amount of sleep that normal animals do. The lesions disrupt the circadian pattern but do not affect the total amount of sleep.

Figure 9.25 shows the suprachiasmatic nuclei in a cross section through the hypothalamus of a mouse; they appear as two clusters of dark-staining neurons at the base of the brain, just above the optic chiasm. (See *Figure 9.25.*) The suprachiasmatic nuclei of the rat consist of approximately ten thousand small neurons, tightly packed into a volume of between 0.1 and 0.3 mm^3 (Meijer and Rietveld, 1989).

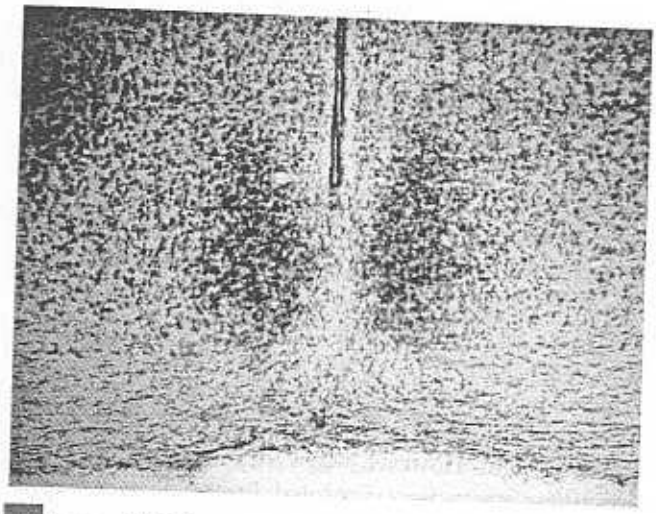


Figure 9.25

A cross section through a rat brain, showing the location and appearance of the suprachiasmatic nuclei. Cresyl violet stain. (Courtesy of Geert DeVries, University of Massachusetts.)

The dendrites of these neurons form synapses with one another—a phenomenon that is found only in this part of the hypothalamus and that probably relates to the special function of these nuclei. A group of neurons is found clustered around the capillaries that serve the SCN. These neurons contain a large amount of rough endoplasmic reticulum, which suggests that they may be neurosecretory cells (Card, Riley, and Moore, 1980; Moore, Card, and Riley, 1980). Thus, some of the control that the SCN exerts over other parts of the brain may be accomplished by the secretion of neuromodulators.

Because light is the primary zeitgeber for most mammals' activity cycles, we would expect that the SCN receives fibers from the visual system. Indeed, anatomical studies have revealed a direct projection of fibers from the retina to the SCN: the *retinohypothalamic pathway* (Hendrickson, Wagoner, and Cowan, 1972; Aronson et al., 1993). If you look carefully at Figure 9.25, you can see small dark spots within the optic chiasm, just ventral and medial to the base of the SCN; these are cell bodies of oligodendroglia that serve axons that enter the SCN and provide information from the retina. (See *Figure 9.25.*)

circadian rhythm (*sur kay dee un* or *sur ka dee un*) A daily rhythmical change in behavior or physiological process.

zeitgeber (*tsite gay ber*) A stimulus (usually the light of dawn) that resets the biological clock responsible for circadian rhythms.

suprachiasmatic nucleus (SCN) (*soo pra ky az mat ik*) A nucleus situated atop the optic chiasm. It contains a biological clock responsible for organizing many of the body's circadian rhythms.

The photoreceptors in the retina that provide photic information to the SCN appear to be neither rods nor cones—the cells that provide us with the information used for visual perception. Mice with a genetic disorder that causes degeneration of retinal photoreceptors—total degeneration of rods and near-total degeneration of cones—are still as sensitive to light as those of normal mice, even though they are totally blind (Foster et al., 1991; Jiminez et al., 1996). These results suggest that there is a special photoreceptor that is responsible for synchronization of diurnal rhythms. Indeed, Freedman et al. (1999) found that targeted mutations against genes necessary for production of both rods and cones did not disrupt the synchronizing effects of light. However, when they removed the mice's eyes, these effects *were* disrupted. Provencio et al. (2000) may have found the photochemical and the receptive cells responsible for these effects. They discovered a chemical that they named *melanopsin,* which is produced by a gene on chromosome 10 in humans. In the human, mouse, and monkey eye, cells containing this opsin are found not in the region that contains rods and cones, but in the region where amacrine cells and ganglion cells are located. In fact, the melanopsin-containing cells are located in a region of cells that project to the SCN.

Pulses of light that reset an animal's circadian rhythm trigger the production of Fos protein in the SCN, which indicates that the light initiates a period of neural activity in this nucleus (Rusak et al., 1990, 1992). The synaptic connections between the retina and the SCN appear to be glutamatergic; drugs that block glutamate receptors prevent a period of bright light from stimulating Fos production and resetting circadian rhythms (Abe, Rusak, and Robertson, 1991; Vindlacheruvu et al., 1992).

Besides receiving visual information directly from the retina via the retinohypothalamic pathway, the SCN also receives such information indirectly, from the **intergeniculate leaflet (IGL)**, a part of the lateral geniculate nucleus (Aronson et al., 1993; Moore and Card, 1994). (You will recall from Chapter 6 that the *dorsal* lateral geniculate nucleus sends visual information to the striate cortex.) The IGL receives photic information from the retina; in fact, the axons of the retinohypothalamic pathway divide near the optic chiasm and send one collateral to the SCN and another to the IGL. The terminal buttons of the neurons that connect the IGL to the SCN corelease GABA and a substance called **neuropeptide Y.** The connection between the IGL and the SCN (the *geniculohypothalamic pathway*) appears to play a role in resetting circadian rhythms; electrical stimulation of the IGL leaflet or microinfusion of neuropeptide Y directly into the SCN shifts the timing of circadian rhythms (Albers and Ferris, 1984; Rusak, Meijer, and Harrington, 1989). Damage to the geniculohypothalamic pathways reduces, but does not abolish, the effects of changes in the light–dark cycle on an animal's circadian rhythms (Harrington and Rusak, 1986). Thus, both the direct pathway from the retina to the SCN and the indirect pathway through the thalamus mediate the effects of light as a zeitgeber.

Evidence suggests that the IGL plays a special role in mediating the effects of zeitgebers other than light. Although light is the most potent stimulus for resetting circadian rhythms, other environmental stimuli, such as loud noises or sudden changes in temperature, can do so, too. In addition, an animal's own activity can affect its circadian rhythm. For example, if a hamster is suddenly given access to a running wheel, its burst of activity in the wheel will advance or retard the animal's circadian rhythm, according to the time of day during which the access occurs (Reebs and Mrosovsky, 1989; Wickland and Turek, 1991). Wickland and Turek (1994) found that this effect was abolished by lesions of the IGL. Thus, it appears that the geniculohypothalamic tract connecting the IGL with the SCN is the sole pathway for at least one zeitgeber. More recently, Amir and Stewart (1996) found that zeitgebers could be classically conditioned. They found that after a neutral stimulus had been paired with bright lights, this stimulus could itself serve as a zeitgeber, provoking the production of Fos in the SCN and resetting circadian activity rhythms. It would be interesting to see whether damage to the IGL would disrupt this effect, too.

How does the SCN control drinking, eating, sleep cycles, and hormone secretion? Neurons of the SCN project caudally to the midbrain and to other hypothalamic nuclei, dorsally to other diencephalic regions, and rostrally to other hypothalamic nuclei and to the septum. If all of these connections are severed by large semicircular knife cuts around most of the SCN, circadian rhythms are disrupted (Meijer and Rietveld, 1989). However, we cannot conclude that the effects result from damage to efferent axons of the SCN. For one thing, knife cuts do not simply sever axons; they also cut blood vessels and interrupt patterns of blood flow. In addition, transplantation studies suggest that the control that the SCN exerts over some functions may be mediated by the secretion of chemical signals.

Lehman et al. (1987) destroyed the SCN and then transplanted in their place a new set of suprachiasmatic nuclei obtained from donor animals. The grafts succeeded in reestablishing circadian rhythms, even though very few efferent connections were observed between the graft and the recipient's brain. More recent studies have shown that the

intergeniculate leaflet (IGL) A part of the lateral geniculate nucleus that receives information from the retina and projects to the SCN.

neuropeptide Y A peptide released by the terminals of the neurons that project from the IGL to the SCN.

transplant need not even be placed in the normal location of the SCN. Aguilar-Roblero et al. (1994) found that SCN tissue restored circadian rhythms in a recipient animal if it was transplanted into the lateral ventricle, dorsal third ventricle, or caudal third ventricle adjacent to the cerebral aqueduct. The fact that the placement of the transplant was not critical suggests that the circadian rhythms may be controlled by chemicals secreted by the SCN tissue and carried to the critical regions of the brain through the cerebrospinal fluid. But the most convincing evidence comes from a transplantation study by Silver et al. (1996). Silver and her colleagues first destroyed the SCN in a group of hamsters, abolishing their circadian rhythms. Then, a few weeks later, they removed SCN tissue from donor animals and placed it in tiny semipermeable capsules, which they then implanted in the animals' third ventricles. Nutrients and other chemicals could pass through the walls of the capsules, keeping the SCN tissue alive, but the neurons inside the capsules were not able to establish synaptic connections with the surrounding tissue. Nevertheless, the transplants reestablished circadian rhythms in the recipient animals. The identity of the chemical signal is not yet known.

Recently, LeSauter and Silver (1999) discovered that a subregion of the SCN composed of neurons that contain a particular calcium-binding protein (calbindin-D_{28K}) is critical for circadian rhythms controlling circadian activity cycles. Neurons in this region receive direct input from the retina, and most of them increase their production of Fos protein when the animal is exposed to light (Silver et al., 1996). Lesions of the SCN that spare this subregion do not affect circadian activity cycles, but lesions that destroy it do. In addition, transplants of SCN tissue restore circadian activity cycles in recipient animals with SCN lesions only if the grafts contain neurons from this subregion. These results suggest that the circadian clock may reside in these neurons; what functions are performed by the rest of the SCN are not known. (See *Figure 9.26.*)

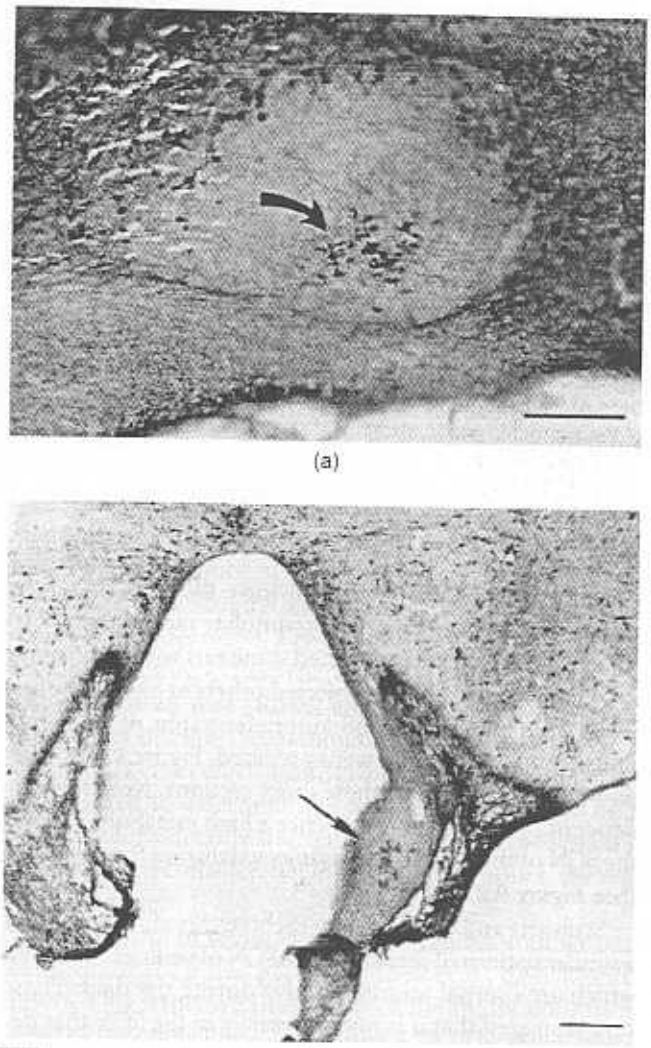


Figure 9.26

A cluster of neurons in the SCN that are responsible for circadian activity rhythms. (a) Photomicrograph of neurons in the SCN stained for the presence of calbindin$_{28K}$. (b) Photomicrograph of transplanted SCN tissue in a rat whose SCN was previously destroyed. The graft, which contains a small group of neurons containing calbindin$_{28K}$ (arrow), restored circadian activity cycles to the recipient animal.

(From LeSauter, J., and Silver, R. *Journal of Neuroscience*, 1999, *19*, 5574–5585.)

The Nature of the Clock

All clocks must have a time base. Mechanical clocks use flywheels or pendulums; electronic clocks use quartz crystals. The SCN, too, must contain a physiological mechanism that parses time into units. After years of research, investigators are finally beginning to discover the nature of the biological clock in the SCN.

First, let us examine some evidence that the SCN does, in fact, contain a clock. So far, we have seen that zeitgebers act through their connections with the SCN. We have also seen that circadian rhythms require that the animal have an intact SCN or a transplant placed in or near the lateral or third ventricles. However, I have not yet described evidence that proves that a clock is located there; the clock could be located elsewhere but fail to run unless it is exposed to chemicals secreted by the SCN.

Several studies have demonstrated daily activity rhythms in the SCN, which indicates that the circadian clock is located there. A study by Schwartz and Gainer (1977) nicely demonstrated day–night fluctuations in the activity of the SCN. These investigators injected rats with radioactive 2-deoxyglucose (2-DG). As you will recall from Chapter 5, this chemical is structurally similar to ordinary glucose; thus, it is taken up by cells that are metabolically active. However,

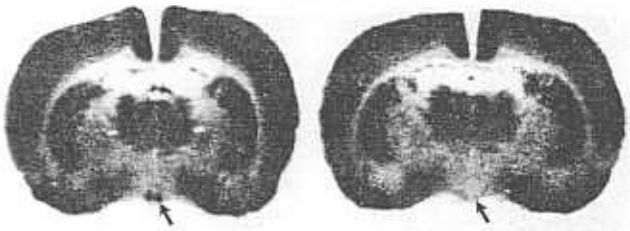


Figure 9.27

Autoradiographs of cross sections through the brains of rats that had been injected with carbon-14-labeled 2-deoxyglucose during the day (*left*) and the night (*right*). The dark region at the base of the brain (*arrows*) indicates increased metabolic activity of the suprachiasmatic nuclei.

(From Schwartz, W. J., and Gainer, H. *Science, 1977, 197,* 1089–1091. Reprinted with permission.)

it cannot be utilized, nor can it leave the cell. Therefore, metabolically active cells will accumulate radioactivity.

Schwartz and Gainer injected some rats with radioactive 2-DG during the day and injected others at night. The animals were then killed, and autoradiographs of cross sections through the brain were prepared. Figure 9.27 shows photographs of two of these cross sections. Note the evidence of radioactivity (and hence a high metabolic rate) in the SCN of the brain that was injected during the day (*left*). (See *Figure 9.27.*)

Schwartz and his colleagues (Schwartz et al., 1983) found a similar pattern of activity in the SCN of squirrel monkeys, which are diurnal animals (active during the day). These results suggest that it is not differences in the SCN that determine whether an animal is nocturnal or diurnal but differences elsewhere in the brain. The SCN keeps track of day and night, but it is up to mechanisms located elsewhere to determine when the animal is to be awake or asleep.

The "ticking" of the biological clock within the SCN could involve interactions of circuits of neurons, or it could be intrinsic to individual neurons themselves. Evidence suggests the latter—that each neuron contains a clock. Several studies have succeeded in keeping individual SCN neurons alive in a culture medium. For example, Welsh et al. (1995) removed tissue from the rat SCN and dissolved the connections between the cells with papain, an enzyme sometimes used as a meat tenderizer. The cells were placed on top of an array of microelectrodes so that their electrical activity could be measured. Although these neurons did reestablish synaptic connections with each other, they displayed individual, independent, circadian rhythms in activity. Figure 9.28 shows the activity cycles of four neurons. As you can see, all showed circadian rhythms, but their periods of peak activity occurred at different times of day. (See *Figure 9.28.*)

As we have just seen, evidence indicates that "ticking" occurs in individual neurons. But the activity cycles of neurons in the SCN of an intact animal are all synchronized—their peaks of activity occur at the same time each day. What synchronizes these cycles? The most obvious answer would seem to be the synaptic connections between them. However, studies have shown this explanation to be incorrect. For example, Bouskila and Dudek (1993) prepared slices of the rat hypothalamus that included the SCN and kept them alive in a culture medium. They found that the activity cycles of the neurons were all synchronized. The investigators then placed the slices in a culture medium that contained no calcium. As we saw in Chapter 2, the release of neurotransmitter requires the entry of calcium into the terminal button; thus, the lack of extracellular calcium blocks synaptic transmission. Despite the

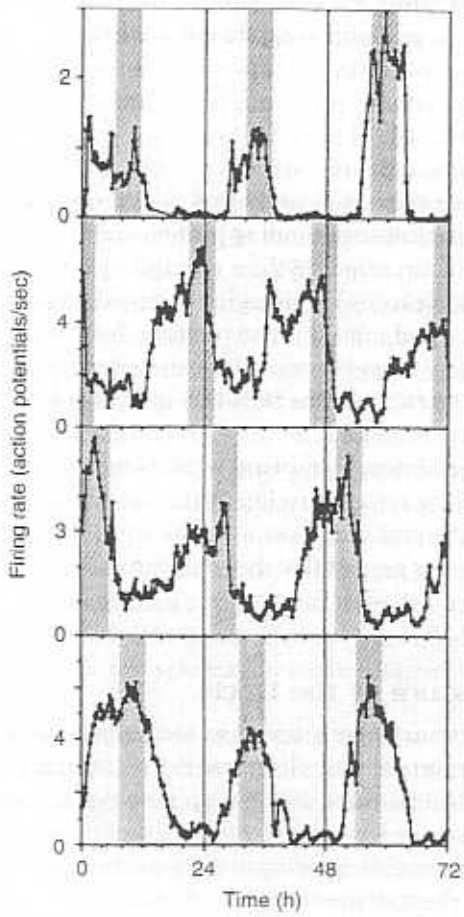


Figure 9.28

Firing rate of individual SCN neurons in a tissue culture. Color bars have been added to emphasize the daily peaks. Note that although each neuron has a period of approximately one day, their activity cycles are not synchronized.

(From Welsh, D. K., Logothetis, D. E., Meister, M., and Reppert, S. M. *Neuron, 1995, 14,* 697–706.)

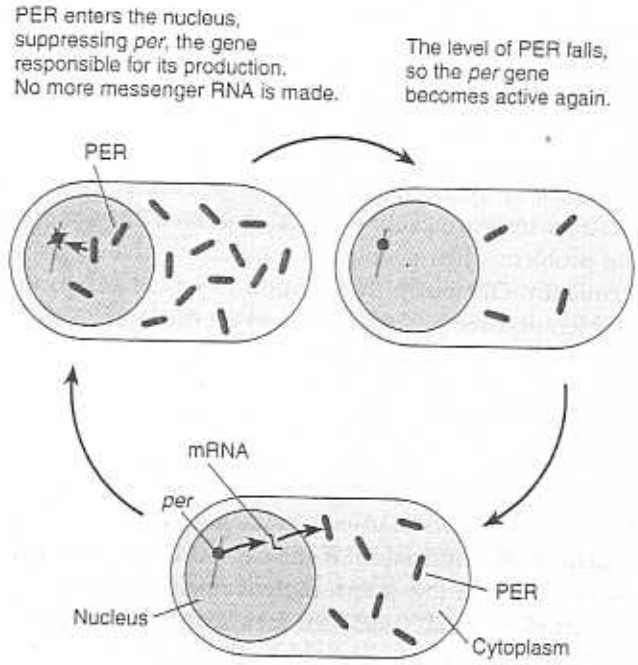


Figure 9.29

A schematic explanation of the hypothesized role of PER and TIM in control of circadian rhythms in the fruit fly.

absence of synaptic activity, the activity cycles of the SCN neurons in the slice remained synchronized. The most likely explanation is that the neurons (or perhaps the glial cells that surround them) release chemicals that synchronize their activity.

What causes intracellular ticking? For many years investigators have believed that circadian rhythms were produced by the production of a protein that, when it reached a certain level in the cell, inhibited its own production. As a result, the levels of the protein would begin to decline, which would remove the inhibition, starting the production cycle again. Studies with *Drosophila melanogaster*, the common fruit fly, have found just such a mechanism (Hunterensor, Ousley, and Sehgal, 1996; Lee et al., 1996; Myers et al., 1996; Zeng et al., 1996). At the beginning of a cycle, two genes, *per* and *tim*, become active and cause the production of two proteins: PER and TIM (short for *period* and *timeless*). When a sufficient level of these proteins accumulates, they bind with other proteins in the nucleus and turn off the *per* and *tim* genes. Eventually, the levels of PER and TIM decline, and the *per* and *tim* genes become active again, beginning the next cycle.

Researchers have discovered genes in rodents that are very similar to the *per* and *tim* genes in fruit flies. However, only the PER protein is found in appreciable amounts in the SCN. Furthermore, the levels of PER (actually, there are three variants of this protein) vary across the day–night cycle, suggesting that the mechanism responsible for the ticking of the mammalian clock may have evolved long ago (Sangoram et al., 1998, Zylka et al., 1998; Zheng et al., 1999). (See *Figure 9.29.*)

Control of Seasonal Rhythms: The Pineal Gland and Melatonin

Although the SCN has an intrinsic rhythm of approximately 24 hours, it plays a role in much longer rhythms. (We could say that it is involved in a biological calendar as well as a biological clock.) Male hamsters show annual rhythms of testosterone secretion, which appear to be based on the amount of light that occurs each day. Their breeding season begins as the day length increases and ends when it decreases. Lesions of the SCN abolish these annual breeding cycles; the animals' testes then secrete testosterone all year (Rusak and Morin, 1976). Possibly, the lesions disrupt these annual cycles because they destroy the 24-hour clock against which the daily light period is measured to determine the season. That is, if the light period is considerably shorter than 12 hours, the season is winter; if it is considerably longer than 12 hours, the season is summer.

The control of seasonal rhythms involves another part of the brain: the **pineal gland** (Bartness et al., 1993; Moore, 1995). This structure sits on top of the midbrain, just in front of the cerebellum. (See *Figure 9.30.*) The pineal gland secretes a hormone called **melatonin**, so named because it has the ability in certain animals (primarily fish, reptiles, and amphibians) to turn the skin temporarily dark. (The dark color is produced by a chemical known as *melanin.*) In mammals melatonin controls seasonal rhythms. Neurons in the SCN make synaptic connections with neurons in the *paraventricular nucleus of the hypothalamus* (the PVN). The axons of these neurons travel all the way to the spinal cord, where they form synapses with preganglionic neurons of the sympathetic nervous system. The postganglionic neurons innervate the pineal gland and control the secretion of melatonin.

In response to input from the SCN, the pineal gland secretes melatonin during the night. This melatonin acts back

pineal gland (*py nee ul*) A gland attached to the dorsal tectum; produces melatonin and plays a role in circadian and seasonal rhythms.

melatonin (*mell a tone in*) A hormone secreted during the night by the pineal body; plays a role in circadian and seasonal rhythms.

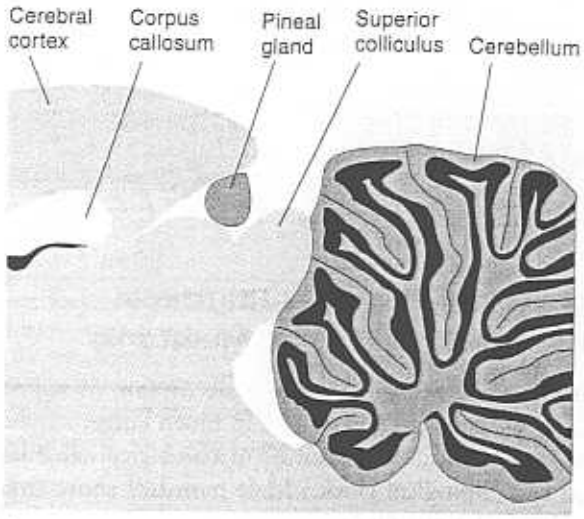


Figure 9.30

The pineal gland, located on the dorsal surface of the midbrain. (Adapted from Paxinos, G., and Watson, C. *The Rat Brain in Stereotaxic Coordinates*. Sydney: Academic Press, 1982. Redrawn with permission.)

on various structures in the brain (including the SCN, whose cells contain melatonin receptors) and controls hormones, physiological processes, and behaviors that show seasonal variations. During long nights a large amount of melatonin is secreted, and the animals go into the winter phase of their cycle. Lesions of the SCN, the paraventricular nucleus (PVN), or the pineal gland disrupt seasonal rhythms that are controlled by day length—and so do knife cuts that interrupt the neural connection between the SCN and the PVN, which indicates that this is one function of the SCN that is mediated through its neural connections with another structure. Furthermore, although transplants of fetal suprachiasmatic nuclei will restore circadian rhythms, they will not restore seasonal rhythms, because the transplanted tissue does not establish neural connections with the PVN (Ralph and Lehman, 1991).

Changes in Circadian Rhythms: Shift Work and Jet Lag

When people abruptly change their daily rhythms of activity, their internal circadian rhythms, controlled by the SCN, become desynchronized with those in the internal environment. For example, if a person who normally works on the day shift begins working on a night shift or if someone travels east or west across several time zones, his or her SCN will signal the rest of the brain that it is time to sleep during the work shift (or the middle of the day, in the case of jet travel). This disparity between internal rhythms and the external environment results in sleep disturbances and mood changes and interferes with people's ability to function during waking hours.

Jet lag is a temporary phenomenon; after several days, people who have crossed several time zones find it easier to fall asleep at the appropriate time, and their daytime alertness improves. Shift work can present a more enduring problem when people are required to change shifts frequently. Obviously, the solution to jet lag and to the problems caused by shift work is to get the internal clock synchronized with the external environment as quickly as possible. The most obvious way to start is to try to provide strong zeitgebers at the appropriate time. If a person is exposed to bright light before the low point in the daily rhythm of body temperature (which occurs an hour or two before the person usually awakens), the person's circadian rhythm is delayed. If the exposure to bright light occurs after the low point, the circadian rhythm is advanced (Dijk et al., 1995). In fact, several studies have shown that exposure to bright lights at the appropriate time help to ease the transition (Boulos et al., 1995). Houpt, Boulos, and Moore-Ede (1996) have even developed a computer program that helps to determine the optimal pattern of light exposure to minimize the effects of jet travel between various parts of the world. Similarly, people adapt to shift work more rapidly if artificial light is kept at a brighter level and if their bedroom is kept as dark as possible (Eastman et al., 1995).

As we saw in the previous subsection, the role of melatonin in seasonal rhythms is well established. Studies in recent years suggest that melatonin may also be involved in circadian rhythms. As we saw, melatonin is secreted during the night, which, for diurnal mammals such as ourselves, is the period during which we sleep. But although our species lacks strong seasonal rhythms, the daily rhythm of melatonin secretion persists. Thus, melatonin must have some functions besides regulation of seasonal rhythms.

Recent studies have found that melatonin, acting on receptors in the SCN, can affect the sensitivity of SCN neurons to zeitgebers and can itself alter circadian rhythms (Gillette and McArthur, 1995; Starkey et al., 1995). Researchers do not yet understand exactly what role melatonin plays in the control of circadian rhythms, but they have already discovered practical applications. Melatonin secretion normally reaches its highest levels early in the night, at around bedtime. Investigators have found that the administration of melatonin at the appropriate time (in most cases, just before going to bed) significantly reduces the adverse effects of both jet lag and shifts in work schedules (Arendt et al., 1995; Deacon and Arendt, 1996). Bedtime melatonin has even helped synchronize circadian rhythms and improved the sleep of blind people for whom

light cannot serve as a zeitgeber (Skene, Lockley, and Arendt, 1999).

interim summary

Our daily lives are characterized by cycles in physical activity, sleep, body temperature, secretion of hormones, and many other physiological changes. Circadian rhythms—those with a period of approximately one day—are controlled by biological clocks in the brain. The principal biological clock appears to be located in the suprachiasmatic nuclei of the hypothalamus; lesions of these nuclei disrupt most circadian rhythms, and the activity of neurons located there correlates with the day–night cycle. Light, detected by special cells in the retina that are not involved in visual perception, serves as a zeitgeber for most circadian rhythms. That is, the biological clocks tend to run a bit slow, with a period of approximately 25 hours. The sight of sunlight in the morning is conveyed from the retina to the SCN—directly and via the IGL of the lateral geniculate nucleus. The effect of the light is to reset the clock to the start of a new cycle.

Individual neurons, rather than circuits of neurons, are responsible for the "ticking." Studies with tissue cultures suggest that synchronization of the firing patterns of individual neurons is accomplished by means of chemical communication between cells, perhaps involving astrocytes. In the fruit fly, two genes, *tim* and *per*, are responsible for circadian rhythms. These genes' proteins (TIM and PER) bind, travel to the nucleus, and inhibit further protein synthesis until they disintegrate and the cycle begins again. Studies with rodents suggest that a similar mechanism exists in mammals.

The SCN and the pineal gland control annual rhythms. During the night the SCN signals the pineal gland to secrete melatonin. Prolonged melatonin secretion, which occurs during winter, causes the animals to enter the winter phase of their annual cycle. Melatonin also appears to be involved in synchronizing circadian rhythms: The hormone can help people to adjust to the effects of shift work or jet lag and even synchronize the daily rhythms of blind people for whom light cannot serve as a zeitgeber.

suggestedreadings

Hastings, J. W., Rusak, B., and Boulos, Z. Circadian rhythms: The physiology of biological timing. In *Neural and Integrative Animal Physiology*, edited by C. L. Prosser. New York: Wiley-Liss, 1991.

Horne, J. *Why We Sleep: The Functions of Sleep in Humans and Other Mammals.* Oxford: Oxford University Press, 1988.

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Mancia, M., and Marini, G. *The Diencephalon and Sleep.* New York: Raven Press, 1990.

Moorcroft, W. H. *Sleep, Dreaming, and Sleep Disorders: An Introduction.* Lanham, MD: University Press of America, 1993.

Schwartz, W. J. *Sleep Science: Integrating Basic Research and Clinical Practice.* Basel: Karger, 1997.

Webb, W. *Sleep: The Gentle Tyrant,* 2nd ed. Bolton, MA: Anker, 1992.

suggestedwebsites

The Sleep Well

http://www.stanford.edu/~dement/alphaindex.html

The topic of sleep is the focus of this site. The Sleep Well site provides a number of links to basic research on sleep and to sites that cover sleep disorders.

SleepNet

http://www.sleepnet.com/

SleepNet contains a forum on sleep issues, a set of links to sleep lab sites and to sleep disorders. In addition, the site contains a column written by the sleep scientist Dr. William Dement.

Basics of Sleep Behavior

http://bisleep.medsch.ucla.edu/sleepsyllabus/

This site provides coverage on a number of sleep lecture topics including NREM and REM sleep, chemical and neuronal control of sleep, and sleep functions.

National Centers on Sleep Disorders Research

http://www.nhlbi.nih.gov/about/ncsdr/

This NIH site provides an interactive quiz on sleep, and contains a series of fact sheets and education materials on sleep and sleep disorders.

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