Chapter 10

Sleep in Animals: A State of Adaptive Inactivity

Jerome M. Siegel

Chapter Highlights

- In most adult animals sleep is incompatible with mating and feeding. Many researchers view animals as being highly vulnerable to predation during sleep. Why do animals devote from 2 to 20 hours of the day to sleep, in what appears to be a nonproductive state? Why has evolution preserved this state?The presence of sleep in nearly all animals and the enormous variation in sleep time across species are best explained as adaptations to ecologic and energy demands.
- Sleep is not a maladaptive state that needs to be explained by undiscovered functions (which nevertheless undoubtedly exist). Rather, the major function of sleep is to increase behavioral efficiency. Greater waking activity does not necessarily lead to increased numbers of viable offspring and, hence, genetic success. Rather, genetic success is closely linked to the efficient use of resources and to the avoidance of risk. Thus, inactivity can reduce predation and injury. It also reduces brain and body energy consumption. As often stated, energy conservation is not a sufficient explanation for sleep, because the energy saved in a night's sleep in humans is only equivalent to that contained in a slice of bread. In the wild, however, most animals are hungry and are seeking food most of the time they are awake. If ample food is available, the population of a species quickly expands until faced again with food scarcity, a phenomenon that is illustrated by the great increase in the human population.
- The ability of sleep to conserve energy when food is scarce constitutes a major survival benefit even if only a small amount of energy is saved. Conversely, if food is available but is time-consuming to acquire, it is highly advantageous for animals to be able to reduce sleep time without behavioral impairment. Similarly, it is highly advantageous to reduce or eliminate sleep to allow migration and to respond to certain other needs. Several examples of extended periods of elimination or substantial sleep reduction without rebound have recently been documented and appear to be strongly linked to species success.
- Many researchers have assumed that predation risk is increased during sleep—that more animals are killed per hour during sleep than during waking. However there is scant evidence to support this contention. Most animals seek safe sleeping sites, often underground, in trees or in groups that provide communal protection. Those large herbivores that cannot find safe sleeping sites appear to require smaller amounts of sleep and to sleep less deeply. Large animals that are not at risk for predation, such as big cats and bears, can sleep for long periods, often in unprotected sites, and appear to sleep deeply.

ADAPTIVE INACTIVITY

Sleep should be viewed in the context of other forms of so-called *adaptive inactivity*. Most forms of life have evolved mechanisms that permit the reduction of metabolic activity for long periods of time when conditions are not optimal. In animals, this usually includes a reduction or cessation of movement and sensory response. The development of dormant states was an essential step in the evolution of life, and dormancy continues to be essential for the preservation of many organisms. Many species have evolved seasonal dormancy patterns that allow them to anticipate periods that are not optimal for survival and propagation (predictive dormancy, including hibernation). In other species, dormancy is triggered by environmental conditions (consequential dormancy). Many organisms spend most of their lifespan in dormancy, becoming active only when conditions are optimal. A continuum of states of adaptive inactivity can be seen in living organisms including plants, unicellular and multicellular animals, and animals with and without nervous systems.[1]

In the plant kingdom, seeds often are dormant until the correct season, heat, moisture, and pH conditions are present. A documented example of markedly delayed emergence was production of a healthy tree from a lotus seed after a 1300-year period of dormancy.[2] In another, more recent report, a 2000-year-old date palm seed produced a viable sapling.[3] Some forms of vegetation can germinate only after fires that may come decades apart. These include the giant sequoias native to the U.S. Southwest, as well as many other species of trees and grass. Most deciduous trees and plants have seasonal

periods of dormancy during which they cease photosynthesis, a process called abscission. These periods of dormancy enhance plant survival by synchronizing growth to optimal conditions. Clearly this mechanism has evolved to time germination to optimal conditions. Energy savings is not the only reason for dormancy in plants or animals.

Many unicellular organisms (protozoans) have evolved to live in environments that can sustain them for only portions of the year, because of changes in temperature, water availability, or other factors. Their survival requires that they enter dormant states that can be reversed when optimal conditions reappear.

A tiny colony of yeast trapped inside a Lebanese weevil covered in ancient Burmese amber for up to 45 million years has been brought back to life and used to brew a modern beer.[4] Rotifers, a group of small multicellular organisms of microscopic or submicroscopic size (up to 0.5 mm long), have extended dormant periods lasting from days to months in response to environmental stresses, including lack of water or food.[5,6]

Parasites can become dormant within the host animal's tissues for years, emerging during periods when the immune system is compromised.[7] Some invertebrate parasites have extended dormant periods, defending themselves by forming a protective cyst.[8] In some cases the cyst can be dissolved and the parasite activated only by digestive juices. Many sponges have a similar dormant state that allows them to survive suboptimal conditions by being encased in "gemmules."

Insect dormancy or diapause can be seasonal, lasting several months; anecdotal reports indicate that under some conditions, diapause can last for several years to as long as a century.[9] This can occur in an embryologic, larval, pupal, or adult stage. During diapause, insects are potentially vulnerable to predation, as are some sleeping animals. Passive defense strategies are employed, such as entering dormancy underground or in hidden recesses, having hard shells, and tenacious attachment to substrates. In a few cases, insects have evolved a vibrational defensive response that is elicited when pupae are disturbed. Land snails and slugs can secrete a mucous membrane for protection and enter a dormant state when conditions are not optimal.[10]

Reptiles and amphibia that live in lakes that either freeze or dry seasonally and snakes that live in environments with periods of cold or extreme heat have the ability to enter dormant states (called *brumination* in reptiles). These dormant periods may occur just during the cool portion of the circadian cycle or may extend for months in winter.[11] *Estivation* is a form of dormancy that occurs during warm periods, typically during summer. It allows reptiles, amphibia, fish, and insects[12-16] to emerge with the first rains from what had been a barren, apparently lifeless lakebed.

In the mammalian class, a continuum of states ranging from dormancy to continuous activity can be seen. Small animals that cannot migrate long distances and live in temperate or frigid environments often survive the winter by hibernating. Some bats and many species of rodents, marsupials, and insectivores hibernate. This condition is entered from, and generally terminates in, non–rapid eye movement (NREM) sleep periods. During *hibernation,* body temperature can be reduced to below 10° C, down to as low as –3° C, with greatly reduced energy consumption.[17,18] Animals are quite difficult to arouse during hibernation, with full arousal taking many minutes. Consequently, hibernators are vulnerable to predation and survive hibernation by seeking protected sites. *Torpor*[17] is another form of dormancy that can be entered by mammals and birds daily. Torpor is entered and exited through sleep and can recur in a circadian rhythm or can last for weeks or months. Animals in shallow torpor are less difficult to arouse than hibernating animals but are still unable to respond quickly when stimulated. Some other mammals such as bears enter extended periods of sleep in the winter during which their metabolic rate and body temperature are reduced by 4° to 5° C,[19] but they remain more responsive than animals in torpor.

Sleep can be seen as a form of adaptive inactivity lying on this continuum. What is most remarkable about sleep is not the unresponsiveness or vulnerability it creates but rather its ability to reduce activity and body and brain metabolism but still allow a high level of responsiveness relative to the states of dormancy just described. The often-cited example of a parent's arousing at a baby's whimper but sleeping through a thunderstorm illustrates the ability of the sleeping human brain to continuously process sensory signals during the sleep period and trigger complete awakening to significant stimuli within a few hundred milliseconds. This capacity is retained despite the great reduction in brain energy consumption achieved in sleep relative to quiet waking.[20,21]

Adolescent humans are less responsive than adults to stimuli presented during sleep, as anyone who has lived with teenagers can attest. This trait may have been selected for by evolution, because protection from predators normally is provided by older members of the family group who also tend to the nocturnal needs of infants. The inactivity of children benefits the group by reducing their relatively large portion of the family's food needs and diverting food energy to growth, rather than activity.

Some animals that live in climates with a pronounced seasonal reduction in food or light availability or a periodic increase in threat from predators may need to migrate to survive. Many species of birds do this, as do certain species of marine mammals (see later). Although some may maintain circadian rhythms of activity during migration, others remain continuously active for weeks or months. Some vertebrate species do not ever appear to meet the behavioral criteria for sleep, remaining responsive, or responsive and active, throughout their lifetime.[22]

Humans with insomnia typically are not sleepy during the day despite a reduced (or in many cases normal) duration of nighttime sleep. With respect to their sleep pattern, they may be viewed as falling closer to migrating animals or short-sleeping animals, in contrast with humans with sleep disturbed by sleep deprivation, sleep apnea, or pain, who are sleepy during the day.[23] Patients with restless legs syndrome are similarly unlikely to be sleepy during the day despite low levels of nightly sleep. Conversely, many people with hypersomnia appear to need more sleep and in fact sleep more deeply, rather than being the victims of a shallow or disrupted sleep that is compensated for by extended sleep time. Perhaps such persons may be expressing genes and behaviors that were highly adaptive in distant phylogenetic ancestors needing to reduce energy consumption.

To summarize, evolution has produced a wide range of forms of diurnal or seasonal "adaptive inactivity," some of which are accompanied by a virtual cessation of metabolism

and responsiveness. Clearly, evolution rewards judicious activity, not continuous activity. Sleep often is viewed as a liability because of the associated reduced alertness in comparison with quiet waking. However, seen in the context of adaptive inactivity shown by most species, what is most notable about sleep in humans is its intermediate status, between the highly inactive unresponsive states seen in rotifers, insects, and hibernating mammals (which show little neuronal activity during hibernation) and the virtually continuous periods of activity and wakefulness that have been seen in migrating birds and cetaceans.

QUANTITATIVE ANALYSES OF THE CORRELATES OF SLEEP DURATION IN MAMMALS

Many studies have attempted to correlate the data that have been collected on sleep duration in mammals with physiologic and behavioral variables, to develop hypotheses regarding the function of sleep. The data on which these studies are based are not ideal. Only approximately 70 mammalian species have been studied with sufficient measurements to determine the amounts of REM and NREM sleep over the 24-hour period. These are by no means a random sample of the more than 5000 mammalian species. Rather, they are species that are viable and available for study in laboratories or, in some instances, for noninvasive (and less accurate) studies in zoos.

In laboratories, animal subjects for sleep studies typically are fed ad libitum and are housed at relatively invariant, thermoneutral temperatures and on artificial light cycles. These environments differ greatly from those in which they evolved. Digital recording and storage technologies now exist that will enable the collection of polygraphic data on animals in their natural environments,[24] but they have not yet been widely used. Such observations are necessary to determine the variation in sleep times caused by hunger, response to temperature changes, predation and the other variables that have driven evolution. Very few of these animals have been tested for arousal threshold, the nature and extent of sleep rebound, and other aspects of sleep whose variation across species may potentially contribute to an understanding of sleep evolution and function. An important issue in comparing sleep times in animals is determining sleep depth. In humans, sleep depth, as assessed by either arousal threshold or EEG amplitude, increases after sleep deprivation and often is greater during early stages of development when total sleep time is greatest. Can sleep time be profitably compared across animals without incorporating information on sleep depth? Can it be assumed that animals that sleep for longer periods also sleep more deeply, as is true across human development, or is the reverse more likely—that short-sleeping animals sleep more deeply as has been hypothesized[25]? It would be best not to make either assumption; any conclusions should be based on hard evidence about these dimensions of sleep.

One of the earliest studies comparing REM and NREM sleep durations with physiologic variables found that sleep duration was inversely correlated with body mass.[26,27] A subsequent analysis found that this relationship applied only to herbivores, not to carnivores or omnivores.[28] This study also showed that, as a group, carnivores slept more than omnivores, who in turn slept more than herbivores (Figure 10-1). In an early study, a significant negative correlation was found between brain weight and REM sleep time (but not total sleep time). A point worthy of emphasis is that this latter correlation was extremely small, accounting for only 4% of the variance in REM sleep time (Figure 10-2). The largest correlation emerging from these early studies was that between body or brain mass and the *duration* of the sleep cycle—that is, the time from the start of one REM sleep period to the start of the next, excluding interposed waking. This correlation accounted for as much as 80% of the variance in sleep cycle time between animals and has held up in subsequent studies in mammals. Sleep cycle duration is approximately 10 minutes in mice, 90 minutes in humans, and 120 minutes in elephants. Because sleep is linked to a reduction in body temperature[29] and reduces energy usage, it has been hypothesized that energy conservation may be a function of sleep.[30]

Several studies have reanalyzed the phylogenetic data set with the addition of data on the few more recently studied animals. These studies took a variety of strategies to extract relations from this data set. Lesku and colleagues[31] used a method of "independent contrasts" in an attempt to control for the relatedness of species being compared. Inclusion of many rodent species in earlier analyses would give the data for those animals a disproportionate effect on conclusions. These workers confirmed previous findings of a negative relationship between basal metabolic rate (which is correlated with body mass) and sleep time. In contrast with earlier and subsequent studies of the same data set, they reported a positive correlation between REM sleep and relative brain mass and a negative relationship between REM sleep time and predation risk.

Another study, confining its analysis to studies that met the investigators' more rigorous criteria, found that metabolic rate correlates negatively rather than positively with sleep quotas,[32] in contrast with earlier studies.[27] This result is not inconsistent with some earlier work.[28] They also reported that neither adult nor neonatal brain mass correlates positively with adult REM or NREM sleep times, differing from earlier studies.[27,32] In agreement with earlier analyses, animals with high predation risk were found to sleep less.[28,33] In keeping with the concept of some fixed need for an unknown function performed only during sleep, the researchers proposed that short-sleeping species sleep more intensely to achieve this function in less time, but they presented no experimental evidence for this hypothesis.

A notable feature of the studies by Lesku and Capellini and their coworkers is that both excluded animals that the investigators concluded had unusual sleep patterns. So the echidna, which combines REM and NREM features in its sleep,[34] was eliminated from the analysis. The platypus, with the largest amount of REM sleep of any animal yet studied,[35] also was excluded from this analysis, as it was from another study focusing on brain size relations.[36] The dolphin and three other cetacean species and two species of manatee were excluded from the Lesku et al. study because of their low levels of REM sleep and presence of unihemispheric slow waves. Including these species in such analyses would undoubtedly negate or reverse the positive relationship reported between brain size and REM sleep, because the platypus exhibits the largest amount of REM sleep time of any studied animal and one of the smallest brain sizes and the dolphin, which appears to have little or no REM sleep, has a larger brain size than humans.[37,38] As discussed further on, these "unusual" species that have been excluded from previous

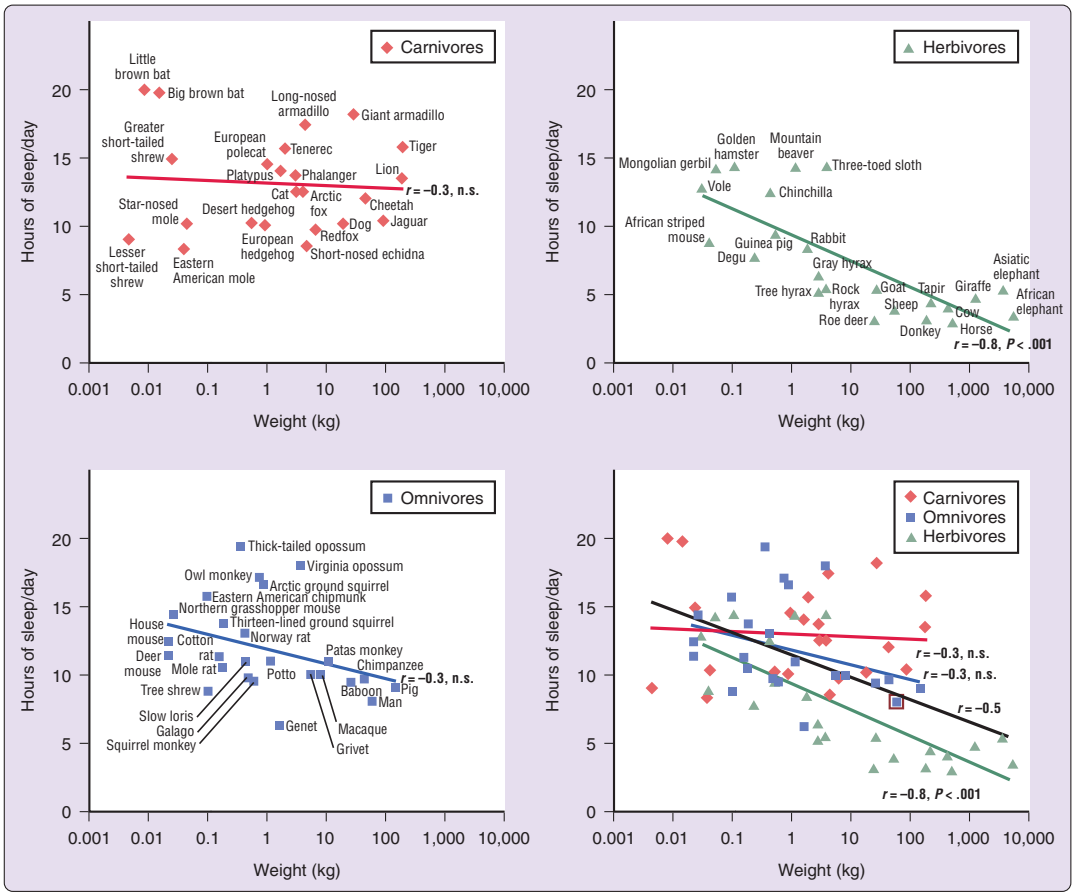

Figure 10-1 Sleep Times in Mammals. Sample data plotted by color: **A,** carnivores, *dark red*; **B,** herbivores, *green*; **C,** omnivores, *gray*. Sleep times in carnivores, omnivores, and herbivores differ significantly, with carnivore sleep amounts significantly greater than those for herbivores. Sleep amount is an inverse function of body mass over all terrestrial mammals (*black line*). This function accounts for approximately 25% of the interspecies variance (**D**) in reported sleep amounts. Herbivores are responsible for this relation, because body mass and sleep time were significantly and inversely correlated in herbivores but not in carnivores or omnivores. (From Siegel JM. Clues to the functions of mammalian sleep. *Nature* 2005;437:1264–71.)

analyses may in fact hold important clues to the function of sleep across species.

In considering the possibility of universal functions of sleep across species, from humans to *Drosophila*, it is important to appreciate the presence of REM and NREM sleep in birds. A correlational analysis of sleep parameters in birds paralleling the studies done in mammals found no relationship between brain mass, metabolic rate, relative metabolic rate, maturity at birth, and total sleep time or REM sleep time.[39] All values for these parameters were found to be "markedly nonsignificant." The only significant relation found was a negative correlation between predation risk and NREM sleep time (but not REM sleep time), in contrast with the relation reported earlier in mammals between predation risk and REM sleep time (but not NREM sleep time). This lone significant relation explained only 27% of the variance in avian NREM sleep time.

To summarize, a variety of correlation studies reach disparate and often opposite conclusions about the physiologic and functional correlates of sleep time. Of note, with the exception of the strong relationship between sleep cycle length and brain and body mass, all of the "significant" correlations reported explain only a small portion of the variance in sleep parameters, throwing into question whether the correlational approach as currently used is getting at the core issues of sleep function. Despite similar genetics, anatomy, cognitive abilities, and physiologic functioning, closely related mammalian species can have very different sleep parameters, and distantly related species can have very similar sleep parameters. Many such examples exist despite the relatively small number of species in which REM and NREM sleep times have been determined (Figure 10-3). For example, the guinea pig and baboon hasve the same daily aonouts of REM and NREM sleep.[40]

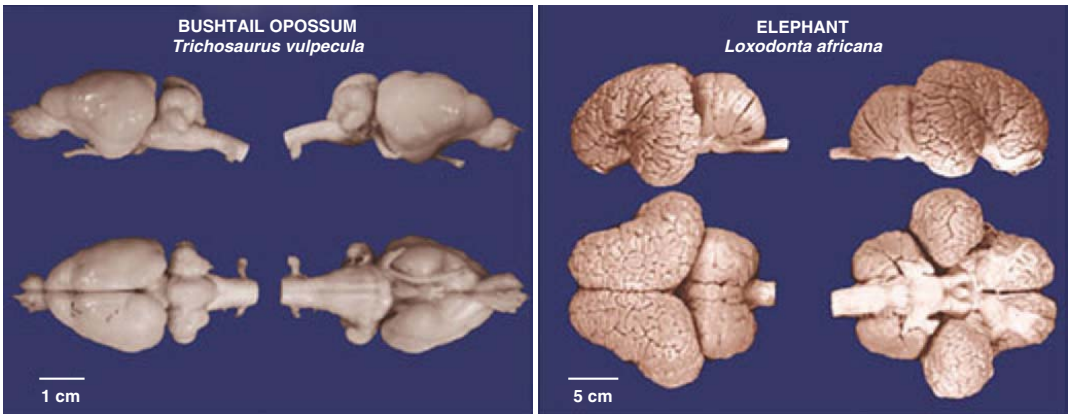

Figure 10-2 Sleep amount is not proportional to the relative size of the cerebral cortex or to the degree of encephalization, as illustrated by these two examples. (From Siegel JM. Clues to the functions of mammalian sleep. *Nature* 2005;437:1264–71.)

THE DIVERSITY OF SLEEP

Overview

On the assumption that sleep satisfies an unknown yet universal function in all animals, some work has been carried out in animals whose genetics and neuroanatomy are better understood and more easily manipulated than in mammals. Much of this work has focused on the fruit fly, *Drosophila melanogaster.* These animals appear to meet the behavioral definition of sleep. Their response threshold is elevated during periods of immobility, but they will rapidly "awaken" when sufficiently intense stimuli are applied. They make up for "sleep" deprivation with a partial rebound of inactivity when left undisturbed. However, major differences between the physiology and anatomy of these organisms and those of mammals make it difficult to transfer insights gleaned from studies of *Drosophila* sleep to human sleep. The *Drosophila* brain does not resemble the vertebrate brain. Octopamine, a major sleep-regulating transmitter in *Drosophila,* does not exist in mammals. Hypocretin, a major sleep-regulating transmitter in mammals, is not produced by *Drosophila.*[40] *Drosophila* flies are not homeotherms, whereas thermoregulation has been closely linked to fundamental aspects of mammalian sleep.[28,29,41] There is no evidence for the occurrence of a state resembling REM sleep in *Drosophila.* Thus the neurochemistry, neuroanatomy, and neurophysiology of sleep must necessarily differ between *Drosophila* and humans and other mammals. Any commonality of sleep phenomena would have to be restricted to cellular level processes. Two studies have shown that *Drosophila* sleep and sleep rebound are markedly impaired by genetic alteration of a potassium current that regulates neuronal membrane excitability.[42,43] Regulation of potassium currents may be a core function of sleep, or it may instead affect the excitability of circuits regulating activity and quiescence, much as such currents affect seizure susceptibility.[44,45]

Caenorhabditis elegans, a roundworm with a nervous system much simpler than that of *Drosophila,* has also been investigated for sleep like behavior.[46] *C. elegans* reaches adulthood in 60 hours and has periods of inactivity during this maturation, called "lethargus," occurring before each of the four molts it undergoes before reaching maturity. Stimulation of *C. elegans* during the lethargus period produced a small but significant decrease in activity during the remainder of the lethargus period but did not delay the subsequent period of activity or increase quiescence overall, phenomena that differ from the effects of sleep deprivation in mammals. It is not clear if adult *C. elegans* shows any aspect of sleep behavior.[47]

Fundamental species differences in the physiology and neurochemistry of sleep have been identified even within the mammalian line. Although many similarities have been recognized, the EEG aspects of sleep also differ considerably between humans, rats, and cats, the most-studied species.[48-50] Human stage 4 NREM sleep is linked to growth hormone secretion. Disruption of stage 4 sleep in children is thought to be a factor in the pathogenesis of short stature. In dogs, however, growth hormone secretion normally occurs in waking, not sleep.[51] Melatonin release is maximal during sleep in diurnal animals, but is maximal in waking in nocturnal animals.[52] Erections have been shown to be present during REM sleep in humans and rats[53]; the armadillo, however, has erections only in NREM sleep.[54] Blood flow and metabolism differ dramatically between neocortical regions in adult human REM sleep,[55] although most animal sleep deprivation and sleep metabolism studies treat the neocortex as a unit. Lesions of parietal cortex and certain other regions prevent dreaming in humans, even in subjects who continue to show normal REM sleep as judged by cortical EEG activity, rapid eye movements, and suppression of muscle tone.[56] Children younger than 6 years of age do not generally report dream mentation, perhaps because these cortical regions have not yet developed.[57] These findings make it questionable whether nonhuman mammals that exhibit REM sleep, all of which have cortical regions whose structure differs from that in adult humans, have dream mentation.

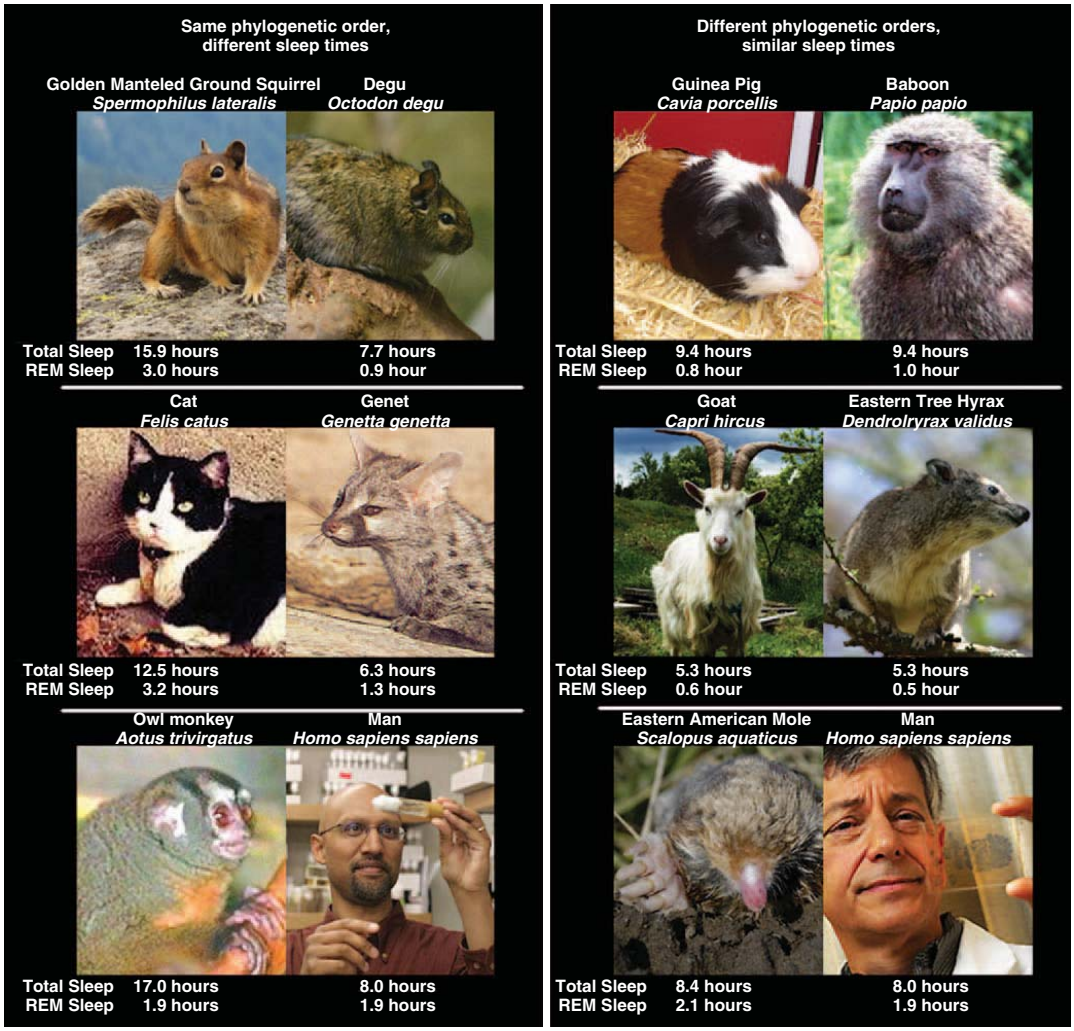

Figure 10-3 Mammalian phylogenetic order is not strongly correlated with sleep parameters. **Left,** Three pairs of animals that are in the same order but have very different sleep parameters. **Right,** Three pairs of animals from different orders with similar sleep amounts. Mammalian sleep times are not strongly correlated with phylogenetic order. (From Allada R, Siegel JM. Unearthing the phylogenetic roots of sleep. *Curr Biol* 2008;18:R670–9.)

Reindeer

Reindeer are ruminants. Like some other ruminants, they appear to remain active over the entire circadian cycle to an extent not seen in most carnivores and omnivores. A study examined the activity of two species of reindeer living in polar regions where they experience periods of continuous darkness in the winter and continuous light in the summer. Activity was monitored for an entire year. It was found that the circadian rhythm of melatonin and circadian rhythms of behavioral activity dissipated in winter and summer. Activity time ranged from 22% to 43% greater in summer than in winter (calculated from data obtained in studies by- van Oort and Tyler).[58,59] EEG recording and arousal threshold tests were not done; however, the activity changes suggest that major changes in sleep duration occur seasonally.

Walrus

A study of the walrus revealed that these animals frequently become continuously active for periods of several days even when fed ad libitum and under no apparent stress.[60] Animals living in marine environments may not be as strongly affected by circadian variables because their evolution has been shaped by tidal and weather features that do not adhere to 24-hour cycles.

Sleep in Cetaceans: Dolphins and Whales

REM sleep is present in all terrestrial animals that have been studied, but signs of this state have not been seen in cetaceans, which are placental mammals. These animals show only unihemispheric slow waves (USWs), which can be confined to one hemisphere for 2 hours or longer. The eye contralateral to the hemisphere with slow waves typically is closed, although covering the eye is not sufficient to produce slow waves.[35,61] These animals never show persistent high-voltage waves bilaterally. Sometimes they float at the surface during USW activity. Often, however, they swim while USWs are being produced (Figure 10-4). When they swim during USW activity, no asymmetry in their motor activity is observed, in contrast with the behavior seen in the fur seal (see further on). Regardless of which hemisphere is showing slow wave activity, they tend to circle in a counterclockwise direction (in the northern hemisphere[62]). No evidence has been presented for elevated sensory response thresholds contralateral to the hemisphere that produces slow waves. Indeed, a substantial elevation of sensory thresholds on one side of the body presumably would be quite maladaptive, in light of the danger of collisions while moving. Similarly, brain motor systems must be bilaterally active to maintain the bilaterally coordinated movement that they exhibit during USW activity. As indicated by these findings, forebrain and brainstem sensory and motor activity must differ radically during USW from that seen in terrestrial mammals during sleep (see Chapter 8)[63,64] The one study of USW rebound after USW deprivation in dolphins produced very variable results, with little or no relation between the amount of slow waves lost in each hemisphere and the amount of slow waves recovered when the animals were subsequently left undisturbed.[65] In two other studies it was shown that dolphins are able to maintain continuous vigilance 24 hours/day, responding at 30-second intervals, for 5 and for 15 days with no decline in accuracy. At the end of this period, no detectable decrease of activity or evidence of inattention or sleep rebound, such as would be expected of a sleep-deprived animal, was seen.[22,66,67]

USWs would be expected to save nearly one half of the energy consumed by the brain that is saved during bihemispheric slow wave activity.[20,21] USWs are well suited to the dolphin's group activity patterns. Because dolphins and other cetaceans swim in pods, the visual world can be monitored by dolphins on each side of the pod, and the remaining dolphins merely have to maintain contact with the pod. In routine "cruising" behavior, this can be done with only one eye, allowing the other eye and connected portions of the brain to reduce activity, as occurs in USWs. This hypothesis needs to be explored by electroencephalographic observations of groups of cetaceans in the wild.

In some smaller cetaceans, such as the harbor porpoise[68] and Commerson's dolphin,[69] motor activity is essentially continuous from birth to death—that is, they never float or sink to the bottom and remain still. These animals move rapidly, and it is evident that they must have accurate sensory and motor performance and associated brain activation to avoid collisions. It is difficult to accept this behavior as "sleep" without discarding all aspects of the behavioral definition of sleep.[22]

All studied land mammals have been reported to show maximal sleep and maximal immobility at birth, leading to the conclusion that sleep is required for brain and body development. Newborn killer whales and dolphins, however, are continuously active. In captivity, they swim in tight formation and turn several times a minute to avoid conspecifics in the pool and pool walls. During this period the calves learn to nurse, breathe, and swim efficiently. Although some USWs might be present at these times, the eyes are open bilaterally when they surface, at average intervals of less than 1 minute, indicating that any slow wave pattern could not last longer than this period.[70] Sleep interruption at such intervals can be lethal to rats,[71] and human sleep is not restorative if interrupted on such a schedule.[72] The cetacean mothers also cease eye closure at the surface and during floating behavior and are continuously active during the postpartum period. No loss of alertness is apparent during the "migratory" period. In the wild, mother and calf migrate together, typically for thousands of miles, from calving to feeding grounds. Sharks, killer whales, and other predatory animals target the migrating calves, and a high level of continuous alertness is necessary for both mother and calf during migration. The maternal and neonatal pattern could be described as "sleep" with well-coordinated motor activity, accurate sensory processing, and effective response to threats in the environment, and without the likelihood of any EEG slow waves or prolonged eyelid closure. This designation, however, does not comport with the accepted behavioral definition of sleep.[73] Thus both cetaceans and migrating birds (see later) greatly reduce sleep time during migrations without any sign of degradation of physiologic functions, sluggishness, loss of alertness, or impairment of cognitive function.

Sleep in Otariids: Eared Seals

On land, sleep in the fur seal generally resembles that in most terrestrial mammals. The EEG is bilaterally synchronized, and the animal closes both eyes, appears unresponsive, and cycles between REM and NREM sleep. By contrast, when the fur seal is in the water, it usually shows an asymmetric pattern of behavior, with one of the flippers being active in maintaining body position, while the other flipper is inactive. During these periods, the fur seal has a high-voltage EEG, with slow waves in one hemisphere with the contralateral eye generally closed. The other eye generally is open or partially open, with an activated, waking-like EEG pattern (Figure 10-5). Therefore, unlike in the dolphin, it appears that one half of the brain and body may in some sense be "asleep" and the other half "awake." Microdialysis studies showed that during asymmetric sleep, the waking hemisphere has significantly higher levels of acetylcholine release than the sleeping hemisphere.[74] By contrast, levels of serotonin,[75] histamine, and norepinephrine,[76] transmitters traditionally considered to be linked to arousal, do not differ between the hemisphere with high-voltage EEG activity and the hemisphere with a low-voltage EEG pattern. This work indicates that acetylcholine has a unique role in mediating the waking EEG in this species, and probably in other mammals, including humans.

Sleep in Monotremes

The mammalian class can be subdivided into three subclasses: placentals, marsupials, and monotremes. There are just three extant monotreme species: the short-beaked and long-beaked echidna and the platypus. Fossil and genetic evidence indicates that the monotreme line diverged from the other mammalian lines approximately 150 million years ago and that

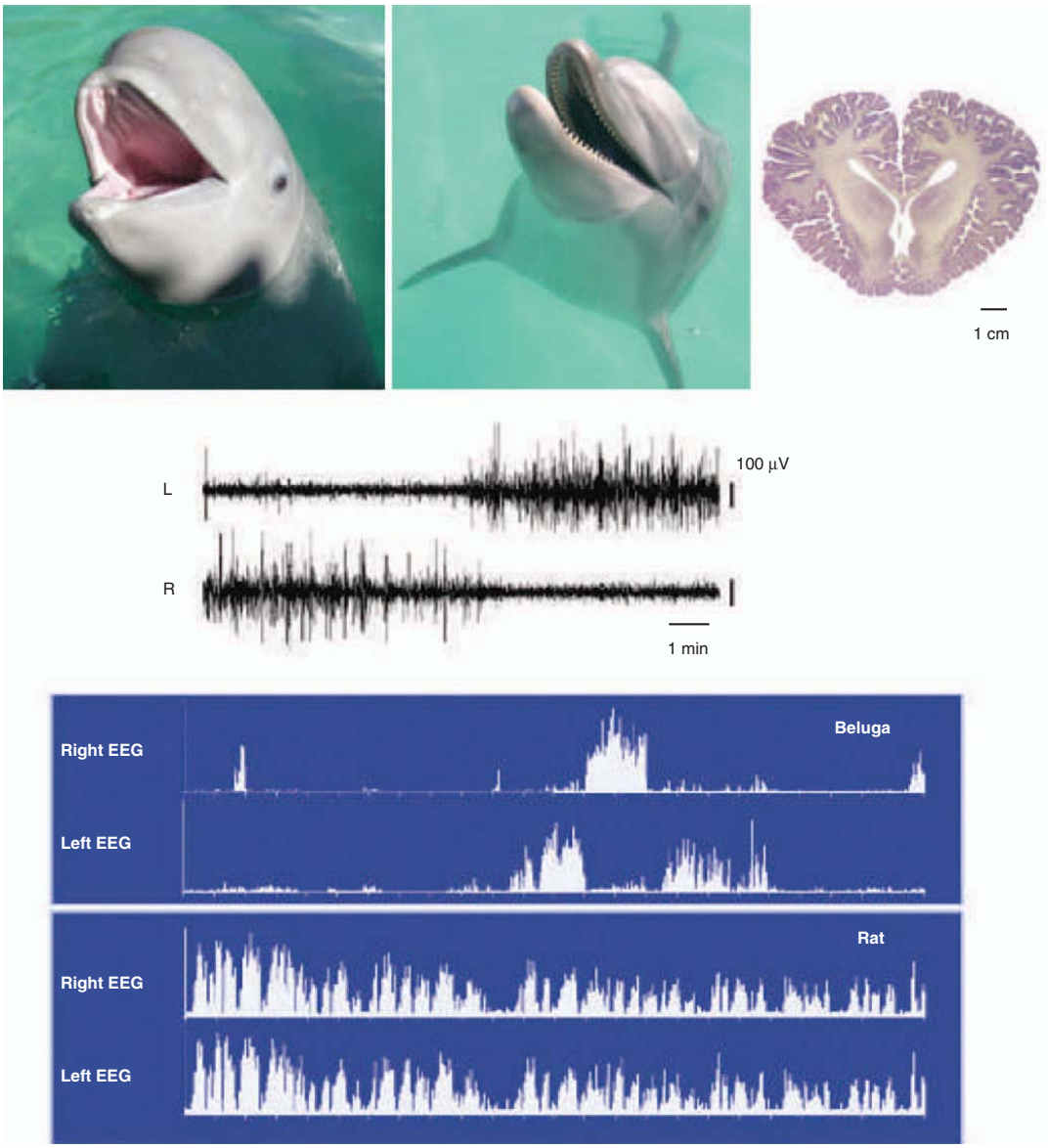

Figure 10-4 Cetacean Sleep; Unihemispheric Slow Waves in Cetaceans. **Top,** Photos of immature beluga (*left*), adult dolphin, and section of adult dolphin brain. Electroencephalogram (EEG) of adult cetaceans, represented here by the beluga, during sleep. All species of cetacean for which sleep EEGs have been recorded so far have demonstrated unihemispheric slow waves. *Top traces* show left and right EEG activity. The spectral plots show 1- to 3 Hz power in the two hemispheres over a 12-hour period. The pattern in the cetaceans contrasts with the bilateral pattern of slow waves seen under normal conditions in all terrestrial mammals, represented here by the rat (*bottom traces*). (From Siegel JM. Clues to the functions of mammalian sleep. *Nature* 2005;437:1264–1271.)

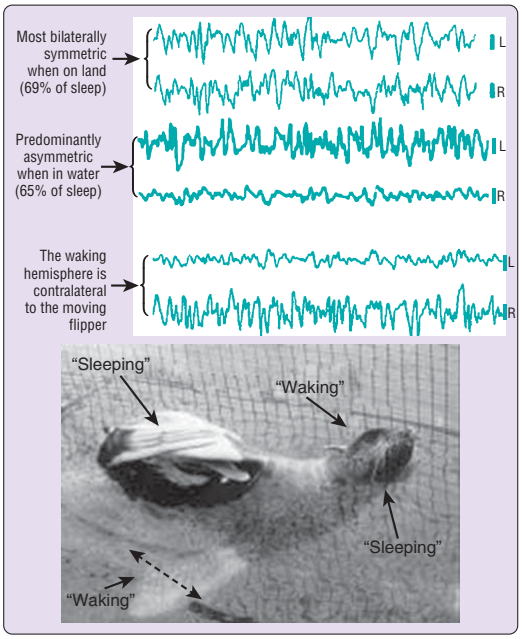

Figure 10-5 Fur Seal Sleep. On land, fur seals usually sleep like terrestrial mammals, with bilateral EEG synchrony and REM sleep (*not shown*). When in water, however, they typically show asymmetric slow wave sleep, with a sleep-like EEG pattern in one hemisphere and a waking-like EEG in the other hemisphere. Unlike in the dolphin, the asymmetric EEG of the fur seal is accompanied by asymmetric posture and motor activity, with the flipper contralateral to the hemisphere showing low-voltage activity used to maintain the animal's position in the water and the other flipper and its controlling hemisphere showing "sleep." EEG, Electroencephalogram.

both echidna species are derived from a platypus-like ancestor.[77-80] The monotremes have shown a remarkably conservative evolutionary course since their divergence from the two other mammalian lines. For example, fossil teeth from *Steropodon galmani* dated at 110 million years ago show many similarities to the vestigial teeth of the present-day platypus, *Ornithorhyncus anatinus*.[81] Analyses of fossilized skull remains indicate remarkably little change in platypus morphology over at least 60 million years.[81,82] The low level of speciation throughout the fossil record is another indicator of the uniquely conservative lineage of monotremes. The 150 million years of platypus evolution has produced no species radiation, apart from the echidna line, and only two living and one extinct species of echidna have been documented. Although monotremes are distinctly mammalian, they do display a number of reptilian features, making study of their physiology a unique opportunity to determine the commonalties and divergences in mammalian evolution.[78,83,84]

This phylogenetic history led to an early study of the echidna to test the hypothesis that REM sleep was a more recently evolved sleep state. No clear evidence of the forebrain low-voltage EEG acctivity that characterizes sleep was seen in this study, leading to the tentative conclusion that REM sleep evolved in placentals and marsupials after the divergence of the monotreme line from the other mammals.[85] This issue was subsequently reexamined using single-neuron recording techniques, in addition to the EEG measures employed in the earlier studies. REM sleep is generated in the mesopontine brainstem (see Chapter 8) and is characterized by a highly variable burst-pause activity of brainstem neurons. This activity is responsible for driving the rapid eye movements, twitches, and other aspects of REM sleep. The investigators recorded from these brainstem regions in unrestrained echidnas to see if this activation was absent throughout sleep. Instead of the slow, regular activity that characterizes brainstem neurons in many nuclei during NREM sleep in placental mammals,[63,64] the echidna showed the irregular activity pattern of REM sleep throughout most of the sleep period[34,86] (Figure 10-6). It appeared that the brainstem was in a REM sleep–like state while the forebrain was in an NREM sleep state.

These interesting findings led to the performance of additional electrophysiologic studies of sleep in the platypus. In this work, the platypus was found to have pronounced phasic motor activity typical of that seen in REM sleep (see Video 10-1).[87] This intense motor activity could occur while the forebrain EEG exhibited high-voltage activity,[35] similar to the phenomenon seen in the echidna. Not only was the motor activity during sleep of intensity equal to or greater than that seen in REM sleep in other animals, but the daily amount of this REM sleep state was greater than that in any other animal. However, unlike in adult placental and marsupial mammals, the signs of REM sleep were largely confined to the brainstem (Figure 10-7). This observation indicates some resemblance to the conditions in most mammals that are born in an immature (altricial) state, which do not show marked forebrain EEG activation during REM sleep early in life (see the chapters on development, in Section ••). The tentative conclusion reached in the initial studies of the echidna, that the monotremes experienced no REM sleep and that REM sleep was a recently evolved state, had to be reversed. Apparently, a brainstem manifestation of REM sleep probably was present in the earliest mammals, perhaps in very large amounts. It may be the brainstem quiescence of NREM sleep, along with the cortical EEG desynchrony of REM sleep, that are the most recently evolved aspects of sleep in the mammalian line.

Birds

Birds have REM sleep that appears physiologically very similar to that seen in mammals, although REM sleep values tend to be lower than total sleep values in mammals.[39] Many bird species migrate over long distances. The effect of this migratory behavior on sleep has been studied in the white-crowned sparrow (*Zonotrichia leucophrys gambelii*). These birds, even when confined in the laboratory, decrease sleep time by two thirds during the periods when they would normally be migrating.[88] Of note, this is a common feature of cycles of adaptive inactivity. A ground squirrel that normally hibernates in the winter will enter a state of torpor at the appropriate season even when maintained in a laboratory under constant conditions.[89]

During the migratory period, the sparrow's learning and responding were unimpaired or improved. In these birds, sleep was not deeper by EEG criteria than that seen when they were not migrating, despite its greatly reduced duration. Their sleep latency did not differ from that during nonmigrating periods.[88]

A recent study of sleep in birds presented an novel and important example of "adaptive" sleep suppression. It was

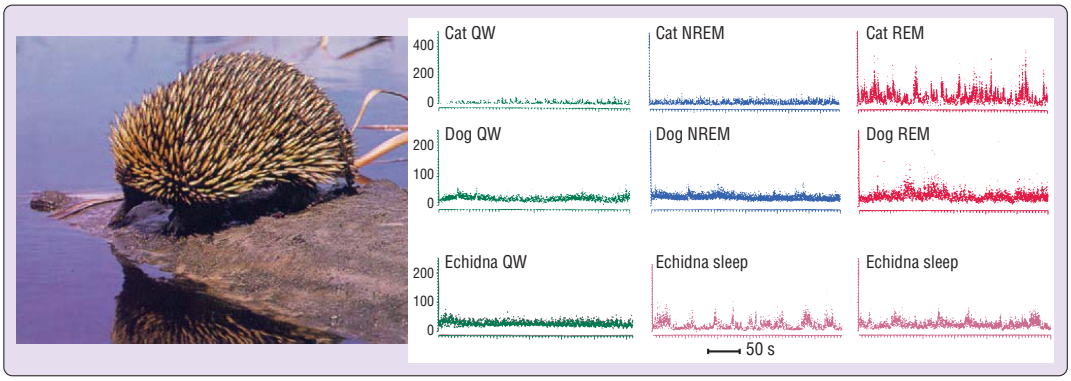

Figure 10-6 **Brainstem Activation during Sleep in the Echidna.** Instantaneous compressed rate plots of representative units recorded in nucleus reticularis pontis oralis of the cat, dog, and echidna. Each point represents the discharge rate for the previous interspike interval. In cat quiet waking (QW) and NREM sleep, the discharge rate is low and relatively regular. The rate increases and becomes highly variable during REM sleep. A similar pattern can be seen in a unit recorded in the dog. In the echidna, sleep is characterized by variable unit discharge rates, as is seen in REM sleep, but this occurs while the cortex is showing high-voltage activity. (From Siegel JM, Manger P, Nienhuis R, et al. The echidna Tachyglossus aculeatus combines REM and nonREM aspects in a single sleep state: implications for the evolution of sleep. *J Neurosci* 1996;16:3500–6.)

found that many polygynous pectoral sandpipers, which breed during a period of continuous summer light, cease sleeping or greatly reduce sleep during breeding. Furthermore, the males with the greatest reduction in sleep sired the most offspring—a unique and dramatic example of adaptive sleep loss increasing genetic propagation.[90] What was most surprising, in view of the strength of this selective benefit, was that *any* males remained sleeping during the breeding period. It was speculated that the continuously active males would be at a competitive disadvantage if their food was scarce after the breeding season relative to those that saved energy by sleeping. In periods of reduced food availability, it is the second group of birds that would survive to mate the next year, leading to a dynamic balance between birds with these two behaviors.[91]

Studies in the ostrich, considered to be in many respects a "primitive" bird, provided novel support for the link between bird and mammalian sleep. It was found that sleep in the ostrich resembles that in the platypus and echidna, with rapid eye movements and muscle tone suppression, brainstem aspects of REM sleep occurring with high-voltage EEG activity, resembling the weak or nonexistent EEG voltage reduction seen in monotremes, whereas their brainstem shows the neuronal activity activation and rapid eye movements that characterize REM sleep.[92]

The observations in monotremes and birds suggest that the reptilian common ancestor of both mammals and birds exhibited REM sleep or a closely related precursor state, rather than the previously advanced speculation that REM sleep must have evolved twice, based on the conclusion that monotremes did not have REM sleep. Although scattered early reports claimed to have identified REM sleep in reptiles, these findings have not been replicated.[28] In the experience of my own research group, when the same recording techniques used in the echidna were appplied in the turtle in a search for evidence of REM sleep, no evidence of phasic brainstem neuronal activity during quiescent states in this reptile was found.[93]

SLEEP REBOUND

The phenomenon of sleep rebound[94] is not always seen. When fur seals go in the water for extended periods, as they do in winter, REM sleep time is greatly reduced. Little or no rebound of lost REM sleep occurs when the animals return to land, even after several weeks in the water.[95] In the cases of the dolphins and killer whales mentioned previously, a near-total abolition of "sleep-like behavior" for periods of several weeks during migration is followed by a slow increase back to baseline levels, with no rebound. The same phenomenon is seen in migrating white sparrows, a migratory species that has been carefully studied under laboratory conditions.[88] In human studies, persons with bipolar disorder in a "manic" phase greatly reduce sleep time for extended periods, and persuasive evidence for progressive degradation of performance, physiologic function, or sleep rebound during this period is lacking. Zebra fish can be completely deprived of sleep for more than three days by placing them in continuous light but show no rebound when returned to a "12-12" light-dark cycle.[96] By contrast, when they are deprived by repetitive tactile stimulation, they do show rebound, suggesting that the deprivation procedure rather than the sleep loss underlies the rebound.

Typically, 30% or less of sleep time lost during deprivation is recovered in the human and rodent, in which the phenomenon has been most extensively studied. A similar percentage of rebound is seen in other species including some invertebrates.[97] One may ask why, if sleep is essentially a maladaptive state, animals that have the ability to regain lost sleep in 30% of the time it would normally have taken have not evolved shorter sleep times to take advantage of the adaptive benefits of increased waking. If sleep is viewed as a form of adaptive inactivity, however, this paradox vanishes. A small sleep rebound may be necessary to compensate for processes that can occur only, or optimally, in sleep, but for the most part,

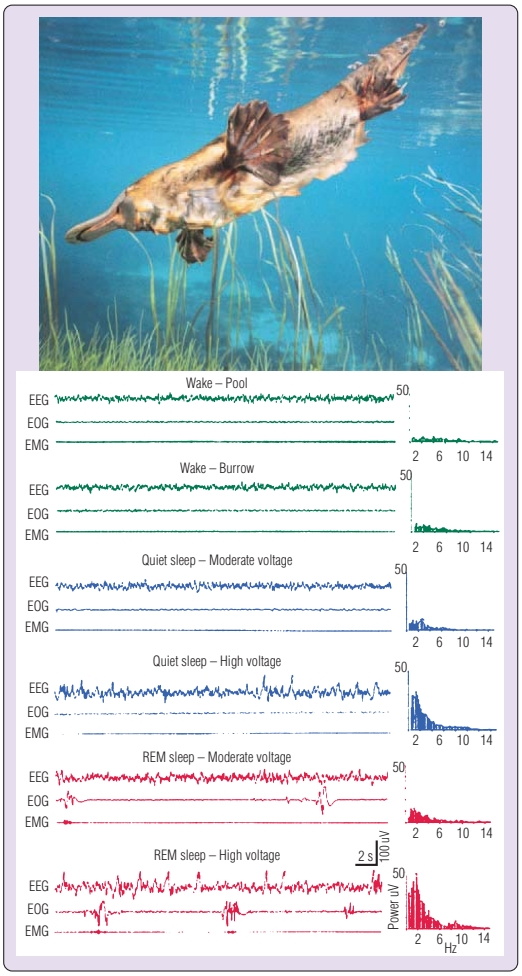

Figure 10-7 **Brainstem REM Sleep State in the Platypus.** Rapid eye movements and twitches can occur while the forebrain is showing a slow wave activity pattern. EEG, EOG, EMG, and EEG power spectra of samples shown of sleep-wake states in the platypus. EEG, Electroencephalogram; EMG, electromyogram; EOG, electrooculogram. (From Siegel JM, Manger PR, Nienhuis R, et al. Sleep in the platypus. *Neuroscience* 1999;91(1):391–400.)

sleep time is determined in each species by the evolved tradeoffs between active waking and adaptive inactivity.

The variation in rebound within and across species needs to be more carefully studied. Some aspects of rebound have been shown to be due to the deprivation procedure, rather than to the sleep loss itself. For example, stressing rats by restraint can produce increased REM sleep even when no sleep has been lost. This effect is mediated by the release of pituitary hormones.[98,99] It is possible that in some species, other aspects of rebound are driven by changes in hormonal release linked to sleep deprivation,[1] rather than by some intrinsic property of sleep.

CLINICAL PEARL

Although sleep and sleep stages differ in amount between species, human sleep does not appear to be qualitatively unique. This factor makes animal models suitable for the investigation of many aspects of pharmacology and pathology in sleep science.

SUMMARY

Sleep can be seen as an adaptive state, benefiting animals by increasing the efficiency of their activity. Sleep does this by suppressing activity at times associated with maximal predator risk and permitting activity at times of maximal food and prey availability and minimal predator risk. It also increases efficiency by decreasing brain and body metabolism. However, unlike the dormant states employed in plants, simple multicellular organisms, and ectothermic organisms, and the hibernation and torpor employed in some mammals and birds, sleep allows rapid arousal for tending to infants, dealing with predators, and responding to environmental changes. A major function of REM sleep may be to allow rapid awakening with alertness, by means of periodic brainstem activation. Many organisms can reduce sleep for long periods of time without rebound during periods of migration or other periods in which a selective advantage can be obtained by continuous waking.

The big brown bat specializes in eating mosquitoes and moths that are active from dusk to early evening. The big brown bat typically is awake only approximately 4 hours a day.[27] Not surprisingly, this waking is synchronized to the period when its insect prey species are active. It is not likely that this short waking period, one of the shortest yet observed, can be explained by the need for some time-consuming unknown process that occurs only during sleep and requires 20 hours to complete. This extremely brief period of wakefulness can be more easily explained by the ecologicl specializations of this bat. Similarly, "sleep" in ectothermic animals is most likely to be determined by temperature and other environmental variables, rather than any information processing or physiologic maintenance requirement. An approach that takes the environmental conditions in which each species evolved into account can better explain the variance in sleep time among mammals.

Many vital processes occur in both waking and sleep, including recovery of muscles from exertion, control of blood flow, respiration, growth of various organs, and digestion. Some processes may occur more efficiently in sleep but can also occur in waking. It has been claimed that sleep has an essential role in learning, but further investigations have disputed such claims.[101-105] It is highly probable that some functions have migrated into or out of sleep in various animals. Neurogenesis,[106] synaptic downscaling,[107] immune system activation,[108] and reversal of oxidative stress[109,110] may be accomplished in sleep in mammals. It remains to be seen if these or any other vital functions can be performed only in sleep. As suggested by the available evidence, however, such functions cannot explain the variation of sleep amounts and the apparent flexibility of sleep physiology within and between

animals. Viewing sleep as a period of well-timed adaptive inactivity that regulates behavior may better explain this variation.

ACKNOWLEDGEMENT

Work on which this chapter is based was supported by the Medical Research Service of the Department of Veterans Affairs, the National Institutes of Health, and the National Science Foundation.

Selected Readings

Schmidt MH. The energy allocation function of sleep: a unifying theory of sleep, torpor, and continuous wakefulness. *Neurosci Biobehav Rev* 2014;**47**:122–53.

Siegel JM. Clues to the functions of mammalian sleep. *Nature* 2005;**437**: 1264–71.

Siegel JM. Sleep viewed as a state of adaptive inactivity. *Nat Rev Neurosci* 2009;**10**:747–53.

A complete reference list can be found online at https://ExpertConsult.inkling.com/.

References

1. Siegel JM. Sleep viewed as a state of adaptive inactivity. *Nat Rev Neurosci* 2009;**10**(10):747–53.
2. Shen-Miller J, Schopf JW, Harbottle G, et al. Long-living lotus: germination and soil γ-irradiation of centuries-old fruits, and cultivation, growth, and phenotypic abnormalities of offspring. *Am J Bot* 2002;**89**(2): 236–47.
3. *National Geographic News*. Viable 2000 year old date palm seed. <http://newsnationalgeographic.com/news/2005/11/1122_051122_old_seed.html>; Nov. 5, 2005 [accessed 2009].
4. 45 million year old viable yeast. *Food In The Fort* blog, <http://www.foodinthefort.com/tag/raul-cano/>; 2009.
5. Caprioli M, Santo N, Ricci C. Enhanced stress resistance of dormant bdelloids (rotifera). *J Gravit Physiol* 2002;**9**(1):235–6.
6. Ricci C, Caprioli M, Fontaneto D. Stress and fitness in parthenogens: is dormancy a key feature for bdelloid rotifers? *BMC Evol Biol* 2007; **7**(Suppl. 2):S9.
7. Di Cristina M, Marocco D, Galizi R, et al. Temporal and spatial distribution of Toxoplasma gondii differentiation into bradyzoites and tissue cyst formation in vivo. *Infect Immun* 2008;**76**(8):3491–501.
8. Pozio E. Foodborne and waterborne parasites. *Acta Microbiol Pol* 2003;**52**(Suppl.):83–96.
9. Brusca RC, Brusca GJ. *Invertebrates*. Sunderland (Mass.): Sinauer Associates; 1990.
10. Li D, Graham LD. Epiphragmin, the major protein of epiphragm mucus from the vineyard snail, Cernuella virgata. *Comp Biochem Physiol B Biochem Mol Biol* 2007;**148**(2):192–200.
11. Krohmer RW, Bieganski GJ, Baleckaitis DD, et al. Distribution of aromatase immunoreactivity in the forebrain of red-sided garter snakes at the beginning of the winter dormancy. *J Chem Neuroanat* 2002;**23**(1): 59–71.
12. Kaiya H, Konno N, Kangawa K, et al. Identification, tissue distribution and functional characterization of the ghrelin receptor in West African lungfish, Protopterus annectens. *Gen Comp Endocrinol* 2014;**14**:10.
13. Lehmann T, Dao A, Yaro AS, et al. Seasonal variation in spatial distributions of Anopheles gambiae in a Sahelian village: evidence for aestivation. *J Med Entomol* 2014;**51**(1):27–38.
14. Chen M, Zhang X, Liu J, Storey KB. High-throughput sequencing reveals differential expression of miRNAs in intestine from sea cucumber during aestivation. *PLoS ONE* 2013;**8**(10):e76120.
15. Sun J, Mu H, Zhang H, et al. Understanding the regulation of estivation in a freshwater snail through iTRAQ-based comparative proteomics. *J Proteome Res* 2013;**12**(11):5271–80.
16. Reilly BD, Schlipalius DI, Cramp RL, et al. Frogs and estivation: transcriptional insights into metabolism and cell survival in a natural model of extended muscle disuse. *Physiol Genomics* 2013;**45**(10):377–88.
17. Swoap SJ. The pharmacology and molecular mechanisms underlying temperature regulation and torpor. *Biochem Pharmacol* 2008;**76**(7): 817–24.
18. Geiser F. Reduction of metabolism during hibernation and daily torpor in mammals and birds: temperature effect or physiological inhibition? *J Comp Physiol [B]* 1988;**158**(1):25–37.
19. Hissa R, Siekkinen J, Hohtola E, et al. Seasonal patterns in the physiology of the European brown bear (Ursus arctos arctos) in Finland. *Comp Biochem Physiol A Physiol* 1994;**109**(3):781–91.
20. Nofzinger EA, Nissen C, Germain A, et al. Regional cerebral metabolic correlates of WASO during NREM sleep in insomnia. *J Clin Sleep Med* 2006;**2**(3):316–22.
21. Raichle ME, Mintun MA. Brain work and brain imaging. *Annu Rev Neurosci* 2006;**29**:449–76.
22. Siegel JM. Do all animals sleep? *Trends Neurosci* 2008;**31**(4):208–13.
23. Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 4th ed. Philadelphia: Saunders; 2005.
24. Rattenborg NC, Voirin B, Vyssotski AL, et al. Sleeping outside the box: electroencephalographic measures of sleep in sloths inhabiting a rainforest. *Biol Lett* 2008;**4**(4):402–5.
25. Capellini I, Nunn CL, McNamara P, et al. Energetic constraints, not predation, influence the evolution of sleep patterning in mammals. *Funct Ecol* 2008;**22**:847–53.
26. Zepelin H, Rechtschaffen A. Mammalian sleep, longevity and energy metabolism. *Brain Behav Evol* 1974;**10**:425–70.
27. Zepelin H, Siegel JM, Tobler I. Mammalian sleep. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 4th ed. Philadelphia: Saunders; 2005. p. 91–100.
28. Siegel JM. Clues to the functions of mammalian sleep. *Nature* 2005; **437**(7063):1264–71.
29. McGinty D, Szymusiak R. Keeping cool: a hypothesis about the mechanisms and functions of slow-wave sleep. *Trends Neurosci* 1990;**13**: 480–7.
30. Berger RJ, Phillips NH. Energy conservation and sleep. *Behav Brain Res* 1995;**69**(1–2):65–73.
31. Lesku JA, Roth TC, Amlaner CJ, Lima SL. A phylogenetic analysis of sleep architecture in mammals: the integration of anatomy, physiology, and ecology. *Am Nat* 2006;**168**(4):441–53.
32. Capellini I, Barton RA, McNamara P, et al. Phylogenetic analysis of the ecology and evolution of mammalian sleep. *Evolution* 2008;**62**(7): 1764–76.
33. Allison T, Cicchetti DV. Sleep in mammals: ecological and constitutional correlates. *Science* 1976;**194**:732–4.
34. Siegel JM, Manger P, Nienhuis R, et al. The echidna Tachyglossus aculeatus combines REM and nonREM aspects in a single sleep state: implications for the evolution of sleep. *J Neurosci* 1996;**16**:3500–6.
35. Siegel JM, Manger PR, Nienhuis R, et al. Sleep in the platypus. *Neuroscience* 1999;**91**(1):391–400.
36. Savage VM, West GB. A quantitative, theoretical framework for understanding mammalian sleep. *Proc Natl Acad Sci U S A* 2007;**104**(3): 1051–6.
37. Patzke N, Spocter MA, Karlsson KA, et al. In contrast to many other mammals, cetaceans have relatively small hippocampi that appear to lack adult neurogenesis. *Brain Struct Funct* 2015;**220**(1):361–83.
38. Dell LA, Patzke N, Bhagwandin A, et al. Organization and number of orexinergic neurons in the hypothalamus of two species of Cetartiodactyla: a comparison of giraffe (Giraffa camelopardalis) and harbour porpoise (Phocoena phocoena). *J Chem Neuroanat* 2012;**44**(2):98–109.
39. Roth TC, Lesku JA, Amlaner CJ, Lima SL. A phylogenetic analysis of the correlates of sleep in birds. *J Sleep Res* 2006;**15**(4):395–402.
40. Allada R, Siegel JM. Unearthing the phylogenetic roots of sleep. *Curr Biol* 2008;**18**(15):R670–9.
41. Rechtschaffen A, Bergmann BM, Everson CA, et al. Sleep deprivation in the rat: X. Integration and discussion of findings. *Sleep* 1989;**12**: 68–87.
42. Cirelli C, Bushey D, Hill S, et al. Reduced sleep in Drosophila Shaker mutants. *Nature* 2005;**434**(7037):1087–92.
43. Koh K, Joiner WJ, Wu MN, et al. Identification of SLEEPLESS, a sleep-promoting factor. *Science* 2008;**321**(5887):372–6.
44. Gargus JJ. Ion Channel functional candidate genes in multigenic neuropsychiatric disease. *Biol Psychiatry* 2006;**60**(2):177–85.
45. Steinhäuser C, Seifert G. Glial membrane channels and receptors in epilepsy: impact for generation and spread of seizure activity. *Eur J Pharmacol* 2002;**447**(2–3):227–37.
46. Raizen DM, Zimmerman JE, Maycock MH, et al. Lethargus is a Caenorhabditis elegans sleep-like state. *Nature* 2008;**451**(7178):569–72.
47. Zimmerman JE, Naidoo N, Raizen DM, Pack AI. Conservation of sleep: insights from non-mammalian model systems. *Trends Neurosci* 2008; **31**(7):371–6.
48. Bergmann BM, Winter JB, Rosenberg RS, Rechtschaffen A. NREM sleep with low-voltage EEG in the rat. *Sleep* 1987;**10**(1):1–11.
49. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Public Health Service. Washington (D.C.): U.S. Government Printing Service; 1968.
50. Sterman MB, Knauss T, Lehmann D, Clemente CD. Circadian sleep and waking patterns in the laboratory cat. *Electroencephalogr Clin Neurophysiol* 1965;**19**:509–17.
51. Takahashi Y, Ebihara S, Nakamura Y, Takahashi K. A model of human sleep-related growth hormone secretion in dogs: effects of 3, 6, and 12 hours of forced wakefulness on plasma growth hormone, cortisol, and sleep stages. *Endocrinology* 1981;**109**:262–72.
52. Redman JR. Circadian entrainment and phase shifting in mammals with melatonin. *J Biol Rhythms* 1997;**12**(6):581–7.
53. Hirshkowitz M, Schmidt MH. Sleep-related erections: clinical perspectives and neural mechanisms. *Sleep Med Rev* 2005;**9**(4):311–29.
54. Affanni JM, Cervino CO, Marcos HJ. Absence of penile erections during paradoxical sleep. Peculiar penile events during wakefulness and slow wave sleep in the armadillo. *J Sleep Res* 2001;**10**(3):219–28.
55. Braun AR, Balkin TJ, Wesensten NJ, et al. Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. *Science* 1998;**279**(5347):91–5.
56. Solms M. Dreaming and REM sleep are controlled by different brain mechanisms. *Behav Brain Sci* 2000;**23**(6):843–50.

57. Foulkes D. Home and laboratory dreams: four empirical studies and a conceptual reevaluation. *Sleep* 1979;**2**(2):233–51.
58. van Oort BE, Tyler NJ, Gerkema MP, et al. Where clocks are redundant: weak circadian mechanisms in reindeer living under polar photic conditions. *Naturwissenschaften* 2007;**94**(3):183–94.
59. van Oort BE, Tyler NJ, Gerkema MP, et al. Circadian organization in reindeer. *Nature* 2005;**438**(7071):1095–6.
60. Lyamin OI, Kosenko PO, Vyssotski AL, et al. Study of sleep in a walrus. *Dokl Biol Sci* 2012;**444**:188–91.
61. Lyamin OI, Mukhametov LM, Siegel JM. Relationship between sleep and eye state in Cetaceans and Pinnipeds. *Arch Ital Biol* 2004;**142**(4): 557–68.
62. tafne GM, Manger PR. Predominance of clockwise swimming during rest in Southern Hemisphere dolphins. *Physiol Behav* 2004;**82**(5): 919–26.
63. Siegel JM, Tomaszewski KS. Behavioral organization of reticular formation: studies in the unrestrained cat. I. Cells related to axial, limb, eye, and other movements. *J Neurophysiol* 1983;**50**:696–716.
64. Siegel JM, Tomaszewski KS, Wheeler RL. Behavioral organization of reticular formation: studies in the unrestrained cat: II. Cells related to facial movements. *J Neurophysiol* 1983;**50**:717–23.
65. Oleksenko AI, Mukhametov LM, Polykova IG, et al. Unihemispheric sleep deprivation in bottlenose dolphins. *J Sleep Res* 1992;**1**:40–4.
66. Ridgway S, Carder D, Finneran J, et al. Dolphin continuous auditory vigilance for five days. *J Exp Biol* 2006;**209**(Pt 18):3621–8.
67. Branstetter BK, Finneran JJ, Fletcher EA, et al. Dolphins can maintain vigilant behavior through echolocation for 15 days without interruption or cognitive impairment. *PLoS ONE* 2012;**7**(10):e47478.
68. Mukhametov LM. Sleep in marine mammals. *Exp Brain Res* 2007;**8**: 227–38.
69. Mukhametov LM, Lyamin OI, Shpak OV, et al. Swimming styles and their relationship to rest and activity states in captive Commerson's dolphins. *Proceedings of the 14th biennial conference on the biology of marine mammals*, Vancouver, Nov. 27-Dec. 3, 2002, p.152.
70. Lyamin O, Pryaslova J, Lance V, Siegel J. Animal behaviour: continuous activity in cetaceans after birth. *Nature* 2005;**435**(7046):1177.
71. Rechtschaffen A, Bergmann BM. Sleep deprivation in the rat: an update of the 1989 paper. *Sleep* 2002;**25**(1):18–24.
72. Bonnet MH. Sleep deprivation. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 3rd ed. Philadelphia: WB Saunders; 2000. p. 53–71.
73. Gnone G, Moriconi T, Gambini G. Sleep behaviour: activity and sleep in dolphins. *Nature* 2006;**441**(7096):E11. [comment on Lyamin OI, Pryaslova J, Lance V, Siegel JM. Sleep behaviour: sleep in continuously active dolphins. Nature 2005;**435**(7046):1177]
74. Lapierre JL, Kosenko PO, Lyamin OI, et al. Cortical acetylcholine release is lateralized during asymmetrical slow-wave sleep in northern fur seals. *J Neurosci* 2007;**27**(44):11999–2006.
75. Lapierre JL, Kosenko PO, Kodama T, et al. Symmetrical serotonin release during asymmetrical slow-wave sleep: implications for the neurochemistry of sleep-waking states. *J Neurosci* 2013;**33**(6):2555–61.
76. Lapierre JL, Kosenko PO, Korneva SM, et al. Cortical norepinephrine release is not lateralized during asymmetrical slow-wave sleep in the fur seal. *Sleep* 2013;**36**:155.
77. Clemens WA. Diagnosis of the class mammalia. In: Walton DW, Richardson BJ, editors. *Fauna of Australia. Mammalia*, vol. 1B. Canberra (A.C.T., Australia): Australian Government Publishing; 1989. p. 401–6.
78. Westerman M, Edwards D. DNA hybridization and the phylogeny of monotremes. In: Augee M, editor. *Platypus and echidnas*. Mosman (N.S.W., Australia): Royal Zoological Society of NSW; 1992. p. 28–34.
79. Flannery TF. Origins of the Australo-Pacific mammal fauna. *Aust Zool Rev* 1989;**1**:15–24.
80. Warren WC, Hillier LW, Marshall Graves JA, et al. Genome analysis of the platypus reveals unique signatures of evolution. *Nature* 2008; **453**(7192):175–83.
81. Archer M, Jenkins F, Hand S, et al. Description of the skull and nonvestigial dentition of a miocene platypus (Obdurodon dicksoni n. sp.) from Riversleigh, Australia, and the problem of monotreme origins. In: Augee M, editor. *Platypus and echidnas*. Mosman (N.S.W., Australia): Royal Zoological Society of New South Wales; 1992. p. 15–27.
82. Pascual R, Archer M, Ortiz J, et al. The first non-Australian monotreme: an early Paleocene South American platypus (Monotremata, Ornithorhynchidae). In: Augee M, editor. *Platypus and echidnas*. Mosman (N.S.W., Australia): Royal Zoological Society of New South Wales; 1992. p. 1–14.
83. Griffiths M. *The biology of the monotremes*. New York: Academic Press; 1978.
84. Kemp T. *Mammal-like reptiles and the origin of mammals*. London: Academic Press; 1982. p. 1–363.
85. Allison T, Van Twyver H, Goff WR. Electrophysiological studies of the echidna, Tachyglossus aculeatus. I. Waking and sleep. *Arch Ital Biol* 1972;**110**:145–84.
86. Siegel JM, Manger P, Nienhuis R, et al. Novel sleep state organization in the echidna: implications for the evolution of REM and nonREM sleep. *Sleep Res* 1994;**23**:37.
87. Siegel JM. *REM sleep in the platypus, UCLA Neuropsychiatric Institute website*, <http://www.npi.ucla.edu/sleepresearch/media.php>; 2009.
88. Rattenborg NC, Mandt BH, Obermeyer WH, et al. Migratory sleeplessness in the white-crowned sparrow (Zonotrichia leucophrys gambelii). *PLoS Biol* 2004;**2**(7):E212.
89. O'Hara BF, Watson FL, Srere HK, et al. Gene expression in the brain across the hibernation cycle. *J Neurosci* 1999;**19**(10):3781–90.
90. Lesku JA, Rattenborg NC, Valcu M, et al. Adaptive sleep loss in polygynous pectoral sandpipers. *Science* 2012;**337**(6102):1654–8.
91. Siegel JM. Suppression of sleep for mating. *Science* 2012;**337**(6102): 1610–11.
92. Lesku JA, Meyer LC, Fuller A, et al. Ostriches sleep like platypuses. *PLoS ONE* 2011;**6**(8):e23203.
93. Eiland MM, Lyamin OI, Siegel JM. State-related discharge of neurons in the brainstem of freely moving box turtles, Terrapene carolina major. *Arch Ital Biol* 2001;**139**:23–36.
94. Tobler I. Phylogeny of Sleep Regulation. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 5th ed. St. Louis: Elsevier; 2011. p. 112–25.
95. Lyamin OI, Oleksenko AI, Polyakova IG, Mukhametov LM. Paradoxical sleep in northern fur seals in water and on land. *J Sleep Res* 1996;**5**(Suppl. l):130.
96. Yokogawa T, Marin W, Faraco J, et al. Characterization of sleep in zebrafish and insomnia in hypocretin receptor mutants. *PLoS Biol* 2007;**5**(10):2379–97.
97. Tobler I. Phylogeny of sleep regulation. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 4th ed. Philadelphia: Saunders; 2005. p. 77–90.
98. Zhang JX, Valatx JL, Jouvet M. Hypophysectomy in monosodium glutamate-pretreated rats suppresses paradoxical sleep rebound. *Neurosci Lett* 1988;**86**:94–8.
99. Rampin C, Cespuglio R, Chastrette N, Jouvet M. Immobilization stress induces a paradoxical sleep rebound in rat. *Neurosci Lett* 1991;**126**: 113–18.

REVIEW QUESTIONS

1. Dormant states include:
   A. Sleep
   B. Abscission
   C. Hibernation
   D. Diapause
   E. All of the above
2. Hibernation is entered from a state of:
   A. REM sleep
   B. NREM sleep
   C. Cataplexy
   D. Waking
3. With respect to sleep amounts, three phylogenetic groups of animals arranged in *descending* order, from those that sleep the most to those that sleep the least, are:
   A. Carnivores, omnivores, herbivores
   B. Herbivores, omnivores, carnivores
   C. Marsupials, placentals, monotremes
   D. Marsupials, monotremes, placentals
4. Which animal experiences the *most* REM sleep?
   A. Platypus
   B. Dolphin
   C. Human
   D. Big brown bat
5. Which statement regarding sleep time is *true*?
   A. Fur seals greatly reduce REM sleep when in water.
   B. Dolphins experience REM sleep only in the first week of life.
   C. Primates, as a group, devote a higher percentage of their sleep time to REM sleep than any other mammalian order.
   D. Smaller cetacean (dolphin and whale) species sleep more than larger cetaceans.
6. Animals that can go without sleep for long periods of time without sleep rebound include:
   A. Dolphin
   B. Polygynous pectoral sandpipers
   c. Manic humans
   D. Killer whales
   E. All of the above
7. Which animal experiences the *least* amount of REM sleep?
   A. Platypus
   B. Dolphin
   C. Human
   D. Big brown bat
8. Which of the following statements regarding phylogenetic sleep differences is *true*?
   A. Human REM and NREM sleep amounts are neither higher nor lower than REM or NREM sleep amounts in other animals.
   B. Dolphins experience REM sleep only in the first week of life.
   C. Primates, as a group, devote a higher percentage of their sleep time to REM sleep than any other mammalian order.
   D. Smaller cetacean (dolphin and whale) species sleep more than larger cetaceans.
9. Humans with insomnia:
   A. Frequently fall asleep during the day
   B. Make up for lost sleep with substantial sleep rebounds
   C. Are not sleepy during the day
   D. Have a reduced lifespan

ANSWERS

1. **E.**
2. **B.**
3. **A.**
4. **A.**
5. **A.**
6. **E.**
7. **B.**
8. **A.**
9. **C.**