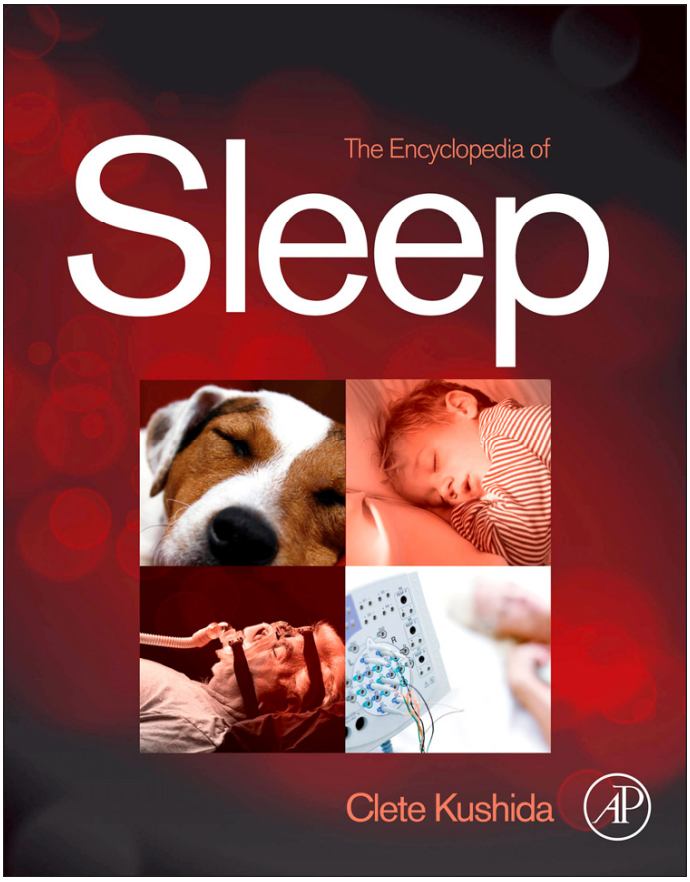

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Evolution of Sleep (Sleep Phylogeny)

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Glossary

Adaptive: Leading to propagation of the species.
Brain stem: The portion of the brain located above the spinal cord.
Electroencephalogram: An amplified recording of the weak electrical potentials generated by brain activity.
Forebrain: The portion of the brain located above the brain stem.
Hibernation: A state of greatly reduced metabolic activity and body temperature lasting for days or weeks.
Phylogeny: The study of relatedness of organisms. In sleep research, this term is commonly used to refer to the study of the distribution of sleep duration and the comparison of the characteristics of sleep across species.
Torpor is a state of reduced metabolic activity lasting for as little as a few hours.

The idea that sleep saves energy and 'knits up the raveled sleeve of care,' that is, has a restorative function, is hundreds, perhaps thousands of years old. But starting in the 1950s, with the discovery of rapid eye movement (REM) sleep and, later, with extensive studies of sleep deprivation in rats, a new idea became dominant. This idea was that sleep was universal and performed a mysterious function, vital for life, in virtually all multicellular or even unicellular organisms. However, 50 years of work have revealed frustratingly little evidence for any such function. In particular, the data that have been gathered in the past 5 years cannot be explained within this paradigm. These data include the finding that adult and newborn dolphins and related cetaceans go without sleep for weeks with no ill effects and findings by other workers that sleep is greatly reduced during migration, and that this reduction does not generally lead to major physiological effects. It now appears that many species reduce sleep for long periods of time under normal conditions and that others do not sleep at all, in the way sleep is conventionally defined. New evidence suggests that humans with less sleep than average do far better, in terms of longevity, than humans with more sleep than average. Sleep does not seem to have a unique, essential role in memory consolidation, despite claims to the contrary. These new findings lead to the conclusion that sleep itself, by regulating behavior and energy expenditure, is highly adaptive and can be most accurately viewed from an evolutionary perspective.

Sleep in Mammals

Sleep physiology has been most thoroughly studied in humans, and in the cat, rat, and mouse. In these animals, two distinct kinds of sleep can be identified, non-REM sleep and REM sleep. These states are readily discriminated by recordings of the electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG).

In waking, the EEG recorded from neocortical regions is characterized by low-voltage activity. Neuronal recording reveals that the low voltage is not a sign of inactivity, but is rather associated with very high rates of neuronal action potentials occurring asynchronously, so the excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) driving this activity tend to cancel out when large electrodes are used to record EEG from the brain surface or, in humans, from the scalp.

In contrast, non-REM sleep is characterized by an overall decline of neuronal activity and metabolism in the neocortex and an even greater decline in the subcortical regions. However, because the activity of neurons tends to be synchronized by a dynamic interaction between thalamus and cortex during non-REM sleep, the amplitude of electrically recorded activity increases. The frequency of the summated EPSPs and IPSPs of this activity ranges from below 1 Hz to over 15 Hz in humans. Non-REM sleep in humans can be subdivided into four stages. Stages 1–3 are characterized by a progressive elevation in voltage. Stage 4 has the highest-voltage EEG activity, and the lowest frequencies, with power under 4 Hz, predominating. Typically, stage 4 decreases with age and individuals over 40 years of age have little or none of this state.

REM sleep is characterized by an increase in metabolic activity back to waking levels. The neocortical EEG is also quite similar to that seen in waking, as neuronal activity tends to be asynchronous, as in waking. Most brain neurons, for instance, forebrain neurons, have maximal activity in waking; they greatly decrease activity in non-REM sleep and increase activity to waking levels during REM sleep.

The physiological correlates of sleep are not confined to the brain. In non-REM sleep, heart rate and respiration slow down and become very regular. Muscle tone (EMG) is reduced. Body temperature falls and is regulated at the lower level.

In REM sleep, tone in most muscles, apart from those that move the eyes and the diaphragm, is for the most part absent. REMs and twitching, absent in non-REM sleep, occur. Heart rate, blood pressure, and respiration become irregular. Body temperature appears to be unregulated and drifts toward environmental temperature.

Endocrine hormones are released in particular sleep states or in relation to circadian phase; however, this varies in a species-specific way across mammals and does not appear to be a universal feature of sleep.

Normally, non-REM sleep occurs at sleep onset and is followed by REM sleep, with REM sleep latency being approximately an hour in humans. REM sleep amounts are greatest at

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the end of the sleep period. There is a circadian modulation of REM sleep tendency, such that if normal individuals initiate sleep at typical awakening times, for example, 7–8 a.m., they will have a greatly shortened REM sleep latency. In narcolepsy, latency to REM sleep is greatly reduced at all hours, making this a common diagnostic criterion for this disorder.

Extensive work has been done to localize the mechanisms responsible for generating sleep. The most important conclusion to emerge from these studies is that the 'core' generating mechanisms of non-REM sleep are in the forebrain, specifically in the thalamus, hypothalamus, and in the basal forebrain regions just in front of the hypothalamus. Stimulation of these regions can induce sleep and lesions of them can produce a profound insomnia. Certain neurons within this region are inactive in waking but highly active in sleep, with subsets of these neurons being activated by sleep deprivation and discharging shortly before sleep onset.

In contrast, the mechanisms generating REM sleep are located in the brain stem, specifically in the pons and caudal midbrain.

Several theories purporting to explain sleep–waking cycles have claimed that sleep-active and wake-active neurons become reciprocally active by virtue of their direct synaptic interactions. However, it is unlikely that sleep initiation, maintenance, and termination can be explained solely by such direct interactions. The implicated waking and sleep-active groups have direct connections and information can be relayed between these groups within milliseconds. Yet sleep is a cycle lasting 90 min in humans, with non-REM stages progressing to REM stages and then to waking. Within REM sleep, there is a gradual buildup of phasic activity, a period of elevated and irregular brain stem and forebrain activity and then a series of stereotyped changes including a reduction of REM, an EMG increase followed by awakening or by a progression into non-REM sleep. Unit recording reveals cyclical changes within the key cell groups corresponding to the progression of EEG changes, rather than rapid state transitions.

In order to explain the gradual time course of brain activity changes, physiological or neurochemical changes with a comparable time course have been sought. It has been found that sleep-active neurons respond to heat by inducing sleep and lowering brain temperature. Therefore non-REM sleep may have a role in the thermoregulation of the brain. There may also be chemical cues driving these neurons. A large number of chemicals thought to accumulate during waking have been hypothesized to be important in triggering activity in these cells, including adenosine released by high levels of energy consumption, prostaglandins, nitric oxide, and interleukins. However, it is not clear if any or all of these changes are necessary or sufficient to trigger or terminate this state.

Although most of the critical brain mechanisms mediating non-REM sleep are in the forebrain and those generating REM sleep are in the brain stem, the forebrain and brain stem interact in the generation of both these sleep states. For example, brain stem arousal systems antagonize forebrain sleep-inducing regions so that an intact animal has much less non-REM sleep than one in which the connections between brain stem and forebrain are severed. There are also important interactions between forebrain regions and the brain stem REM sleep generator. The loss of hypocretin neurons, all of which are located in the hypothalamus, is responsible for the disease of narcolepsy. The most unusual symptom of this disorder results from a dysregulation of the brain stem muscle tone inhibitory mechanism. This causes the suppression of muscle tone that normally characterizes REM sleep to occur in waking. This triggering can cause the awake narcoleptic to experience a profound muscle tone suppression, in extreme cases causing a fall to the ground, even though alertness is maintained.

Sleep in Birds

Birds appear to have sleep states resembling those in mammals. Higher-voltage EEG can be observed in quiescent states and is punctuated by relatively brief REM sleep episodes. Little work has been done on the mechanisms responsible for generating sleep in birds. It cannot be assumed that these are identical to those in mammals. To put this into context, circadian rhythm control has been investigated in birds and its anatomical substrates differ substantially from those seen in mammals.

Sleep Amounts in Mammals and Birds

The sleep durations of animals vary widely. Some animals such as the giraffe sleep as little as 2 h a day. Others such as the opossum sleep 18 h a day. Humans typically have 7–8 h of sleep a day with 4 h in REM sleep. It was hypothesized that differences in sleep across species were correlated with some physiological feature of each animal, such as body mass, brain size, intelligence, body temperature, or life span. If so, this would have been a starting point for determining the physiological function of sleep. However, although some weak relations were found across mammals, these relationships mostly evaporated as the collected data and analysis techniques increased in quality and amount. Significant relations explained only a very small portion of the variance and even these relations appear to be largely a function of the mathematical treatment of the data. Measures that attempt to factor in sleep 'intensity' to explain the variability of sleep duration across species do not appear to solve this problem, as animals that sleep longer also appear to sleep more deeply.

A further problem with this approach is that to the extent that very weak and variable relations between the above physiological variable and sleep state have been claimed in mammals, none of these relations appears to hold in birds. Thus, this work does not appear to be leading to convincing evidence for a simple physiological explanation for sleep time or sleep stage duration across species (**Figure 1**).

An important recent development has been the appreciation of the differences between land mammals and marine mammals. Dolphins never show the long periods of bilaterally symmetrical high-voltage EEG activity that are used for identification of non-REM sleep in land mammals. Rather one hemisphere exhibits a sleep-like EEG while the other exhibits a wake-like EEG. Convincing evidence for REM sleep has not been seen in these marine mammals. Other subsequently studied cetacean species have shown the same unihemispheric sleep waves and apparent lack of REM sleep. The animals may be mobile and responsive during this EEG pattern,

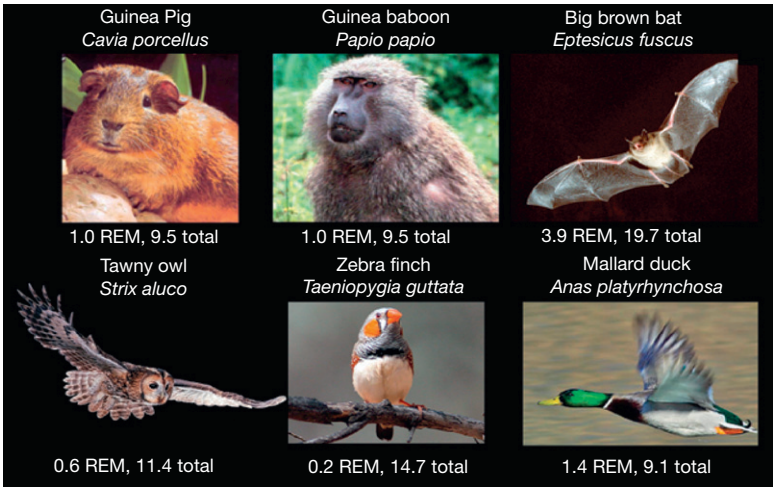

Figure 1 Sleep time is not strongly related to physiological variables. Examples of reported mammalian and bird sleep amounts are shown (see Siegel 2001, 2005, 2008, 2009 for further examples). Noteworthy is the similarity of sleep parameters in the guinea pig and baboon, animals that dramatically differ in almost every physiological parameter, and the very high level of sleep in the big brown bat and the variability of REM sleep parameters in birds. A variety of studies have attempted to correlate total sleep times and REM sleep times or percentages with physiological variables, for example, metabolism, life span, brain/body weight ratio, and altricial–precocial status. (Early studies concluded that animals that were born in a relatively immature, helpless state (altricial) had more REM sleep as adults; however, later studies have disputed this.) Recent studies have found that relations between physiological variables and sleep duration disappear or reverse depending on which animals are included and excluded and how the data are handled. The few studies finding significant relations between sleep and physiological variables have found correlations that explain very little of the enormous variance in sleep parameters across homeotherms (Siegel, 2009). Credits for pig and baboon in Siegel 2001; Bat, billbatboy ca.; Owl, Kim Taylor; Zebra finch, central pet; Mallard, U Michigan Zoology.

making tenuous any assumption that this is 'sleep,' of the kind that is seen in most land mammals studied. This asymmetrical EEG pattern may be related to the apparent lack of REM sleep in these mammals.

Studies in land mammals have generally shown that REM sleep amounts are greatest at birth. Therefore it was thought that REM sleep in dolphins might be observed if they were examined shortly after birth. However, when this was done, it was surprising to find that, unlike land mammals, both newborn dolphins and their mothers were continuously active 24 h day for weeks after birth. Similar observations were made in killer whales. In the wild, the postpartum period is characterized by migration over long distances from birthing grounds to feeding grounds. Dolphins and even killer whales are subject to predation at these times, so sensorimotor responsiveness is even more important for these species during migration than when they are in familiar waters. Although further studies are necessary, all indications are that they migrate while in a highly aroused state, rather than a 'sleep swimming' state. The healthy fur seal and walrus, under controlled ad libitum feeding conditions, will often spontaneously stay awake for 24–48-h periods, as indicated by both behavioral and EEG observations, a behavior only rarely observed in land mammals.

Interesting observations in the white crowned sparrow, a bird that migrates long distances, produced similar results. When these birds are kept caged in the laboratory they show greatly reduced sleep and increased activity during the periods when they would be migrating in the wild. This period of greatly reduced sleep and greatly increased activity and wing flapping lasts for several weeks. Despite this, there is no increased sleep after this period to 'make up' for lost sleep. This was also seen in observations of cetaceans. It can be shown that lack of rebound sleep was also seen after the period of postpartum activity in cetaceans.

The Effects of Sleep Deprivation

Sleep deprivation studies have been performed for over 100 years in an effort to find 'the' or 'a' function for sleep. Unfortunately, although such studies are simple in concept, the execution and interpretation of such studies are fraught with difficulty. Some of the earliest studies were done by Manacéine in 1894. She showed that long-term sleep deprivation, attempting to totally eliminate sleep, could be lethal in the dog. However, other studies using the same species found little lethality, possibly a function of the method of deprivation used. A relatively short period of recovery sleep was sufficient to dissipate sleepiness. With the advent of computer EEG scoring, an attempt was made to deprive rats of all sleep or of just non-REM sleep or REM sleep by forcing them to walk when sleep was detected. Total deprivation was not possible since the automatic scoring and the arousal technique required a period of sleep before sleep could be interrupted. This technique produces increasingly frequent arousals from sleep as the deprivation period progresses. These arousals may contribute to the pathologies observed. These included a reduction in grooming, skin lesions, hyperthermia, infection, and ultimately death. Signs of oxidative stress and degenerative changes have been seen in certain brain regions. However, similar effects have not been seen in rats deprived of sleep by other techniques, in

mice, or in other animals. In the early sleep deprivation studies in dogs, temperature did not change, whereas it increased greatly in the rats deprived by the 'disk over water' technique.

Voluntary sleep deprivation automated in humans does not produce marked physiological effects. The best studied case observed the effects of 11 days of supervised self-deprivation of sleep in a 17-year-old individual. The primary resulting symptom was sleepiness, which reversed after a 14-h recovery sleep. Large studies have examined the relation between life span and sleep duration in humans. It was found that humans reporting sleep times of 7 h have the longest life span. Humans reporting more than 7 h of nightly sleep have a shorter life span, but there is relatively little shortening of life span in humans who have less than 7 h of sleep. Only the very small percentage of humans with sleep times of less than 5 h have an appreciable shortening of life span, but this is far less than the reduced life span of humans with 9 or more hours of sleep, who constitute a much larger group. It can be claimed that long sleep is a response to some underlying pathology, accounting for earlier death, but there is so far no direct evidence supporting this. It remains to be seen if reducing sleep in long sleepers has a beneficial effect. However, the popular expectation that short sleep is correlated with short life span and long sleep with greater longevity is not supported by the existing literature. Sleep times in infants have been found to vary across cultures, with infants in Asian cultures having substantially shorter sleep times, of up to 1.7 h, than those in predominantly Caucasian cultures.

A disorder called fatal familial insomnia (FFI) is often presented as proof that sleep loss causes death in humans as it does in rats deprived by the forced walking method. However, FFI is a prion disease that affects all body organs and brain cells. There is little evidence that sleep induced by sedation can greatly extend life in FFI patients. Conversely, 'sleeping sickness' is frequently fatal. But this is an infectious disease and it is unlikely that it is the increased sleep that is responsible for death.

Sleep-Like States in Other Organisms: Do All Animals Sleep Like Humans?

Following on the assumption that sleep is a universal state, many researchers have focused on studying sleep-like states in reptiles, fish, or invertebrates. Invertebrates such as *Drosophila* and *Caenorhabditis elegans*, and fish such as the zebrafish have the great advantage of allowing relatively easy manipulation of the genome. Clearly, most of these species have states of reduced responsiveness. It is also clear that they cannot all have the same mechanisms controlling sleep that mammals have because their neuroanatomy, neurochemistry, and autonomic physiology differ greatly from those of mammals. Thermoregulatory systems have been shown to be intimately involved in sleep control, as outlined earlier, limiting the relevance of systems regulating activity and inactivity in poikilothermic animals. Nevertheless, it is likely that some neuronal mechanisms responsible for increasing and decreasing activity in invertebrates are operational in mammals. When one considers that adenosine and gamma-aminobutyric acid, transmitters crucially involved in mammalian sleep cycle control, are also present in invertebrates, the utility of investigating active and inactive state control mechanisms becomes obvious. However, the differences that are already known must also be appreciated. Octopamine, one of the most common transmitters in *Drosophila*, which has been implicated in the control of rest and activity states, does not exist in mammals. Conversely, hypocretin (also called orexin), the transmitter whose deficiency causes narcolepsy, does not exist in *Drosophila*. So, it is as naive to expect exact parallels between mammalian sleep states and invertebrate states of inactivity as it is to expect that there will be no commonalties between the mechanisms causing inactivity in vertebrates and invertebrates.

Is Sleep Vital for Memory Consolidation?

Despite early findings that sleep duration and REM sleep time are not related to intelligence in humans or to brain/body weight ratio across species, the idea that sleep is for memory consolidation is so intriguing and has received so much publicity that it has nearly become standard wisdom. However, recent well-controlled studies have undermined this idea.

REM sleep figures in many hypotheses that sleep functions to process and reinforce memories. One idea was that REM sleep represented an opportunity for reinforcing facts learned during the day or rehearsing motor tasks. It was claimed that during REM sleep there was a 'replay' of patterns of activity experienced in learning, presumably allowing the patterns to be 'stamped in,' thereby aiding in consolidation. The actual evidence for this is quite weak, as has been discussed elsewhere. This hypothesis predicts and requires that REM sleep deprivation should prevent or slow memory consolidation. However, this does not appear to be the case. Although stress and sleepiness are always a potential confound in sleep deprivation studies, they have not been properly controlled in studies of learning in REM sleep. A very large body of clinical observation had previously found that individuals taking monoamine oxidase inhibitors, who had had little or no REM sleep for years, had no apparent cognitive or learning difficulties. Millions of individuals have taken such drugs. It was speculated that learning problems might have been present but were overlooked. Therefore, a recent study used two different drug treatments to greatly reduce or completely suppress REM sleep after learning tasks. Testing was done immediately after the REM sleep–suppressed nights and also after sufficient time had passed so that all drugs were out of the body. No effect on learning was seen and, surprisingly, learning of certain tasks actually seemed to have significantly improved after REM deprivation.

Other studies have focused on the role of non-REM sleep in learning, typically procedural learning, that is, motor or sensorimotor learning. These studies have either lacked sleep deprivation conditions or have been plagued by poor control for circadian phase or for performance deficits caused by sleepiness. Several recent studies have rigorously controlled for these variables. These studies have found that as these controls are instituted, the sleep effects diminish. Students of learning have long known that 'learned' tasks can be interfered with if subsequent learning is attempted, as opposed to periods of doing other things or simply relaxation or reduction of sensory input reduction. It is well known that 'cramming' is not as efficient as

distributed learning and separation of learning sessions by sleep may be as effective as separation by waking. However, current evidence does not support the prior claim that sleep is required for consolidation of procedural tasks or has any advantage for memory consolidation over quiet waking states.

Why Do Animals Sleep?

The adaptive function of sleep does not appear to operate at the cellular level. The enormous variety of sleep times in closely related animals and the similar sleep times in animals that are physiologically very different (e.g., guinea pig and baboon) is at variance with such a cellular explanation (**Figure 1**).

Although Darwin put great effort into a discussion of the adaptive function of body size and anatomical features, exemplified by his analysis of beak shape in birds, he scarcely mentioned sleep. However, the adaptive value of sleep is enormous. Elephants sleep very little and they spend most of their waking hours in nearly continuous eating. The low caloric density of their food requires this. Indeed, the waking time of herbivores is inversely related to their body mass. In contrast, predators such as lions have significantly higher levels of sleep than herbivores when they are not food-deprived, that is, in zoos where they seldom go hungry. Some animals will reduce sleep when they are hungry, an adaptive response when food can be found. Other animals will reduce activity when food is scarce to conserve energy. Migrating animals frequently do not have the opportunity to sleep or eat during migrations. It is interesting to observe that current evidence suggests that they make up for the lack of feeding and weight loss by increased food intake before or after reaching their destination. However, they do not appear to make up for the lost sleep. Surviving species are those who have developed cellular mechanisms to cause them to adapt their sleep and activity levels to food shortages, migrations, predator avoidance, changes in light levels, inclement weather, and the many challenges to species survival.

Testing this hypothesis will require studies of how animals sleep over long periods of time in their natural environment, rather than the laboratory or zoo studies that have been favored in the past. Fortunately, modern electronics makes such studies increasingly practical.

Sleep time clearly differs across species and these differences must result from differences in the functioning or inputs to the critical groups for non-REM and REM sleep generation. Although the author's analysis indicates that the sleep function is not exerted at the cellular level, the *regulation* of sleep time is clearly exerted at a cellular level by critical cell groups located in the basal forebrain, hypothalamus, and brain stem. The regulation of these cell groups and their interaction remains to be understood.

Acknowledgments

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See also: **Background:** Sleep in Birds; **Sleep and the Nervous System:** NREM Sleep: Anatomy and Physiology; REM Sleep Anatomy and Physiology.

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