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Sleep is a mysterious, intricate biological symphony which is composed and conducted by the genetics, anatomy, physiology, neurochemistry, environment, and psychology of living organisms. The phenomenon of sleep is not a uniquely human experience, and with many variations on a theme, it is ubiquitous throughout the animal kingdom. In order to understand why we sleep and why there are perturbations which result in sleep disorders, it is of importance to study sleep in many different living organisms, including those with a long phylogenetic history, which may shed light on the origins of sleep. However, one might reasonably ask how can the study of sleep in diverse creatures such as insects, reptiles, birds, and dolphins—organisms so unlike ourselves—contribute to our knowledge about human sleep? At first glance the immediate answer would appear to be “not much.” However, to entertain the possibility that the study of animal sleep is inconsequential or even irrelevant in understanding human sleep and its disorders would be shortsighted. The identification and study of model organisms such as the fruit fly (*Drosophila melanogaster*), for example, have produced a dramatic explosion in our molecular and genetic knowledge about the mechanisms controlling the expression of sleep. These findings reverberate with new insights across the entire spectrum of sleep disorders medicine. Although the exact functions and purposes of sleep still remain unknown, many pieces of the sleep puzzle derived from phylogenetic studies have laid the foundation for unraveling these mysteries.

Most animal sleep studies have been performed in familiar mammals, and a recent review [1] underlines the fact that primarily mice, rats, cats, and dogs have been used experimentally to construct animal models of human sleep disorders. However, the literature is rich with studies of unusual mammalian and nonmammalian species which, although displaying remarkable variations in environment, evolutionary history, behavior, life span, anatomy, and physiology, exhibit the

behavioral characteristics of sleep and provide clues to the origins of sleep. At least from a behavioral standpoint, sleep appears to be a universally conserved phenomenon, and as we shall see, genetic and molecular aspects of sleep have also been conserved. Insects, fish, amphibians, reptiles, and invertebrates as well as mammals including egg laying monotremes (platypus and echidna), marine-dwelling cetaceans (whales, dolphins, porpoises) and pinnipeds (seals), marsupials (kangaroo, possum), and placental mammals all display behavioral sleep. Documentation of distinctive electrophysiology, which can be different from that of mammals, may also accompany behavioral sleep in nonmammals. By studying living organisms with a long history in the fossil record, clues to the role of sleep in species survival as well to the function of sleep might be obtained. There are several recent detailed reviews on behavioral and electrophysiological characteristics of mammalian and nonmammalian sleep [2–6]. Here, we will not recapitulate these details, but rather draw upon relevant studies from the animal literature to explore how clues from phylogenetic studies have contributed to the understanding of human sleep and human sleep disorders.

The Definition of Sleep

The first task in understanding sleep mechanisms is to define sleep. There are two different approaches to this definition, behavioral and electrophysiological. The behavioral definition of sleep is well established, and behavioral criteria have been used to identify sleep in diverse insects, invertebrates, mammalian, and nonmammalian organisms. These criteria include (1) a species specific posture; (2) behavioral quiescence; (3) increased arousal thresholds; (4) state reversibility to distinguish sleep from coma or torpor; and (5) a homeostatic response to sleep deprivation, i.e., an increase in sleep amount following sleep deprivation. In mammals, there are distinctive electrophysiological events which accompany behavioral sleep and which distinguish sleep

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from wakefulness. During nonrapid eye movement (NREM) sleep, the EEG is characterized by high amplitude slow waves as well as by other distinctive wave forms such as sleep spindles and K complexes. In humans, NREM sleep has been subdivided into three or four separate sleep stages with specific EEG waveform criteria detailed for each stage [7, 8]. Rapid eye movement (REM) sleep alternates in a cyclical fashion with NREM sleep. REM sleep is characterized by a low amplitude EEG similar to that of waking, skeletal muscle atonia, and rapid eye movements. REM sleep is a period of intense physiological activity in a sleeping organism and other distinctive events during REM sleep include vivid dreaming in humans, increased single neuron firing in the brain, increases in brain temperature, and penile erections. REM sleep is also referred to as paradoxical sleep (PS) recognizing the incongruity of this active physiology in a sleeping organism.

Since there is a close correspondence between the distinctive electrophysiological markers of mammalian sleep and behavior, electrophysiology is generally a more efficient means, rather than continuous visual observation of behavior, in defining mammalian sleep. However, as we shall see, although the behavioral criteria for sleep may be met, the electrophysiological expression of sleep is often different in nonmammalian species.

In comparison with mammals, there are relatively few electrophysiological studies which have been performed during behavioral sleep in nonmammalian organisms. Furthermore, there is controversy as to whether the “true” indicators of electrophysiological sleep are present since nonmammalian electrophysiology is quite different from that of mammals. The high amplitude slow waves defining mammalian NREM sleep have not been reliably observed during nonmammalian behavioral sleep with the exception of birds [9]. Similarly, REM sleep has not been rigorously documented in nonmammals, again with the exception of brief bouts of avian REM sleep usually lasting less than 10 s. In mammals, the thick neocortical layer responsible for generating slow wave activity, is absent in nonmammals, making it unlikely that slow waves can be generated without this anatomical substrate. There are some scattered observational reports of REM sleep in nonmammals, but most studies have not presented rigorous or convincing evidence for REM sleep.

There is, however, a variety of other electrophysiological correlates associated with behavioral sleep in invertebrates and nonmammalian vertebrates. A sampling reveals a decline in local field potentials during behavioral sleep in fruit flies [10, 11], spindle-like activity during quiescence in the frog [12], isolated spikes and spike trains during behavioral quiescence in the octopus [13], spikes during behavioral wakefulness and waves of 15–20 Hz during

behavioral sleep in the crayfish [14], and high amplitude spikes during behavioral sleep which disappear with behavioral waking in turtles, tortoises, lizards, and caiman [15–18].

These findings, which are dissimilar to the electrophysiology of mammalian sleep, have prompted debate as to whether the sleep of nonmammalian organisms is the same state as mammalian sleep and whether it is logical or scientifically reasonable to impose the mammalian criteria for sleep on nonmammalian species [19–21]. Other electrophysiological findings which further complicate the picture include reports of high amplitude slow waves characteristic of mammalian NREM sleep occurring during behavioral sleep in young caimans [22], REM sleep in lizards [23], high amplitude slow waves during waking in lizards [24], and high amplitude spikes during reptilian behavioral sleep which appear to be analogous to ventral hippocampus spikes recorded during NREM sleep in mammals [25]. Libourel and Herrel [4] have recently suggested that explanations for these varied findings in reptiles may be the result of differences between natural or seminatural recording conditions and laboratory conditions, differences in habituation to the recording environment, differences in electrophysiological recording techniques, methodological differences in evaluating arousal responses, and differences in electrode placements since no stereotaxic atlases of reptilian brains are available to ensure consistency of electrode placement. This debate surrounding sleep in reptiles is central to the question of whether nonmammalian organisms sleep if they do not exhibit mammalian electrophysiology. Rather than attempt to resolve this issue, examples from phylogenetic sleep studies will be used to evaluate the contribution of phylogeny to human sleep.

Model Organisms in the Study of Sleep

The revolution in our current knowledge about the neurochemical, molecular, and genetic bases for sleep has been propelled forward at an extraordinary rate by the introduction of model organisms, primarily the fruit fly (*Drosophila melanogaster*), and round worms (*Caenorhabditis elegans*) as well as the zebrafish (*Danio rerio*) (Figs. 9.1, 9.2, 9.3). Compared to mammals, there are a number of features which make these organisms both practical and scientifically desirable for study. There is economic and logistical ease in maintaining large colonies, and a short life span as well as short reproductive cycles allow for the rapid evaluation of experimental manipulations. Increased statistical power can be achieved as the result of a large number of available subjects, and there is the potential for rapid replication of results in genetically identical organisms under similar

conditions. Furthermore, the presence of drosophila appendages such as wings and legs allow for observations of complex behaviors. The most significant scientific advantage is the relatively small number of neurons (approximately 100,000) in the adult drosophila brain as compared to the staggeringly large number of neurons (approximately 86 billion) in the adult human brain [26, 27]. The drosophila genome has been mapped with shared homologues identified in humans [28–31]. In addition, the neurotransmitters which have been demonstrated to play a role in the control of human sleep, including serotonin, dopamine, acetylcholine, GABA, and epinephrine (the equivalent of octopamine in drosophila), and in the case of zebrafish, orexin, are present [32, 33].

A model organism is a model only if, despite strong genetic similarities to humans, there is evidence that behavior meets the criteria for sleep. *Drosophila* quiescence does fulfill the criteria established for behavioral sleep [34, 35]. Behavioral quiescence, a stereotypic posture, elevated arousal thresholds, state reversibility with stimulation, and a homeostatic response to deprivation of rest, i.e., rest increased following the period of rest deprivation are present. This homeostatic response to deprivation is independent of at least one central clock gene, indicating that the homeostatic response is not simply a circadian response rather than a response to rest deprivation. Additional evidence for the similarity between *drosophila* quiescence and human sleep includes a similar response to drugs including caffeine, modafinil, and methamphetamine [36–38]. Antihistamines increase quiescent periods in *drosophila* similar to drowsiness in humans [35]. Finally, there are age-related changes in sleep similar to the changes in sleep amounts across the human life span [35, 39].

Drosophila is the organism which has arguably received the most attention as a model system for the genetic and molecular study of sleep. However, zebrafish (*D. rerio*) also offer similar biological and behavioral properties with respect to sleep for consideration as a model organism [40, 41]. Another proposed model organism is the round worm (*C. elegans*). During lethargus, a quiescent behavioral state which occurs after each of four molts, the behavioral criteria for sleep, including a homeostatic response to rest deprivation and elevated arousal thresholds, are present [42, 43]. There is genetic and molecular conservation between *drosophila* and *C. elegans* [44, 45]. A recent study also provides evidence that quiescence during molts in another worm, the tobacco hornworm (*Manduca sexta*), meets the behavioral criteria for sleep [46]. Thus, these model organisms with their practical and experimental advantages may have the potential to observe, and perhaps unlock, the underlying mechanisms controlling the expression of sleep.

Optimal Sleep and Mortality

The ill effects of insufficient sleep may be witnessed on some of the principal organic functions, but it is the brain and nervous system that suffer chiefly in the first instance. The consequences of a too protracted vigil are too well known to be mistaken, and many a person is suffering, unconscious of the cause, from the habit of irregular and insufficient sleep.

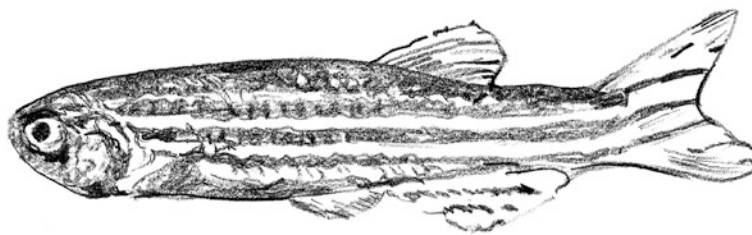
William A. Hammond, 1866 [47].

The consequences of insufficient sleep have long been a subject of debate and discussion. Still today, some of the most common questions asked of sleep clinicians revolve around sleep quality and sleep amounts: How many hours of sleep per night are necessary for good health, is a lack of

Fig. 9.1 The Fruit Fly
(*drosophila melanogaster*)



Fig. 9.2 The Zebra Fish (*danio reiro*)



sleep harmful, and will inadequate amounts of sleep or poor quality sleep affect longevity? As we shall see, there are data to suggest that too little or too much sleep may impact health and life span in humans. For example, persistent, but not intermittent, self-reported insomnia is associated with an increased risk of all-cause mortality over a 20-year follow-up period, suggesting that decreased sleep amounts negatively impact life span [48]. In contrast, prolonged sleep amounts have been associated with an increased risk of fatal and nonfatal stroke [49], conversely suggesting that increased sleep amounts negatively impact health. Although studies of sleep in nonhuman organisms reveal significant variations in sleep amounts, there are no data available which shed light on the impact of these variations in promoting species survival and longevity. As we shall see, however, there are examples of “natural” sleeplessness in the animal world, and most importantly the genetic manipulation of model organisms has advanced our knowledge about the mechanisms controlling sleeplessness.

One approach to addressing the question of whether there are optimum amounts of sleep associated with a long life span would be to examine the relationship between sleep amounts and mortality in large populations. A systematic relationship between human sleep and mortality was first described over 30 years ago [50], and since that time a body of epidemiological literature has accumulated which suggests fairly consistently that short and, somewhat inconsistently, that long sleep amounts are associated with increased mortality as well as with diseases such as obesity, diabetes, hypertension, and cardiovascular disease [51–55]. Typically, the best survival curves are associated with about 7 h of sleep per night. Shorter sleep times are variably defined in these studies as 4–6 h per night and long sleep times as more than 8–9 h per night, raising the question of whether the common recommendation of a minimum of 8 h of sleep per night is appropriate [56]. Of note is that in virtually all epidemiological studies, sleep duration was assessed by subjective estimates and not overnight sleep studies utilizing polysomnography, suggesting the possibility of subjective over- and underestimates of sleep duration which could bias results. Also, it cannot be determined in these epidemiological studies whether short and long sleep durations are the direct cause of increased mortality or whether short and long

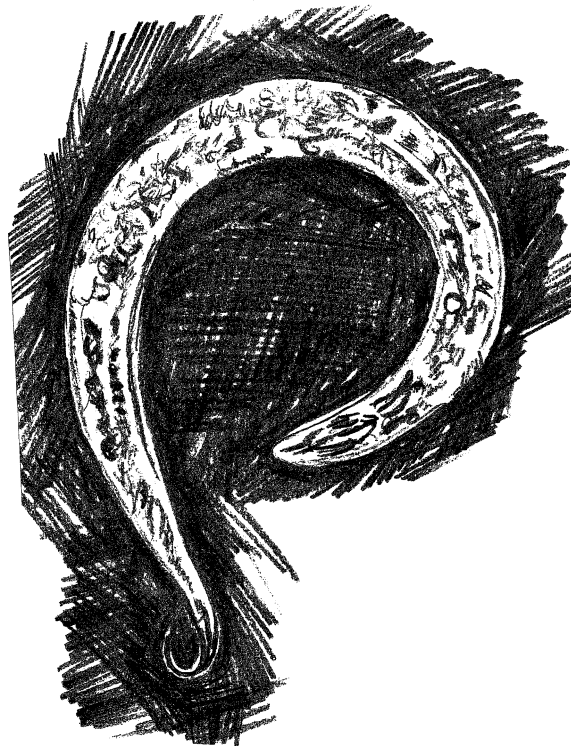


Fig. 9.3 The Round Worm (*caenorhabditis elegans*)

sleep durations are the product of an underlying intervening condition which in turn is responsible for these associations with mortality.

The most extensive and rigorous review of the literature addressing the question of optimal sleep time was recently performed by a panel of sleep experts assembled by the American Academy of Sleep Medicine and the Sleep Research Society [57]. The consensus of the panel was that less than 6 h of sleep is inadequate to support optimal health, but no consensus could be reached about the effects of 9 h or more on optimal health. The final consensus was that 7 h was the minimum amount of daily sleep necessary to support optimal health. However, no consensus could be reached about an upper maximum threshold of sleep for optimal health. This is not surprising. A careful review of the epidemiological studies supporting a relationship between sleep duration and mortality raises the issue of, for example, how

variable methodologies for determining total sleep time may weaken the conclusions which can be drawn from the U-shaped curve characteristic of the relationship between sleep duration and mortality [58]. Also of interest in these considerations of mortality and sleep duration is the demonstration of a dose–response relationship between hypnotic sleep medications typically used to treat short sleep and an increased mortality risk as well as an increased cancer risk for the most frequent users of hypnotics [59]. These findings suggest that intervening variables, inconsistently assessed in epidemiological studies, may contribute substantially to the association between sleep duration and mortality.

Human epidemiological studies, although inviting speculation about the predictive value of sleep amounts in determining life span, do not reveal the biological mechanisms responsible for this relationship. There are age-related changes in *drosophila* sleep similar to the sleep fragmentation and decreased sleep amounts observed in aging humans, suggesting that *drosophila* may shed light on the mechanisms mediating sleep and longevity in humans [39]. Several genetically engineered *drosophila* mutants, including *Minisleep (mns)*, *Hyperkinetic (Hk)*, *Sleepless (sss)*, and *Insomniac (inc)*, have been developed which have markedly reduced sleep amounts in comparison with wild-type flies [60–62]. Life span in these short sleeping flies is reduced, suggesting that sleep duration has a direct relationship to longevity. Of note is that waking behavior was not impaired in mutant strains. These mutations are mediated by *Shaker*, a gene which encodes for the voltage dependent potassium channel. Another short sleeping mutant, *fumin (fmn)*, which has a mutation in the dopamine transporter gene (DAT), does not show a reduced life span nor do these flies exhibit a homeostatic response to sleep deprivation [63]. There is substantial evidence from a number of studies to indicate that dopaminergic systems have a major role in the expression of arousal and sleep [36, 64]. Mutations of the *amnesiac (amn)* gene, which has a role in the adenylate cyclase/cAMP signaling pathway, are associated with fragmented sleep and, similar to *fmn*, are not associated with a rebound in quiescence following deprivation [65]. Of note is that a high-calorie diet in *fmn* mutants results in further reductions in sleep amounts and reduced longevity, suggesting that accelerated aging and shortened sleep are impacted by increased caloric intake [66]. Also time-restricted feeding with food access limited to 12 h per day in wild-type flies, although not changing caloric intake, is associated with improvements in sleep and ameliorates an age-related cardiac decline [67]. These studies indicate that there are a number of different factors which affect the expression of sleep. Also of interest are mutations in genes which would not seem to play a role in sleep expression such as the fragile X mental retardation gene (*Fmr1*). Overexpression of

drosophila Fmr1 results in shortened sleep, whereas the loss of *Fmr1* is associated with significantly longer sleep amounts as compared to control flies. In neither mutant was there a homeostatic response to sleep deprivation, and of particular interest relevant to the human epidemiological studies is that life span is reduced in both the short and long sleeping *Fmr1* mutants [68]. Finally, it is most likely that there is not a single dedicated “sleep gene,” but that other genes more broadly controlling cellular and neuronal functions also control the expression of sleep. An example is the demonstration that decreasing cyclin A, a protein which regulates the progression of cells through the cell cycle, results in decreased total sleep and a decrease in the homeostatic response to sleep deprivation [69]. More recently, a sleep regulating protein *redeye (rye)* which interacts with *sss* has been identified in short sleeping mutants and after sleep deprivation in wild-type *drosophila* [70].

The cellular mechanisms controlling sleep in humans are virtually unknown. The complaint of insomnia, difficulty falling and staying asleep typically with resulting daytime fatigue, affects approximately 30 % of the population in varying degrees of severity [71]. Not only physiological factors, but the contribution of psychological factors to this disorder, make it a daunting task to untangle the mechanisms which are involved in the expression of human sleeplessness. There are two disorders characterized by shortened sleep which have been identified in this category of sleep difficulties and which have a known genetic basis. The first is advanced sleep phase syndrome in which affected family members have a mutation of the *hPER2* clock gene involved in controlling the timing of sleep. Although the sleep cycle is regular in affected family members, there is a four hour advance of sleep, temperature, and melatonin rhythms in affected as compared to unaffected family members [72]. A second disorder of sleeplessness with a known genetic basis is fatal familial insomnia. This disorder is a rare, inherited, progressive neurodegenerative disease in which there is a progressive inability to sleep eventually culminating in total sleeplessness and death [73]. Autopsy findings reveal selective bilateral neuronal loss and reactive gliosis of the anterior and dorsomedial thalamic nuclei with an accumulation of prion protein. In affected individuals, there is a single mutation on the prion protein gene *PRNP* at position 178 combined with a mutation at position 129 [74]. Although these are two very specific instances of sleep difficulty, there is, however, evidence to suggest that short sleepers do carry a gene with a specific *DEC2* (also known as *BhLHE41*) mutation. This mutation was identified in a family with two individuals who had lifelong short sleep averaging 6.25 h per day as compared to noncarrier family members who averaged 8.06 h per day [75]. Subsequent work has identified other mutations of *BHLHE41* associated with decreased total sleep time and with fewer average

lapses in performance on a psychomotor vigilance task, suggesting resistance to the effects of sleep deprivation [76].

Despite this large body of literature which suggests that sleep and longevity are related, there continues to be no clear answer to the question of whether there is an optimal amount of sleep which can promote maximum longevity in humans. Additionally, understanding the genetic and cellular mechanisms responsible for human sleeplessness is clearly in its infancy. There are, of course, no formulas to translate the equivalency of *drosophila* sleep minutes which can be manipulated by these mechanisms into human sleep hours. As previously noted, at least some of the ambiguity in human studies may be related to subtle differences in survey questioning about sleep amounts which result in subjective under- or overestimation of sleep time [58].

There are also variables identified from *drosophila* studies which may interact with genetics to potentially affect sleep with respect to longevity including social enrichment or isolation, environmental conditions, diet, methods of evaluating quiescence, and climates and altitudes [77–82]. There is also recent evidence that variations in population density during normal *drosophila* larval development affect sleep duration in adults, but not in *amn* mutants, suggesting lifelong cellular changes in sleep controlling mechanisms dating from infancy as the result of environmental exposures [83]. Although not as intensively studied as *drosophila*, other mammals and non-mammals also demonstrate that environment and social experience may affect the expression of sleep. For instance, sleep in honey bees is increased by exposure to the bee colony environment in comparison with isolated bees [84]. Electrophysiological recordings of unrestrained sloths in the rain forest reveal that total sleep time is substantially less than under laboratory conditions [85]. The threat of predation and social status may also play a significant role in determining sleep amounts in mammals [86–88]. In reptiles, young caimans recorded in a colony exhibited differing electrophysiology from caiman recorded in isolation, suggesting that these differences in environment and socialization may have affected the expression of sleep [17, 22].

The most striking example of the evolutionary effects of habitat upon sleeplessness is illustrated by studies in the Mexican cavefish (*Astyanax mexicanus*) [89, 90]. Surface- and cave-dwelling populations of these fish differ remarkably in daily sleep amounts with surface fish averaging over 800 min and three different cave-dwelling populations averaging 110–250 min per day. Blockade of B-adrenergic receptors with propranolol produced dose-dependent increases in cave fish sleep without any effect at any dose on sleep of surface-dwelling fish. Adrenergic antagonists did not affect sleep in surface dwellers, but cavefish sleep increased significantly in response to the B1 antagonist atenolol. The number of catecholamine neurons is conserved in cavefish as opposed to surface-dwelling fish, suggesting

that an increase in the adrenergic arousal system in cavefish as compared to surface dwellers has occurred during evolution. Other recent fish studies have examined circadian rhythmicity in aging killifish (*Nothobranchius*) as well as the induction of quiescence by melatonin in the three spot wrasse (*Halichoeres trimaculatus*) [91, 92].

In summary, much of the appeal of the findings from human epidemiological studies resides in the simplicity of the U-shaped curve which suggests that the relationship between longevity and sleep is straightforward. Both short sleep and long sleep are associated with increased mortality. However, as we have seen from the animal literature, these data are fraught with many potentially uncontrolled and confounding genetic, environmental, and ecological factors which have the potential to alter this relationship. An unambiguous answer to the question of how much sleep and under what conditions are necessary for optimal longevity remains unanswered.

Pharmacological Development

A significant advantage of utilizing model organisms to explore the molecular basis of sleep lies in their well-studied genome which is amenable to precise manipulation. Another potentially productive area in which these model organisms may be of substantial benefit is in the area of developing new and focused pharmacological treatments for human diseases, including sleep disorders [30]. For example, approximately 70 % of human genes have at least one zebrafish orthologue, and as a result, zebrafish have been extensively used to develop human disease models [28, 93]. The correspondences between the human genome and the genomes of model systems suggest that model organisms could be instrumental in developing in vivo drug treatments at a molecular level for modifying or treating human sleep disorders. Zebrafish are sensitive to major classes of drugs including anxiolytics, hypnotics, and stimulant among others which could potentially be used to treat disordered sleep [33, 40]. In addition, the cost of screening pharmacologically active compounds is substantially less expensive in an organism such as the zebrafish so that an increased number of compounds can be economically evaluated. New effects and mechanisms of drug action on waking and quiescence produced by similar major neurotransmitter pathways in both zebrafish and mammals, and identification of poorly understood compounds can be rapidly assessed.

Cross-translational studies between model organisms and humans also open new avenues for the discovery of waking and sleep biomarkers which may have practical application. One example is the discovery of salivary amylase as a biomarker for sleepiness and sleep drive in both *drosophila* and humans utilizing cross-translational studies [38, 94]. The

potential applications of such a “sleepiness marker” are far reaching. For example, multiple sleep latency testing (MSLT), a series of daytime nap tests spaced throughout the day according to a standard protocol, is currently the standard electrophysiological assessment tool for objectively evaluating a patient’s subjective complaint of sleepiness. The maintenance of wakefulness test (MWT) is used in a similar protocol to evaluate daytime alertness [95]. With further elaboration of the salivary amylase findings, convenient, rapid, cost-effective alternatives to the MSLT and MWT could potentially be developed for objective assessment of sleepiness and alertness in settings where polysomnography is unavailable. Another practical application of these findings may be the assessment of drowsy drivers similar to breathalyzer assessments of alcohol consumption or the assessment of persons such as air traffic controllers, bus drivers, or train conductors whose occupations require a high degree of alertness to ensure public safety.

The utilization of model organisms for development of effective pharmacological treatments and sleep-related biomarkers is still in development. However, as knowledge about sleep mechanisms continues on a rapid, steep trajectory, it is not unreasonable to anticipate that the practical application of this knowledge will also follow.

Sleep Disorders

Narcolepsy

The mechanisms underlying the expression of narcolepsy were virtually completely unknown until the serendipitous discovery by Dr. William Dement of a dog with what appeared to be cataplectic attacks similar to the cataplectic attacks demonstrated by human narcoleptic subjects [96]. Since that time, understanding the etiology of narcolepsy has arguably been primarily the result of discoveries in animal research [97, 98]. The cardinal symptoms of narcolepsy include excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis, and cataplexy, a sudden loss of muscle tone with strong emotions. Electrophysiologically, narcolepsy is diagnosed by the rapid onset of REM sleep, typically with a latency of less than 15 min as compared to the 60- to approximately 90-min latency to the onset of REM sleep in normal subjects. Narcolepsy, in conjunction with a history of clinical symptoms, is diagnosed by the rapid onset of REM sleep during a protocol of daytime nap testing [95]. Based on epidemiological studies in several countries, the prevalence of narcolepsy has been estimated at between 25 and 50 per 100,000 persons [99]. Of all the sleep disorders, the genetics, neuropharmacology, and molecular mechanisms of narcolepsy appear to be the best understood [100]. The

discovery of orexin (hypocretin) deficiency resulting from the loss of orexigenic neurons in narcoleptic dogs, mice, and humans and the close association of the human leukocyte antigen DQB1*0602 and DQA1*0102 in almost all narcoleptics has led to the conclusion that narcolepsy is an autoimmune disease [101]. However, the mechanisms by which orexin is depleted are unknown. Potential environmental triggers for the development of narcolepsy which have been identified include upper airway infections and the H1N1 flu vaccine in genetically susceptible individuals [102, 103].

Gene therapy clinical trials are now being performed for a variety of human diseases including cancer, cardiovascular disease, Parkinson’s disease, and cystic fibrosis [104]. Hypothalamic gene replacement therapy in orexin-deficient mice improves sleep quality and the timing of REM sleep, but does not improve cataplexy [105]. Conversely, gene transfer into the zona incerta in orexin-deficient mice improves cataplexy, but not sleep fragmentation [106]. There are no data on gene replacement in narcoleptic humans, but the findings in mice suggest that this approach may be a promising one. As the result of this research in narcolepsy, a new sleeping medication, suvorexant, has been developed as a treatment for insomnia. Suvorexant is a dual orexin 1 and orexin 2 receptor antagonist which dose dependently enhances sleep in humans [107, 108]. Suvorexant was approved for human use by the Food and Drug Administration in August, 2014. Of interest is a detailed account of suvorexant’s approval process which appeared in the popular press [109].

A major stumbling block in the use of model organisms to study narcolepsy is the absence of REM sleep. Birds are the only nonmammalian organism to display convincingly behavioral and electrophysiological signs of REM, but avian REM sleep bouts are brief, lasting only a few seconds. Could it be possible that REM sleep is present in *drosophila* or zebrafish and that it has simply been missed? This seems unlikely particularly in light of a recent detailed video analysis of zebrafish eye movements and respiration during sleep which did not uncover any credible evidence for the presence of REM [110]. Additionally, the limited behavioral repertoire of model organisms precludes their usefulness in evaluating, for example, cataplexy or sleep paralysis which are major signs of narcolepsy. The *drosophila* brain does not contain orexin. However, zebrafish have a distribution of orexin expressed in the brain in a fashion similar to that of mammals [111]. Overexpression of orexin in zebrafish results in elevated motor activity, decreases in arousal thresholds, and shortened, disturbed sleep in the dark [111, 112]. During the course of evaluating zebrafish hypocretin receptor mutants, Yokogawa et al. [112] made several interesting observations with respect to sleep. Normal adult zebrafish maintained under constant light conditions have an almost complete suppression of sleep. A homeostatic

rebound response to this sleep deprivation was not observed, and a progressive return to sleep occurred over the course of one to two weeks. Following sleep deprivation in response to electrical stimulation, there was no homeostatic response when animals were released into light, but a homeostatic rebound occurred with release into darkness. Additionally, exposure to light during the last 6 h of the biological night produced a marked suppression of sleep without a homeostatic rebound with release into darkness.

Although the orexigenic substrate of the zebrafish brain parallels that of the mammalian brain, the zebrafish is not a particularly enlightening model organism to elaborate upon mechanisms controlling narcolepsy. None of the model organisms studied to date would appear to serve as a model for narcolepsy. Furthermore, the unusual response of zebrafish sleep to light with sleep suppression and to the absence of a homeostatic response following sleep deprivation suggests that there are components of zebrafish sleep which should not be considered as a model substrate for sleep disorders.

Sleep Apnea

The cardinal symptoms of obstructive sleep apnea (OSA) are well known and unmistakable in their presentation: loud snoring and pauses in respiration terminated by explosive snores, breath holding episodes witnessed by a bed partner, and excessive daytime sleepiness resulting from the arousals terminating often hundreds of respiratory pauses during sleep. Severe OSA is a risk factor for arterial hypertension, heart failure, stroke, pulmonary hypertension, and maternal morbidity [113, 114]. A familial component has been described in several studies [115–117]. There are two reports of a naturally occurring model of sleep apnea in the English bulldog which has a crowded upper airway anatomy similar to sleep apnea patients [118] and in obese miniature pigs [119]. Nonmammalian species have not been observed to have sleep apnea, and model organisms have not been developed for experimental evaluation of this disorder.

The experimental research on sleep apnea has been focused on the induction of sleep apnea in dogs, rats, and mice by artificially occluding the airway and exposure to repetitive hypoxemia [120–123]. The cardiovascular and neurochemical consequences of sleep apnea have been described in these experimental models, but the genetic and cellular components of sleep apnea are not well understood. OSA is a complex disease process with multiple interactive factors including age, weight, gender, arterial and pulmonary hypertension, cardiovascular disease, and metabolic disorders. It is almost certainly the case that there are multiple cellular and genetic components contributing to the expression of OSA. A gene encoding the allele APOEε4 which is

essential for cholesterol metabolism and transport has been associated with OSA in adults and children. However, a meta-analysis of studies reporting an association between APOE and sleep apnea concluded that the association is weak [124]. Another meta-analysis of OSA genetic association studies revealed that TNFA rs1800629, which may also be associated with heart disease and heart failure as well as chronic obstructive pulmonary disease, was significantly associated with OSA [125]. These authors concluded that studies examining OSA genetics did not typically provide robust evidence. Thus, the complexity of OSA presents significant challenges in understanding the genetics of this disorder, and at least at the present time, a model organism with a well-known genome combined with the symptoms of OSA does not appear to be on the horizon.

Restless Legs Syndrome (RLS)

Clinical symptoms of RLS include restless, creeping, crawling, uncomfortable sensations in the legs during sedentary activities with a worsening of these sensations beginning in the evening. They are accompanied by an irresistible urge to move the legs for temporary relief. Typically, there is a worsening of the sensations at sleep onset which results in substantial difficulty falling asleep. Key factors in the expression of RLS are iron deficiency and the involvement of the dopaminergic system in regulating iron metabolism, although the mechanism of this relationship is not clearly understood. Currently, dopamine agonists, such as ropinirole and pramipexole, which enhance brain dopamine, are the treatments of choice for RLS [126]. Prevalence, depending upon the complexity of survey questions, ranges between 9.4 and 15 % querying RLS as a single symptom. This range changes somewhat to 3.9–14.3 % utilizing the criteria of the International Restless Legs Syndrome Study Group [127, 128]. Inclusion of stricter diagnostic criteria such as the frequency and severity of symptoms results in decreased estimates of prevalence.

Genome-wide association studies (GWAS) have opened a new window onto the genetic underpinnings of human RLS. GWAS studies in both European and US populations have identified genomic loci which are associated with restless legs syndrome including *MEIS1*, *BTBD9*, and *MAP2K5/LBXCOR1* on chromosomes 2p, 6p, and 15q [129–131]. Animal models have been proposed for the study of restless legs syndrome. Mice and rats with lesions of the A-II dopaminergic nucleus which projects to the spinal cord have demonstrated an increase in locomotor activity [132, 133]. Spontaneously hypertensive rats exhibit increased motor activity, suggesting a possible model for the study of RLS [134]. One study in *C. elegans* demonstrated that the *MEIS1* worm orthologue increased ferritin expression and human

cells cultured in iron-deficient conditions revealed decreased MEIS1 expression, lending further support to the role of these genes in iron metabolism [135].

Animal studies are typically the catalyst for human research. However, the discovery of these potential RLS loci via human GWAS provided a reverse “human to animal” stimulus for the development of a *drosophila* RLS model [136]. As described above, the diagnosis of RLS in humans is accompanied by reports of an irresistible urge to move the legs for relief of discomfort. Of course, these sensations cannot be communicated by *drosophila*, but movement can be operationally used to infer the presence of RLS. Genetic alteration of the fly homologue *dBTD9* which corresponds to human *BTBD9* resulted in fragmented sleep characterized by a decrease in the duration of sleep bouts and an increase in the number of sleep bouts and waking after sleep onset, suggesting the sleep fragmentation of RLS patients. However, sleep duration in flies per 24-h period was not different between mutants and controls. Although flight and negative geotaxis were normal in mutants, when confined to a restricted space flies were hyperlocomotive, reminiscent of the movements experienced by RLS patients during the forced immobility test (FIT) [137]. Uninterrupted bouts of walking were also longer in mutants. Comparing dopamine levels in mutants and controls, mutants revealed a 50 % reduction in dopamine, suggesting a relationship between alterations between *BTBD9* and maintenance of normal dopamine levels. Also of note is that treatment with pramipexole, a dopamine agonist, restored sleep consolidation in mutants to control levels, again suggesting a significant role for dopamine in the expression of RLS. *dBTD9* is also implicated in the regulation of iron metabolism and ferritin homeostasis.

These genetic explorations into the expression of RLS in a model system provide evidence of the complex relationship between specific genes and the role of dopamine in regulating ferritin levels. Ideally, with further studies more effective treatments for RLS will be discovered.

Unusual Sleep Disorders

There is a group of unusual sleep disorders, the parasomnias, in which the distinction between waking and sleep becomes blurred and waking behavior appears to intrude into sleep. Included in this group of disorders are confusional arousals, REM behavior disorder (RBD), sleep walking, and sleep-related eating disorders [138]. Complex vigorous motor activity which can become violent in the case of RBD and loud vocalizations may accompany these disorders. Not a great deal is known about the prevalence of parasomnias, but sleep walking, for example, is relatively common with a lifetime prevalence estimated at 29.2 % [139]. RBD is rarer with a prevalence of 2.01 % and subclinical RBD estimated at 4.95 % in a Korean elderly population [140]. Due to the complexity of behavior in parasomnias, no animal models

have been developed to study these disorders, and not surprisingly no naturally occurring animal models of parasomnias have been identified. However, early studies in cats revealed “dream enacting” behavior following pontine tegmental brainstem lesions, reminiscent of the vocalizations and motor movements in RBD [141, 142].

Can sleep and wakefulness be present in the same brain at the same time? This possibility seems counterintuitive to our normal experience since we typically dichotomize states of alertness as being either waking or sleep and the transition between them as drowsiness, often euphemistically described as being half awake or half asleep. The parasomnias suggest that the comingling of sleep and waking in the same neural substrate is possible, and insights from animal studies are of benefit in shedding light on this issue.

There are a number of examples in the animal literature in which “nonquiescent” or literally “motorically active” sleep is present, suggesting that sleep can be compatible with behavior typically present during waking. For example, nocturnal “sleep swimming” fish inhabiting coral reefs in the Red Sea vigorously move the dorsal, pectoral, and caudal fins in fixed body positions at a frequency of strokes approximately twice the rate with daytime swimming outside the coral reef [143]. This behavior may function to aerate the reef and assure healthy corals. Captive dolphin and killer whale neonates and their mothers remain continuously active and do not exhibit signs of behavioral sleep for several months postpartum with gradually increasing periods of behavioral quiescence which eventually return to normal amounts, but do not exceed normal amounts, of behavioral sleep [144, 145]. Dolphins are able to maintain continuous vigilance with accurate echolocation for a testing period of up to 15 days [146]. In the laboratory birds demonstrate marked decreases in EEG defined sleep during the migration season, and data from freely moving swifts equipped with data loggers during a 200-day nonstop flight suggest that sleep occurs during periods of decreased activity during flight [147–149].

There is the possibility that these animals are unique and simply do not sleep. However, this would be contrary to findings from virtually all other living organisms. Alternatively, a variant of sleep may be present which coexists with waking and which allows for sustained vigilance in the presence of physiological sleep. In fact, there is a unique form of sleep, unihemispheric sleep, a state in which one hemisphere of the brain exhibits waking EEG activity simultaneously with sleeping EEG activity in the other hemisphere. Unihemispheric sleep has been recorded in dolphins [150], whales [151], fur seals [152], and birds [9]. Only NREM sleep has been observed in whales and dolphins, whereas in birds and seals REM sleep is present. Of interest is a recent demonstration of decreased orexin bouton density in the cerebral cortex of a porpoise and a whale compared to ten mammalian species [153]. The presence of

unihemispheric sleep offers the significant advantages of an ability for part of the brain to sleep during long-distance migration while maintaining sentinel functions in monitoring the environment [148, 154].

Unihemispheric sleep is clearly an unusual form of physiological sleep. However, there are recent human electrophysiological studies utilizing scalp, intracerebral EEG, and unit recordings which suggest the possibility that there are also coexisting regional differences in human sleep and waking. For example, detailed sleep electrophysiological studies have demonstrated that 85 and 75.8 % of sleep spindles and slow waves, respectively, have been detected in less than half of brain recording sites [155]. This regionality of sleep waveforms, along with the demonstration of unihemispheric sleep in animals, suggests that parasomnias such as sleep walking or RBD may be a manifestation of simultaneously occurring waking and sleep processes. There is also further evidence from intracerebral recordings that motor cortex activation lasting from 5 to more than 60 s can occur simultaneously with an increase in slow wave activity in the dorsolateral prefrontal cortex [156]. Also relevant in this regard is the finding that human sleep spindles recorded in the hippocampus precede the sleep spindles and K complexes characteristic of Stage 2 sleep recorded from neocortical scalp electrodes [157]. Similarly in cats, increases in ventral hippocampus spikes precede the onset of NREM sleep, also suggesting that sleep processes may begin in different brain regions at different times in both animals and humans, strengthening the similarities between these electrophysiological processes [25]. Studies in both the echidna, a primitive egg laying mammal considered the basal stock of living mammals, and the ostrich, a basal bird, demonstrate that elements of both NREM and REM sleep may be simultaneously present during behavioral sleep [158, 159]. Further illustrating the simultaneous presence of different physiological states in humans are data from a single subject with stereotaxically implanted electrodes who experienced confusional nocturnal arousals [160]. During these episodes, there was localized activation of the motor, cingulate, insular, temporopolar, and amygdalar cortices in the presence of slow waves recorded from the frontal and parietal dorsolateral cortices and in the presence of spindles recorded from the hippocampal cortex.

Parasomnias are very poorly understood, and the triggers which initiate waking-like behaviors during sleep are completely unknown. There are no readily available animal preparations in which to study these unusual behaviors. Unihemispheric sleep in marine-dwelling mammals and birds hints that there is a capacity for simultaneous expression of both waking and sleeping electrophysiology in the same brain. However, the mechanisms controlling the expression of unihemispheric sleep may be controlled by different, more orderly processes than the processes which result in the often explosive behavior and vocalizations

which accompany many of the human parasomnias. Nonetheless, the parasomnias suggest that sleep and waking may be the manifestation of simultaneous waking and sleep.

Conclusions

Although the behavioral and electrophysiological parameters of sleep have been described in great detail in many living organisms, the cellular origins of sleep are still elusive. Studying living organisms is unlikely to provide a definitive answer to the question of how sleep originated, and the behavioral or cellular origins of sleep cannot be preserved in the fossil record. There is one speculative observation that a dinosaur fossil from the Cretaceous era (between 145 and 65.5 million years ago) has been preserved in an avian-like sleeping posture [161]. Sleep is undoubtedly an ancient behavior which has been conserved through evolution, but the crucial life sustaining functions it serves to maintain its presence in many different species is unclear.

Knowledge about sleep mechanisms has rapidly evolved by utilizing model organisms as the genetic and molecular substrates for the study of mechanisms controlling sleep. Even though there are tremendous benefits to the utilization of these organisms, there are also a number of issues which are raised.

Considerations in the Use of Model Organisms

A major question is whether model organisms can truly serve as models for the exploration of human sleep mechanisms and sleep disorders. As we have seen, there is a remarkable correspondence among the genetic, neurochemical, and cellular operations of model organisms and humans. However, it is obvious that the complexity of human behavior and the unexplored cellular effects of human emotions and psychology upon sleep cannot be unraveled by model organisms. The clinical understanding of human sleep disorders relies not only upon the patient's descriptions and environment, but also on observations of witnesses to the patient's symptoms. For example, can it be assumed that frequent movements of the fruit fly's legs are a model for the uncomfortable sensations described by patients in restless legs syndrome? Thus, even though a model may produce a wealth of information about the "technical" aspects of sleep, this does not ensure that this model is necessarily the model for human discovery. Is human NREM sleep the homologue of behavioral sleep in model organisms? There have been no convincing data which have demonstrated the presence of REM sleep in model organisms, and electrophysiological correlates of human NREM sleep have not been described. This absence of some electrophysiological sleep correlate of behavior is a

significant drawback for an organism modeling human sleep. Also, there have been a large number of studies, particularly in *Drosophila*, to suggest that short sleep has adverse effects upon life span. What is the translation factor between old age in “*Drosophila* days” and “human years?” What is the translation factor between short or long *Drosophila* “sleep minutes” and short or long human “sleep hours?” These questions are probably unanswerable. Finally, there are some aspects of sleep in model organisms which are different from human sleep characteristics such as the absence of a homeostatic rebound in sleep following deprivation of quiescence in some mutant flies or the suppression of sleep upon exposure to light and the lack of a subsequent homeostatic response in zebrafish.

These questions should not, of course, discourage the use of model organisms in discovering clues to the cellular and genetic mechanisms of human sleep. There has been a massive increase in understanding the cellular basis of sleep, almost completely unknown just a few years ago, as the result of complex cellular manipulations performed in these organisms. It seems unlikely that model organisms will provide us with a “true” model of sleep disorders such as sleep apnea or narcolepsy, and their major utility may lie in being model organisms for understanding the cellular and genetic basis of sleep.

Besides enlightening our understanding of the cellular mechanisms controlling sleep, another area of interest with respect to the use of model organisms is the demonstration of positive and negative effects of social isolation or enrichment upon sleep. These findings suggest that greater attention should be devoted to exploring the impact of environmental factors in assessing human sleep problems. Furthermore, it would be of interest in these studies to determine in model organisms the effects of, for example, predation or threat on sleep in a controlled environment.

Treatments for Human Sleep Disorders Resulting from the Use of Model Organisms

Ideally, understanding the genetic and cellular mechanisms controlling human sleep would be fruitful in yielding more effective treatments for human sleep problems. There has been one recent addition to the armamentarium of sleeping medications, suvorexant, which was developed directly as the result of research in narcolepsy and the identification of orexigenic neurons in the expression of waking and sleep. The identification of salivary amylase as a marker for sleepiness which arose from cross-translational studies in *Drosophila* and humans may also potentially find a practical use in the more widespread identification of sleepiness. With continued research into the details of sleep mechanisms revealed by the use of model organisms, it is anticipated that these findings will translate into practical applications.

Phylogenetic Studies and Human Sleep

The remarkable diversity in sleep behavior and electrophysiology in nonmammalian organisms has provided an array of clues which sheds light upon the understanding of normal and disturbed human sleep. One of the most interesting examples of diversity in animal sleep is the unihemispheric sleep of cetaceans which challenges the notion that sleep is a global state affecting all areas of the brain in the same manner and at the same time. Organisms which display unusual sleep-related behavior such as sleep swimming fish, cetaceans, and their offspring which do not exhibit behavioral sleep for several continuous months after birth, and the demonstration of prolonged, continuous flight in birds offer hints that there may be clues in nature for at least some human sleep complaints of short sleep. New monitoring techniques such as high-resolution video monitoring, in vivo calcium imaging, and multielectrode recording probes hold promise for more refined analyses of behavior and electrophysiology in nonmammalian species [110, 162, 163]. Additionally, behavioral and electrophysiological studies of animals in their own habitats utilizing new technologies will expand our understanding of the diversity of sleep.

Sleep studies in animals have unquestionably enhanced our appreciation of the behavioral, molecular, and environmental factors which govern the expression of sleep, and, in turn, these studies have provided insight into the factors influencing human sleep and its disorders. The biological symphony of sleep continues to be performed throughout nature, and ongoing scientific exploration on a variety of fronts will only continue to enlighten our understanding of this intricate, universal composition.

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