
Overview

Sleep Mechanisms in Health and Disease

Linda A. Toth, DVM, PhD* and Krishna Jhaveri, MD

Excess sleepiness, abnormal sleep patterns, non-restorative sleep, and fatigue are becoming increasingly pervasive in modern society. Identifying substances and mechanisms that modulate sleep and vigilance during health and disease is a critical prelude to eventual development of interventions to prevent or alleviate these disabling problems. A unified interdisciplinary approach that includes neurophysiology, neuroanatomy, neurochemistry, and molecular biology will promote elucidation of the complex biology of sleep. Integration of basic sleep physiology with modern genetic techniques will eventually lead to identification of specific genes and substances involved in regulation of various facets of sleep. The review presented here highlights recent progress in defining the anatomy and physiology of sleep-wake regulatory systems, delineating the role of homeostatic and circadian process in regulating sleep and wakefulness, and establishing the relationship of sleep and sleep disorders to other medical conditions. Particular emphasis is placed on reviewing the interactions between sleep, infectious challenge, and host defense response, and on identifying mechanisms that contribute to variation in sleep patterns among various strains of inbred mice.

Sleep is a ubiquitous biological phenomenon that has been documented in all mammalian and avian species studied to date (223). Humans spend about a third of their lives asleep, whereas other species of animals spend variable amounts of time asleep. Periods of rest that appear to be analogous to sleep also are observed in fish, insects, and other organisms (25, 81, 83, 167, 225). The evolutionary persistence of and amount of time devoted to sleep in various species suggests that it has an important biological function; however, the precise function of sleep remains an issue of speculation and debate among sleep researchers (3, 51, 89, 218). At an intuitive level, sleep appears to be restorative in nature, but the identity of what actually becomes restored in a physiologic sense remains elusive. For example, sleep may promote recovery of normal cognitive performance via mechanisms such as removal of metabolites (143, 157). Sleep also promotes maintenance of homeostasis by conservation of energy (e.g., reduced basal metabolic rate, oxygen utilization, and glucose metabolism; conservation of glycogen) (13, 132, 224). Some physiologic processes appear to occur principally during sleep. For example, functions as diverse as release of growth hormone and memory consolidation either occur predominantly during sleep or are dependent on occurrence of sleep (140, 210). The "physiologic rest" provided by sleep may also promote immune function (110, 204). Another postulated role for sleep is maintenance of neural plasticity (83, 87, 111, 165). Sleep can also be viewed as having an adaptive function that links rest-activity cycles to the ecologic niche and physiologic capabilities of individual species (219). For example, nocturnal, diurnal, and crepuscular patterns of sleep and wakefulness may optimize a species' evolutionary success at foraging and avoiding predators.

Unwanted alterations in the normal behavioral or physiologic patterns of sleep occur in many, if not all people at one time or another during their lives. Problems with sleep range from insomnia and non-restorative sleep to excess daytime sleepiness, and include life-threatening conditions, such as sleep apnea, cataplexy, and narcolepsy. The impact of sleep disruption and excess sleepiness is an important problem from economic and public health perspectives (91, 211). Because of the prevalence, resultant health complications, and lost productivity associated with inadequate sleep, cost implications of sleepiness and sleep disorders are immense (91). For example, sleep or sleepiness is implicated in numerous accidents ranging from single-car collisions to catastrophic incidents, such as the Exxon Valdez disaster (2, 27, 48, 121, 150). Sleep loss can also impair performance. For example, recent studies indicate that resident physicians who develop fatigue and decreased attention span in association with lack of sleep while working prolonged schedules pose a possible risk to the well being of their patients (23, 92, 212). Sleep loss and the resultant increase in sleepiness also contribute to disturbances in mood, reduced quality of life, and perhaps, altered disease resistance. Learning more about the causes and regulation of sleep may lead to development of interventions that may prevent or control sleep disturbances and, thus, improve the quality of life for many people.

A widely held model of sleep regulation invokes the interaction of two processes that together control sleep duration and timing (17, 38). The first process is a homeostatic component that responds to physiologic need. This component is considered to mediate the occurrence of compensatory "recovery" sleep that typically follows periods of prolonged wakefulness. The second process is a circadian timing component that promotes adaptation to the environment. Extension of this so-called "two-process" model to include a behavioral component introduces flexibility that allows the organism to voluntarily modify the

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Department of Pharmacology, Southern Illinois University School of Medicine,
Springfield, Illinois 62794.
*Corresponding author.

amount and timing of sleep and wakefulness to adjust to environmental and psychological demands (219). The ultimate importance of sleep is dramatically illustrated by findings that chronic sleep deprivation (SD) of rats for two to three weeks is associated with eventual hypothermia, weight loss despite increased food intake, and ultimately, death (152). These adverse outcomes indicate that sleep is important and indeed vital to the maintenance of biological equilibrium (86).

What Is Sleep?

The state of sleep reflects a complex amalgamation of physiologic and behavioral processes. Sleep is characterized by perceptual disengagement from and lack of responsiveness to the environment (26), and is usually associated with a species-specific sleep posture, selection of location, and circadian timing. An important characteristic of sleep is its quick reversibility into wakefulness, which distinguishes sleep from the pathologic condition of coma. Sleep typically occurs with a spontaneous periodicity that is essentially independent of environmental cues, such as variation in ambient light or temperature (223). In addition, homeostatic regulation adjusts the amount and depth of sleep as a function of preceding wakefulness. The process of sleep is regulated by interactions of multiple anatomic and neurochemical processes within the central nervous system.

The occurrence of sleep is inferred on the basis of a variety of criteria that range from simple observation of posture, behavior, and/or eye state to almost complete reliance on the electroencephalogram (EEG) (134). For clinical and experimental purposes, vigilance states and stages of sleep are defined principally on the basis of characteristic patterns of the EEG, eye movement (as detected by electrooculography and the resulting electrooculogram [EOG]), and muscle tone (measured by electromyography and a resulting electromyogram [EMG]). This collection of records is known as a polysomnogram, and the recording process is called polysomnography. Polysomnographic profiles define three distinct states of vigilance: wakefulness, rapid-eye-movement sleep (REMS; also called paradoxical sleep, desynchronized sleep, and, in infants, active sleep), and non-rapid-eye-movement sleep (NREMS; also called synchronized sleep, and, in infants, quiet sleep). NREMS can be further subdivided into four stages (26, 37). These stages are distinguished principally on the basis of characteristic properties of EEG frequency bands and waveforms. Stage-1 sleep marks the transition from waking to sleep. This stage is characterized by slowing of the EEG frequency, reduction in muscle tone, and low arousal threshold. Stage-2 sleep is characterized by the occurrence of sleep spindles (7- to 14-Hz bursts that reflect thalamocortical synchronization), K complexes (large biphasic waves with ultra-low rhythm that reflect initial cortical synchronization), a higher arousal threshold, and, as stage 2 progresses, the gradual appearance of high-amplitude slow waves in the EEG. Sleep stages 3 and 4 are characterized by predominance of high-amplitude signals in the slow-frequency (delta frequency band, or < 4-Hz) component of the EEG, and hence, are often called slow-wave sleep (SWS) or delta sleep. In animal studies, the term SWS is often used to encompass all stages of NREMS. In humans, stages 3 and 4 are sometimes called "deep sleep" because arousal thresholds are typically highest during these stages (26). A reverse progression into lighter stages of NREMS typically precedes entry into REMS. REMS is characterized by a

low-voltage fast EEG with relative theta predominance (generating a "sawtooth" pattern in the EEG in some instances), skeletal muscle atonia, and phasic eye movements. In humans, the arousal threshold during REMS is variable (26). In contrast, cats have high arousal thresholds during REMS, resulting in the designation in some publications of REMS as "deep sleep" in cats. During REMS, cats also show ponto-geniculo-occipital (PGO) waves, which reflect rapid eye movements; however, PGO waves are not usually detectable in humans (26).

The phrase "sleep architecture" refers to the pattern of transition across episodes of waking, REMS, and stages of quiet sleep during a specific time interval. In humans, the relevant interval is usually the eight-hour period designated for sleep. During sleep, humans tend to cycle from NREMS into REMS with a periodicity of about 90 min, with REMS episodes becoming longer in duration as the night progresses. Sleep architecture is influenced by age and health status and varies across species (67). For example, some species (e.g., many carnivores) engage in consolidated bouts of sleep, with long individual episodes of NREMS and REMS, whereas other species (e.g., many rodents) show short bouts of NREMS and REMS with frequent arousals and many state transitions (80, 219). Because of the frequent spontaneous arousals of rodents under normal conditions, imposed brief episodes of forced wakefulness (e.g., during cage changing) are unlikely to have adverse effects on animal well being, just as an occasional brief arousal during the night will have little or no important impact on human well being.

Many physiologic processes change during the various stages of the sleep-wake cycle (67, 135, 138, 139, 223). Compared with quiet wakefulness, NREMS is characterized by assumption of a thermoregulatory posture, cessation of voluntary muscle activity, reduced anti-gravity muscle tone, and reduced energy expenditure. REMS is characterized by muscle atonia, myoclonic twitches, and rapid eye movements, indicating a substantial difference in motor control and activation between REMS and NREMS. In general, NREMS is characterized by physiologic stability, in which cardiovascular, respiratory, and thermoregulatory statuses are essentially consistent with a state of postural and motor quiescence. In contrast, REMS is characterized by high variation in and blunted homeostatic regulation of physiological functions, particularly when viewed from the perspective of muscular atonia and behavioral inactivity. The specific cardiovascular changes that occur during NREMS and REMS vary depending on the species and the level of activation during the preceding period of wakefulness (139, 214). Respiration also varies across vigilance states, with some variations depending on the species (136, 139, 142, 170). Reduced respiratory rate and ventilation during NREMS in humans and animals is consistent with a state of reduced energy expenditure (139). In contrast, during REMS, the respiratory rate is irregular (106, 170, 174). Sleep is also associated with altered thermoregulatory function. In general, compared with regulation during wakefulness, thermoregulation during NREMS occurs relative to a lower hypothalamic regulatory set point (172), although physiologic mechanisms of regulation are similar. In contrast, REMS is associated with absence of thermoregulatory responsiveness, effectively resulting in functional poikilothermy (139).

Sleep and the Circadian Clock

Most animal species, including humans, exhibit a 24-h rhythm

in various physiologic and behavioral processes, including sleep and wakefulness, body and brain temperature, and metabolism. An internal biological pacemaker that is typically synchronized with solar day and night controls this rhythm. The principal circadian clock function of the central nervous system resides in the suprachiasmatic nucleus (SCN), which regulates the circadian timing of sleep, wakefulness, and other processes (75). The rhythm maintained by the circadian pacemaker is endogenous to the organism and persists independent of the external environment. For example, animals housed under constant light or constant darkness have quasi-circadian patterns of functioning that depend solely on internal pacemakers, as opposed to external cues related to light (75). Such cycles are termed “free-running.” The endogenous free-running rhythm normally maintains a period that is close to 24 h (i.e., “*circa dia*,” or “about a day”). However, the rhythm can be modified or reset by environmental inputs (126).

Dissociations between the endogenous circadian rhythm and external cues can result in decreased attention span, increased daytime sleepiness, and increased risk of accidents (48). For example, the tendency of the biological clock to maintain its normal ‘diurnal’ rhythm can lead to extreme tiredness in shift workers. Prolonged shift work may eventually result in collapse of the circadian rhythm and can potentially contribute to gastrointestinal and coronary illnesses, leading to increased mortality (115). Similarly, travel across multiple time zones causes chronobiological disruption due to the discrepancy between solar and biological clocks, commonly referred to as “jet lag.” The prevailing circadian rhythm will usually accommodate only a few hours of change per day, and consequently, several days or even a week of acclimation may be necessary for physiologic and functional adaptation to a new solar rhythm (159).

Established endogenous circadian rhythms and environmentally elicited or externally imposed changes in cycles occur in response to and/or in synchrony with changes in gene transcription and translation in the SCN and related brain regions. Oscillatory cycles of gene transcription and translation in SCN correspond temporally with behavioral and physiologic rhythms (133, 181) and provide the basic driving mechanism that underlies oscillatory circadian regulation in the brain and, indirectly, in peripheral cells, tissues, and organ systems. Genes that influence the circadian period (e.g., *Clock*, *period*) are typically assessed by determining the periodicity of peaks and ebbs in spontaneous locomotor activity under conditions of constant light or constant darkness. Genes that influence circadian rhythms may secondarily influence the timing of sleep during the normal 24-h cycle, and some have been documented to influence sleep quality, duration, and homeostasis in mice and flies (82, 105, 129, 167).

Measurement of Sleep in Animals

For polysomnographic assessment of sleep in humans, electroencephalographic and electromyographic electrodes and other monitoring devices are placed temporarily by use of adhesive or other devices, whereas in animals, such instrumentation is usually implanted surgically to prevent displacement and to reduce artifacts related to movement. Standard guidelines for surgery apply to implantation of such devices (33, 68). However, allowing full recovery of animals from the non-specific effects of surgery is essential to acquiring accurate data, because pat-

terns of sleep are exquisitely sensitive to disruption by factors, such as pain, illness, anorexia, drug therapy, and general or non-specific stress. A minimal recovery period of at least one week is probably necessary to allow stable resumption of presurgical circadian patterns of food and water intake and locomotor activity (79).

In most animal studies, electroencephalographic and other electrophysiologic data are collected via flexible electrical tethers that connect the implanted electrodes to data acquisition equipment. Although these tethers generally appear to induce little or no restriction of normal behavior, animals must nonetheless be given time to adjust to the tether before data acquisition is initiated. Usually, three to seven days are permitted for acclimation (205). Telemetric collection of electroencephalographic signals has recently been used for sleep studies in mice (186), but this technique is not yet in widespread application. Sleep patterns are also sensitive to environmental influences. Therefore, animals used in studies of sleep are generally maintained under conditions of accurately controlled ambient temperature, light:dark exposure, and noise attenuation.

EEG and EMG patterns and associated physiologic measurements are generally translated into states and patterns of vigilance by using computer-assisted scoring algorithms that are typically subjectively verified for accuracy by an experienced human scorer. Data from all species, including humans, can be scored in similar manner. To illustrate a typical scoring algorithm, Fig. 1 shows a sample computer screen display (EegScore, Quality Software, Springfield, Ill.) of data collected from a mouse. The traces from bottom to top show EEG delta (1- to 4-Hz) wave amplitudes (DWA), EEG theta (4- to 8-Hz) amplitudes (TWA), EMG amplitudes, and the ratio of theta-to-delta amplitudes (TDR). This algorithm requires the scorer to select threshold values that reflect SWS (DWA), locomotor activity (EMG), and REMS (TDR) for each individual animal. Vigilance states in the scored data are displayed using color-coding of the DWA trace. Intervals in which DWA exceeds the SWS threshold in the absence of movement are considered to be periods of SWS, and are shown in blue. REMS, which is shown in red, is characterized by a decrease in DWA to below the SWS threshold while TWA remains high, resulting in a high TDR. At all other times, the animal is considered to be awake, which is shown in white. The figure thus shows a mouse that engaged in a bout of SWS, displayed brief arousal in association with movement, re-entered SWS, passed into an episode of REMS, then awakened and moved. Data are usually collected continuously throughout the entire duration of an experiment. Vigilance states are typically assessed across time intervals that range from four to 60 sec, depending on the species and the necessary precision of assessment. For statistical analysis and graphical presentation, data are then usually summarized across intervals ranging from one to 24 h.

Recent Advances in the Neurobiology of Sleep and Wakefulness

Basic overviews of the neurobiology of sleep are available in many standard textbooks. However, several important recent findings that have revolutionized and invigorated the study of sleep mechanisms and regulation are summarized below.

Neuronal basis of the EEG. In general, the high-voltage, low-

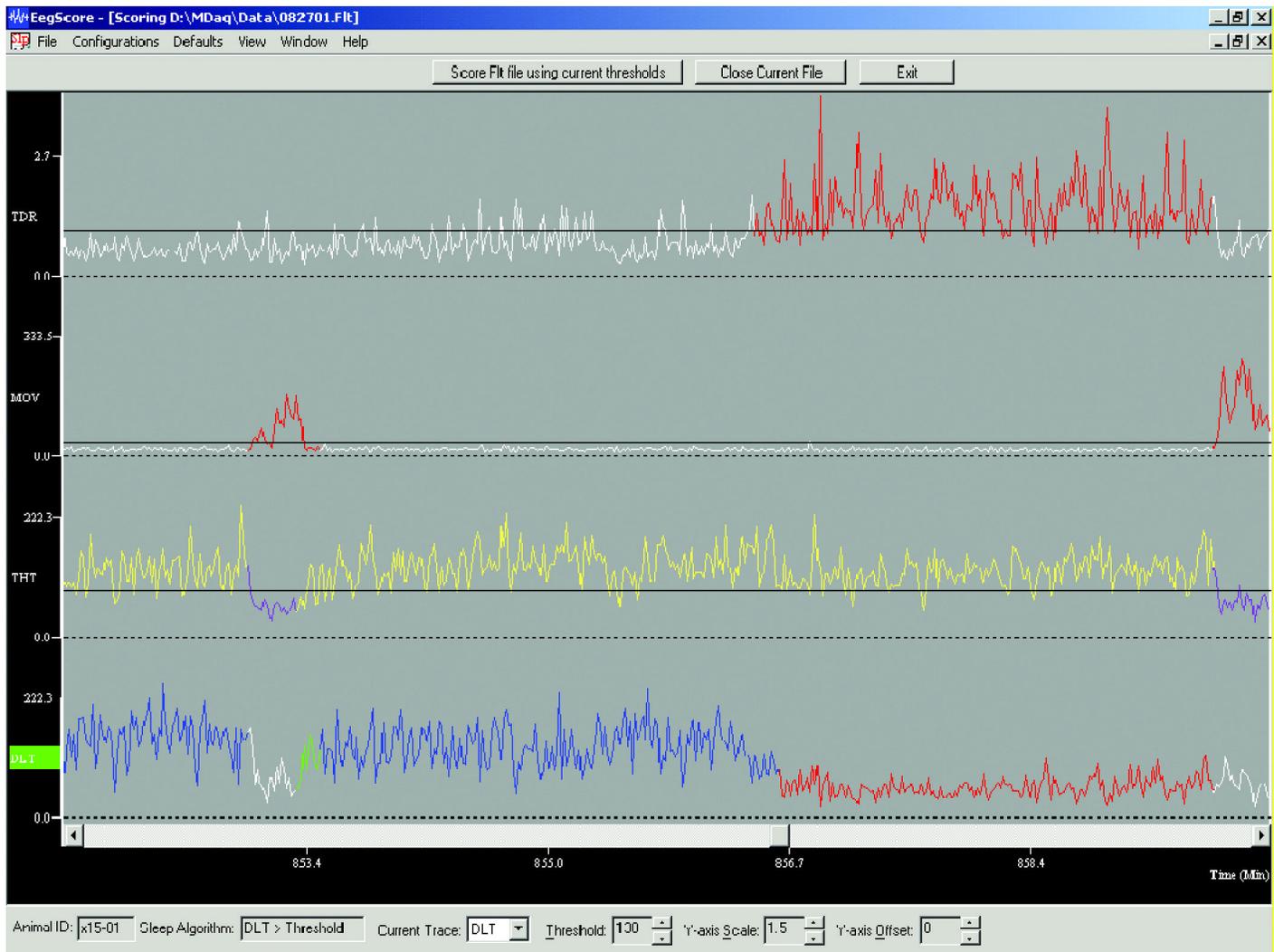


Figure 1. Polysomnographic-based sleep scoring algorithm for animal studies. See text for detailed explanation.

frequency electroencephalographic waves that characterize NREMS reflect synchronization of neuronal firing, whereas the low-voltage, fast-frequency waves that occur during waking and REMS sleep reflect desynchronized neuronal activity. The waking or desynchronized EEG mainly consists of activity in so-called beta (14- to 30-Hz) and gamma (30- to 50-Hz) frequency ranges. Sleep spindles, which are characteristic of stage-2 sleep, occur with a 10- to 12-Hz frequency and develop as a result of interactions between thalamocortical neurons and γ -aminobutyric acid (GABA) neurons in the nucleus reticularis of the thalamus (171, 178). The cholinergic systems of the brainstem and basal forebrain (BF) are the major components of the ascending reticular activating system that acts at the thalamic nucleus reticularis to maintain electroencephalographic desynchronization and arousal. Extensive *in vivo* and *in vitro* evidence suggests that the target neurons in the thalamus respond to cholinergic agonists in manner consistent with electroencephalographic activation (97, 166, 177). However, other brainstem reticular projections to thalamus, and noradrenergic and serotonergic projections from locus coeruleus (LC) and raphe nuclei, respectively, also have important roles in regulation of sleep and arousal (96).

The generation of cortical slow waves (i.e., delta, or low-fre-

quency 0.5- to 4-Hz waves) depends on the activity and membrane polarization state of thalamocortical neurons (124, 178, 179). During wakefulness, depolarizing inputs to these neurons from mesopontine and BF neurons suppress electroencephalographic slow-wave activity (24). Noradrenergic and serotonergic inputs from LC and raphe nuclei, respectively, also contribute to hypopolarization of thalamocortical neurons. However, depolarizing inputs from LC and raphe gradually diminish as sleep deepens, and during REMS, their neuronal activity stops, leaving mesopontine and BF cholinergic inputs as the only depolarizing influences on the thalamocortical network. Delta waves become oscillatory during sleep and in the absence of activating or arousing inputs. Cortical and thalamocortical neurons develop simultaneous hyperpolarization in association with spontaneous transitions from less synchronized to more synchronized states with greater delta power in the EEG (180). Thus, during SWS, neocortical and thalamic neurons fire in phase, and electroencephalographic synchronization results from active inhibition of thalamocortical neurons (180).

Advances in understanding the electrophysiologic basis for synchronous activity in the sleep EEG (5, 178), coupled with increasingly sophisticated approaches to EEG analysis (1, 57, 130),

have indicated that the EEG is influenced by previous and ongoing experiences of the animal (18, 65). However, some aspects of the EEG are heritable traits (11, 176). In mice, assessment of spectral power spectra in various electroencephalographic frequency bands across different vigilance states has revealed strain differences in the peak theta frequency of the EEG during SWS and REMS (60). The gene that regulates the frequency of theta oscillations in mice was recently identified as short-chain acyl-coenzyme A dehydrogenase (*Acads*) (184).

Ventrolateral preoptic area. Most neurons in the brain decrease their firing rate during NREMS. However, neurons in at least one discrete brain region, the ventrolateral preoptic area (VLPO), increase their activity during sleep, as documented using *c-fos* immunohistochemical analysis and neuronal recording (169, 182). GABAergic and galaninergic efferents project from VLPO to the tuberomammillary nucleus (TMN) (168), which contains ascending histaminergic neurons that are considered to be important in mediating arousal (hence accounting for the drowsiness that often accompanies use of antihistaminergic drugs). Neurons of the TMN are tonically active during waking, are less active during NREM sleep, and cease firing during REMS (161). Neurons projecting from VLPO may induce sleep by inhibiting wake-promoting neurons in the TMN. These neuronal systems are hypothesized to interact in inhibitory and excitatory feedback loops to prevent abrupt or unstable sleep-wake state transitions (161).

Molecular mechanisms of sleep. Numerous endogenous mediators and systems are postulated to form inter-regulatory networks that cumulatively influence the sleep-wake cycle (66, 78, 112). A brief review of data concerning the potential role of transcription factor nuclear factor κ B (NF κ B) in the regulation of sleep provides an example of the complex molecular inter-relationships that modulate vigilance. NF κ B shows diurnal variation in its activation state, with cortical concentrations being highest during the light phase of the circadian cycle in association with the somnolent period of rodents (30). Activation of NF κ B in the cortex also increases after SD (30), and administration of NF κ B inhibitory peptide reduces time spent in NREMS (114). Some sleep-enhancing cytokines (e.g., interleukin [IL]-1 and tumor necrosis factor- α [TNF α]) activate NF κ B (160), whereas cytokines associated with enhanced arousal (e.g., IL-10 and IL-4) reduce NF κ B activation (31, 217). Activation of NF κ B increases expression of nitric oxide synthase 2 and cyclooxygenase 2, which results in increased production of nitric oxide and prostaglandin D₂ (PGD₂), respectively. The latter two substances both promote sleep (77, 98). Administration of a nitric oxide synthase inhibitor suppresses the recovery of sleep that normally occurs after SD in rats (156).

The substances involved in sleep regulation are likely to vary in concentration and function across different brain regions during different phases of the sleep-wake cycle, and the dominant sleep-regulatory factor may vary in different neuronal populations. Furthermore, specific neuronal populations probably interact with multiple sleep-regulatory substances, and the magnitude and nature of sleep responses will depend on local concentrations of these substances and on the pharmacokinetics of their interactions with receptors on specific neurons (111). The complex network of humoral and neuronal regulatory circuitry coupled with the numerous and highly pleiotropic substances that modulate sleep and wakefulness complicate efforts to delin-

eate the mechanisms of sleep initiation and maintenance.

Adenosine. Adenosine has long been considered a potential sleep-modulatory substance because of the well-known ability of caffeine, an adenosine antagonist, to promote wakefulness. Results of microdialysis studies have indicated that in BF, a brain region implicated in the control of arousal and sleep initiation, the release of adenosine gradually increases with the duration of wakefulness and decreases during subsequent sleep, suggesting that extracellular concentrations of adenosine reflect sleepiness and perhaps promote sleep (144). Because adenosine is a by-product of ATP metabolism, this hypothesis is congruent with energy recovery as a function of sleep. Administration of adenosine analogues into the BF can increase NREMS and cortical slow-wave activity, and administration of caffeine prevents these effects (13, 147). The adenosine that accumulates in BF during prolonged wakefulness appears to act via the A1 adenosine receptor (A1AR). A six-hour period of forced wakefulness is associated with increased A1AR mRNA concentrations in rat BF, corresponding with increased release of adenosine (9). Microdialysis perfusion into rat BF of an antisense oligonucleotide directed against A1AR mRNA caused significant reduction in NREMS (188).

Adenosine systems also interact with other sleep-regulatory substances and systems. For example, administration of PGD₂ into the rostral BF increases extracellular adenosine release in a dose- and time-dependent manner (163). Type-2a adenosine receptor agonists mimic the somnogenic effects of PGD₂ (78). In addition, signal transduction pathways associated with the A1AR cause activation of NF κ B (9). Adenosine also influences the inhibitory neurotransmitter GABA in BF and inhibits arousal-related cholinergic neurons in BF and in laterodorsal and pedunculo pontine tegmental nuclei (148).

Functional genomics of sleep. Despite qualitative similarities across strains, direct comparisons of the sleep patterns of various inbred strains of mice reveal quantitative differences in daily amounts and patterns of SWS and REMS (41, 61, 63, 93, 158, 183, 205, 207, 209) (Fig. 2). These differences are typically rather modest in magnitude, but are nonetheless statistically valid and have sometimes been corroborated in independent laboratories. For example, numerous research groups have documented that C57BL/6 mice generally have greater amounts of SWS and REMS than do BALB/c mice, particularly during the light (resting) phase of the circadian cycle (41, 63, 158, 183, 205, 209). Others have documented strain-related differences in the relationship between sleep patterns and the light:dark cycle (61, 207).

Results of several studies have documented altered sleep in mice with targeted mutations of genes that are implicated in the regulation of sleep. For example, mice with targeted mutations ("knock-outs") of specific serotonin receptors or transcription factors have different patterns of sleep than do genetically intact mice (19, 59). Mice that lack the prion protein gene, which is implicated in the human condition of fatal familial insomnia (28), have alterations in both sleep and circadian activity (190). Altered patterns of sleep also were reported in mice with targeted deletions of genes for receptors of the sleep-modulatory cytokines IL-1 and TNF (55, 56). Thus, this so-called candidate gene approach to the identification of sleep-regulatory mechanisms can reveal apparent gene-related influences on sleep. However, the interpretation of data collected from knock-out mice can be complicated by potential developmental compen-

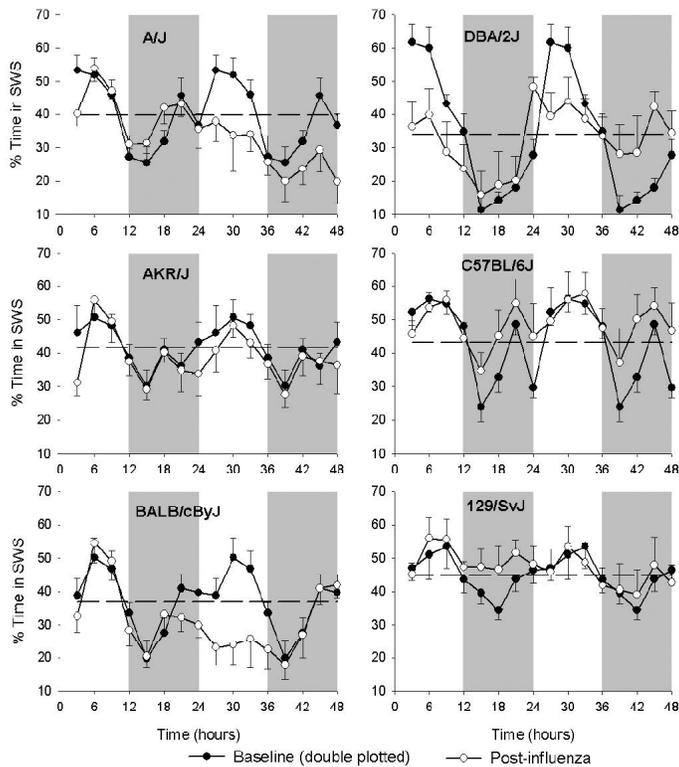


Figure 2. Percentage of time spent in slow-wave sleep before and after influenza virus inoculation. Slow-wave sleep (SWS) was monitored for 24 h before (filled circles) and 48 h after (open circles) inoculation of mice with influenza virus. The y-axis indicates the percentage of time spent in SWS during three-hour intervals. The x-axis indicates the time (in hours) after inoculation. Twenty-four hour baseline values are double-plotted over 48 h of postinoculation values to facilitate visual comparisons. Shaded regions denote the dark phase of the 24-h cycle. The horizontal dashed lines denote average values during the 24-h baseline period. Use of analysis of variance (ANOVA) revealed significant differences across strains in the percentage of time spent in SWS during the baseline period (adapted from 207).

sation for the missing gene and/or substance and by variation in the genetic background of knock-out and control strains. Many targeted mutations are studied in mice with mixed and variable genetic backgrounds. Even if mutations are transferred onto inbred genetic backgrounds, these strains still retain congenic genomic segments surrounding the transferred deletion (69). Genetic background can clearly influence the expression of complex behavioral or physiologic phenotypes (35, 215, 216). For example, the free-running circadian periods of *Clock* mutant mice vary depending on the genetic background strain (104). Because of such caveats, declaring a gene to be a major effect factor contributing to genetic variation in a complex phenotype on the basis of the study of knock-out mice can be problematic.

Technical considerations will probably be an important variable in achieving consensus between various independent studies that involve use of a genetic approach to identify sleep regulatory genes or mechanisms (34, 213, 215, 216). Even subtle variations in experimental technique can influence detection and analysis of behavioral phenotypes (34). Animals used for the study of sleep are typically implanted with various arrays of recording devices to permit the assessment of sleep and other physiologic parameters. The specific complement of instrumentation could influence the amount of sleep or activity measured,

compared with that in mice with a different complement of instrumentation. For example, implantation of telemetry transmitters for data collection can itself alter exercise capacity in mice (15). Gene expression and its behavioral impact also are subject to environmental influences (70, 215), and environmental factors can clearly influence the amount of sleep exhibited by mice. For example, environmental temperature differentially affects the amounts of SWS and REMS in C57BL/6 and BALB/c mice (158). Thus, findings in different studies may be influenced by the surgical preparation, the environment, and even by the precise scoring algorithm used to quantify sleep per se.

Orexin and narcolepsy. Results of positional cloning studies recently indicated that canine narcolepsy is caused by a mutation in the *hypocretin (orexin) receptor 2 (Hcrtr2)* gene (119). This landmark finding was almost simultaneously corroborated by an independent report that mice with a targeted mutation of the *orexin* gene also exhibit a narcoleptic-like phenotype (29). Orexinergic neurons, which are located predominantly in the posteriolateral region of the hypothalamus, appear to facilitate ascending arousal systems; loss of these neurons appears to destabilize waking, promoting development of narcolepsy (161). By firmly documenting an association between specific gene mutations and a sleep disorder, that work has established the usefulness of genetic approaches to the study of sleep, sleep propensity, and sleep disorders. Those animal data have spurred intense investigation into the role of orexins in regulating vigilance under normal conditions and in contributing to the symptoms of narcolepsy and, perhaps, other sleep disorders (185, 187). Building on the initial discoveries in animals, studies conducted in humans with narcolepsy have indicated the absence of orexin in the hypothalamus and cerebrospinal fluid (131, 141, 189).

Health Implications of Sleep and Sleep Loss

Sleep and host defense. A situation that is often anecdotally associated with changes in sleep and sleepiness is the state of infectious disease. People suffering from common infectious conditions such as “colds” or “the flu” often report symptoms such as increased sleepiness or poor-quality sleep. Persistent fatigue and excess sleepiness also are being reported with increasing frequency as long-term adverse effects of infectious and inflammatory diseases, such as human immunodeficiency virus infection and hepatitis (39, 42, 74). In addition, sleep is commonly viewed as having protective or curative properties that can help one to avoid or recover from infections, leading to statements like “you’d better get some sleep, or you’re going to get sick” or “if you don’t get some rest, you’re never going to get better.”

Increased sleep propensity during microbial infections and a resultant increase in time spent asleep may confer survival advantages during infectious disease. One likely advantage is reduced energy utilization due to inactivity and lower metabolic rate (223). Such energy conservation may help the host to maintain metabolic homeostasis despite the metabolically costly generation of fever during periods of infection-related anorexia. Because animals typically seek a protected location for sleep, increased somnolence may also promote survival by causing the animal to remain in a safe location during periods of disease-related debilitation (76, 162). Sleep also is postulated to promote immune responses, and could perhaps in that way confer an additional host benefit during infectious disease (110). Indeed, rab-

Table 1. Model systems used to study infection- and inflammation-related changes in sleep

Species	Microbial challenge	Selected references
Mouse	Influenza virus	54, 205
	Newcastle disease virus	192
	Rabies virus	72
	Immune-mediated hepatitis	194
	<i>Candida albicans</i>	201
	Microbial products (LPS, poly I:C)	192, 202
Rat	<i>Trypanosoma</i> species	7, 73
	Scrapie	10
	Brewer's yeast	100
	Microbial products (LPS, MDP)	94, 117
Rabbit	Bacteria, fungi, trypanosomes	197, 198
	Influenza virus	102
	Microbial products (LPS, MDP, poly I:C)	103, 113, 108
Cat	Feline immunodeficiency virus	145
	Creutzfeld-Jakob agent	71
	Feline herpesvirus	195
Human	Microbial products (LPS)	84
	Fatal familial insomnia (prion mediated)	127
	Various medical conditions ("colds," HIV, trypanosomiasis, viral encephalitis)	22, 40, 47, 90, 173, 221

LPS = Lipopolysaccharide; MDP = muramyl dipeptide; poly I:C = polyribosinic:polyribocytidilic acid; HIV = human immunodeficiency virus.

bits that develop a robust enhancement of sleep after microbial challenge are more likely to survive than are those that show little or no enhanced sleep (206). However, sleep during microbial infections may also engender some disadvantages for the host. Prolonged somnolence is likely to reduce opportunities for food and water consumption, thereby exacerbating energy deficits that accrue due to fever and anorexia. In addition, excess sleep or sleepiness is associated with reduced arousal and inattention to the environment, which could have detrimental consequences if prolonged unnecessarily. Thus, an appropriate balance between sleep and arousal during the infectious state would perhaps achieve the optimal survival advantage.

The influence of infectious or inflammatory challenge on sleep in humans and animals has been investigated (Table 1). In rabbits, challenge with a variety of infectious organisms induces an initial phase of increased sleep that is followed by a phase of reduced sleep (197-199). Infected rabbits develop fevers with about the same time course as they develop increased sleep, but results of numerous studies have indicated that fever and sleep are dissociable and that the increased sleep propensity is not dependent on development of fever (109, 197)). The biphasic sleep response does not develop as a result of recovery from the infection, as rabbits generally are blood culture positive and their hemogram is abnormal throughout the period of altered sleep. Furthermore, the decrease in sleep is not simply a rebound due to the earlier excess amount of sleep. If rabbits are prevented from sleeping during the phase of increased sleep, they nonetheless enter the period of reduced sleep at about the same postinoculation time as do clinically normal rabbits, without recovering the imposed sleep debt (203). This observation indicates that the sleep decrease, like the sleep increase, is an actively triggered physiologic process that is not simply occurring in response to a previous period of rest. Various physiologic mechanisms are postulated to mediate the sleep increase and the sleep decrease phases of the response. For example, pro-inflammatory cytokines that promote sleep (e.g., IL-1, TNF) may predominate the internal milieu during the early stage of

infection, whereas anti-inflammatory cytokines that promote arousal (e.g., IL-10, IL-4) may predominate later. The precise temporal pattern of sleep alterations depends on the type of infective agent and the route of inoculation, and manipulating hormonal, immunologic, and environmental variables can cause qualitative and quantitative variations in the response (191, 196, 198-200).

Different inbred strains of mice have substantial variation in their sleep responses during infection (205, 207, 208) (Fig. 2). For example, C57BL/6 mice inoculated intranasally with influenza virus have a pattern characterized by excess sleep during the normal active phase, whereas infected BALB/cBy mice have reduced sleep during the normal rest phase of the circadian cycle. Similar strain differences in sleep also occur in mice that are immunized against the virus (205). However, both strains experience equivalent hypothermia, reduced locomotor activity, histologic pneumonia, and pulmonary viral titers (205). After infection, both strains of mice have increased numbers of SWS bouts, shorter epochs of SWS, reduced EEG slow-wave amplitude during SWS, and a blunted circadian rhythm of sleep (205). These changes imply that the infected mice experience a light plane of sleep, and that their sleep is fragmented. Similar sleep changes develop in rabbits inoculated intranasally with *Pasteurella multocida*, a natural respiratory tract pathogen of rabbits (199).

The potential role of immune modulatory substances in the generation of altered sleep during infectious disease can be illustrated by considering C57BL/6 and BALB/c mice. These strains differ in the production and release of interferon (IFN) that is elicited in response to some viral challenges (43, 149). IFN is known to cause sleep or sleepiness after exogenous administration in humans and animals (193), and is a potential mediator of altered sleep during viral infections. In mice, IFN production is regulated in part by the *Ifi* gene (43, 149). The C57BL/6 strain of mice has an *Ifi* allele that promotes high IFN production, whereas BALB/c mice have an allele associated with low IFN production. Congenic B6.C-H28 mice, which have the BALB/c allele for low IFN production on the C57BL/6 genetic background, have C57BL/6-like sleep responses after challenge with influenza virus, but have BALB/c-like responses after challenge with avian Newcastle disease paramyxovirus (192). These data indicate that the critical factor mediating alterations in sleep can vary depending on the challenge organism and illustrate how murine genetic variants can be used to identify the physiologic mechanisms that contribute to behavioral changes in virus-infected mice.

The marked differences in the somnogenic responses of influenza-infected C57BL/6 and BALB/c mice strongly suggested that characterization of sleep patterns in genetically defined mice could reveal information about factors that elicit altered sleep after viral challenge. Analysis of the sleep responses of CXB recombinant inbred strains of mice revealed distinct strain distribution patterns for light-phase and dark-phase sleep phenotypes (193), suggesting that different genetic factors influence influenza-induced sleep responses during light and dark phases of the circadian cycle. Linkage analysis revealed a quantitative trait locus, *Srip11* (sleep response to influenza, light phase 1), associated with the change in SWS (208). The 95% confidence interval of *Srip11* incorporates the 21- to 31-cM portion of chromosome (Chr) 6. Genes that are located within this

interval and that could theoretically influence sleep phenotypes include *Ghrhr* (growth hormone-releasing hormone receptor), *Crhr2* (corticotropin-releasing hormone receptor 2), *Npy* (neuropeptide Y), and *Cd8a* (an epitope on cytotoxic T lymphocytes). Recent evidence suggests that *Ghrhr* may be the critical gene that underlies *Srtp1*, and thereby contributes to generation of the BALB/cBy phenotype (4).

Sleep deprivation. Most people have at one time or another experienced the adverse impact of sleep loss on cognitive performance, mood, learning, and quality of life. Sleepiness and fatigue are commonly associated with lack of productivity, increased numbers of accidents, and operational errors (2, 44, 118). Sleepiness and poor sleep quality also broadly influence human perceptions of general health status and quality of life (8, 20, 95, 99). Sleep loss is increasingly becoming recognized as an important public health problem.

Short-term sleep loss in humans typically does not have severe adverse physiologic consequences other than increasing sleepiness and causing impaired performance of some tasks (49, 88, 128). These effects are rapidly reversed by a period of sleep. In rats, biologically significant effects of total SD develop gradually and include progressive debilitation, development of ulcerative lesions on tail and paws, weight loss despite hyperphagia (indicative of increased energy expenditure), decreased body temperature, intestinal bacterial overgrowth and translocation, and, after 11 to 23 days, death in association with septicemia (52, 53, 152). This process of gradual deterioration begins within five days of total SD and precedes signs of overt morbidity (53). The penetration of bacteria into normally sterile tissues during prolonged SD implies development of immune insufficiency and abnormal host defense, and suggests that SD could render healthy individuals susceptible to disease, as well as exacerbate existing disease or complicate recovery in patient populations.

Results of studies in rabbits indicate that reduced or fragmented sleep after microbial challenge is associated with poor prognosis, whereas increased sleep is correlated with a favorable clinical outcome (206). Associations between absent or diminished sleep, reduced EEG amplitude, and imminent death also occur in aged mice in advance of spontaneous death (220) and in mice with fatal experimentally induced rabies (72). Several correlation studies indicate relationships between sleep and longevity in humans (46, 107, 122, 222). However, despite common beliefs that SD can increase susceptibility to or retard recovery from microbial infections, or, conversely, that sleep increases disease resistance or promotes recovery, these relationships have not been studied extensively, and published data are conflicting. For example, a recent study indicates that restriction of sleep impairs antibody generation by healthy human subjects who receive vaccination against influenza virus (175). Similarly, results of a study of influenza-infected mice indicate that SD retards viral clearance and development of a protective antibody response (21); however, others have not confirmed this finding (154, 204). Other data indicate that short-term sleep deprivation may promote some host defense functions (12, 50, 153).

Discrepancies in literature may be related at least in part to technical considerations that impact the conduct and interpretation of studies of sleep loss. Maintenance of wakefulness, whether enforced or voluntary, usually entails a waking posture, movement, cognition, perhaps the presence of light, perhaps auditory or tactile stimulation, and all of the underlying

physiologic processes implied by these activities. In addition, inducing SD in animal studies involves, to variable degrees, imposition of non-specific stress, which may interact with sleep loss. For example, SD-related changes in viral clearance could be related to sleep loss per se, but might also be impacted by stress-induced activation of the glucocorticoid system (85). Similarly, chronic stress that is associated with sleep loss impairs the immune response to influenza vaccination in elderly adults, although the contributory influence of sleep loss per se, as opposed to those of other physiologic perturbations associated with stress, is not clear (101).

The principal approaches used to induce SD in animals are the so-called "gentle-handling" technique, the "flowerpot" technique (32, 146), the "disk-over-water" technique (14, 152), and forced locomotion (58, 125, 151). The "gentle handling" method is perhaps the strategy that is used most commonly. This approach requires the experimenter to physically arouse the animal whenever it assumes a sleep posture or enters an EEG-defined sleep state. Despite its apparent simplicity and its widespread use, the "gentle handling" method of inducing SD has several disadvantages. One disadvantage is the requirement for continual labor-intensive animal observation, which effectively limits the duration of imposed SD. Another major disadvantage is the high likelihood that repeated disturbance of the animal could cause non-specific stress, which clouds interpretation of the data. In contrast to the gentle-handling method, the other three methods can be easily imposed for long periods and may, therefore, create some animal-use concerns. Such considerations have been reviewed recently (33).

Perspectives. Recent progress in defining the anatomy and physiology of sleep-wake regulatory systems should promote our understanding of how homeostatic and circadian drives can induce rapid and discrete changes in behavioral state. An interdisciplinary and unified approach that includes neurophysiology, neuroanatomy, neurochemistry, and molecular biology will promote elucidation of the complex biology of sleep. Integration of basic sleep physiology with modern genetic techniques will undoubtedly allow identification of specific genes and substances involved in the regulation of various facets of sleep. Industrial, governmental, and professional organizations are increasingly recognizing the importance of adequate sleep and the detrimental impact of sleep loss and sleepiness, although public awareness may be lagging (45, 155). At present, increased availability of recommendations to promote public well being in this area is probably warranted in many arenas.

Fatigue and disturbed sleep are common troubling problems for many healthy persons, as well as for persons experiencing chronic disease and associated therapies for conditions that include cancer, HIV/acquired immune deficiency syndrome (AIDS), musculoskeletal diseases, and hepatitis (6, 16, 36, 42, 64, 74, 99, 116, 123). Increased knowledge about the interactions between sleep and immune function could have important health implications, particularly for patients who experience disruptions in normal patterns of sleep in association with either their primary disease or their therapy. Sleep disruption can be profound in hospitalized patients and nursing home residents (62, 120, 122, 164). For example, patients spend less than one percent of the night in SWS during the five- to eight-day period after open-heart surgery (137). The development of valid animal models for evaluating the relationship among sleep,

sleep loss, and susceptibility to or recovery from disease is an important goal.

Current data suggest that normal sleep and various sleep disorders have a genetic basis or are influenced by genetically determined physiologic or environmental predispositions. Excess sleepiness, abnormal sleep patterns, non-restorative sleep, and fatigue are becoming increasingly pervasive in modern society. Identifying substances and mechanisms that modulate sleep and vigilance in animals during health and disease should ultimately contribute to a better understanding of the processes that control normal sleep and contribute to sleep disorders, allow the eventual identification of mechanisms that cause fatigue, excess sleepiness, or poor sleep, and promote the eventual development of interventions to prevent or alleviate these disabling medical conditions.

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