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Overview

Animal Models of Sleep Disorders

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Problems with sleep affect a large part of the general population, with more than half of all people in the United States reporting difficulties with sleep or insufficient sleep at various times and about 40 million affected chronically. Sleep is a complex physiologic process that is influenced by many internal and environmental factors, and problems with sleep are often related to specific personal circumstances or are based on subjective reports from the affected person. Although human subjects are used widely in the study of sleep and sleep disorders, the study of animals has been invaluable in developing our understanding about the physiology of sleep and the underlying mechanisms of sleep disorders. Historically, the use of animals for the study of sleep disorders has arguably been most fruitful for the condition of narcolepsy, in which studies of dogs and mice revealed previously unsuspected mechanisms for this condition. The current overview considers animal models that have been used to study 4 of the most common human sleep disorders—insomnia, narcolepsy, restless legs syndrome, and sleep apnea—and summarizes considerations relevant to the use of animals for the study of sleep and sleep disorders. Animal-based research has been vital to the elucidation of mechanisms that underlie sleep, its regulation, and its disorders and undoubtedly will remain crucial for discovering and validating sleep mechanisms and testing interventions for sleep disorders.

Abbreviations: CSF, cerebrospinal fluid; MSLT, multiple sleep latency test; NREMS, non-rapid-eye-movement sleep; REMS, rapid-eye-movement sleep; RLS, restless legs syndrome; OxR, orexin receptor; OSA, obstructive sleep apnea; SOREMSP, sleep-onset rapid eye movement sleep period; SWS, slow-wave sleep

Sleep Disorders

Problems with sleep affect a large part of the general population, with more than half of the people in the United States reporting difficulties with sleep or excessive sleepiness at some time during their lives and with about 40 million affected on a chronic basis.[113,119] During the past 30 y, knowledge about sleep physiology and the health consequences of sleep loss and sleep disorders has grown substantially. This information—together with growing awareness of the causal or contributory effect of sleep loss and sleepiness on catastrophic accidents, motor vehicular accidents, and performance—has heightened awareness of the effects of insufficient sleep on health, safety, mood, productivity, and quality of life.[10,56] However, societal and individual efforts to limit or manage sleep loss can be offset by the personal or societal needs or desires to extend waking hours and limit sleep time. Compounding this problem, more than 80 specific sleep disorders have been identified by the American Academy of Sleep Medicine,[5] and medically defined sleep disorders are prevalent in society. However, for a variety of reasons, many sleep disorders go unrecognized, undiagnosed, or untreated (for examples, see references 134 and 192). Identifying and managing the adverse consequences of sleep loss is further complicated in that personal, subjective estimates of sleep amount and quality, the severity of sleepiness, and the likelihood of falling asleep often correlate poorly with validated objective measures of sleep, sleepiness, alertness, and performance (for examples, see references 7, 10, 146, 213, 214, 223, and 232).

Sleep is a complex physiologic process that is influenced by many internal and external factors, such that problems with sleep are often related to specific personal circumstances, and complaints about inadequate sleep are rooted (at least to some extent) in the subjective assessment of the affected person. These subjective and circumstantial aspects of sleep complicate the study of sleep disorders in any model other than humans. However, advances in managing the distress and debilitation associated with sleep disorders undoubtedly will require the use of animals for delineation of the underlying physiology of sleep, identification and validation of the causes and mechanisms of sleep disorders, and the development and preliminary testing of new therapeutic approaches. Exemplifying this relationship, 2 landmark independent studies that used either genetically altered mice or dogs with spontaneous narcolepsy discovered that disruptions in orexinergic neuronal systems represent a previously unknown underlying mechanism for narcolepsy and thereby suggested new therapeutic strategies.[32,121] The current overview considers animal models that have been used to study 4 of the most common human sleep disorders: insomnia, narcolepsy, restless legs syndrome, and sleep apnea (Figure 1).

General Considerations in Studying Sleep in Animals

In most mammals and birds, waking and various stages of sleep can be defined based on electroencephalography (Figure 2;

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	Insomnia	Narcolepsy	Sleep apnea	Restless legs syndrome
Definition	Persistent difficulty in falling or staying asleep	Excessive sleepiness associated with cataplexy and other REMS phenomena	Intermittent, somewhat cyclical reductions or cessations in airflow during sleep	Sensorimotor disorder characterized by overwhelming urge to move the legs when they are at rest, usually accompanied by unpleasant sensations
Prevalence	50%, occasional; 22%, frequent	0.05% of population	18 million adults in the United States	About 10% of adults in the United States
Features	Duration, acute or chronic; etiology, primary or secondary (comorbid); nocturnal timing, sleep onset or early arousal	With or without cataplexy	Central or obstructive; often associated with snoring and obesity	Primary (familial) or secondary (comorbid); worsens with inactivity, including during sleep
Adverse outcomes	Unwanted daytime sleepiness or fatigue; cognitive impairment, mood disturbances	Excessive daytime sleepiness, cataplexy, sudden sleep onset, sleep paralysis, hypnogogic hallucinations	Sleep disruption, daytime sleepiness or fatigue; cardiovascular, metabolic, and neuropathologic complications	Uncontrollable leg movements, uncomfortable or painful feelings in legs, interference with sleep
Treatments	Sleep hygiene, hypnotic medications, cognitive behavioral therapy	Stimulant and antidepressant medications, sodium oxybate	Weight loss, continuous positive airway pressure, oral appliances, sleep, hygiene, surgery	Diet, exercise, medication (dopamine agonists, opioids)

Figure 1. Common sleep disorders.

reviewed in reference 210). Electroencephalography provides an objective and functional marker of sleep, can be measured in freely moving or naturally sleeping animals under controlled laboratory conditions or in a naturalistic environment, and supports studies of the pharmacologic and physiologic manipulation of sleep.[159] Electroencephalography is often used to assess sleep in combination with measurement of body and brain temperature, other physiologic systems (for example, respiration), brain and blood chemistry, and brain functioning.[48] However, specific electroencephalography-based features of sleep vary across species; for example, some species show single-hemisphere sleep, and some monotremes appear to lack features that characterize rapid-eye-movement sleep (REMS) in placental and marsupial mammals.[2,116,117] In contrast to birds and mammals, reptiles and amphibians have higher amplitude cortical activity during waking states than they do in quiescent states, and they do not appear to have REMS (reviewed in references 2 and 181). However, although electroencephalography-defined sleep architecture can vary among species, many features, including key homeostatic, circadian, and neurochemical modulations of sleep, are similar across species.[159,217]

In addition to an electroencephalography-based definition, sleep can be defined behaviorally as a regulated state of reduced movement and sensory responsiveness (that is, behavioral quiescence and an elevated arousal threshold that respond to homeostatic regulation).[2,231] Behaviorally defined states that appear analogous to electroencephalography-defined sleep have been identified in both mammalian and nonmammalian organisms, the latter including fish, flies, nematodes, and birds.[41,196]

The daily amount of sleep and its placement within the 24-h day are fundamental characteristics of sleep in animals and have been evaluated in over 150 animal species, including invertebrates, fish, amphibians, reptiles, birds, and 14 orders of mammals in over 200 studies using behavioral methodology or electroencephalography (or both) in laboratory and field studies.[27,231] However, the daily duration, cyclical organization, diurnal timing, and other features of sleep vary extensively among animal species.[2,27,45,231] Indeed, even inbred strains of laboratory mice show variation in these properties of sleep.[80,211] Furthermore, commonly used rodents generally are preponderantly awake during the dark phase and asleep during the light phase. Species with a higher basal metabolic rate on a body-weight basis appear to spend a relatively larger total percentage of time in slow-wave sleep (SWS), suggesting an energy conservation role for this sleep state.[115,230] In comparison, other species spend relatively less time in REMS, suggesting a diminished neurophysiologic role for REMS in those animals.[231] However, such species-related comparative assessments of sleep and its features may generate different relationships and conclusions depending on how the analysis is conducted and interpreted.[117,182,183,197,198] For example, when controlled for phylogeny, an assessment based on 4 common sleep indices (body mass, brain mass, basal metabolic rate, and gestation period) and an ecological variable (a measure of predation risk based on vulnerability associated with the sleep site) found interspecies support for a neurophysiologic role for REMS, but no support for an energy conservation function for SWS,[116,117] in contrast to previous analyses that did not consider phylogeny.[230,231]

Effective use of animals to study normal sleep and sleep disorders must consider known similarities and differences between human and animal sleep patterns (Figure 3). For example, in adult humans and in nonhuman primates, the circadian distribution of sleep tends to be consolidated and normally monophasic (perhaps diphasic with consideration of napping and segmented sleep), whereas it is polyphasic and relatively fragmented in rats, mice, and cats. Therefore, within a night's sleep, humans pass through 4 to 6 cycles of nonrapid eye-movement sleep (NREMS; often referred to as SWS in animals) and

	Behavioral features			Electrophysiologic features		
	Thought	Movement	Eyes	EEG	Electromyelogram	Electrooculogram
NREMS–SWS	Some mental activity; no memory unless awakened	Infrequent, involuntary	Closed; slow or no movement	Synchronized, slow frequency, high amplitude	Reduced	Slow or absent
REMS–PS	Illogical mental activity; memory only if awakened	Inhibited	Closed; rapid movement	Desynchronized, fast frequency, low amplitude	Inhibited	Rapid
Waking	Logical mental activity; memory	Frequent, voluntary	Open; directed movement	Desynchronized, fast frequency, low amplitude	Present, purposeful	Present, directed

Figure 2. Behavioral and electrophysiologic features of vigilance states. PS, paradoxical sleep

	Human	Rat	Mouse	Cat	Dog
Primary diurnal sleep phase	Dark	Light	Light	Dark	Dark
Sleep pattern	Monophasic or diphasic	Polyphasic	Polyphasic	Polyphasic	Polyphasic
Daily sleep duration	7–8 h	12–15 h	12–15 h	12–13 h	9–14 h
Length of sleep bouts	6–8 h	10–14 min	2–4 min	78 min	45 min

Figure 3. General characteristics of normal sleep in humans and 4 commonly used model species.[27,51,108,132,212,231]

REMS (also referred to as paradoxical sleep, due to the associated cortical activation), whereas in rats, mice, and cats, NREMS–REMS cycles are much shorter and occur periodically throughout the 24-h day. Furthermore, environmental factors, including temperature and photoperiod, can substantially alter these parameters.[27] For example, a recent study reported that mice living in a natural environment are not explicitly nocturnal, exhibit feeding activity that is predominantly and sometimes exclusively diurnal, and show a negligible modulatory influence of specific genes on activity timing as compared with seasonal influences.[43]

The restorative properties of sleep depend on its duration, quality, and continuity. For example, sleep fragmentation, as occurs in persons with sleep apnea, disrupts normal sleep architecture, reduces the amount of time spent in the deeper stages of sleep, and reduces the restorative benefit of sleep. Although patients with sleep apnea may not complain of insomnia, the impaired continuity of their sleep causes a variety of problems, including fatigue and daytime sleepiness. In comparison, sleep in rodents is highly fragmented even under normal conditions, with normal individual sleep bouts of less than 5 min in mice.

Despite many differences in sleep between animals and humans, the many commonalties have made animal studies fundamental to past and future research on sleep.[48,231] Translational animal models have supported the investigation of sleep and sleep disorders in ways that are not possible in human volunteers, thereby expanding our understanding of sleep neurophysiology and regulation and facilitating the development of new treatments for sleep disorders.[48,159]

Insomnia

Insomnia is the most commonly reported sleep-associated problem, affecting as much as 50% of the adult population periodically and 10% to 15% chronically.[141] Insomnia is characterized by complaints that include difficulty in falling asleep, frequent awakening from sleep, waking too early and having trouble falling back to sleep, and nonrestorative sleep. These problems occur despite adequate opportunity to sleep and result in daytime sleepiness or fatigue and performance impairment. Insomnia can be characterized in terms of duration (acute or chronic), cause (primary or secondary), type (psychophysiologic, paradoxical, inadequate sleep hygiene, comorbid, and idiopathic), and timing during the night (initial or onset, middle, late, or mixed).[162] Several theoretical frameworks have been developed to explain the basis for insomnia (reviewed in reference 162), and available animals models of insomnia generally derive from the demonstrated efficacy of known approaches to insomnia management in those models.[184] The growing body of information on the physiology of sleep supports a reasonably circumscribed list of general pathophysiologic mechanisms of primary insomnia that encompass 4 broad candidate areas: 1) disruption of sleep homeostatic regulation; 2) disruption of the circadian clock; 3) disruption of intrinsic systems responsible for the expression of sleep; and 4) enhancement of extrinsic systems that can alter normal sleep–wake regulation.[184]

A model that incorporates several of these theoretical features involves exposure of rats to a stressful environment; this experience is followed several hours later by sleep disturbances similar to those of people with stress-induced insomnia (prolonged sleep latency, reduced sleep duration, frequent arousals and fragmentation of sleep, high-frequency electroencephalographic activity during NREMS).[28] Careful and detailed examination of behavior, immunohistochemistry, and specific brain lesions indicates that rats exposed to this situation develop simultaneous activation of arousal and sleep-promoting regions in the brain.[28] In particular, specific limbic regions appear to activate brainstem arousal systems and subsequently the cerebral cortex, generating high-frequency activity in the electroencephalogram.[28] Similarly, insomnia in people can occur in association with inappropriate arousal from sleep, increases in the high-frequency component in the electroencephalogram, abnormal hormone secretion, and autonomic and metabolic activation in both brain and the periphery.[19]

Rodent genetic models purported to represent insomnia have been proposed on the basis of strain-related differences in the 24-h amount and diurnal distribution of sleep.[14,44,80,180] For example, as compared with other mouse strains, DBA/2J mice spend more time awake during a 24-h period, have relatively low electroencephalographic δ power (theoretically related to low sleep

drive) both over the 24-h day and during the light (rest) phase, and show a relatively high number of brief awakenings and SWS episodes.[63,80] These characteristics (a low amount of sleep that is shallow and fragmented) resemble those of some patients with insomnia,[80] suggesting the possibility that DBA/2J mice may be a useful model of insomnia.

Various strains of *Drosophila* created by laboratory selection also vary in the amount, pattern or proportion of time spent in a behavioral state that appears analogous to electroencephalography-defined sleep in mammals.[195] So-called insomnia-like (ins-l) flies sleep less than do normal flies, appear to have difficulty initiating and maintaining sleep, and show evidence of daytime cognitive impairment.[194] These flies also are hyperactive, are hyperresponsive to environmental perturbations, and show other features that may be related to their sleep phenotype.[194] Whole-genome profiling of ins-l flies has identified differential expression of at least 2 genes that are upregulated in human subjects after acute sleep deprivation.[194] Ins-l flies may be useful for the identification of genes and molecules that contribute to sleep regulation, genetically driven sleep need, and insomnia.[194]

Administration of caffeine has been proposed as a simple and effective model of sleep-onset insomnia. The effects of caffeine on sleep in humans and animals include increased arousal, prolonged latency to sleep onset, reduced total sleep time and efficiency, and reduced build-up of sleep pressure during waking.[18,96,109,160,169,184,227] Furthermore, sleep-promoting agents attenuate or reverse caffeine-induced sleep disruptions in rats and people.[151,160]

Some circadian clock genes influence sleep (reviewed in reference 86). For example, a point mutation in the human clock gene *Per2* produces the rare advanced sleep-phase syndrome, whereas a functional polymorphism in *Per3* is associated with the more frequent delayed sleep-phase syndrome.[86] Furthermore, an association study revealed a higher recurrence of insomnia in patients homozygous for Clock polymorphisms.[86,193] Selective breeding of mice was used to create an early-running (indicative of spontaneous early awakening) genetic variant.[225] In these variant mice, the onset of the daily wheel-running bout precedes dark onset by several hours, and pharmacologic treatment at appropriate circadian times normalizes diurnal patterns of running.[225]

Finally, some models using brain lesions also result in at least temporary reductions in sleep that may mimic some features of insomnia. For example, lesions of the ventrolateral preoptic nucleus, which contains neurons that are active during sleep, cause significant reductions in both the amount and depth of NREMS; these effects persist for at least 3 wk after the lesion.[125]

An ideal animal model of insomnia would mimic the main characteristics of human insomnia: the animal would display reductions in the amount or quality of sleep at times when sleep would normally be expected and would accrue sleep debt or display sleepiness or tiredness during the normal active phase. Therefore, modeling insomnia in animals requires the creation of a situation in which the subject does not initiate sleep at the appropriate circadian phase, despite being given sufficient opportunity to sleep, and subsequently develops a sleep debt, or a need for recuperative sleep. Few (if any) models convincingly achieve these conditions. For example, in typical experimental sleep deprivation, animals are actively prevented from engaging in sleep despite having the desire and ability to sleep. Rodent models of disrupted sleep generally involve perturbation of the animal or its situation, commonly via imposition of a stressor (for example, immobilization, an altered environment, social stress, fear and fear conditioning, sensory stimulation; reviewed in reference 180). Finally, consideration of the temporal organization of sleep and waking is crucial to developing models for testing sleep-promoting drugs. For example, because many commonly studied rodent species are relatively active during the dark phase and somnolent during the light phase, administration of sleep-inducing agents during the light phase may mask or minimize sleep-inducing properties, whereas administration during the dark phase would test a drug's effects in animals that are active and showing little or no sleep pressure.

The question remains of whether currently available models actually represent insomnia, because one cannot determine whether the animals trying unsuccessfully to sleep or simply are not sleeping. Furthermore, people with insomnia often report sleep problems that are not confirmed on polysomnography, indicating a substantial subjective perceptual component in many cases of this disorder.[90,223,232] Nonetheless, data obtained from model systems clearly have extended our understanding of the brain mechanisms that underlie sleep and wakefulness and the processes that contribute to the homeostatic and circadian regulation of sleep. This knowledge would be unavailable without the careful assessment of sleep in animals.

Sleep Apnea

Sleep-disordered breathing refers to intermittent, somewhat cyclical reduction or cessation of airflow during sleep. This common condition affects at least 18 million Americans.[50] In the specific disorder known as sleep apnea, airflow stops during sleep. The 2 forms of sleep apnea are obstructive and central, which respectively occur with or without obstruction of the upper airway; obstructive sleep apnea (OSA) is by far the most common type, often occurring in association with snoring. In the presence of a collapsible airway, sleep-induced loss of tonic input to the upper airway dilator muscle motor neurons allows the pharyngeal airway to collapse.[50] The sleeping subject generally reacts to this airway obstruction by awakening; sleep then resumes, leading to repeated cycling of sleep, intermittent hypoxia, and arousal throughout the night.[50] Numerous comorbid conditions, including diabetes and cardiovascular disease, are associated with sleep-disordered breathing and OSA. Predisposing factors are obesity, large necks in men, menopause in women, and physical abnormality of the upper airway. The health consequences of OSA include systemic and pulmonary hypertension, stroke, coronary artery disease, and cardiac arrhythmias.[50] In addition, intermittent hypoxemia and sleep disruption can negatively affect insulin sensitivity and glucose regulation and may contribute to the development of metabolic syndrome independent of obesity.[216] Neurocognitive effects of OSA include daytime sleepiness and impaired memory and concentration; persistent (perhaps permanent) cognitive impairment and neural injury may develop in association with sleep apnea despite long-term therapy, particularly when sleep apnea develops in association with or as a consequence of concurrent comorbid conditions.[50,120,216]

Sleep-disordered breathing and OSA are not reported frequently in animals but do appear spontaneously in some species and strains. A natural animal model of OSA is English bulldogs, which have been used to study upper airway anatomy and physiology and the pharmacologic treatment of OSA. English bulldogs have an enlarged soft palate and narrow oropharynx and

display many of the clinical features of OSA, including snoring, sleep-disordered breathing, oxyhemoglobin desaturation during sleep, frequent arousal from sleep, and hypersomnolence with shortened sleep latencies.[91,92] However, OSA in English bulldogs is not related to obesity, as it often is in humans. Obese Yucatan minipigs have been proposed as a model of obesity-related sleep apnea; obese pigs exhibit considerably more apnea and oxyhemoglobin desaturation than do their lean counterparts.[123] Although the upper airways of nonhuman primates have structural and functional similarities to those of humans, spontaneous OSA has not been reported in any nonhuman primate species to date to our knowledge. However, cynomolgus macaques that received intradermal liquid collagen injections in the uvula, tongue, and lateral pharyngeal walls developed hypopnea and reduced REMS.[163] Sprague–Dawley and spontaneously hypertensive rats exhibit sleep-related central apnea that has been exploited experimentally.[29,30]

Noninvasive models of intermittent hypoxemia expose animals to repetitive hypoxia and oxygenation, which occur in both obstructive and central apnea (reviewed in reference 49). Depending on the species, animals are either ventilated with a mask or placed in a ventilated cage or chamber; in either case, they breathe nitrogen-enriched air (to create hypoxia) alternating with oxygen or normal air.[49] By creating intermittent hypoxemia, these models allow evaluation of oxygen desaturation, hypercapnia, sustained hypoxia, and sleep fragmentation.[77,168,186] The models typically apply the stimulus of intermittent hypoxemia during the sleep-dominant phase of the diurnal cycle and create moderate to severe oxygen desaturation, thereby mimicking severe forms of human sleep apnea (reviewed in reference 49). In human patients, the severity of sleep apnea is assessed based on both desaturation of arterial oxygen and the frequency of respiratory events (apnea or hypopnea).[4,49] Therefore, modeling different severities of sleep apnea requires reproduction of both the appropriate frequency of intermittent hypoxemia cycles and sufficient oxygen desaturation to be comparable to those in human patients. An advantage of intermittent hypoxemia models is that they permit exposures that can be extended over months, allowing the investigation of chronic consequences that might occur in humans.[187,188,235]

OSA has been modeled in a variety of species by using surgical tracheostomy and subsequent intermittent occlusion of the endotracheal tube.[25,71,73,105,110,166,190,221] These models produce predictable, reliable, and modifiable obstructive apneas that are compatible with concurrent neural manipulation and hemodynamic measurements. Rodents are often exposed to hypoxia for a fixed period of time during the light (somnolent) phase, with normoxia during the dark (active) phase. Although many studies do not link exposure to intermittent hypoxemia with sleep or sleep onset, some studies monitor the animal's sleep–wake state and generate airway obstruction in association with sleep and release this constraint during arousal.[24,87,101] For example, one study produced obstructive apnea in conscious rats by using an inflatable balloon implanted in the trachea.[191] When deflated, the tracheal implant did not notably impair normal breathing, yet apneic episodes of as long as 16 s in duration could be created during sleep.[191]

Mice have increasingly been used to study interactions between sleep and respiration. C57BL/6J mice show spontaneous apnea, postsigh apnea, and irregular breathing with apnea during reoxygenation after acute hypoxia.[226] These mice have been used, for example, to assess the relationships among obesity, age, and pharyngeal mechanical and neuromuscular control.[167] C57BL/6J mice can also be used to develop pharmacologic and genetic approaches to improving irregular breathing and apnea.[226] New Zealand obese and New Zealand white mice and respiratory-gated MRI of the pharynx have been used to determine the effect of obesity on pharyngeal airway size during inspiration and expiration.[21,22] As compared with lean New Zealand white mice, New Zealand obese mice have a significantly smaller airway, greater parapharyngeal fat pad volumes, and a greater volume of other upper-airway soft tissue structures.[22] Pharyngeal airway cross-sectional area is greater during inspiration than expiration in New Zealand obese mice, whereas the reverse occurs in New Zealand white mice, supporting the idea that pharyngeal airway patency in obese subjects depends on airway dilation during inspiration and may be vulnerable to sleep-associated loss of neuromuscular pharyngeal activation.[21,22]

Animals have been used to study the neurochemical regulation of pharyngeal motor neuron activity and airway patency and, because oxyhemoglobin saturation patterns correlate with neural injury, have facilitated investigation of how OSA can cause neurobehavioral and cognitive impairment independent of comorbidities.[50,120,216] Neurons and neuronal groups that are more metabolically active are typically the most vulnerable to hypoxic injury.[120] Long-term exposure of adult mice to cycles of hypoxia and reoxygenation results in irreversible impairments that develop in association with vacuolization in the perikarya and dendrites and markedly impaired c-*fos* activation in both noradrenergic locus coeruleus and dopaminergic ventral periaqueductal gray wake neurons, with a 40% loss of catecholaminergic wake-related neurons after 6 mo of exposure.[235] In contrast, cholinergic, histaminergic, orexinergic, and serotonergic wake-related neurons seem unperturbed.[235] The use of animals to identify molecular pathways for oxidative, inflammatory, and organelle injury related to neural dysfunction provides an avenue for the development of interventions that may prevent or even reverse neural injury from sleep apnea.[120,216]

Current animal models of intermittent hypoxemia have several drawbacks. In many cases, the models mimic severe human OSA and may be less applicable to most clinical OSA.[49] In addition, animals exposed to intermittent hypoxemia develop hypocapnia, whereas human OSA is characterized by hypercapnia.[49,103] Although CO_2 supplementation in rats does not modify hypertensive effects of intermittent hypoxemia,[78] CO_2 levels may influence other effects of intermittent hypoxemia and OSA. Furthermore, human OSA typically is associated with obesity, which is not always considered in animal studies. In addition, OSA causes sleep fragmentation, which may have independent effects on metabolism. Models for studying OSA-associated sleep fragmentation have been developed in animals.[13,25,88,165,218] However, these models may not achieve reliable or reproducible arousals during the course of chronic exposure; for example, sleep changes induced by long-term exposure to intermittent hypoxemia in animals may be less durable than are effects on blood pressure.[76,77,88,95,105,147,168,219] Thus, exposure of animals to intermittent hypoxemia produces repeated arousals and changes in sleep architecture that are comparable to those in clinical OSA, yet the effects may not be persistent, limiting their use for studying long-term metabolic consequences of OSA.

Narcolepsy

Narcolepsy is characterized by 4 cardinal symptoms: excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations (reviewed in reference 1). Cataplexy is the most characteristic feature of narcolepsy and consists of sudden muscle atonia during wakefulness. Cataplexy is triggered by emotions and varies in presentation, ranging from complete postural collapse to attacks that affect only facial muscles, neck, arms or legs. Episodes of cataplexy last from a few seconds to 10 min and are associated with a waking or a REMS-like electroencephalogram. Most narcoleptic patients also have disturbed sleep, including sleep fragmentation, prolonged NREMS–REMS cycles, periodic limb movements during sleep, and comorbidities such as OSA. The excessive daytime sleepiness of narcolepsy is associated with episodes of an irresistible urge to sleep (sleep attacks).

Narcolepsy is clinically categorized as occurring with cataplexy, without cataplexy, or secondary to another medical disorder. The diagnosis usually requires patient assessment with polysomnography both at night and during a multiple sleep latency test (MSLT).[5] The MSLT involves 5 nap opportunities scheduled 2 h apart during the day time, beginning 1.5 to 3 h after awakening. Key diagnostic features of the MSLT are the latencies of sleep onset and REMS. If REMS occurs in less than 15 min, then the epoch is defined as a sleep-onset REMS period (SOREMSP). A MSLT consistent with narcolepsy reveals a mean sleep latency of less than 8 min and 2 or more SOREMSP after minimally sufficient sleep on the previous night.

The most likely cause for narcolepsy has been identified as the degeneration of hypothalamic neurons that contain the peptide orexin, which is also called hypocretin. The landmark discovery of the role of orexin in narcolepsy was based on the study of narcoleptic dogs and observations of orexin-deficient mice.[32,121] Narcoleptic patients have low levels of orexin A in their CSF.[20] Two other peptides (dynorphin and neuronal-activity–related pentraxin [NARP]) colocalize with orexin in neurons and may contribute to narcolepsy.[42] In addition, most narcoleptic patients with cataplexy are positive for a specific MHC class II allele, HLA-DQB1*0602.[122]

Canine models. In addition to humans, spontaneous narcolepsy has been described in dogs, cats, and horses.[57,106,127,138,202] Affected dogs show attacks of cataplexy that may be partial or involve full collapse; electroencephalographic recordings show normal electrical activity and sleep stages but also document SOREMSP.[138] Canine narcolepsy with cataplexy has now been identified in several breeds, with Doberman pinschers and Labrador retrievers showing familial forms (autosomal recessive) and other breeds showing sporadic narcolepsy.[31,70,79] Familial cases generally have early onset with mild symptoms, whereas sporadic cases have varied onset and more severe symptoms.[33] Cataplexy in dogs is evaluated with a highly standardized food-elicited cataplexy test in which 12 pieces of canned dog food are placed on the ground in a semicircular pattern at 30-cm distances.[179] A normal dog eats all of the food in approximately 10 s, whereas a narcoleptic dog exhibits episodes of partial or complete cataplexy before eating all the food. Another test involves play-elicited cataplexy, in which 2 dogs are brought into a room and allowed to freely interact with each other and with toys.[17]

Three stages of cataplexy have been described in narcoleptic dogs.[107] The first stage consists of muscle atonia, a waking-like electroencephalogram, and retained visual tracking; the second stage is characterized by REMS with hippocampal theta activity; and the third stage shows mixed-frequency and -amplitude electroencephalographic activity prior to a transition to wakefulness or sleep. Sleep recordings have revealed similar total sleep time in normal and narcoleptic dogs.[102] However, narcoleptic dogs spend more time in a drowsy state and, during the canine MSLT, have a shorter sleep latency and higher frequency of SOREMP than do normal dogs.[149] Human narcoleptic patients develop altered ultradian rhythms of sleep, whereas dogs do not.[26,149]

The search for a culprit gene for canine narcolepsy ultimately identified the type II orexin receptor gene (*OxR2*); different mutations of *OxR2* were identified in familial canine narcolepsy in Doberman pinschers, Labrador retrievers and a dachshund family, all of which led to a nonfunctional receptor.[121] Sporadic cases of canine narcolepsy did not have a similar mutation, but did have low levels of orexin in the CSF.[97] In addition to the genetic mutation, other factors may play a role in producing canine narcolepsy. For example, Doberman pinschers with the *OxR2* mutation show evidence of increased microglial expression of MHC II at about 1 mo of age, coinciding with neuronal degeneration in the amygdala and basal forebrain.[203] Treating these narcoleptic dogs with antiinflammatory and immune-suppressive agents beginning before 3 wk of age doubled the time to disease onset and reduced time spent in cataplexy by 90%.[17]

Mouse models. Mice that were genetically engineered to lack orexin were observed to have abrupt transient episodes of behavioral arrest during the dark (active) phase.[32] During these episodes, mice developed electroencephalographic and electromyographic patterns similar to those present during REMS or NREMS with sleep spindles.[32] These mice also had fragmented NREMS, greater amounts of REMS during the dark phase, decreased REMS latency, and multiple SOREMSP.[32] Therefore, the mice show many similarities to human and canine narcolepsy. A consensus report has defined murine cataplexy as an abrupt episode of nuchal atonia lasting at least 10 s, with θ activity dominating the electroencephalogram during the episode, and video recordings documenting immobility; at least 40 s of wakefulness must precede the episode.[189] Mouse cataplexy can be triggered by social interaction, locomotor activity, anticipation of food, ultrasonic vocalizations, wheel running, and group housing.[36,65,158]

Like narcoleptic Dobermans, *OxR2* knockout mice are only mildly symptomatic; their patterns of sleep and behavior correspond to the excessive daytime sleepiness and cataplexy of human narcolepsy.[224] *OxR1* knockout mice have moderate sleep fragmentation without cataplexy, whereas mice that lack both *OxR1* and *OxR2* have a phenotype similar to that of orexin null mice.[137,224] A caveat of studies using mice with constitutive gene deletions is that phenotypes may be confounded by developmental compensation, and therefore administration of inhibitors of OxR has been used to model narcolepsy; however, neither an OxR1 selective nor a dual OxR antagonist produced cataplexy in rodents, although they did increase REMS.[23] In addition to fragmentation of sleep and waking, mice with ablation of orexinergic neurons or OxR develop reductions in locomotion, feeding, drinking, and energy expenditure.[234]

In human narcolepsy, the loss of dynorphin and NARP signaling from orexin neurons likely contributes to the production of the disease.[42] Therefore, the most accurate model may require loss of orexin neurons rather than loss of only the orexin gene. A cytotoxic transgene, the N-terminal truncated cDNA for human

ataxin 3, can be used to ablate orexin neurons.[89] Mice with ablation of orexin neurons exhibit behavioral arrest, sleep fragmentation, and SOREMSP, as well as obesity beginning at 12 to 15 wk of age.[89] Genetic background, diet, and sex all appear to influence the phenotype of narcoleptic mice.[81]

Rat models. Injection of orexin B conjugated to the ribosomal toxin saponin into the rat hypothalamus leads to loss of over 90% of orexinergic neurons, with concurrent loss of other substances such as melanocyte concentrating hormone.[82] Rats treated in this manner spend more time in NREMS and REMS during the dark phase but spend less time in REMS during the light phase, with multiple SOREMSP.[82]

Transgenic rats that express a human ataxin-3 fragment under control of the human prepro-orexin promoter (orexin–ataxin 3 rats) develop almost complete loss of orexin neurons by 17 wk of age in association with sleep fragmentation, less wakefulness during dark phase, changes in REMS duration during both light and dark phases, a shortened REMS latency, multiple SOREMSP, and brief periods of atonia and postural collapse in association with electroencephalographic characteristics of wakefulness, resembling cataplexy.[16] Orexin levels in the CSF fall dramatically by 2 to 4 wk, with levels in regions of the cortex of less than 1% of levels in control rats.[233] The orexin–ataxin 3 rats retain some orexin neurons in the lateral hypothalamus and can double their CSF orexin levels in response to sleep deprivation, but even these elevated levels are still much lower than are basal levels in control rats.[16]

Another method of reducing levels of orexin or orexin receptors is through use of antisense RNA or RNA interference technology. In contrast to chemical destruction or gene deletion, the effects of interfering RNA are selective and reversible and have a fast onset. A study using microdialysis perfusion of *oxR2* antisense RNA into the pontine reticular formation of rats for 3 d produced more time in REMS and more episodes of cataplexy.[208] Targeting of prepro-orexin mRNA by injecting short interfering RNA into the perifonicial hypothalamus of rats resulted in suppressed expression of preproorexin, increased REMS during the active phase and cataplexy-like behavior, with no effect on NREM sleep.[35] Microinjection of small interfering RNA targeting the orexin type 1 receptor into the locus coeruleus of rats increased REMS during the dark phase.[34]

Restless Legs Syndrome

Restless legs syndrome (RLS) is a common disorder, with a reported prevalence of 5% to 15% in the general population.[228] RLS is more common in women than in men, and although it may develop at any age, it is more common in older adults.[150] RLS appears to have a familial predisposition.[62] The essential criteria for the diagnosis of RLS are 1) an urge to move the legs, accompanied or caused by unpleasant sensations in the legs; 2) onset or worsening of the urge during rest or inactivity; 3) partial or total relief by movement; and 4) worsening of symptoms during the evening or night as compared with the day.[3]

The underlying pathophysiology of RLS has not yet been elucidated completely. However, human studies have revealed 2 major impairments. First, functional brain imaging and autopsy studies have revealed abnormalities of the dopaminergic system.[39,60] In addition, dramatic improvement occurs after administration of dopaminergic agonists and symptoms are worsened by dopaminergic antagonists, supporting involvement of the dopaminergic system.[228] Second, the severity of RLS symptoms is inversely correlated with iron levels in serum and CSF.[139] CSF ferritin is decreased in patients with RLS, and imaging studies indicate reduced iron content in the striatum and red nucleus.[139] In addition, autopsies of brains of humans with RLS have shown reduced ferritin and iron staining and increased transferrin staining but decreased numbers of transferrin receptors.[38] Furthermore, serum ferritin levels correlate strongly and inversely with RLS symptom severity,[59] although because not everyone with iron deficiency develops RLS, other factors must also be important. The site of pathology in RLS within the nervous system remains elusive; however the preponderance of lower extremity involvement and development of RLS after spinal cord injury suggests involvement of the spinal cord, the circadian pattern of variation of symptoms suggests an associated dysfunction in circadian control areas, and the unpleasant sensory component suggests malfunction of antinociceptive mechanisms.[9,207]

Based on these features, several types of animal models have been evaluated with regard to RLS. One category involves animals with dopamine-related deficits in brain function. For example, the hypothesis that the diencephalic spinal tract (A11 dopamine cell cluster) is involved in the pathogenesis of RLS[37,154,171] has been tested by using the neurotoxin 6-hydroxydopamine to induce bilateral depletion of diencephalic A11 dopaminergic nuclei in rats.[154,155] Although some of the physical signs and response to treatment in rats were consistent with clinical RLS in humans,[154,155] the subjective aspects (for example, 'unpleasant sensations' or 'an urge to move') cannot be convincingly assessed in rats, and therefore the lesion may only partially mimic the clinical features of RLS. Dopamine systems may also be relevant to the circadian activity abnormalities of RLS because the suprachiasmatic nucleus of the hypothalamus projects to the A11 dopaminergic nucleus.

Mice with iron deficiency show marked increases in wake time in the 4-h period prior to light onset, yet their sleep and wake time is normal during the 12-h light period.[47] The period of increased wakefulness corresponds to the diurnal time point at which RLS symptoms maximally disrupt sleep onset and progression in humans, suggesting that iron-deficient mice may provide a potentially useful animal model for RLS.[47]

Finally, models of dopamine deficiency and iron deficiency have been combined. For example, among mice maintained on iron-deficient diets prior to the induction of bilateral lesions of the A11 nucleus by using 6-hydroxydopamine, locomotor activity was greatest in the group with both iron deprivation and lesions, and this hyperactivity was ameliorated by appropriate pharmacologic treatment.[128,170] In a genetic model, D3 receptor knockout mice display a phenotype consistent with the symptoms of RLS, iron-deficient D3 receptor knockout mice show greater acute and persistent pain responses than those in control mice, and responses are greater in mice with both deficiencies.[55] Furthermore, iron-deficient mice show a period of increased locomotor activity before the light (rest) phase; this timing resembles the increased restlessness of RLS patients prior to sleep.[55] Iron-deficient D3 receptor knockout mice develop this increased activity 3 to 4 h earlier than do mice with only iron deficiency.[55]

In summary, several animal models of RLS have been proposed. The key features include iron deficiency and dopaminergic deficit either due to genetic or pharmacologic manipulation. The changes in locomotor activity, circadian rhythm, and sensory responses in these models seem to mimic some of the clinical features of RLS.

However, RLS is a subjective clinical diagnosis based on symptoms reported by patients. The urge to move, unpleasant sensations, and amelioration of these perceptions by movement are key features that pose a major challenge for additional investigation of this condition in animal models.

Other Animal Models for the Study of Sleep Physiology and Sleep Disorders

Increasing awareness of the importance of sleep to normal health and functioning, together with growing numbers of new research tools and genetically altered animals, has led to the identification of animals with sleep abnormalities that have not yet been linked to specific sleep disorders. However, such models may nonetheless be valuable in contributing to improved understanding of sleep physiology and pathophysiology and may eventually become associated with specific sleep disorders. For example, the study of 'hippocampal ripples' in rodents could lead to improved understanding of the mechanisms that link sleep to learning and memory.[64,83,209,222] Numerous other models offer similar possibilities, including, for example, mice that show alterations in normal sleep, behavioral features such as anxiety, and various gene deletions or insertions.[8,58,75,100,143] Other approaches can also be used to model human sleep disorders. For example, rats with spinal cord injury show leg movements during sleep and may be a model for the study of periodic leg movement during sleep in paraplegic patients.[66] Male and female rodents can be evaluated to determine sex-associated effects in sleep processes and sleep disorders (for examples, see references 6, 140, and 161), as some sleep disorders show a significant sex-associated bias.[61,164,172]

Management of Animals Used to Study Sleep Disorders

Many external and internal factors can influence sleep in animals and people. Environmental cues and stimuli that are relevant to the use of animals for the study of sleep and sleep disorders include light exposure and photoperiod (for example, variation in light intensity or in the duration of the light and dark phases within each 24-h cycle, the use of light:dark cycle lengths that exceed or are less than 24 h, exposure to constant dim light or darkness, exposure to light during the dark phase, on–off ramping of lighting to mimic dawn–dusk), ambient temperature (including influences of cage mates and bedding), noise, vibration, and disruptions in the home environment (for example, changing or moving the cage). For example, in a recent study, 3 different methods of transferring mice to another cage (forceps transfer, gentle transfer with gloved hands, and a passive transfer technique that did not involve active handling) had transient effects on serum corticosterone concentrations and were associated with altered open-field behaviors when mice were tested later on the same day; these findings indicate that the occurrence of cage change can influence both physiology and patterns of activity.[175] In addition, the frequency at which cages are changed, the type of bedding, and even the color of the caging used can influence the animals and the data collected, including their circadian rhythms and the amount of sleep they engage in.[46,118,185] With adequate ventilation and bedding, even cages that appear dirty to observers may not have significant or even measurable adverse effects on mice.[185] Furthermore, because rodents are olfactory-oriented animals, disruption of the olfactory environment in the cage is likely to constitute a significant environmental perturbation that can disrupt stable patterns of activity and behavior.[175] The social environment can affect sleep also, as illustrated in a recent study showing that pair-housed and individually housed mice show differences in their recuperative response to sleep deprivation.[104] Finally, the regulation of ambient light exposure is crucial, as dramatically illustrated in a recent report in which the inadvertent exposure of finches to an abnormal light cycle was associated with the development of clinical illness that resolved when the lighting was corrected.[200] Therefore, environmental stability must be controlled carefully by both the husbandry and research staffs to ensure the collection of valid results with minimal numbers of animals. These issues apply to all research that uses animals but are particularly crucial for studies of sleep.

General animal health is important to studies of sleep. Infection, pain and stress, even when subclinical, can alter normal patterns or parameters of sleep and activity in animals and people.[54,99,215] Because unintended health problems can alter sleep and confound data interpretation, sleep researchers are generally alert for the development of unanticipated changes in the health of their animals and are motivated to correct such problems. Animals that are being used to study sleep and associated behaviors are generally carefully, and often remotely and continuously, monitored for many behavioral and physiologic parameters that reflect overall health. These markers of health and illness can include patterns of sleep, locomotor activity, temperature, and food intake. Indeed, behavioral changes such as reduced activity or food intake are perhaps the most common initial signs of health impairment in clinical veterinary medicine. Because objective measurement of these parameters often occurs continuously in animals on sleep studies, many studies of sleep require surgical implantation of electroencephalographic, electromyographic, and other recording electrodes, which are then monitored by using either tethering or telemetry (for examples, see references 12, 11, 15, 67, 98, 142, 152, 153, 176, 204, and 205). Although appropriate attention to postsurgical care is important to obtaining valid data, many analgesic and antiinflammatory drugs have well documented effects on sleep,[52,126,157,220] and their use may confound the interpretation of data for some studies. Therefore, studies that require surgery must be designed to ensure that ample time is provided so that the effects of drugs used in association with surgery have dissipated before data collection begins.

Some approaches to monitoring sleep rely on assessment of movement or posture (for examples, see references 53, 74, 133, 156, and 201). Although these methods allow high-throughput processing of mice (for example, for drug evaluation or screening of mutant mice) and do not require surgery, they require validation prior to use in animals that may have inherent or treatment-induced alterations in activity, posture, size, and anatomic characteristics. In addition, behavioral assessment does not provide information on alterations in the electroencephalogram and electromyogram that are crucial to the assessment of genetic and pathologic perturbations of sleep. Therefore, some methods of assessing sleep may not be suitable for particular research questions.

Many studies of sleep and sleep disorders use a period of experimental sleep deprivation as a test situation. In general, both people and animals engage in a period of excess sleep, known as a sleep rebound or recuperative sleep, after an enforced delay in the

normal anticipated time of sleep onset. The sleep rebound reflects the normal homeostatic regulation of sleep and is influenced by genetics, environment, and circadian timing. In general, acute short-term sleep loss has no significant adverse health effects, although it can acutely alter glucose metabolism, cause sleepiness, and impair performance in some tasks.[94,145] However, the health effect of chronic disruption of sleep is increasingly being recognized and is currently an important topic of study.[114,228] Several approaches have been used to disrupt sleep in laboratory animals. The most widely used method is the so-called 'gentle-handling' technique, which has been applied to rodents, rabbits, and cats and causes loss of both NREMS and REMS. In this approach, the animals are under continuous observation and, whenever they either enter a state of behaviorally or electroencephalography-defined sleep, they are physically roused by actions such as tapping on the cage, providing novel objects, or gentle prodding. As the duration of the deprivation period increases, particularly beyond a few hours during the species' normal rest phase, the intensity or frequency of arousal interventions must be increased to maintain waking. These interventions can be quantified to generate a measure of sleepiness or sleep drive. In some cases, experimenters use repeated brief episodes of handling applied before sleep deprivation to habituate the animals to this procedure. However, a study using 6 d of repeated brief (3 min) handling of C57BL/6J mice during the light phase reported reductions in rest time on all handling days, increased serum corticosterone levels after 6 d (but not 1 d) of handling, and altered subunit composition of NMDA receptors in hippocampus.[124] Therefore, mice do not appear to habituate to daily brief handling over a 6-d period, and daily handling may alter measures of sleep homeostasis, stress, and receptor composition and signaling.[124]

Two long-standing approaches to creating chronic sleep disruption are the so-called 'disk-over-water' approach, which can produce either total sleep or REMS deprivation,[15,177,178] and the 'flower-pot' or 'platform' technique, which produces REMS deprivation but also influences SWS.[84,129,135,136] Increasingly common approaches to reducing sleep involve automated tactile stimulation,[144,173,174] forced locomotion,[13,15,72,111,112,130,131] or other automated interventions.[148,199] Unlike the gentle-handling method, automated methods can easily be imposed for long periods, potentially creating concern about animal wellbeing during the study. For example, rats develop nonspecific signs of illness after 5 or more days of total sleep deprivation.[68,69] However, sleep is a highly resilient physiologic process, and animals that experience sleep loss or disruption generally recover without obvious harmful after-effects as soon as they are given the opportunity to sleep.

Interpretation of data collected under all approaches to sleep deprivation or fragmentation requires careful consideration of potential nonspecific effects of the activating stimulus, including both the sensory stimulus used (for example, exposure to novel objects) and the requirement for movement. Many studies incorporate an activity-control group comprising animals that are required to perform equivalent amounts of locomotion over a shorter time period, thereby allowing sufficient time for consolidated sleep (for examples, see references 85 and 205).

Conclusion

Animal-based research has been invaluable with regard to the elucidation of mechanisms that underlie sleep, its regulation, and its disorders. Although subjective aspects of sleep complicate the use of animals for the study of some types of disorders, animals undoubtedly will remain crucial for discovering and validating sleep mechanisms and testing interventions for sleep disorders. Indeed, additional species are now being evaluated with regard to improving the alignment of human and animal sleep characteristics and thereby creating more valid models (for examples, see references 40 and 93). However, the use of any of these model systems requires careful control of nonspecific aspects of the environment to ensure the collection of valid, interpretable data.

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