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Many faces of sleep regulation: beyond the time of day and prior wake time

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Abstract

The two-process model of sleep regulation posits two main processes regulating sleep: the circadian process controlled by the circadian clock and the homeostatic process that depends on the history of sleep and wakefulness. The model has provided a dominant conceptual framework for sleep research since its publication ~40 years ago. The time of day and prior wake time are the primary factors affecting the circadian and homeostatic processes, respectively. However, it is critical to consider other factors influencing sleep. Since sleep is incompatible with other behaviors, it is affected by the need for essential behaviors such as eating, foraging, mating, caring for offspring, and avoiding predators. Sleep is also affected by sensory inputs, sickness, increased need for memory consolidation after learning, and other factors. Here, we review multiple factors influencing sleep and discuss recent insights into the mechanisms balancing competing needs.

Keywords

sleep; two-process model; circadian clock; sleep homeostasis; motivation

Introduction

The widely accepted two-process model of sleep regulation postulates that a process controlled by the circadian clock (Process C) interacts with a homeostatic process (Process S) to govern the timing and intensity of sleep [1,2]. Process S, reflecting sleep debt, increases during wakefulness and dissipates during sleep, and a transition to sleep or wake is triggered when Process S reaches the upper or lower threshold, respectively. Process C regulates the daily cycling of the thresholds according to the time of day [3]. EEG slow

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Conflict of Interest

The authors declare no conflict of interest.

wave activity (SWA) and rebound sleep are the primary indicators of Process S [4], while body temperature and melatonin rhythms serve as major indicators of Process C [1,2]. The model successfully accounts for the timing and intensity of sleep in a variety of experimental conditions. It has been highly influential and has provided a dominant framework for sleep research for decades [2,5–7].

The molecular and neural basis of circadian rhythms has been studied extensively, and the highly conserved machinery of the molecular oscillators has been elucidated in detail [8]. In mammals, the circadian oscillators in the suprachiasmatic nuclei (SCN) of the hypothalamus synchronize the peripheral clocks [9]. The SCN influences sleep-wake timing in part through downstream subparaventricular zone-dorsomedial hypothalamic pathways acting on the ventrolateral preoptic area (VLPO) and the lateral hypothalamus (LH), as well as the paraventricular nuclei of the hypothalamus acting on the LH [10]. In *Drosophila*, ~150 neurons in the central brain that contain the molecular clock machinery serve as the neural substrates for the circadian clock [11]. Among these, several clusters have been shown to affect sleep, including the ventral lateral neurons (LNvs), dorsal lateral neurons, and dorsal neuron group 1 (DN1), likely by acting on downstream targets such as the ellipsoid body and the pars intercerebralis [12].

In contrast to the circadian mechanisms, the molecular and neural mechanisms of sleep homeostasis remain elusive despite recent advances. In mammals, homeostatic control of sleep involves molecules such as adenosine, which increases during wake, promotes sleep, and acts on multiple brain regions [13]. Numerous brain regions in mammals involved in sleep regulation have been identified, facilitated by optogenetic and chemogenetic approaches in recent years [14,15]. However, the brain regions identified thus far are generally active when animals are either awake or asleep and may be involved in switching between wake and sleep states rather than sleep homeostasis [16]. On the other hand, several studies point to subsets of central complex neurons as a putative sleep homeostat in *Drosophila* [14]. Whether there are functionally analogous neuronal groups in mammals is unknown. Interestingly, recent mammalian and *Drosophila* studies show that calcium signaling in astrocytes reflects changes in sleep need after deprivation [17,18], suggesting a conversed mechanism of sleep homeostasis.

Although the circadian and homeostatic processes are central to sleep regulation, and the time of day and prior wake time are the primary factors affecting the two processes, it is also critical to consider other factors influencing sleep (Figure 1) [19–21]. Sleeping organisms cannot engage in essential behaviors such as eating, foraging, mating, caring for offspring, avoiding predators, and locomotion. Moreover, sensory inputs can interrupt or promote sleep, and certain conditions such as illness, fatigue, or increased need for memory consolidation after learning, may induce sleep. Thus, it is likely that organisms continually monitor various internal drives and environmental conditions to determine whether to sleep or engage in other behaviors. The preceding list of factors impacting sleep, while incomplete, underscores the need to go beyond the time of day and prior wake time for understanding sleep regulation.

The various sleep-regulatory factors may influence sleep in part through their effects on the circadian clock and sleep homeostat. Circadian rhythms can be modulated by temperature, nutrition, immune challenges, social interactions, and mechanosensory stimulation, among other factors [22–26]. Similarly, the sleep homeostat and its response to sleep deprivation can be affected by stress, social cues, and infections [27–29]. Process C and Process S are separable, but there is evidence of interaction between them [6]. For example, sleep deprivation or increased sleep pressure can affect the magnitude of circadian changes elicited by light [30–32] and SCN neuronal activity [33,34]. Conversely, clock genes may impact the homeostatic control of sleep pressure and the response to sleep deprivation [35,36]. Several recent reviews have covered the circadian and homeostatic mechanisms of sleep regulation [10,12,14]. Here, we focus on some of the other factors influencing sleep as well as recent advances in understanding the genetic and neural mechanisms balancing various drives.

Nutrition

Proper nutrient intake is vital for the survival of an individual. Not surprisingly, food scarcity has a marked influence on sleep in several species. For example, food deprivation leads to reduced sleep in rodents and flies, presumably to allow extra time for foraging [37–40]. The striking reduction in sleep amount in cave-dwelling fish populations of *A. mexicanus* compared to their surface counterparts is also likely due to food scarcity and the increased need for foraging in caves [41]. The effects of starvation on sleep, however, may depend on the duration of food deprivation. In *C. elegans*, short-term starvation leads to heightened arousal and foraging behavior, but long-term food deprivation leads to increased sleep [42]. Human studies also suggest that acute and long-term starvation have different effects on sleep [43–45].

Consistent with sleep suppression by starvation, there is an increased propensity for sleep after meals. While human studies yielded variable results, perhaps due to differences across individuals and the amount and type of food consumed [46–50], a recent *Drosophila* study has documented acute sleep-promoting effects of food consumption in more controlled settings [51]. Rodent studies have also found that a high caloric diet increases rapid eye movement (REM) sleep and alters sleep architecture [52–54]. This section reviews the molecular and neural mechanisms of sleep regulation by the metabolic state, focusing on recent advances from rodent and fly studies.

Sleep suppression by starvation—Ghrelin, a “hunger hormone” that promotes food intake, is upregulated during fasting [55]. Notably, Ghrelin administration is sufficient to stimulate wakefulness in rodents [56,57], suggesting that it is involved in sleep suppression by food deprivation. Neuropeptide Y (NPY)- and Agouti-Related Peptide (AgRP)-expressing neurons mediate Ghrelin signaling, and those in the hypothalamic arcuate nucleus induce appetite-related behavior [55]. Activation of AgRP neurons increases wakefulness, while their inhibition suppresses sleep changes caused by food deprivation [58]. Some rodent studies have also shown that NPY promotes wakefulness and feeding behavior [59–62], although other studies have shown that it induces sleep states [63,64]. *Drosophila* studies provide supporting evidence that Neuropeptide F (NPF), the ortholog to

mammalian NPY, contributes to sleep regulation by food deprivation [65,66]. NPF signaling can also increase wake behavior, and starvation-induced sleep loss requires NPF [66]. Subsets of NPF-expressing neurons in the circadian network and the fan-shaped body, a known sleep center, suppress sleep when activated [66], making them good candidates for sleep regulation by food deprivation. Overall, these studies point to a significant role for the Ghrelin/AgRP/NPY pathway in sleep suppression by starvation.

Orexin (Hypocretin) peptides were first discovered as regulators of feeding behavior in rodents [67]. The subsequent discovery of an Orexin Receptor mutation in narcoleptic dogs and narcolepsy in Orexin knockout mice indicated their role in maintaining wakefulness [68,69]. Orexins are expressed in the LH, a brain region regulating feeding, sleep, and motivated behaviors. Therefore, Orexin neurons are well suited for mediating the effects of food deprivation on sleep. Indeed, ablation of Orexin-expressing neurons abolishes fasting-induced increases in arousal [70]. Further evidence for the role of Orexin in the interaction between hunger and sleep comes from the Mexican cavefish, in which Orexin neurons mediate sleep suppression in the cave populations relative to surface populations [71].

Recent experiments in mice have demonstrated the role of Calretinin (CR), a calcium--binding protein, and CR-expressing neurons in the Paraventricular thalamus (PVT^{CR+}) in starvation-induced wakefulness [72]. PVT^{CR+} neurons become activated in response to starvation, and their optogenetic activation promotes wakefulness. Significantly, chemogenetic inhibition of PVT^{CR} neurons, specifically those projecting to the bed nucleus of the *stria terminalis* (BNST), attenuates starvation-induced arousal. These findings show that PVT^{CR+} neuronal activity reflects the arousal state under starvation and that the PVT-BNST pathway is critical for sleep suppression by starvation.

The first study documenting dramatically decreased sleep in starved flies found that two clock genes, *Clk* and *Cyc*, limit starvation-induced sleep loss [40]. Subsequent studies in *Drosophila* have identified several molecules and neurons involved in the process, including the Adipokinetic Hormone (AKH) pathway, which is analogous to the Glucagon pathway in mammals [73]. AKH Receptor-expressing neurons integrate information from AKH-expressing neurons and Insulin-producing cells (IPCs) for starvation-induced hyperactivity [74], and one of the *Drosophila* Insulin-like proteins, Dilp2, is necessary for starvation-dependent changes in arousal threshold [75]. Forkhead Box-O (FOXO), which regulates synaptic plasticity, functions downstream of AKH in the starvation-induced remodeling of dorsal projections of the small-LNv (s-LNv) clock neurons [73]. It would be interesting to determine if the role of circadian genes, *Clk* and *Cyc*, in limiting the starvation-induced sleep suppression is linked to the AKH/FOXO pathway's role in remodeling the s-LNv dorsal projections.

The conserved RNA/DNA binding protein Translin is upregulated in starved flies and functions in Leukokinin (Lk)-expressing neurons for starvation-induced sleep suppression [76]. Strikingly, a single pair of Lk-expressing neurons is required to integrate sleep and metabolic state, likely through the action of Lk neuropeptide on IPCs in the central brain [77]. Also, increased serine during starvation acts as a wake-promoting factor through

cholinergic neurotransmission [78], suggesting that serine metabolism in the brain regulates starvation-induced sleep suppression.

Metabolic control of sleep may also involve the circadian process. Work from the beginning of the 20th century showed that rats kept under constant light conditions with a regularly scheduled access to food showed anticipatory increases of locomotor activity before mealtime [84]. This phenomenon is controlled by food entrainable oscillators (FEOs), although their exact locations are unknown [85,86]. Whereas the SCN controls most behavioral outputs that occur in a circadian fashion, the FEOs can be entrained independently of the SCN [87–89].

How the nutritional regulation of sleep is integrated with the circadian and homeostatic processes requires further investigation.

Nutrient-specific sleep regulation—In addition to starvation, specific dietary components can affect sleep. Human studies assessing the effect of diet on sleep have found that a diet high in plant-derived foods, whole grains, legumes, and seafood and low in processed food is associated with improved sleep quality [79,80]. In *Drosophila*, dietary protein (provided mainly by yeast in the laboratory food) modulates sleep amount in a sex-dependent manner [81], and protein consumption leads to postprandial sleep through Lk Receptor neurons [51]. Furthermore, the absence of dietary protein increases sleep depth, a phenomenon dependent on the Dilp2 signaling pathway [75]. In addition to dietary protein, sugar content influences sleep amount and architecture through gustatory receptors [82], and dietary fatty acids promote sleep independently of taste perception [83].

Nutrition also modulates the balance between sleep and other behaviors, as discussed in detail below. In both rodents and fruit flies, metabolic control of sleep involves multiple molecular and neuronal pathways. How the various pathways work together to meet metabolic and sleep needs remains to be investigated.

Reproduction

Reproduction is essential for species survival; therefore, it acts as a strong motivational drive capable of robust sleep modulation. Several vertebrate and invertebrate examples illustrate the animals' adaptive sleep reduction to enhance successful mating and offspring survival.

Mating—A striking example of sleep loss by sex drive comes from a study of arctic sandpipers [90]. Male sandpipers markedly reduce their sleep to compete for females during 3 weeks of female fertility. Notably, males that sleep the least produce the most offspring, highlighting the benefits of sacrificing sleep to satisfy reproductive needs and challenging the view that sleep loss necessarily leads to decreased performance.

Like sandpipers, flies also reduce sleep in a sexual context. Male flies paired with female flies forgo a lot of nighttime sleep to engage in courtship [28,91]. However, courtship does not always outcompete sleep. Sleep-deprived males (with high sleep drive) and sexually satiated males (with decreased sex drive) favor sleep over mating [91]. Thus, the decision between sleep and courtship depends on the relative strength of sleep and sex

drive. Intriguingly, male sleep loss due to a sexual partner does not lead to homeostatic sleep rebound when the partner is removed [28]. Further, female pheromones can suppress rebound sleep that typically follows mechanical sleep deprivation, implying that sexual arousal can override homeostatic sleep drive. The fact that sexually aroused flies and sandpipers maintain reduced sleep for several days or weeks suggests plastic sleep needs depending on the context. Animals that lose sleep voluntarily to meet other pressing needs may sleep more efficiently, obviating the need for rebound sleep.

Recent studies in mice and flies have begun to identify the neural mechanisms by which sex drive competes with sleep drive. A study in mice showed that dopaminergic ventral tegmental area (VTA) neurons mediate wakefulness in the presence of salient stimuli, including a sexual partner [92]. Activation of VTA neurons promotes wakefulness and suppresses sleep, while their inhibition promotes sleep-related nesting behavior. VTA neurons are critical for arousal in response to not only sexual partners but also other ethologically relevant salient stimuli related to food and predators. These findings reveal a central role for the VTA dopaminergic circuit in integrating multiple arousal signals to decide between sleep and wakefulness.

Drosophila studies have also identified several neuronal populations, including dopaminergic neurons, involved in sexually motivated male sleep reduction [28,91,93–96]. At the center are male-specific Fruitless (Fru)-expressing P1 neurons, known primarily for integrating external sensory cues and internal sex drive to control courtship and mating behaviors [97,98]. However, P1 neuron activation also leads to sleep suppression [28,91,96], demonstrating the close link between sleep and courtship regulation. P1 neurons act downstream of a subset of octopaminergic neurons and upstream of a pair of dopaminergic neurons [91,93]. The circadian DN1 neurons function upstream and downstream of P1 neurons [96] and may provide the circadian input to the courtship and sleep balance.

Post-mating offspring care—Species survival relies on proper care of the offspring resulting from successful mating. Post-mating behavioral changes, including altered sleep patterns, have been observed in several species. Sleep changes can occur before and after the birth of the offspring.

Various sleep-related disorders have been documented in pregnant women, including restless legs syndrome, frequent awakenings, daytime sleepiness, and insomnia [99–102]. These problems may be attributable to the hormonal changes as well as physical discomfort. Pregnancy-related sleep changes have also been reported in rodents, although the exact nature of the sleep alterations is unclear. Studies have found a reduction in REM and non-REM (NREM) sleep during the light phase [103,104]. However, two studies showed that pregnancy generally increase NREM and REM sleep [104,105], whereas a third study found decreased sleep [103]. The mechanisms underlying these changes are not yet known but may involve hormones [106–108]. Notably, mating with vasectomized males results in nighttime sleep changes in female rats for up to 12 days post mating, similar to the duration of altered sleep observed in pregnant females [109]. This result implies that post-mating sleep changes in rodents are, at least in part, independent of fertilization.

Females of diverse *Drosophila* species exhibit post-mating sleep suppression [110–114]. This sleep suppression occurs even when the males lack sperm [110,111], suggesting that post-mating sleep changes in insects, as in rodents, are independent of fertilization. Sex Peptide and its receptor in the female's SPSN-SAG neuronal circuit convey information about the mating status from the periphery to the central brain to elicit several behavioral changes, including increased egg laying, reduced sexual receptivity, and decreased sleep [111,115]. The reduced sleep may be due to egg laying or foraging for proper food substrates for egg laying.

In addition to prenatal care, postnatal offspring care can also lead to sleep reduction. Postpartum sleep reduction in humans can last more than 12 weeks [116,117], with maternal-infant co-sleeping generally leading to poorer sleep quality in the mothers than sleeping separately [118–120]. Whether postpartum sleep reduction is due only to the baby waking up the adult or also to an internal regulation of the adult's sleep pattern, is unknown. In dolphins and killer whales, both mothers and offspring suppress rest behavior for several months after birth [121,122]. The early postpartum period in rodents is also associated with increased wakefulness and decreased NREM sleep [103,105], in part due to the external stimuli stemming from the pups [103]. Interestingly, maternal nursing in rabbits acts as a synchronizing factor on their offspring through brain regions that are not part of the central circadian oscillator, resembling the findings of the FEOs and suggesting that reproductive demands recruit novel neuronal substrates to regulate rest-activity patterns [123–125]. An invertebrate example of sleep regulation due to offspring care comes from worker bumble bees, which reduce their sleep amount in the presence of larvae and pupae [126]. Interestingly, bees show no apparent sleep rebound when the pupae are removed, suggesting, that this type of sleep loss does not lead to homeostatic recovery, as seen with sleep loss by sexual encounters in male flies.

Predator avoidance

Animals are vulnerable to predation during sleep, and thus they restrict sleep to certain places and times of the day to mitigate this danger. The circadian organization of rest-activity cycles is plastic, since the appearance of a novel predator or the disappearance of the threat can lead to changes in the diurnality/nocturnality of the prey [127,128]. In addition, sleep undergoes plastic changes depending on recent encounters with predators. For example, rats show increased wake time and decreased NREM and REM sleep after being chased by a simulated predator [129]. Some species regulate other aspects of sleep to facilitate predator avoidance. Mallard ducks located on the edges of a group exhibit increase unihemispheric NREM sleep and orient their opened eye away from the group's center [130,131]. This ability allows the ducks in the periphery to better detect predators during sleep.

To our knowledge, the potential effects of predator avoidance on invertebrate sleep have not been investigated. However, given the recent demonstration of an internal state resembling fear [132], *Drosophila* could serve as an attractive model to uncover the molecular and neural mechanisms of sleep regulation by fear.

Migration/locomotion.

Migration in search of food, reproductive niches, or warmer weather can take several days, and it is sometimes associated with alterations in the amount or characteristics of sleep. For example, sleep in migratory birds is dramatically reduced during the migratory season [133–135], and episodes of unihemispheric sleep can occur in flight [135]. Performance on a cognitive task is preserved in white-crowned sparrows with reduced sleep during the migratory season, while sleep restriction during the non-migratory season impairs performance on the same task [134], suggesting that birds show resistance to the effects of sleep loss during migration.

The daily organization of rest-activity cycles is also affected by migration in songbirds, with the appearance of nocturnal activity during migration in otherwise diurnal animals [136]. This phenomenon appears to be controlled by a circadian oscillator that is independent of the one controlling diurnal activity [137]. Moreover, the circadian clock is responsive to seasonal changes in photoperiod, which controls migratory behaviors [138,139], suggesting that the circadian process mediates behavioral changes needed to accomplish the migration process, including nighttime sleep suppression.

Locomotion and physical activity also impact sleep in animals that do not migrate. In rodents, spontaneous activity affects the circadian organization of rest-activity rhythms [reviewed in 140], and voluntary wheel-running activity can consolidate sleep-wake cycles by increasing wakefulness during the active phase of the animal [141–143]. The study of how voluntary activity affects sleep is of particular interest since there is evidence that exercise also improves sleep quality in humans [144]. Finally, a certain level of constant locomotion is needed to assure optimal respiration in some species of sharks and cetacean mammals. Although sleep has not been described in cartilaginous fish that constantly swim [145], unihemispheric sleep in cetacean mammals allows them to fulfill their respiratory and sleep needs [146], pointing to the diverse regulatory effects that physical activity and locomotion can have on sleep.

Sensory stimulation

Multiple sensory inputs such as light, temperature, and food influence sleep, in part by entraining the circadian clock [147–149]. Besides its role in entraining the circadian clock [150], light directly affects sleep, which is referred to as masking [151]. In nocturnal rodents, light can promote sleep when applied during the dark, active phase, while dark pulses applied in the light phase can have the opposite effect [151]. In mammals, the direct effects of light on sleep rely on intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin [152–154]. These cells connect with brain structures, including the SCN, the intergeniculate leaflet (IGL), as well as with sleep regulatory neurons within the preoptic area (POA) [155,156]. Light induces the activation of both POA and IGL (among other regions downstream iPRGC), and GABAergic IGL and POA neurons have an important role in light-induced sleep promotion in rodents [156,157]. Moreover, light may also affect the homeostatic process since melanopsin-deficient mice show reduced SWA both at baseline and after sleep deprivation [154].

Sensory inputs can influence sleep both positively and negatively. Sensory gating filters out many sensory stimuli during sleep, but intense or salient stimuli such as a loud noise from an alarm clock or food-associated odor can interrupt sleep. On the other hand, certain stimuli such as rocking and soothing sounds can help us fall asleep. In this section, we focus on the latter, i.e., sleep promotion by sensory stimulation.

Anecdotal observations suggest that babies like to be rocked to sleep, and humans of all ages tend to fall asleep during long car rides. Experimental studies have confirmed that rocking promotes sleep in infants, adults, and mice [158–162]. Studies in adult humans found that lying on a bed rocking at 0.25 Hz reduced sleep latency and increased the duration of deep sleep [161,162]. Rocking increased the EEG power of slow wave activity (SWA), believed to reflect sleep need [163], and spindle activity, thought to be involved in sensory gating and memory consolidation [164–166]. Consistent with the well-known effects of sleep on memory consolidation, rocking also improved declarative memory in humans [161].

The first study showing that rocking promotes sleep in a non-human species involved the mouse [159]. Rocking mice at 1 Hz accelerates sleep onset, increased NREM sleep, and decreases wake time. The rocking effects on sleep depends on the maximum linear acceleration instead of the rocking frequency. Mutant mice that cannot encode linear acceleration due to missing otoliths, small particles in the inner ear, do not exhibit rocking-induced sleep changes, suggesting that the vestibular otolithic organs mediate the rocking effects [159].

Gentle vibration also promotes sleep in *Drosophila* [167]. Flies exhibit reduced sleep after vibration (‘negative rebound’), suggesting vibration-induced sleep contributes to sleep homeostasis. Additionally, flies show reduced arousability during vibration-induced sleep relative to baseline sleep, indicating that sleep during vibration is deeper than baseline sleep. Elevated arousal through the circadian clock, increased dopamine signaling, and reduced GABA signaling attenuate vibration-induced sleep [167], pointing to the suppression of arousal as a potential mechanism for sleep induction by vibration.

Repetitive acoustic stimuli or white noise can also enhance sleep SWA in humans [158,168–171]. Whether stimulation in other sensory modalities such as vision and olfaction can promote sleep has received relatively little attention. While some studies found that olfactory stimulation can promote sleep in humans and rats [172], another study found little effects of olfactory stimuli on human sleep [168]. Moreover, deprivation of olfactory stimulation reduces sleep in flies, consistent with sleep-promoting effects of olfactory inputs, whereas activation of olfactory receptor neurons or presentation of several odorants fails to elicit sleep increase in flies [173]. Differences in the odorants and delivery methods may account for the variable results. Intriguingly, disrupting flight in flies by cutting wings increases sleep through wing chemosensory neurons [174], suggesting that chemosensory stimulation associated with flight promotes sleep. Further investigation of the effects of stimuli in multiple modalities may provide insights into the mechanisms of sleep induction by sensory stimulation and determine whether different modalities with distinct peripheral sensory organs converge on the same central sleep circuits.

Two mechanisms of how repetitive sensory stimulation promotes sleep have been proposed: synchronization and habituation. The synchronization model suggests that sensory stimulation synchronizes neural activity and enhances sleep SWA [161,175]. The model is consistent with the finding that synchronizing brain activity through transcranial direct current stimulation and magnetic stimulation of the cortex can enhance sleep SWA [176–178]. Also consistent with the model are the sleep-promoting effects of rocking and brief tones delivered at low frequencies (≤ 1.5 Hz) in humans and mice [159,161,162,168]. Notably, a human rocking study found that slow oscillations and spindles tend to occur at specific time points relative to the rocking cycles, supporting the idea that rhythmic stimulation entrains brain oscillations. However, these studies did not test sensory stimuli outside the frequency range of SWA, leaving open the possibility that mechanisms other than the synchronization of brain activity to low-frequency stimuli may play a role in sleep induction.

The habituation model proposes that habituation, a form of simple non-associative learning, mediates sleep induction by repetitive stimuli [158,179,180]. The model suggests that habituation leads to a reduction in arousal and an increase in sleep through a common inhibitory mechanism. The finding that vibration-induced sleep in *Drosophila* requires GABA signaling, the primary inhibitory neurotransmission system, is consistent with the model [167]. More direct support for the model comes from the finding that flies fall asleep faster and sleep longer over multiple blocks of continuous vibration, and the improvement during continuous vibration does not generalize to intermittent vibration [167]. This finding demonstrates stimulus specificity, ruling out sensory adaptation and motor fatigue, and supports the view that habituation is involved in sleep induction by vibration. Furthermore, vibrations ranging from 3–200 Hz can induce sleep in flies [167], suggesting that synchronizing the brain activity to stimuli of a specific frequency range is not required for sleep induction. However, the habituation and synchronization models are not mutually exclusive, and determining their relative contributions under different stimulus conditions may be a promising future direction.

Learning/Memory

One of the essential functions of sleep is to enhance learning and memory. Numerous studies investigated the link between sleep and learning/memory and have shown an evolutionarily conserved role for sleep in facilitating learning and memory consolidation [181]. Almost all studies focused on how sleep influences learning and memory, as discussed in recent review articles [181,182]. A smaller number of studies showed that learning and related processes also influence sleep, demonstrating that the relationship is bi-directional. Here we focus on the effects of learning on sleep.

Sleep or SWA increases after learning tasks in several species [182]. Humans performing a rotation adaptation task, a learning paradigm in which people adapt to a systematic rotation imposed on a visuomotor task, show increased sleep SWA after rotation compared to no-rotation control tasks [183]. Notably, the increase in SWA is localized to the cortical regions relevant for the rotation adaptation task [184], suggesting local regulation of sleep based on synaptic changes associated with learning. Visual perceptual learning that depends

on a restricted population of orientation-selective neurons in the occipital cortex increases the number of slow waves initiated in the area [185], further supporting local control of post-learning sleep. Sleep SWA in rats also increases locally after learning a task involving the motor cortex[186] and after locally infusing BDNF to induce synaptic potentiation [187]. In addition, sleep SWA in humans is elevated in cortical areas that are active during wakefulness [183,188,189], suggesting that sleep is locally regulated in a neural activity-dependent manner.

Related studies in *Drosophila* found that sleep is significantly increased following courtship conditioning, a learning and memory paradigm in which male flies learn to suppress their courtship behaviors following unsuccessful mating attempts toward a mated female [190–192]. Additionally, flies raised in a socially enriched environment sleep significantly more than those kept in isolation [193–196]. Socially enriched flies also show increased pre- and post-synaptic protein levels, suggesting that increased synaptic strength mediates the sleep increase following social enrichment [197]. Importantly, learning and memory mutants with impaired cAMP and ERK signaling do not exhibit sleep increase following social enrichment [193,197,198], suggesting that common molecular mechanisms underlie social enrichment-induced sleep and learning and memory processes.

The effects of cognitive tasks and social interaction on sleep may be mediated in part by their ability to entrain the circadian clock [199,200]. In nocturnal rats, the daily performance of a cognitive task requiring sustained attention during the light phase yields a diurnal activity pattern that persists for days in the absence of cognitive training [200]. Similarly, daily administration of foot shocks to rats alters their feeding and activity from the dark to the light phase, which is maintained in a free-running condition [201]. Interestingly, daily cognitive training can entrain SCN-lesioned animals, suggesting cognition entrainable oscillators outside the SCN [200], reminiscent of the FEOs.

Together, these studies demonstrate that learning, neural activity, and social behavior promote sleep, likely to meet the increased need for memory consolidation. However, as discussed below, a recent study reported an exciting discovery of sleep-independent memory under starvation conditions [202].

Sickness

Sickness caused by various conditions such as infection, excessive heat or cold, and injury results in various behavioral changes, including decreased activity, altered sleep, anorexia, reduced social interaction, cognitive impairments, among others [203–206]. While these responses generally have adaptative advantages such as reducing energy expenditure and promoting the recovery process, prolonged or exacerbated sickness responses can be detrimental [204,207]. This section reviews mechanisms of several types of sickness-induced sleep, focusing on insights from invertebrate studies [208].

Infection and immune response—The effects of inflammation on sleep in mammals have been reviewed elsewhere [209,210]. They include increased NREM sleep, decreased REM sleep, and sleep fragmentation. These changes are mediated by humoral factors such as Interleukins, Interferon and Tumor Necrosis Factor and activation of certain neural

circuits such as the vagal circuit [209,210]. The effects of infection and immune response on sleep are observed in invertebrates as well. In *Drosophila*, infection with gram-negative bacteria increases baseline sleep, mediated by the Nuclear Factor-κβ-like transcription factor *relish* and the clock gene *period* [211,212]. Interestingly, a recently identified sleep gene, *nemuri*, encodes an antimicrobial peptide and has a role in infection-induced sleep increase in flies [213]. Further, intra-thoracic injections of human tumor necrosis factor and astrocytic expression of its *Drosophila* homolog Eiger promote sleep suggesting a conserved role for the molecular actors in sleep changes upon immune activation [214].

Viral infections with the pathogenic *Drosophila* C Virus also lead to increased sleep [215]. However, infections with *S. pneumoniae* and non-pathogenic immune activation via upregulation of the pattern recognition protein PGRP-Lca lead to reduced sleep [216,217]. Whether the divergent results are due to different experimental approaches or varying sleep responses elicited by activating distinct immune pathways remains to be investigated. Notably, proinflammatory markers are associated with the progression of several neurodegenerative diseases [218], which in turn are linked to disrupted sleep regulation [219].

Injury—Traumatic brain injury (TBI) is associated with a variety of sleep disturbances, including excessive daytime sleepiness, increased sleep need, insomnia, and sleep fragmentation in humans [220,221], mice [222], and flies [223]. A peripheral injury can also influence sleep. The removal of antennae or wings in flies increases daytime sleep for several hours [174,224]. Removing other sensory organs or silencing olfactory receptor neurons does not cause increased sleep, suggesting that post-injury sleep is not due to sensory deprivation or inflammatory response. Notably, pre-synaptic active zones of the severed neurons are removed within hours after injury, unlike the Wallerian degeneration of severed axons that requires several days [224]. Mutations that protect neurons from Wallerian degeneration attenuate post-injury sleep, and depriving flies of post-injury sleep impairs the removal of both active zones and axons, suggesting a bidirectional relationship between neural injury and sleep [224].

Cellular stress—Features of sleep such as behavioral quiescence and reduced response to sensory stimuli suggest that sleep may provide an opportunity for restorative processes. Consistent with the view, cellular stress leads to increased sleep in several species to facilitate the recovery from cellular damage. In *C. elegans*, several manipulations that lead to cellular stress, including noxious heat, cold, hypertonicity, tissue damage and UV light, increase sleep [225,226]. Stress-induced sleep is independent of the sensation of the stressor and is a response to the cellular damage [227], and likely restores protein homeostasis and promotes cellular recovery [225]. The current model of stress-induced sleep in *C. elegans* is that cellular stress promotes the release of LIN-3/EGF, which activates the ALA neuron, leading to increased sleep via the NLP-8, FLP-24, and FLP-13 neuropeptides [225,228,229]. FLP-13 acts through the GPCR MLSR-1, which inhibits wake-promoting neurons [230]. Interestingly, FLP-13 peptides are related to *Drosophila* FMRFa peptides, and flies mutant for FMRFa or its receptor show decreased sleep increase upon heat stress [231], suggesting a conserved mechanism for stress-induced sleep.

Endoplasmic reticulum (ER) stress, a form of cellular stress, also influences sleep [232,233]. Overexpression of immunoglobulin binding protein (BiP), an indicator of ER stress, elicits exaggerated recovery sleep after sleep deprivation in *Drosophila*, while reduced BiP activity has the opposite effect [234]. In addition, inducing ER stress leads to fragmented sleep, whereas relieving ER stress ameliorates sleep fragmentation in aged animals [235]. The role of ER stress regulators in sleep is likely conserved since activating Eukaryotic Initiation Factor 2α, an ER response related pathway, promotes sleep in rats [236,237], and inhibiting the ER kinase PERK reduces sleep in flies and zebrafish [238].

Reactive oxygen species—A proposed function of sleep is removing excess reactive oxygen species (ROS) that accumulate during wakefulness [239]. Studies involving acute sleep restriction have found inconsistent effects on antioxidant response and ROS accumulation in the brains of mice and rats [224,240–246]. However, recent studies show that chronic sleep loss is consistently associated with increased ROS. First, diverse short-sleeping fly mutants exhibit reduced survival after oxidative challenge, while inducing sleep in wild-type flies by genetic and pharmacological means increases resistance to oxidative stress [246]. Second, sleep loss elevates mitochondrial ROS in sleep-promoting neurons in *Drosophila* [247]. Third, sleep loss causes lethality through ROS accumulation in the gut of flies and mice [248]. These findings support the view that ROS accumulates during wakefulness and decreases during sleep.

Interestingly, overexpression of antioxidant genes in neurons reduces sleep in flies [246], suggesting that ROS plays a role in regulating sleep. A recently proposed mechanism states that accumulated ROS oxidates a cofactor for Hyperkinetic, a subunit of the Shaker potassium channel, and slows the inactivation of the A-type current to enhance the excitability of sleep-promoting neurons, thereby promoting sleep [247].

Nutritional modulation of the balance between competing needs

As we presented in previous sections, sleep is suppressed by various competing needs, such as reproduction, foraging, predator avoidance, and migration. However, the decision to sleep or not is unlikely to be a simple choice between two alternative behaviors. Several recent studies have revealed the complexity of sleep regulatory mechanisms by considering multiple factors simultaneously. We provide four examples of how an organism's nutritional state can modulate the trade-off between sleep and other demands.

Sleep vs. courtship.—Whereas well-fed male flies are willing to forgo most of their nighttime sleep in favor of courtship when paired with females [28,91], protein-deprived males are less inclined to give up sleep to pursue sexual partners [93]. Although protein-deprived males are less likely to sacrifice sleep at night to engage in courtship, they are willing and able to court and mate during the day (Figure 2). These data suggest that flies engage in a sophisticated cost-benefit analysis to decide when to sleep or court. Since protein is necessary for potential offspring to survive, malnourished males may reason that even a successful mating is not likely to produce live offspring and choose sleep over courtship at night. But if they are already awake during the day, they may decide it is worth the effort to court in case protein becomes available later.

Predator avoidance vs. energy conservation.—Warblers, small migratory songbirds, cannot make their long-distance migration in one leg and make stopovers to rest and forage to restore energy reserves. The birds must reconcile competing needs for sleep, energy restoration/conservation, and predator avoidance during the stopovers. Ferretti et al. investigated sleep and metabolic patterns in garden warblers at a Mediterranean stopover site [249]. They found that songbirds in poor metabolic conditions sleep with the head tucked in their feathers, whereas those in good metabolic conditions sleep with a normal posture. They determined that birds that sleep with the head tucked in reduce energy consumption but respond slower to the noise of a potential predator than those that sleep with a normal posture. Thus, birds in poor metabolic conditions are willing to adopt an unsafe sleep posture to conserve energy, suggesting a trade-off between energy consumption and predator avoidance (Figure 2). Warblers adjust their sleeping posture, which impacts both processes, depending on their metabolic conditions.

Memory consolidation vs. foraging.—The need to sleep for memory consolidation is also affected by food availability [202]. Whereas well-fed flies increase their sleep after olfactory conditioning, starved flies do not. Moreover, post-training sleep deprivation in fed flies leads to poor memory consolidation, but memory is unaffected by sleep deprivation in starved flies. Distinct neural circuits mediate memory in fed vs. starved conditions. This plasticity in memory circuits may allow flies in a food-scarce environment to remember food-associated cues without giving up foraging [202].

Recovery from cellular stress vs. foraging.—Whereas food deprivation reduces sleep to allow time for foraging [38–41], cellular stress by noxious stimuli such as UV light and heat increases sleep to promote recovery from damage [225,228,230]. A study in *C. elegans* investigated the combined effects of starvation and cellular stress on sleep and found that food deprivation severely suppresses stress-induced sleep [250]. Interestingly, whereas mutant worms with defective stress-induced sleep exhibit shortened lifespan under a well-fed condition, food deprivation protected the mutant worms against the lethal effects of cellular damage [225]. This finding suggests that food deprivation inhibits stress-induced sleep, in part by reducing the need for sleep. Analogous to sleep-independent memory consolidation discussed above [202], recovery from cellular stress may involve distinct cellular pathways in fed and starved conditions.

These examples of nutritional modulation of the tradeoff between competing needs suggest that sophisticated cost-benefit analyses underlie the decision to sleep or not to sleep.

Concluding remarks

As our survey of the literature shows, sleep is strongly influenced by several factors beyond the time of day and prior wake time. Sleep is also influenced by many other factors not covered in this review, such as, exercise, aging, and neurodegeneration, anxiety and other emotions, and human-specific requirements such as jobs and deadlines [129,130,134,144,251–254]. To fully understand how sleep is regulated in health and diseases, it will be advantageous to investigate sleep in various contexts while simultaneously manipulating multiple variables.

Manipulation of specific groups of cells has identified numerous sleep-regulatory neuronal groups in mice, flies, and worms [12,255,256], and uncovered the involvement of glia in sleep regulation [257]. The diversity of sleep-regulatory loci may reflect the many factors that control sleep and explain why many neurodegenerative and neurodevelopmental diseases are linked to sleep disruptions [258]. While most of these loci were identified because their manipulation influences baseline sleep, others influence sleep only in specific circumstances [58,77,91]. Which neurons and glia are activated under various conditions and how they integrate diverse sleep-relevant information are important topics for future research.

A recurring theme in this review is that sleep loss does not necessarily lead to homeostatic rebound sleep or negative consequences. Starvation-induced sleep loss does not lead to rebound sleep [75] or poor memory consolidation [202] and can provide resistance to stress-induced lethality [250]. Similarly, sleep loss due to sexual activities does not result in rebound sleep or poor mating performance [28,90]. These results demonstrate plasticity in sleep regulation in that the physiological need for homeostatic rebound sleep depends on the context of sleep loss. Interestingly, sleep-dependent and sleep-independent memory consolidation employ distinct neural circuits [202]. Switching to alternative neural circuits or molecular pathways may also provide resistance to sleep loss in other contexts, which would be an important topic for future investigation.

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Abbreviations:

AgRP	Agouti-Related Peptide
AKH	Adipokinetic Hormone
BDNF	Brain-derived neurotrophic factor
BiP	Immunoglobulin binding protein
BNST	Bed nucleus of the stria terminalis
cAMP	Cyclic Adenosine mono-phosphate
CR	Calretinin
DN1	dorsal neuron group 1
EGF	Epidermal growth factor
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
FEO	Food entrainable oscillator

FOXO	Forkhead Box-O
GPCR	G protein-coupled receptors
IGL	Intergeniculate leaflet
IPCs	Insulin-producing cells
ipRGCs	Intrinsically photosensitive retinal ganglion cells
LK	Leukokinin
NPF	Neuropeptide F
NPY	Neuropeptide Y
NREM	Non-rapid eye movement
PERK	Phosporilated-extracellular signal-regulated kinase
PGRP-Lca	Peptidoglycan-recognition protein LCa
POA	Preoptic area
PVT	Paraventricular thalamus
REM	Rapid eye movement
s-LNv	Small ventral lateral neurons
SWA	Slow wave activity
VLPO	Ventrolateral preoptic area
VTA	Ventral tegmental area

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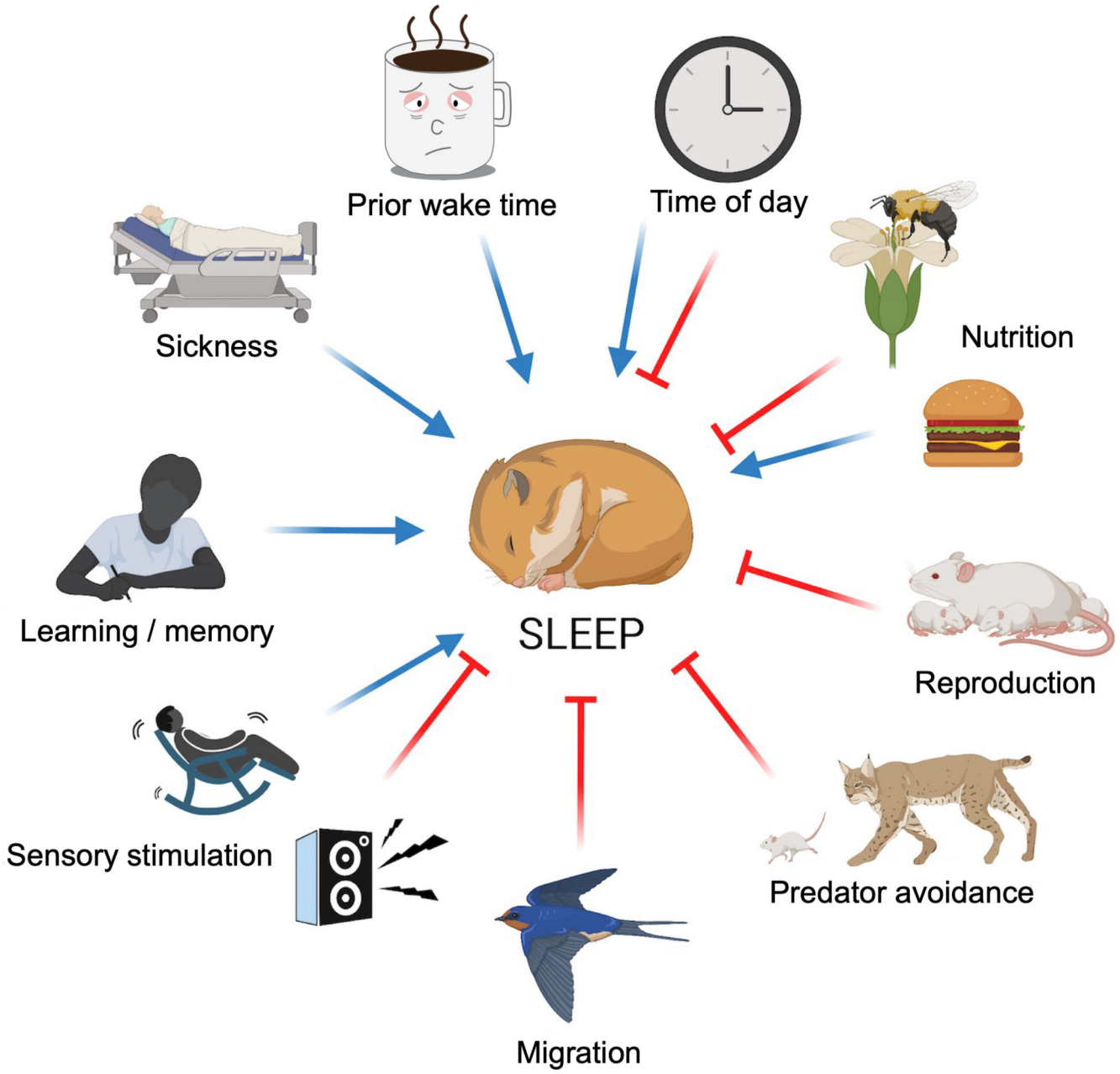

Figure 1. Multiple factors influencing sleep.

In addition to the time of day and prior wake time, sleep is strongly influenced by other factors, a subset of which is depicted. Blue arrows indicate sleep promotion, and red lines indicate sleep suppression. The separate arrows and lines do not represent independent processes. The various factors may influence sleep in part through their effects on the circadian and homeostatic processes.

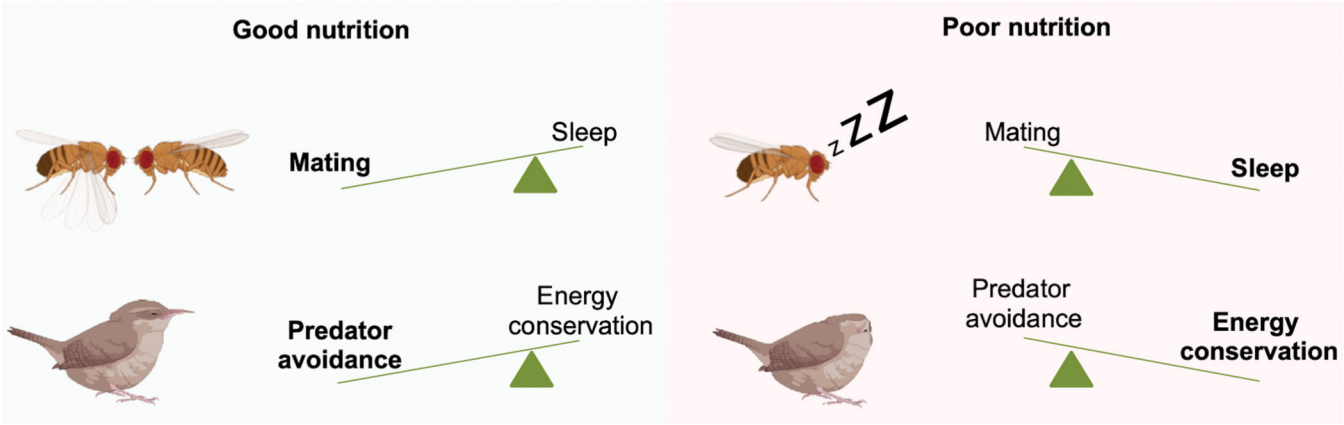

Figure 2. Nutrition modulates the balance between competing needs.

The nutritional status shifts the balance between sleep and other needs. Top: Under good nutritional conditions, male flies forgo their nighttime sleep to engage in reproductive behaviors. Lack of dietary protein, needed for offspring survival, causes males to reduce their nighttime courtship in favor of sleep [93]. Bottom: Garden warblers in good nutritional conditions choose to sleep in an untucked position, which allows for higher alertness and predatory avoidance. Poorly nourished warblers sleep with their heads tucked under the feathers, which favors energy conservancy over predator avoidance [249].