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To sleep or not to sleep: neuronal and ecological insights

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Abstract

Daily, animals need to decide when to stop engaging in cognitive processes and behavioral responses to the environment, and go to sleep. The main processes regulating the daily organization of sleep and wakefulness are circadian rhythms and homeostatic sleep pressure. In addition, motivational processes such as food seeking and predator evasion can modulate sleep/wake behaviors. Here, we discuss the principal processes regulating the propensity to stay awake or go to sleep—focusing on neuronal and behavioral aspects. We first introduce the neuronal populations involved in sleep/wake regulation. Next, we describe the circadian and homeostatic drives for sleep. Then, we highlight studies demonstrating various effects of motivational processes on sleep/wake behaviors, and discuss possible neuronal mechanisms underlying their control.

Introduction

Animals, including nematode worms, bees, flies, fish, rodents, humans, and even birds during migration, alter between wake and sleep states, throughout their lives. During wakefulness, animals engage in various adaptive and motivated behaviors, including foraging, courting, mating, parenting, and predator evasion. Sleep is a state of quiescence with reduced responsiveness to external stimuli, yet it is restorative and recruits essential mechanisms for homeostatic balance. How do animals decide whether and when to alternate between sleep and wakefulness? The two main processes that regulate the daily organization of sleep and wake periods are circadian rhythms and homeostatic sleep pressure [1,2]. The circadian clock (~24 hours long) synchronizes sleep to an appropriate time of day, while the homeostatic sleep process is responsible for maintaining a species-specific daily sleep balance. In addition, motivational processes such as food and mate seeking, and predator evasion can powerfully modulate sleep and wake states. Animals can stay awake for extended periods, sleep longer, sleep lighter, or sleep with only half of their brain (unihemispheric sleep) in response to different internal and external conditions. Here, we will review the principal processes that regulate the propensity to stay awake or go to sleep, focusing on studies investigating neuronal and ecological aspects.

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Neuronal circuitry of sleep/wake state regulation

In mammals, birds, and reptiles, there are three general states of vigilance: wakefulness, non-rapid eye movement (NREM) sleep, and rapid-eye movement (REM) sleep—that differ in behavior, physiology, and brain electrical activity. Over the last century numerous studies have contributed to the identification of distinct neuronal populations in the mammalian brain that participate in the regulation of sleep/wake states. It is currently understood that subcortical neuromodulatory neurons in the brainstem, midbrain, hypothalamus, and basal forebrain interact with each other, the thalamus, and the cortex to drive behavioral, physiological, and electrocortical sleep/wake states. Key components of the wake regulatory systems are the: (1) monoaminergic neurons (including noradrenergic, dopaminergic, serotonergic, and histaminergic) of the locus coeruleus (LC), ventral tegmental area (VTA), dorsal raphe nucleus (DRN), and tuberomammillary nucleus (TMN); (2) cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), and basal forebrain (BF), and (3) hypocretinergic (Hcrt; also known as orexinergic) neurons of the lateral hypothalamus (LH) [3]. A balance between activity in wake-promoting and sleep-promoting neurons [4•], such as the GABAergic neurons of the ventrolateral preoptic area (VLPO) and brainstem, has been hypothesized as a model to understand sleep-to-wake transitions [5].

Remarkably, the sleep/wake regulatory mechanisms and neuromodulatory systems involved are highly conserved among the animal kingdom [6,7•]. For example, in both mammals and insects, dopaminergic (mammals: [8••,9••]; insects: [10,11]), noradrenergic (mammals: [12]; insects: [13]), and histaminergic (mammals: [14]; insects: [15]) transmissions promote wakefulness, while GABAergic (mammals: [4•]; insects: [16,17]) and serotonergic (mammals: [18]; insects: [19]) transmissions promote sleep. This conservation suggests an ancient and common origin for sleep [6].

Circadian regulation of sleep/wake states

Animals typically sleep in a specific phase of the day, for example, night in diurnal species. This pattern of sleep/wake organization follows the light-dark cycle, but also persists in the absence of environmental cues—demonstrating the existence of an internal regulatory mechanism. This internal rhythm is generated by a circadian clock (~24 hours long), that regulates numerous physiological and behavioral processes including the sleep/wake cycle. The circadian clock can be synchronized to the environment by different cues (or *Zeitgebers*) [5,20], such as light [21], temperature [22], food availability [23], and social interactions [24,25]. Internal clocks are advantageous to animals, enabling them to predict daily recurring events – even in the absence of environmental cues – and aligning their internal processes to the environment [20,26], as for feeding and metabolism [27]. In mammals, overt rhythmicity is coordinated by the central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus [28], although various circadian oscillators are present throughout the brain [29,30]. It is hypothesized that the major output region of the SCN in regard to sleep/wake regulation is the dorsomedial nucleus of the hypothalamus, which heavily innervates sleep- and wake-promoting nuclei via the subparaventricular zone [28,31]. Nonetheless, the precise roles of the SCN in sleep/wake

state synchronization, sleep structure and sleep quality, as well as the role of additional circadian oscillators in sleep/wake regulation, remain to be elucidated.

Homeostatic regulation of sleep/wake states

As for other homeostatically regulated processes, such as hunger and thirst, the need for sleep accumulates as wakefulness is extended and only dissipates during sleep. How is this regulation attained? Recent studies in *Drosophila* provided important insights regarding the mechanisms and circuits that mediate the homeostatic drive, and raise the intriguing possibility that sleep need is sensed by a master control center [32••]. In mammals, the precise identity, location of action, and mechanisms of the homeostatic regulation of sleep remain unclear. More than a century ago, researchers discovered that the cerebrospinal fluid of sleep deprived animals contained substances that promote sleep [33,34]. Among the proposed substances and mechanisms involved in promoting sleep are the neuromodulator adenosine, and its receptors A1 and $A2_A$, as well as cytokines such as interleukin-1 and tumor necrosis factor-α, prostaglandin D_2, and Nitric oxide (NO) [35–37]. A recent forward-genetics screen in mice revealed two sleep mutants, *Sleepy* and *Dreamless* [38••]. *Sleepy* is a gain-of-function mutant of Sik3 serine-threonine protein kinase involved in the transduction of the mTOR pathway [38••]. *Sleepy* mutants show increased NREM sleep amount. *Dreamless* mutants, that have a mutation in the sodium leak channel NALCN, show a decrease in REM sleep amount and episode duration [38••]. Although the precise mechanisms by which these mutations modulate sleep need are still unclear, the use of an unbiased forward-genetics approach in mammals will likely lead to major insights into the pathways and mechanisms of sleep regulation.

Motivational control of sleep/wake states

Motivational processes can powerfully modulate the propensity to stay awake or go to sleep. When motivated, humans can stay awake and engage in various cognitive and physical activities far beyond their physiological bed time while ignoring the circadian and homeostatic sleep drives. In the wild, foraging and mating opportunities and the presence of predators drive motivational responses and modulate arousal. Animals can stay awake for extended periods, sleep longer, sleep lighter, or show unihemispheric sleep in response to different internal and external conditions (Figure 1).

Hunger can drive arousal and locomotor activity and suppress sleep [39–41,42••,43], probably to favor foraging behavior. The presence of predators or predator cues can also modulate sleep/wake states [44], reduce sleep [45] or induce frequent arousals [46–48]. The motivation to mate and reproduce is a strong driving force in animals' behavior, yet limited studies examined the capacity of this motivation to drive wakefulness. One notable study not only demonstrated that the motivation to mate can powerfully affect sleep and wake states, but that this plasticity increases the fitness of animals [49]. Male polygynous pectoral sandpipers (*Calidris melanotos*) are able to greatly reduce sleep duration, to as little as 2 hours/day during a 3-week period of same-sex competition for access to fertile females [49]. Remarkably, the males that slept the least had the highest breeding success—measured as the number of young sired [49].

Birds can significantly reduce their daily sleep duration over long migratory [50] and foraging [42••] flights. For example, great frigatebirds (*Fregata minor*) can spend only 0.7 hour/day sleeping while on foraging flight in contrast to 12.8 hours/day while on land [42••]. In addition to sleep suppression, birds (and other animals, see below) can show unihemispheric sleep; during which only one of the hemispheres engages in slow-wave activity, while the other is in the awake state and the eye contralateral to the awake hemisphere is open [51]. Unihemispheric sleep enables the individual to simultaneously engage in two otherwise mutually exclusive tasks; sleep and attention [51]. Mallard ducks (*Anas platyrhynchos*) undergo unihemispheric sleep while under the risk of predation [52,53], and other birds during long flights [54•]. Marine mammals show unihemispheric sleep [55] allowing them to keep swimming and breathing, and taking continuous care of young. Interestingly, other mammals, including rodents and humans, can show local slow-wave sleep in cortical areas [56–58], as well as in individual neurons [59] while behaviorally awake.

What are the neuronal mechanisms underlying the arousal response in face of various environmental and homeostatic processes? LH Hcrt neurons have been suggested to mediate the increase in wakefulness in response to stressful conditions [60–62], including reduced food availability [63]. The Hcrts are two neuropeptides, Hcrt-1 and Hcrt-2, produced from a single precursor and are expressed in a glutamatergic neuronal population in the LH. Hcrt neurons project to most sleep/wake regulatory nuclei, which express either, or both, of the two Hcrt receptors [64]. Transgenic mice in which Hcrt neurons are ablated (Hcrt ataxin3 mice) do not show an increase in wakefulness or locomotion following fasting [63]. In addition to integrating cues from the environment, Hcrt neurons are critical regulators of brain reward function, in part by modulating VTA dopaminergic neurons [65,66]. VTA dopaminergic neurons are principal regulators of motivational processes [67], and regulate sleep/wake states and arousal in face of various ethologically-relevant salient stimuli [8••]. Chemogenetic [68] inhibition of VTA dopaminergic neurons prevent the maintenance of wakefulness even in the presence of a potential mate, palatable food and predator scent [8••]. Future studies examining the necessity of the different sleep/wake regulatory circuits to arousal if face of various motivational processes should deepen our understanding of the link between motivational processes and sleep/wake regulation.

Individuals can vary in their capacity to regulate arousal in response to specific internal and external needs (for example, Ref. [49]), possibly due to differences in their underlying neuronal machinery. It would be of interest to examine the costs and benefits of this capacity in various ecologically-relevant conditions. For example, whether individuals with a higher capacity to stay awake and suppress their sleep to favor motivational processes (such as mate seeking) will show disadvantages in other aspects (such as attentional processes). In addition, it would be of interest to examine whether reward-related ecologically-relevant demands (such as mate seeking), that reduce or fragment sleep, result in minor negative consequences on animal physiology as compared to stressful or lab-induced sleep disturbances [54•]. Future studies comparing the consequences of sleep/wake disturbances under different naturalistic environments should increase our understanding of the evolution of sleep/wake cycles.

Motivation to sleep

Animals do not just fall asleep, literally speaking, but rather prepare themselves for sleep, and display species-specific behaviors [69–71]. Lizards [72], birds, rodents [73], great apes [74,75], humans, and even fish [76] among many others, search for a safe and comfortable place to sleep, may build a nest or a bed, take a species-specific posture, and engage in other behaviors, such as grooming, before going to sleep. In the wild, the selection of a sleeping site could have a strong impact on fitness, as the sites may provide protection from predation, shelter from thermal challenges, access to food resources, and be advantageous for territorial defense [44,69]. Remarkably, the neuronal substrates regulating this sleep-preparatory phase remain poorly understood. Our recent findings suggest that during this sleep-preparatory phase the motivational state of animals is shifted from wake-related goal-directed behaviors to sleep-related but still goal-directed behaviors, such as nest-building [8••]. Moreover, our data suggest that neurotransmitter systems/brain circuits involved in wake-related behaviors, such as VTA dopaminergic neurons [8••], need to be suppressed for animals to prepare for sleep. Although the term *motivation* has traditionally been used to describe the drive to engage in wake-related behaviors, there seems to be a *motivation to sleep* that could recruit distinct neuronal circuits and behavioral repertoires—with the ultimate goal of attaining sleep [8••,77].

Consolidating sleep/wake states

Once animals enter wakefulness or sleep, they need to maintain the behavioral and physiological state for the duration necessary to fulfill its physiological purposes. A failure to prevent unwanted transitions between wakefulness and sleep could result in severe fitness consequences. For example, the survival of animals could be at risk if a predator defense behavior would be interrupted by unexpected transitions to sleep. In addition, the restorative and memory consolidation functions of sleep are dependent upon proper consolidation of sleep [78–80]. How do sleep/wake regulatory circuits maintain the boundaries between the vigilance states? The Hcrt system is hypothesized to orchestrate the structural organization of sleep/wake states. Hcrt LH neurons are essential for the stability of arousal, and malfunction of the Hcrt network fragments sleep and wake states. The loss of Hcrt-producing neurons or their receptors in rodents, canines, and humans is associated with narcolepsy/cataplexy—a neurological disorder characterized by an inability to control the boundaries between sleep/wake states [64]. In narcoleptics, periods of wakefulness are interrupted by unexpected sleep episodes, and REM-like episodes co-exist with conscious wakefulness [64]. Transgenic mice lacking Hcrt neurons or Hcrt receptor R2 show increased arousal state transitions, but do not vary in the total daily duration of sleep and wake states from control animals. Optogenetic [81] stimulation of Hcrt LH neurons in mice increases the probability for a sleep-to-wake transitions [82], whereas optogenetic, chemogenetic, or pharmacological inhibition of Hcrt neurons induces sleep [83–85].

Conclusions

During the last decades, major advances have been made in characterizing the neuronal populations participating in sleep/wake regulation. It is now possible to further explore how

information from the diverse sleep/wake regulatory populations is integrated to control overt arousal, and how diverse external and internal inputs modulate the regulatory capacities of these circuits. In addition, relatively little is known on the neuronal mechanism regulating sleep under natural or semi-natural conditions. Outstanding questions remain, including how distinct sleep/wake regulatory populations regulate arousal in naturalistic environments, how different selective pressures modulate sleep behavior, and what are the contributions of sleep to survival and reproduction in the wild.

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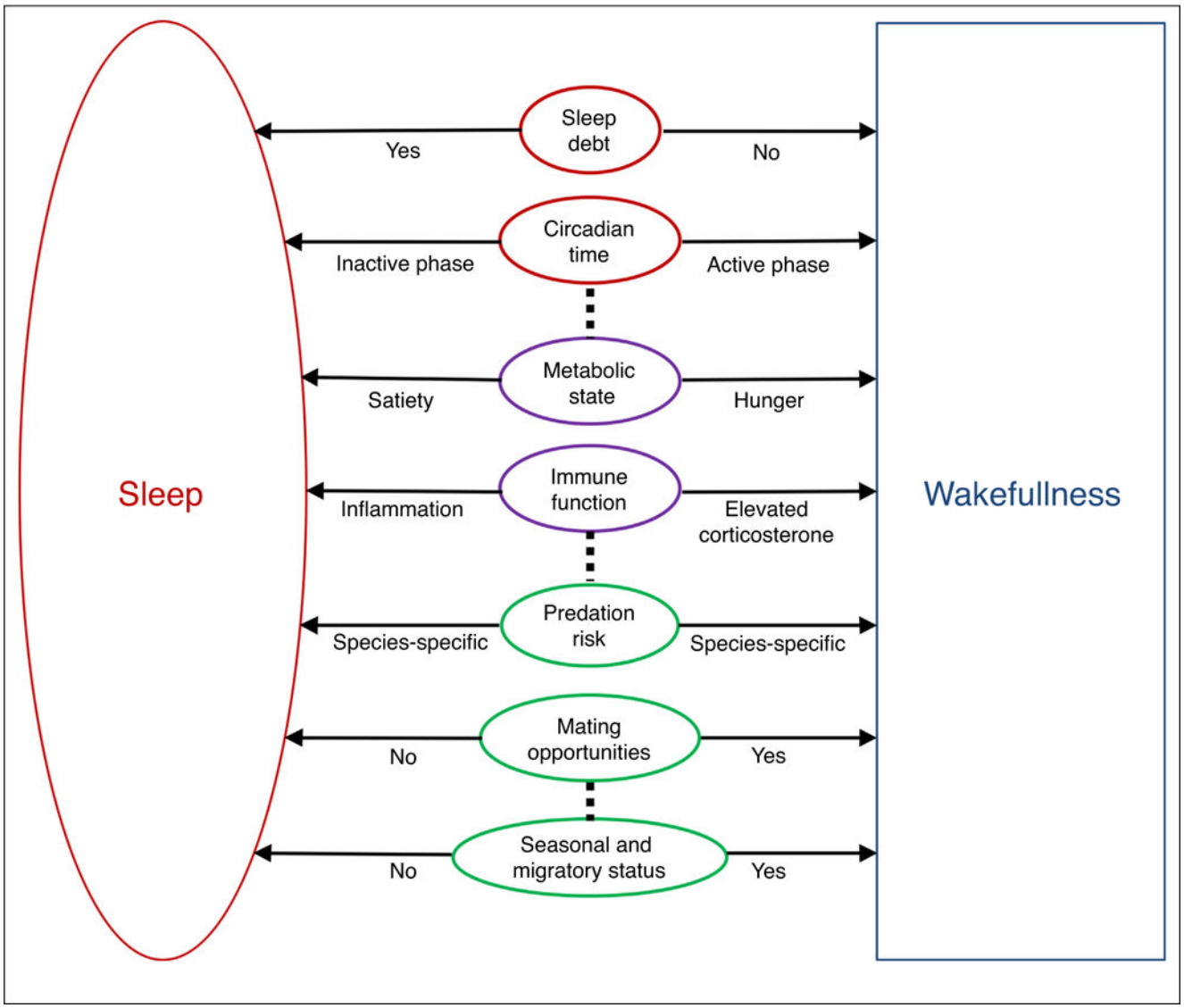

Figure 1.

A schematic of the main factors controlling sleep/wake states. Multiple internal and external signals can modulate the propensity of animals to stay awake or to go to sleep. Distributed networks in the brain integrate these often-conflicting variables to generate a coherent output that results in consolidated sleep.