HHS Public Access

Author manuscript

Semin Cell Dev Biol. Author manuscript; available in PMC 2022 June 01.

Published in final edited form as:

Semin Cell Dev Biol. 2022 June ; 126: 3–14. doi:10.1016/j.semcdb.2021.05.034.

Sleep timing and the circadian clock in mammals: Past, present and the road ahead

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Abstract

Nearly all mammals display robust daily rhythms of physiology and behavior. These approximately 24-h cycles, known as circadian rhythms, are driven by a master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus and affect biological processes ranging from metabolism to immune function. Perhaps the most overt output of the circadian clock is the sleep-wake cycle, the integrity of which is critical for health and homeostasis of the organism. In this review, we summarize our current understanding of the circadian regulation of sleep. We discuss the neural circuitry and molecular mechanisms underlying daily sleep timing, and the trajectory of circadian regulation of sleep across development. We conclude by proposing future research priorities for the field that will significantly advance our mechanistic understanding of the circadian regulation of sleep.

Keywords

Circadian rhythms; Sleep; Suprachiasmatic nucleus; Clock genes

1. Introduction

The success of a species is highly dependent on its ability to adapt to environmental pressures. As a consequence of the rotation of the Earth around its own axis and the sun, life evolved under multiple rhythmic environmental regimes, including both seasonal and daily changes in light exposure. As a result, nearly every species on Earth has developed a biological timekeeping system that can anticipate these changes and organize physiology and behavior in a way that is advantageous for the organism [1]. Biological rhythms of approximately 24 h, called circadian rhythms, are highly conserved among mammalian species and provide a temporal order for behavioral and physiological processes, the most

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overt of these being daily cycles of sleep and wake. Most mammals display bouts of sleep that are consolidated to a single phase of the environmental light-dark (LD) cycle, and this timing is highly influenced by the circadian clock. In this review, we provide a broad overview of the molecular, neural circuit and developmental mechanisms underlying the circadian regulation of sleep and pose several avenues for further investigation necessary to bridge critical gaps in our understanding.

1.1. The mammalian circadian clock

Circadian clocks in mammals, and indeed all species, have three key characteristics: they are endogenous to the organism, they can synchronize to environmental cycles (entrainable), and their intrinsic period remains relatively constant regardless of external temperature (temperature compensated) [1]. These characteristics allow organisms to both align their biological rhythms with environmental cycles, a process called entrainment, and to maintain rhythmicity in the absence of external time cues.

Virtually every mammalian cell contains its own molecular circadian clock constituted by a transcriptional-translational feedback loop (TTFL) in which translated proteins inhibit the activation of their own promoters, thus halting their continued production [2]. Eventually these proteins degrade and inhibition of their own transcription ceases, starting the loop over again. The proteins CLOCK and BMAL comprise the positive arm of the TTFL, and form heterodimers that promote the transcription of Period (PER1, PER2, PER3) and Cryptochrome (CRY1, CRY2) genes. PER and CRY proteins then heterodimerize and inhibit the activity of CLOCK/BMAL heterodimers, thus negatively regulating their own transcription. This primary clock mechanism is supported by a secondary feedback loop, in which retinoic acid receptor-related orphan receptors (RORs) and the transcriptional repressor REV-ERBα activate and inhibit the expression of BMAL1, respectively [2].

In mammals, the coordination of this symphony of circadian oscillators throughout the body is driven by the master circadian pacemaker housed in the suprachiasmatic nuclei (SCN), a small bundle of about 20,000 neurons in mice, and 50,000 neurons in humans, located in the ventral hypothalamus [3]. The molecular clockwork drives circadian rhythms in gene expression and excitability in SCN neurons [4,5], and these individual neuronal oscillators coordinate SCN-level rhythms through a combination of synaptic transmission and gap junction-mediated electrical coupling [3]. The SCN is synchronized to environmental LD cycles by way of light input from intrinsically photosensitive retinal ganglion cells (ipRCGs) in the retina [6]. These ipRGCs send direct projections to and increase activity of SCN neurons via release of glutamate and pituitary adenylate cyclase-activating peptide. This glutamatergic signaling underlies light-induced phase--shifting of SCN activity [7,8], and light exposure induces an acute increase in expression of the clock gene *Per1*, presumably leading to phase shifts in the molecular clockwork of SCN neurons [9]. Remarkably, the SCN is able to sustain circadian rhythmicity of neural activity in the absence of environmental cues or input from other regions of the brain [10].

Although the precise anatomy and cellular composition of the SCN differs slightly between mammalian species, the core features of the SCN network are thought to be well conserved across placental mammals [11]. Despite the fact that over 90% of SCN neurons express

the inhibitory small neurotransmitter GABA, the SCN is highly heterogeneous, expressing a wide array of neuropeptides, cytokines and small neurotransmitters [3,12]. The SCN is roughly divided into two functional and anatomical subregions [13]: the ventro-lateral SCN (vlSCN) or “core”, which expresses the neuropeptide vasoactive intestinal polypeptide (VIP) and is highly light-responsive [14,15]; and the dorsal-medial SCN (dmSCN) or “shell”, containing arginine vasopressin (AVP) neurons that are strong intrinsic circadian oscillators. VIP neurons in the vlSCN receive dense glutamatergic inputs from ipRGCs, providing information about the presence or absence of environmental light. The vlSCN then relays light information to AVP neurons in the vlSCN, synchronizing their intrinsic oscillations to external environmental light and maintaining synchrony of the SCN neural network. Although this coupling mechanism between vl- and dmSCN is incompletely understood, evidence suggests that both GABA [16] and VIP [14,17] signaling are critical for maintaining network synchrony. Neurons in the dmSCN both send GABAergic and glutamatergic axonal projections to nuclei throughout the brain and release humoral factors such as Prokineticin-2 [18], signals which together provide a temporal order for daily cycles of sleep and wake. Although useful, recent work reveals the core-shell model to be an oversimplification [19,20]. Additional neuropeptides found in the SCN include gastrin-releasing peptide (GRP), Neuromedin-S (NMS) [21], substance P, somatostatin cholecystokinin and neurotensin, and it is typical for SCN neurons to co-express multiple neuropeptides [5].

2. Clocks, sleep and the mammalian brain

2.1. A mysterious state of being

The most overt output of the circadian clock is sleep, a reversible state of unconsciousness characterized by behavioral inactivity and reduced responsiveness to external sensory stimuli [22]. Although sleep is a highly conserved behavior in mammals and indeed virtually every animal species on earth, its precise functions and the evolutionary pressures that selected for it remain unclear [23]. Despite this fact, sleep has been shown to be critical in maintaining physiological processes including memory consolidation [24], immune function [25] and metabolism [26].

In mammals, sleep is typically classified as one of two primary stages that alternate throughout a sleep bout: rapid eye-movement (REM) sleep and non-rapid eye-movement (NREM) sleep. These two stages have distinct physiological signatures which can be measured using a combination of electroencephalography (EEG) and electromyography (EMG) in both humans and animals. NREM sleep is characterized by synchronous, high amplitude waves oscillating in the delta frequency range (0.5–4 Hz) as measured by EEG, and reduced muscle tone as measured by EMG. REM sleep is characterized by mixed frequency, low voltage amplitude waves, high power in the theta frequency range (6–10 Hz) and complete muscle atonia [22]. In humans, sleep is consolidated into a single primary bout happening at approximately the same time of day, in which NREM sleep is highly concentrated at the beginning of the sleep cycle, and REM sleep at the end [22]. In commonly studied mammalian model organisms such as mice and rats, sleep bouts are more fragmented and occur at multiple times throughout the day, although more sleep occurs

during the day than at night [27]. The duration of the primary sleep bout and the timing of ultradian cycling between sleep stages varies between mammalian species, though in humans sleep duration is approximately 8 h and a full sleep stage cycle takes 90–110 min [22].

2.2. Sleep in the brain

The key brain regions involved in sleep and wake initiation and maintenance are well-studied. A brief overview of this neural circuitry is provided here and reviewed extensively by Scammell et al. [28].

There are two primary pathways involved in the initiation and maintenance of wakefulness, both of which originate from the brainstem and hypothalamus. The first is a dorsal pathway arising from cholinergic neurons in the pedunculopontine nucleus (PPT) and laterodorsal tegmental nuclei (LDT) of the pons [29,30]. These regions, which are highly active during wakefulness and REM but less so during NREM [31], project to and activate thalamic relay neurons that enable processing of sensory and motor information by the cortex. These neurons also send sparse projections to the cortex itself, and activation of PPT has been shown to promote fast EEG activity characteristic of wakefulness [32] and disrupt slow-wave EEG activity during NREM sleep [33]. Additionally, the cholinergic basal forebrain (BF) provides direct input to distinct subregions throughout the cortex and is implicated in initiating and maintaining arousal [34,35]. The second wake-promoting pathway arises from monoaminergic neurons in the rostral brainstem and caudal hypothalamus. Although each of these groups differs slightly in their targets and mechanisms of action, they share similar firing patterns such that they are highly active during wake, fire slowly during NREM and are quiescent during REM [28]. The first of these is the noradregenergic locus coeruleus (LC), which projects broadly to the thalamus, cortex and multiple hypothalamic areas and receives input from several wake-promoting areas [36], making it a critical node in the sleep-wake regulatory network. Wake-promoting serotoninergic neurons in the dorsal and median raphe send and receive projections from regions involved in sleep-wake maintenance [28,37]. Dopamine neurons in the ventral tegmental area (VTA) [38] and ventral periaqueductal gray (vPAG) [39] have also been shown to modulate arousal, and a recently-discovered population of dopaminergic neurons in the dorsal raphe promotes wakefulness [40]. Finally, wake-active histamine neurons in the tuberomammillary nucleus (TMN) of the posterior hypothalamus project widely throughout the brain and have been demonstrated to promote sustained arousal under certain behavioral conditions [41].

Among sleep-promoting brain regions, the ventrolateral preoptic area (VLPO) and median preoptic area (MnPO) stand out as key players. Both regions are highly active during NREM sleep, send GABAergic inhibitory projections to hypothalamic and brainstem nuclei that promote wakefulness as part of the ascending arousal system, and receive afferents from the wake-active monoaminergic brain regions described above [42,43]. Additionally, lesions of the VLPO and surrounding areas result in profound sleep loss [44] and activation of the VLPO has been demonstrated to promote NREM sleep [45]. Recent work has also identified a population of GABAergic neurons in the substantia nigra reticulata that promotes the transition from wake to sleep states, primarily by way of NREM sleep initiation [46].

Historically, the study of REM sleep-promoting brain regions has focused primarily on the pons, including subpopulations of the primarily cholinergic PPT and LDT [47, 48], the glutamatergic sublaterodorsal nucleus (SLD) [49] and the GABAergic ventral medulla [50]. More recently, researchers have identified REM-active neurons in subregions of the hypothalamus including melanin-concentrating hormone-expressing neurons in the lateral hypothalamus (LH) [51] and a subpopulation of galanin-expressing neurons in the largely GABAergic dorsomedial hypothalamus (DMH) involved in transitions between NREM and REM [52].

The reciprocal connections between nodes throughout the sleep-wake regulatory circuitry comprise a self-reinforcing loop where activity from wake-promoting regions inhibits sleep-promoting regions and vice versa. This observation led to the conceptual model of the sleep-wake regulatory network as a flip-flop switch, first proposed by Saper and colleagues [53]. In electrical engineering, a flip-flop switch can be used to produce sharp transitions between discrete states but requires a stabilizing force to prevent uncontrolled switching. Orexin-expressing neurons in the LH are critical for maintaining wakefulness and have been hypothesized to serve this role [54]. These neurons are wake-active [55] and send excitatory projections to cortex, brainstem and monoaminergic centers comprising the wake-promoting pathways described above [56], thus promoting arousal but not inhibiting the sleep-promoting action of the VLPO [54].

2.3. The two-process model of sleep regulation

Although the flip-flop switch model accounts for transitions between wakefulness and states of sleep with great precision, an additional framework is needed to describe patterns of sleep and wake on longer timescales. Our understanding of sleep timing is often framed in the context of the two-process model of sleep regulation, which posits that sleep is controlled by the interactions of separate circadian and homeostatic processes [57,58]. Circadian regulation of sleep (Process C) is driven by the circadian pacemaker, such that sleep drive oscillates with a periodicity that is typically entrained to the environmental LD cycle [57,59]. In humans, this is manifested as an increase in circadian arousal during the late afternoon and early evening, and as decrease in circadian wakefulness towards the end of the sleep bout.

Homeostatic regulation of sleep (Process S) on the other hand is driven by sleep debt, or how long an individual has been awake. Sleep pressure increases with time spent awake until the individual falls asleep and decreases the longer an individual has been asleep [57,60]. Indeed, it is well documented in both human [61,62] and animal models [63] that sleep drive increases during periods of sleep deprivation, Although sleep pressure may be hard to quantify, there are EEG signatures that have been validated as reliable markers of the Process S increase [58, 64]. First, during extended wakefulness, the EEG power within a range of frequencies that spans across theta and alpha waves (6.25–9 Hz) increases with the time of wakefulness [65]. Second, the EEG delta power (0.25 and 4.0 Hz) during NREM sleep at the beginning of the recovery sleep after extended wakefulness increases with the previous time spent [60]. This delta power at the initiation of sleep and its decay

through recovery sleep have become signature metrics of the increase of process S during wakefulness and its decrease during recovery sleep, respectively.

Much of what we understand about the two-process model of sleep regulation was gleaned from landmark studies performed in the 1980's investigating sleep in both rodents and human subjects. Seminal work by Tobler et al. [66], Mistlberger et al. [67] and Trachsel et al. [68] provided key evidence that these two processes are distinct by demonstrating that in SCN-lesioned nocturnal rats, the rhythmicity of sleep-wake cycles was abolished without altering the total amount of daily sleep time. Remarkably, these animals displayed increased NREM sleep during a rebound period following sleep deprivation, suggesting the integrity of Process S was left intact. Similar results were observed in studies of sleep and circadian behavior in diurnal squirrel monkeys with SCN lesions. Unlike nocturnal animals, SCN-ablated squirrel monkeys not only lost their circadian regulation of sleep but also slept more, providing evidence for the opponent sleep regulatory process model, in which process C induces wakefulness and process S sleep [69,70].

In humans, experiments in which subjects were placed in specialized laboratory conditions absent of environmental time cues established that sleep, body temperature and endocrine rhythms followed a circadian rhythm [71–74]. Additionally, while shifting the phase of the clock with light exposure affected times at which subjects were likely to fall asleep, these manipulations did not have an effect on the depth of sleep [75]. Although the contribution of the human SCN in circadian sleep regulation could not be directly established in these early studies, later work showed that human sleep patterns were consistent with a model in which Process C is driven by a single circadian pacemaker [76]. This work led to the development of a forced-desynchrony protocol in which participants were placed in an LD and rest-activity cycle that the circadian pacemaker cannot entrain to, resulting in the primary sleep bout occurring at different circadian times on each subsequent day of the experiment [61]. Similarly, nap protocols requiring that participants take 30-min naps followed by 60-min periods of wakefulness at different time points over 24–48 h established that wakefulness is also modulated in a circadian fashion [77]. These paradigms provided experimental frameworks in which to test predictions of the two-process model in humans, and demonstrated that the two processes make parallel contributions to sleep timing [71–73,75], including that the timing of REM sleep specifically is coupled to Process C [61,73,78].

While the two processes are clearly able to work independently, there is increasing evidence that they also influence each other and that Process S may have more influence over Process C than vice versa. For example, in both humans and rodent models, the magnitude of phase shifts induced by changes in the LD cycle are attenuated during periods of sleep deprivation [79,80]. Although some evidence indicates that clock genes may influence sleep depth and that SWS is modulated by circadian phase, more research is needed to determine if and how the circadian clock influences Process S [81].

2.4. Neuronal mechanisms of circadian sleep regulation

The SCN is the primary driver of Process C [59]. Following key experiments demonstrating the necessity of the SCN for circadian rhythmicity of sleep in both nocturnal rodents and

diurnal primates, researchers developed a greater understanding of the mechanisms by which the SCN affects sleep timing. While there is heterogeneity in the activity rhythms of both single neurons and neuronal ensembles within the SCN [4], on average SCN neurons display peak firing rates during the subjective day in both diurnal and nocturnal mammals [82]. Simultaneous recording of EEG/EMG and SCN neural activity in rats revealed that the SCN is more active during REM sleep than NREM sleep [83], and SCN lesion studies suggest that the SCN facilitates transitions to REM sleep during the rest phase of the LD cycle [84]. Later work used long-term, continuous recording of EEG/EMG to evaluate sleep in a rodent model of the forced desynchrony protocols pioneered in humans [85]. Under this forced desynchrony protocol, animals were placed into a 22-h LD cycle that the circadian pacemaker is unable to entrain to, and as a result displayed two different rhythms of sleep, locomotor activity and core body temperature – one rhythm that was synchronized to the environmental LD cycle, and another that oscillated with a period longer than 24 h and did not entrain to the LD cycle. These rhythms were associated with rhythmic clock gene expression within the vl- and dmSCN, respectively. Under these conditions, researchers found that REM sleep was the sole sleep stage that oscillated with a > 24 h period [86]. Later experiments demonstrated that REM sleep propensity was associated with rhythmic clock gene expression in the dmSCN, specifically [87].

Given the clear role for the SCN in sleep timing, it is reasonable to suppose that the SCN should send strong projections to the sleep-wake regulating brain regions described above (Fig. 1). However, the SCN sends only sparse direct projections to sleep- and wake-active neuronal populations such as the VLPO [88] and orexinergic LH [89], but forms indirect contacts with these and other sleep-relevant regions via strong projections to the subparaventricular zone (SPZ) [90]. The SPZ densely innervates the heterogeneous DMH, and GABAergic DMH neurons project to and inhibit the VLPO, while glutamatergic DMH neurons excite the LH [91]. In this indirect fashion, the SCN is hypothesized to exert its influence over the timing of sleep-wake rhythms. Indeed, the relay stations provided by the SPZ are necessary for the circadian regulation of sleep, as lesions of the ventral SPZ eliminate circadian rhythmicity of sleep without altering total sleep time [90], and lesions of the DMH reduce the amplitude of circadian rhythms of sleep while slightly increasing total sleep time [91]. It has recently been shown that the SCN also promotes wakefulness via GABAergic projections to corticotropin-releasing factor neurons in the paraventricular nucleus of the hypothalamus (PVN), which then excite orexin neurons in the LH. Disruption of this circuitry has been shown to reduce wakefulness and amplitude of circadian sleep-wake rhythms [92]. Interestingly, stimulation of a subset of *Brnb3*-expressing ipRGCs that do not project to the SCN are sufficient to acutely promote sleep possibly via sparse projections to the VLPO but are not required for circadian photoentrainment of sleep [93], highlighting one avenue by which the environmental LD cycle can drive sleep timing while bypassing the master clock.

In addition to primary connections from retinal ipRGCs to the ventral core of the SCN via the retinohypothalamic tract (RHT), there are two major afferent pathways leading to the SCN: the serotonergic median raphe and the intergeniculate leaflet (IGL). The median raphe plays a key role in maintaining wakefulness as described above, and its role in mediating circadian behavior is reviewed extensively elsewhere [94]. The neuropeptide Y

(NPY)-expressing IGL projects to the SCN via the geniculohypothalamic tract and has been shown to regulate entrainment and phase resetting of the SCN [95]. However, the IGL also sends and receives projections between critical sleep-wake regulatory centers including the DMH, VLPO, SPZ and PAG, suggesting it may serve as an important point for relaying information between the SCN and the broader sleep-wake network [96]. The SCN also receives more modest direct projections from sleep-wake regulatory centers including the DMH, LC, SPZ, TMN and the arcuate nucleus of the hypothalamus (ARC), the latter of which has a prominent role in modulating circadian rhythms of sleep and metabolism [97].

In addition to synaptic transmission, humoral factors released by the SCN play a key role in maintaining circadian rhythmicity. In a landmark study by Silver et al., researchers demonstrated that SCN grafts housed in a semi-permeable capsule that prevented axonal outgrowth were able to restore behavioral circadian rhythmicity in SCN-lesioned animals, suggesting that diffusible factors play a key role in circadian sleep regulation [98].

2.5. The night hormone

The rhythmic release of the pineal hormone melatonin also plays a role in the timing of sleep in mammals [99]. The SCN regulates the timing of melatonin release via a multisynaptic projection connecting the PVN and the superior cervical ganglion of the spinal cord, and terminating in the pineal gland (Fig. 1). In both diurnal and nocturnal animals, melatonin release peaks during the night and is lowest during the day [100] and light inhibits its secretion, giving rise to the nickname the “night hormone.” Melatonin can phase shift and entrain behavioral circadian rhythms in both nocturnal rodent models [101] and humans [99], although contrary to popular belief, exogenous administration of melatonin is likely to only have a modest sleep-promoting effect [102]. Melatonin plays a direct role in rhythmically downregulating core body temperature (CBT) [103], and in humans low CBT is necessary for transitions from wakefulness to sleep [104]. Indeed, the acute effects of melatonin on sleepiness have been observed to be coincident with this dip in CBT [105]. Importantly, the effects of melatonin on sleep in humans are also time-dependent, such that administration of exogenous melatonin during the day when endogenous melatonin levels are low is sleep-promoting [106,107], whereas nighttime administration has been shown to depend more on dosage and vary between subjects [99]. Similar sleep-promoting effects have also been reported in three different species of diurnal non-human primates [108]. As a result, melatonin has been used to induce phase shifts of sleep in therapeutic contexts ranging from blindness [109], jet lag, shift work, insomnia and circadian rhythm disorders [110].

Despite modest sleep-promoting effects in diurnal animals, melatonin is unlikely to promote sleep in nocturnal animal models in fact may induce opposite effects. Melatonin has been shown to have wake-promoting effects when administered during the daytime in rats [111, 112], and there is evidence to suggest that endogenous melatonin is not necessary for proper timing and consolidation of sleep bouts in the rat [113]. Many strains of nocturnal mice commonly used as animal models in studies of circadian rhythms display little or no endogenous secretion of melatonin [114], and the effects of exogenous administration of melatonin on sleep in these mice remains controversial [115].

2.6. Sleep and the molecular circadian clockwork

In mammalian species from mice to humans, the core circadian clock genes comprising the molecular TTFL have been shown to be critical in the circadian regulation of sleep (Table 1). The first mammalian circadian clock gene to be identified, named *Clock*, was isolated and cloned in mice by Joseph Takahashi and colleagues [116] in the late 1990's. This work opened the door to a flurry of discoveries about the roles of *Clock* and other mammalian circadian clock genes in assembling the molecular TTFL, and its essential nature in generating and sustaining circadian rhythms [117–119].

Following these discoveries, researchers began to study the roles of clock genes in sleep regulation, although a clear picture of clock gene knockouts effects on circadian rhythms of sleep has yet to emerge. Mice containing a double knockout of the *cryptochrome* genes *Cry1* and *Cry2* not only lack circadian rhythmicity in constant conditions, they display a greater amount of NREM sleep and higher sleep consolidation, suggesting a role for clock genes in both homeostatic and circadian regulation of sleep [120]. Single and double knockouts of the *Period* genes *Per1* and *Per2* are similarly arrhythmic, but display typical amounts of NREM, REM and wake, as well as preserved homeostatic sleep regulation [121,122]. Mice with the Δ*19 Clock* mutation exhibit reduced amounts of NREM sleep but retain circadian rhythmicity of sleep [123]. Similarly, mice lacking the transcription factor *Npas2*, a paralog of *Clock* in brain regions outside of the SCN, display normal circadian rhythms of sleep but altered amounts of NREM sleep and sleep homeostasis [124]. *Bmal1* knockout mice, which lack circadian rhythmicity under constant conditions [119], also display a multitude of sleep disturbances including reduced amplitude of circadian rhythms of sleep, sleep fragmentation, increased total sleep time and reduced homeostatic sleep response [125]. Interestingly, a primate-specific variable-number tandem-repeat polymorphism in *PER3* is associated with an altered homeostatic sleep response but normal circadian rhythms of sleep in mice [126]. These seemingly contradictory results obviate the complex roles of individual TTFL components in regulating not only sleep timing but quality and duration.

It is important to note that these initial studies employed global deletion or mutations of core clock genes, which are not solely expressed in the SCN. Although the SCN coordinates cell- and tissue-level circadian rhythms throughout the entire organism, several other sleep-relevant brain regions display circadian oscillations in neuronal activity and gene expression themselves, including the ARC, DMH, and VTA [127]. Such oscillations, both in SCN and extra-SCN brain regions, drive rhythms of cellular processes including expression and modulation of receptors and ion channels that drive neuronal excitability [128], as illustrated by a recent study in which mice containing an excitatory cortical neuron-specific deletion of *Clock* displayed epileptic seizures during SWS [129]. Beyond the brain, clock gene expression in organs ranging from the lungs to the liver is necessary for a variety of physiological functions, the disruption of which may have marked effects on sleep.

Such observations make interpretation of results from global clock gene mutant mice more difficult and highlight the need for region and cell type-specific approaches to study the role of clock genes in the circadian regulation of sleep. For example, more recent studies have demonstrated that deletion of *Bmal1* in *Syt10*-expressing neurons, which are abundant in the SCN [130], or the forebrain [131] is sufficient to abolish circadian rhythms of locomotor

activity in mice. Similar behavior was observed following deletion of *Bmal1* in NMS neurons [21], which are localized to the SCN. Finally, another study found that deletion of *Bmal1* from VIP SCN neurons reduced the amplitude of circadian rhythms of sleep [132].

The importance of clock gene expression in extra-SCN brain regions was further highlighted by recent work demonstrating that deletion of *Bmal1* in forebrain neurons outside of the SCN increased NREM sleep duration during the dark phase and altered daily timing of both NREM and REM sleep [133]. Clock gene expression in tissues outside of the brain likely also play a role in sleep regulation, as rescue of *Bmal1* expression in skeletal muscle tissue in *Bmal1* knockout mice was sufficient to curb associated deficits in sleep duration but not timing [134]. Further region-specific studies of clock gene expression and sleep, as well as investigation of the effects of different sleep states and perturbations on clock gene expression in regions beyond the SCN, will reveal much needed greater insights into how the molecular TTFL regulates sleep timing.

These characterizations of circadian clock genes in animal models also paved the way for greater understanding of their role in human sleep regulation [135]. Such insights first came from investigations of different chronotypes, which describe an individual's preferred sleep timing. The distribution of chronotypes throughout the population is approximately normal, such that extreme morning "larks" will rise at the same time late "owls" fall asleep and most people display a more conventional sleep schedule, although these preferences change across the lifespan and under environmental influences like light exposure and timed feeding [136].

Familial advanced sleep phase syndrome (ASPS) is an inheritable disorder in which patients have an extreme early chronotype with a 4-h advance of sleep, melatonin and core body temperature rhythms [137]. In 2001, the first example of an association between a clock gene mutation and sleep timing in humans came to light when ASPS was attributed to a missense mutation in the human *PER2* gene, saddling patients with an extremely short circadian period [138]. When researchers introduced a similar *Per2* mutation in transgenic mice, the mice displayed the same shortened circadian period of behavior [139]. More recently, ASPS was associated with mutations in *CRY2* [140] and *TIMELESS*, the latter of which has been studied extensively in *Drosophila* but is less well understood in mammals [141]. Delayed sleep phase syndrome (DSPS), in which people tend to be extreme late chronotypes, is associated with a short length polymorphism in the clock gene *PER3*, while the longer length allele was associated with morningness [142]. DSPS has also been associated with a gain-of-function mutation of *CRY1,* and patients with this mutation also displayed an elongated period of molecular circadian rhythms [143]. More recently, genome-wide association studies (GWAS) leveraging large genomic datasets and actigraphy-derived measures of sleep timing have suggested contributions for known clock genes, and several non-clock genes, to determining chronotype [144]. While GWAS studies are limited in their reproducibility and ability to establish causal relationships between loci and circadian behaviors, they provide potentially promising new lines of inquiry for researchers working to understand the genetics underlying the circadian regulation of sleep.

3. Sleep and the clock during development

Rhythms of sleep and wake, at both the circadian and ultradian scales, are hardly static throughout the lifespan. Indeed, both chronotype and the nature of ultradian sleep cycles undergo marked changes from infancy and early childhood to adolescence [145], and these changes are likely to play a significant role in several aspects of brain function and development [146]. While adult sleep duration is approximately 8 h per day, infants spend up to 16 h of their day sleeping with more rapid cycling between sleep stages. More typical ultradian rhythms of sleep do not emerge until children are school-age [145], such that ultradian cycle length increases while cycle number decreases as children progress through early childhood [147]. While circadian rhythms of core body temperature and melatonin secretion may emerge as early as 6 months [148], unlike adults toddlers may display REM sleep during daytime naps [149], suggesting that the development of circadian regulation of sleep during childhood may be more complex.

Surprisingly little is known about the mechanisms underlying these developmental transitions in sleep regulation [150]. A review from Blumberg & colleagues proposes a framework for studying the developmental trajectory of bidirectional interactions between brainstem and hypothalamic circuitry driving ultradian, circadian and homeostatic sleep regulation, using early postnatal rats as a model system [150]. While some qualitative differences in the manifestation of sleep exist at earlier developmental time points, such as the emergence of EEG delta activity at postnatal day 11 (P11) [151] and a reliance on the mother for entrainment of behavioral circadian rhythms until P8 [152], young rats display rapid ultradian cycling between sleep stages consistent with the flip-flop switch model, and evidence suggests these transitions are mediated by circuitry contained entirely within the brainstem during the early postnatal period [150]. Additionally, the distribution of sleep and wake bouts across the 24-h day display a predictable progression throughout development [150], with marked circadian regulation of sleep emerging by P17, well before sleep homeostasis [153].

These observations make young rats a highly tractable and fruitful model system in which to study the mechanisms of both circadian and ultradian sleep regulation. Researchers have found that rats display day-night cycling of sleep and wakefulness as early as P2, but unlike in adult rats, the duration of both sleep and wake bouts were shorter during the night [154]. Later work demonstrated that lesioning the SCN or DMH in rats at age P8 was associated with the fragmentation of wake bouts and disruption of wake bout distribution later in life, but the same was not true for sleep bouts [155]. Finally, differences in the developmental trajectory of connectivity between the SCN and ventral SPZ have been associated with differences in activity timing between diurnal and nocturnal rats [156].

One disadvantage of rats as model systems is the relative lack of readily available transgenic models and tools for the manipulation and imaging of neural activity. Mouse models meet this requirement, however due to technical difficulties in measuring sleep in perinatal mice, relatively few studies have characterized quantitative and qualitative changes in sleep across development. One notable exception demonstrated that orexin receptors were necessary for normal consolidation of sleep and wake bouts in mice between P12 and P21 [157]. Another

study evaluated sleep architecture and homeostatic sleep regulation in adolescent mice and found a decrease in REM sleep and increase in NREM sleep relative to adults. Interestingly, while increases in delta sleep typical of a normal homeostatic sleep response were observed in adolescent mice, the magnitude of this increase showed high inter-individual variability until approximately P42 [158]. More recently, a comprehensive survey of sleep in mouse pups at different time points between P7 and P21 demonstrated that the emergence of both qualitative EEG features and consolidation of sleep stages largely mirrors the developmental trajectory of sleep features observed in rats and humans, although the study did not evaluate circadian regulation of sleep [159]. Increased understanding of sleep during development in the mouse, combined with the large transgenic toolbox available in mouse models, provides a new opportunity to characterize developmental mechanisms underlying the circadian regulation of sleep.

In addition to the behavioral and physiological studies described above, understanding the development of circadian sleep regulation calls for a comprehensive picture of the developing SCN. However, despite our knowledge of adult SCN anatomy and physiology, comparatively little attention is paid to unraveling the mechanisms of SCN development and its connectivity to sleep-relevant brain regions [160, 161]. The development of SCN cellular differentiation, patterning, rhythmicity, afferents and paracrine signaling are relatively well-studied, but little is known regarding the development of SCN efferents [160]. Because both direct and indirect projections from the SCN to brain regions in the sleep-wake regulatory network play key roles in sleep timing, characterizations of SCN efferents from a developmental perspective will be key to understanding the circadian regulation of sleep during development.

4. Advancing to the next phase – future directions for sleep and the circadian clock

4.1. Uncovering new roles for the master pacemaker in sleep regulation

In recent years, researchers have begun to elucidate mechanisms by which the SCN may exert a more direct influence over sleep timing. A report by Collins et al. [162] demonstrated that nighttime optogenetic stimulation of a subset night-active SCN neurons that co-express VIP and NMS is sufficient to acutely promote sleep in mice, while stimulating or inhibiting these neurons during the day has no effect on sleep. The peak of activity in these neurons was coincident with the daily “siesta” - a brief bout of sleep typically observed as a lull in locomotor activity occurring towards the end of the activity period in behavioral studies of circadian rhythms – and the timing of the siesta was dependent on an intact molecular clockwork in SCN VIP neurons. The authors thus hypothesized that SCN VIP neurons are responsible for timing the siesta such that this brief bout of sleep boosts wakefulness during the wake-maintenance zone, a brief period of wakefulness at the end of the activity bout [163]. Interestingly, another study found that while *Bmal1* expression in SCN VIP neurons was necessary for normal amplitude of circadian sleep-wake rhythms, chemogenetic stimulation of these neurons during the night did not have an acute sleep- or wake-promoting effect [132]. These studies highlight the need for further inquiry into the role of these neurons in directly regulating sleep timing.

Elucidating a potential direct role for the SCN in circadian sleep regulation will be aided by better understanding of specific cell types within the SCN, and specific genetic tools with which to target them. A recent study employed single-cell RNA sequencing (scRNA-seq) of mouse SCN and identified 5 distinct SCN neuronal cell types, largely confirming our current understanding of the anatomy and function of the master clock [19] while simultaneously revealing greater heterogeneity than was previously appreciated [20]. Each cell type expressed genes encoding at least two primary neuropeptides and were demonstrated to play different roles in mediating circadian behavior. For example, *Grp*$^{+}$/*Vip*$^{+}$ neurons were highly photo-responsive but displayed weak intrinsic circadian oscillations in gene expression, while *Avp*$^{+}$/*Nms*$^{+}$ and *Cck*$^{+}$/*C1q13*$^{+}$ neurons displayed opposite behavior. Some cell types also oscillated at different phases with respect to other cell types, which the authors suggest could have a cell type-specific effect on the regulation of the SCN's downstream neuronal targets. Based on these observations, the authors developed a Cre-recombinase reporter mouse in which *Vip*$^{+}$/*Nms*$^{+}$ SCN neurons specifically could be fluorescently labeled, thus allowing for a thorough characterization of their spatiotemporal distribution throughout the nucleus. Such emphasis on specific SCN cell types has already begun to reveal surprising insights about their differential contributions to regulating circadian rhythms. Shan et al. recently described the development of a Cre-inducible bioluminescent reporter mouse line in which rhythms of *Per2* expression in AVP and VIP neurons of the SCN can be monitored simultaneously in different color channels [164]. Using this reporter mouse, the researchers found that in *ex vivo* SCN slice preparations, *Bmal1* expression was necessary and sufficient for maintaining circadian rhythmicity of *Per2* expression in AVP neurons, but not in VIP neurons.

Such lines of inquiry highlight the need for further investigation into the roles of specific SCN cell types in the circadian regulation of sleep. Evaluating sleep behavior in mice in which individual cell types are targeted for excitation, inhibition, imaging and/or genetic manipulation represents an especially promising direction for the field [165]. For example, recent work demonstrated that in vivo optogenetic manipulation of either the whole SCN or VIP neurons specifically is sufficient to entrain circadian rhythms of locomotor activity and CBT in mice [166]. Such cell type-specific manipulations of SCN neurons have also borne fruit in understanding how reciprocal connections between the SCN and downstream hypothalamic areas can acutely regulate behavior. In 2016, Gizowski et al. demonstrated that excitatory peptidergic signaling from SCN AVP neurons to the organum vasculosum lamina terminalis (OVLT) gates the timing of anticipatory water intake prior to sleep in mice. Optogenetic stimulation of SCN AVP neurons outside of the normal water intake period resulted in an acute increase in water drinking behavior [167]. Conversely, excitatory GABAergic signaling from osmo-sodium-sensing neurons in the OVLT to SCN AVP neurons conveyed information about systemic osmolality and could shift the phase of the circadian clock. Optogenetically stimulating this pathway phase shifted the locomotor activity bout and lowered CBT [168]. Similar characterizations of functional synaptic contacts between specific SCN cell types and sleep-relevant targets such as the SPZ, DMH and VLPO will deepen our understanding of how the circadian clock drives sleep timing. However, caution should be taken when interpreting the effects of manipulating SCN neuronal activity on sleep. The SCN is remarkable in its ability to regulate the 24-h

timing of virtually all behavioral and physiological outputs, and its regulation of sleep could be indirect by affecting other outputs and not necessarily the generation of sleep or wakefulness. For instance, the activity modulation of SCN neurons essential to sustain CBT rhythms would not only change the circadian rhythm of CBT but also affect the temperature-dependent modulation of sleep.

4.2. Long-term monitoring of sleep architecture

Much of what we understand about the circadian regulation of sleep comes from animal studies measuring locomotor activity, as relatively few studies evaluate sleep rhythms for longer than a few days. In 1985, Richardson et al. employed continuous, tethered EEG/EMG recording in mice for durations of 60–280 days and studied sleep architecture under conditions including baseline LD cycles, constant darkness and following light pulses that shifted the phase of the circadian clock [169]. This work revealed great insight into the daily distribution of wakefulness, NREM and REM during these conditions, and largely reflected sleep behaviors observed in human forced desynchronization studies. Importantly, the rhythms of electrographically measured sleep differed from rhythms of locomotor activity as measured by wheel-running, highlighting the caveats of inferring sleep timing from locomotor activity alone, to say nothing of the ability to evaluate timing of sleep stages. Later work employed long-term sleep monitoring to demonstrate that the timing of REM sleep is coupled to an oscillator in the dmSCN in rats, as described above [87]. Other studies have used a combination of continuous and longitudinal monitoring of EEG/EMG to evaluate changes in sleep stage timing under conditions inducing chronic disruption to the circadian system such as LD cycles differing from 24 h [170] and serial jet lags [171] in mice. Most recently, continuous sleep monitoring in mice during a single jet lag paradigm revealed that the primary bout of sleep re-entrains to the new LD cycle faster than the daily siesta [172].

The paucity of studies employing long-term sleep monitoring likely stems from technical difficulties associated with chronic tethered recordings and a lack of standardization of methods for automatic sleep stage classification. This latter point is especially important, as manual sleep staging is labor-intensive and error prone. Automatic sleep stage classification has been an active area of research since the 1960’s, with proposed methods demonstrating a range of accuracy and level of adoption by the field [173]. More recent approaches leveraging machine learning and datasets from variety of animal models and experimental conditions have shown promise in both offline and real-time classification of sleep stages performed with user-friendly graphical interfaces [174–176]. Long-term, continuous sleep monitoring becomes far more practical when aided by these methods. Such experiments, when combined with systems neuroscience tools described above and newly described non-invasive methods for chronic imaging of peripheral clock gene expression in freely behaving mice [177] will be invaluable to furthering our understanding of how the circadian clock regulates sleep.

4.3. Bringing circadian regulation of sleep into the light

A key limitation in current approaches to understanding the circadian regulation of sleep is that nocturnal rodents are the most widely used animal models in the field. As a result,

some insights we acquire with these models are unlikely to directly translate to humans and other diurnal animals. While sleep and circadian behavior in diurnal mammals such as the squirrel monkey and Nile grass rat [178] are well-studied, they are far less represented in the field than nocturnal mice, which have historically been more easily amenable to genetic manipulation. Although SCN physiology is similar in nocturnal and diurnal animals, it must regulate sleep in opposite directions during equivalent phases of the LD cycle. Similarly, light stimulates and inhibits sleep in nocturnal and diurnal species, respectively [179,180]. “ON/OFF” switches that distinguish these effects between diurnal and nocturnal models have been proposed. However, these switches remain to be identified and are likely a convenient oversimplification of how sleep is temporally organized.

With the advent of low-cost sequencing technologies like scRNA-seq and CRISPR-Cas-based gene editing methods, as well as behavioral paradigms that induce diurnality in nocturnal animals [181], the development of diurnal transgenic animal models becomes more tractable. Additionally, increasingly sophisticated wireless data loggers that can capture EEG, EMG, CBT and locomotor activity are allowing for sleep monitoring in unconventional model systems, including animals in the wild [182]. Leveraging these technologies to develop new model systems will fill crucial gaps in our understanding of circadian sleep regulation in diurnal mammals.

4.4. Conclusions

Many important questions remain unanswered in the field of circadian sleep regulation, from how the SCN drives sleep to occur at different times of day in diurnal versus nocturnal animals, to how the clock responds to internal and external environmental factors to modulate sleep timing in a flexible manner. While addressing these questions remains a tantalizing endeavor for basic researchers, the importance of developing a mechanistic understanding of Process C goes well beyond the bench, as we now know that disruptions of sleep and circadian rhythms are associated with metabolic disorders [26], cancer [183], mental health disorders [184], neurological disease (e.g., epilepsy), and neurodegenerative diseases (i.e, Parkinson’s and Alzheimer diseases) [185]. Additionally, there is increasing public understanding that artificial lighting [186], socioeconomic disparities [187], daylight savings time [188] and societal constraints [189] impact sleep timing. Recent advances described above promise to help resolve longstanding questions and reveal mechanistic insights into how and why the circadian clock gates the timing of sleep.

Funding

This work was supported by NIH awards R01 NS110012 and R01 NS108934 to HOD, a CURE Sleep & Epilepsy grant NINDS award R01 NS102796-01 to FK, and Washington Research Foundation Innovation Graduate Fellowship in Neuroengineering to RS.

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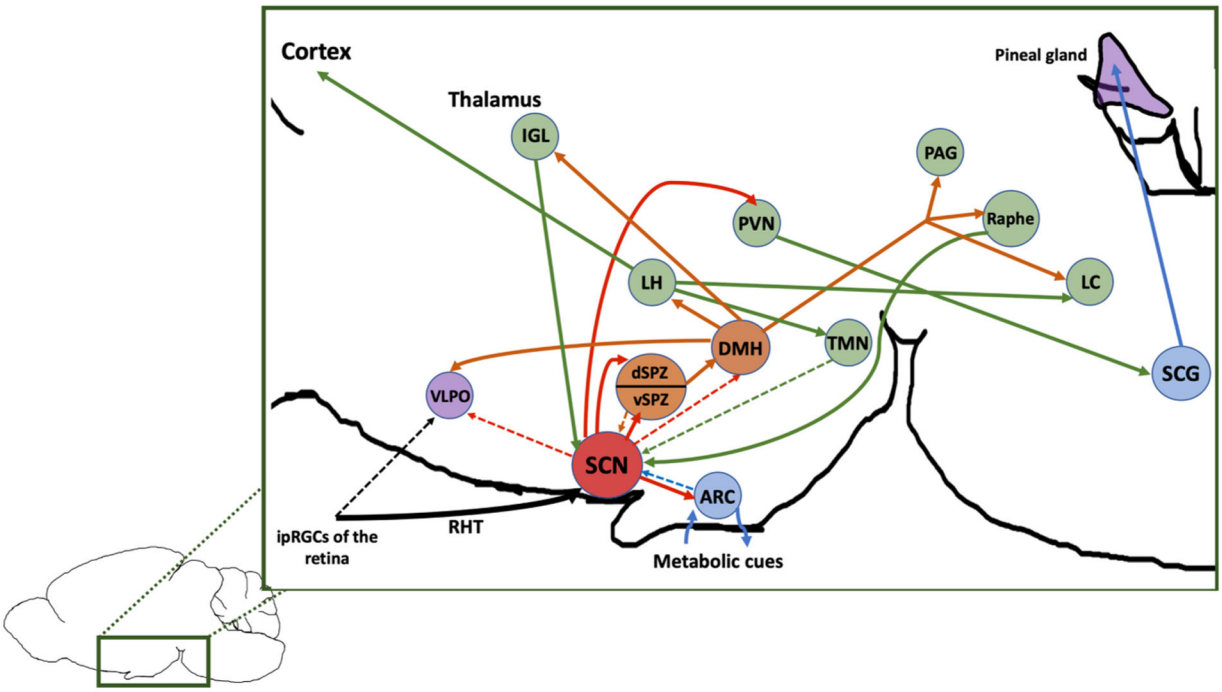

Fig. 1.

Simplified diagram of connections between the master circadian clock and sleep-wake circuitry. Diagram is color-coded as follows: Red = SCN, Green = generally wake-promoting, Purple = generally sleep promoting, orange = both, blue = neutral/other role, dotted lines = sparse projections. Abbreviations: ipRGCs, intrinsically photosensitive retinal ganglion cells; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; ARC, arcuate nucleus of the hypothalamus; VLPO, ventrolateral preoptic nucleus; dSPZ, dorsal subparaventricular zone; vSPZ, ventral subparaventricular zone; DMH, dorsomedial hypothalamus; TMN, tuberomammillary nucleus; LH, lateral hypothalamus; PVN, paraventricular nucleus; IGL, intergeniculate leaflet; PAG, periaqueductal gray; LC, locus coeruleus; SCG; spinal cervical ganglion.

Table 1

Summary of the effects of circadian clock gene mutations on sleep and circadian rhythms.

Gene	Species	Manipulation or mutation	Region	Phenotype	Reference
Cry1/Cry2	Mouse	Double knockout	Global	• Sleep rhythms abolished • Increased NREM duration • Higher sleep consolidation	[120]
Per1/Per2	Mouse	Double knockout	Global	• Sleep rhythms abolished • Sleep duration and homeostatic regulation intact	[121, 122]
Per2	Mouse	Human *PER2* mutation associated with advanced sleep phase	Global	Shortened circadian period of activity	[139]
Per3	Mouse	Human *PER3* mutation associated with changes in sleep timing and sleep rebound	Global	• No change in sleep timing or amount • Altered time course of EEG delta and theta power profiles during sleep rebound	[126]
Clock	Mouse	Δ*19* mutation	Global	Reduced NREM duration	[123]
Clock	Mouse	Knockout	Excitatory cortical neurons	Seizures during NREM sleep	[129]
Npas2	Mouse	Knockout	Global	• Altered NREM EEG • Slowed sleep need accumulation and compromised REM recovery after sleep deprivation (SD) in females • Compromised NREM recovery after SD in males	[124]
Timeless	Mouse	Human *TIM* mutation associated with advanced sleep phase	Global	• Advanced phase of sleep-wake rhythms • Altered responsiveness to light pulses	[141]
Bmal1	Mouse	Knockout	Global	• Sleep rhythms abolished • Sleep fragmentation • Reduced homeostatic sleep response • Increased total sleep time	[125]
Bmal1	Mouse	Knockout	*Syt10*-expressing neurons	Activity rhythms abolished	[130]
Bmal1	Mouse	Knockout	Forebrain neurons including SCN	Activity rhythms abolished	[131]
Bmal1	Mouse	Knockout	NMS SCN neurons	Activity rhythms abolished	[21]
Bmal1	Mouse	Knockout	VIP SCN neurons	Reduced amplitude of circadian rhythms of sleep	[132]

Gene	Species	Manipulation or mutation	Region	Phenotype	Reference
Bmal1	Mouse	Knockout	Forebrain neurons excluding SCN	Increased NREM during dark phase	[133]
Bmal1	Mouse	Knockout	VIP SCN neurons	Disrupted daily siesta	[162]
Bmal1	Mouse	Knockout	AVP SCN neurons	Loss of tissue-level *Per2* expression rhythms in *ex vivo* SCN culture	[164]
Bmal1	Mouse	Knockout, rescue	Expression rescued in skeletal muscle	Recovery of normal sleep duration but not timing	[134]
PER2	Human	Missense mutation	Global	Advanced sleep phase syndrome (ASPS)	[138]
CRY2	Human	Missense mutation	Global	ASPS	[140]
TIMELESS	Human	Nonsense mutation	Global	ASPS	[141]
PER3	Human	Short length polymorphism	Global	Delayed sleep phase syndrome (DSPS)	[142]
PER3	Human	Longer length polymorphism	Global	Extreme morningness	[142]
CRY1	Human	Gain-of-function mutation	Global	DSPS	[143]