

Circadian rhythms and sleep—the metabolic connection

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Abstract The circadian system coordinates mammalian physiology and behavior with the environmental light–dark cycle. It allocates sleep to the inactivity phase using various mechanisms involving neurotransmitters, nuclear receptors, and protein kinases. These pathways are related to metabolism, indicating that the circadian system and sleep are connected via metabolic parameters. This suggests that organs other than the brain may “sleep.” A hypothetic view on this aspect is presented providing a different perspective on sleep regulation.

Keywords Nuclear receptors · Neurotransmitters · Protein kinases · Metabolism · AMPK · Cell death · Apoptosis · Adenosine · ATP release · Catecholamines · cGMP · Circadian rhythm · Gene expression · Liver · Neuroendocrinology · Protein kinase · Sleep apnea

Introduction

Life on earth has been exposed to a periodic occurrence of light and darkness during its evolution. This steady change of light and darkness has been incorporated in the form of a circadian rhythm in order to schedule biochemical and physiological processes to their optimal phase during the 24 h of a day (for the molecular makeup, see [66], this issue). In mammals, a day can roughly be divided into an

activity phase, during which physical activity is predominant, and a rest phase, during which repair mechanisms become active and brain function alters into a state of sleep. Hence, sleep is a periodically occurring state of rest and lack of interaction with the environment. However, sleep appears to be more than simply switching off wakefulness; it appears to be a highly regulated process involving mainly two mechanisms: (1) a homeostatic process regulating the increase for readiness to fall asleep during wakefulness and the decrease of sleep intensity during sleep and (2) a circadian process that schedules sleep and wakefulness to the appropriate times within 1 day and is mostly independent of previous sleep/wake episodes [9].

These two mechanisms describe sleep at the systemic level. However, in the last decade, the circadian system could be analyzed in a very systematic manner due to the identification of genes making up transcriptional–translational autoregulatory feedback loops building the base for a clock mechanism at the cellular level. This has paved the way to analyze mice with mutations in specific clock genes and their effect on sleep parameters [58, 66]. Circadian parameters were most of the time affected; however, homeostatic parameters, such as delta power, have been affected only in a few cases [21, 79]. This indicates that at the molecular level, additional mechanisms determine the homeostatic contribution to sleep.

Deciphering the molecular base of sleep has been very difficult. This may have several reasons. First, it is very likely that the homeostatic and circadian processes are interlaced to some degree, which makes it difficult to clearly separate the two processes and the mechanisms involved. Second, the definition of sleep is focused on the brain and its activity, since lack of sleep manifests first in lack of interaction with the environment due to changes in brain activity. However, due to the reasons mentioned

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above, the influence of the circadian component on sleep is becoming better understood. The influence of circadian rhythms on neurotransmitter expression and their action on sleep via their receptors is an emerging topic [71]. Regulation of neurotransmitter expression directly via clock components binding to E-boxes in promoters of the corresponding genes [35] as well as indirect regulation via nuclear receptors modulated by clock components such as PER2 [63] may shed new light on the interaction between circadian rhythms and sleep. Furthermore, binding of neurotransmitters to their receptors uncovers a variety of signaling pathways that are potentially involved in the activation of genes important for sleep regulation such as, for example, metabolic regulators (adenosine) and regulators of neuronal plasticity [2].

Neurotransmitters, sleep, and circadian rhythms

Neurotransmitters serve to modulate brain activity in either a positive or negative manner. There are two main groups of neurotransmitters, those that facilitate sleep and those that facilitate arousal.

Excitatory neurotransmitters such as noradrenaline, serotonin, histamine, acetylcholine, and orexin are released during wake from their respective neurons in the locus ceruleus, dorsal raphe/thalamus, tuberomammillary nucleus/posterior hypothalamus, basal forebrain/lateral tegmentum, and lateral hypothalamus, respectively. At the same time, the release of inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA) and galanin from the ventrolateral preoptic nucleus (VLPO) is suppressed to favor the state of wakefulness.

Orexin-A and orexin-B (hypocretin-1 and hypocretin-2) are excitatory neuropeptide hormones that stimulate wakefulness and energy expenditure and are thought to stimulate food intake [17, 60]. Interestingly, orexin immunoreactivity shows diurnal variation in the rat central nervous system [72] and in cerebrospinal fluid of humans [26, 61] suggesting that this peptide may be regulated by the circadian clock mechanism or mechanisms for clock adaptation. This is supported by the findings that dark pulses activate orexin neurons [47]. Hence, there may be a reciprocal relationship between circadian cues and arousal-promoting signals arising from orexin neurons. However, it remains to be seen whether the orexin promoter can be modulated by clock components providing a direct link between circadian and arousal-promoting signals.

Sleep-promoting signals such as melatonin, glycine, GABA, and adenosine are released from the pineal gland, the spinal cord, and the VLPO or accumulate in the basal forebrain in the case of adenosine. This happens in an ordered fashion. First, all aminergic and cholinergic neuro-

transmitters and orexin (see above) are inhibited through VLPO-mediated GABA and galanin release. This decreases arousal. Then, acetylcholine originating from neurons in the brainstem, midbrain, and basal forebrain is released as well as orexin. GABA and galanin that are released from the brainstem and VLPO act to inhibit the aminergic brainstem neurons (for detailed mechanism of sleep state switching, see [62]).

The switch from wake to sleep appears to correlate with the accumulation of the ATP breakdown product adenosine during wakefulness [6]. This occurs especially in the basal forebrain and correlates with sleep pressure. Adenosine inhibits GABAergic basal forebrain neurons, which act to inhibit the sleep-promoting neurons of the VLPO. Disinhibition of the VLPO promotes release of GABA and galanin, which in turn inhibit the arousal-promoting system in the brainstem, midbrain, and basal forebrain, thereby initiating sleep. Hence, it appears that sleep may have a metabolic function to avoid buildup of metabolic waste that may be harmful for the cell (see below). Of note here is that metabolic parameters also intersect with circadian rhythms [27].

In the pineal gland, melatonin production rises after the activity period via activation of pineal beta-adrenergic receptors activated by noradrenaline. This results in elevation of adenosine monophosphate (5'-AMP) and increases the synthesis of the rate-limiting enzyme of melatonin synthesis, the arylalkylamine-*N*-acetyltransferase (*Aanat*) (reviewed in [32]). There is evidence that the synthesis of *Aanat* mRNA is regulated by the circadian clock by translational mechanisms [38]. Direct interaction of clock components with the E-box present in the promoter of the *Aanat* gene appears to modulate its expression also transcriptionally in a time-dependent fashion [29]. This highlights additional interactions between circadian rhythms and sleep regulation. Taken together, it appears that several neurotransmitters involved in the regulation of sleep are directly regulated by clock components and hence represent intersections between circadian rhythms and sleep.

Nuclear receptors, sleep, and circadian rhythms

Nuclear receptors are proteins that bind organic compounds such as hormones and translocate upon ligand binding into the nucleus of a cell. There they directly bind to DNA and regulate expression of genes and therefore are classified as transcription factors. The heme binding nuclear receptor REV-ERB α (NR1D1) [82] is part of the circadian clock machinery [55] and may influence sleep patterns via alterations in the circadian component of sleep. However, animals lacking this nuclear receptor have not been tested for sleep parameters.

Since nuclear receptors are transcription factors, there is the possibility that they may affect expression of important neurotransmitters affecting sleep. Recently, the nuclear receptor germ cell nuclear factor (aka NR6A1) was identified to regulate orexin transcription [73]. However, whether absence of NR6A1 in the brain affects sleep remains to be demonstrated. The levels of non-peptide neurotransmitters such as dopamine and serotonin may be modulated by nuclear receptors via transcriptional regulation of rate-limiting enzymes responsible for their synthesis and/or degradation. Nurr1 (NR4A2) directly transactivates the promoter of the tyrosine hydroxylase gene (TH), which encodes for the rate-limiting enzyme in dopamine synthesis [37]. Interestingly, this nuclear receptor interacts with the clock protein PER2 [63], which modulates NR4A2 activity [59]. Hence, TH expression may be affected by the circadian clock. Furthermore, it appears that clock components regulate the promoter of the *Maoa* gene [28], which encodes for the rate-limiting enzyme for dopamine degradation. This may be one of the reasons why mice with mutations in clock genes display alterations in sleep parameters [20, 22, 39, 44]. The regulation of dopamine by nuclear receptors may also affect noradrenaline synthesis, since this molecule is synthesized from dopamine by the enzyme dopamine β -hydroxylase. The synthesis of the other catecholamine that affects sleep, serotonin, is controlled by tryptophan hydroxylase-2 in the brain [84]. This enzyme is regulated by the estrogen receptor beta (NR3A2) within serotonergic neurons of the dorsal raphe nuclei [19] indicating the involvement of nuclear receptors in regulation of production of this neurotransmitter. Interestingly, it appears that under certain conditions the estrogen receptor beta (NR3A2) may interact with PER2 [24], and therefore, its activity is possibly influenced by the clock mechanism.

Retinoids (including vitamin A) appear to modulate sleep regulation probably by affecting the homeostatic component of sleep (reviewed in [65]). Sleep deprivation (SD) leads to changes in gene expression in the brain. One gene that is significantly affected by SD is transthyretin [65], a critical transporter protein for retinol. Genetic linkage analysis in various mouse strains with varying slow wave sleep (SWS) revealed that retinoic acid receptor beta (RAR β aka NR1B2) may be linked to changes in SWS. Analysis of mice mutant in the *Rarb1* gene revealed that this is indeed the case [46]. Hence, it appears that retinoic acid-mediated transcriptional events affect cortical synchrony during sleep. Consistent with this finding is the observation that a vitamin A-deficient diet causes attenuation of delta oscillations, a correlate of sleep depth and sleep need in the electroencephalogram (EEG) of SWS [65]. In conclusion, it appears that RARB and its ligand are modulating the homeostatic component of

sleep. Of note is that RARB receptors have been hypothesized to play an important role in the mesolimbic dopaminergic pathway [40], which is involved in addiction processes and regulation of mood [50]. The other receptor that can bind retinoids, retinoic X receptor alpha (NR2B1), heterodimerizes with Nurr1 (NR4A2) and NGFI-B (Nur77 aka NR4A1) [53]. Since Nurr1 regulates TH, retinoids may affect the synthesis of dopamine [42]. Hence, retinoids may affect sleep via regulation of dopamine production. How the Nurr1 interacting clock gene PER2 is involved in this process remains to be determined.

Protein kinases, sleep, and circadian rhythms

Protein kinases play an important role in the circadian clock mechanism [76]. A mutation in casein kinase I δ (CKI δ) leads to familial advanced sleep phase syndrome [80], by affecting phosphorylation of a specific serine residue in the clock protein PER2 and hence disturbing the circadian component of sleep.

The light-mediated resetting mechanism of the circadian clock involves a number of kinases, including CKI. There is genetic evidence that cGMP-dependent protein kinase II (PKGII) modulates the size of resetting in response to light [51]. In contrast, cGMP-dependent protein kinase I (PKGI) regulates the timing and quality of sleep and wakefulness but not resetting of the circadian clock [43]. Interestingly, the *Caenorhabditis elegans* homolog of PKGI appears to influence lethargus, a sleep-like state in these animals [57]. Since cGMP-dependent protein kinases can mediate nitric oxide (NO) signaling in the nervous system, NO may influence parameters of sleep. In accordance with this hypothesis is the observation that NO affects recovery sleep [36].

The MAP-kinase signaling pathway is involved in the resetting of the circadian clock machinery in response to light (reviewed in [31]) and also appears to affect sleep. For example, selective increase of rapid eye movement (REM) sleep in HIV-infected subjects can be prevented by an inhibitor of the ERK activating enzyme MEK [18]. Hence, the MAP-kinase pathway appears to be involved in REMS regulation. Additionally, there is genetic evidence that protein kinase A (PKA) signaling plays a role in the maintenance of sleep [30]. This is also supported by the finding of a single nucleotide polymorphism in the phosphodiesterase 4D (PDE4D) gene that is associated with sleepiness in humans [25]. PDE4D reduces cAMP levels and thereby reduces PKA activity. REM sleep deprivation leads to activation of PKA in the pedunculopontine tegmental nucleus [16], a critical area of the brainstem for the regulation of REM sleep. Hence, activation of PKA

seems to be a critical step for the homeostatic regulation of REM sleep.

Glycogen synthase kinase 3 β (GSK3 β) phosphorylates and stabilizes the clock component and nuclear receptor Rev-erb α [81]. This may be linked to the observation that transgenic mice overexpressing GSK3 β exhibit severe fragmentation of the sleep–wake cycle without showing deviancy in total duration of vigilance states [1]. In humans, a single nucleotide polymorphism in the promoter of GSK3 β is associated with response to total sleep deprivation in bipolar depression [5]. Taken together, it appears that GSK3 β may modulate sleep–wake organization and recovery sleep. However, a mechanistic chain of events is still lacking.

Calcium/calmodulin-dependent protein kinase IV (CaMKIV), which is involved in synaptic plasticity [78], synaptic homeostasis [33], and learning and memory [23], is up-regulated following sleep [13]. Overexpression of CaMKIV in mice selectively enhances 4–7.5 Hz oscillation power during trace fear learning and 1–4 Hz delta oscillations during subsequent sleep [67]. This emphasizes a role for CaMKIV in the control of learning and sleep-related EEG oscillations.

The mRNA of another calcium/calmodulin-dependent protein kinase, CaMKK2, is increased after 6 h of SD. This kinase is an activator of adenosine monophosphate (AMP)-activated protein kinase (AMPK), a sensor and central mediator of metabolic signals. Consequently, AMPK is phosphorylated, and p-AMPK is increased after SD [12] and hence leads to higher AMPK activity. Pharmacological treatment of mice with AMPK inhibitor and activator modulated EEG delta power indicating that AMPK is involved in the regulation of sleep depth and sleep homeostasis [12]. Recent investigations also point to an involvement of AMPK in the regulation of the circadian oscillator. The clock protein CRY1 is phosphorylated and destabilized by AMPK [41] affecting the oscillator mechanism of the clock. Also, CKI ϵ is activated by AMPK, which leads to PER2 degradation and phase advance in the circadian expression of clock genes [75]. Deletion of AMPK leads to changes of circadian rhythms in a tissue- and isoform-specific manner [74]. Since AMPK is a nutrient sensor, it appears that metabolic status may affect the circadian component of sleep via CRY1 and PER2 phosphorylation linking metabolism and sleep.

Adenosine plays an important role in sleep regulation [6, 56]. Extracellular ATP is rapidly degraded by ectonucleotidases [85], some of which are expressed in a time-dependent fashion [83]. The resulting adenosine accumulates in the extracellular space and is taken up by astrocytes via equilibrative nucleoside transporters [4]. Inside the cell, adenosine is phosphorylated by adenosine kinase (ADK) to 5'-AMP. Hence, ADK drives the influx of adenosine into the

astrocytes and regulates the abundance of extracellular adenosine, and therefore, ADK is the primary enzyme regulating adenosine metabolism in rodents [8, 48]. In accordance with the notion of adenosine being an important sleep regulator, overexpression of the cytoplasmic isoform of ADK altered sleep physiology in mice [52]. Interestingly, however, reduced expression had no major effect on sleep [52].

Taken together, the above illustrates the importance of protein kinases in sleep and circadian clock regulation. Most likely, more protein kinases and phosphatases, the counterplayers of kinases, are involved in the regulation of sleep.

Metabolism, an intersection between the circadian and the homeostatic process of sleep?

Most of the neurotransmitters, nuclear receptors, and protein kinases that regulate sleep are involved in the regulation of metabolism as well. Therefore, metabolism may be the focal point between the regulation of the circadian and homeostatic process of sleep. In 1995, Benington and Heller [6] proposed that during wake, metabolism is increased in the brain, leading to a rise in adenosine levels. Adenosine is an inhibitory neuromodulator in the central nervous system, inhibiting neuronal activity of excitatory (e.g., cholinergic and glutamatergic) as well as inhibitory (e.g., GABAergic) neurons [70]. The rate of adenosine formation increases when the supply-to-demand ratio for oxygen is decreasing. In other words, if more oxygen is needed than can be supplied as observed in hypoxia, neuronal activity is shut down (for review, see [54]). This may be important to protect neurons from self-destruction and to minimize cell damage [15]. Interestingly, adenosine levels increase during SD in the basal forebrain of rats, but not in the thalamus, dorsal raphe nucleus, pedunculo-pontine tegmental nucleus, and preoptic area (for review, see [54]). This regionally specific rise in adenosine in response to SD supports the hypothesis that adenosine promotes sleep via modulation of neuronal activity in the basal forebrain.

However, it is not clear how extracellular ATP levels are regulated. The ATP produced in mitochondria leads to a steady-state cytosolic concentration of ATP of about 10 mM. Extracellular ATP is approximately 10 nM under basal conditions. Hence, the ATP gradient for ATP secretion or efflux is about 10^6 -fold. Interestingly, this gradient is 100 times greater, yet opposite, to the gradient for calcium entry into cells. Therefore, if a pathway is activated or a channel opened for ATP release, ATP would exit the cell down a very favorable gradient. It should be emphasized, however, that only 1% or less of the intracellular ATP pool is

necessary to activate its own or its derivative's receptors. Thus, extracellular ATP signaling can occur without compromising cellular metabolism or essential enzymatic reactions (reviewed in [64]).

After conversion of ATP to adenosine and uptake of adenosine into the cell, ADK phosphorylates adenosine to 5'-AMP (see above). 5'-AMP signals to the cell that energy should be mobilized from the organism's storage sites. This molecule allosterically regulates the following key metabolic, (catabolic and anabolic) enzymes. On the catabolic side, AMPK is activated by 5'-AMP, which leads to increase in nicotinamide phosphoribosyl transferase, and intracellular NAD⁺ levels rise. This enhances SIRT1 activity leading to deacetylation of its targets such as PGC-1 α [10, 11] to increase fatty acid oxidation. The rate-limiting enzyme of glycolysis, phosphofructokinase, is positively regulated by 5'-AMP dictating the catabolism of glucose. Glycogen catabolism is also positively regulated by 5'-AMP via activation of the rate-limiting enzyme glycogen phosphorylase, which liberates glucose from glycogen. Anabolic reactions such as gluconeogenesis, however, are inhibited by 5'-AMP by negative regulation of fructose-1,6-diphosphatase (reviewed in [45]). Taken together, 5'-AMP activates catabolic pathways and inhibits anabolic pathways. This is in line with the view that adenosine promotes sleep. During inactivity, energy will be supplied by the body's stores, and hence, catabolic pathways need to be activated. Interestingly, many of the enzymes highlighted here are involved in the regulation of the circadian system.

The liver is the central organ for metabolic regulation. Patients with liver cirrhosis display fragmented sleep, delayed sleep habits, take longer to fall asleep, and nap frequently during the day [7, 14]. The pathophysiology of these abnormalities is unknown, but patients with liver cirrhosis might be interesting to study from the point of view of a disturbed circadian system. Under the assumption that cirrhotic patients do not have a circadian rhythmically active liver, these patients model a clock system with disturbance of peripheral but not central clocks. Hence, the importance of peripheral circadian liver metabolic rhythms can be studied in terms of their relevance for sleep. In this context, the metabolism of melatonin, a sleep-promoting molecule, synthesized in the pineal gland has been studied. Melatonin is transformed to 6-sulphatoxymelatonin (aMT6s) in the liver [3, 34] and is excreted in the urine. Abnormalities in the rhythm of both plasma melatonin and urinary aMT6s have been observed in patients with cirrhosis, and this may contribute to sleep disturbances [68, 69]. A significant association has been observed between aMT6s profiles and delayed sleep timing in patients with cirrhosis [49] indicating at least a disturbance of the circadian component of sleep in these patients.

The hourglass and “sleeping” cells

The circadian as well as the homeostatic component of sleep are related to metabolism. This is probably one of the reasons why the two processes cannot be clearly separated from each other. In contrast to the circadian component, the mechanistic workings of the homeostatic component are far from understood. The following hypothesis may aid in better understanding and investigating the homeostat in the future. The homeostat may be viewed as a counter of the filling state of a metabolic trash bin. During the active phase, metabolism is mainly running in one direction, and toxic products such as, for example, peroxides may accumulate. Under normal conditions, the circadian component will signal the appropriate time for the organism to inverse the biochemical pathways and regenerate its enzymes and detoxify the cells which have accumulated toxic products (e.g., peroxides). This will put the cell back to its initial metabolic state in a circadian fashion (Fig. 1). However, the circadian signal may be overruled by prolonged activity or sleep deprivation, which may be necessary under extreme circumstances. As a consequence, toxic metabolic products accumulate. In other words, the trash bin fills up over the normal levels limited by the circadian signal. This still can be tolerated, but a safety mechanism needs to be in place to define the maximal levels of toxic substances allowed in the cell to protect it from destruction. Such a metabolic meter will ultimately force the cell to go into the “regenerative” state, irrespective of other signals. The initial state of the cell will be reached via such an hourglass mechanism-like process (Fig. 1). This may happen in all cell types. However, neurons are

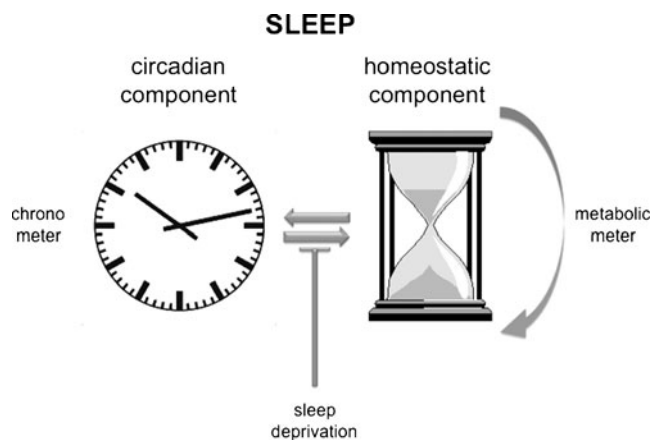


Fig. 1 A circadian and a homeostatic component regulate sleep in mammals. The circadian component corresponds to a chronometer (*left*) whereas the homeostatic component corresponds to a metabolic meter with an hourglass-like mechanism. The two components interact but can be uncoupled by sleep deprivation

somewhat special in this respect, because they are more sensitive to toxic substances than other cell types. This may be the reason why this effect is seen first in the brain in the form of shutting down the awake state of brain activity.

Recently, “local” sleep in the brain of rats was observed [77]. After a long period of awake state, cortical neurons were observed to go briefly “offline” accompanied by slow wave sleep in the local EEG. The switch to go “offline” appeared to affect only some areas in the brain but not others at a given time, indicating the existence of “local sleep.” The incidence of this process appeared to increase with the duration of the awake state, and animals showed an overall “awake” EEG. Hence, local populations of neurons may fall asleep without affecting the awake appearance of the animal, although impairing its motor performance slightly. This local regulation of sleep in individual neurons will allow the animal to have some neuronal circuits still running while others are idling. This would help the animal to perform task important for survival for a longer period than predicted by the circadian timer. These observations are in line with the view presented above to rest “tired” metabolically exhausted neurons and allow them to regenerate, avoiding accumulation of cytotoxic substances. It remains to be seen whether such neurons die, when not allowed to rest, which would be a prediction of the model postulated above.

The model presented above would also predict that basically all cells and organs have the potential to sleep. However, the central position of the brain allows it to regulate the function of other organs via neuronal and hormonal signaling. Therefore, the brain may be communicating “sleep” to organs before they are instructed by their own metabolic meter to go into a “regenerative” state. Hence, sleep may not be observed in organs under normal circumstances. Under stressful conditions, however, when cells in peripheral organs are “overused” and not allowed to regenerate (e.g., liver cirrhosis), cells will die as a consequence. These cells will then be replaced with newly differentiated cells originating from local progenitor cells. This process is less efficient in the brain and hence, metabolic control is more stringent in this tissue. Although the hypothesis described here has many appealing facets, it is certainly simplistic. Nevertheless, the view presented here may be useful to look at sleep from a different perspective.

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