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A metabolic–transcriptional network links sleep and cellular energetics in the brain

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Abstract

This review proposes a mechanistic link between cellular metabolic status, transcriptional regulatory changes and sleep. Sleep loss is associated with changes in cellular metabolic status in the brain. Metabolic sensors responsive to cellular metabolic status regulate the circadian clock transcriptional network. Modifications of the transcriptional activity of circadian clock genes affect sleep/wake state changes. Changes in sleep state reverse sleep loss-induced changes in cellular metabolic status. It is thus proposed that the regulation of circadian clock genes by cellular metabolic sensors is a critical intermediate step in the link between cellular metabolic status and sleep. Studies of this regulatory relationship may offer insights into the function of sleep at the cellular level.

Keywords

Nicotinamide adenine dinucleotide; Adenosine triphosphate; Slow wave activity; Sleep; Circadian; Adenosine monophosphate-activated protein kinase; Glycogen; Sirtuin; Poly(ADP)ribosyl polymerase; Peroxisome proliferator-activated receptor

Introduction

The field of sleep research has gained profound insights from molecular genetic and classical genetic studies over the past decade (reviewed in Refs. [1–3]). Sleep loss triggers a large scale change in transcriptional regulatory networks [4, 5], including the circadian clock genes [6, 7]. However, a link between these transcriptional changes and the restorative function of sleep remains elusive. Published studies document that sleep/wake cycles are sensitive to, and paralleled by, changes in cellular metabolic status in the brain (reviewed in Refs. [4, 8, 9]). Others demonstrate that cellular metabolic sensors regulate circadian clock gene function (reviewed in Refs. [10–12]). Still others demonstrate that circadian clock genes regulate sleep/wake cycles and molecular responses to sleep loss in a manner that extends beyond their role in the generation of 24-hour rhythms (reviewed in Ref. [13] and Landgraf et al., this issue). This article seeks to unite these three themes in a unitary conceptual framework. The three themes converge to provide a framework whereby the interrelations of cellular metabolism, transcriptional regulatory events and sleep/wake-related changes in neuronal activity are united as a functional entity within the brain (Fig. 1). By this proposed mechanism, the detection of cellular metabolic status by the transcriptional network centered around circadian clock genes regulates sleep states to maintain metabolic

homeostasis in the brain. Future efforts might exploit the interrelationship of circadian clock genes, sleep and cellular energetics for therapeutic benefit.

Sleep–wake cycles are accompanied by profound shifts in cerebral metabolism (reviewed in Ref. [14]). A reduction in the rate of cerebral glucose metabolism during nonrapid eye movement sleep (NREMS) relative to wakefulness is a reliable finding in positron emission tomography studies on human subjects. Estimates of the reduction in cerebral glucose metabolism during NREMS relative to wakefulness range from 12% [15] to 30% [16] to 44% [14]. This relationship does not apply for rapid eye movement sleep, a state in which the cerebral cortex is as active as it is during wake both electroencephalographically and metabolically [17, 18]. Since the majority of time spent asleep is in NREMS, the overall conclusion stands that sleep is a state of reduced metabolic demand in the brain.

What is the electrophysiological basis for the reduction in cerebral metabolism during sleep relative to wakefulness? Slow oscillations in the electroencephalogram (EEG) during NREMS are accompanied by oscillations in cerebral cortical neurons between an up (depolarized) state in which the cell is excitable and engages in burst firing, and a down (hyperpolarized) state in which the cell is silent. The cooccurrence of slow (1 Hz) waves and down state/up state alternations during NREMS is now a well-documented feature of NREMS in rodents [19, 20], cats [21, 22] and humans [23]. The alternation of firing between up and down states during NREMS contrasts with the tonic up states that occur during wakefulness. These silent down states may in fact be critical to the reduced metabolism that occurs during NREMS. Action potentials necessitate energy expenditure, as ion fluxes must be countered by energy efficient [24] but nonetheless energy-consuming [25, 26] mechanisms that repolarize the cell.

There are caveats to this conceptual model of sleep as a mediator of cellular energetic functions. The model focuses largely on cerebral cortical EEG dynamics as a key readout for understanding sleep function. EEG dynamics are influenced by a complex system of subcortical regulatory centers. Some of these centers promote, and others inhibit, slow EEG activity (reviewed in Refs. [27, 28]). Still others serve REM sleep regulatory functions (reviewed in Ref. [29]). In accordance with their roles, these subcortical regulatory centers have their own state-specific activity patterns. These subcortical centers are likely to contribute to sleep-related changes in brain metabolic status, both through their effects on the cortical EEG, and changes in their own metabolic demand. Additionally, the 1-Hz slow waves associated with alternating up and down states should not be confused with what has traditionally been thought of as the EEG marker for sleep homeostasis, delta (0.5–4 Hz) activity [30]. Slow waves and delta activity are concordant in at least two senses. First, both are prominent in NREMS and rare during wake and REMS. Second, slow waves are most likely to occur on a large spatial scale early in the sleep period, when delta activity and sleep need are highest [23]. Just as delta power dissipates across a night's sleep, the global span [23] and amplitude [31] of up/down states (also described as on/off states [23]) decreases with the discharge of sleep need. Nonetheless, there is evidence that these two types of NREMS-related activity are the products of distinct neuronal events. Whereas the decline in delta power across a night's sleep, presumed to reflect the discharge of sleep need, occurs incrementally across NREMS episodes, EEG power at frequencies below 1 Hz exhibits a

distinct pattern of decline [31]. Therefore, it should not be assumed that any function attributed to 1 Hz up/down oscillations, including possibly a cellular energetic function, is in a 1:1 relationship with 0.5–4 Hz EEG power dynamics, the traditional and widely applied measure of sleep homeostasis.

The regulatory mechanisms that enforce the relationship between sleep and cellular metabolism are not fully characterized, but are likely to be related to the synthesis and use of adenosine triphosphate (ATP), an essential energy source for maintaining the cell membrane ionic concentration gradients critical for neuronal excitability. Down states during NREMS are defined by a precipitous decline in the occurrence of action potentials. The decline in the number of action potentials curtails demand for ATP-dependent membrane repolarization mechanisms [25]. There is thus considerable appeal to the notion that sleep serves an essential function for brain metabolism. However, what is the evidence that metabolic demand is a driving force in the regulation of sleep, as opposed to an epiphenomenon coincident to but independent of sleep regulation? There is evidence, reviewed below, that a number of metabolic status indicators vary across sleep states within the brain, and that these metabolic status indicators regulate sleep via their effects on cellular metabolic sensors. The mechanisms that mediate the relationship between molecular sensors of cellular metabolic status and sleep are ill-defined. While changes in the cellular metabolic status of neurons can occur on a timescale of seconds, regulatory changes in EEG-defined sleep occur on the scale of minutes to hours. Metabolically-induced transcriptional changes may bridge these timescales, transducing short-term cellular changes to long-term changes in sleep states. Beginning from this assumption, one can inquire about the effects of metabolic changes on transcriptional regulation. The circadian transcriptional regulatory machinery is well-positioned to transduce short-term metabolic changes into longerterm changes in the macromolecular composition of the cell. We now consider the relationships of a panel of cellular metabolic sensors to sleep/wake cycles and how the relationships between these sensors and sleep might be mediated by clock genes.

AMPK: a metabolic indicator for cellular energy charge

ATP is the primary energy currency of the cell. It is the cellular fuel that offers the greatest amount of potential energy in the oxidative metabolic chain [32, 33]. In the production of ATP, adenosine is the backbone for a series of energy transfer reactions. Consumption of glucose, fatty acid, or amino acid-derived fuels by the citric acid cycle results in the sequential attachment of phosphate groups to this adenosine backbone to form adenosine monophosphate (AMP), adenosine diphosphate (ADP) and ATP. Subsequent reversal of this set of reactions removes these phosphate groups, yielding energy to perform work such as the operation of ion pumps that produce the ion concentration gradients necessary for action potentials. NREMS is paralleled by a reduced ATP flux relative to wakefulness [34, 35]. Sleep loss, by contrast, causes in the brain an increase in the expression of the mitochondrial genome [36], an indication that the requirement for ATP use is increased during wake relative to sleep.

The regulation of ATP metabolism is highly tuned by an elaborate set of regulatory mechanisms [37], including the activity of the adenosine monophosphate-activated protein

kinase (AMPK; reviewed in Ref. [38]). When the AMP/ATP ratio increases due to consumption of ATP (a decrease in cellular “energy charge”), AMPK is phosphorylated by upstream kinases and initiates changes in the cell that slow ATP consumption. This mechanism appears to be at work in the brain in association with sleep; temporal patterns of AMPK phosphorylation provide evidence that this metabolic sensor reacts to changes in sleep/wake states. AMPK phosphorylation in the brain is reduced during times of day when sleep predominates [34]. Enforced wake caused an increase in phosphorylated AMPK (pAMPK) [34, 39].

With its wide-ranging impact on cellular regulatory pathways [38], it is hard to imagine that sleep/wake-related changes in AMPK activity would not impact on sleep physiology. Indeed, AMPK does appear to affect sleep physiology. An AMPK inhibitor attenuated NREMS slow wave activity (SWA) during spontaneous sleep, while an activator enhanced it [39]. These data demonstrate that AMPK is a driver of sleep need. How are the effects of AMPK activation mediated? Multiple mechanisms may be at play, but one may involve the product of the canonical clock gene cryptochrome 1 (*cry1*). It is a target for phosphorylation by AMPK. Phosphorylation by AMPK destabilizes Cry1 protein [40], preventing it from performing its transcriptional inhibitory function. The effect of AMPK activation on sleep [39] is similar to *cry1/cry2* double gene knockout, which increases time spent in NREMS, NREMS consolidation and NREMS SWA [41]. The degradation of Cry proteins, analogous to gene knockout, may contribute to the SWA-promoting effect of pharmacological activation of AMPK [39].

NAD(P)H:NAD(P)⁺: a metabolic indicator for redox status

The synthesis of ATP requires oxidation–reduction reactions at several stages of carbohydrate metabolism and during the citric acid cycle. As intermediates are oxidized, a pool of cellular nicotinic adenine dinucleotides (NAD) undergoes reduction. NAD harboring an additional phosphate group (NADP) also serves as a reducing agent; NAD and NAD(P) are collectively labeled as NAD(P). A high rate of ATP production will alter the NAD(P)H:NAD(P)⁺ ratio. This ratio, therefore, provides a metabolic indicator of changes in cellular redox status in parallel with metabolic load. Given the sleep state-dependence of ATP production in the brain, it seems likely that the ratios of NAD(P)H:NAD(P)⁺ should also vary with sleep states.

So what evidence indicates that cellular redox status, and with it the ratio of NAD(P)H:NAD(P)⁺, varies across sleep cycles? Several papers have found evidence of oxidative stress occurring after sleep loss. Upregulation of glutathione and glutathione peroxidase occurs in the rat brain as a consequence of sleep deprivation [42]. Upregulation of this antioxidant pathway presumably serves to counteract the oxidative load associated with the SD-related increase in glycolytic enzyme activity (documented by both Refs. [42] and [43]). Increased lipid peroxidation and oxidized glutathione, additional measures of oxidative stress, have also been observed in the brains of sleep deprived mice [44]. That sleep loss accelerates metabolic pathways involving oxidation reactions can be inferred based on the effects of SD on transcripts related to oxidant defenses [5, 8]. These data are compatible with the concept that cellular oxidative stress is a consequence of sleep loss.

Oxidative stress caused by sleep loss may feed into cellular metabolic regulation through NAD(P)-sensing proteins. The positive transcriptional regulator of clock-related transcripts, NPAS2, is impacted by oxidative stress and the NAD(P)H:NAD(P)⁺ ratio [45]. The molecular basis for effects of redox status on the clock mechanism was not clear at the time of its discovery, but latter observations on the effect of the NAD-sensing histone deacetylase SIRT1 on transcriptional regulatory clock genes [46] may be relevant to the matter. SIRT1 protein undergoes circadian oscillations and is necessary for high amplitude oscillations in *bmal1*, *dbp* and *period2* (*per2*) gene expression in an in vitro fibroblast model of circadian clock function. In SIRT1-deficient mice, positive regulators Bmal1 and Clock are downregulated at the protein level and the negative regulators Per2 and Cry1 are upregulated. SIRT1 protein binds to Per2, Bmal1 and Clock and deacetylates Per2 protein, resulting in a reduction of the half-life of Per2 protein [46]. Collectively, these results demonstrate that SIRT1 deacetylation of Per2 is required for the timely degradation of Per2 protein and subsequent derepression of *per* and *cry* transcripts. In the absence of SIRT1-dependent deacetylation, Per2 protein remains in the cell longer, decreasing the amplitude and increasing the period of circadian oscillations. All of these effects occur in interaction with the transcriptional regulator, Clock, which is a histone acetyltransferase (HAT; [47]). SIRT1, as a histone deacetylase (HDAC) counteracts the enzymatic activity of Clock.

Being NAD⁺-sensitive [48], SIRT1 is positioned to modulate the clock gene network in concert with cellular redox state. Also, given the previously cited evidence that cellular redox status varies with sleep state, SIRT1 might be expected to contribute to sleep regulation. Data from SIRT1-deficient mice support this notion. SIRT1-deficient mice exhibit a failure to sustain state consolidation, characterized by reductions in time awake, wake episode duration and NREMS SWA [49]. That said, histochemical data reported in the same study document degeneration of wake-promoting subcortical nuclei in SIRT1-deficient mice. Whether the sleep phenotype is secondary to the degeneration, as opposed to an acute consequence of SIRT1-deficiency, cannot be determined based on these data alone. Studies on the acute effects of SIRT1 inhibitors (a number of which are available [50]) on sleep might advance this line of work.

Poly ADP-ribose polymerase (PARP): a secondary sensor of both cellular energy charge and redox status

ADP-ribosylation is a posttranslational modification that regulates the activities of dynamic proteins in the cell. PARPs are a family of enzymes capable of ADP ribosylation of target proteins [51]. PARPs exert some of their influence on cellular function as transcriptional regulatory proteins. PARP activity is regulated by both AMPK-dependent phosphorylation [52] and SIRT1 [53, 54], the potential clock gene- and sleep-regulatory functions which are mentioned above. So as a potential mediator of the cellular response to changes in both energy charge and redox status, PARPs have the potential to modulate cellular physiology in accordance with sleep state.

Indeed, there is evidence that PARP activity regulates sleep state. The acute response to the PARP inhibitor minocycline includes a period of insomnia lasting hours [55]. Additionally, minocycline strongly suppresses EEG slow wave activity in the cerebral cortex both after

sleep deprivation [55] and in spontaneous sleep conditions in humans [56] and mice [57]. The somnolytic effect of this PARP inhibitor is indicative of a potential sleep-promoting role for PARP activity. It is possible that SIRT1 and PARP act antagonistically in sleep/wake regulation. SIRT1 activation, in association with a shift in redox status, inhibits PARP and (whether through this mechanism or independently) supports wake-promoting mechanisms. Reduced SIRT1 activity occurring as a consequence of a wake-dependent increase in oxidative stress, liberates PARP-1, and consequent PARP enzymatic/transcriptional activity that promote sleep. This argument hinges on the assumption that the sleep-suppressing effect of minocycline is mediated by PARP inhibition. It is a significant caveat, however, that the effects of minocycline may be mediated through other mechanisms (such as the antibiotic effect of this tetracycline derivative). Given this caveat, it would be very informative to study the sleep phenotype of PARP-1 deficient mice, and its modulation (or lack thereof) by minocycline.

Like other metabolically driven enzymes, PARP activity regulates the circadian clock proteins [58]. In the liver, at least, PARP activity (as measured by protein ADP-ribosylation) is circadian. PARP-1 binds to, and ADP-ribosylates, the Clock protein. Genetic deficiency for PARP-1 depresses Clock/Bmal1-dependent transcription and, thereby, alters the daily cycle of gene expression in the liver and its entrainment by restricted feeding.

Glycogen metabolism: availability of substrates for the citric acid cycle

The citric acid cycle, a source of ATP needed for cellular work, is initiated with the consumption of an energy substrate, which in the brain is typically derived from glycolytic processing of a glucose-derived substrate. Benington and Heller proposed that the energy challenge posed by wakefulness obligates the depletion of glycogen stores, which in turn obligates the replenishment of those glycogen stores through sleep [9]. Some earlier observations indicated that sleep facilitated the synthesis of glycogen within the brain [59]. Glycogen levels are, however, inconsistently affected by short-term sleep loss (reviewed in Ref. [8]). It may not be the concentration of glycogen, but rather its rate of turnover, which increases and decreases in concert with wake and sleep, respectively [60, 61].

Glycogen synthase kinases, including glycogen synthase kinase β (GSK3 β), are essential to the regulation of cellular glycogen stores. GSK3 β provides negative feedback to prevent the synthesis of glycogen when glycogen stores are sufficient or glucose supplies must be diverted to other uses [62]; it phosphorylates glycogen synthase, thereby suppressing the synthesis of glycogen. GSK3 β , like AMPK, is sensitive to cellular metabolic status and enforced wakefulness, and affects sleep. The phosphorylation of GSK3 β increases in synaptosomes during enforced wakefulness [63]. GSK3 β overexpression in mice disrupts the consolidation of NREMS [64]. The role of GSK3 β as a kinase extends beyond regulation of glycogen synthase into the realm of clock genes. It was first implicated in circadian rhythmicity through fruit fly studies. The *Drosophila* orthologue of GSK3 β phosphorylates the Clock protein TIMELESS, and overexpression of GSK3 β shortens circadian period in *Drosophila* [65]. Similar observations were subsequently made in studies on mammalian tissues [66]. Overexpression of GSK3 β shortens circadian period in cultured mammalian cells while pharmacological inhibition lengthens it. These effects of GSK3 β manipulations

on the clock may be mediated by phosphorylation of Period proteins; the same study demonstrated direct interactions of mammalian GSK3 β with Per2, GSK3 β -dependent phosphorylation of Per2 and GSK3 β -dependent nuclear entry of Per2 [66].

Peroxisome proliferator-activated receptors (PPARs): sensors of lipid metabolism

Fatty acids, like glucose derivatives, can fuel the production of ATP through the citric acid cycle. Lipids endogenous to the central nervous system are known regulators of sleep [67] and lipid species have been demonstrated to vary in cerebrospinal fluid in association with sleep loss [68, 69]. PPARs, a family of transcriptional regulatory nuclear receptors, are sensitive to the endogenous sleep-promoting lipids anandamide [70] and oleylethanolamide [71], and therefore, mediate transcriptional responses related to fatty acid metabolism [72]. Two members of the PPAR family of receptors, PPARs α and γ , share in common with the above described metabolic sensors the ability to influence both the circadian clock and sleep–wake cycles. Chronic administration of dietary bezafibrate, the antihyperlipidemic PPAR α agonist, increases NREMS SWA during the light phase in rodents [73]. This effect, which is phenomenologically similar to sleep deprivation, is compatible with a role for this transcriptional regulator in the sleep homeostat. However, the effect cannot be attributed to the brain with certainty as the treatment was systemic. The effects of PPAR α agonist administration on sleep might be mediated by changes in the circadian clock gene network. PPAR α binds to the *bmal1* promoter, and its binding is necessary for the circadian expression of *bmal1* in the rodent liver (though not in the suprachiasmatic nucleus). Fenofibrate, another PPAR α agonist, upregulates *clock* gene expression in vitro [74]. PPAR γ is also a positive regulator of *bmal1* transcription [75] and may contribute to the sleep/wake effects of PPAR agonists.

A missing link: how might a transcriptional feedback loop modulate neuronal excitability in association with sleep/wake states?

One missing link in this story is embodied by the question: are the effects of metabolic sensors on sleep/wake regulation mediated by their effects on circadian clock protein function, or by other means? If the effects are mediated by clock mechanisms, then how does a molecular feedback loop of the clock regulate neuronal excitability, the final common path of sleep regulation? We know from the data reviewed in this volume [76] and elsewhere [13] that spontaneous and experimentally induced genetic variations in circadian clock gene loci impact sleep homeostasis. However, the molecular and electrophysiological mechanisms by which the clock component proteins affect changes in sleep is a crucial gap in the current state of knowledge. The circadian clock, in its simplest most fundamental form, is a negative feedback loop consisting of a network of transcriptional regulatory proteins that regulate the transcription of their own genetic loci. Clock output pathways driven by the positive regulators of this feedback loop are a potential source of insight. Genetic disruption of the positive transcriptional components of the feedback loop present obvious circadian phenotypes, but additionally exhibit alterations in EEG measures associated with sleep homeostasis. Both NPAS2-deficient and Clock mutant mice exhibit

reduced time in NREMS. The sleep phenotype of *Bmal1*-deficient mice increased NREMS bout duration and EEG delta activity relative to controls is, on its face, opposite those of NPAS2-deficient and *Clock* mutant mice. This discrepancy might reflect the fact that *Clock* and NPAS2, unlike *Bmal1*, overlap functionally. Loss of functional *clock* alleles can be compensated by NPAS2 expression [77, 78], and vice versa, whereas there is no compensatory change (at least in terms of circadian behavior) in response to the loss of *bmal1*. Therefore, the sleep phenotypes associated with *Clock* and NPAS2 mutations represent perturbed transcriptional networks, whereas that of *bmal1* deficiency represents total disruption of the network.

So which clock outputs are relevant to sleep phenotypes? The fact that a significant portion of the genome is regulated by the circadian clock [79, 80] is at once a testament to the importance of this regulatory regime and a curse to those who seek a mechanistic link between the molecular clock components and sleep homeostasis. The identification of sleep regulatory loci extends beyond the core clock components to at least one transcriptional target of *Clock* and *Bmal1*, DEC2. A point mutation of the DEC2 gene identified in humans and subsequently engineered into mice confers reduced time asleep relative to the wild type allele [81]. Still, it will be a challenge to trace a path from these molecular events associated with the clock to the excitability of the cerebral cortex at the EEG level. Evidence that the clock can regulate neuronal excitability is rare but present. For instance, neuropeptide-induced *period1* expression drives an increase in the excitability of suprachiasmatic neurons in vitro [82] albeit through a still uncertain mechanism. Based on this observation, it can be hypothesized that clock genes regulate sleep state-specific changes in excitability in a cell-endogenous manner. The details of this regulatory path await characterization.

Synthesis and outlook

Sleep has long been posited to have a function in regulating brain metabolic status. Given the restorative effects on brain function that are attributed to sleep, there is considerable intellectual appeal to this line of reasoning. This review has described the evidence that metabolic indicators vary within the brain across sleep/wake cycles. It has identified metabolic sensors in the cell that mediate the effects of these indicators on cell function. It has described, for each such sensor, the evidence that the sensor affects sleep. Additionally, it has described the effects of these metabolic sensors on circadian clock protein function.

Segregation of enzymatic processes is necessary to prevent futile cycles of production and consumption and to generate the concentration gradients that build potential energy in the cell [62]. When spatial segregation is not possible, temporal segregation may suffice [83]. The transcriptional–translational loop that composes the circadian clock may have been adapted for this purpose in areas of the brain outside the SCN to enforce the temporal segregation of distinct metabolic processes into sleep and wake. It is a challenge to identify a cellular metabolic substrate for “sleep” if one defines sleep as a property of cell networks, which even the most reductionist models of sleep do [84, 85]. However, inasmuch as these network properties are influenced by metabolically responsive clock molecules, it should be possible to do so. The availability of tools to study cellular metabolic status in brain-derived tissues and in the brain itself with increasing temporal and spatial resolution (for example,

Refs. [34, 86, 87]) will continue to drive inquiries within this conceptual framework. These technological improvements can be coupled with the increasingly elegant genetic manipulations that characterize studies of clock gene function (for example, Refs. [88, 89]). From a biomarker discovery standpoint, the regulatory networks described in this review may contribute to the tremendous interindividual variability in sleep need in the general population. From a therapeutic standpoint, manipulating the response of the cell to energetic status through clock genes and sleep-related waveforms may provide novel therapeutic inroads in stroke and other conditions impacted by abnormalities in the processing of glycolytic fuels.

Abbreviations

NREMS	Nonrapid eye movement sleep
SWA	Slow wave activity
EEG	Electroencephalographic/electroencephalogram
ATP	Adenosine triphosphate
ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate-activated protein kinase
cry	Cryptochrome
per	Period
NAD	Nicotine adenine dinucleotide
HDAC	Histone deacetylase
PARP	Poly ADP-ribose polymerase
GSK3b	Glycogen synthase kinase 3b
PPARs	Peroxisome proliferator-activated receptors

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Fig. 1.

Proposed interrelationships of metabolic status, cellular metabolic sensors, transcriptional regulatory circadian clock genes, and the sleep–wake cycle. Intensive use of neuronal circuits during wakefulness poses a metabolic challenge that is manifested by changes in the relative concentrations of metabolic status indicators in the cell. Metabolic sensor proteins react to these changes by altering the concentrations or activities of transcriptional regulatory clock proteins. Changes in transcriptional regulatory clock protein levels or their functional activities alter the propensity for sleep. Sleep alters the metabolic status of the cell in a manner that reverses the metabolic challenge posed by wakefulness.