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Circadian Blueprint of Metabolic Pathways in the Brain

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Abstract

The circadian clock is an endogenous, time-tracking system that directs multiple metabolic and physiological functions required for homeostasis. The master or "central" clock located within the suprachiasmatic nucleus (SCN) in the hypothalamus governs peripheral clocks present in all systemic tissues, contributing to their alignment and ultimately to temporal coordination of physiology. Accumulating evidence reveals the presence of additional clocks in the brain and suggests the possibility that circadian circuits may feedback to these from the periphery. Here, we highlight recent advances on the communications between clocks and discuss how they relate to circadian physiology and metabolism.

Graphical Abstract

In addition to the central pacemaker, the mammalian brain contains additional circadian clocks whose function illustrates how systemic homeostasis relies on the coordinated communication between clocks.

Circadian rhythms govern an extensive variety of behavioral, physiological and metabolic functions in virtually all life forms, from bacteria to plants, invertebrates and mammals. These rhythms are largely controlled by the circadian clock, a molecular machinery operating in all cells (Figure 1). The organization of the mammalian circadian clock is based on transcriptional-translational feedback loops. Central to the core clock are the transcription factors CLOCK and BMAL1, which heterodimerize and drive the expression of a large number of clock-controlled genes (CCGs) by binding to E-boxes, the most common promoter element on the genome. Because of this, the molecular clock directs the expression of an estimated 10-15 % genes in all organs and tissues[1, 2]. Importantly, through the interplay between the clock and tissue-specific transcriptional pathways, the overlap of CCGs in each organ is relatively small, underscoring the concept that a very large fraction of the genome has the potential of being regulated in a circadian manner[3]. Among the CCGs there are the genes encoding the repressors period (PER) and cryptochrome (CRY) whose accumulation results in inhibition of CLOCK:BMAL1-driven transcription. PER and CRY repressors are subsequently degraded through clock-dedicated proteasome circuits, leading to new transcription cycles. In addition to this central circuit, the orphan nuclear receptors

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Competing Interests

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ROR and REV-ERB contribute to the clock mechanism by generating an additional regulatory loop. Finally, a variety of signaling pathways influence core clock regulators by inducing several post-translational modifications that ultimately lead to changes in clock control[4].

The exquisite control of circadian gene expression by the clock is associated to chromatin remodeling. The very first observation of circadian chromatin transitions illustrated that H3-Ser10 phosphorylation occurs in SCN neurons in response to a light stimulus and is linked to the activation of clock genes[5]. Subsequently, a number of chromatin remodelers have been found to display circadian activity[6]. Among the chromatin remodelers involved in circadian control, the nicotinamide adenine dinucleotide (NAD^+)-dependent SIRT1 deacetylase deserves special mention. Indeed, SIRT1 and other members of the so-called 'sirtuin' family provide a relevant molecular link between metabolism, epigenetics and the circadian clock[7].

Virtually every tissue in our body harbors a functional molecular clock and coordination among clocks is crucial for optimal timekeeping and physiology. Here, we discuss the relationship between circadian clocks and metabolic homeostasis. First we describe some evidence on newly discovered brain clock functions and their implication for circadian physiology. We then examine the complex network of output and feedback signals that couples brain clocks to the peripheral metabolic framework. We conclude by discussing the current understanding of how nutrition affects circadian physiology and how this relates to brain functions.

Clocks in the brain

Mechanisms of SCN entrainment

The mammalian circadian system is a hierarchical network of oscillators, where the master or "central" clock is in the suprachiasmatic nuclei (SCN) of the hypothalamus that receives photic information via the retino-hypothalamic tract. The central clock connects with peripheral clocks present in all systemic tissues, contributing to their coordinated functions. The combination of this interplay and environmental cues ensures temporally coordinated physiology. The SCN comprises about 20,000 interconnected neurons capable of generating diurnal rhythms in neuronal activity, which persist in the absence of external timing cues. The SCN is sub-divided into two main nuclei, the "core" and "shell", diverse for neuronal projections, expression of neuronal peptides and activation in response to light. "Core" and "shell" neurons form circuits that are coupled via firing of action potentials and release of neuropeptides. Well-characterized SCN neuropeptides are vasoactive intestinal polypeptide (VIP) synthesized by ventrolateral "core" neurons and arginine vasopressin (AVP) released from neurons in the dorsal "shell"[8, 9]. Signaling of both VIP and AVP is critical for establishing and synchronizing firing as well as behavioral rhythms[10–13].

A feature of the central circadian system is its heterogeneity. Transcriptional analysis of single-cell SCN neurons highlighted the complexity of the signaling network underlying synchronization of the master clock[14]. Hence, in addition to the known coupling mechanism within the SCN, numerous others are likely to help regulate circadian period. In this respect, astrocytes, which make up a substantial fraction of the cells in the SCN, are responsible for a

variety of functions within the CNS. Astrocytes provide energy supply through glucose/glycogen pathways[15], regulating neurovascular coupling via release of vasoactive molecules[16] and playing an active role in synaptic transmission by actively releasing synaptically active molecules including glutamate, ATP and GABA[17]. Rat astrocytes display rhythmic expression of clock genes[18, 19] as well as cyclic ATP release in culture[20], indicating that astrocytes indeed have a functional clock. Moreover, pharmacological inhibitors of glial activity affect rhythms of SCN neuronal firing and of diurnal behavioral rhythms[21], thereby suggesting that glial cells could play a role as synchronizers of circadian networks within the SCN. In support of this notion, several animal models have proven the importance of SCN astrocytes for rhythmic entrainment and circadian physiology[22–24]. The behavioral phenotypes highlighted by these studies denote the importance of reciprocal interactions between glial and neuronal cells in the context of circadian circuitry. Indeed, in *vitro* co-culture experiments showed that synchronous astrocytes are able to entrain rhythmicity in neurons with a mechanism that is mediated by GABA (γ-aminobutyric acid) and GABAA receptor signaling[22]. GABA is the most abundant neurotransmitter in the SCN, where it acts as a primary synchronizing signal[25] and is able to communicate phase information to distinct SCN populations[26]. Astrocytes also express GABA transporters and receptors and activation of both results in increased intracellular Ca^{2+} concentration[27, 28], a marker of metabolic activation associated with the release of various gliotransmitters, including glutamate[29]. Notably SCN astrocytic intracellular Ca^{2+} levels rise during the circadian night displaying an oscillatory pattern that is anti-phasic with that of SCN neurons. Astrocyte Ca^{2+} oscillation is coupled with release of high levels of glutamate into the extracellular space which leads to inhibition of SCN neuronal activity through pre-synaptic activation of GABAergic neurons[23].

Another fundamental feature of astrocytes is to supply metabolic substrates to neurons through the proposed “astrocyte to neuron lactate shuttle” (ANLS) mechanisms[30]. Glucose consumption in the SCN is rhythmic[31] and brain lactate concentrations show daily variations peaking during the active phase[32], possibly suggesting the existence of a rhythmic “neurometabolic coupling” mechanism among astrocytes and neurons throughout the SCN (Figure 2). Moreover, given that glutamate is a key mediator of astrocyte time keeping[23], it is worthy to note that glutamate uptake by astrocytes can trigger a cascade of events ultimately leading to production and release of lactate into the extracellular space[15]. Further underlying the link between astrocyte glutamate metabolism and circadian physiology, the astrocytic glutamate transporter EAAT1 displays rhythmic expression in the SCN that is deregulated in *Per2* mutant mice[33]. Importantly, astrocyte lactate trafficking is crucial for the activity of orexin neurons and for the regulation of sleep-wake cycles[34]. Thus, it is tempting to speculate that lactate shuttling may also be involved in promoting SCN neuronal firing and circadian pacemaking.

Clocks in other hypothalamic nuclei

In addition to the SCN, the hypothalamus is subdivided into several interconnected nuclei, which include the dorsomedial nucleus of the hypothalamus (DMH), ventromedial nucleus of the hypothalamus (VMH), arcuate nucleus (ARC) and paraventricular nucleus of the hypothalamus (PVH). These nuclei control numerous physiological processes that display

diurnal rhythmicity, including sleep-wake cycles, energy expenditure, thermoregulation, glucose and lipid metabolism, and feeding behavior[35]. In addition to receiving projections from the SCN, extra-SCN hypothalamic sites harbor their own circadian oscillator capable of sustaining autonomous circadian rhythms[36]. Although the functional significance of these non-SCN brain clocks remains elusive it is thought that they play a central role in gating some behavioral and physiological processes during the 24 hours, acting in synchrony or independently from the master clock (Figure 3).

Both ARC and DMH are critical in governing feeding behavior[37] and most likely act in synchrony with the SCN to generate feeding rhythms. Circadian activity of α-MSH neurons in the ARC is controlled by the SCN[38] and, vice versa ventromedial ARC neurons convey feeding related signals to the SCN[39]. In the ARC orexigenic and anorexigenic peptides neuropeptide Y (*Npy*), agouti-related peptide (*Agrp*), pro-opiomelanocortin (*Pomc*) as well as cocaine and amphetamine regulated transcript (*Cart*) are expressed in a diurnal manner[40, 41]. Notably, targeted disruption of NPY signaling in the ARC leads to profound effects on daily patterns of activity and feeding[4243]. In the DMH NPY is important for the maintenance of energy homeostasis through a mechanism that involves both food intake and energy expenditure modulation[44]. Additionally, NPY regulates rhythmic expression of a subset of genes in the liver[45]. Yet, it is unclear whether the observed changes in cyclic gene expression are driven by central or peripheral NPY signaling. Further studies may help clarify whether this neuropeptide may play a key role in coupling central and peripheral clocks.

While a direct link between rhythmic expression of these neuropeptides and the molecular clock has not been proven, targeted genetic alteration of clock core genes generates animals with disrupted circadian rhythms, characterized by alteration in feeding behavior as well as energy homeostasis (Table 1). CLOCK mutant mice are hyperphagic and display significant increased food intake during the day, which is coupled with decreased expression of orexigenic transcripts in the hypothalamus[46]. Likewise, global loss or mutation of other core clock components, including *Bmal1*, *Per1*, *Per2* and *Cry1/2*, leads to disruption in feeding behavior[47–52]. Moreover, central clocks are not solely implicated in rhythmic feeding behavior regulation, but appear to be involved in the control of energy expenditure as well. For example, mice with ablation of either *Rev-erbα* or *Per2* genes display a faulty thermogenic response due to impaired activity of brown adipose tissue (BAT)[53, 54]. These mice mutants carry the ablation of the circadian gene in all cells, thereby being unable to distinguish between peripheral or centrally controlled regulatory mechanisms. While this type of genetic models of clock disruption have been instrumental for the understanding of circadian physiology, a major limitation stands in their inability to characterize distinct functions of the clock in specific areas of the brain. In the case of *Rev-erbα,* brain specific deletion results in constant elevated body temperature[55], suggesting that REV-ERBα may be instrumental for central regulation of circadian energy balance.

The strategy of ablating clock function uniquely in specific neuronal populations has remarkable potential to unravel specialized circadian circuits. Indeed, a targeted approach to delete *Bmal1* specifically in Sf1-neurons of the hypothalamic VMH led to the discovery of an unrecognized function of the hypothalamic clock in regulating circadian energy

expenditure[56]. This finding most likely relates to the well-known diurnal oscillations in body temperature[57], though it remains unclear how this rhythmicity is achieved. Activity of the BAT, the main thermogenic organ, is under the control of a central neuronal circuitry that resides in several hypothalamic nuclei[58]. While the existence of a SCN-SNS (Sympathetic nervous system)-BAT circuitry implicated in rhythmic body temperature control has been suggested[59], coordinated activity between the SCN and ARC has been shown to be critical for BAT thermogenesis[60]. In this respect, the consequences of ablating *Bmal1* in the VMH represent a demonstration that a specialized, SCN-independent hypothalamic clock orchestrates diurnal energy expenditure and thermogenesis[56]. Given the intimate relationship between the VMH and glucose/insulin homeostasis[61], it is tempting to speculate that the clock within the VMH could be also involved in generating daily rhythms in glucose levels and/or tolerance and integrate these with thermogenesis.

Clocks intrinsic to other hypothalamic nuclei are likely to contribute to various aspects of circadian physiology. For example, a recent study highlighted the importance of the enzyme O-GlcNAc transferase (OGT) in the PVN for feeding behavior regulation[62]. In peripheral tissues OGT rhythmically O-GlcNAlates and stabilizes BMAL1 and CLOCK, ultimately affecting circadian oscillations[63]. Thus, OGT could act as nutritional sensor conveying information to the clock machinery in the CNS and thereby play a role in circadian regulation of energy balance and feeding behavior.

Further studies aimed at deciphering the relative roles of extra-SCN hypothalamic clocks with appropriate genetic models will be critical to unravel the relationship between circadian rhythms and metabolic homeostasis.

Metabolic coupling of central and peripheral clocks

As illustrated above, the central clock within the SCN appears to operate within a network of hypothalamic oscillators to orchestrate many aspects of physiology and behavior. Several pathways governing cellular and systemic metabolism are intimately interconnected to the circadian system[64, 65]. Indeed, optimal timing of diurnal metabolic processes is obtained via tight control of central output signals, whereas peripheral cellular metabolism is suspected to feedback to the hypothalamus[66].

SCN output to peripheral clocks

Together with the autonomic nervous system, endocrine signals are key mediators of rhythmic physiology. The first clue suggesting that SCN output signals may operate through paracrine endocrine signaling was obtained by transplanting SCN grafts into animals lacking a central pacemaker[67–69]. Subsequently, parabiosis experiments between SNC-lesioned and intact animals further confirmed that circulating factors could drive rhythms in peripheral tissues[70]. These findings are in keeping with the notion that secretion of several endocrine factors is diurnal and driven by the central clock[71]. One of the best examples is the release of cortisol from the hypothalamic-pituitary-adrenal (HPA) axis. In fact, under normal physiological conditions blood glucocorticoid levels oscillate as a result of endogenous clock function[72]. The central clock in the SCN regulates HPA rhythms via two main mechanisms: projections from the SCN to the paraventricular nucleus (PVN) drive rhythmic

secretion of adrenocorticotropin hormone (ACTH)[73], which in turn regulates circadian release of corticoids from the adrenal cortex; additionally, the SCN is connected to the adrenal gland via the autonomous nervous system (ANS), enabling the central clock to modulate adrenal sensitivity to ACTH, as well as light-induced adrenal activation[74, 75]. Additionally, circadian production of glucocorticoid is gated through the peripheral adrenal clock[76–78]. Glucocorticoids play a central role in energy balance and have been implicated in circadian metabolic control because of their ability to entrain peripheral clocks[78–81]. In the liver, glucocorticoids synchronize circadian expression by directly activating clock genes via glucocorticoid response elements (GRE) present in their regulatory regions[80]. Moreover, glucocorticoids can activate BAT thermogenesis in humans[82] and a recent study determined that human BAT activity is rhythmic[83]. Interestingly, the peak of thermogenic activity in BAT is in phase with the secretion of cortisol, suggesting that glucocorticoids might play a role in driving rhythmic body temperature. Peripheral oscillators are extremely sensitive to temperature changes; hence temperature cycles can also function as output entraining signals for peripheral clocks[84–86]. Accordingly, temperature increase triggers heat shock factor 1 (HSF1) mediated transcription of the *Per2* gene by binding to a HSE site within its promoter[87]. Conversely, low temperatures induce expression of the RNA binding protein CIRBP, which post-transcriptionally regulates CLOCK and possibly *Rorα* and *Per3*[88].

Central coordination of peripheral metabolism is also obtained through secretion of the sleep-promoting hormone melatonin. Melatonin is released by the pineal gland throughout the day-night cycle under tight control of the SCN[89]. Underlying the ability of melatonin to entrain peripheral rhythms, melatonin receptors are expressed in several peripheral tissues[90] and rhythmic exposure of cultured adipocytes to melatonin is sufficient to synchronize the expression of clock genes[91]. In pancreatic beta cells melatonin regulates insulin secretion by reducing cytosolic cAMP and cGMP levels, thus directly influencing diurnal glucose and insulin blood levels[92–94]. Accordingly, pinealectomized animals loose diurnal rhythmicity of insulin secretion and glucose tolerance[95, 96]. More recently, human mutations in the melatonin receptor 1b gene *MTNR1B* have been identified. Subjects with the *MTNR1B* variant have hyper activation of melatonin signaling, resulting in impaired insulin release, hyperglycemia and increased risk to develop type 2 diabetes (T2D)[97].

Together these findings demonstrate that the SCN relies on a variety of output signals to synchronize peripheral clocks and contributes to a large network of oscillators working together to drive circadian physiology.

Daily rhythms in glucose metabolism

Many aspects of glucose homeostasis are circadian: first, glucose plasma levels are rhythmic both in rodents and humans[98]; also, it is well established that glucose uptake into the brain follows a circadian rhythm[31]; lastly, glucose tolerance displays daily variations[99]. Supporting the notion that the central clock drives circadian plasma glucose metabolism, SCN-lesioned mice display no rhythm in glucose nor insulin levels[100]. Importantly, peak of plasma glucose levels at the onset of the active period is detected even when mice receive 6 meals per day every 4 hours[101], indicating that glucose oscillations are driven by the central clock and are thereby independent from feeding rhythms.

Nevertheless, diurnal glucose homeostasis involves not only the central clock but also peripheral clocks in liver, pancreas, muscle and adipose tissue. Via the gluconeogenic pathway, the liver is the main source of endogenous glucose, and is thus the most plausible candidate for diurnal glucose control. Loss of hepatic circadian rhythms by liver-specific ablation of *Bmal1* causes severe hypoglycemia during the active phase, suggesting that the liver clock is necessary for diurnal glucose homeostasis[102]. Moreover, hypothalamic clocks signal to the liver through the sympathetic and parasympathetic nervous system[103, 104]. It has been demonstrated that central administration of the GABAA receptor antagonist bicuculline induces activation of hypothalamic orexin neurons, which in turn triggers hepatic glucose production[105]. Orexins are critical modulators of the sleep/wake cycle as well as of energy and glucose metabolism[106] and are thus thought to operating by connecting the clock and glucose rhythmicity. In fact, by signaling to orexin neurons in the perifornical area (PF) via the DMH, the SCN controls rhythmic release of orexin[107, 108]. Notably, levels of orexin in the cerebrospinal fluid (CSF) peak at the onset of the active phase[109] alongside increase in hepatic glucose production. Recent evidence further supports the essential nature of the orexin system for glucose plasma rhythms: intracerebroventricular delivery of orexin modulates plasma glucose levels in a time-dependent manner by affecting cyclic hepatic gluconeogenesis[110]. Additionally, orexin-null mice, while maintaining a normal feeding behavior, completely loose daily rhythms in glucose levels[110]. In keeping with this observation, narcoleptic patients are characterized by a total lack of the orexin system[111] and show features of metabolic syndrome including impaired glucose tolerance and obesity[112, 113].

Metabolic feedback from peripheral tissues to the central clock

As discussed above, the SCN coordinates a wide array of physiological and metabolic processes, including feeding behavior. By driving 24-h feeding rhythms, the central clock regulates the nutritional status of peripheral organs. In turn, feeding schedule can function as potent timing cue for peripheral clocks, modulating local metabolism and signaling. Because the clock needs to continuously adjust to external stimuli to maintain correct timing of circadian physiology, it needs to rely on and integrate feedback signals from peripheral clocks. Indeed, it is thought that autonomous rhythms of the SCN are fortified and enhanced through central and peripheral feedback mechanisms **(**Figure 4**)**.

How peripheral metabolic signals may be conveyed to the central clock? The hypothalamus serves as the principal relay center for metabolic feedback from the periphery. AMP-activated protein kinase (AMPK) is an essential cellular energy sensor and within the hypothalamus AMPK is involved in regulating whole-body energy status[114]. Moreover, hypothalamic activity of AMPK is responsive to feeding-fasting cycles[115]. In the arcuate hypothalamic nucleus (ARC), AMPK activity is inhibited by leptin[115], an anorexigenic hormone whose levels display diurnal variations[116] and whose rhythms are governed by the clock in the adipose tissue[117]. More importantly, the central clock in the SCN finely tunes sensitivity of ARC neurons to circulating leptin[117]. Additionally to leptin another adipokine, namely adiponectin, exhibits diurnal rhythms in WAT and serum and is controlled in a circadian manner in adipose tissue[118, 119]. Via its receptor AdipoR1 expressed in the ARC, adiponectin is also able to elicit central effects that are similar but opposite to those induced

by leptin. In fact, in the hypothalamus adiponectin activates AMPK and this activation is associated with increased food intake and suppressed energy expenditure[120]. The opposite nature of these two adipokines argues for a complementary role of leptin and adiponectin in driving rhythmic activation of AMPK. Accordingly, kinase activity of AMPK is robustly rhythmic in the hypothalamus[121] as well as in the liver where it phosphorylates and triggers degradation of CRY1[122]. Activation of AMPK may be then conveyed to the SCN via neuronal projections from the ARC, which constitute the main communication route of metabolic information to the central clock[39]. Thus, a leptin/adiponectin/AMPK axis may signal metabolic feedback cues to the SCN via the ARC. In support of this scenario, targeted deletion of AMPK, as well as adiponectin and leptin receptor expressing neurons in the ARC, lead to profound disruption of feeding behavior[42, 115, 120, 121]. Additionally, AMPK regulates the mammalian-target-of-rapamycin (mTOR) pathway, which is a major nutrient sensing pathway that displays rhythmic activity in several tissues, including the SCN[123]. Notably, work in fruit flies[124] and in mammals[125] illustrates that manipulation of TOR/mTOR signaling directly affects the endogenous clock in the SCN, thereby linking nutrient sensing mechanisms to circadian timekeeping.

Another metabolic sensor capable of conveying metabolic inputs to the SCN is SIRT1. In peripheral tissues SIRT1 influences several metabolic processes by deacetylating key metabolic factors including proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), peroxisome proliferators activated receptor (PPAR)-γ and forkhead box O1 (FOXO1)[126]. SIRT1 also deacetylates the core clock proteins BMAL1 and PER2 and is thus intimately coupled to circadian regulation[127, 128]. This coupling is further strengthened by the fact that sirtuins use the cellular metabolite nicotinamide adenine dinucleotide (NAD^+) as a cofactor, the levels of which oscillate and consequently define cyclic activity of SIRT1[129, 130]. SIRT1 is highly expressed in several hypothalamic nuclei where it plays a key role in energy homeostasis. In POMC neurons, SIRT1 is required for long-term control of body weight balance[131] and in the ARC it regulates feeding behavior as well as body weight[132]. In support of a role of SIRT1 as a metabolic sensor communicating the nutritional status to the endogenous clock, SIRT1 expressed in the VMH has been shown to be crucial for the adaptation of the central clock to feeding cues[133]. This concept is further corroborated by the fact that hypothalamic SIRT1 is induced by fasting[134], suggesting that activity of this deacetylase changes as a consequence of feeding-fasting cycles. Peripheral activity of SIRT1 may also modulate circadian function in the brain. Indeed, a study reports that SIRT1 controls the secretion of extracellular NAMPT (eNAMPT) from the adipose tissue into the circulation. Circulating eNAMPT appears to maintain NAD^+ levels in the hypothalamus and adipose tissue-specific deletion of eNAMPT has profound effects on hypothalamic function. In line with the rhythmic activity of SIRT1, circulating levels of eNAMPT seem to display diurnal oscillation in mice[135] and may thus affect rhythmic levels of NAD^+ in the hypothalamus.

Feeding-fasting cycles can additionally modulate the levels of other metabolic regulators associated to the circadian system. Importantly, fasting rapidly increases the circulating levels of fibroblast growth factor 21 (FGF21), a metabolic regulator produced in the liver under the control of PPARα and that plays an central role in the adaptation to fasting[136, 137]. However, it is yet unclear whether hepatic expression and circulating concentrations of

Fgf21 are rhythmic. A study reported that *Fgf21* expression is circadian in the liver, peaking during the fasting phase and under direct control of the circadian machinery[138]. However, transactivation of *Fgf21* by BMAL1/CLOCK was not confirmed by an independent study[139] and serum levels of FGF21 are relatively stable under normal feeding regimens[137], displaying a 24-h oscillatory pattern only following prolonged fasting[140, 141]. Nevertheless, FGF21 is able to modulate directly the central clock by activating β-Klotho signaling in the SCN. This activation induces reduction of insulin levels, increase of systemic corticosterone and changes in locomotor activity[142]. Therefore, FGF21 signaling appears to be critical for the central clock to detect and consequently gate adaptive responses to nutritional states.

Overall, how the SCN responds to peripheral metabolic signals remains ill-defined and needs further investigation. Nonetheless, experimental indications argue for a system where the SCN is reciprocally connected to other biological clocks via a complex network of output and feedback signals. These reciprocal interactions seem to be crucial for maintaining circadian rhythmicity and metabolic homeostasis. Misalignement and consequent loss of synchrony has pronounced consequences on health[143].

Food and biological clocks

Food acts as a potent synchronizer for peripheral clocks. Restricting food access to rodents exclusively during the day shifts the phase of circadian gene expression within peripheral tissues, whereas the SCN remains entrained to the light-dark cycle[144]. Consequently, changes in feeding habits may lead to the uncoupling of peripheral tissues from the master clock, possibly causing metabolic alterations[145]. These metabolic perturbations are similar to those occurring in shift workers who are subjected to abnormal eating schedules and have a misalignment of the sleep/wake and feeding/fasting cycles to the light-dark cycle. Importantly, mounting data indicates that misalignment of the internal clocks can have negative effects on health and possibly contribute to the development of a variety of pathologies, including neurodegerative disorders.

Feeding time

Numerous evidences from mouse studies highlight the importance of feeding time for peripheral rhythmicity and metabolic fitness[64] (Table 2). Mice receiving a high fat diet (HFD) display blunted rhythms in feeding behavior consuming the majority of food intake during the rest period. Changes in feeding behavior occur before the increase in body weight, arguing that circadian disruption is a key factor in the development of obesity and metabolic disease[146]. Accordingly, CLOCK mutant mice also exhibit increased food consumption during the day and have a larger predisposition to develop metabolic syndrome[46]. Rescue of CLOCK in the liver of mutant mice restores hepatic circadian rhythms as well as diurnal feeding rhythms and reduces their sensitivity to HFD[147]. Imposing a feeding rhythm to *Cry1*/*Cry2*-deficient mice by restricting food access exclusively to the night is sufficient to rescue hepatic transcriptional rhythms[148]. Similarly, *Per1*^{S714G} mutated mice that exhibit altered feeding patterns and increased sensitivity to obesity, greatly benefit from restricting food access to nighttime[52]. Indeed restoring feeding/fasting rhythms with light/dark cycle has many metabolic benefits. In mice fed a HFD, time-

restricted feeding (TRF) completely prevents and reverts the adverse metabolic effects of HFD even though the mice consume equivalent levels of calories[149, 150]. Further consolidating the implications of feeding time on metabolic fitness, 30% caloric restriction ad libitum has different outcomes on body weight depending on if the diet is consumed in the day-time or night, with the latter being associated with reduced body weight [151].

Recent evidence translates the murine observations on restricted feeding and circadian synchrony to humans. A 13-day laboratory protocol explored the effects of meal timing on human physiological rhythms. In this study, delaying mealtime by 5 hours did not affect daily rhythms of plasma melatonin and cortisol, indicating that the SCN was not affected. However, the authors were able to observe significant changes in the phase of plasma glucose rhythms as well as a 1-hour delay of *Per2* expression in WAT[152]. Results from this study thus provide convincing evidence that meal timing can affect diurnal rhythms in peripheral tissues uncoupling them from the central clock in human subjects. In another study, the eating pattern of healthy adults was monitored and correlated with metabolic parameters such as caloric intake and BMI. Whereas there was no correlation between daily eating duration and BMI, restricting the eating interval from about 14 hours to 10 hours over 16 weeks led to a reduction in body weight as well as BMI[153]. Therefore, adjusting daily behavior favoring alignment of activity, food intake and light exposure can support beneficial outcomes on metabolic homeostasis.

Food composition

Besides to the time of feeding also the quality and quantity of food we consume can affect our circadian and metabolic physiology. There are a number of studies delineating how food composition can affect and rewire the molecular clock. We will provide a brief summary on how these nutritional regimens reprogram circadian biology.

High-fat diet—An early study had shown that feeding mice HFD ad libitum altered both the behavior as well as the expression of clock genes in peripheral tissues[146]. It has been shown that excessive caloric intake can affect the SCN leading to a disrupted response to light[154], though it is yet unclear how nutritional cues affect the central clock. Remarkably, HFD rewires circadian metabolism in several tissues, including the medial prefontal cortex (mPFC) and the SCN in the brain[155]. In the liver HFD generates a widespread remodeling of the hepatic circadian clock, leading to profound reprogramming of specific metabolic pathways. Specifically HFD affects the liver circadian transcriptome and metabolome in three ways: abolition of previously oscillating transcripts and metabolites, shift in phase of metabolites that oscillated in both feeding conditions and induction of newly oscillating transcripts and metabolites. Mechanistically, HFD causes the impairment of CLOCK-BMAL1 chromatin recruitment at CCGs promoters, and induces de novo oscillation of surrogate transcriptional pathways, such for example the regulator PPARγ[156]. In the CNS activation of PPARγ is linked to energy balance regulation and contributes to the hyperphagic phenotype observed in animals fed HFD[157]. Interestingly the PPARγ ligand arachidonate is strongly increased in the serum of HFD-fed animals[158]; continuous activation of central PPARγ could explain why mice fed a HFD display dampening of their feeding rhythms.

Calorie restriction—Calorie restriction (CR) is best known for its beneficial effects on aging and lifespan. While aging in associated with changes in circadian physiology, how the aging process affects circadian rhythms remains poorly understood. Given that CR is able to reverse aging-associated homeostatic decay, it is a potent tool to try to dissect molecular mechanism occurring during aging and lifespan extension. This is exemplified by two studies that employed CR to investigate how aging influences circadian rhythms in peripheral tissues[159, 160]. Aging was associated with a tissue-specific rewiring of circadian function, mainly involving DNA repair mechanisms in adult stem cells[160] and protein deubiquitination and cell-cycle biological processes in the liver[159], whereas the expression of core clock genes remained unchanged in all the examined cell types. Moreover, the authors found that CR generated a widespread reprogramming of circadian transcription and that a portion of the reprogrammed genes overlapped with those oscillating in young mice. In the liver, CR exerted most of its action on NAD^+ metabolism and global protein acetylation. Decline in total NAD^+ levels is a common feature of aging and has been observed in peripheral tissues[161] as well as in the brain[162]. Stressing the relationship between NAD^+ and aging is the observation that supplementation with precursors that replenish the NAD pool can restore and reverse some aspects of age-associated decay[163].

Most of the aspects of CR are mediated by the sirtuins. Accordingly, many hepatic genes regulated by CR overlapped with SIRT1 target genes, suggesting that the CR-mediated circadian rewiring may go through SIRT1[159]. Additionally to its role in regulating circadian physiology in peripheral tissues[164], SIRT1 has also been implicated in circadian control in the SCN where it acetylates and consequently regulates the activity of BMAL1[165]. Aged mice show a decline of the levels of SIRT1 in the SCN that is associated with an impaired adaptation to a “jet lag” paradigm. This phenotype is rescued in mice with brain-targeted overexpression of SIRT1[164]. It would thus be of interest to explore the outcomes of CR on the central clock and SIRT1 activity in the SCN. One would predict that CR might modulate NAD metabolism also in the CNS, leading to activation of SIRT1 and improved entrainment fitness of the SCN. Intriguingly, a report suggests that CR may affect the temporal organization of the SCN and its response to light[166]. Moreover, CR was recently shown to generate a self-imposed temporal restriction of food intake as well as changes in locomotor activity[151].

Ketogenic Diet—Ketogenic diet (KD) consists in a low carbohydrate and high-fat diet that induces endogenous ketogenesis. KD stimulates a metabolic response similar to that induced by fasting and calorie restriction: dependence on fatty acids and production of ketone bodies, which are used as an energy source by the brain and other tissues.

Ketone bodies can be sensed by the hypothalamus and stimulate food intake by inducing the expression of hypothalamic orexigenic neuropeptides[167]. Interestingly, ketone bodies released from the liver seem to be required for daily food anticipation via feedback to the hypothalamus[168]. Additionally, βOHB can modulate phase and amplitude of clock genes in the brain[169].

Notably, ketone bodies are not only a source of energy, but can also have a role as epigenetic regulators. Specifically, β-hydroxyl-butyrate (βOHB) operates as an endogenous inhibitor of

HDACs[170], linking its changing levels to the degree of histone acetylation. Moreover, KD can modulate circadian oscillations in peripheral tissues via a βOHB-driven chromatin remodeling mechanism[171]. Indeed, robust serum βOHB oscillation induces rhythmic histone acetylation in the gut by inhibiting HDAC activity[171]. It is interesting to note that βOHB not only influences protein acetylation, but it also may function as a cofactor for another histone modification associated with transcriptional activation, namely β-hydroxyl-butyrylation. This newly discovered histone modification is induced upon fasting and it has been shown to mark several clock genes in the liver[172].

KD is used in children to treat recurrent epilepsy. Recent evidences suggest that it could be additionally used as a therapeutic strategy for neuronal pathologies characterized by abnormal energy utilization, including neurodegenerative disorders like Alzheimer and Parkinson disease[173]. Accordingly, feeding mice KD for a long period of time improves memory in aged mice[174]. Of note, the presence of a functional circadian oscillator in the hippocampus, argues for a role of the clock in neuronal plasticity and memory formation[175]. This is further underscored by the fact that uncoupling of SCN oscillators leads to memory processing impairment[22, 176]. Whether health-promoting effects of KD in the brain are linked to central clock mechanisms remains to be elucidated.

Altogether, feeding regimens powerfully influence rhythmic transcription by enhancing and disrupting oscillations, or even by inducing *de novo* oscillations of otherwise non-cyclic genes. Yet, the specific contribution of the molecular clock to these processes is not fully elucidated. Two independent studies carried out in *Drosophila melanogaster* investigated whether the beneficial effects of TRF[177] and dietary restriction (DR)[178] on aging are dependent on a functional endogenous oscillator. Notably, flies carrying mutations for clock components showed attenuated responses to both dietary interventions, arguing that in *Drosophila* a functional clock is required for optimal response to feeding cues. Experiments in the mouse show that food-driven rhythmic gene under TRF seems to be in large part independent of a functional clock[148]. Additionally, a functional clock cannot generate rhythmic expression of nutrient responsive genes in the absence of nutritional cues[148]. Importantly, in the absence of a functional clock, TRF is not able to restore completely oscillation and amplitude of food-driven transcripts and KD-mediated circadian reprogramming of a subset of genes is blunted[171]. Thus, the endogenous clock is able to integrate nutritional cues. Therefore, food-driven circadian rewiring is likely to be mediated by both clock-independent metabolic regulators and the molecular clock, suggesting that adaptation to nutritional challenges involves the synergy of the two. Further investigations carried out on clock mutant animals and under free-running conditions are thus warranted to shed light on the reciprocal interaction between nutrition and endogenous clocks.

Conclusions and future directions

The past two decades have witnessed extensive advances in characterizing the molecular mechanisms of circadian clocks. While the connections between the clock and cellular metabolism have revealed some conceptually novel leads[65, 179], the comprehension of how peripheral clocks connect to the brain and neuronal metabolism remains limited. In addition, the presence of several extra-SCN brain oscillators begs the question of how these connect to

the SCN and possibly with the periphery. Recent technological advances have allowed editing circadian regulators in specific brain areas and cell types thus helping the identification of novel circadian circuits. In light of these recent discoveries, important questions need to be addressed: how are brain clocks aligned for proper cyclic function? Are these brain clocks operating in concert to convey messages to the periphery? How does this network of brain clocks respond to extrinsic inputs such as metabolic signals, drugs and food? We have highlighted a number of potential links coupling central brain clocks to metabolic signaling pathways. Studies aimed at investigating how brain clocks adapt to environmental cues will provide further insights on how this complex network operates. High-throughput approaches will again prove valuable to dissect the specificity, plasticity and communications between clocks.

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Glossary

Promoter element:
proximal DNA regulatory element immediately upstream of the transcription start site (TSS)

Chromatin transitions:
Promoter elements are governed by specific epigenetic modifications that can shift from an “active” accessible state to a “repressed” state and vice versa.

Oscillator:
timing system composed of transcriptional and translational feedback loops with an endogenous periodicity of approximately 24 hours

Hyperphagic:
abnormal increase of food consumption

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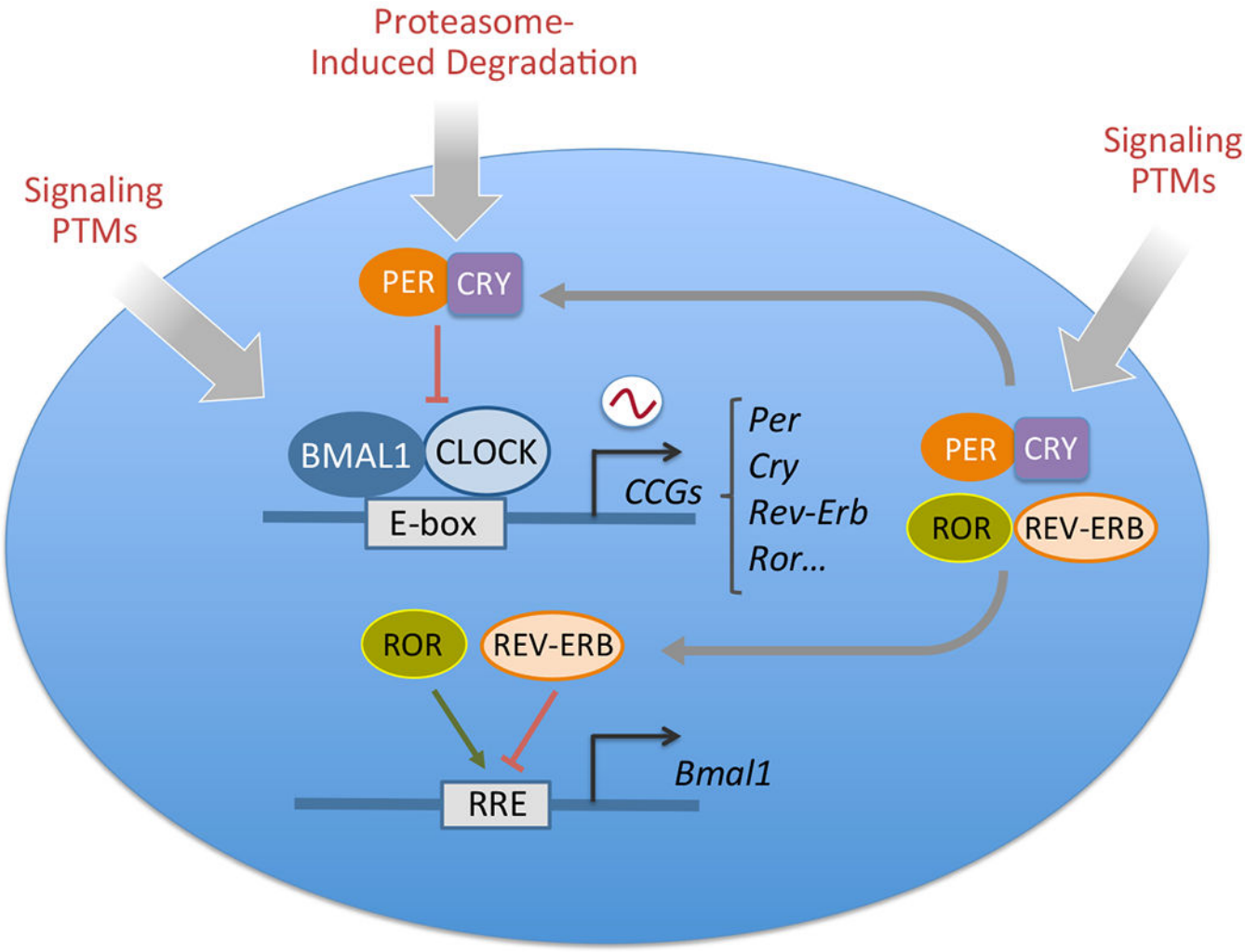

Figure1: Molecular Organization of the Mammalian Circadian Clock

The mammalian molecular clock consists of a positive loop driven by the transcriptional activators CLOCK and BMAL1 and a negative feedback loop driven by the repressors period (PER) and cryptochrome (CRY) proteins. In mammals there are three PER proteins and two CRYs. CLOCK and BMAL1 activate the expression of clock-controlled genes (CCGs) through binding to E-box elements in their promoters. Among the CCGs are *Per* and *Cry* genes whose products dimerize and translocate into the nucleus where they inhibit CLOCK:BMAL1 activity. PERs and CRYs undergo a number of post-translational modifications that result in proteasome-induced degradation with a 24 hour rhythmicity, ultimately allowing the start of a new circadian cycle. CLOCK:BMAL1 also induce the activation of *Rev-Erb* and *Ror* genes that give rise to a secondary loop by binding to responsive promoter elements (RRE) and inhibit and activate respectively *Bmal1* transcription. Most of the molecular clock components are additionally regulated through various signaling pathways that post-translationally modify the core clock. Post-translational modifications (PTMs) include acetylation, phosphorylation, O-GlcNAcylation and SUMOylation (See Ref 181 for an overview). Together these transcriptional-translational regulatory loops generate the circadian output.

∿ indicates oscillation.

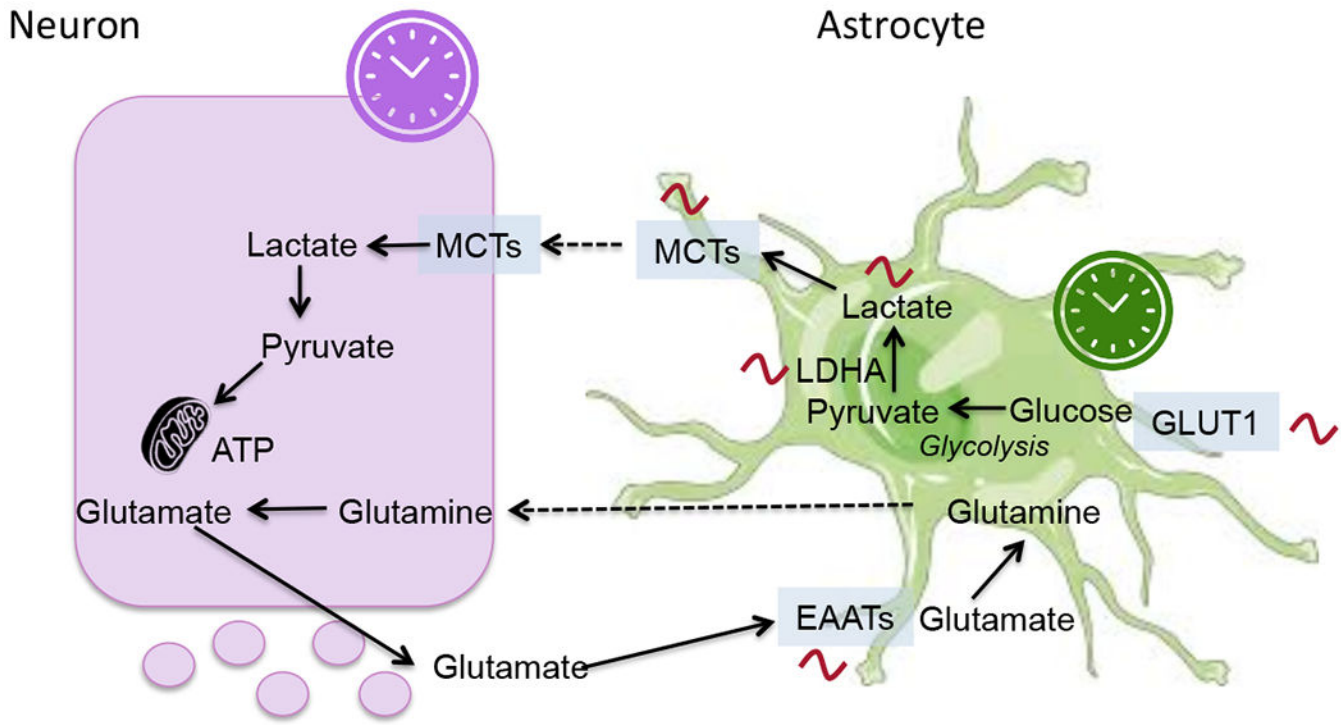

Figure 2: Metabolic coupling of neurons and astrocytes

Glutamate is released at neuronal excitatory synapses and up-taken by astrocytes through glial-specific glutamate transporters (EAATs). Glutamate uptake by astrocytes triggers an increase in glycolysis, enhancing influx of glucose from blood vessels via glucose transporters (GLUTs) expressed in astrocytes. Part of the glucose is metabolized to lactate via pyruvate by the lactate dehydrogenase isoenzyme A (LDHA) and transported outside the astrocytes via monocarboxylate transporters (MCTs). Once transferred to neurons, lactate is oxidized to produce ATP. Both neurons and astrocytes have an autonomous circadian clock. Several of these enzymes display daily rhythms in the SCN (see the Circadiomics web portal as a reference[182]). Additionally, lactate levels show diurnal variations. We propose a model where circadian neurometabolic coupling contributes to SCN function.

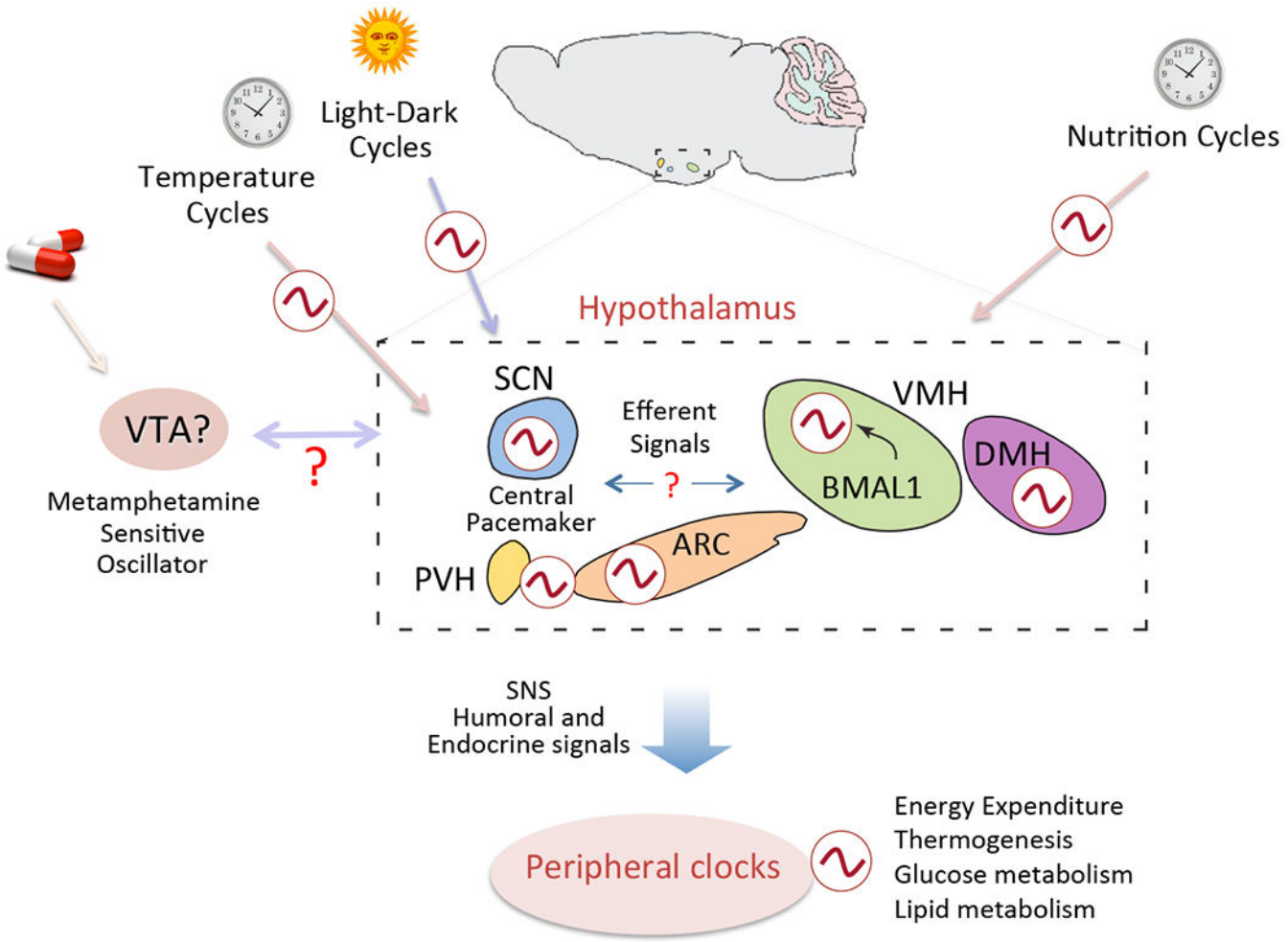

Figure 3: Network of hypothalamic oscillators

Representative illustration of how external cues and output signals are integrated within the hypothalamic network of oscillators. The hypothalamic SCN is the master regulator, whereas extra-SCN hypothalamic nuclei harbour their own independent circadian oscillator. It is hypothesized that extra-SCN clocks operate in concert with the SCN to gate circadian physiology during the 24 hour cycle. Clocks in the arcuate nucleus (ARC), dorsomedial hypothalamus (DMH) and ventromedial hypothalamus (VMH) integrate external cues such as temperature cycles and nutrition cycles. Central output signals are conveyed to peripheral tissues via the sympathetic nervous system (SNS) as well as through humoral factors thereby regulating peripheral metabolism and energy homeostasis. Light is the main entrainment signal for the suprachiasmatic nucleus (SCN). Additionally, oscillators sensitive to other external cues, such as food and drugs of abuse, have been hypothesized. The location and functional relationships among brain oscillators remains to be elucidated. PVH, paraventricular nucleus of the hypothalamus; VTA, ventral tegmental area.

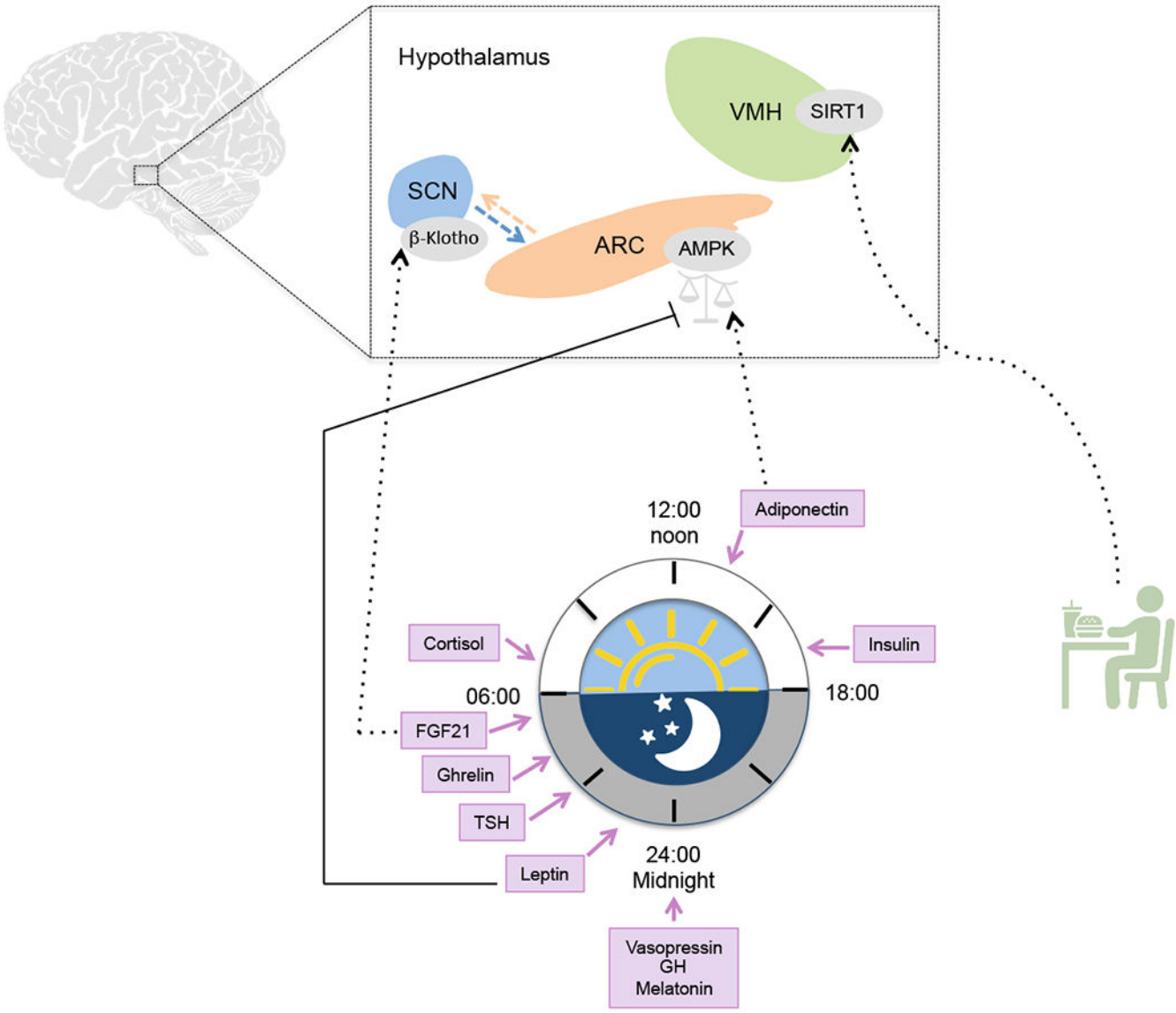

Figure 4: Interplay between peripheral and central clocks

Endocrine signals are central mediators of circadian physiology and circulating levels of several endocrine factors oscillate over the course of the day, including cortisol, insulin, ghrelin, TSH, vasopressin, growth hormone (GH) and melatonin. Peripheral tissues coordinate the diurnal secretion of factors that provide positive and negative feedback inputs to the brain clocks. Hypothalamic diurnal activity of AMP-activated protein kinase (AMPK) is finely tuned via the opposite action of two adipokines: leptin and adiponectin. The metabolic regulator fibroblast growth factor 21 (FGF21) is secreted from the liver and modulates directly the central clock in the SCN by inducing activation of β–Klotho receptors. Oscillation of other humoral factors such as ghrelin may also provide peripheral feedback to central clocks. Metabolic cues are also conveyed to the brain through the action of the metabolic sensor SIRT1. In the ventromedial hypothalamus (VMH) SIRT1 is key for

the adaptation of the central clock to feeding. ARC, arcuate nucleus. Dotted arrows indicate activation. Solid arrows indicate inhibition.

Table1.

Effect of clock disruption on behavior and metabolism

Gene	Animal Model	Phenotype	Comment	Reference
CLOCK	*Clock* Δ19 mutant	Hyperphagic Obese	Decreased expression of orexigenic transcripts	46
BMAL1	Null mice	Arrhythmic feeding	No effect on FAA	47
BMAL1	VMH specific deletion	Decreased body weight	Affects BAT circadian activity	56
BMAL1	Liver specific deletion	Hypoglycemia	Arrhythmic expression of hepatic glucose regulatory genes	102
Per1	S714G mutant	Advanced food intakeIncreased sensitivity to obesity	Feeding uncoupled from energy expenditure	52
Per2	Null mice(Per2Brdm1)	Absence of diurnal feeding rhythmsImpaired BAT activity	Loss of α-MSH diurnal rhythmsAltered lipid metabolism	48, 53
Cry1/Cry2	shRNA,Null mice	Absence of diurnal feeding rhythmsHyperglycemia	Feeding behavior rescued by TRF	50, 148
Reverbα	Null mice	Absence of diurnal rhythms of BAT activity	Higher Ucp1 expression in BAT	54

FAA, food anticipatory activity; BAT, brown adipose tissue; α-MSH, α–melanocyte-stimulating hormone; TRF, Time restricted feeding

Table2.

Effects of dietary interventions and diurnal rhythms

Dietary Intervention	Model	Circadian Phenotype	Molecular Effectors	Reference
Day-time restricted feeding	WT mice*cry1*$^{-/-}$*; cry2*$^{-/-}$ mice	Restored 24-h rhythms of gene expression in liver	Metabolic responsive TFs	148
Fat supplemented diet restricted to 12-h/day	WT *Drosophila* clk, cyc, per, tim mutant *Drosophila*	Increased amplitude of oscillating transcriptsImproved cardiac function	Endogenous clock	177
5-h delay in meal time	Male human subjects	Phase delay of plasma glucose rhythmsPhase shift Per2 expression in adipose tissue	NR	152
HFD	WT mice	Lengthening of circadian periodBlunted rhythmic gene expression	NR	146
HFD	WT mice	Loss and gain of oscillation of transcripts and metabolites in the liver	BMAL1 PPARγ	156
HFD	WT mice *Scap*$^{-/-}$ mice *Pparα*$^{-/-}$ mice	Remodeling of circadian enhancers Gain of oscillation of de novo lipogenesis and FA oxidation	SREBP PPARα	180
HFD restricted to 8-h/day	WT mice	Reduced BW gainImproved hepatic glucose metabolismReduced hepatic steatosisEnhanced oscillation of clock genes and of metabolic sensors	NR	149
DR	WT *Drosophila*per, tim mutant *Drosophila*	Enhanced amplitude of cycling genesGain of oscillation of medium chain triglycerides	Endogenous clock	178
CR	Young and old WT mice	Enhanced amplitude of clock genes in liverIncreased protein acetylationChanges in NAD^+ metabolism	SIRT1	159
CR	Young and old WT mice	Phase advance of clock genes in SCs “Adult” like rhythmic gene expression in aged SCs	NR	160
KD	WT mice	Lower amplitude of clock genes in the brainHigher amplitude of clock genes in liverIncreased basal locomotor activity	NR	169
KD	WT mice CLOCK$^{-/-}$ mice	Loss of RER rhythmsGain of oscilation of liver cholesterol levelsGain of oscillation of free FAs in the gutEnhanced amplitude of CCGsGain of oscillation of serum βOHB levels	BMAL1 PPARα	171

NR non reported; WT wild-type; TFs transcription factors; clk clock; cyc cycle; tim timeless; per period; BW body weight; NAD^+ nicotinamide adenine dinucleotide; SCs stem cells; RER respiratory exchange ratio; FAs fatty acids; CCGs clock controlled genes; βOHB β–Hydroxybutyrate; HFD high-fat diet; DR dietary restriction; CR calorie restriction; KD ketogenic diet;