The Tissue Clock Network: Driver and Gatekeeper of Circadian Physiology

Circadian rhythms are integrated outputs of central and peripheral tissue clocks interacting in a complex manner – from drivers to gatekeepers

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In mammals, a network of cellular circadian clocks organizes physiology and behavior along the 24-h day cycle. The traditional hierarchical model of circadian clock organization with a central pacemaker and peripheral slave oscillators has recently been challenged by studies combining tissue-specific mouse mutants with transcriptome analyses. First, a surprisingly small number of tissue rhythms are lost when only local clocks are ablated and, second, transcriptional circadian rhythms appear to be regulated by a complex mix of local and systemic factors. As reviewed here, these findings suggest a more integrated model of clock network interaction with the central pacemaker as the main source of behavioral and systemic–physiological rhythms and peripheral clocks controlling some local rhythms while at the same time acting as gatekeepers that temporally adjust cellular responses to external stimuli.

1. Introduction

Life on Earth is strongly influenced by the 24-h rotation of our planet around its axis. In order to adapt physiology and behavior to the corresponding dramatic, but, with regard to their recurrence, highly predictable changes in environmental conditions, most species have developed internal timekeeping mechanisms to track (day-) time.[1] Such circadian clocks (from Latin “circa diem” means “around the day”) are found in all cells of the body and are based on interlocked transcriptional-translational feedback loops of a set of core clock genes characterized by prominent circadian oscillations in mRNA and protein abundance. Most clock genes encode transcription factors or transcriptional regulators. Rhythmic activation through circadian promoter elements: E-boxes, D-boxes, and retinoid acid-related orphan receptor response elements (ROREs)—drives the expression of large programs of tissue-specific clock output genes, so-called clock-controlled genes (Ccg), that translate clock time into physiological meaningful signals (Figure 1).[2]

Naturally, all these clocks need to be coordinated—not only within specific organs but between all systems of an organism—and synchronized to external time to sufficiently fulfill their purpose along the 24-h cycle. In mammals, this task is implemented by a main circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN). The SCN clock is directly entrained by the external light–dark cycle and transmits this information to subordinate clocks throughout the body to align physiological functions with external time.[3] The circadian standard model suggests a sequential system in which the SCN acts like an orchestral director that coordinates the timing of otherwise independent cellular oscillators throughout the body, to ensure temporal coherence and the expression of overt rhythms (Figure 2A).[4] Of note, according to this model peripheral oscillators are both necessary and sufficient to drive tissue rhythms.

The transfer of the circadian information from the SCN to peripheral oscillators is conducted via neuronal as well as humoral pathways but also factors like body temperature and behavior, for example the sleep/wake cycle, influence the rhythm of peripheral clocks. The influence of such external factors on the circadian transcriptome rhythms, for example, in specific organs—or even specific cell types within these organs, as was shown for pancreatic alpha and beta cells—is widely accepted in the field but challenges the proposed simplicity of the sequential circadian model.[5–10] Especially under the assumption that the large majority of the transcriptional rhythms is controlled at the cellular (clock) level, as transcriptome analysis in rodents indicates, the question of how non-SCN rhythmic signals modulate and synchronize peripheral clocks becomes pressing.[11]

Importantly, in theory, an influence of peripheral clocks on rhythmic physiological outputs is not absolutely essential. As long as (centrally derived) input into the target tissue is rhythmic this would be sufficient to regulate tissue responses in a time-of-day dependent manner (Figure 2B). As a combination of these
two scenarios and an extension to the hypothesis of the sequential model, peripheral clocks could also act as gatekeepers, that, by regulating tissue responsiveness to external stimuli, for example, from the SCN, modulate physiological outputs in a circadian fashion (Figure 2C). In this integrated model, peripheral clocks would be sufficient but not essential for peripheral rhythm generation. Such circadian gating would allow for retaining a certain centralized control over internal circadian time while at the same time permitting tissue-specific modulation of responses to external demands. In this paper we review the current literature on circadian network coordination with regard to these three modes of tissue clock action and highlight the hypothalamus–pituitary–adrenal (HPA) axis as a prominent example of peripheral gatekeeping. Furthermore, we re-interpret experiments on tissue-specific clock manipulation under this perspective and devise experiments to test the mechanisms of circadian networking.

2. A Combination of Local and Systemic Time Cues Regulates Circadian Output Rhythms

The traditional, but arguably a bit oversimplified, view of the circadian system in mammals is its partition into two main parts. On the one hand the clock in the SCN, defined as the master clock and the main central pacemaker of the system, and on the other hand, every other clock in the organism. The advantage of such a hierarchical concept is that external rhythmic time cues are processed centrally, and the circadian information can be passed in a very coordinated fashion to all downstream oscillators, a process that ensures a tight system synchronization. The instructive role of the SCN for tissue rhythmicity is illustrated by the observation that a considerably higher amount of cycling transcripts is detectable when tissues are harvested directly from the organism as compared to explants or cultured cells.[12] In line with that, transcriptome rhythms in the liver—but also other peripheral tissues—show second- and third-order harmonics, meaning rhythmic oscillations with a 12- or 8-h period, in vivo. These ultradian rhythms are strongly dampened ex vivo, indicating that they are centrally regulated or at least enforced.[12] Even though peripheral tissue clock genes continue to show expression rhythms in vitro, these display considerable dampening after some days in culture in the absence of external time cues.[11] Another example is the epidydimal white adipose tissue, in which around 6% of transcripts are rhythmic, but the vast majority of them lose their rhythms after genetic deletion of the SCN clock, indicating a significant role of the master clock or master clock-derived signals for circadian tissue regulation. Of note, at the same time, a distinct set of gene transcripts gains rhythmicity only after master clock ablation. This observation may be explained by a counteractive temporal regulation by both local and systemic cues. Once SCN-derived rhythms are ablated local counterregulatory signals may overshoot, leading to a rhythmic regulation of target gene expression.[14]

This observation already points out some limitations of the sequential model as it does not really allow for an integration of systemic signals into rhythmic tissue output. Of significance in this context are food availability and diurnal feeding patterns, which, despite their impact on circadian rhythms, are not necessarily synced with the light/dark cycle. In mice, more that 80% of rhythmically expressed transcripts in the liver lose their rhythm during fasting,[15] more than 70% under arrhythmic feeding conditions.[16] Furthermore, timed feeding cues can restore physiological rhythms in the absence of a functional tissue clock.[15] The core clock oscillator in the liver, for instance, remains functional under fasting and re-feeding as well as arrhythmic feeding conditions, though some changes in amplitude and phasing of core clock gene expression may occur. It is possible that these are at least partly caused by feeding/fasting related changes in plasma insulin levels.[16,17]

Greenwell et al. identified a set of genes in the liver that remains rhythmic under night-restricted, ad-libitum and arrhythmic feeding conditions, but loses its rhythm in brain and muscle ARNT-like 1 (Bmal1 or Arntl) deficient mice, which suggests (tissue-) clock dependency.[16] Looking in general at the amounts of cycling gene transcripts on individual tissue level, using RNA sequencing and microarray hybridization,[11,18] surprisingly little consistency of Cpg identity across different cell types was found, despite the thousands of oscillating genes detectable in each tissue.[11,18–20] Those genes consistently found as being rhythmically expressed across tissues mainly comprise the core clock machinery itself, its regulators and their immediate downstream targets.[19] However, recent evidence suggests that the role of local clock proteins in the controlling of rhythmically expressed genes is far less dominant, and that clock protein transcription factors such as CLOCK/BMAL1 might rather increase the chance for binding of other transcription factors at close enhancer sites—a
Figure 2. Alternate modes of circadian network interaction. A) Sequential mode: the SCN pacemaker is reset by light and entrains peripheral clocks through systemic timing signals. Tissue clocks subsequently drive rhythms in local physiological processes through transcriptional programs. B) SCN-driven mode. The SCN pacemaker is reset by light and regulates rhythmic physiological functions through neuronal and humoral signals. C) Gating mode: peripheral clocks adapt local tissue responses to SCN-derived systemic cues, thus modulating physiological rhythms in a time- and tissue-specific manner.

process that then initiates circadian gene transcription. Epigenetic modulation may mediate this process, and extensive analysis of RNA-, ChIP-, and MethyC-sequencing data by Vollmers et al. and others revealed rhythmic oscillations of histone modifications as well as rhythmic expression of non-coding and regulatory RNAs. Overall, a more integrated system comprising different oscillatory inputs might better explain the experimental data on peripheral circadian regulation described above.

3. Adrenocortical Clocks Gate Adrenocorticotropin Responses to Control Glucocorticoid Rhythms and Stress Responses

The complexity with which circadian clocks within a system can interact with each other to create rhythms, can be illustrated by the example of the HPA axis. On the first glance, the system seems to follow a classic hierarchical structure. Hypophysiotropic neurons of the paraventricular nucleus (PVN) of the hypothalamus produce corticotiberin (CRH), which stimulates the pituitary to release adrenocorticotropin (ACTH) into the blood stream. ACTH is transported to the adrenal cortex where it initiates the production and release of glucocorticoids (GCs)—mainly cortisol in humans and corticosterone in rodents. Overactivation is prevented by a feedback loop in which GCs inhibit the production of CRH and ACTH, respectively. GC feedback to the pituitary results in the characteristic pulsatile GC secretion rhythm with periods of approximately 90 min. This pulsatility is overlaid by a very robust 24-h oscillation with peak time at the beginning of the activity phase (Figure 3). The circadian compound of the GC rhythm is most likely evoked by arginine vasopressin (AVP) immunoreactive projections from the SCN to a sub-population of CRH-producing neurons in the PVN. In rodents, the adrenal release of GCs is acutely increased by the infusion of an AVP antagonist in the PVN which suggests that the transfer of time-of-day information from the SCN is achieved

Figure 3. Circadian regulation of the HPA axis. Rhythmic release of arginine vasopressin (AVP) from the SCN regulates CRH (corticoliberin) release from the paraventricular nucleus of the hypothalamus (PVN). In the pituitary, the CRH signal triggers release of adrenocorticotropin (ACTH) into the blood. ACTH induces glucocorticoid (GC) release from the adrenal cortex, which negatively feeds back on ACTH and CRH production in the pituitary and the brain, respectively. Bottom: the 24-h GC release profile in humans is characterized by circadian (dotted line) and pulsatile (90-min) rhythms and peaks in the early morning.
via neuronal control of rhythmic CRH production in the hypothalamus. In line with this, ACTH rhythms are closely connected to endogenous CRH concentrations. Plasma ACTH shows a pulsatile and diurnal rhythm with highest concentrations at the beginning of the activity phase, that is, the evening in nocturnal rodents such as rats and the morning in humans. Thus, SCN lesions in rats lead to an overall reduction of plasma ACTH concentrations and the loss of rhythmic changes over the day as well as a loss in circadian GC rhythm. Also, immunoneutralization of CRH erases the circadian component of plasma ACTH, however, baseline ACTH is still detectable even without any CRH signal. In addition, stimulation of the adrenal through autonomic innervation may be involved in circadian GC regulation, either via direct innervation of the adrenal cortex or mediated by the adrenal medulla.

Importantly, the transplantation of foetal SCN grafts into aged rats, which otherwise show a loss of rhythmicity in CRH and POMC mRNA expression, cannot normalize the average level of POMC mRNA. Indeed, a general diurnal rhythm in PVN and anterior pituitary is restored, but not the exact temporal pattern of CRH mRNA found in young rats. In contrast, serum corticosterone concentrations are diurnally rhythmic independent of the age of the host or the SCN transplant. These data clearly suggest circadian regulation downstream of the SCN. Another example is the connection between ACTH and GC rhythms, which are highly synchronized, even though ACTH normally shows a lower amplitude compared to GCs indicating that other factors—probably at the level of ACTH reception in the adrenal—must be involved in this process. Indeed, hypophysectomised rats show low GC plasma concentrations without daily alterations. However, substitution of thyroxine and ACTH in the hypophysectomised rats re-establishes rhythmic GC production. It appears that the adrenal processes ACTH and thyroxine signals differently depending on the time of day and thereby may create the observed GC rhythm—a classic gating mechanism.

Transplantation studies of adrenal tissues between clock-deficient and -proficient mice strengthen this view, but adrenocortical clock function itself seems dispensable for GC rhythmicity. Overall, these findings imply that adrenal clocks are sufficient, but not necessary to create HPA axis rhythms. Moreover, PVN, pituitary and adrenal rather interpret systemic (SCN-derived) signals in line with the above-proposed gating model.

4. Tissue Clock Knockouts Yield Various Phenotypes

In recent years, several tissue-specific clock gene mutant mouse models have been generated to study the contribution of tissue clocks to physiological rhythm regulation (Table 1). In all cases, the phenotypes of these animals reveal a complex interaction of local and systemic signals in the regulation of physiological functions of the given tissue. Moreover, systemic interventions such as time-restricted feeding are capable of reversing the phenotype in some of these tissue clock mutants. With regard to the HPA axis, GC rhythms are dampened with elevated baseline levels in Per1 mutant animals while loss of Per2 has no effect on GC profiles. Mice carrying a mutated Per2 and no cryptochrome 1 (Cry1) gene also show a disrupted circadian clock and no rhythmic activity in constant darkness (DD). In these mice, the ACTH rhythm is also blunted. Instead, steady-state ACTH concentrations in the midst between normal peak and trough values are measured. Following from that, also the corticosterone rhythm is gone, but corticosterone concentrations in mutant mice are overall low. These data suggest that not only the ACTH signal is pivotal for the production of corticosterone, but also the circadian clock in the adrenals itself plays a role, which is ablated in Per2/Cry1 mutant animals and therefore cannot differentially respond to ACTH. Ex vivo data show an intrinsic rhythm

| Tissue | Mouse model | Phenytoypes | Reference |
|--------|-------------|-------------|-----------|
| Adipocytes | Arntl-flx/aP2-Cre | Obesity, shift in food intake rhythm, reduction in polyunsaturated fatty acids | [55] |
| Adrenal | Adrenal transplantation (Per2loxP/+)Cre1−/−adrenal in wildtype host | Rhythmic ACTH in LD and DD, dampened corticosterone secretion rhythm in LD and DD | [44] |
| Adrenal cortex | Mct2-KS-Bmal1 transgenic | Dampened circadian corticosterone rhythm | [49] |
| Brain | Arntl-flx/Nes-Cre | Disrupted oscillation of clock genes in the cortex, astrogliosis, abnormal response to novelty | [66] |
| Gonadotropes | Arntl-flx/GR1-Cre | Oestrous cycle instability, increased luteinizing hormone and gonadotropin levels | [67] |
| Hepatocytes | LAP-tTA/TRE-Nrl1d1 transgenic | Extensive loss of rhythm transcripts, robust oscillation of mPer2 | [54] |
| Hepatocytes | Arntl-flx/Alb1-Cre | Hypoglycaemia restricted to the fasting period, lower resting blood glucose | [53] |
| Pancreatic β cells | Arntl-flx/Pdx-Cre | Normal circadian activity, feeding rhythms, body weight and composition, elevated ad lib glucose levels, impaired glucose tolerance, reduced insulin secretion starting with 2–4 month | [58] |
| Pancreatic β cells | Arntl-flx/GRI-Cre-ERα | Hyperglycemia, impaired glucose tolerance and hypoinsulinemic diabetes, normal wheel-running, period length, food intake and body weight | [59] |
| Skeletal muscle | Arntl-flx/MicIfCre | Impaired insulin-stimulated glucose uptake, reduced glucose oxidation | [60] |
| Skeletal muscle | Arntl-flx/Hus-Cre-ERα | Reduced sensitivity to insulin, reduced glucose oxidation | [60] |
| Skeletal muscle | Arntl-flx/ACTA-rtTA-TRE-Creα | Reduced HIF1α activity, reduced anaerobic glycolysis | [60] |
of responses in adrenal slices, with increased corticosterone release at times when plasma GCs are at their natural high. When arrhythmic adrenals from Per2/Cry1 double mutant mice are transplanted into adrenalectomized wild-type mice and vice versa, GC rhythms are dampened. Overall this indicates that the adrenal clock is able to evoke a rhythmic corticosterone production without the input of a functional SCN as long as an entraining light stimulation is available.[44] On the other hand, genetic approaches to deleting adrenal clock function provided mixed results. Son and colleagues used a mouse line expressing CRE recombinase from the ACTH receptor (Mc2r) promoter to generate mice with an adrenal-specific knockout of Bmal1. They found that the adrenal STAR protein, involved in cholesterol transport and steroidogenesis, and corticosterone content showed diurnal rhythms under light–dark conditions (LD), which were abolished in DD. Further analysis revealed that the rhythmic transcription of Star is evoked by the binding of the CLOCK/BMAL1 heterodimer at a distal E-box element. This underlines the pivotal role of the adrenal clock machinery for sustaining the corticosterone rhythm through rhythmic regulation of Star.[49] In contrast, mice with specific deletion of Bmal1 in the adrenal cortex using another CRE recombinase driver (Cyp11a1) show no impairment in GC secretion under basal and stressed conditions.[45] Finally, a third paper using an aldosterone synthase-controlled CRE driver to delete Bmal1 found complex alterations in daily GC rhythms and stress responses depending on light–dark conditions and gender of the mice.[50,51]

4.1. Liver Clocks Control Rest Phase Blood Glucose Levels

The knockout of BMAL1 is of specific interest, because Bmal1 appears to be the only essential component of the molecular clockwork in mice. Bmal1 deficient animals show no behavioral circadian rhythm under DD conditions and the GC levels throughout the day are severely dampened.[52] A hepatocyte-specific Bmal1-deficient mouse model depicts an impaired liver clock with increased Cry1 expression and loss of Bmal1-dependent genes such as D-site albumin promoter binding protein (Dbp) and nuclear receptor 1d1 (Nrd1 or Rev-erba). These liver clock knockout mice show normal locomotor activity, feeding behavior and body fat content as well as unaltered GC and glucagon levels. However, hypoglycaemia restricted to the fasting period and exaggerated glucose clearance in the presence of normal sensitivity to and production of insulin is detected. These data suggest a defect in hepatic glucose export during the fasting phase that may be explained by the loss of rhythmicity of the glucose transporter 2, a BMAL1-dependent Cog that normally exhibits highest expression during the fasting phase.[19] While these findings underline the importance of the local liver clock for glucose homeostasis, they may also be interpreted as defective gating since hepatic glucose export is a response to low blood glucose levels. In line with this, Kornmann and colleagues, using liver-specific overexpression of REV-ERBα to repress Bmal1, showed that even in the absence of a functional liver clock rhythmic expression of some genes—including the core clock component Per2—is retained, indicating that these oscillations are driven at least partly by circadian signals from outside the liver.[54]

4.2. Adipose Tissue Clocks Regulate Lipolysis and Central Appetite Rhythms

The specific deletion of Bmal1 in adipocytes leads to a dampened rhythmicity of Nr1d1 and Per3 expression in white and Per2, Per3 and Dbp in brown adipose tissue. Adipocyte clock knockout mice show adiposity compared to controls under regular as well as high-fat diet condition. The increase of fat mass correlates with higher leptin concentrations in the plasma, an important satiety signal of the hypothalamus.[55] Despite high leptin levels, food intake is increased in the mutants specifically in the light phase suggesting temporally regulated leptin resistance.[56] Metabolomic analyses reveal a reduced adipose production of polyunsaturated fatty acids (PUFAs) during the fasting period, which are signals directly processed in the hypothalamus and promoting satiation. These data suggest an adipose clock-driven oscillation of PUFA production and, potentially, a circadian gating of PUFAs production in response to fasting signals during the normal rest phase. The lack of PUFA surge during the fasting phase triggers the hypothalamus to promote rest phase feeding, which in turn causes obesity.[53]

4.3. Loss of Pancreas Clock Function Promotes Hypoinsulinemia

Mice with a specific loss of Bmal1 only in pancreatic islets show normal circadian activity, feeding rhythms as well as body weight and composition, but already at the age of 2–4 months suffer from hyperglycaemia, impaired glucose tolerance and decreased insulin secretion. This mirrors the phenotype of the (global) Clock[6] and mutant mouse with its reduced glucose-stimulated insulin secretion.[57,58] Tamoxifen induced loss of Bmal1 in beta cell islets in adult animals likewise leads to the development of hyperglycaemia, impaired glucose tolerance and hypoinsulinemia. Transcriptome analysis in beta cell clock knockout mice revealed a loss of rhythmicity in genes involved in exocytosis, vesicle trafficking, tethering and fusion. Many of them were identified as direct transcriptional targets of CLOCK:BMAL1, underlining the importance of the local clock machinery in islet physiological rhythms.[59]

4.4. Muscle Clocks Regulate Glucose Uptake and Hypoxia Responses

Mice with a Bmal1 deletion in the skeletal muscle show normal survival and growth, unaltered muscle histology and an increased weight of hind limb muscles. Moreover, these mice show normal circadian rhythms of locomotor activity, but activity levels are increased during the dark phase. Muscle clock loss leads to reduced insulin sensitivity while fasting blood glucose levels and glucose tolerance remain unchanged. These alterations in tissue insulin responses correlate with reduced expression of the insulin-dependent glucose transporter GLUT4 and a decrease in glucose oxidation rate.[60] Another important pathway, presumably gated by the local circadian clock in the skeletal muscle, is the hypoxia pathway including the transcription factor hypoxia-induced factor 1 alpha (HIF1α). Peek et al.
Figure 4. Examples of tissue clock gating in circadian physiology. The SCN regulates circadian rhythms in systemic physiological signals such as metabolic levels (e.g., glucose, oxygen) or hormone secretion (e.g., ACTH or insulin). These signals are temporally integrated by the tissue clock machinery regulating expression of genes encoding for response mediators such as hormone receptors or signaling proteins. Such local temporal fine-tuning (i.e., gating) allows for tissue-specific temporal interpretation of centrally or externally controlled signals (ACTH, adrenocorticotropic; Glut1/2, glucose transporter 1/2; Fasn, fatty acid synthase; Pparγ, peroxisome proliferator activated receptor gamma; M3r, muscarinic receptor 3; StaR, steroid acute regulatory protein; Ldha, lactate dehydrogenase A; Mct4, lactate transporter 4).

using an inducible skeletal muscle-specific Bmal1 knockout model, demonstrated an impaired oxygen consumption rate, a reduction in exercise-dependent glycolytic lactate production and reduced HIF1α target gene expression in skeletal muscle after deletion of Bmal1. The fact that an exercise challenge in mice leads to different degrees of hypoxia induction via HIF1α, dependent on the time of day, further underlines the role of the muscle circadian clock in this context. Interestingly, hypoxia may itself act as a (tissue-specific) zeitgeber to coordinate tissue clock phase coherence across the body.

5. Tissue Clock Rescue Reveals Local Clock-Dependent and -Independent Transcriptional Rhythms

To further dissect the interplay between central and peripheral clocks, the groups of Paolo Sassone-Corsi and Salvador Aznar Benitah created a mouse model in which Bmal1 expression (and, thus, clock function) can be restored in a specific tissue in an otherwise Bmal1-deficient animal by expression of CRE recombinase. In the resulting tissue clock rescue model, expressing functional BMAL1 only in the epidermis, an oscillation of the epidermal clock machinery was observed with a preserved phase, but a slight reduction in amplitude compared to wildtype animals under light–dark conditions. In DD however, rescue mice lose their rhythmic regulation completely, emphasising that the epidermis requires light—or another light-driven signal—as a synchronizer of tissue physiology. For the epidermis it remains a possibility that light directly synchronises the clock via detection by keratinocytes, but this cannot be a generalised mechanism because comparable characteristics were observed for the liver and adrenal transplants that are not subject to direct light exposure. Together, these data show that—at least under rhythmic environmental conditions—peripheral clocks are sufficient to drive physiological tissue rhythms. However, only a limited number of the transcripts shown to be rhythmic in control animals were retained in the rescue mouse models, which in turn suggests that for the remaining output rhythms systemic signals are essential. These findings clearly show that light is a functional zeitgeber for peripheral tissues such as liver, skin and adrenal, independent of the SCN pacemaker. To which extent a rescued tissue clock function may be capable of gating responses to external stimuli, however, has not yet been tested.

6. Conclusions and Outlook

In biological systems, multilevel regulatory networks are essential in adapting the organism to a complex and dynamic environment. We have made the case that a combination of systemic
control, local rhythm generation, and circadian gating describes the involvement of tissue clocks in physiological control. This is not a trivial assumption, since it determines the way how we understand the necessity of peripheral clocks for physiological homeostasis and their value as targets of therapeutic intervention.

Considering the plethora of signals peripheral tissues receive, it makes perfect sense to leave the principle temporal control of the body to a central and less-exposed pacemaker while using local clocks to adjust and modulate tissue responses in a time- and context-dependent manner (Figure 4). The SCN fits this description as its dominant zeitgeber is the light dark cycle—arguably the most reliable source of time information available—while it is shielded from most other time signals. In contrast, peripheral tissues integrate temporal information from local clocks with systemic factors and external stimuli to adapt physiological functions such as energy metabolism.

Interestingly, while this integrated model leaves less control with the peripheral clocks themselves, it may provide interesting new points of attack in the clinical context. Many chronic diseases are characterized by altered responses to external stimuli. For example, in diabetic patients, either insulin secretion in response to elevated glucose levels (type-1) or glucose disposal in response to insulin stimulation (type-2) are inhibited. Similarly, in many psychiatric diseases responses to external stressors are pathologically altered. In both cases, circadian regulation has been implicated and clocks in the CNS or metabolic tissues may be targets for therapeutic approaches. Indeed, the tissue-specificity of a given target response may be an advantage for such clock-mediated therapies.

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Conflict of Interest
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