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Introduction

Daily rhythms in nature, such as the opening and closing of flowers or our patterns of sleep and wakefulness and their association with the perpetual alteration of night and day, were recognized in antiquity although their origins were not questioned until the eighteenth century. The French Astronomer Jean-Jacques d'Ortous de Mairan conducted an investigation into whether the leaves of the Mimosa plant opened in response to light.[1] While de Mairan's experiments were the first to question the origin of such daily rhythms, Augustin Pyramus de Candolle is credited with the first suggestion that they arose through an internal timekeeping mechanism. In 1832, de Candolle concluded that the rhythm of Mimosa leaf folding and unfolding observed under constant light conditions must come "from within the plant",[2] and because rhythms observed under such conditions express a period of only approximately 24 hours, they have come to be called "circadian" rhythms, from the Latin circa "about" and dies "day". Almost a half a century later Charles Darwin came to a similar conclusion regarding leaf movements, writing further that "we may conclude that the periodicity of their movements is to a certain extent inherited".[3] As time progressed, investigators became increasingly aware that not only plants, but all organisms including humans displayed daily rhythms that were generated by an internal time-keeping system or endogenous biological clock.[4-8]

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The Suprachiasmatic Nucleus is a Circadian Oscillator

The suprachiasmatic nucleus (SCN) is the primary circadian oscillator in the brain, and is located in the ventral periventricular zone of the hypothalamus, dorsal to the optic chiasm and medial to the anterior hypothalamic area. Each of the paired suprachiasmatic nuclei is composed of a heterogeneous group of ≈10,000 interconnected small neurons that express circadian rhythms in both gene expression and in the rate of action potential firing.[9] Although recognized early on as a distinct hypothalamic nucleus in a variety of species,[10] its function remained unspecified until the demonstration of a retinal projection terminating in the SCN, the retinohypothalamic tract (RHT).[11,12] Such a projection was thought to be a critical component of clock function, since it would enable direct synchronization with the environmental day/night cycle, so identification of the RHT focused attention on this region of the anterior hypothalamus as a potential site of the biological clock.

SCN ablation studies were then conducted, with the observation that complete destruction of the SCN rendered animals arrhythmic. This led to the suggestion that the SCN was indeed the site of at least one component of a circadian clock that is normally entrained by retinal signals transmitted via the RHT.[13,14] SCN metabolic activity, electrophysiological recording of the SCN both *in vivo* and *in vitro*, and transplantation of fetal anterior hypothalamic tissue containing the SCN into SCN-lesioned hosts of the same or different species subsequently confirmed that: (1) the SCN is the site of a circadian oscillator whose neurons rhythmically alter their metabolism and firing rate and (2) the SCN is required for the expression of behavioral circadian rhythms (Fig. 1).[15-22] However, there was also an indication from some transplantation studies that the circadian timing system may be composed of a distributed multi-oscillator system[21] and, as discussed below, it is now recognized that almost all cells and tissues in the body are circadian clocks.[23-25]

The SCN Molecular Circadian Oscillator is Linked to the Neural Activity Rhythm

Insights into the molecular mechanisms of the mammalian SCN circadian clock emerged from work conducted in the fruit fly. These studies identified three mutant alleles of a single gene (*period*) that had the properties of either increasing or decreasing the circadian period or of eliminating circadian rhythmicity altogether.[26] Following the discovery of the mammalian homologue of *per* in 1997,[27,28] great strides have been made in defining the core molecular components that underlie the generation of circadian oscillations in the SCN.[29]

The cell autonomous circadian oscillations of SCN neurons are generated by two interlocking transcription/translation feedback loops that function together to generate high amplitude circadian rhythms of gene expression. Four integral clock proteins form the core of the SCN molecular clock: two activators (CLOCK and BMAL1) and two repressors (PER and CRY) as well as kinases and phosphatases that regulate the localization and stability of these integral clock proteins. CLOCK and BMAL1 dimerize in the cytoplasm of SCN neurons, and following translocation to the nucleus, they initiate transcription of target genes including *per* and *cry* by binding to E-box elements within the enhancer and promoter

sequences of these genes. A feedback loop results from the translocation of PER:CRY heterodimers back to the nucleus where they repress their own transcription by acting on the CLOCK:BMAL1 complex. As PER and CRY proteins are degraded via ubiquitin-dependent pathways, repression on CLOCK:BMAL1 is eased and the cycle is repeated. Post-translational modifications play an important role in establishing the circadian period of the oscillation. An additional interlocking feedback loop involves the positive regulator, ROR and the negative regulator, REV-ERBα that adds robustness to the oscillations and helps to maintain accurate circadian timing (Fig. 2).[29]

Circadian oscillations in core clock genes must be linked to the functional output of the SCN, the daily fluctuation of spontaneous action potential firing of SCN neurons. Firing is greatest during the day (6-10 Hz) and low at night (<1 Hz) without regard to whether the behavior of the organism is diurnal or nocturnal.[16-18,30-32] Alterations in components of the molecular clock that increase or decrease the period of the cycle alter the frequency of the spontaneous firing rate of SCN neurons, while elimination of the molecular oscillation abolishes the firing rate rhythm. These findings support the interpretation that the intracellular molecular clock drives the expression of rhythms in the frequency of action potential firing in SCN neurons.[33,34] *Per1* may play an important role in the link as there is a positive correlation between *Per1* promoter activity and spike frequency in individual SCN neurons, suggesting a fixed phase relationship between molecular clock and electrical activity.[35,36] However, the precise causal link between the molecular oscillations of clock genes within SCN neurons and their rhythm of neuronal firing rate remains unclear.

Ion channels play a major role in neuronal excitability and several ion channels in SCN neurons appear to be under circadian clock control.[33,37] Ionic mechanisms that appear to contribute to the oscillation in SCN firing include persistent Na^+ currents, L-type Ca^{2+} currents, hyperpolarization-activated currents (I_H), large-conductance Ca^{2+} activated K^+ (BK) currents and fast delayed rectifier (FDR) K^+ currents although much remains to be learned.[38] There have been suggestions that membrane ion currents may also feedback to regulate the molecular clock, perhaps via voltage-dependent regulation of Ca^{2+} currents and subsequent second-messenger action of intracellular Ca^{2+} on gene transcription.[39-41] Fluxes in intracellular calcium are important for light-induced resetting of the SCN clock (see below), but recent work has shown that rhythmic electrical activity does not appear to be required for molecular oscillations in invertebrate clock neurons.[42] It is clear, however, that rhythmic spontaneous firing of the SCN clock is the critical functional output of the SCN and is required for overt behavioral rhythmicity.[43]

The RHT Entrains the SCN Circadian Clock to the Day/Night Cycle

The SCN circadian oscillator derives functional utility from its ability to be entrained to the day/night cycle. Simply stated, entrainment of the SCN oscillator to the day/night cycle means that the period of the endogenous SCN circadian oscillation becomes equal to that of the light/dark cycle.[44] Entrainment provides a predictable and appropriate phase relationship to the day/night cycle, in effect enabling recognition of local time, and thus the SCN circadian oscillator is said to function as a biological clock.[45] It is important to note that entrainment differs from simple synchronization to changes in the light/dark cycle as the

rhythm generation is neither passive nor driven and entrainment therefore allows for great plasticity and adaptive potential.[9] This plasticity is evidenced, for example, by the change in the phase angle of entrainment to the light/dark cycle in the golden hamster that occurs with seasonal changes in day length.[46]

Entrainment is accomplished by a daily resetting of the SCN clock such that the light-induced phase shift of the clock is equal in magnitude to the difference between the free-running period of the endogenous SCN oscillation (observed under constant conditions such as constant darkness, DD) and the period of the environmental light/dark cycle (i.e., typically 24 h but not restricted to this period). This mechanism is described empirically by the response of animals free-running under DD conditions and exposed briefly to light at different phases of the circadian cycle. The response of the SCN to brief light pulses is phase dependent: light exposure during the subjective day (i.e., the times when the animal would normally be exposed to daylight) has virtually no effect on the phase of the free-running circadian rhythm. In contrast, light exposure early in the subjective night produces phase delays in circadian rhythms, whereas light exposure late in the subjective night results in phase advances.

The phase response curve (PRC) to brief light pulses plots the amplitude of the phase shift as a function of the phase of the rhythm at the time of the light stimulation with the onset of activity arbitrarily defined as circadian time (CT) 12.[47] Effective light pulses can be as brief as 1 s and as dim as 0.05 lux.[48,49] Thus, entrainment is critically dependent on phase shifts occurring at dusk and/or dawn as the portion of the circadian day sensitive to light is coincident with the twilight transitions in the day/night cycle. Since light experienced around dusk (or light offset under laboratory conditions) produces phase delays, it is therefore the prominent photic cue used for entrainment when the period of the endogenous SCN circadian oscillation is < 24 h, as is typical for most strains of laboratory mouse. Light exposure late in the subjective night results in phase advances of the SCN and thus light around dawn (or light onset in the laboratory) is the salient photic cue used to reset the SCN clock of organisms with a period > 24 h such as most strains of laboratory rat, as well as humans.[50,51]

Although it is clear that signals transmitted from the retina to the SCN via the RHT are necessary for entrainment, the photoreceptors or the type of retinal ganglion cell (RGC) that mediated the effects of light on the SCN clock were unresolved until relatively recently. Since the pioneering descriptions of the vertebrate retina by Santiago Ramón y Cajal in the late 1800s, it was believed that the retinal rods and cones were the only photoreceptors in mammals.[52] Keeler, in 1927, provided the first suggestion that a non-rod, non-cone photoreceptor might exist when he reported that some mice, despite having no photoreceptors in the outer retina[53] retained their ability to constrict the iris in response to light stimulation (i.e., the pupillary light reflex, PLR).[54] Although it was suggested that RGCs might somehow be light sensitive and therefore be responsible for the observed behavior of the iris, Keeler's prescient suggestion did not gain traction. Reports of mice lacking rods and cones but retaining their ability to entrain their circadian activity rhythms to a light/dark cycle appeared many decades later.[55,56] Additional studies in the late 1990s using transgenic mice lacking rod and cone photoreceptors, reported that these animals also

retained several irradiance-dependent responses including photoentrainment of their circadian locomotor behavior, the PLR, and light-induced suppression of nocturnal pineal melatonin secretion.[57,58] Although these studies and other reports[59-62] provided strong support for the existence of a non-rod, non-cone photoreceptor in the mammalian retina, the prospect that a third photoreceptor in the retina had been missed for over a century was met with considerable skepticism.[63]

SCN-projecting RGCs express melanopsin and are intrinsically photosensitive

Using cultured dermal melanophores from *Xenopus laevis*, Provencio and colleagues identified the photopigment responsible for the light-induced dispersion of melansomes.[64] This opsin, now called melanopsin, is a member of the opsin family of G-protein coupled receptors and it shares the greatest sequence homology to octopus (invertebrate) rhodopsin. Importantly, melanopsin mRNA was expressed in frog dermal melanophores, in the brain and in the retina, but not in typical retinal photoreceptors.[64] In mammals, melanopsin was found to be expressed in the ganglion cell layer of the retina, providing the basis for the suggestion that RGCs expressing the novel mammalian opsin were directly photosensitive.[65] These findings were soon extended by the demonstration that melanopsin was expressed in SCN-projecting RGCs.[66]

The prediction that SCN-projecting RGCs were photosensitive was borne out in early 2002 through a set of landmark reports by Berson, Hattar, Yau and colleagues.[67,68] Berson and coworkers recorded from SCN-projecting RGCs in the rat retina and showed that when these neurons were isolated pharmacologically and physically from all rod and cone synaptic input, they depolarized and generated action potentials in response to photic stimulation; that is, these ganglion cells were intrinsically photosensitive.[67] Importantly, it was also shown that these intrinsically photosensitive retinal ganglion cells (ipRGCs) expressed melanopsin.[68] The discovery of melanopsin by Provencio and colleagues and the reports describing ipRGCs in the rodent retina laid the foundation for what has become an exciting and rapidly growing new subdivision of retinal biology.[63,69-72]

Multiple ipRGC subtypes with widespread axonal projections.

Since the initial description of ipRGC projections to the SCN via the RHT, it has become evident that there are multiple morphological and physiological ipRGC subtypes that send their axons to many areas of the brain, and their diverse functions are actively being investigated. At least five ipRGC subtypes have now been described (M1-M5) and there are preliminary reports of additional subtypes.[70] M1 ipRGCs (initially identified as the SCN-projecting RGCs)[67] have the greatest abundance of melanopsin protein in the plasma membrane and the most robust intrinsic response to light stimulation among all the ipRGC subtypes. In addition to the melanopsin-mediated intrinsic response to light, all ipRGCs receive rod and cone photoreceptor inputs via bipolar cells. In dim light, rods and cones drive ipRGCs whereas the response to bright light is an integration of photoreceptor drive and melanopsin-mediated depolarization. At least two ipRGC subtypes (M1 and M2) innervate the mouse SCN and the vast majority of these (≈ 80%) are of the M1 subtype,[73]

although the functional significance of these two ipRGC subtypes innervating the SCN remains to be determined. M1 ipRGCs can be further parsed based on their expression of the Brn3b transcription factor; Brn3b-negative ipRGCs innervate the SCN.[74] Brn3b-positive M1 ipRGCs send collaterals to the intergeniculate leaflet (IGL), a component of the circadian timing system[75] and to the olivary pretectal nucleus (the midbrain nucleus that regulates the PLR), the medial amygdala, lateral habenula, and superior colliculus.[76,77]

SCN Circadian Gating of Responses to Light Stimulation

Illumination of the retina evokes excitatory postsynaptic currents (EPSCs) in a subpopulation of SCN neurons. These responses have long latencies and are sustained,[78] similar to the responses of M1 ipRGCs to light.[79] The light-induced EPSCs are the result of glutamate release from the RHT and are mediated by both ionotropic and metabotropic glutamate receptors. Where examined to date, the location of these indirectly light-responsive neurons in the SCN has been found to correspond to the terminal field of the RHT, primarily within the ventral and lateral aspects of the SCN, although species differences in the RHT terminal field exist and RHT fibers can be found throughout almost all of the SCN in several species.[77,80] The excitatory response to NMDA is larger during the night than during the day whereas AMPA/kainite-induced currents do not show a day/night difference.[81,82] In addition to glutamate, most (if not all) SCN-projecting ipRGCs also synthesize pituitary adenylate cyclase-activating polypeptide (PACAP)[83] and PACAP may act as a modulator of the glutamatergic input to the SCN.[84] Recent work has reported that when the vesicular glutamate transporter has been selectively knocked out in ipRGCs (Vglut2 conditional knock-outs), mice retain the ability to entrain to light/dark cycles, albeit not normally,[85] indirectly suggesting that RHT release of PACAP alone may be sufficient to entrain the SCN to the light/dark cycle.[85-87]

Obrietan and colleagues have provided evidence that p42/p44 mitogen-activated protein kinase (MAPK) signal transduction plays an important role in gating the responsiveness of the SCN to light. The MAPK pathway in the SCN is induced by light in a phase-dependent manner, couples light to transcriptional activation, and mediates light-induced phase shifts.[88-91] MAPK activation is also triggered by glutamate and PACAP.[92] The Ras-like G-protein Dexras1 also appears to be a critical factor in this process. Dexras1 null mice exhibit a restructured PRC to light at night and a loss of gating to photic resetting during the subjective day.[93] The exact mechanisms by which the SCN clock gates its responses to light, shifting its phase during the subjective night but not during the subjective day, remains to be fully elucidated.

The study of light-induced SCN gene activity resulting in pacemaker resetting was initiated by the seminal observation that light induces a rapid and transient expression of the transcription factor c-Fos within the SCN during the same circadian phases that light shifts the SCN oscillation.[94,95] The *Per* genes (*Per1* and *Per2*) in the SCN are photo-inducible with a phase dependence similar to that of light-induced behavioral phase shifts, suggesting that light-induced induction of *Per* is a pivotal component of phase resetting.[96,97] Daan and colleagues[98] offered an intriguing 2-component molecular model for light-induced phase shifting in the SCN, inspired by earlier work suggesting that *Per1* mediated phase advances

and *Per2* mediated phase delays. However, a subsequent analysis of phase shift responses to light in mice lacking functional *Per* (*Per1* and *Per2*) or Cry (*Cry1* and *Cry2*) genes revealed that all 4 genotypes of mice retain the capacity for both advancing and delaying responses to light.[99] Thus, the molecular mechanism underlying the biphasic response of the SCN to light also remains to be determined.

RHT stimulation increases SCN neuron spike rate and intracellular calcium levels when the spike rate is low at night, and it has been suggested that the light-evoked increase in Ca^{2+} may play a role in shifting the molecular oscillations.[100,101] Although light has little effect on the SCN clock during the subjective day, light stimulation can substantially boost the firing rate of individual SCN neurons that display rhythmic baseline firing (i.e., clock cells).[32] However, this increase in spiking activity during the subjective day does not translate into clock gene (*Per1* or *Per2*) induction and resetting of the molecular clock. The resistance of the clock to phase shift during the subjective day may be because intracellular calcium levels have plateaued at a high level during this phase of the circadian cycle.[100] Indeed, light-evoked increases in action potential firing during the subjective day do little to further increase intracellular calcium levels in SCN clock cells.[101] As in mammals, the pacemaker cells in the marine snail *Bulla gouldiana* respond to light stimulation at all phases of the circadian cycle, while light-induced phase shifts of the circadian pacemaker are restricted to the subjective night. An examination of this model system has shown that light shifts the snail pacemaker only during the subjective night because depolarization of clock cells opens calcium channels during the night when these channels are normally closed.[102] Thus, after even very bright light stimulation during the subjective day, the increase in SCN action potential firing rate may have little influence on SCN molecular clock function. Nevertheless, the increased SCN output at this phase may be sufficient to alter the activity of descending autonomic circuits if the light stimulation is of sufficient duration and intensity.[103]

SCN Functional Organization

The SCN oscillator is composed of thousands of autonomous cellular oscillators that are coupled in a complex neural network that is critically important for the generation of coherent circadian rhythms.[104] In addition, the left and right SCN are coupled to each other, and under certain conditions, each SCN can function as an independent clock.[105,106] The vast majority of SCN neurons synthesize GABA, and there is an extensive GABAergic plexus throughout the SCN, consistent with intra-SCN communication.[104] In addition, all GABAergic neurons use at least one additional peptide neurotransmitter (vasoactive intestinal polypeptide, VIP; vasopressin, VP; gastrin-releasing peptide, GRP; substance P, SP; somatostatin, SS; calbindin, CALB; calretinin, CALR; enkephalin, ENK; neurotensin, NT; or cholecystokinin, CCK).[80] There are considerable species differences in the clustering of peptide-expressing cells in the SCN,[80] but based on the rat model in which VIP neurons are located primarily ventrolaterally and VP cells are found primarily in the dorsomedial aspect, the SCN has historically been divided into two subdivisions.[80] The geniculohypothalamic tract (GHT) arising from neuropeptide-Y (NPY) neurons in the IGL and the RHT arising from ipRGCs, terminate primarily, although not exclusively, in the ventrolateral VIP subdivision in the rat. Another organizational scheme that has arisen is the

'core and shell'[107] although it has been suggested that this an over simplification of SCN functional organization.[80] The distribution of VIP and VP neurons in the SCN appears to be dependent both on the circadian phase when the tissue is examined and the species being studied, with considerable overlap in the distribution of these peptide-expressing neurons (see Morin and Allen, 2006 for a comprehensive review).[80] Interactions among SCN neurons are required for robust and coherent SCN function, with GABA and VIP playing a prominent role, while the coupling between regional SCN pacemakers may be dependent on the photoperiodic environment.[108-111]

Although GABA is typically associated with inhibitory post-synaptic responses in the mature brain, GABA-evoked excitation has been reported in the SCN of adult animals. Indeed, GABA-evoked excitation during the day was originally suggested to contribute to the higher level of firing rate of SCN neurons noted during this phase of the circadian cycle.[112] However, now it is unclear whether GABA-evoked excitation is restricted to particular phases of the circadian cycle and/or to particular cell types or sub-regions of the nucleus.[113,114] The cellular mechanisms underlying GABA-evoked excitation in the SCN is unknown although it is well documented that the expression and function of cation-chloride cotransporters are responsible for the shift in GABAergic responses during development.[115] There is a heterogeneous distribution of cation-chloride cotransporters within the SCN[116,117] although it is not known if their expression and/or function, regulated by the WNK-SPAK/OSR1 kinase complex, is under circadian regulation.[118] It was recently suggested that GABA-evoked excitation in the SCN may be regulated by day length and therefore may play a role in seasonal adjustments of SCN activity.[119]

Serotonergic Modulation of Photic Input to the SCN

The SCN receives a robust serotonergic input arising from ascending projections of serotonin (5-HT) neurons in the median raphe nucleus that modulates RHT input.[120,121] Although SCN neurons express several serotonin receptor subtypes, the best-documented mechanism by which 5-HT alters the response of the SCN to light is via presynaptic 5-HT_{1B} receptors located on RHT terminals, inhibiting ipRGC glutamate release.[122-126] This inhibitory function might suggest that knocking out 5-HT_{1B} receptors would enhance the effect of light on SCN-mediated behavior. However, mice lacking 5-HT_{1B} receptors have an attenuated response to light,[127] most likely because 5-HT_{1B} receptors are also located presynaptically on GABAergic terminals in the SCN.[128] Thus, although 5-HT_{1B} receptor KO mice have increased glutamatergic transmission via the RHT, there is apparently a concomitant increase in GABAergic transmission within the SCN that may 'spillover' to attenuate RHT input via $GABA_B$ receptors also located presynaptically on RHT terminals.[129] The attenuated response to light in the 5-HT_{1B} receptor KO mouse results in a delayed phase angle of entrainment compared to wild-type mice under short-day (winter-like) conditions, whereas entrainment to standard 12L:12D conditions is unaffected.[130] Thus the circadian response to light in mice lacking 5-HT_{1B} receptors phenocopies people suffering from recurring winter depression or seasonal affective disorder (SAD), who typically manifest a phase-delayed circadian system.[131] Various lines of clinical evidence point to a significant role for 5-HT in the pathophysiology of SAD and alterations in the

function of 5-HT_{1B} receptors have been shown to be associated with depression-like states.[132,133]

Outputs from the SCN

SCN temporal signals drive rhythms in behavior, physiology, metabolism and hormone secretion. This function is accomplished via the three major output pathways that exit the SCN: 1) a rostral pathway into the medial preoptic area which continues into the paraventricular nucleus of the thalamus (relaying SCN signals to the medial prefrontal cortex);[134,135] 2) a pathway that runs caudally along the base of the brain to the retrochiasmatic area and into the capsule of the ventromedial nucleus; and 3) the largest of these pathways that travels in an arc dorsally and caudally giving off terminals along the way to innervate the area immediately dorsal to the SCN, the ventral subparaventricular zone (vSPZ) and to a region ventral to the paraventricular hypothalamic nucleus (PVN), the dorsal subparaventricular zone.[134,136] Some of these fibers continue caudally to the dorsomedial nucleus of the hypothalamus (DMH), which in turn participates in the regulation of the hypocretin/orexin system[137] helping to consolidate wakefulness (see Chapter 2). SCN projections into the periventricular portion of the PVN convey circadian signals to descending circuits that synapse in the pre-ganglionic sympathetic neurons of the spinal cord that regulate many autonomic functions, including rhythmic pineal melatonin secretion.[138,139] There are also sparse projections to corticotropin releasing hormone (CRH) cells in the PVN that contribute to the circadian rhythm of corticosterone secretion and to the ventrolateral preoptic nucleus (VLPO) which promotes sleep.[134]

The SPZ is an especially important relay for SCN signals and lesions in this area reduce the amplitude or disrupt multiple circadian rhythms, including rhythmic sleep, body temperature, locomotor activity and neural activity in structures outside the SCN. The SPZ may be the region in the hypothalamus that translates SCN signals to determine whether an animal's behavior is nocturnal or diurnal.[140] As an integration site of SCN signals with other homeostatic drives, the SPZ allows for plasticity in the timing of behavior. An example of such behavioral plasticity is seen when food access is restricted to a few hours in daytime. Under these conditions, locomotor activity shifts phase from the night into the day and eventually causes nocturnal torpor (natural hypothermia).[141,142]

Although homogeneous in its cytoarchitecture, the SPZ can be divided into functional quadrants that are interconnected to each other and the SCN. The dorsal subdivision is critical for relaying SCN signals regulating body temperature rhythms whereas the ventral subdivision appears more important for relaying SCN signals that control rhythms of sleep and locomotor activity.[143-145] The medial region of the SPZ receives afferent fibers mainly from the dorsomedial aspect of the SCN. On the other hand, the lateral SPZ receives signals from the ventrolateral SCN and also RHT afferents that extend beyond the boundaries of the SCN. These extra-SCN retinal inputs to the lateral SPZ may be part of a functional subdivision of the RHT [146] and may have contact with neuroendocrine cells in the hypothalamus, providing direct input to neuroendocrine and autonomic circuits as a parallel pathway for photic regulation of homeostatic regulation.[103, 147]

The SCN regulates peripheral circadian oscillators

Over the past decade it has become clear that the SCN is not the only circadian oscillator in mammalian systems. Several regions of the brain outside the SCN have the capacity to generate circadian oscillations in neural activity and virtually all organs of the body contain autonomous circadian oscillators.[148-152] The oscillators outside the SCN utilize the same core clock genes that generate circadian oscillations in the SCN, and 5-10% of the transcriptome in peripheral tissues display circadian rhythms (i.e., up to ≈10% of the genes are clock-driven genes) although the subset of rhythmic transcripts is distinct among the various tissues, reflecting their specific functions.[153] The most significant difference between the SCN oscillator and the vast majority of peripheral oscillators is that the latter depend on SCN-derived signals to maintain sustained rhythms due to the lack of strong coupling between cells in peripheral tissues compared to the tightly coupled neural network of the SCN.

In addition, while photic cues entrain the SCN and contribute to coupling among SCN neurons, peripheral tissues have no direct access to signals from the retina and thus are dependent on the SCN both for entrainment to the day/night cycle and for maintaining intercellular coupling. However, the full scope and nature of the SCN-regulated signals that entrain and couple peripheral oscillators are not completely understood. For example, rhythms in body temperature that are regulated by the SCN may play an important role in maintaining synchrony between cells in peripheral organs.[154,155] Yet another example is observed in daily feeding rhythms: restricting the feeding of a nocturnal animal to daytime hours alone shifts the phase of clock gene RNA expression in the liver and other peripheral tissues, while the SCN remains normally entrained to the light:dark cycle.[156]

Lastly, a crucially important temporal signal that helps maintain synchrony among peripheral (and central) oscillators is the SCN-regulated daily rhythm in glucocorticoids (cortisol in humans and corticosterone in rodents). Glucocorticoids are potent transcriptional regulators. The robust corticosterone rhythm is critically important in synchronizing subordinate circadian oscillators in the periphery. This is accomplished through the action of glucocorticoid receptors (GRs) on glucocorticoid-responsive elements within the promoter and enhancer sequences of the *Per1* and *Per2* genes.[157-159] The rhythmic expression of a diverse set of genes in the CNS is dependent on rhythmic corticosterone secretion[160-166], although there are no GRs in the SCN. It has been shown that manipulation of corticosterone rhythms alters the speed of re-entrainment to shifted light:dark cycles[167,168] and rhythmic regulation of GRs leads to phase dependent changes in the sensitivity to glucocorticoids,[169] emphasizing the need for the coordination of central and peripheral oscillators. Serotonin synthesis in the dorsal raphe nucleus is dependent on the high amplitude corticosterone rhythm,[164,170] and flattening in the cortisol rhythm due to increased basal levels is common for patients suffering from major depression.[171-174] Moreover, there may also be an association between the daily cortisol rhythm and seasonal affective disorder: SAD patients may have both the phase delayed circadian system noted above, and also a reduced daily cortisol rhythm.[175] Indeed, recent studies using animal models with entrainment to winter-like (short-day) cycles have observed that when animals exhibit behavioral activity rhythms

that are substantially delayed under these conditions, the amplitude of the corticosterone rhythm is reduced by 50%.[176]

Studies such as those reported herein, and many others currently underway, continue to reinforce the notion that the precise regulation of circadian timing, whether driven or merely coordinated by the central circadian pacemaker in the SCN, is crucial to the sustenance of both physical and mental health. Much work remains to be done to uncover the full range of the mechanisms through which this regulation is effected, but each discovery yields new opportunities to help restore the temporal balance that is required to live in harmony with the ineluctable cyclicity of the earth's rotation.

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LIST OF ABBREVIATIONS

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid
BK	large-conductance Ca^{2+} activated K^+ currents
BMAL1	brain and muscle ARNT-like 1
Brn3b	Brain-specific homeobox/POU domain protein 3B
CALB	calbindin
CALR	calretinin
CCK	cholecystokinin
CLOCK	circadian locomotor output cycles kaput
CNS	central nervous system
CRH	corticotropin releasing hormone
CRY	cryptochrome
CT	circadian time
DD	constant darkness
DMH	dorsomedial nucleus
ENK	enkephalin
EPSCs	excitatory postsynaptic currents
FDR	fast delayed rectifier K^+ currents
GABA	gamma-aminobutyric acid
GHT	geniculohypothalamic tract
GR	glucocorticoid receptor
GRP	gastrin-releasing peptide

IGL	intergeniculate leaflet
I_H	hyperpolarization-activated currents
ipRGC	intrinsically photosensitive retinal ganglion cell
KO	knockout
M1, M2	ipRGC subtypes
MAPK	p42/p44 mitogen-activated protein kinase
NMDA	N-methyl-D-aspartate
NPY	neuropeptide Y
NT	neurotensin
OSR1	oxidative stress-related kinase 1
PACAP	pituitary adenylate cyclase-activating polypeptide
PER	period
PLR	pupillary light reflex
PRC	phase response curve
PVN	paraventricular nucleus
REV-ERBα	orphan nuclear receptor
RGC	retinal ganglion cell
RHT	retinohypothalamic tract
ROR	retinoid-related orphan receptor
SAD	seasonal affective disorder
SCN	suprachiasmatic nucleus
SP	substance P
SPAK	sps1-related proline/alanine-rich kinase
SPZ	subparaventricular zone
SS	somatostatin
VIP	vasoactive intestinal polypeptide
Vglut2	vesicular glutamate transporter 2
VLPO	ventrolateral preoptic nucleus
VP	vasopressin
WNK	lysine deficient protein kinase 1
5-HT	serotonin

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KEY POINTS

- The suprachiasmatic nucleus (SCN) is the primary circadian oscillator in the brain responsible for temporal coordination.
- A set of clock genes forms interlocking transcription/translation feedback loops.
- A rhythm in SCN neural activity represents the functional output of the clock.
- The SCN is entrained to the day/night cycle via the retinohypothalamic tract.
- A recently discovered retinal ganglion cell photoreceptor innervates the SCN.

SYNOPSIS

There is a growing recognition that the coordinated timing of behavioral, physiologic and metabolic circadian rhythms is a requirement for a healthy body and mind. In mammals, the primary circadian oscillator is the hypothalamic suprachiasmatic nucleus (SCN), which is responsible for circadian coordination throughout the organism. SCN neurons express a core set of clock genes with interlocking transcriptional/translational feedback loops that underpin SCN rhythmicity. Retinal signals, transmitted from intrinsically photosensitive retinal ganglion cells via the retinohypothalamic tract, entrain the SCN circadian clock to the environmental day/night cycle. The SCN, in turn, maintains global circadian synchrony of localized tissue-based circadian clocks in the periphery via connections with the autonomic circuits innervating peripheral organs. The SCN also maintains synchrony in and between tissue-based circadian clocks throughout the body by its regulation of rhythmic secretion of hormones such as the glucocorticoids. Temporal homeostasis is now recognized as a complex interplay between rhythmic clock gene expression in brain regions outside the SCN and in peripheral organs, controlled by the integration of SCN efferent signals directly in the brain and indirectly via autonomic circuits together with the high amplitude daily cortisol rhythm. Abnormalities in this intricate circadian orchestration may alter sleep patterns and contribute to the pathophysiology of affective disorders.

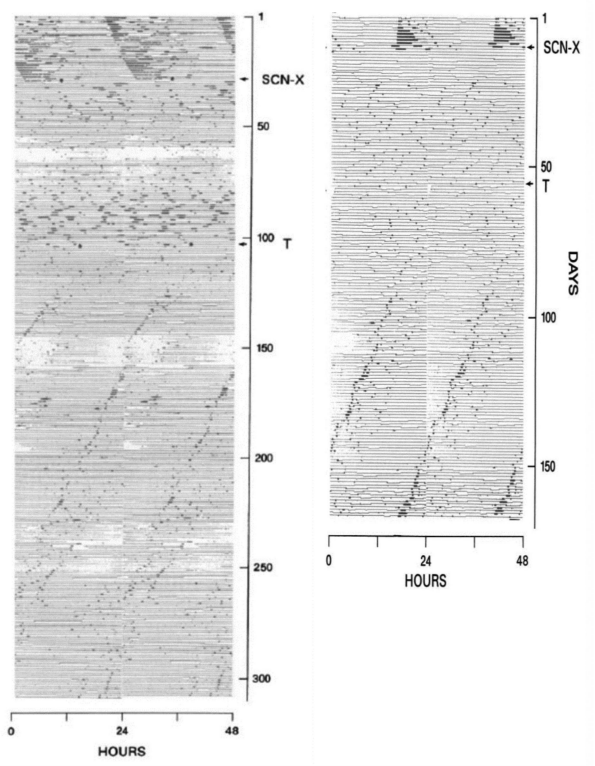

Figure 1.

Anterior hypothalamic heterografts restore circadian behavior to arrhythmic SCN-lesioned hosts. Wheel-running activity record of SCN-lesioned hamsters bearing a fetal mouse anterior hypothalamic (AH) heterograft (left) or a fetal rat AH heterograft (right). Note that the period of the restored circadian rhythm on the left is typical of that of an intact mouse (i.e., < 24h), but the restored rhythm on the right is not typical of that of an intact rat (i.e., > 24h). SCN-X indicates day of complete, bilateral SCN lesion. T indicates day of fetal AH implantation.

Adapted from Sollars PJ, Kimble DP, Pickard GE. Restoration of circadian behavior by anterior hypothalamic heterografts. J Neurosci 1995; 15:2109-2122; with permission.

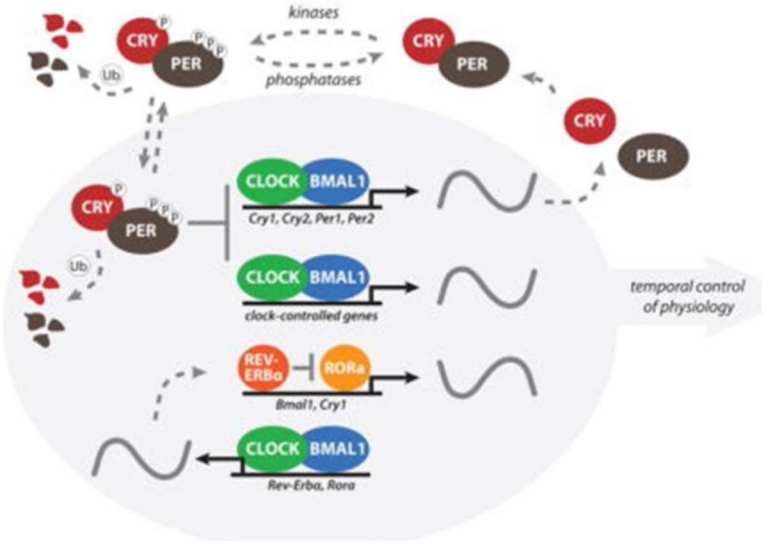

Figure 2.

Molecular architecture of the mammalian circadian clock.

From Partch CL, Green CB, Takahashi JS. Molecular architecture of the mammalian circadian clock. Trends Cell Biol. 2014; 24:90-99; with permission.