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Review

The suprachiasmatic nuclei as a seasonal clock

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ABSTRACT

In mammals, the suprachiasmatic nucleus (SCN) contains a central clock that synchronizes daily (i.e., 24-h) rhythms in physiology and behavior. SCN neurons are cell-autonomous oscillators that act synchronously to produce a coherent circadian rhythm. In addition, the SCN helps regulate seasonal rhythmicity. Photic information is perceived by the SCN and transmitted to the pineal gland, where it regulates melatonin production. Within the SCN, adaptations to changing photoperiod are reflected in changes in neurotransmitters and clock gene expression, resulting in waveform changes in rhythmic electrical activity, a major output of the SCN. Efferent pathways regulate the seasonal timing of breeding and hibernation. In humans, seasonal physiology and behavioral rhythms are also present, and the human SCN has seasonally rhythmic neurotransmitter levels and morphology. In summary, the SCN perceives and encodes changes in day length and drives seasonal changes in downstream pathways and structures in order to adapt to the changing seasons.

1. Introduction

The rotation of the Earth on its axis, combined with the Earth's annual revolution around the Sun, causes both daily and seasonal fluctuations in photoperiod, light intensity, temperature, and food availability. Many organisms have evolved an innate clock that produces circadian rhythms (i.e., rhythms with a period (revolution time) of approximately 24 h) that enables them to anticipate and accommodate these cyclic changes in the environment. The internal clock is an adaptation to the environment, and it increases the organism's likelihood of survival (i.e., the organism's fitness) (DeCoursey and Krulas, 1998). Animals that are synchronized to both daily and annual cycles can anticipate and prepare for changes in food availability and ambient temperature, as well as the presence of predators, mating opportunities, and social interactions. Most animals have a clear 24-h rhythm in terms of their physiological functions, including body temperature, hormone production and secretion, behavioral activity, and sleep. Besides a circadian rhythm, many animals also display a seasonal rhythm. Seasonal breeding animals such as squirrels, hamsters and sheep experience drastic changes in behavior, reproductive physiology and metabolism. Other animals, like mice and rats display altered behavioral activity patterns in response to changing day lengths (Fig. 2A and F).

In mammals, the central clock that synchronizes these 24-h rhythms is located in the suprachiasmatic nucleus (SCN), a bilateral structure comprised of approximately 10,000 neurons (Abrahamson and Moore, 2001). The SCN is located in the ventral periventricular zone of the anterior hypothalamus, dorsal to the optic chiasm, in close proximity to the third ventricle. The SCN is required for the generation of overt circadian rhythms, and is synchronized to the external day-night cycle by light (Ralph et al., 1990). Light information reaches the SCN through a monosynaptic pathway from the retina to the SCN; this pathway is known as the retinohypothalamic tract (RHT). Thus, the SCN is the first and most rostral structure in the brain to receive photic information on photoperiod. Because of its central role in detecting and encoding photic information, the SCN is indispensable for regulating daily and seasonal rhythms.

The molecular mechanism that underlies rhythm generation is based upon interconnected positive and negative feedback loops that regulate the transcription of core clock genes and the function of these genes' protein products. The transcription factors Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle ARNT-like protein 1 (Bmal1) promote the transcription of target genes, including the Period (*Per1*, *Per2*, and *Per3*) and Cryptochrome (*Cry1* and *Cry2*) gene families. In turn, the Per and Cry proteins repress CLOCK/Bmal1-mediated gene transactivation. The nuclear receptors ROR (α, β, and γ), PPARα, and REV-ERB (α and β) comprise an additional regulatory loop. Results obtained from experiments using dissociated SCN cells revealed that individual cells have a circadian rhythm in their firing rate, with a wide range

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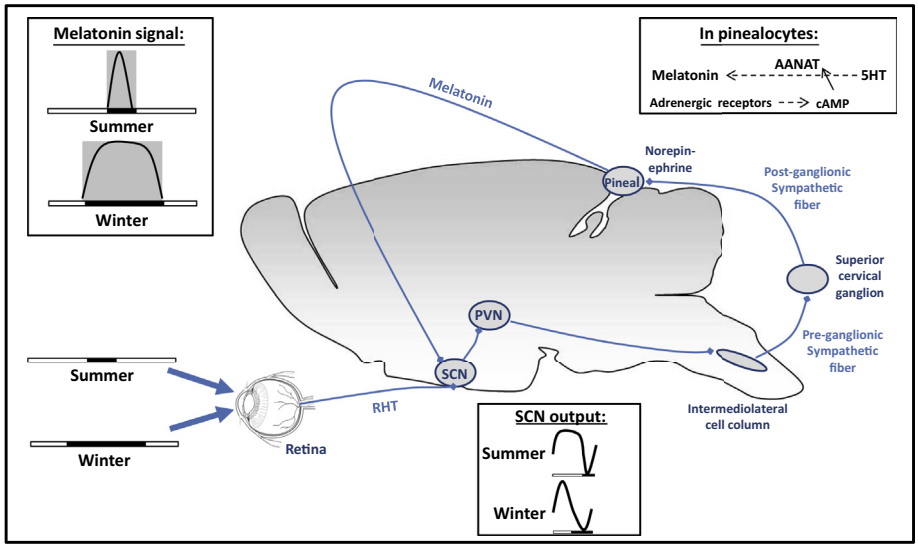

Fig. 1. Schematic overview of the pathway regulating seasonal melatonin secretion. Light synchronizes the master clock with the external day-night cycle, and photic information received by the retina reaches the suprachiasmatic nuclei (SCN) via the retinohypothalamic tract (RHT). The external photoperiod influences the electrical activity of the SCN, thereby enabling the SCN to code for long summer days and short winter days. This photoperiodic information is then transmitted from the SCN to the pineal gland via a polysynaptic efferent pathway that travels through the paraventricular nucleus (PVN) to the intermediolateral cell column of the thoracic spinal cord, to the superior cervical ganglion, and finally to the postganglionic adrenergic fibers that innervate the pineal gland. Norepinephrine is released from these sympathetic nerve endings at night, stimulating postsynaptic β1 and α1 adrenergic receptors on the pinealocytes, causing a large increase in intracellular cAMP levels. This increase in cAMP activates serotonin *N*-acetyltransferase (AANAT). Oscillating levels of activated AANAT result in the rhythmic synthesis and secretion of melatonin. During short summer nights (i.e., long photoperiod), the nocturnal melatonin signal is compressed temporally; in contrast, the signal is relatively prolonged during long winter nights (i.e., short photoperiod). These photoperiod-induced changes in melatonin secretion have wide-reaching effects on seasonal animal physiology and behavior.

of intrinsic periods (ranging from 22 h to 28 h) (Herzog et al., 1998; Shirakawa et al., 2000; Welsh et al., 1995). These results gave rise to the notion that individual SCN neurons are autonomous single-cell oscillators driven by their intrinsic molecular feedback loops (Welsh et al., 1995).

In the past decade, it has become increasingly evident that the SCN's ability to regulate seasonal rhythms is dependent upon the plasticity of the SCN's neuronal network. By adjusting the phase relationship among single cell oscillators, the SCN can code for short winter days and long summer days, respectively. Thus, the SCN's ability to encode photoperiod information requires the presence of a functional neuronal network. Hence, this is in contrast, with the SCN's ability to produce circadian rhythms, which is a cell autonomous property. By encoding photoperiod information, the SCN creates an internal representation of day length, and this representation is transmitted to other brain nuclei, including the pineal gland, which plays a major role in the regulation of seasonal reproduction cycles by releasing melatonin. A schematic overview of the pathway regulating melatonin secretion is shown in Fig. 1. In this chapter, we will review the changes that occur within the SCN under the influence of a changing photoperiod. We will first describe the characteristic light response properties of SCN neurons, that are essential to measure the length of the day. Next, we will discuss the SCN's heterogeneous organization and the role of the SCN in storing photoperiod information. We will then review several of the SCN's efferent pathways that are involved in seasonal responses, including the pathways that lead to the pineal gland, which plays a key role in regulating breeding cycles. Finally, we will review the evidence showing that the human clock has seasonal rhythmicity.

2. The SCN as a luminance detector

Irradiance detection is one of the SCN's primary functions (Morin and Allen, 2006; Meijer and Schwartz, 2003). By detecting changes in ambient illumination levels, the clock becomes properly phased relative to the external day-night cycle and is therefore attuned to gradual changes in day length; this information is then used as an indication of the changing seasons. The SCN's ability to respond in a sustained fashion (i.e., without adaptation) to environmental light is nearly unique to the SCN and is typical of some of the non-image-forming visual centers in the brain (Foster and Hankins, 2007; Lucas, 2013). Irradiance detection is based on the complementary actions of melanopsin, rods, and cones (van Diepen et al., 2013; Lall et al., 2010; Altimus et al., 2008; Drouyer et al., 2007). Melanopsin alone is sufficient for photic entrainment (Freedman et al., 1999; Foster et al., 1991), and in the absence of rods and cones, sustained responses can be recorded from ip-retinal ganglion cells (ipRGCs) and cells in the SCN (Berson et al., 2002; Hattar et al., 2002; Wong, 2012). In the absence of melanopsin, however, sustained responses are preserved in the SCN, and although the SCN's phase-shifting capacity is reduced, animals entrain normally to the light–dark cycle (Ruby et al., 2002; Panda et al., 2002). These findings underscore the presence of overlapping tasks of rods, cones, and melanopsin.

Recordings within the SCN have revealed the presence of a subpopulation of cells that are acutely affected by light stimuli. In nocturnal rodents, including rats, hamsters and mice, approximately 25% of the SCN's cells are excited by light stimuli, and a smaller population has a reverse response and is inhibited—or silenced completely—by light (Meijer et al., 1998; Brown et al., 2011; Aggelopoulos and Meissl, 2000; Nakamura et al., 2004). In diurnal animals, the percentage of light responsive cells is lower, and relatively more cells are light suppressed (Meijer et al., 1989; Jiao et al., 1999).

The magnitude of the change in the discharge rate of both light-activated and light-inhibited SCN neurons is a function of light intensity (Meijer et al., 1998; Aggelopoulos and Meissl, 2000). The intensity-response curve is sigmoidal with a working range centered around the light intensities that occur at dawn and dusk. This working range is relatively narrow compared to the range of light intensities that actually occurs in the environment;

consequently, changes in environmental illumination are translated into a signal that indicates "day" versus "night", whereas the SCN can discriminate only poorly between light intensities that occur throughout the day (for example, to determine whether it is a sunny day or a cloudy day). The SCN's ability to detect changes in illuminance is a prerequisite to determine the length of the day and thus changes in photoperiod.

3. SCN network plasticity

The combined electrical activity of individual SCN neurons is integrated to produce electrical activity oscillations at the SCN network level. This output signal has a sinusoidal-like waveform pattern and oscillates with ~24-h precision. The peak of the SCN's electrical output is during the day, and the trough is during the night. This rhythm is typical of the SCN and is present in both diurnal and nocturnal species. *In vivo* electrophysiology recordings in the SCN of freely moving mice revealed that transitions in behavior from rest to activity—and vice versa—occur at half-maximal levels of the SCN's electrical activity rhythm (Houben et al., 2009).

Compelling evidence suggests that plasticity in the SCN's neuronal network plays a major role in the SCN's ability to adjust to changes in the photoperiod. *In vivo* recordings of SCN discharge rate in freely moving mice showed that after the animals are moved to continuous darkness, the SCN's electrical activity waveform is retained for many circadian cycles (Houben et al., 2009; Vanderleest et al., 2007). Thus, the SCN has a "memory" for photoperiod. During both long and short photoperiods, increasing electrical activity triggers the offset of behavioral activity when it reaches the 50% level and decreasing electrical activity triggers the onset of behavioral activity when the 50% level is reached. Thus, the SCN's waveform—and in particular, the peak width of the waveform—stores photoperiodic information (Houben et al., 2009). Waveform changes are preserved and measurable *in vitro* (Mrugala et al., 2000; Jagota et al., 2000). Following a change to a short photoperiod, the peak of the SCN's electrical activity pattern is compressed (i.e., the peak width becomes narrower), whereas changing to a long photoperiod broadens the peak width (Mrugala et al., 2000). *In vitro* single-cell recordings from acute SCN slices obtained from both mice and rats that were entrained to a 12-h photoperiod revealed that individual cells are active for a relatively short period of time (*ca.* 4–5 h) (Schaap et al., 2003; Brown et al., 2006). The majority of neurons were active throughout midday, some neurons were active at dawn and dusk, and relatively few neurons during the night (Vanderleest et al., 2007; Schaap et al., 2003). These findings revealed that the electrical activity patterns of individual cells differ from the electrical activity waveform of the entire SCN network, and indicate that the waveform of the SCN rhythm is determined by the temporal distribution of the single-cell activity patterns (Vanderleest et al., 2007; Schaap et al., 2003; Rohling et al., 2006; Brown and Piggins, 2009).

When entrained to a short photoperiod, the individual electrical activity patterns have a narrow phase distribution, meaning that the peak in their activity is close in time (i.e. around midday), whereas the patterns are more widely distributed when entrained to a long photoperiod. The narrow phase distribution of subpopulation activity patterns in a short photoperiod explains the compression of electrical activity waveforms measured at the population level in the SCN (Vanderleest et al., 2007) (Fig. 2G–J). Likewise, the electrical activity in the SCN of mice entrained to a long photoperiod has a decompressed peak SCN waveform, which can be explained by the wide distribution of subpopulation activity patterns (Vanderleest et al., 2007; Mrugala et al., 2000) (Fig. 2B–E). Importantly, the individual electrical activity patterns in short photoperiods are remarkably similar to the activity patterns in long photoperiods (Vanderleest et al., 2007; Schaap et al., 2003; Rohling et al., 2006; Brown and Piggins, 2009). Thus, the electrical activity pattern at the SCN population level is determined by the phase relationship between the individual SCN neurons (Vanderleest et al., 2007; Schaap et al., 2003; Rohling et al., 2006; Brown and Piggins, 2009). Furthermore, the single-cell electrical activity profiles in the dorsal SCN differ between long photoperiods and short photoperiods while this difference is not present in the ventral SCN (Brown and Piggins, 2009). Computational studies found that differences in single-unit activity profiles in the dorsal SCN are not sufficient to explain the waveform changes at the SCN network level (Brown and Piggins, 2009; Rohling et al., 2006). Moreover, molecular studies revealed that the single-cell expression patterns—measured by measuring *Per1* expression—do not differ between long and short photoperiods (Naito et al., 2008). Together the studies support the hypothesis that the phase distribution of single cells plays a key role in seasonal adaptation by the SCN (Brown and Piggins, 2009). Fig. 2 provides an illustrative overview of the seasonal information processing by the circadian system.

Molecular and electrophysiology studies revealed differences in regional organization within the SCN; molecular expression patterns are more region-specific, whereas electrical activity profiles are more homogenous. Anatomically, the SCN can be divided in two major sub-regions, namely the ventrolateral and dorsomedial regions (Van den Pol, 1980). The ventrolateral SCN contains vasoactive intestinal polypeptide (VIP)-expressing neurons, whereas the dorsomedial SCN contains predominantly arginine vasopressin (AVP)-expressing neurons (Morin and Allen, 2006). γ-aminobutyric acid (GABA) is the most common neurotransmitter in the SCN and is expressed in both sub-regions (Moore et al., 2002). In the past two decades, it has become increasingly clear that several neurotransmitters in the SCN, including VIP, GABA, and gastrin-releasing peptide (GRP), are involved in the synchronization of individual neurons. Below, we will discuss the sub-regional photoperiodic differences in clock gene profiles and the importance of neurotransmitters in seasonal encoding of the SCN.

3.1. Rostro-caudal axis

As mentioned above, anatomically the SCN can be divided in a ventrolateral and dorsomedial region, however, in seasonality also the rostral and caudal SCN can be distinguished from each other and exhibit differences in their response to change in day length (Johnston, 2005; Inagaki et al., 2007; Hazlerigg et al., 2005; Yan and Silver, 2008). For example, Hazlerigg and colleagues reported a difference between the rostral and caudal expression patterns of Per2, Rev-erbα, and D-site albumin promoter binding protein (Dbp) in the SCN of Siberian hamsters (*Phodopus sungorus*, also known as the Djungarian hamster) following exposure to a long photoperiod (16 h light:8 h dark) (Hazlerigg et al., 2005). Although the peak time of RNA expression in the rostral SCN was unaffected—or delayed slightly relative to midday—following exposure to a long photoperiod, the peak expression of all three genes was advanced in the caudal SCN. In contrast, the expression patterns of these genes were similar in the rostral and caudal SCN of Siberian hamsters that were previously housed in a short photoperiod (8 h light:16 h dark), and RNA levels peaked at approximately the same time in both sub-regions (Hazlerigg et al., 2005). Furthermore, SCN gene expression studies demonstrated that photoperiod regulates SCN gene expression of the E-box-regulated genes (Per1, Per2, Cry1, Rev-erbα, AVP and Dbp), while Bmal1 and Cry2 are not affected (Johnston et al., 2005). Based on these findings, a multiple-oscillator model was proposed in which the caudal and rostral SCN encode information regarding the time at which dawn and dusk occur, respectively. Thus, as the photoperiod is lengthened, the

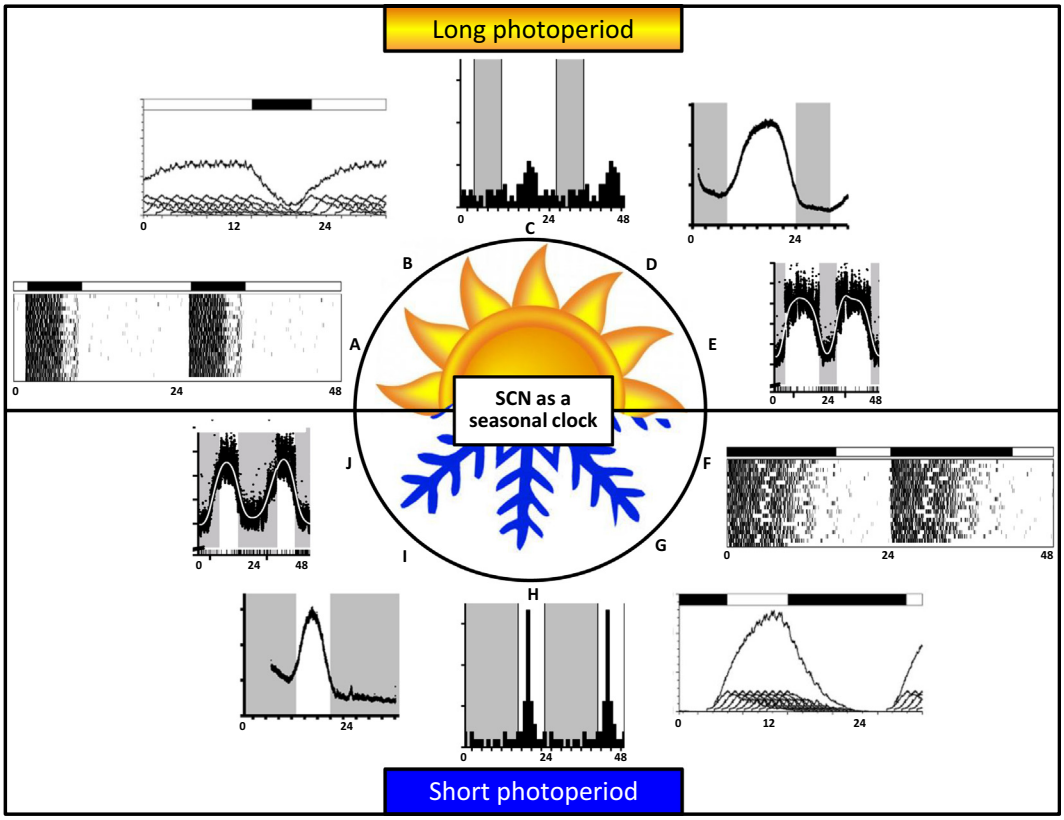

Fig. 2. The SCN's ability to regulate seasonal rhythms is dependent upon the plasticity of the SCN's neuronal network. The graphs should be read in a clockwise manner. In a long photoperiod (upper panel), animals display compressed activity patterns in accordance with the light–dark cycle (A; double plotted actogram). In long days, there is relatively weak phase synchronization among the individual SCN neurons and subpopulations of SCN neurons; accordingly, the distribution of neuronal activity patterns is wider (B; average single unit activity plotted as a function of time in h and C; double plotted histogram of SCN neuronal subpopulation activity peak times plotted as a function of time in h). Both *in vitro* (D; multiunit activity in Hz plotted as a function of time in h) and *in vivo* (E; multiunit activity in Hz plotted as a function of time in h) measurements of electrical activity in the SCN of mice entrained to a long photoperiod reveal a decompression of the peak in the SCN waveform, consistent with the wide distribution of subpopulation activity patterns observed in long days. In short photoperiods (lower panel), animals have long bouts of nocturnal activity (F double plotted actogram). Electrical recordings of small populations of SCN neurons show that in short days, these subpopulations are relatively phase-synchronized. Consequently, the distribution of single-cell activity is narrow and reveals a clear peak in individual activity at midday (G; average single unit activity plotted as a function of time in h and H; double plotted histogram of SCN neuronal subpopulation activity peak times plotted as a function of time in h). The narrow phase distribution of the patterns of subpopulation activity in a short photoperiod causes a compression of the electrical activity waveform, measured at the SCN network level both *in vitro* (I; multiunit activity in Hz plotted as a function of time in h) and *in vivo* (J; multiunit activity in Hz plotted as a function of time in h). Adapted with permission from Vanderleest et al. (2007) and Schaap et al. (2003) (Copyright (2003) National Academy of Sciences, U.S.A. and Elsevier).

caudal SCN tracks dawn, and the rostral SCN tracks dusk (Johnston, 2005). Long-term *in vitro* measurements of circadian rhythms in the clock gene *Per1* in the SCN of mice that were previously exposed to either a long, medium, or short photoperiod revealed three oscillating SCN sub-regions; one sub-region is located in the caudal SCN, and the other two sub-regions are located in the rostral SCN (Inagaki et al., 2007). The circadian oscillation in *Per1* expression in the caudal SCN was phase-locked to the offset of behavioral activity in all three photoperiods; in contrast, the oscillation of the rostral SCN was phase-locked to the onset of behavioral activity. The *Per1* expression pattern in the rostral SCN was unimodal in short and medium photoperiods; however, in long photoperiods, a bimodal pattern emerged, suggesting the presence of a second oscillator in the rostral SCN (Inagaki et al., 2007).

3.2. Ventral versus dorsal SCN

Because nearly all light-responsive cells are concentrated in the retinorecipient ventrolateral SCN (i.e., the "core" SCN), this sub-region is acutely affected by light (Antle and Silver, 2005; Bryant et al., 2000; Tanaka et al., 1997; Yan et al., 2007). Light increases the expression of *c-fos*—measured as *c-fos* mRNA and c-Fos protein immunoreactivity (c-Fos-ir)—in the ventrolateral SCN in rats, mice and hamsters (Jac et al., 2000; Silver et al., 1996; Colwell and Foster, 1992; Ebling et al., 1991). Moreover, the ventral SCN has light-induced alterations in clock gene expression (Yan et al., 1999; Dardente et al., 2002; Kuhlman et al., 2003; Karatsoreos et al., 2004; Schwartz et al., 2000) and acute responses in electrical activity (Kuhlman et al., 2003; Shibata et al., 1984a,b; Groos and Mason, 1980; Meijer et al., 1986, 1992). The up-regulation of *c-fos* expression following a light pulse is dependent on the circadian phase (i.e. the time of the cycle) and occurs exclusively during subjective night (Sumova et al., 1995; Travnickova et al., 1996; Illnerova et al., 2000). In rats that are first entrained to a long photoperiod and subsequently housed in continuous darkness, the interval for *c-fos* mRNA expression and c-Fos-ir in the ventral SCN in response to a light pulse was significantly shorter than in rats from short photoperiods (Sumova et al., 1995). The after effects of photoperiod on the interval of *c-fos* expression indicates that the ventral SCN has a memory of the previous photoperiod (Sumova et al., 2004). Moreover, in hamsters a striking difference in c-Fos expression in the ventral SCN during the dark phase was found between hamsters housed in a long and short photoperiods (Yan and Silver, 2008).

The dorsomedial sub-region of the SCN (i.e., the "shell" of the SCN) does not receive direct light input (Jac et al., 2000;

Schwartz et al., 2000; van den Pol, 1991; Guido et al., 1999a,b; Sumova et al., 1998); instead, this sub-region receives non-photic input from the cortex, basal forebrain, and hypothalamus (Jac et al., 2000; van den Pol, 1991; Cagampang et al., 1994). To synchronize with the external light–dark cycle, the dorsomedial SCN is dependent on projections from the ventral SCN. The functional difference between the various sub-regions of the SCN becomes clear in the case of temporal asynchrony between the SCN and the external light–dark regimen, which is triggered by exposure to a shift in the external cycle (de la Iglesia et al., 2004; Albus et al., 2005). Although the ventral SCN adapts rapidly to a new external cycle, the dorsal SCN requires several days to resynchronize (Yan and Silver, 2008; Reddy et al., 2002; Nagano et al., 2003). Accordingly, the dorsal SCN lacks a light-induced up-regulation of *c-fos* mRNA levels; however, the dorsal SCN has spontaneous rhythmic expression of *c-fos* and the protein product c-Fos (Sumova et al., 1998). This rhythmic expression of *c-fos* in the dorsal SCN persists in continuous darkness for at least two cycles, in contrast to the light-induced *c-fos* expression rhythm in the ventral SCN. The spontaneous *c-fos* expression rhythm in the dorsal SCN may represent rhythmic intrinsic neuronal activity that is driven by a molecular feedback loop (Sumova et al., 1998). Rhythms in *c-fos* expression—and c-Fos protein levels—adapt to the external photoperiod. In rats entrained to a long photoperiod, the dorsal SCN had a longer c-Fos-ir interval compared to the dorsal SCN of rats that were entrained to a short photoperiod (Sumova et al., 2000). The extension of the c-Fos-ir interval was attributed solely to an earlier morning onset of high c-Fos-ir expression in long days (approximately 7 h) compared to short days, as the evening decline in c-Fos levels occurred at approximately similar times under both light regimens (Sumova et al., 2000). Thus, the seasonal adaptation of *c-fos* mRNA and c-Fos protein patterns in the dorsal SCN reflects seasonal adaptation of the dorsal SCN's molecular clock machinery. Like the ventral SCN, the dorsal SCN also has photoperiod memory (Sumova et al., 2000). Thus, even though the ventral SCN receives direct light input, the dorsal SCN is indirectly affected by it and both sub-regions adjust to the photoperiod in a similar time frame (Sumova et al., 2004, 2000). It is difficult to reconcile the rostral-caudal differences in the SCN observed under different photoperiods with the anatomical organization of the SCN, which is mainly specified along the ventro-dorsal axis.

3.3. Neurotransmitters involved in seasonal encoding

Several neurotransmitters are involved in synchronization and in the coupling between SCN neurons; therefore, each of these transmitters may play a key role in seasonal encoding of the SCN. The primary neurotransmitter in the ventral SCN is VIP. In the ventral SCN, VIP-expressing cells receive light information from the retina, and they project to the dorsal SCN (Abrahamson and Moore, 2001; Antle et al., 2009). The *in vivo* and *in vitro* application of VIP can mimic the light-induced responses of the SCN (Reed et al., 2001; Piggins et al., 1995), and applying VIP to SCN neurons isolated from VIP-deficient mice can restore synchrony in the clock neurons (Maywood et al., 2011; Aton et al., 2005). Furthermore, the absence of VIP or its receptor (VIP2R, also known as VPAC2) attenuates the SCN's electrical activity (Brown et al., 2007) and molecular rhythmicity (Maywood et al., 2011). In mice, the loss of either VIP or VPAC2 causes behavioral disruptions such as the loss of a coherent circadian rhythm in continuous darkness, as well as changes in the ability to entrain to various light–dark cycles (Aton et al., 2005; Colwell et al., 2003; Harmar et al., 2002; Ciarleglio et al., 2009). The importance of VIP in seasonal adaptation of the SCN became obvious from *in vivo* electrophysiological SCN measurements in freely-moving VIP knockout mice. VIP knockout mice housed in a long, medium or short photoperiod showed no differences in SCN peak width after release in darkness and hence, lost the ability to encode photoperiodic information (Lucassen et al., 2012).

The GRP-expressing SCN cells are located in the ventral subregion of the SCN and play a role in transducing light-related information to other regions in the SCN (Gamble et al., 2007; Antle et al., 2005). The *in vitro* application of GRP to SCN slices mimics the phase-shifting response to light (McArthur et al., 2000) and can increase synchronization among SCN neurons in SCN slices from VIP receptor-deficient mice (Maywood et al., 2011, 2006). Thus, GRP may be involved in both synchronization and coupling between SCN neurons, and its role should be further explored.

The majority of neurons in the dorsal SCN contain the neuropeptide AVP. The expression of AVP (measured as mRNA and peptide production) is rhythmic (Cagampang et al., 1994). Moreover, the rhythm of AVP expression is driven by the intrinsic molecular feedback loop of the core clock machinery. The rhythm of AVP expression is also subject to changes in photoperiod. The SCN of rats housed in a long photoperiod had significantly longer AVP expression interval compared to the SCN of rats housed in a short photoperiod (Sumova et al., 2000; Tournier et al., 2007). Furthermore, SCN slices obtained from hamsters housed in a long photoperiod reached higher peak levels of AVP expression than slices obtained from hamsters housed in a short photoperiod (Tournier et al., 2007). Finally, the *in vitro* application of AVP restored both rhythmicity and synchrony in SCN obtained from VIP-deficient mice (Maywood et al., 2011), and these effects may have been mediated by changes in intracellular calcium levels (Irwin and Allen, 2010).

The role of GABA in synchronization in the SCN was examined in desynchronized SCN (obtained from mice that were entrained to an extremely long photoperiod, i.e., 20 h). In SCN slices were $GABA_A$ signaling was blocked desynchrony among the SCN cells was maintained, while untreated SCN slices regained synchrony (Evans et al., 2013). This indicates that $GABA_A$ signaling promotes resynchronization in long days (Evans et al., 2013). GABA is the most prevalent neurotransmitter in the SCN, and the SCN has both classic GABAergic inhibition and GABAergic excitation (Albus et al., 2005; Choi et al., 2008; De and Pennartz, 2002; Wagner et al., 2001; Irwin and Allen, 2009). *In vitro* experiments revealed that GABAergic excitation is functionally important for synchronizing the dorsal and ventral SCN (Albus et al., 2005). Recently, the influence of photoperiod on the ratio between GABAergic excitation and GABAergic inhibition was examined. Remarkably, in the SCN of mice that were housed previously in long days, slightly more GABAergic neurons were excitatory (40%) than inhibitory (36%); in contrast, in the SCN of mice that were housed in short days, a higher percentage of GABAergic neurons were inhibitory (52%) than excitatory (28%) Farajnia et al., 2014. The ratio between excitatory and inhibitory GABAergic neurons changed by blocking the Cl^- cotransporter NKCC1 using bumetanide, which suggests the involvement of NKCC1 in seasonal adaptation. Whether photoperiod also affect GABAergic inhibitory-excitatory balance in other brain regions should be investigated in future studies. The finding that photoperiod alters the balance in dopamine and somatostatin underscores the potential large influence of photoperiod on neurotransmitter signaling in the brain (Dulcis et al., 2013).

3.4. Phase shifts

In early studies, Elliott and Pittendrigh found that light pulses triggered a larger shift in running-wheel activity in hamsters entrained to short days as compared to long days (Pittendrigh et al., 1984). Later studies performed in mice and hamsters have supported these findings (Vanderleest et al., 2009; Evans et al., 2004; Refinetti, 2002). Moreover, the effect of light on the SCN

can be mimicked *in vitro* by applying a glutamate receptor agonist. *In vitro*, an NMDA pulse caused a significantly larger delay in the SCN of mice from a short photoperiod compared to the SCN of mice from a long photoperiod (Vanderleest et al., 2009). In addition, after advancing the light–dark cycle, the high-amplitude SCN rhythms in mice entrained to a short photoperiod advanced significantly more than the low-amplitude SCN rhythms in mice entrained to a long photoperiod (Ramkisoensing et al., 2014).

These findings are unexpected in view of the current knowledge that the amplitude of the SCN rhythm is larger in short days than in long days. The limit-cycle oscillator theory is often used to model the phase-shifting behavior of oscillators. A special property of the limit cycle is that the original rhythm (period) is restored when it is perturbed, and predicts that in general oscillators with high amplitude shift to a lesser degree than low-amplitude oscillators in response to an external perturbation of a given magnitude (Arnol'd and Levi, 1988; Winfree, 2000; Pittendrigh et al., 1991). Based on this prediction, one would have expected that low-amplitude SCN rhythms—as occur in long days—would have a larger phase shift than high-amplitude SCN rhythms.

One possible way to reconcile this discrepancy between theory and experimental observations is to take into consideration the differences in synchronization in long and short days (Vanderleest et al., 2009). In a more synchronized SCN neuronal population (i.e., in short days), the majority of the individual cells will respond with a common phase-shifting response to an external perturbation, which will lead to a large shift at the ensemble network level. If the neuronal population of the SCN is less synchronized, the individual cells will have divergent phase-shifting responses, resulting in a smaller shift in the SCN network. Simulation studies have recapitulated precisely the experimental observations and demonstrated that the synchrony among individual cells determines the phase-shifting response of the SCN network (Vanderleest et al., 2009). Thus, although the limit-cycle oscillator theory may well predict the behavior of an *individual* oscillator, it cannot predict the behavior of a *network* of oscillators

4. SCN efferent pathways

4.1. Peripheral clocks

In vertebrates, most peripheral cell types contain endogenous circadian oscillators (Yoo et al., 2004; Yamazaki et al., 2000; Balsalobre et al., 1998; Nagoshi et al., 2004; Welsh et al., 2004). For example, tissue explants obtained from heart, lung, and liver have revealed oscillations in the expression of their clock genes (Yoo et al., 2004; Yamazaki et al., 2000). The molecular mechanism underlying these peripheral clocks is the same mechanism that underlies the central clock. However, non-transcriptional oscillations could also play a role as shown by peroxiredoxins that undergo ~24-h redox cycles in erythrocytes (O'Neill and Reddy, 2011).

The SCN synchronizes the peripheral clocks via humoral and neuronal outputs (Kalsbeek et al., 2006, 2010; Vujovic et al., 2008), and when input from the SCN is lost, the peripheral clocks rapidly become desynchronized (Yoo et al., 2004; Yamazaki et al., 2000). Synchronization of peripheral clocks to the light–dark cycle is essential for maintaining seasonal physiology. Exposing rats to a different photo affects the expression of *Per1* in the liver and *Per2* in the lung and heart (Bendova and Sumova, 2006). Exposing Syrian hamsters (*Mesocricetus auratus*, also known as the golden hamster) to either short or long days significantly changes the circadian expression of *Per1* in the lung and heart, as well as the clock-controlled gene *Dbp* in the heart (Carr et al., 2003). The expression profiles of clock genes in the SCN and peripheral tissues are differentially altered by photoperiod (Carr et al., 2003; Sumova et al., 2002). The rhythm of clock gene expression in the SCN adjusts to the transition from long to short days primarily by phase-advancing the expression decline; in contrast, the expression of Rev-erbα in the liver—as well as the rhythm of locomotor activity—adjusts to the same transition by advancing the onset of activity. Exposing an animal to short days for several months causes the animal to revert to a long photoperiod-like physiology. Although the rhythm of clock expression in peripheral tissues reflects long day-like behavior, the expression profile of clock genes in the SCN continues to reflect short days, resulting in a clear dissociation between the SCN and the peripheral clocks (Carr et al., 2003). This functional dissociation suggests that regulation of the peripheral clocks by the photoperiod is not driven solely by the SCN and/or melatonin and is likely under the control of other factors such as food intake and/or locomotor activity. Indeed, placing animals on a restricted feeding regimen can entrain the liver independent of the SCN and the light–dark cycle (Stokkan et al., 2001; Parkanova et al., 2012).

4.2. Neural and humoral pathways

The SCN signals to both intrahypothalamic and extrahypothalamic target areas via efferent neural pathways. Anatomical studies using anterograde and retrograde tracers in the rat brain identified the following six primary efferent projections from the SCN (Watts and Swanson, 1987; Watts et al., 1987; Stephan et al., 1981; Berk and Finkelstein, 1981; Swanson and Cowan, 1975): (i) fibers that terminate in the zone between the SCN and the paraventricular nucleus (PVN), as well as the periventricular nucleus and anterior hypothalamic area (with some axons continuing dorsally and terminating in the mid-rostrocaudal parts of the PVN, and some axons terminating caudally in the dorsomedial nucleus); (ii) rostrally directed fibers that terminate in the ventral parts of the medial preoptic area and anteroventral periventricular nucleus; (iii) anterodorsally oriented fibers that traverse the medial preoptic nucleus (including adjacent regions) and terminate ventrally in the intermediate lateral septal nucleus; (iv) fibers that run caudal to the third group and terminate in the preoptic continuation of the bed nucleus of the stria terminalis, as well as in the parataenial nucleus and rostral part of the PVN; (v) laterally directed fibers that traverse the optic tract and terminate in the ventral lateral geniculate nucleus; and (vi) fibers that extend posteriorly through the anterior hypothalamic and retrochiasmatic areas and terminate between the arcuate nucleus and ventral parts of the ventromedial nucleus, as well as in adjacent parts of the lateral hypothalamic area.

In Siberian hamsters, obstruction of the dense efferent projections that originate in the dorsal tips of the SCN and traverse dorsomedially and dorsocaudally does not block short-day melatonin signals, suggesting that these projections are not the route that the SCN uses to transmit photoperiod information to other areas of the central nervous system (Song et al., 1998). Other projections that might be responsible for transmitting the short-day signal include the rostrally and caudally traversing fibers along the ventral surface of the brain (Song et al., 1998). An additional pathway may involve humoral output from the SCN. The SCN's exocrine function has been suggested based on experiments in which SCN transplants restored circadian activity rhythms in SCN-lesioned animals and animals that were arrhythmic due to other factors (Tousson and Meissl, 2004; Silver et al., 1990; Lehman et al., 1987; Earnest et al., 1999). Encapsulating the transplanted SCN, which prevents neural outgrowth, did not prevent the restoration of circadian rhythmicity, suggesting that humoral signals diffuse from the transplanted SCN (Silver et al., 1996). Moreover, the structural integrity of the SCN seems unnecessary for maintaining

rhythmicity, as even micropunches are sufficient to restore activity patterns (LeSauter et al., 1996). Even though locomotor rhythm can be restored by SCN transplants, the transplants are unable to restore the reproductive response to day length (Lehman et al., 1987), suggesting that neural efferent pathways are necessary for transmitting information regarding day length from the SCN.

4.3. Melatonin

4.3.1. Melatonin signaling

The SCN conveys photoperiodic information to the pineal gland via a polysynaptic efferent pathway as shown in Fig. 1. This pathway runs from the paraventricular nucleus of the hypothalamus, to the intermediolateral cell column of the thoracic spinal cord, to the superior cervical ganglion, and finally to the postganglionic adrenergic fibers that innervate the pineal gland. During night time, norepinephrine is released from these sympathetic nerve endings and stimulates postsynaptic β1 and α1 adrenergic receptors on pinealocytes, triggering a large increase in intracellular cyclic adenosine monophosphate (cAMP) levels Klein et al., 1970. This increase in cAMP activates serotonin *N*-acetyltransferase (also known as arylalkylamine *N*-acetyltransferase, or AANAT), a key regulatory enzyme in the melatonin biosynthesis pathway (Klein and Weller, 1970a). Oscillations in the level of AANAT cause the rhythmic synthesis and secretion of melatonin (Klein and Weller, 1970b). In both diurnal (i.e., day-active) as well as nocturnal (i.e., night-active) animals, melatonin levels are high during the dark phase. Upon exposure to light, AANAT levels decrease rapidly, in turn reducing melatonin levels. When entrained to a long photoperiod, the light-induced decrease in AANAT is advanced by an earlier dawn, whereas the dark-induced increase in AANAT is delayed by a later dusk. As a result, the duration of the nocturnal melatonin signal is compressed during the relatively short nights in the summer and expanded during the long winter nights (Illnerova and Vanecek, 1980). Thus, the temporal pattern of melatonin levels serves as a humoral signal conveying information regarding both the time of day and day length. Photoperiod-induced changes in melatonin secretion have wide-reaching effects on seasonal animal physiology and behavior, as the MT1 and MT2 melatonin receptors are distributed widely throughout the body, including the central nervous system, heart, endocrine system, and immune system. Because the SCN expresses high levels of melatonin receptors, melatonin serves as a feedback system on the clock (Duncan et al., 1989; Maywood et al., 1995; McArthur et al., 1991). Melatonin has been shown to inhibit glucose uptake by the SCN as well as inhibit SCN single-unit activity during the late subjective day (Cassone et al., 1987, 1988; Shibata et al., 1989). Furthermore, melatonin can mediate a phase advance in the central clock at the late subjective day and late subjective night (Hunt et al., 2001). However, the precise role of this hormone in the circadian system is still a subject of debate. Pinealectomy (removal of the pineal gland) has only limited effects on mammalian circadian rhythmicity (Morin, 1993); moreover, C57Bl/6 mice—a melatonin-deficient inbred mouse strain (Ebihara et al., 1986)—have normal locomotor activity rhythms (Roseboom et al., 1998; Schwartz and Zimmerman, 1990). In contrast, giving daily injections of melatonin can restore—at least partially—circadian activity patterns in animals housed in continuous conditions (Cassone et al., 1986a,b; Cassone, 1992; Armstrong et al., 1986; Chesworth et al., 1987), but only if the SCN is intact (Cassone et al., 1986a).

4.3.2. The seasons and melatonin

Melatonin is secreted at night, and the duration of melatonin production reflects the length of the dark period (i.e., the scotoperiod); thus, daily melatonin secretion is prolonged in the winter (when nights are longer) as compared to the summer (Illnerova and Vanecek, 1985). In the laboratory setting, seasonal responses can be evoked by the administration of exogenous melatonin (Bartness et al., 1993). For example, long-lasting pulses of melatonin in pinealectomized Siberian hamsters elicit a short day-like response, thus mimicking winter even in hamsters that are housed in a long photoperiod (Bartness and Goldman, 1988). This result has been confirmed in hoofed animals with intact melatonin signaling. Prolonging the melatonin signal by giving oral or intramuscular melatonin to sheep and deer housed in long days triggers a short day-like reproductive response (Bubenik, 1983; Nett and Niswender, 1982; English et al., 2014; Kennaway et al., 1984; Poulton et al., 1987). Using radiolabeled melatonin as a tracer, several high-affinity binding sites for melatonin have been identified in the Siberian hamster brain; these sites include the paraventricular nucleus, the stria medullaris, the nucleus reuniens, the pars tuberalis (PT), and the SCN Duncan et al., 1989; Weaver et al., 1989. Quantitative autoradiography has revealed that the density of melatonin receptors in the SCN of Syrian hamsters is lower in short photoperiods than in long photoperiods (Schuster et al., 2001). The SCN of hedgehogs, however, has a similar number of melatonin-binding sites under both long and short photoperiods (Gauer et al., 1993). Moreover, unlike in the Syrian hamster, changing the photoperiod does not affect melatonin receptor density in the SCN of Siberian hamsters, although the amplitude of the melatonin peak is higher under short photoperiods than under long photoperiods (Schuster et al., 2001; Recio et al., 1996). Consistent with this finding, Siberian hamsters lack a circadian rhythm in melatonin binding in the SCN (Schuster et al., 2001; Recio et al., 1996). In contrast, in the rat SCN, melatonin receptors fluctuate daily, with increased receptor density during the day and decreased density at night (Gauer et al., 1993; Tenn and Niles, 1993). In summary, photoperiod affects the level of melatonin-binding sites in the SCN of Syrian hamsters, but not in the SCN of hedgehogs or Siberian hamsters, while the effect of photoperiod in the rat has yet to be investigated.

The pars tuberalis (PT) in the pituitary gland expresses the highest density of melatonin receptors of any tissue and is the most conserved site of expression across mammalian species. The PT plays a role in mediating some of the seasonal photoperiod-induced responses in mammals, including the photoperiod-induced regulation of prolactin (Ross and Morgan, 2002; Morgan, 2000). In short photoperiods, the density of melatonin receptors is reduced in the PT of both Syrian hamsters and Siberian hamsters (Schuster et al., 2001). This short photoperiod-induced decrease in melatonin-binding capacity is directly determined by the duration of the nocturnal melatonin signal (Messager et al., 1999; Gauer et al., 1994; Stanton et al., 1991). Thus, the short photoperiod-induced reduction in melatonin receptor density in the PT of both Syrian hamsters and Siberian hamsters—and in the SCN of Syrian hamsters—is likely due to a long-term, gradual melatonin-induced inhibition of melatonin receptor gene expression (Schuster et al., 2001).

5. Seasonal physiology and the SCN

5.1. Hibernation and the SCN

Hibernation is an energy-conserving strategy used by many species to cope with annually recurring periods of cold and/or food shortage. For most mammalian hibernators, the hibernation season is marked by prolonged intermittent periods of hypometabolism that generally last 4–10 days, with brief recurrent returns to euthermic body temperature lasting approximately 6–24 h (Ruby, 2003). When hibernating (i.e., in a state of deep torpor), body temperature, cardiac function, and respiratory rate are reduced, muscle tone is more relaxed, and the animal adopts a heat-conserving "curled-up" body position.

The hibernation season for the golden-mantled ground squirrel (*Spermophilus lateralis*) lasts approximately six months (from autumn through winter) and is spent in an underground hibernaculum. This period of deep torpor interrupted by spontaneous periods of arousal eventually turns to a state of continuous arousal during spring and summer. The body weight of these squirrels also follows a seasonal rhythm: in the summer, they increase their food intake and fat mass, and in the winter these fat reserves are depleted gradually despite the animal's reduced energy expenditure. When these squirrels are transferred to a constant photoperiod and temperature condition, this annual rhythm in body weight change persists (Heller and Poulson, 1970). Lesioning the SCN can disrupt the animal's natural annual rhythm in body mass, but only when the animal is exposed to temperatures similar to temperatures experienced during the winter (Ruby et al., 1998). When SCN-lesioned squirrels are housed at 23 °C, only ~20% of the animals display disruptions in their annual body mass rhythm (Zucker et al., 1983; Lee and Zucker, 1991). Interestingly, experiments that measured the uptake of radiolabeled 2-deoxyglucose in ground squirrels revealed that during hibernation, the SCN is more metabolically active relative to other brain regions (Kilduff et al., 1982); indeed, of the 96 brain structures that were studied, the only brain regions with a metabolic rate higher than the SCN during deep hibernation were the paratrigeminal nucleus (which integrates visceral and somatic information) and the cochlear nucleus (Kilduff et al., 1990). The uptake of 2-deoxyglucose by the SCN increased when the animal entered hibernation and remained high throughout the entire hibernation period (Kilduff et al., 1989). As the animal returned to its euthermic state, the uptake of 2-deoxyglucose by the SCN declined abruptly. In the SCN, expression of the light-responsive transcription factor c-Fos increases during deep hibernation and peaks during arousal from hibernation (Bitting et al., 1994; Revel et al., 2007). Complete—or even partial—ablation of the SCN disrupts the animal's normal hibernation pattern and the weight loss that usually occurs during hibernation (Ruby et al., 1998, 1996; Dark et al., 1990). These results suggest that the SCN plays an important functional role in hibernation. However, the SCN's role in hibernation might not be circadian per se, as the clock genes *Per1*, *Per2*, and *Bmal1*, as well as the clock-controlled gene *AVP*, do not oscillate in the SCN of hibernating European hamsters (*Cricetus cricetus*, also known as the common hamster or black-bellied hamster). Moreover, hibernating marmots and European hamsters do not have rhythmic plasma melatonin levels or rhythmic AANAT expression (Revel et al., 2007; Florant et al., 1984). However, because these experiments were performed at different ambient temperatures and in a variety of species and/or strains, the results are difficult to compare. Nevertheless, although its exact role remains unclear, the SCN seems to be required for establishing annual hibernation patterns and the related rhythmic fluctuations in body weight.

5.2. Seasonal breeding

Seasonal breeders adapt their reproductive cycle to the changing seasons in order to maximize reproductive success and offspring survival. Many species of birds, voles, mice, and hamsters breed in the spring and have a gestation period of only several weeks; thus, these species are classified as so-called "long-day breeders". On the other hand, goats, sheep, and deer breed in the autumn and have a gestation period of approximately six months; thus, these species are classified as "short-day breeders". The offspring of both long-day breeders and short-day breeders are born in the spring and/or summer, when food is abundant. These seasonal breeders primarily use the changing photoperiod as a breeding calendar, as this is the most reliable seasonal environmental cue to indicate the time of year. Seasonal reproduction is regulated by both luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which together regulate seasonal changes in gonad size. Exposing male hamsters to a short photoperiod causes gonadal regression, which is accompanied by the cessation of spermatogenesis and a decline in testosterone secretion. Photoperiod also affects the body weight of hamsters, although the effect differs among species. For example, in short days, Syrian hamsters gain weight, whereas Siberian hamsters lose weight (Bittman et al., 1991; Bartness and Wade, 1984; Wade and Bartness, 1984). This opposite effect of photoperiod on weight change in two different hamster species represents different strategies used to cope with food shortage during the winter months (for review, see Morgan et al. (2006)); Syrian hamsters accumulate fat prior to the winter, and that added fat is then utilized in the winter; in contrast, Siberian hamsters reduce their food intake prior to the winter in order to acclimate their energy requirements to accommodate the reduced food availability during the winter months.

5.2.1. Seasonal breeding and the SCN

Exposure to artificial light during the subjective night suppresses the circadian rhythms of activity and SCN output (Coomans et al., 2013; Fonken et al., 2013; Ohta et al., 2005; Shuboni and Yan, 2010). Even ecologically relevant levels of seemingly dim light—similar to the levels of light pollution produced in urban areas (i.e., approximately 5 lux)—can affect the circadian system in rodents (for review, see Fonken and Nelson (2014)). For example, these low levels of illumination during the night prevent short-day responses in reproduction and body mass in Siberian hamsters (Ikeno et al., 2014). In addition, lesioning the SCN disrupts the photoperiod-induced responses to short day exposure in both Syrian hamsters and Siberian hamsters (Bittman et al., 1991; Rusak and Morin, 1976; Stetson and Watson-Whitmyre, 1976). Melatonin secretion is also disrupted by lesioning the SCN; however, the lack of photoperiod-induced response after SCN lesioning cannot be attributed exclusively to disrupted melatonin signaling. The infusion of exogenous melatonin to mimic short days does not elicit short day-like responses in gonad size or body weight in SCN-lesioned Siberian hamsters (Bartness et al., 1991). In contrast, the nocturnal infusion of melatonin does cause short-day-like gonad atrophy in SCN-lesioned Syrian hamsters (Maywood et al., 1990).

The mink is a short-day breeder that becomes sexually inactive when day length exceeds 10 h and reaches peak sexual activity in February. Complete destruction of the SCN in minks abolishes the short day-evoked increase in testicular activity, comparable to the studies performed in long-day breeders (Maurel et al., 1991). Testicular regression in summer is not triggered by day length and, in line with this, is not abolished by lesioning the SCN (Maurel et al., 1991; Boissin-Agasse et al., 1986). Thus, in the mink, the SCN regulates testicular activity under short day conditions, but does not regulate testicular regression during long days.

5.2.2. Prolactin

Most species of seasonally breeding mammals have a seasonal pattern of prolactin secretion, with peak secretion occurring in the spring and/or summer and the nadir occurring in the autumn and/or winter (for review, see Curlewis (1992)). Prolactin (also known as luteotropic hormone or luteotropin) is a polypeptide hormone that is both synthesized in and secreted from lactotrophs, specialized cells in the anterior pituitary gland. Prolactin is best known for its role in stimulating the production of milk in female mammals; however, more than 300 separate biological activities have been attributed to prolactin involving reproduction, immune responses, angiogenesis, osmoregulation, metabolism, and behavior. In addition to seasonal fluctuations, prolactin secretion follows a diurnal cycle and the ovulatory cycle. In rats, stimulating the

uterine cervix (either through mating or by artificial stimulation) induces the twice-daily secretion of prolactin secretion (Smith and Neill, 1976; Gorospe and Freeman, 1981; Butcher et al., 1972). The diurnal surge in prolactin secretion begins in the afternoon (between 1 pm and 3 pm), peaks in the early evening (between 5 pm and 7 pm), and returns to basal levels by midnight. The nocturnal surge begins at 1 am, peaks in the early morning (between 3 am and 7 am), and returns to basal levels by 11 am. The ovulatory cycle of prolactin secretion in female rats includes a pre-ovulation surge in prolactin in the afternoon of the proestrus phase, and this surge coincides with an estradiol-induced surge in luteinizing hormone.

Surges in prolactin secretion occur in response to hypothalamic dopaminergic inhibition and in response to stimulation by hypothalamic-releasing neurohormones such as oxytocin and thyrotropin-releasing hormone. Several studies suggest that prolactin secretion is controlled by the coordinated activity of neuroendocrine dopamine and oxytocin, both of which are controlled by daily output from the SCN. Exposing rats to continuous light, which inhibits SCN output by ~50% (Coomans et al., 2013), suppresses the abovementioned cervix-stimulated prolactin surge (Pieper and Gala, 1979; Bethea and Neill, 1979). Lesioning the SCN abolishes both the mating-induced prolactin surge and the cervical stimulation-induced prolactin surge (Jakubowski and Terkel, 1986; Kawakami and Arita, 1981; Kawakami et al., 1980; Bethea and Neill, 1980). Furthermore, knocking down the clock genes *Per1*, *Per2*, and *CLOCK* within the SCN, thereby disrupting the circadian rhythmicity in behavior and physiology, blocks the proestrus and estradiol-induced prolactin surges (Poletini et al., 2007). Inhibiting the neurotransmitter VIP in the SCN by injecting antisense oligonucleotides disrupts both the prolactin surge induced by cervical stimulation and the estradiol-induced surge in ovariectomized rats (Harney et al., 1996; Egli et al., 2004; Kennett et al., 2008). In addition, administration of vasopressin to the medial preoptic area during a prolactin surge suppresses this surge (Palm et al., 2001). The SCN transmits circadian information via vasopressin-containing fibers to estrogen receptor-containing neurons in the medial preoptic area and/or via VIP-containing projections to dopaminergic and/or oxytocinergic neurons in the paraventricular nucleus and the periventricular nucleus, thereby controlling the timing of the circadian surge in prolactin (and likely the seasonal surge in prolactin as well). Thus, the SCN plays a role in regulating prolactin, thereby coordinating seasonal physiology.

6. The seasons and the human SCN

In human populations, a wide variety of seasonal rhythms have been reported (Halberg et al., 1983; Aschoff, 1981), including seasonal fluctuations in birth rate (Roenneberg and Aschoff, 1990), blood pressure (Imai et al., 1996), and sleep (Kohsaka et al., 1992); for review, see Foster and Roenneberg (2008)). On the other hand, other studies failed to detect significant differences in human physiology as a result of changing photoperiod (for review, see Bronson (2004)). For example, measuring plasma melatonin levels in healthy urban subjects revealed no difference in the duration of elevated night melatonin levels between the summer and winter seasons (Illnerova et al., 1985). However, the melatonin rhythms were phase-delayed by approximately 1.5 h in the winter compared to the summer. It is likely that the use of artificial light in modern society limits the ability of the circadian system to synchronize to naturally occurring changes in day length, thereby attenuating our photoperiod-induced seasonal physiology (Wehr et al., 1995). Furthermore, one-fourth of the world's population practices daylight saving time (in which the clock is changed by one hour twice a year), which disrupts the seasonal adaptation of the human circadian system to the changing photoperiod when the clocks are advanced in the spring (i.e., at the start of summer time) (Kantermann et al., 2007).

A few studies reported seasonal changes in the human SCN. For example, a study of postmortem brain specimens found that serotonin (5-HT) levels have seasonal fluctuations, particularly in the hypothalamus (Carlsson et al., 1980). Specifically, the concentration of 5-HT peaked in October–November and reached a nadir in December–January. Consistent with this finding, similar seasonal patterns have been reported for L-tryptophan (a precursor of serotonin) in the blood (Maes et al., 1995), as well as 5-HT and its metabolites in the cerebrospinal fluid (Brewerton et al., 1988). Another study using single-photon emission computed tomography (SPECT) found a seasonal rhythm in the availability of serotonin transporter binding sites in the hypothalamus of healthy female subjects (Neumeister et al., 2000). Brain-derived neurotrophic factor (BDNF), which interacts closely with 5-HT in both neuronal functioning and plasticity, also fluctuates seasonally in humans (Molendijk et al., 2012). The reductions in 5-HT concentration and transporter binding sites during the winter coincide with an increased prevalence of depression during this same period. 5-HT is strongly involved in the regulation of circadian rhythms by the SCN. For example, the SCN receives robust serotonergic projections from the midbrain raphe nuclei, and changes in 5-HT affect circadian behavior and neuroendocrine rhythms in rodents. The seasonal fluctuations in 5-HT levels may reflect changes in serotonergic projections to the SCN, which induce seasonal rhythmicity in both physiology and behavior.

Seasonal changes in SCN morphology have been identified using postmortem brain tissue obtained from young subjects (males and females 6–47 years of age). In early autumn (i.e., from August through October), the number of vasopressin-containing and VIP-containing neurons was significantly higher than in late spring/early summer (i.e., from April through June) (Hofman and Swaab, 1992, 1993; Hofman et al., 1993). The SCN-PVN axis is essential for relaying photoperiodic information to other parts of the body. The volume of the PVN also fluctuates seasonally, peaking in the spring (Hofman and Swaab, 1992). In contrast, other brain regions that are not involved in the temporal organization of biological processes do not fluctuate seasonally, suggesting that seasonal changes in morphology are limited to brain regions that play a role in the transmission of photoperiod-related information. As one ages, the seasonal fluctuation in SCN morphology is progressively reduced (Hofman and Swaab, 1995); for example, the annual fluctuation in vasopressin-containing neurons in the SCN diminishes in elderly people (i.e., in individuals 50–95 years of age). This observation is consistent with other perturbations in the circadian system observed in aging humans and other mammals, including fragmented activity patterns and a decline in neuronal activity in the SCN (Meijer et al., 2012; Farajnia et al., 2012; Nakamura et al., 2011).

7. Conclusions

It is becoming increasing clear that in addition to orchestrating circadian rhythmicity, the SCN also plays an important role in seasonal physiology. The unique light response characteristics of SCN neurons enables these cells to measure the length of the day (i.e., the photoperiod). This information is then encoded by the SCN by adjusting the level of phase synchrony among the individual SCN neurons. At the molecular level, the regional organization is clearly heterogeneous, whereas at the level of electrical activity, changes in phase synchrony are integrated and measurable throughout the SCN. The ensemble electrical activity of the entire SCN reflects the length of the day. Thus, the ability of the SCN to

encode photoperiod information is dependent on the integrity of the neuronal network. Seasonal changes in certain physiological functions are regulated by structures that lie downstream of the SCN. The SCN projects to intrahypothalamic and extrahypothalamic target areas, and it projects indirectly to numerous endocrine systems in our body. Despite the widespread use of artificial light, many studies report the presence of seasonal rhythms in humans, although other studies found no evidence of such rhythms. In the human SCN, seasonal rhythms are well documented. Whether seasonal rhythms are important to humans, and whether they contribute to our health and/or fertility, are open questions that must be addressed.

Conflict of interest

The authors have no conflict of interest to declare.

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References

Abrahamson, E.E., Moore, R.Y., 2001. Suprachiasmatic nucleus in the mouse: retinal innervation, intrinsic organization and efferent projections. Brain Res. 916, 172–191.
Aggelopoulos, N.C., Meissl, H., 2000. Responses of neurones of the rat suprachiasmatic nucleus to retinal illumination under photopic and scotopic conditions. J. Physiol. 523 (Pt 1), 211–222.
Albus, H., Vansteensel, M.J., Michel, S., Block, G.D., Meijer, J.H., 2005. A GABAergic mechanism is necessary for coupling dissociable ventral and dorsal regional oscillators within the circadian clock. Curr. Biol. 15, 886–893.
Altimus, C.M., Guler, A.D., Villa, K.L., McNeill, D.S., Legates, T.A., Hattar, S., 2008. Rods-cones and melanopsin detect light and dark to modulate sleep independent of image formation. Proc. Natl. Acad. Sci. USA 105, 19998–20003.
Antle, M.C., Silver, R., 2005. Orchestrating time: arrangements of the brain circadian clock. Trends Neurosci. 28, 145–151.
Antle, M.C., Kriegsfeld, L.J., Silver, R., 2005. Signaling within the master clock of the brain: localized activation of mitogen-activated protein kinase by gastrin-releasing peptide. J. Neurosci. 25, 2447–2454.
Antle, M.C., Smith, V.M., Sterniczuk, R., Yamakawa, G.R., Rakai, B.D., 2009. Physiological responses of the circadian clock to acute light exposure at night. Rev. Endocr. Metab. Disord. 10, 279–291.
Armstrong, S.M., Cassone, V.M., Chesworth, M.J., Redman, J.R., Short, R.V., 1986. Synchronization of mammalian circadian rhythms by melatonin. J. Neural Transm. Suppl. 21, 375–394.
Arnol'd, V.I., Levi, M., 1988. Geometrical Methods in the Theory of Ordinary Differential Equations. Springer-Verlag, New York.
Aschoff, J., 1981. Annual rhythms in man. In: Handbook of Behavioral Neurobiology, volume 4th ed. Plenum, New York, pp. 475–487.
Aton, S.J., Colwell, C.S., Harmar, A.J., Waschek, J., Herzog, E.D., 2005. Vasoactive intestinal polypeptide mediates circadian rhythmicity and synchrony in mammalian clock neurons. Nat. Neurosci. 8, 476–483.
Balsalobre, A., Damiola, F., Schibler, U., 1998. A serum shock induces circadian gene expression in mammalian tissue culture cells. Cell 93, 929–937.
Bartness, T.J., Goldman, B.D., 1988. Peak duration of serum melatonin and short-day responses in adult Siberian hamsters. Am. J. Physiol. 255, R812–R822.
Bartness, T.J., Wade, G.N., 1984. Photoperiodic control of body weight and energy metabolism in Syrian hamsters (*Mesocricetus auratus*): role of pineal gland, melatonin, gonads, and diet. Endocrinology 114, 492–498.
Bartness, T.J., Goldman, B.D., Bittman, E.L., 1991. SCN lesions block responses to systemic melatonin infusions in Siberian hamsters. Am. J. Physiol. 260, R102–R112.
Bartness, T.J., Powers, J.B., Hastings, M.H., Bittman, E.L., Goldman, B.D., 1993. The timed infusion paradigm for melatonin delivery: what has it taught us about the melatonin signal, its reception, and the photoperiodic control of seasonal responses? J. Pineal Res. 15, 161–190.
Bendova, Z., Sumova, A., 2006. Photoperiodic regulation of PER1 and PER2 protein expression in rat peripheral tissues. Physiol. Res. 55, 623–632.
Berk, M.L., Finkelstein, J.A., 1981. An autoradiographic determination of the efferent projections of the suprachiasmatic nucleus of the hypothalamus. Brain Res. 226, 1–13.
Berson, D.M., Dunn, F.A., Takao, M., 2002. Phototransduction by retinal ganglion cells that set the circadian clock. Science 295, 1070–1073.
Bethea, C.L., Neill, J.D., 1979. Prolactin secretion after cervical stimulation of rats maintained in constant dark or constant light. Endocrinology 104, 870–876.
Bethea, C.L., Neill, J.D., 1980. Lesions of the suprachiasmatic nuclei abolish the cervically stimulated prolactin surges in the rat. Endocrinology 107, 1–5.
Bitting, L., Sutin, E.L., Watson, F.L., Leard, L.E., O'Hara, B.F., Heller, H.C., Kilduff, T.S., 1994. C-fos mRNA increases in the ground squirrel suprachiasmatic nucleus during arousal from hibernation. Neurosci. Lett. 165, 117–121.
Bittman, E.L., Bartness, T.J., Goldman, B.D., DeVries, G.J., 1991. Suprachiasmatic and paraventricular control of photoperiodism in Siberian hamsters. Am. J. Physiol. 260, R90–R101.
Boissin-Agasse, L., Jacquet, J.M., Lacroix, A., Boissin, J., 1986. Circadian participation in the photoregulation of testis activity and prolactin secretion in the mink, a short-day breeder. J. Biol. Rhythms 1, 231–241.
Brewerton, T.D., Berrettini, W.H., Nurnberger Jr., J.I., 1988. Linnoila, M: Analysis of seasonal fluctuations of CSF monoamine metabolites and neuropeptides in normal controls: findings with 5HIAA and HVA. Psychiatry Res. 23, 257–265.
Bronson, F.H., 2004. Are humans seasonally photoperiodic? J. Biol. Rhythms 19, 180–192.
Brown, T.M., Piggins, H.D., 2009. Spatiotemporal heterogeneity in the electrical activity of suprachiasmatic nuclei neurons and their response to photoperiod. J. Biol. Rhythms 24, 44–54.
Brown, T.M., Banks, J.R., Piggins, H.D., 2006. A novel suction electrode recording technique for monitoring circadian rhythms in single and multiunit discharge from brain slices. J. Neurosci. Methods 156, 173–181.
Brown, T.M., Colwell, C.S., Waschek, J.A., Piggins, H.D., 2007. Disrupted neuronal activity rhythms in the suprachiasmatic nuclei of vasoactive intestinal polypeptide-deficient mice. J. Neurophysiol. 97, 2553–2558.
Brown, T.M., Wynne, J., Piggins, H.D., Lucas, R.J., 2011. Multiple hypothalamic cell populations encoding distinct visual information. J. Physiol. 589, 1173–1194.
Bryant, D.N., LeSauter, J., Silver, R., Romero, M.T., 2000. Retinal innervation of calbindin-D28K cells in the hamster suprachiasmatic nucleus: ultrastructural characterization. J. Biol. Rhythms 15, 103–111.
Bubenik, G.A., 1983. Shift of seasonal cycle in white-tailed deer by oral administration of melatonin. J. Exp. Zool. 225, 155–156.
Butcher, R.L., Fugo, N.W., Collins, W.E., 1972. Semicircadian rhythm in plasma levels of prolactin during early gestation in the rat. Endocrinology 90, 1125–1127.
Cagampang, F.R., Okamura, H., Inouye, S., 1994. Circadian rhythms of norepinephrine in the rat suprachiasmatic nucleus. Neurosci. Lett. 173, 185–188.
Cagampang, F.R., Yang, J., Nakayama, Y., Fukuhara, C., Inouye, S.T., 1994. Circadian variation of arginine-vasopressin messenger RNA in the rat suprachiasmatic nucleus. Brain Res. Mol. Brain Res. 24, 179–184.
Carlsson, A., Svennerholm, L., Winblad, B., 1980. Seasonal and circadian monoamine variations in human brains examined post mortem. Acta Psychiatr. Scand. Suppl. 280, 75–85.
Carr, A.J., Johnston, J.D., Semikhodskii, A.G., Nolan, T., Cagampang, F.R., Stirland, J.A., Loudon, A.S., 2003. Photoperiod differentially regulates circadian oscillators in central and peripheral tissues of the Syrian hamster. Curr. Biol. 13, 1543–1548.
Cassone, V.M., 1992. The pineal gland influences rat circadian activity rhythms in constant light. J. Biol. Rhythms 7, 27–40.
Cassone, V.M., Chesworth, M.J., Armstrong, S.M., 1986a. Entrainment of rat circadian rhythms by daily injection of melatonin depends upon the hypothalamic suprachiasmatic nuclei. Physiol. Behav. 36, 1111–1121.
Cassone, V.M., Chesworth, M.J., Armstrong, S.M., 1986b. Dose-dependent entrainment of rat circadian rhythms by daily injection of melatonin. J. Biol. Rhythms 1, 219–229.
Cassone, V.M., Roberts, M.H., Moore, R.Y., 1987. Melatonin inhibits metabolic activity in the rat suprachiasmatic nuclei. Neurosci. Lett. 81, 29–34.
Cassone, V.M., Roberts, M.H., Moore, R.Y., 1988. Effects of melatonin on 2-deoxy-[1-14C]glucose uptake within rat suprachiasmatic nucleus. Am. J. Physiol. 255, R332–R337.
Chesworth, M.J., Cassone, V.M., Armstrong, S.M., 1987. Effects of daily melatonin injections on activity rhythms of rats in constant light. Am. J. Physiol. 253, R101–R107.
Choi, H.J., Lee, C.J., Schroeder, A., Kim, Y.S., Jung, S.H., Kim, J.S., Kim, d.Y., Son, E.J., Han, H.C., Hong, S.K., Colwell, C.S., Kim, Y.I., 2008. Excitatory actions of GABA in the suprachiasmatic nucleus. J. Neurosci. 28, 5450–5459.
Ciarleglio, C.M., Gamble, K.L., Axley, J.C., Strauss, B.R., Cohen, J.Y., Colwell, C.S., McMahon, D.G., 2009. Population encoding by circadian clock neurons organizes circadian behavior. J. Neurosci. 29, 1670–1676.
Colwell, C.S., Foster, R.G., 1992. Photic regulation of Fos-like immunoreactivity in the suprachiasmatic nucleus of the mouse. J. Comp. Neurol. 324, 135–142.
Colwell, C.S., Michel, S., Itri, J., Rodriguez, W., Tam, J., Lelievre, V., Hu, Z., Liu, X., Waschek, J.A., 2003. Disrupted circadian rhythms in VIP- and PHI-deficient mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 285, R939–R949.
Coomans, C.P., van den Berg, S.A., Houben, T., van Klinken, J.B., van den Berg, R., Pronk, A.C., Havekes, L.M., Romijn, J.A., van Dijk, K.W., Biermasz, N.R., Meijer, J.H., 2013. Detrimental effects of constant light exposure and high-fat diet on circadian energy metabolism and insulin sensitivity. FASEB J. 27, 1721–1732.
Curlewis, J.D., 1992. Seasonal prolactin secretion and its role in seasonal reproduction: a review. Reprod. Fertil. Dev. 4, 1–23.

Dardente, H., Poirel, V.J., Klosen, P., Pevet, P., Masson-Pevet, M., 2002. Per and neuropeptide expression in the rat suprachiasmatic nuclei: compartmentalization and differential cellular induction by light. Brain Res. 958, 261–271.
Dark, J., Kilduff, T.S., Heller, H.C., Licht, P., Zucker, I., 1990. Suprachiasmatic nuclei influence hibernation rhythms of golden-mantled ground squirrels. Brain Res. 509, 111–118.
De, J.M., Pennartz, C., 2002. Circadian modulation of GABA function in the rat suprachiasmatic nucleus: excitatory effects during the night phase. J. Neurophysiol. 87, 834–844.
de la Iglesia, H.O., Cambras, T., Schwartz, W.J., Diez-Noguera, A., 2004. Forced desynchronization of dual circadian oscillators within the rat suprachiasmatic nucleus. Curr. Biol. 14, 796–800.
DeCoursey, P.J., Krulas, J.R., 1998. Behavior of SCN-lesioned chipmunks in natural habitat: a pilot study. J. Biol. Rhythms 13, 229–244.
Drouyer, E., Rieux, C., Hut, R.A., Cooper, H.M., 2007. Responses of suprachiasmatic nucleus neurons to light and dark adaptation: relative contributions of melanopsin and rod-cone inputs. J. Neurosci. 27, 9623–9631.
Dulcis, D., Jamshidi, P., Leutgeb, S., Spitzer, N.C., 2013. Neurotransmitter switching in the adult brain regulates behavior. Science 340, 449–453.
Duncan, M.J., Takahashi, J.S., Dubocovich, M.L., 1989. Characteristics and autoradiographic localization of 2-[125I]iodomelatonin binding sites in Djungarian hamster brain. Endocrinology 125, 1011–1018.
Earnest, D.J., Liang, F.Q., Ratcliff, M., Cassone, V.M., 1999. Immortal time: circadian clock properties of rat suprachiasmatic cell lines. Science 283, 693–695.
Ebihara, S., Marks, T., Hudson, D.J., Menaker, M., 1986. Genetic control of melatonin synthesis in the pineal gland of the mouse. Science 231, 491–493.
Ebling, F.J., Maywood, E.S., Staley, K., Humby, T., Hancock, D.C., Waters, C.M., Evant, G.I., Hastings, M.H., 1991. The role of N-methyl-d-aspartate-type glutamatergic neurotransmission in the photic induction of immediate-early gene expression in the suprachiasmatic nuclei of the Syrian hamster. J. Neuroendocrinol. 3, 641–652.
Egli, M., Bertram, R., Sellix, M.T., Freeman, M.E., 2004. Rhythmic secretion of prolactin in rats: action of oxytocin coordinated by vasoactive intestinal polypeptide of suprachiasmatic nucleus origin. Endocrinology 145, 3386–3394.
English, J., Poulton, A.L., Arendt, J., Symons, A.M., 2014. A comparison of the efficiency of melatonin treatments in advancing oestrus in ewes. J. Reprod. Fertil. 77, 321–327.
Evans, J.A., Elliott, J.A., Gorman, M.R., 2004. Photoperiod differentially modulates photic and nonphotic phase response curves of hamsters. Am. J. Physiol. Regul. Integr. Comp. Physiol. 286, R539–R546.
Evans, J.A., Leise, T.L., Castanon-Cervantes, O., Davidson, A.J., 2013. Dynamic interactions mediated by nonredundant signaling mechanisms couple circadian clock neurons. Neuron 80, 973–983.
Farajnia, S., Michel, S., Deboer, T., Vanderleest, H.T., Houben, T., Rohling, J.H., Ramkisoensing, A., Yasenkov, R., Meijer, J.H., 2012. Evidence for neuronal desynchrony in the aged suprachiasmatic nucleus clock. J. Neurosci. 32, 5891–5899.
Farajnia, S., van Westering, T.L., Meijer, J.H., Michel, S., 2014. Seasonal induction of GABAergic excitation in the central mammalian clock. Proc. Natl. Acad. Sci. USA 111, 9627–9632.
Florant, G.L., Rivera, M.L., Lawrence, A.K., Tamarkin, L., 1984. Plasma melatonin concentrations in hibernating marmots: absence of a plasma melatonin rhythm. Am. J. Physiol. 247, R1062–R1066.
Fonken, L.K., Nelson, R.J., 2014. The effects of light at night on circadian clocks and metabolism. Endocr. Rev. (20131051).
Fonken, L.K., Aubrecht, T.G., Melendez-Fernandez, O.H., Weil, Z.M., Nelson, R.J., 2013. Dim light at night disrupts molecular circadian rhythms and increases body weight. J. Biol. Rhythms 28, 262–271.
Foster, R.G., Hankins, M.W., 2007. Circadian vision. Curr. Biol. 17, R746–R751.
Foster, R.G., Roenneberg, T., 2008. Human responses to the geophysical daily, annual and lunar cycles. Curr. Biol. 18, R784–R794.
Foster, R.G., Provencio, I., Hudson, D., Fiske, S., De, G.W., Menaker, M., 1991. Circadian photoreception in the retinally degenerate mouse (rd/rd). J. Comp. Physiol. A. 169, 39–50.
Freedman, M.S., Lucas, R.J., Soni, B., Von, S.M., Munoz, M., David-Gray, Z., Foster, R., 1999. Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. Science 284, 502–504.
Gamble, K.L., Allen, G.C., Zhou, T., McMahon, D.G., 2007. Gastrin-releasing peptide mediates light-like resetting of the suprachiasmatic nucleus circadian pacemaker through cAMP response element-binding protein and Per1 activation. J. Neurosci. 27, 12078–12087.
Gauer, F., Masson-Pevet, M., Saboureau, M., George, D., Pevet, P., 1993. Differential seasonal regulation of melatonin receptor density in the pars tuberalis and the suprachiasmatic nuclei: a study in the hedgehog (*Erinaceus europaeus*, L.). J. Neuroendocrinol. 5, 685–690.
Gauer, F., Masson-Pevet, M., Skene, D.J., Vivien-Roels, B., Pevet, P., 1993. Daily rhythms of melatonin binding sites in the rat pars tuberalis and suprachiasmatic nuclei; evidence for a regulation of melatonin receptors by melatonin itself. Neuroendocrinology 57, 120–126.
Gauer, F., Masson-Pevet, M., Pevet, P., 1994. Seasonal regulation of melatonin receptors in rodent pars tuberalis: correlation with reproductive state. J. Neural Transm. Gen. Sect. 96, 187–195.
Gorospe, W.C., Freeman, M.E., 1981. An ovarian role in prolonging and terminating the two surges of prolactin in pseudopregnant rats. Endocrinology 108, 1293–1298.
Groos, G.A., Mason, R., 1980. Maintained discharge of rat suprachiasmatic neurons at different adaptation levels. Neurosci. Lett. 8, 59–64.
Guido, M.E., Goguen, D., De, G.L., Robertson, H.A., Rusak, B., 1999a. Circadian and photic regulation of immediate-early gene expression in the hamster suprachiasmatic nucleus. Neuroscience 90, 555–571.
Guido, M.E., de Guido, L.B., Goguen, D., Robertson, H.A., Rusak, B., 1999b. Daily rhythm of spontaneous immediate-early gene expression in the rat suprachiasmatic nucleus. J. Biol. Rhythms 14, 275–280.
Halberg, F., Lagoguey, M., Reinberg, A., 1983. Human circannual rhythms over a broad spectrum of physiological processes. Int. J. Chronobiol. 8, 225–268.
Harmar, A.J., Marston, H.M., Shen, S., Spratt, C., West, K.M., Sheward, W.J., Morrison, C.F., Dorin, J.R., Piggins, H.D., Reubi, J.C., Kelly, J.S., Maywood, E.S., Hastings, M.H., 2002. The VPAC(2) receptor is essential for circadian function in the mouse suprachiasmatic nuclei. Cell 109, 497–508.
Harney, J.P., Scarbrough, K., Rosewell, K.L., Wise, P.M., 1996. In vivo antisense antagonism of vasoactive intestinal peptide in the suprachiasmatic nuclei causes aging-like changes in the estradiol-induced luteinizing hormone and prolactin surges. Endocrinology 137, 3696–3701.
Hattar, S., Liao, H.W., Takao, M., Berson, D.M., Yau, K.W., 2002. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science 295, 1065–1070.
Hazlerigg, D.G., Ebling, F.J., Johnston, J.D., 2005. Photoperiod differentially regulates gene expression rhythms in the rostral and caudal SCN. Curr. Biol. 15, R449–R450.
Heller, H.C., Poulson, T.L., 1970. Endogenous and exogenous factors controlling reproduction and hibernation in chipmunks (*Eutamias*) and ground squirrels (*Spermophilus*). Comp. Biochem. Physiol. 33, 357–383.
Herzog, E.D., Takahashi, J.S., Block, G.D., 1998. Clock controls circadian period in isolated suprachiasmatic nucleus neurons. Nat. Neurosci. 1, 708–713.
Hofman, M.A., Swaab, D.F., 1992. Seasonal changes in the suprachiasmatic nucleus of man. Neurosci. Lett. 139, 257–260.
Hofman, M.A., Swaab, D.F., 1992. The human hypothalamus: comparative morphometry and photoperiodic influences. Prog. Brain Res. 93, 133–147.
Hofman, M.A., Swaab, D.F., 1993. Diurnal and seasonal rhythms of neuronal activity in the suprachiasmatic nucleus of humans. J. Biol. Rhythms 8, 283–295.
Hofman, M.A., Swaab, D.F., 1995. Influence of aging on the seasonal rhythm of the vasopressin-expressing neurons in the human suprachiasmatic nucleus. Neurobiol. Aging 16, 965–971.
Hofman, M.A., Purba, J.S., Swaab, D.F., 1993. Annual variations in the vasopressin neuron population of the human suprachiasmatic nucleus. Neuroscience 53, 1103–1112.
Houben, T., Deboer, T., Van, O.F., Meijer, J.H., 2009. Correlation with behavioral activity and rest implies circadian regulation by SCN neuronal activity levels. J. Biol. Rhythms 24, 477–487.
Hunt, A.E., Al-Ghoul, W.M., Gillette, M.U., Dubocovich, M.L., 2001. Activation of MT(2) melatonin receptors in rat suprachiasmatic nucleus phase advances the circadian clock. Am. J. Physiol. Cell Physiol. 280, C110–C118.
Ikeno, T., Weil, Z.M., Nelson, R.J., 2014. Dim light at night disrupts the short-day response in Siberian hamsters. Gen. Comp. Endocrinol. 197, 56–64.
Illnerova, H., Vanecek, J., 1980. Pineal rhythm in N-acetyltransferase activity in rats under different artificial photoperiods and in natural daylight in the course of a year. Neuroendocrinology 31, 321–326.
Illnerova, H., Vanecek, J., 1985. Regulation of the circadian rhythm in pineal melatonin production. Physiol. Bohemoslov. 34 (Suppl), 57–61.
Illnerova, H., Zvolsky, P., Vanecek, J., 1985. The circadian rhythm in plasma melatonin concentration of the urbanized man: the effect of summer and winter time. Brain Res. 328, 186–189.
Illnerova, H., Sumova, A., Travnickova, Z., Jac, M., Jelinkova, D., 2000. Hormones, subjective night and season of the year. Physiol. Res. 49 (Suppl. 1), S1–S10.
Imai, Y., Munakata, M., Tsuji, I., Ohkubo, T., Satoh, H., Yoshino, H., Watanabe, N., Nishiyama, A., Onodera, N., Kato, J., Sekino, M., Aihara, A., Kasai, Y., Abe, K., 1996. Seasonal variation in blood pressure in normotensive women studied by home measurements. Clin. Sci. (London) 90, 55–60.
Inagaki, N., Honma, S., Ono, D., Tanahashi, Y., Honma, K., 2007. Separate oscillating cell groups in mouse suprachiasmatic nucleus couple photoperiodically to the onset and end of daily activity. Proc. Natl. Acad. Sci. USA 104, 7664–7669.
Irwin, R.P., Allen, C.N., 2009. GABAergic signaling induces divergent neuronal Ca2+ responses in the suprachiasmatic nucleus network. Eur. J. Neurosci. 30, 1462–1475.
Irwin, R.P., Allen, C.N., 2010. Neuropeptide-mediated calcium signaling in the suprachiasmatic nucleus network. Eur. J. Neurosci. 32, 1497–1506.
Jac, M., Sumova, A., Illnerova, H., 2000. C-Fos rhythm in subdivisions of the rat suprachiasmatic nucleus under artificial and natural photoperiods. Am. J. Physiol. Regul. Integr. Comp. Physiol. 279, R2270–R2276.
Jagota, A., de la Iglesia, H.O., Schwartz, W.J., 2000. Morning and evening circadian oscillations in the suprachiasmatic nucleus in vitro. Nat. Neurosci. 3, 372–376.
Jakubowski, M., Terkel, J., 1986. Female reproductive function and sexually dimorphic prolactin secretion in rats with lesions in the medial preoptic-anterior hypothalamic continuum. Neuroendocrinology 43, 696–705.
Jiao, Y.Y., Lee, T.M., Rusak, B., 1999. Photic responses of suprachiasmatic area neurons in diurnal degus (*Octodon degus*) and nocturnal rats (*Rattus norvegicus*). Brain Res. 817, 93–103.
Johnston, J.D., 2005. Measuring seasonal time within the circadian system: regulation of the suprachiasmatic nuclei by photoperiod. J. Neuroendocrinol. 17, 459–465.

Johnston, J.D., Ebling, F.J., Hazlerigg, D.G., 2005. Photoperiod regulates multiple gene expression in the suprachiasmatic nuclei and pars tuberalis of the Siberian hamster (*Phodopus sungorus*). Eur. J. Neurosci. 21, 2967–2974.
Kalsbeek, A., Palm, I.F., La Fleur, S.E., Scheer, F.A., Perreau-Lenz, S., Ruiter, M., Kreier, F., Cailotto, C., Buijs, R.M., 2006. SCN outputs and the hypothalamic balance of life. J. Biol. Rhythms 21, 458–469.
Kalsbeek, A., Bruinstroop, E., Yi, C.X., Klieverik, L.P., La Fleur, S.E., Fliers, E., 2010. Hypothalamic control of energy metabolism via the autonomic nervous system. Ann. N.Y. Acad. Sci. 1212, 114–129.
Kantermann, T., Juda, M., Merrow, M., Roenneberg, T., 2007. The human circadian clock's seasonal adjustment is disrupted by daylight saving time. Curr. Biol. 17, 1996–2000.
Karatsoreos, I.N., Yan, L., LeSauter, J., Silver, R., 2004. Phenotype matters: identification of light-responsive cells in the mouse suprachiasmatic nucleus. J. Neurosci. 24, 68–75.
Kawakami, M., Arita, J., 1981. Circadian rhythm of prolactin surges induced by stimulation of the uterine cervix in the ovariectomized rat: its sexual differentiation and preoptic regulation. J. Endocrinol. 91, 325–334.
Kawakami, M., Arita, J., Yoshioka, E., 1980. Loss of estrogen-induced daily surges of prolactin and gonadotropins by suprachiasmatic nucleus lesions in ovariectomized rats. Endocrinology 106, 1087–1092.
Kennaway, D.J., Dunstan, E.A., Gilmore, T.A., Seamark, R.F., 1984. Effects of pinealectomy, oestradiol and melatonin on plasma prolactin and LH secretion in ovariectomized sheep. J. Endocrinol. 102, 199–207.
Kennett, J.E., Poletini, M.O., Freeman, M.E., 2008. Vasoactive intestinal polypeptide modulates the estradiol-induced prolactin surge by entraining oxytocin neuronal activity. Brain Res. 1196, 65–73.
Kilduff, T.S., Sharp, F.R., Heller, H.C., 1982. [14C]2-deoxyglucose uptake in ground squirrel brain during hibernation. J. Neurosci. 2, 143–157.
Kilduff, T.S., Radeke, C.M., Randall, T.L., Sharp, F.R., Heller, H.C., 1989. Suprachiasmatic nucleus: phase-dependent activation during the hibernation cycle. Am. J. Physiol. 257, R605–R612.
Kilduff, T.S., Miller, J.D., Radeke, C.M., Sharp, F.R., Heller, H.C., 1990. 14C-2-deoxyglucose uptake in the ground squirrel brain during entrance to and arousal from hibernation. J. Neurosci. 10, 2463–2475.
Klein, D.C., Weller, J., 1970a. Input and output signals in a model neural system: the regulation of melatonin production in the pineal gland. Vitro 6, 197–204.
Klein, D.C., Weller, J.L., 1970b. Indole metabolism in the pineal gland: a circadian rhythm in N-acetyltransferase. Science 169, 1093–1095.
Klein, D.C., Berg, G.R., Weller, J., 1970. Melatonin synthesis: adenosine 3′,5′-monophosphate and norepinephrine stimulate N-acetyltransferase. Science 168, 979–980.
Kohsaka, M., Fukuda, N., Honma, K., Honma, S., Morita, N., 1992. Seasonality in human sleep. Experientia 48, 231–233.
Kuhlman, S.J., Silver, R., Le, S.J., Bult-Ito, A., McMahon, D.G., 2003. Phase resetting light pulses induce Per1 and persistent spike activity in a subpopulation of biological clock neurons. J. Neurosci. 23, 1441–1450.
Lall, G.S., Revell, V.L., Momiji, H., Al, E.J., Altimus, C.M., Guler, A.D., Aguilar, C., Cameron, M.A., Allender, S., Hankins, M.W., Lucas, R.J., 2010. Distinct contributions of rod, cone, and melanopsin photoreceptors to encoding irradiance. Neuron 66, 417–428.
Lee, T.M., Zucker, I., 1991. Suprachiasmatic nucleus and photic entrainment of circannual rhythms in ground squirrels. J. Biol. Rhythms 6, 315–330.
Lehman, M.N., Silver, R., Gladstone, W.R., Kahn, R.M., Gibson, M., Bittman, E.L., 1987. Circadian rhythmicity restored by neural transplant. Immunocytochemical characterization of the graft and its integration with the host brain. J. Neurosci. 7, 1626–1638.
LeSauter, J., Lehman, M.N., Silver, R., 1996. Restoration of circadian rhythmicity by transplants of SCN "micropunches". J. Biol. Rhythms 11, 163–171.
Lucas, R.J., 2013. Mammalian inner retinal photoreception. Curr. Biol. 23, R125–R133.
Lucassen, E.A., van Diepen, H.C., Houben, T., Michel, S., Colwell, C.S., Meijer, J.H., 2012. Role of vasoactive intestinal peptide in seasonal encoding by the suprachiasmatic nucleus clock. Eur. J. Neurosci. 35, 1466–1474.
Maes, M., Scharpe, S., Verkerk, R., D'Hondt, P., Peeters, D., Cosyns, P., Thompson, P., De, M.F., Wauters, A., Neels, H., 1995. Seasonal variation in plasma L-tryptophan availability in healthy volunteers. Relationships to violent suicide occurrence. Arch. Gen. Psychiatry 52, 937–946.
Maurel, D., Boissin-Agasse, L., Roch, G., Herbute, S., Boissin, J., 1991. Suprachiasmatic nucleus lesions abolish photoperiod-induced changes in the testis function and GnRH immunoreactivity in the mink, a short-day breeder. Neuroendocrinology 54, 103–110.
Maywood, E.S., Buttery, R.C., Vance, G.H., Herbert, J., Hastings, M.H., 1990. Gonadal responses of the male Syrian hamster to programmed infusions of melatonin are sensitive to signal duration and frequency but not to signal phase nor to lesions of the suprachiasmatic nuclei. Biol. Reprod. 43, 174–182.
Maywood, E.S., Bittman, E.L., Ebling, F.J., Barrett, P., Morgan, P., Hastings, M.H., 1995. Regional distribution of iodomelatonin binding sites within the suprachiasmatic nucleus of the Syrian hamster and the Siberian hamster. J. Neuroendocrinol. 7, 215–223.
Maywood, E.S., Reddy, A.B., Wong, G.K., O'Neill, J.S., O'Brien, J.A., McMahon, D.G., Harmar, A.J., Okamura, H., Hastings, M.H., 2006. Synchronization and maintenance of timekeeping in suprachiasmatic circadian clock cells by neuropeptidergic signaling. Curr. Biol. 16, 599–605.
Maywood, E.S., Chesham, J.E., O'Brien, J.A., Hastings, M.H., 2011. A diversity of paracrine signals sustains molecular circadian cycling in suprachiasmatic nucleus circuits. Proc. Natl. Acad. Sci. USA 108, 14306–14311.
McArthur, A.J., Gillette, M.U., Prosser, R.A., 1991. Melatonin directly resets the rat suprachiasmatic circadian clock in vitro. Brain Res. 565, 158–161.
McArthur, A.J., Coogan, A.N., Ajpru, S., Sugden, D., Biello, S.M., Piggins, H.D., 2000. Gastrin-releasing peptide phase-shifts suprachiasmatic nuclei neuronal rhythms in vitro. J. Neurosci. 20, 5496–5502.
Meijer, J.H., Schwartz, W.J., 2003. In search of the pathways for light-induced pacemaker resetting in the suprachiasmatic nucleus. J. Biol. Rhythms 18, 235–249.
Meijer, J.H., Groos, G.A., Rusak, B., 1986. Luminance coding in a circadian pacemaker: the suprachiasmatic nucleus of the rat and the hamster. Brain Res. 382, 109–118.
Meijer, J.H., Rusak, B., Harrington, M.E., 1989. Photically responsive neurons in the hypothalamus of a diurnal ground squirrel. Brain Res. 501, 315–323.
Meijer, J.H., Rusak, B., Ganshirt, G., 1992. The relation between light-induced discharge in the suprachiasmatic nucleus and phase shifts of hamster circadian rhythms. Brain Res. 598, 257–263.
Meijer, J.H., Watanabe, K., Schaap, J., Albus, H., Detari, L., 1998. Light responsiveness of the suprachiasmatic nucleus: long-term multiunit and single-unit recordings in freely moving rats. J. Neurosci. 18, 9078–9087.
Meijer, J.H., Colwell, C.S., Rohling, J.H., Houben, T., Michel, S., 2012. Dynamic neuronal network organization of the circadian clock and possible deterioration in disease. Prog. Brain Res. 199, 143–162.
Messager, S., Caillol, M., Martinet, L., 1999. Long-term exposure of hypothalamic explants to melatonin alters the release of gonadotrophin releasing hormone and the density of melatonin binding sites in the pars tuberalis of the male mink (Mustela vison). J. Pineal Res. 26, 17–27.
Molendijk, M.L., Haffmans, J.P., Bus, B.A., Spinhoven, P., Penninx, B.W., Prickaerts, J., Oude Voshaar, R.C., Elzinga, B.M., 2012. Serum BDNF concentrations show strong seasonal variation and correlations with the amount of ambient sunlight. PLoS ONE 7, e48046.
Moore, R.Y., Speh, J.C., Leak, R.K., 2002. Suprachiasmatic nucleus organization. Cell Tissue Res. 309, 89–98.
Morgan, P.J., 2000. The pars tuberalis: the missing link in the photoperiodic regulation of prolactin secretion? J. Neuroendocrinol. 12, 287–295.
Morgan, P.J., Ross, A.W., Mercer, J.G., Barrett, P., 2006. What can we learn from seasonal animals about the regulation of energy balance? Prog. Brain Res. 153, 325–337.
Morin, L.P., 1993. Age, but not pineal status, modulates circadian periodicity of golden hamsters. J. Biol. Rhythms 8, 189–197.
Morin, L.P., Allen, C.N., 2006. The circadian visual system, 2005. Brain Res. Rev. 51, 1–60.
Mrugala, M., Zlomanczuk, P., Jagota, A., Schwartz, W.J., 2000. Rhythmic multiunit neural activity in slices of hamster suprachiasmatic nucleus reflect prior photoperiod. Am. J. Physiol. Regul. Integr. Comp. Physiol. 278, R987–R994.
Nagano, M., Adachi, A., Nakahama, K., Nakamura, T., Tamada, M., Meyer-Bernstein, E., Sehgal, A., Shigeyoshi, Y., 2003. An abrupt shift in the day/night cycle causes desynchrony in the mammalian circadian center. J. Neurosci. 23, 6141–6151.
Nagoshi, E., Saini, C., Bauer, C., Laroche, T., Naef, F., Schibler, U., 2004. Circadian gene expression in individual fibroblasts: cell-autonomous and self-sustained oscillators pass time to daughter cells. Cell 119, 693–705.
Naito, E., Watanabe, T., Tei, H., Yoshimura, T., Ebihara, S., 2008. Reorganization of the suprachiasmatic nucleus coding for day length. J. Biol. Rhythms 23, 140–149.
Nakamura, T.J., Fujimura, K., Ebihara, S., Shinohara, K., 2004. Light response of the neuronal firing activity in the suprachiasmatic nucleus of mice. Neurosci. Lett. 371, 244–248.
Nakamura, T.J., Nakamura, W., Yamazaki, S., Kudo, T., Cutler, T., Colwell, C.S., Block, G.D., 2011. Age-related decline in circadian output. J. Neurosci. 31, 10201–10205.
Nett, T.M., Niswender, G.D., 1982. Influence of exogenous melatonin on seasonality of reproduction in sheep. Theriogenology 17, 645–653.
Neumeister, A., Pirker, W., Willeit, M., Praschak-Rieder, N., Asenbaum, S., Brucke, T., Kasper, S., 2000. Seasonal variation of availability of serotonin transporter binding sites in healthy female subjects as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. Biol. Psychiatry 47, 158–160.
Ohta, H., Yamazaki, S., McMahon, D.G., 2005. Constant light desynchronizes mammalian clock neurons. Nat. Neurosci. 8, 267–269.
O'Neill, J.S., Reddy, A.B., 2011. Circadian clocks in human red blood cells. Nature 469, 498–503.
Palm, I.F., van der Beek, E.M., Swarts, H.J., Van, d.V., Wiegant, V.M., Buijs, R.M., Kalsbeek, A., 2001. Control of the estradiol-induced prolactin surge by the suprachiasmatic nucleus. Endocrinology 142, 2296–2302.
Panda, S., Sato, T.K., Castrucci, A.M., Rollag, M.D., DeGrip, W.J., Hogenesch, J.B., Provencio, I., Kay, S.A., 2002. Melanopsin (Opn4) requirement for normal light-induced circadian phase shifting. Science 298, 2213–2216.
Parkanova, D., Novakova, M., Sosniyenko, S., Sumova, A., 2012. Photoperiodic modulation of the hepatic clock by the suprachiasmatic nucleus and feeding regime in mice. Eur. J. Neurosci. 35, 1446–1457.
Pieper, D.R., Gala, R.R., 1979. The effect of light on the prolactin surges of pseudopregnant and ovariectomized, estrogenized rats. Biol. Reprod. 20, 727–732.
Piggins, H.D., Antle, M.C., Rusak, B., 1995. Neuropeptides phase shift the mammalian circadian pacemaker. J. Neurosci. 15, 5612–5622.

Pittendrigh, C.S., Elliott, J.A., Takamura, T., 1984. The circadian component in photoperiodic induction. In: Photoperiodic Regulation of Insect and Molluscan Hormones. Pitman, London, pp. 26–47.
Pittendrigh, C.S., Kyner, W.T., Takamura, T., 1991. The amplitude of circadian oscillations: temperature dependence, latitudinal clines, and the photoperiodic time measurement. J. Biol. Rhythms 6, 299–313.
Poletini, M.O., McKee, D.T., Kennett, J.E., Doster, J., Freeman, M.E., 2007. Knockdown of clock genes in the suprachiasmatic nucleus blocks prolactin surges and alters FRA expression in the locus coeruleus of female rats. Am. J. Physiol. Endocrinol. Metab. 293, E1325–E1334.
Poulton, A.L., English, J., Symons, A.M., Arendt, J., 1987. Changes in plasma concentrations of LH, FSH and prolactin in ewes receiving melatonin and short-photoperiod treatments to induce early onset of breeding activity. J. Endocrinol. 112, 103–111.
Ralph, M.R., Foster, R.G., Davis, F.C., Menaker, M., 1990. Transplanted suprachiasmatic nucleus determines circadian period. Science 247, 975–978.
Ramkisoensing, A., Gu, C., Van Engeldorp Gastelaars, H.M., Michel, S., Deboer, T., Rohling, J.H., Meijer, J.H., 2014. Enhanced phase resetting in the synchronized suprachiasmatic nucleus network. J. Biol. Rhythms 29, 4–15.
Recio, J., Pevet, P., Vivien-Roels, B., Miguez, J.M., Masson-Pevet, M., 1996. Daily and photoperiodic melatonin binding changes in the suprachiasmatic nuclei, paraventricular thalamic nuclei, and pars tuberalis of the female Siberian hamster (*Phodopus sungorus*). J. Biol. Rhythms 11, 325–332.
Reddy, A.B., Field, M.D., Maywood, E.S., Hastings, M.H., 2002. Differential resynchronisation of circadian clock gene expression within the suprachiasmatic nuclei of mice subjected to experimental jet lag. J. Neurosci. 22, 7326–7330.
Reed, H.E., Meyer-Spasche, A., Cutler, D.J., Coen, C.W., Piggins, H.D., 2001. Vasoactive intestinal polypeptide (VIP) phase-shifts the rat suprachiasmatic nucleus clock in vitro. Eur. J. Neurosci. 13, 839–843.
Refinetti, R., 2002. Compression and expansion of circadian rhythm in mice under long and short photoperiods. Integr. Physiol. Behav. Sci. 37, 114–127.
Revel, F.G., Herwig, A., Garidou, M.L., Dardente, H., Menet, J.S., Masson-Pevet, M., Simonneaux, V., Saboureau, M., Pevet, P., 2007. The circadian clock stops ticking during deep hibernation in the European hamster. Proc. Natl. Acad. Sci. USA 104, 13816–13820.
Roenneberg, T., Aschoff, J., 1990. Annual rhythm of human reproduction: II. Environmental correlations. J. Biol. Rhythms 5, 217–239.
Rohling, J., Wolters, L., Meijer, J.H., 2006. Simulation of day-length encoding in the SCN: from single-cell to tissue-level organization. J. Biol. Rhythms 21, 301–313.
Rohling, J., Meijer, J.H., Vanderleest, H.T., Admiraal, J., 2006. Phase differences between SCN neurons and their role in photoperiodic encoding; a simulation of ensemble patterns using recorded single unit electrical activity patterns. J. Physiol. Paris 100, 261–270.
Roseboom, P.H., Namboodiri, M.A., Zimonjic, D.B., Popescu, N.C., Rodriguez, I.R., Gastel, J.A., Klein, D.C., 1998. Natural melatonin 'knockdown' in C57BL/6J mice: rare mechanism truncates serotonin N-acetyltransferase. Brain Res. Mol. Brain Res. 63, 189–197.
Ross, A.W., Morgan, P.J., 2002. The pars tuberalis as a target of the central clock. Cell Tissue Res. 309, 163–171.
Ruby, N.F., 2003. Hibernation: when good clocks go cold. J. Biol. Rhythms 18, 275–286.
Ruby, N.F., Dark, J., Heller, H.C., Zucker, I., 1996. Ablation of suprachiasmatic nucleus alters timing of hibernation in ground squirrels. Proc. Natl. Acad. Sci. USA 93, 9864–9868.
Ruby, N.F., Dark, J., Heller, H.C., Zucker, I., 1998. Suprachiasmatic nucleus: role in circannual body mass and hibernation rhythms of ground squirrels. Brain Res. 782, 63–72.
Ruby, N.F., Brennan, T.J., Xie, X., Cao, V., Franken, P., Heller, H.C., O'Hara, B.F., 2002. Role of melanopsin in circadian responses to light. Science 298, 2211–2213.
Rusak, B., Morin, L.P., 1976. Testicular responses to photoperiod are blocked by lesions of the suprachiasmatic nuclei in golden hamsters. Biol. Reprod. 15, 366–374.
Schaap, J., Albus, H., Vanderleest, H.T., Eilers, P.H., Detari, L., Meijer, J.H., 2003. Heterogeneity of rhythmic suprachiasmatic nucleus neurons: Implications for circadian waveform and photoperiodic encoding. Proc. Natl. Acad. Sci. USA 100, 15994–15999.
Schuster, C., Gauer, F., Malan, A., Recio, J., Pevet, P., Masson-Pevet, M., 2001. The circadian clock, light/dark cycle and melatonin are differentially involved in the expression of daily and photoperiodic variations in mt(1) melatonin receptors in the Siberian and Syrian hamsters. Neuroendocrinology 74, 55–68.
Schwartz, W.J., Carpino Jr., A., De la Iglesia, H.O., Baler, R., Klein, D.C., Nakabeppu, Y., Aronin, N., 2000. Differential regulation of fos family genes in the ventrolateral and dorsomedial subdivisions of the rat suprachiasmatic nucleus. Neuroscience 98, 535–547.
Schwartz, W.J., Zimmerman, P., 1990. Circadian timekeeping in BALB/c and C57BL/6 inbred mouse strains. J. Neurosci. 10, 3685–3694.
Shibata, S., Oomura, Y., Hattori, K., Kita, H., 1984a. Responses of suprachiasmatic nucleus neurons to optic nerve stimulation in rat hypothalamic slice preparation. Brain Res. 302, 83–89.
Shibata, S., Liou, S., Ueki, S., Oomura, Y., 1984b. Influence of environmental light-dark cycle and enucleation on activity of suprachiasmatic neurons in slice preparations. Brain Res. 302, 75–81.
Shibata, S., Cassone, V.M., Moore, R.Y., 1989. Effects of melatonin on neuronal activity in the rat suprachiasmatic nucleus in vitro. Neurosci. Lett. 97, 140–144.
Shirakawa, T., Honma, S., Katsuno, Y., Oguchi, H., Honma, K.I., 2000. Synchronization of circadian firing rhythms in cultured rat suprachiasmatic neurons. Eur. J. Neurosci. 12, 2833–2838.
Shuboni, D., Yan, L., 2010. Nighttime dim light exposure alters the responses of the circadian system. Neuroscience 170, 1172–1178.
Silver, R., Lehman, M.N., Gibson, M., Gladstone, W.R., Bittman, E.L., 1990. Dispersed cell suspensions of fetal SCN restore circadian rhythmicity in SCN-lesioned adult hamsters. Brain Res. 525, 45–58.
Silver, R., LeSauter, J., Tresco, P.A., Lehman, M.N., 1996. A diffusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. Nature 382, 810–813.
Silver, R., Romero, M.T., Besmer, H.R., Leak, R., Nunez, J.M., LeSauter, J., 1996. Calbindin-D28K cells in the hamster SCN express light-induced Fos. NeuroReport 7, 1224–1228.
Smith, M.S., Neill, J.D., 1976. Termination at midpregnancy of the two daily surges of plasma prolactin initiated by mating in the rat. Endocrinology 98, 696–701.
Song, C.K., Bartness, T.J., 1998. Dorsocaudal SCN microknife-cuts do not block short day responses in Siberian hamsters given melatonin infusions. Brain Res. Bull. 45, 239–246.
Stanton, T.L., Siuciak, J.A., Dubocovich, M.L., Krause, D.N., 1991. The area of 2-[125I] iodomelatonin binding in the pars tuberalis of the ground squirrel is decreased during hibernation. Brain Res. 557, 285–288.
Stephan, F.K., Berkley, K.J., Moss, R.L., 1981. Efferent connections of the rat suprachiasmatic nucleus. Neuroscience 6, 2625–2641.
Stetson, M.H., Watson-Whitmyre, M., 1976. Nucleus suprachiasmaticus: the biological clock in the hamster? Science 191, 197–199.
Stokkan, K.A., Yamazaki, S., Tei, H., Sakaki, Y., Menaker, M., 2001. Entrainment of the circadian clock in the liver by feeding. Science 291, 490–493.
Sumova, A., Travnickova, Z., Peters, R., Schwartz, W.J., Illnerova, H., 1995. The rat suprachiasmatic nucleus is a clock for all seasons. Proc. Natl. Acad. Sci. USA 92, 7754–7758.
Sumova, A., Travnickova, Z., Mikkelsen, J.D., Illnerova, H., 1998. Spontaneous rhythm in c-Fos immunoreactivity in the dorsomedial part of the rat suprachiasmatic nucleus. Brain Res. 801, 254–258.
Sumova, A., Travnickova, Z., Illnerova, H., 2000. Spontaneous c-Fos rhythm in the rat suprachiasmatic nucleus: location and effect of photoperiod. Am. J. Physiol. Regul. Integr. Comp. Physiol. 279, R2262–R2269.
Sumova, A., Sladek, M., Jac, M., Illnerova, H., 2002. The circadian rhythm of Per1 gene product in the rat suprachiasmatic nucleus and its modulation by seasonal changes in daylength. Brain Res. 947, 260–270.
Sumova, A., Bendova, Z., Sladek, M., Kovacikova, Z., Illnerova, H., 2004. Seasonal molecular timekeeping within the rat circadian clock. Physiol. Res. 53 (Suppl 1), S167–S176.
Swanson, L.W., Cowan, W.M., 1975. The efferent connections of the suprachiasmatic nucleus of the hypothalamus. J. Comp. Neurol. 160, 1–12.
Tanaka, M., Hayashi, S., Tamada, Y., Ikeda, T., Hisa, Y., Takamatsu, T., Ibata, Y., 1997. Direct retinal projections to GRP neurons in the suprachiasmatic nucleus of the rat. NeuroReport 8, 2187–2191.
Tenn, C., Niles, L.P., 1993. Physiological regulation of melatonin receptors in rat suprachiasmatic nuclei: diurnal rhythmicity and effects of stress. Mol. Cell. Endocrinol. 98, 43–48.
Tournier, B.B., Dardente, H., Simonneaux, V., Vivien-Roels, B., Pevet, P., Masson-Pevet, M., Vuillez, P., 2007. Seasonal variations of clock gene expression in the suprachiasmatic nuclei and pars tuberalis of the European hamster (*Cricetus cricetus*). Eur. J. Neurosci. 25, 1529–1536.
Tousson, E., Meissl, H., 2004. Suprachiasmatic nuclei grafts restore the circadian rhythm in the paraventricular nucleus of the hypothalamus. J. Neurosci. 24, 2983–2988.
Travnickova, Z., Sumova, A., Peters, R., Schwartz, W.J., Illnerova, H., 1996. Photoperiod-dependent correlation between light-induced SCN c-fos expression and resetting of circadian phase. Am. J. Physiol. 271, R825–R831.
Van den Pol, A.N., 1980. The hypothalamic suprachiasmatic nucleus of rat: intrinsic anatomy. J. Comp. Neurol. 191, 661–702.
van den Pol, A.N., 1991. Glutamate and aspartate immunoreactivity in hypothalamic presynaptic axons. J. Neurosci. 11, 2087–2101.
van Diepen, H.C., Ramkisoensing, A., Peirson, S.N., Foster, R.G., Meijer, J.H., 2013. Irradiance encoding in the suprachiasmatic nuclei by rod and cone photoreceptors. FASEB J. 27, 4204–4212.
Vanderleest, H.T., Houben, T., Michel, S., Deboer, T., Albus, H., Vansteensel, M.J., Block, G.D., Meijer, J.H., 2007. Seasonal encoding by the circadian pacemaker of the SCN. Curr. Biol. 17, 468–473.
Vanderleest, H.T., Rohling, J.H., Michel, S., Meijer, J.H., 2009. Phase shifting capacity of the circadian pacemaker determined by the SCN neuronal network organization. PLoS ONE 4, e4976.
Vujovic, N., Davidson, A.J., Menaker, M., 2008. Sympathetic input modulates, but does not determine, phase of peripheral circadian oscillators. Am. J. Physiol. Regul. Integr. Comp. Physiol. 295, R355–R360.
Wade, G.N., Bartness, T.J., 1984. Effects of photoperiod and gonadectomy on food intake, body weight, and body composition in Siberian hamsters. Am. J. Physiol. 246, R26–R30.
Wagner, S., Sagiv, N., Yarom, Y., 2001. GABA-induced current and circadian regulation of chloride in neurones of the rat suprachiasmatic nucleus. J. Physiol. 537, 853–869.
Watts, A.G., Swanson, L.W., 1987. Efferent projections of the suprachiasmatic nucleus: II. Studies using retrograde transport of fluorescent dyes and

simultaneous peptide immunohistochemistry in the rat. J. Comp. Neurol. 258, 230–252.
Watts, A.G., Swanson, L.W., Sanchez-Watts, G., 1987. Efferent projections of the suprachiasmatic nucleus: I. Studies using anterograde transport of *Phaseolus vulgaris* leucoagglutinin in the rat. J. Comp. Neurol. 258, 204–229.
Weaver, D.R., Rivkees, S.A., Reppert, S.M., 1989. Localization and characterization of melatonin receptors in rodent brain by in vitro autoradiography. J. Neurosci. 9, 2581–2590.
Wehr, T.A., Giesen, H.A., Moul, D.E., Turner, E.H., Schwartz, P.J., 1995. Suppression of men's responses to seasonal changes in day length by modern artificial lighting. Am. J. Physiol. 269, R173–R178.
Welsh, D.K., Logothetis, D.E., Meister, M., Reppert, S.M., 1995. Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. Neuron 14, 697–706.
Welsh, D.K., Yoo, S.H., Liu, A.C., Takahashi, J.S., Kay, S.A., 2004. Bioluminescence imaging of individual fibroblasts reveals persistent, independently phased circadian rhythms of clock gene expression. Curr. Biol. 14, 2289–2295.
Winfree, A.T., 2000. The Geometry of Biological Time. Springer, New York.
Wong, K.Y., 2012. A retinal ganglion cell that can signal irradiance continuously for 10 hours. J. Neurosci. 32, 11478–11485.
Yamazaki, S., Numano, R., Abe, M., Hida, A., Takahashi, R., Ueda, M., Block, G.D., Sakaki, Y., Menaker, M., Tei, H., 2000. Resetting central and peripheral circadian oscillators in transgenic rats. Science 288, 682–685.
Yan, L., Silver, R., 2008. Day-length encoding through tonic photic effects in the retinorecipient SCN region. Eur. J. Neurosci. 28, 2108–2115.
Yan, L., Takekida, S., Shigeyoshi, Y., Okamura, H., 1999. Per1 and Per2 gene expression in the rat suprachiasmatic nucleus: circadian profile and the compartment-specific response to light. Neuroscience 94, 141–150.
Yan, L., Karatsoreos, I., Lesauter, J., Welsh, D.K., Kay, S., Foley, D., Silver, R., 2007. Exploring spatiotemporal organization of SCN circuits. Cold Spring Harb. Symp. Quant. Biol. 72, 527–541.
Yoo, S.H., Yamazaki, S., Lowrey, P.L., Shimomura, K., Ko, C.H., Buhr, E.D., Siepka, S.M., Hong, H.K., Oh, W.J., Yoo, O.J., Menaker, M., Takahashi, J.S., 2004. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. Proc. Natl. Acad. Sci. USA 101, 5339–5346.
Zucker, I., Boshes, M., Dark, J., 1983. Suprachiasmatic nuclei influence circannual and circadian rhythms of ground squirrels. Am. J. Physiol. 244, R472–R480.