Rev Endocr Metab Disord
DOI 10.1007/s11154-009-9121-9

Expression of clock genes in the suprachiasmatic nucleus: Effect of environmental lighting conditions

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Abstract The suprachiasmatic nucleus (SCN) is the anatomical substrate for the principal circadian clock coordinating daily rhythms in a vast array of behavioral and physiological responses. Individual SCN neurons are cellular oscillators and are organized into a multi-oscillator network following unique spatiotemporal patterns. The rhythms generated in the SCN are generally entrained to the environmental light dark cycle, which is the most salient cue influencing the network organization of the SCN. The neural network in the SCN is a heterogeneous structure, containing two major compartments identified by applying physiological and functional criteria, namely the retinorecipient core region and the highly rhythmic shell region. Changes in the environmental lighting condition are first detected and processed by the core region, and then conveyed to the rest of the SCN, leading to adaptive responses of the entire network. This review will focus on the studies that explore the responses of the SCN network by examining the expression of clock genes, under various lighting paradigms, such as acute light exposure, lighting schedules or exposure to different light durations. The results will be discussed under the framework of functionally distinct SCN sub regions and oscillator groups. The evidence presented here suggests that the environmental lighting conditions alter the spatiotemporal organization of the cellular oscillators within the SCN, which consequently affect the overt rhythms in behavior and physiology. Thus, information on how the SCN network elements respond to environmental cues is key to understanding the human health problems that stem from circadian rhythm disruption.

Keywords Circadian rhythms · Light · Clock genes · SCN

1 Introduction

Circadian rhythms in behavior and physiology are controlled by an endogenous circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus [1]. Ablation of the SCN abolishes all measurable circadian rhythms, such as in locomotor activity, eating, drinking, body temperature, and hormone secretions, and transplants of fetal SCN tissue to SCN-lesioned animals restore behavioral rhythms, with the period of the restored rhythm matching that of the donor and not that of the host animal [2]. Within the SCN, circadian oscillations can be measured in metabolic activity, neuropeptide release, electrical activity, and gene expression [3]. The molecular basis for circadian oscillation has been described as an autoregulatory transcription-translation feedback loop made up of a set of clock genes including *Period* (*Per*) *1*, *Per2*, *clock, Bmal1, Cryptochrome (Cry) 1, Cry2, Rev-erb alpha* and *Rora* [3–5]. This molecular clock, while first described for the SCN, also exists in other brain regions, peripheral tissue/organs and even in cultured cell lines [6, 7]. Thus, the current model for the regulation of the circadian system is that the SCN, as the principal circadian pacemaker, sits on top of the hierarchy, synchronizing the other clocks across the brain and body to produce coherent rhythmic behavioral and physiological responses [8, 9].

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Published online: 24 September 2009

Circadian rhythms in an organism are always synchronized to local time, and the most salient environmental cue for setting the phase of circadian rhythms is the day-night/light-dark (LD) cycle [10]. The pathways for light-induced resetting of the circadian clock have been well characterized [11]. Briefly, photic cues are conveyed to the SCN from retina via the retinohypothalamic tract (RHT) [12, 13], and activate NMDA receptors of SCN neurons [14]. The subsequent Ca2+ influx [15–18] and the activation of intracellular and intercellular signaling pathways (reviewed in Antle et al in this issue) alter the pattern of clock gene expressions in the SCN, which results in the resetting of the master circadian clock of the SCN and an array of SCN-dependent rhythmic processes.

Several lines of evidence suggest that photic entrainment of the circadian clock involves acute induction of clock genes *Per1* and *Per2* [3]. A brief light exposure during nighttime causes acute induction in *Per1* and *Per2* expression [19–27]. Blocking *Per* gene induction using antisense oligonucleotides, attenuates light-induced phase shifts of locomotor behavior [28–30]. However, the results from studies using mutant animals are less consistent. Albrecht *et al*. [31] reported the absence of phase advances or delays respectively, in *Per1* or *Per2* mutant mice following a corresponding phase-shifting light pulse. While studies using other *Per* gene mutant lines have shown relatively normal phase shifts after a light exposure [32, 33]. The discrepancy between these studies may originate from the ways in which the mutants were generated, or from the use of different experimental paradigms in testing the phase shifts. It is likely that *Per1* and *Per2* may play complementary or collective roles in mediating photic effect on circadian rhythms. When any deficits occur in one of the genes, the other might be able to partially compensate for the functions affected. Animals deficient in both *Per1* and *Per2* genes do not show circadian rhythms, suggesting the presence of a critical role for *Per* genes in regulating circadian rhythms and in mediating responses of the circadian system to environmental cues [33, 34].

Due to their high amplitude circadian expression and their responsiveness to light, both *Per1* and *Per2* genes are good markers for tracking cellular responses and assessing the phase of circadian oscillators. Because of these features, they have been widely examined in the SCN of various species under a range of lighting conditions. While the initial works merely reported that light induces *Per* gene expression in the SCN, follow up studies, utilizing approaches with higher spatial resolution and various lighting paradigms have revealed that the spatiotemporal regulation of induced and rhythmic *Per* gene expression in the SCN is substantially more complicated and infinitely more interesting than the initial reports suggested. Those observations have uncovered important network properties of the SCN. This review focuses on the studies that explore the responses of the SCN network by examining the expression of clock genes, mostly *Per* genes, under various lighting paradigms, such as acute light exposure, different lighting schedules or duration of light exposure. These results will be discussed under the framework of functionally distinct SCN sub regions and oscillatory groups. The evidence presented here suggests that lighting conditions can affect the clock function by altering the spatiotemporal organization of cellular oscillators within the SCN, which consequently changes the overt rhythms in behavior and physiology.

2 Functionally distinct SCN sub regions

The SCN is a heterogeneous structure that is comprised of different groups of neurons differing in size and morphology, afferent and efferent connections, neuropeptide phenotype, and clock gene expression [12, 13, 24, 27, 35–38]. Although there are species differences in the topography of the SCN that complicate the universal characterization of the SCN [39, 40], there is general agreement that the SCN contains two major compartments based on physiological and functional criteria [41, 42]. One compartment is located in the core or ventrolateral region, receiving heavy retinal input and showing low amplitude circadian oscillations in clock gene expression. The other compartment is located in the shell or dorsomedial region, and shows high amplitude of circadian oscillations (Fig. 1). In most rodent species, the core or ventral SCN region is rich in VIP and GRP expressing neurons, while the shell or dorsal SCN is rich in AVP neurons [42, and references therein]. Intercellular signaling between the two compartments is critical in maintaining the synchrony of SCN cellular oscillators and circadian function within the SCN [43–48].

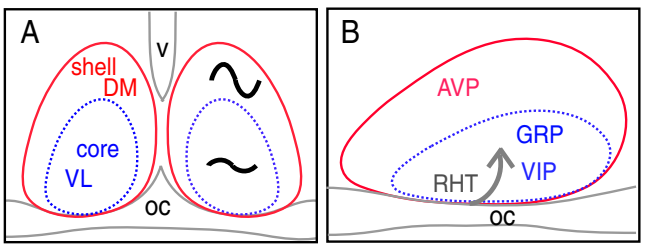

Fig. 1 Anatomically and functionally distinct SCN sub regions. Schematics depict the shell or dorsomedial (DM) region and the core or ventrolateral (VL) region at coronal (**A**) and sagittal (**B**) view of the SCN. The shell SCN region shows high amplitude circadian oscillation in clock gene expression, and is rich in AVP expressing neurons. The core region shows low amplitude circadian oscillation, receives heavy retinal input, and is rich in VIP and GRP cells. oc, optic chiasm; RHT, retinohypothalamic tract; v, third ventricle

Thus, analyzing the clock gene responses in the functionally distinct SCN sub regions, is useful for understanding the intercellular communication that occurs during photic entrainment and for elucidating the responses of the SCN network when the organism is exposed to various lighting conditions. In the studies reviewed here, different terms have been used to describe these two SCN sub regions, sometimes without precise anatomical delineations [39, 40]. In the following discussion, regardless of the terms e.g. core/ventral/ventrolateral and shell/dorsal/dorsomedial used in each original study, the terms "core" and "shell" will be used in reference to the two main subdivisions of the SCN.

3 Acute light exposure

A brief exposure to light can reset the phase of the circadian clock in the SCN. The response of the SCN to light depends on the phase at which the light pulses are applied [49]. The responses to a nighttime light exposure are consistent for both nocturnal and diurnal species. Thus, a light pulse applied in the early night produces phase delays, while the same stimulus presented during the late night produces phase advances. A light pulse applied during the subjective day typically has little or no effect in nocturnal species, but most diurnal animals respond to light pulses during subjective day, and have only a small non-responsive interval, if any at all [50–54]. This circadian gating of responsiveness to photic stimulation is a central feature of all current models of entrainment.

As discussed earlier, light reaches the SCN through the RHT, and the innervation of the SCN by the RHT is predominantly to the core region. Using electrical recording or c-Fos expression, it has been revealed that only a small set (about 30%) of SCN neurons, primarily located in the core SCN region, are directly responsive to light [55–59]. Thus, the photic signals received by the cells in the core region must propagate to the rest of the SCN for the phase shifts of this multi-oscillator network to occur.

Indeed, this intercellular signal transduction is evident in the pattern of light-induced expression of *Per1* and *Per2* in the SCN of many rodent species, such as mice [20, 60], rats [24, 61], hamsters [26, 27] and diurnal grass rats [62]. Although the experimental paradigms, such as the lighting history of the animals, the timing, duration and intensity of the light exposure and the time course, are slightly different among the individual studies, there is a consistent finding, which is that the induction of *Per1* and *Per2* initially occurs in the core SCN, and then spreads into the shell region, with the exact pattern depending on the timing of light exposure (Fig. 2). In the delay zone of the phase response curve, a light pulse induces the expression of both *Per1* and *Per2* genes. At this phase *Per1* expression is restricted in the core SCN while *Per2* expression is initially in the core, but then spreads throughout the SCN. In contrast, after a light pulse in the advance zone, *Per1* is initially induced in the core and then spreads to the shell. The expression of *Per2* following an advancing LP is more variable among different species, and seems to be correlated with the behavioral responses. Specifically, *Per2* induction is present in species that show larger advances, e.g. hamsters, but not in those having smaller behavioral responses, e.g. mice or rats, supporting the view that the two genes have additive effects in mediating behavioral shifts [21, 22, 24, 26, 27, 60, 61]. Taken together, these studies demonstrate that the cells in the core and shell SCN regions are activated sequentially following a photic cue, with distinct spatial patterns of clock gene induction corresponding to different behavioral responses.

The mechanisms underlying the propagation of light-induced *Per* gene expression from the core to the shell SCN are still not well understood. Efforts have been directed to identifying the phenotype of the cells in which *Per* genes are initially induced by light. Co-localization of light-induced *Per* gene with VIP and with GRP, has been shown in mice [38] and in rats [63]. These results are consistent with anatomical studies showing that in these two species, VIP and GRP cells in the SCN are innervated by the RHT [64, 65]. In the rat SCN, some GRP and VIP cells are co-localized [66, 67], and the initial induction of *Per1* gene occurs in only the part of the VIP mRNA expressing region that overlaps with the GRP mRNA expressing one [67]. Therefore, it is likely that the cells showing the initial induction of *Per* gene are those co-expressing VIP and GRP in the SCN. Given that GRP and VIP cells are activated by light, it is possible that these neuropeptides serve as a signal to relay light information from the core to the rest of the SCN. There is evidence to suggest that GRP and VIP do mimic the effects of light, particularly in terms of clock gene expression. *In vitro*, applying either VIP or GRP induces phase-dependent shifts of rhythms in the electrical activity of the SCN [68, 69]. Microinjections of VIP or GRP into the SCN or the third ventricle at night cause elevated *Per1* and *Per2* expression [45, 70, 71]. In hamsters, the GRP induced expression of *Per* gene is restricted to an area dorsal to the core SCN [71], and in mice it is seen in the shell SCN region. [45]. Taken together, these results suggest that VIP and GRP are involved in mediating the photic signals from the direct light-responsive cells to the rest of the SCN.

4 Shifting the LD cycle

An abrupt shift in the LD cycle has profound behavioral and physiological effects as exemplified in jet lag. Jet lag is

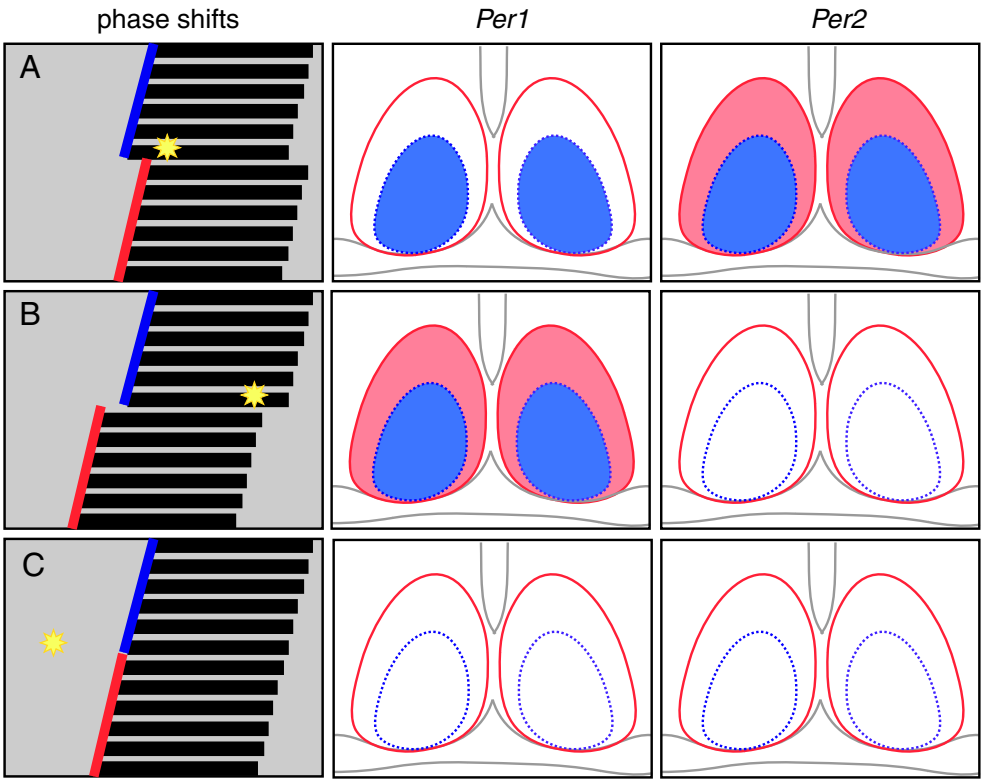

Fig. 2 The photic induction of *Per* genes is phase-dependent. Schematics summarize the results in light-induced *Per1* and *Per2* expression in the SCN of mice and rats. After a phase delaying light pulse (LP) at early night (**A**), light-induced *Per1* expression is restricted in the core SCN while *Per2* expression is in the entire SCN. After a phase advancing LP at late night (**B**), light-induced *Per1* expression is in the entire SCN, and there is no *Per2* induced. After a LP at subjective day (**C**), which does not produce behavioral phase shifts, there is no *Per1* or *Per2* induced in the SCN. In left column, gray shadow indicates darkness, black horizontal bars depict the activity, yellow stars represent LPs, blue and red lines indicate the phase of activity onset before and after the LPs

characterized as a collection of temporary symptoms including fatigue, insomnia, and other physiological, psychological and cognitive disorders commonly seen in trans-meridian travelers. It is well recognized that jet lag is caused by circadian rhythm disruption; specifically, the desynchrony between the internal clock of the body and the local time due to the rapid change of time zone [72, 73]. Jet lag symptoms are also seen in shift workers. However, unlike the travelers who experience jet lag temporarily, shift workers experience long-term dissociation between their internal clock and the environment, which can affect health and well-being [72–74]. Thus, it is of great value to understand the underlying mechanisms mediating the circadian rhythm disruptions that result in health problems. In particular, how the internal clocks respond to shifts of the LD cycle.

Many insights have been obtained regarding to this question by monitoring clock gene expressions in animal models subjected to experimental jet lag, with *desynchrony* being observed at every level of the analysis within the circadian system. Using a rat transgenic line (*Per1-luc*), *Per1* expression was monitored *in vitro* in the SCN and peripheral tissues harvested from animals that had experienced an abrupt shift in their LD cycle [75]. This was the first study demonstrating the reentrainment of peripheral tissues, and the results revealed that the peripheral tissues took much longer to complete a shift than the SCN did, and each tissue readjusted at a different rate. The different reentrainment rates between the SCN and both, peripheral tissues and extra-SCN brain oscillators have been consistently observed in follow up studies [76–78]. Collectively, these studies illustrated a global desynchrony among components of the circadian system, due to the slower adjustment rates of peripheral tissues and the consequent disruption of their normal phase relationship. This temporal disorganization of the circadian system has been proposed as the mechanism underlying the jet lag symptoms, the health issues resulting from shift work [79], and the increased mortality in aged animals when they are exposed to repeated shifts of the LD cycle [80].

More recent observations suggest that the reentrainment of the SCN to a new LD cycle is more complicated, and might be not as fast as initially suggested [75]. In the study by Yamazaki et al using *Per1*-luc rat, it was shown that the SCN adjusted to the new phase rapidly by the first shifted cycle [75]. While the result highlighted the quick response of the SCN, it also raised some questions, such as 1) whether the other clock genes shift in parallel with *Per1*, and 2) whether the individual SCN neurons all shift simultaneously. It is arguable that due to the acute light-responsive nature of the *Per* genes, the quick re-adjustment seen in *Per1* expression may not necessarily reflect the shift of the entire molecular clockwork. Using a similar paradigm, Reddy et al [81] examined the expression of

Per1, *Per2*, along with *Cry1* and *Cry2* in the SCN of mouse following 6 hr phase advance or delay. The expression of both *Per1* and *Per2* shifted to the new phase within the first cycle, consistent with the *in vitro* finding using SCN slice [75]. However, the expression of *Cry1*, which is not acutely up-regulated by light [82], lagged behind following the advances. The results demonstrated a desynchrony between the oscillations of different clock genes that are directly or indirectly light-regulated, which could represent another mechanisms underlying the process of entraining to a new LD cycle as well as one of the causes for jet lag symptoms.

As stated previously, the SCN is a multi-oscillator network consisting of functionally distinct neurons organized into the core and shell sub regions [41, 42]. Further analysis of clock gene expression in the SCN sub regions, revealed another aspect in the responses of the SCN to shifting LD cycle [78, 83, 85]. In mice or rats, the expression of clock genes in the core and shell SCN, which are in phase with each other in LD or constant dark conditions [61, 83, 84], became dissociated between the two regions following shifts in the LD cycle [83, 85]. Using the expression of clock genes *Per1*, *Per2*, *Cry1* mRNA and CRY1 protein as phase markers [83], the results showed that after either a delay or an advance of the LD cycle, the core SCN region first adjusted to the new cycle in 3 or 5 days, respectively, with the shell rejoining the core SCN a few days later. Thus the circadian oscillations of the core and shell regions are temporally desynchronized for days following a shift of the LD cycle. The desynchronized circadian oscillations between the two SCN compartments were also confirmed by an *in vitro* study using brain slice from *Per1*-luc rat [85]. In contrast, in a mouse SCN slice prepared *in vitro*, there were no separable responses attributable to core and shell regions [78]. This may be due to species differences or to difficulties in identifying core and shell region when peptidergic markers are not available. Sub regions of the mouse SCN are not as clear-cut as those of the rat SCN, with the shape and spatial localization varying along the rostral-caudal axis of the nucleus [60, 86]. However, even in mice, following a 6 hr advance in LD cycle, the results did reveal a gradient in the phase-shifting rates of cells along the ventral-dorsal axis, such that cells in the ventral portion of the SCN shifted faster than those in the dorsal region [78]. And the normal phase relationship among the SCN cells was not restored until 14 days after the shift.

Both the core and shell regions send efferent projections to the SCN target regions in the brain [87]. Thus the temporary desynchronization between the two regions may result in conflict output signals from each compartment, which would lead to disregulation in the extra-SCN brain clocks and peripheral tissues, thus disrupting the overt rhythms in behavior and physiology.

5 Effect of photoperiods

In addition to the day-night changes, species from temperate zones also experience seasonal variation in their environments. Accurate prediction of seasonal changes in the environment is crucial for the survival and reproduction of many species [88]. In nature, seasonal changes include food availability, temperature, weather, predator activity, and most importantly, the progressive changes in day-length (photoperiod).

The circadian clock in the SCN plays a critical role in seasonal processes by sensing ambient photoperiod or day-length [89–91]. Several hypotheses have been put forth to account for day-length measurement by the SCN, ranging from mathematical models of external and internal coincidence, molecular morning and evening oscillator models to physiological models of multi-oscillator networks [92–95]. There is a substantial body of literature exploring the impact of day-length on SCN function using c-FOS immunostaining or electrical recording [89, 90, 95, 96], but given the scope of the current review, only studies examining clock gene expression will be discussed.

Expression of clock genes in the SCN depends on photoperiod as seen in the waveform changes, such that the durations of the elevated expressions in *Per* genes and their protein products are expanded in long photoperiods, but compressed in short photoperiods [90]. This is consistent in all species examined, regardless of whether the animals are reproductively photoperiodic [91, 97–100] or not [101–103]. The results on other clock genes, including *Cry1*, *Cry2*, *Bmal1* and *clock* are less consistent, which could either reflect species difference (rat, Syrian hamster, Siberian hamster) or differences in photoperiodic history or condition [91, 99, 103].

Marked regional differences in clock gene expression have been observed along the rostral-caudal axis of *the* SCN, both *in vivo* [91, 100, 104] and *in vitro* [105–107]. In short photoperiod, the rostral and caudal remain in similar phases; while in long photoperiod, the clock gene expression in the caudal phase leads that in the rostral SCN [91, 104–106]. *In vitro* recording of SCN slice from *Per1*-luc mice revealed that the caudal portion was phase-locked to the activity offset, whereas the rostral SCN was phase-locked to the activity onset [104]. However, such correlation between the SCN sub region and activity component was not seen in another *in vitro* study using *Per2*-luc animals [107]. Analyzing the PER1 expression *ex vivo*, at five spatial levels from the rostral to the caudal end of hamster SCN, revealed an orderly phase distribution of the SCN oscillators along the rostral-caudal axis corresponding to day-length [100]. Meanwhile, the core SCN showed low amplitude expression in phase with that in the shell under both long- and short-photoperiods [100]. The results

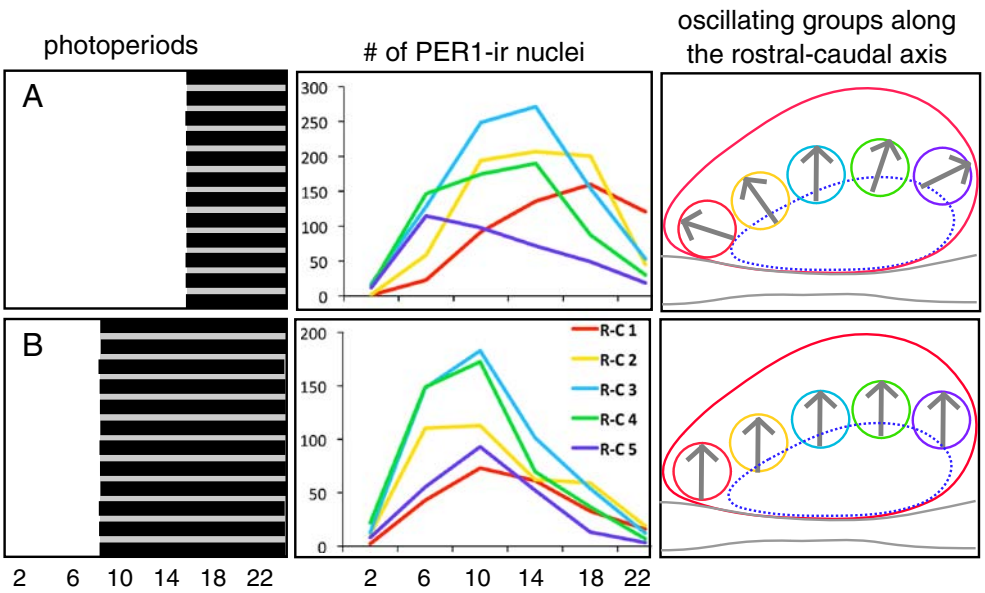

Fig. 3 Spatiotemporal organization of the SCN oscillators under long (A) or short (B) photoperiods. In long photoperiods (**A**), cellular oscillators in the SCN are in different phase organized sequentially along the rostral-caudal (R-C) axis, with the cells in the caudal portion phase lead those in the rostral portion of the SCN. In short photoperiods (**B**), SCN oscillators along the R-C axis remain in similar phase with each other. Line graphs in mid column are re-plotted with data from [100]

demonstrated a gradient in the phase of SCN cell oscillators from the rostral to caudal end of the nucleus, and indicated that day-length determined not only the waveform of the SCN as a whole, but also the phase distribution of individual oscillator cells within the SCN (Fig. 3).

6 Constant light

In many species, constant light (LL) exposure disrupts overt circadian rhythms and induces arrhythmicity [108]. Exposure to LL for 1 day alters the rhythm of c-FOS and PER1, with greater effects in the core than in the shell of rat SCN [109]. After 7 days in LL, *Per2* expression was dampened and PER2 protein rhythm attenuated in mouse SCN [110]. After 50 days in LL, PER2 protein levels were constantly elevated throughout the cycle [111]. Monitoring *Per1* expression within individual SCN neurons *in vitro* has revealed that the attenuation and disruption of the overt rhythm of the SCN is due to desynchrony among individual cell oscillators [112].

LL can also cause "splitting" of circadian rhythms, such that a single daily bout of activity separates into two components, 12 h apart [113]. The anatomical loci responsible for the two activity bouts have been mapped to the bilateral SCN, with the left and right side of the nucleus showing anti-phase circadian oscillations in clock gene expression [112, 114]. In the behaviorally split hamsters housed in LL, in addition to the anti phase oscillation of the bilateral SCN, the core and the shell regions within each side of the SCN also cycle in anti phase [115]. However, in hamsters housed in constant darkness, the neurons in the core SCN do not show rhythms in clock gene expression when measured as a group, likely caused by their phase dispersion [27, 115]. Thus, the long-term constant light exposure appears to be able to synchronize the neurons in the core and reorganize them into anti phase with those in the shell SCN (Fig. 4). It is likely that the changes in the phase relationship between the core and shell region may facilitate the effect of LL, setting off the bilateral SCN lock into anti phase.

Fig. 4 Reorganization of the SCN oscillators in the SCN of behaviorally split hamsters. Constant light induces behavioral "splitting" in hamsters (*left column*). In the SCN of split hamsters, the bilateral SCN became desynchronized with the left and right SCN oscillate in anti phase. Within each side of the SCN, the core and shell region also oscillates in anti phase. Image in mid column is taken, with permission, from [115]. AVP (*red*) and CalB (*blue*) were used as regional markers for the shell and core SCN, respectively

7 Other artificial lighting conditions

The expressions of clock genes have been also examined under other unnatural lighting conditions. One of the most interesting paradigms is the 11:11 LD cycle [116]. In rats exposed to this paradigm, two activity components emerged simultaneously, with one entrained to the 11:11 LD and the other free-runing with the endogenous period typical of the animals. The expression of clock genes *Per1* and *Bmal1* in the SCN of these animals revealed dissociated circadian oscillations in the core and shell regions. Interestingly, the circadian oscillation in the core region corresponded to the entrained activity component, while that in the shell region corresponded to the free-running component. This is a very unique paradigm, which introduces a stable separation between the two compartments of the SCN that can be correlated to behavioral and physiological activities. Using this forced desychronization protocol, it has been shown that the circadian oscillation in the core and shell SCN are correlated with the different stages of sleep [117, 118].

The behavioral bifurcating induced by 24 hr LDLD cycle, is another attractive model in which to examine the corresponding behavioral and physiological functions of the SCN. Under this well-characterized paradigm, hamsters can be induced to bifurcate their circadian activity such that robust wheel-running is expressed in each of the two daily dark phases with a complete inactive phase in between [119, 120]. Although less well characterized than in hamsters, mice also exhibit a comparable, if much less stable, bifurcated activity pattern [119, 121], which is associated with sustained bimodal *Per1* expression within each side of the SCN [121]. In these behaviorally bifurcated animals in LDLD, anti phased oscillation of clock genes expression between the core and shell compartments were also observed in both mice [121] and hamsters (Yan, Silver and Gorman, unpublished result).

8 Overview and conclusions

The regulation of circadian system ensures that our bodily function each occupies an appropriate internal temporal niche, and that the internal processes are synchronized to the local environment. This article reviewed how environmental lighting conditions affect the spatiotemporal organization of the oscillator cells in the SCN, as exemplified by the expression of clock genes. The spatiotemporal reorganization of the oscillator cells, while highlights the functional heterogeneity of the SCN, also reveals substantial flexible and plastic responses of the SCN networks under various environmental lighting conditions. When inappropriately phased, light can disrupt the normal SCN network organization and compromise the coherent and stable phase relationships among circadian oscillators, thus disturbing overt rhythms in a variety of important functions. Problems associated with circadian disruption are well documented in phenomena such as jet lag, shift workers and various sleep disorders, raising wide spread concerns about the long-term health impact derived from these conditions [79]. The insights into the responses of SCN network elements to environmental cues is key to the understanding of the human health problems that stem from circadian rhythm disruption, and for developing effective preventive and therapeutic interventions.

Acknowledgements I would like to thank Drs. Tony Nunez, Michael Antle, Rae Silver and Laura Smale for critical reading and very helpful comments on the manuscript. I am also grateful for the general support of the Psychology Department Startup Fund and the IRGP Award from MSU.

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