

Minireview

Processing of daily and seasonal light information in the mammalian circadian clock

Johanna H. Meijer ^{*}, Stephan Michel, Mariska J. Vansteensel

Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Center, Postal Zone S5-P,
P.O. Box 9600, 2300 RC Leiden, The Netherlands

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Abstract

It is necessary for an organism's survival that many physiological functions and behaviours demonstrate daily and seasonal variations. A crucial component for the temporal control in mammals is the circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Neurons in the SCN generate a rhythm in electrical activity with a period of about 24 h. The SCN receives photic information from photoreceptive ganglion cells in the retina and processes the information, detecting dawn and dusk as well as encoding day-length. Information processing by the SCN is optimized to extract relevant irradiance information and reduce interferences. Neuronal coupling pathways, including GABAergic signalling, are employed to distribute information and synchronize SCN subregions to form a uniform timing signal. Encoding of day-length is manifested in SCN neuronal activity patterns and may be the product of network interactions rather than being based on the single cell.

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The rotation of the earth around its axis causes 24-h changes in environmental conditions, such as temperature, food availability, and light and darkness. In addition, seasonal changes in day-length occur as a consequence of the earth orbiting the sun. In order to cope with and anticipate these changes, most organisms throughout the plant and animal kingdom possess a circadian timing system. In mammals, the main circadian pacemaker is present in the suprachiasmatic nucleus (SCN) (Ralph et al., 1990). This bilateral brain structure is located at the base of the hypothalamus, just above the optic chiasm. It is responsible for 24-h rhythmicity in behaviour and physiology and is also thought to be involved in the adaptation to changing day-length (Ralph et al., 1990; Schwartz et al., 2001). Neurons of the SCN have a genetic basis for rhythm generation. Genes involved in rhythm generation, *clock*, *bmal*,

cryptochrome (*cry*), and *period* (*per*), form intertwined negative feedback loops, which results in a rhythm in expression of about, but not exactly, 24 h (Gachon et al., 2004). Period differences exist between organisms and also between individuals, but for each individual, the endogenous period shows remarkable precision with a variability of only several minutes from day to day.

Entrainment of the endogenously generated rhythm to the 24-h cycle of the environment, as well as adaptation to changing photoperiod, relies on photic information that is carried from the retina, through the optic nerves, to the SCN via fine, unmyelinated fibres. Photic entrainment in mammals is thought to involve at least two clock genes, *mper1* and *mper2* (Zylka et al., 1998). A light-induced rise in *mper1* expression seems to involve phosphorylation of cyclic adenosine monophosphate response element binding protein (CRE) and histone acetylation (Tischkau et al., 2003; Naruse et al., 2004). The activation of *mper1* by light occurs very rapidly (within 10 min) and spreads from the retinorecipient area throughout the SCN within 1–2 h.

^{*} Corresponding author. Fax: +31 71 526 8270.
E-mail address: j.h.meijer@lumc.nl (J.H. Meijer).

Using a fluorescent and bioluminescent reporter system, correlation of a change in membrane properties with an increase in *mper1* expression could be demonstrated on a single cell level (Quintero et al., 2003).

In this minireview, we summarize the current understanding of the effects of light on the mammalian circadian system and illustrate some of the techniques that are used in studies on this topic. We review important findings on retinal circadian photoreception and the direct responses of SCN neurons to retinal illumination, and we describe recent insights in the mechanisms of entrainment as well as photoperiodic encoding.

1. Electrical activity recordings

In the central nervous system, cells communicate by electrical and humoral signalling. Therefore, the protein products of clock genes become functional for central nervous signalling if they lead to changes in membrane potential and thereby to changes in electrical activity and release of neurotransmitters and hormones. Recordings of electrical activity from SCN neurons can be performed using extracellular recording electrodes, for instance low impedance metal electrodes. Such extracellular recordings can be performed in brain slices for extended periods of time. The electrical signals of several microvolts are amplified and counted when above a certain threshold (signal to noise level 3:1). Fig. 1 shows an example of a near 24-h SCN neuronal activity rhythm measured in a slice. In vivo, the electrical activity of SCN neurons can be measured by similar recording techniques. For in vivo recordings, electrodes are implanted in the brain, with the electrode tip aimed at the SCN nuclei. A counter balanced system and swivel allow minimal interference with the animals freedom

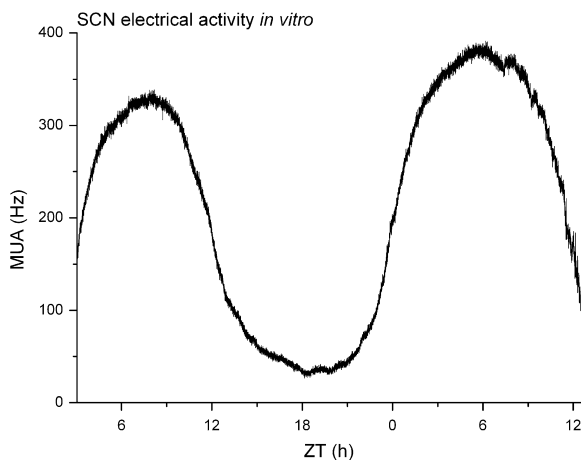


Fig. 1. SCN electrical activity in vitro. The multiunit electrical activity of rat SCN neurons was recorded from a hypothalamic slice preparation and is plotted in 10 s bins. Zeitgeber Time (ZT), based on the light–dark cycle to which the animal was exposed, is given on the *x*-axis. ZT 12 indicates the time of lights off and ZT 0 is the time of lights on. On the *y*-axis, multiunit activity in Hertz is indicated. Note the ~24 h rhythm in the SCN electrical activity, with high levels during the prior light period.

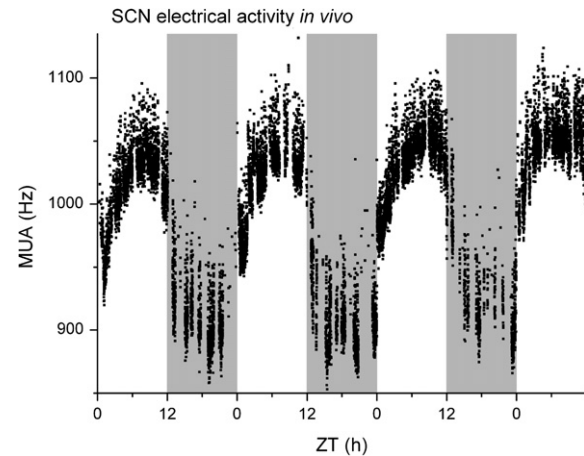


Fig. 2. SCN electrical activity in vivo. Multiunit electrical activity of rat SCN neurons was measured for several days in a freely moving animal using implanted recording electrodes. Multiunit activity is plotted in 10 s bins. Bins that contain movement artefacts were deleted resulting in gaps in the dataset. Zeitgeber Time (ZT) is indicated on the *x*-axis and multiunit activity in Hertz is indicated on the *y*-axis. During recording, the animal was exposed to a 12:12 light–dark cycle. Periods of darkness are indicated in gray. Note that the multiunit electrical activity in the SCN is high during the light period and low during the dark period.

of movement, and in this preparation, the electrical activity can be followed for many days or weeks, without loss of amplitude in the circadian pattern (Fig. 2). While in vitro recordings have the advantage to study the mechanism of the SCN in more detail, in vivo measurements allow study of the response of SCN neurons to photic information, which is the major stimulus that resets the clock and synchronizes it to the environmental light–dark cycle (Takahashi et al., 2001).

2. Entrainment and resetting

The synchronization or entrainment of the circadian rhythm with the environmental cycle under natural light–dark conditions is usually achieved with daily adjustments of the phase and period of the circadian oscillator (Daan, 2000). The effect of light on the circadian rhythm in locomotor activity has been intensively studied in a great number of species (e.g. Daan and Pittendrigh, 1976; Honma et al., 1985). Short light pulses of a few minutes can lead to adjustments in the phase of the circadian rhythm when given during the night. The generation of phase shifts is dependent on the time when the light pulses are given within the circadian cycle. While there is no phase response to light pulses during the day, phase delays of the rhythm occur after light exposure during early night and phase advances can be seen as a result of light pulses during the late night (Pittendrigh, 1988). In addition to this so-called non-parametric entrainment, observations under natural lighting conditions (with dawn/dusk transitions) also suggest a parametric effect of light on the period of the circadian rhythm, i.e. light could accelerate or decelerate the

oscillation at different circadian times (Daan, 2000; Boulos et al., 2002).

A special kind of resetting behaviour is observed after abrupt changes in the phase of the light–dark cycle, which helps to dissect components of the mechanism involved in re-entrainment. Experiments using large, 6-h advances of the light–dark cycle lasting 1 day with subsequent constant darkness, revealed a dissociation of the clock gene *per1* expression rhythm and the electrical activity rhythm of the SCN in vitro (Vansteensel et al., 2003). SCN neuronal activity recordings in freely moving animals under the same conditions further showed a repressive influence of extra-SCN brain areas on resetting processes within the SCN. In rats, bimodal neuronal activity patterns were recorded after 6-h delays of the photoperiod in both ventral and dorsal parts of the SCN (Albus et al., 2005; Fig. 3). Separation of ventral and dorsal parts of the SCN slice by a knife cut disclosed the source of the bimodality with the dorsal SCN rhythm lagging behind the one of the ventral part. These data suggest that the inhibitory influence of extra-SCN areas is mainly affecting the dorsal part of the SCN. Interestingly, application of the GABA_A receptor blocker bicuculline separates the two peaks as effectively as the knife cut suggesting GABA as a putative coupling agent between ventral and dorsal parts of the SCN. Pulsative applications of bicuculline at different circadian times revealed an excitatory effect of GABA in the dorsal part and a mainly inhibitory influence of GABA in the ventral part (Albus et al., 2005). Although an excitatory action of GABA has been previously described in the SCN, this is the first characterization of a possible functional role for interregional coupling within the SCN. The GABAergic pathway would

ensure distribution of the phase information from the ventral part of the SCN and therefore synchronization between dorsal and ventral parts of the SCN. Other coupling mechanisms employing gap-junctions or vasointestinal protein signalling seem to be more important for short distance communication and synchronization between SCN neurons within a subregion (Colwell et al., 2003; Long et al., 2005; Aton and Herzog, 2005; Maywood et al., 2006).

3. Light responsiveness of the circadian clock

In mammals, the light information used for synchronization of the circadian rhythm with the environment (entrainment) reaches the SCN pacemaker exclusively via the eyes as was shown by enucleation studies (Nelson and Zucker, 1981; Meijer et al., 1999; Yamazaki et al., 1999). Interestingly, the circadian light information processed in the retina is not only perceived by the “visual” photopigment rhodopsin, but employs melanopsin, another opsin/vitamin A-based photopigment with maximum sensitivity at 480 nm (Provencio et al., 2000, see for review Peirson and Foster, 2006). Melanopsin has features distinct from rhodopsin and somewhat resembles invertebrate photopigments in that it triggers a depolarization of the cell membrane and may even function as a photoisomerase. Besides its role as a circadian photoreceptor it also seems to be used as an irradiance detector for a number of behavioural and physiological responses to light, like modulation of locomotor activity (masking, Mrosovsky et al., 2001) and pupillary constriction (Lucas et al., 2001). Surprisingly, melanopsin is not expressed in cells of the outer retina where rods and cones are located, but was found in a small number of photoreceptive retinal ganglion cells (Berson et al., 2002). These cells also express pituitary adenylate cyclase activating peptide (PACAP), which is co-released with the neurotransmitter glutamate and modulates the synaptic transmission at the target area in the SCN (Hannibal, 2006; Michel et al., 2006). The relative contribution of rods, cones and melanopsin to circadian photoreception is not yet fully understood. Rodless/coneless mice show unattenuated light-induced phase shifts (Freedman et al., 1999) and melanopsin deficient mice entrain to a light–dark cycle, although they do have attenuated phase resetting responses to short light pulses (Panda et al., 2002). Recent evidence suggests that all photopigments, i.e. rods, cones and melanopsin, are required for proper nonvisual photic responses such as entrainment, masking and pupillary light reflex (Hattar et al., 2003; Panda et al., 2003), and that a modulating influence of visual on non-visual photoreceptors possibly shapes the output of the circadian photoreceptor (Doyle et al., 2006).

From the retina, information on the photic environment is carried to the SCN pacemaker via the retinohypothalamic tract (RHT). In rat, hamster and mouse, the RHT projects mainly to the ventral parts of the SCN, but especially in the hamster and the mouse, retinorecipient

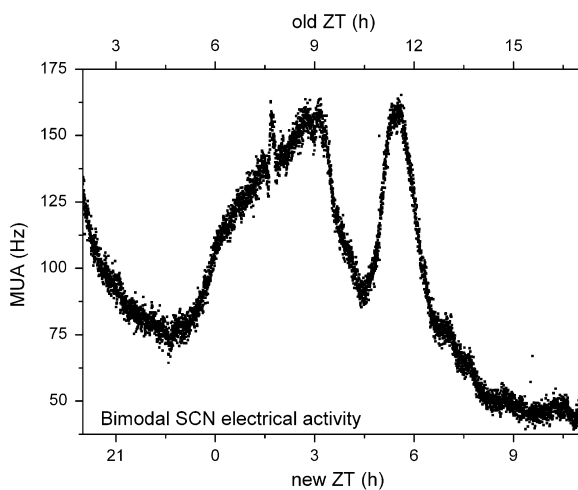


Fig. 3. Bimodal SCN electrical activity. Multiunit electrical activity of the rat SCN was recorded in a slice preparation after the animal was exposed to a 6-h phase delay of the light–dark cycle. On the upper x-axis, ZT of the old, unshifted light–dark cycle is indicated and on the lower x-axis, ZT of the new, 6-h phase delayed, light–dark regime is indicated. On the y-axis, the multiunit activity is indicated in Hertz. The SCN neuronal activity shows a bimodal pattern with one peak that is only slightly shifted and one peak that is almost completely phase delayed and peaks near the new ZT 6.

neurons can also be found in the more dorsal parts (Moore and Lenn, 1972; Card and Moore, 1984; Abrahamson and Moore, 2001). Retinorecipient neurons show sustained responses to retinal illumination, with a short phasic component at the onset of light (Meijer et al., 1998; Fig. 4). The response characteristics contrast with those observed in visual brain areas involved in pattern recognition, but correspond with the sustained responses observed in melanopsin containing ganglion cells (Berson et al., 2002). Besides their sustained response to light, SCN cells code for light intensity (Meijer et al., 1986, 1998). The discharge level is a function of the illumination level. The intensity–response curve is sigmoid, and shows a threshold at around 0.1 lux. This threshold is high as compared to the threshold for vision. Above 0.1 lux, SCN cells code almost linearly for increments in light intensity, and, in rodents, they show saturation at 10–1000 lux, depending on the species. SCN neurons cannot, therefore, discriminate between a cloudy and sunny day (10^5 lux), and also not between a dark and a bright night. Instead, the cells are equipped to differentiate only between day and night. The large range of illumination levels in the environment is translated into an electrical activity signal, indicating light intensities occurring around dawn and dusk. The intensity–response function is not fixed, but changes in the course of the circadian cycle. Recordings at a fixed position within the SCN have shown that the sensitivity to light is highest during the night and lowest during the day. In other words, the sensitivity is optimal when the SCN responds to light information with a phase shift, in order to entrain to the environmental cycle. While responses to low light intensity levels are absent during the day, they become present with higher light intensities. Yet, these light intensities do not cause a shift of the circadian pacemaker. Thus, the ability of the SCN to shift is not determined by the retinal input pathways, but by the phase of the molecular clock at which light is perceived.

4. Photoperiodicity

Many animal species show seasonal rhythms in physiology and behaviour. When rodents are kept on short photoperiods, as in winter, or on long photoperiods, as in summer, their behavioural activity pattern expands or compresses without affecting their total amount of activity (Pittendrigh and Daan, 1976; Refinetti, 2004). The SCN pacemaker is essential to store photoperiodic information. Photic information is perceived by SCN cells, which respond with a sustained increase in discharge rate. After exposure to long or short days for 5 weeks or more, day-length information becomes stably encoded in the SCN and release of animals to constant darkness shows altered behavioural activity patterns for several weeks or more. Multiunit electrical activity recordings in a slice preparation of the SCN show that the photoperiodic information is retained *in vitro* (Schaap et al., 2003). Slices taken from long day animals show broad electrical activity profiles, while slices from short day animals show narrow electrical activity profiles. Similar results are obtained for *per1* expression and cFos immunoreactivity, with broad patterns in long days and narrow patterns in short days (see for review, Sumová et al., 2004).

Several studies have examined the underlying mechanism for the stable encoding of photoperiod information in the SCN. In normal light–dark cycles (LD 12:12) single SCN cells show short electrical activity periods, that do not match the light–dark cycle (Schaap et al., 2003; Brown et al., 2006). Moreover, the oscillations in electrical activity are not completely synchronized in phase, but show clear phase differences (Schaap et al., 2003; Brown et al., 2006). At the molecular level it has been shown that single SCN neurons show phase differences in *per1* expression (Quintero et al., 2003; Yamaguchi et al., 2003). These phase differences may change under long and short photoperiods, with closer phase relations in short days, and wider phase

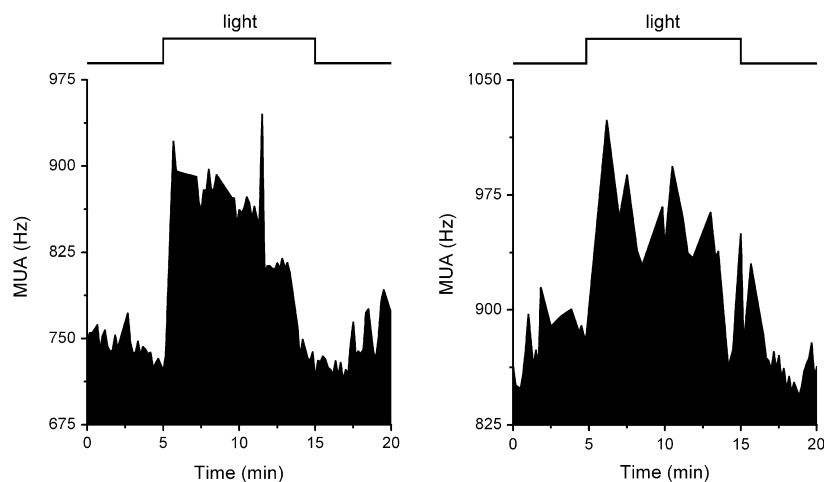


Fig. 4. Light responses of SCN neurons. A 10-min light pulse of ~ 100 lux induces an increase in the multiunit electrical discharge rate of SCN neurons, measured *in vivo* in freely moving rats. The time of the light pulse is indicated by the line on top of the graphs. On the *x*-axis, time is given in minutes and the multiunit activity in Hertz is indicated on the *y*-axis.

relations in long days (Schaap et al., 2003). Changes in phase relation would lead to differences in the broadness of the multiunit activity peaks that are consistent with recorded changes in peak width in rats kept under long and short photoperiods (Schaap et al., 2003; Rohling et al., 2006). While these simulation studies did not require spatial partitioning, Hazlerigg and co-workers (2005) observed that the expression of clock-related genes *per2*, *rev-erba* and *dbp* is differentially regulated in the rostral and caudal SCN. They proposed that the difference between the expression peaks in these parts of the SCN carries seasonal information. These data support the idea that photoperiodic encoding may be a consequence of the structural heterogeneity of the SCN.

In summary, the mammalian circadian system relies heavily on photic information for the adaptation of the endogenously generated rhythms to the 24-h cycle of the environment, as well as to the changing day-lengths in the course of the year. The processing of light information by the circadian system of mammals has evolved on many levels of organization, such as receptors, pathways, processing neurons and genes. The actual light-induced adjustments of the pacemaker and its output require interactions between neuronal populations within the SCN and between the SCN and its periphery. Together, these mechanisms render a highly effective machinery to detect and anticipate information of daily and seasonal changes in the environment.

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