Effects of Illumination on Suprachiasmatic Nucleus Electrical Discharge[a]

GERARD A. GROOS[b,f] AND JOHANNA H. MEIJER[c,d,e]

[b]*Department of Zoology*
University of Groningen
Haren, The Netherlands

[c]*Department of Physiology and Physiological Physics*
University of Leiden
Leiden, The Netherlands

[d]*Department of Psychology*
Dalhousie University
Halifax, Canada

Among the many biological rhythms found in higher vertebrates, those with an annual or a daily period are most prominent. The daily rhythms closely parallel the rotation of the earth around its axis, whereas yearly rhythms follow the revolution around the sun. Both classes of rhythms have developed as an adaptation to the considerable environmental changes that result from the earth's revolution (annual rhythms) and its rotation (circadian rhythms). Vertebrate circadian rhythms are controlled by pacemaker structures in the neuroendocrine system. These pacemakers produce intrinsic circadian oscillations. To adapt to the 24-hour period of the earth's rotation, the pacemakers synchronize to the daily light-dark cycle.[1] Through this process of photic entrainment, the pacemakers maintain a steady phase relation with the solar day. By contrast, many annual rhythms are not self-sustaining. They depend on photoperiodic time measurement, that is, the animal responds to the passing seasons by monitoring the annual changes in the length of the day. In order to time the photoperiod, animals may use a circadian pacemaker. In this case the circadian pacemaker is an integral component of the photoperiodic time measurement system.[1,2] It is a basic tenet that this system is not only capable of monitoring the environmental light-dark cycle for pacemaker entrainment, but also that it receives information about the photoperiod. In this paper we will discuss the major advances in the study of the neural mechanisms of illumination processing by the suprachiasmatic nuclei, a major circadian pacemaker in mammals and a critical component of the mechanism for photoperiodic time measurement.[2]

THE VISUAL AFFERENTS OF THE SUPRACHIASMATIC NUCLEI

In mammals one important circadian pacemaker has been localized in the suprachiasmatic nuclei (SCN) of the hypothalamus.[3-8] These nuclei generate an

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[e]Address for correspondence: Drs. J. H. Meijer, Dept. of Zoology, University of Groningen, P.O. Box 14, 9750 AA Haren, The Netherlands.

[f]Dr. Groos is deceased, March 25, 1985.

intrinsic circadian rhythm that, in a periodic photic environment, is entrained by the light-dark cycle. The SCN rhythm controls the circadian modulation of various biological functions. In rodents, moreover, it has been demonstrated that the SCN pacemaker is essential for photoperiodic time measurement.[2,4] Thus, the SCN control the circadian pattern of pineal melatonin synthesis by way of their efferent neural connections with the sympathetic nervous system.[9] The temporal profile of this pineal hormone, in turn, provides the reproductive system with a humoral signal representing the photoperiod in the environment. The suppression of the high nocturnal melatonin synthesis rate by light is a part of this process that is also mediated by the SCN.[2,4,9] In summary, the SCN exhibit three closely related visual functions: monitoring the daily light-dark cycle for photic entrainment of their pacemaker rhythm, monitoring the actual photoperiod to mediate photoperiodic time measurement, and transmitting photic information to the pineal gland to suppress its elevated nocturnal melatonin level.

Comparative studies have indicated that the vertebrate circadian system can receive photic information through retinal, (para-)pineal and encephalic photoreceptors.[4,10,11] In mammals, however, pineal and encephalic photoreceptive systems are absent.[10] Instead, phototransduction of the day-night cycle occurs exclusively in the retina. The failure of entrainment, the gonadal regression as well as the absence of testicular responses to long day lengths after blinding in rodents attest to the crucial role of the retina in mediating these functions.

From the retina, two neural projections reach the SCN.[12,13] One is a direct, bilateral pathway that leaves the optic chiasm dorsally to terminate along the ventrolateral aspect of the SCN.[14-16] This pathway is known as the retinohypothalamic projection (RHP). The second visual input involves a retinofugal projection to the ventral lateral geniculate nucleus (vLGN).[17,18] A subpopulation of neuropeptide Y (NPY) containing vLGN perikarya in turn sends axons to the SCN.[19-21] This indirect pathway will be referred to as the retino-geniculo-suprachiasmatic projection (RGSP). The terminal field of these peptidergic fibers in the SCN largely overlaps with that of the RHP.[21] Thus, the visual SCN afferents project to the same division of these nuclei.

CHARACTERISTICS OF VISUAL SCN CELLS

The existence of visual cells in the SCN has been amply demonstrated in electrophysiological experiments.[3,22-28] Both single cell and multiple unit recordings show responsiveness of the SCN following retinal illumination[13,22,26,28] as well as after electrical stimulation of the optic nerve.[22,25] The localization of visual SCN cells corresponds fairly well with the known distribution of RHP and RGSP terminals. Visual SCN cells in the hamster, for instance, are predominantly recorded in the lateral and ventral aspects of the nuclei with some cells embedded in the optic chiasm.[26] In each of these regions, retinal or geniculate terminals have been observed in the hamster.[14,21] In the rat, visual cells are mostly found in the caudal SCN.[24] This is consistent with the neuroanatomical evidence for a predominant termination of the RHP in the ventral and caudal part of the SCN in this species.[29] Almost one-third of all spontaneously active SCN cells in the rat and the hamster respond to a sustained increase in retinal illumination.[23,24,26] By contrast, presentation of very brief light flashes (<1 sec.) evokes a response in less than one-tenth of the SCN neurons.[25] This difference in effectiveness of short versus long stimulus durations reflects an outstanding property of visual SCN cells. Sustained illumination is a more adequate stimulus for these cells than light pulses of short duration. This feature is illustrated by a further

characteristic of visual SCN neurons. In all three species studied they respond to whole retinal illumination with a sustained increase or decrease of their discharge rate.[22-24,26] Accordingly they are classified as activated and suppressed cells; activated cells tonically increase, whereas suppressed cells tonically lower their electrical discharge frequency in response to an increment in light intensity (FIGURES 1A–C and 2A,B).[13]

The activated cells are more common than suppressed cells. In the rodent SCN, approximately three times as many activated as suppressed cells are encountered.[23-26] The cell types are not related to separate anatomical regions within the SCN. In fact, they can even be found adjacent to one another (FIGURE 3B). Whether activated or suppressed, visual SCN cells show differences in the details of their response pattern. The latency of response and the mean dark discharge against which the response is expressed vary considerably. Also, tonic responses are sometimes preceded by a brief phasic transient.[24] Once the steady state discharge rate is reached, however, it is maintained at that level for the full duration of retinal illumination.[24] If the steady state discharge for various illumination levels is standardized with respect to the dark discharge, an intensity-response function is obtained (FIGURES 1D and 2C). The intensity-response functions for rat and hamster SCN cells are typically monotonic and exhibit a threshold below which no responses can be detected. At higher

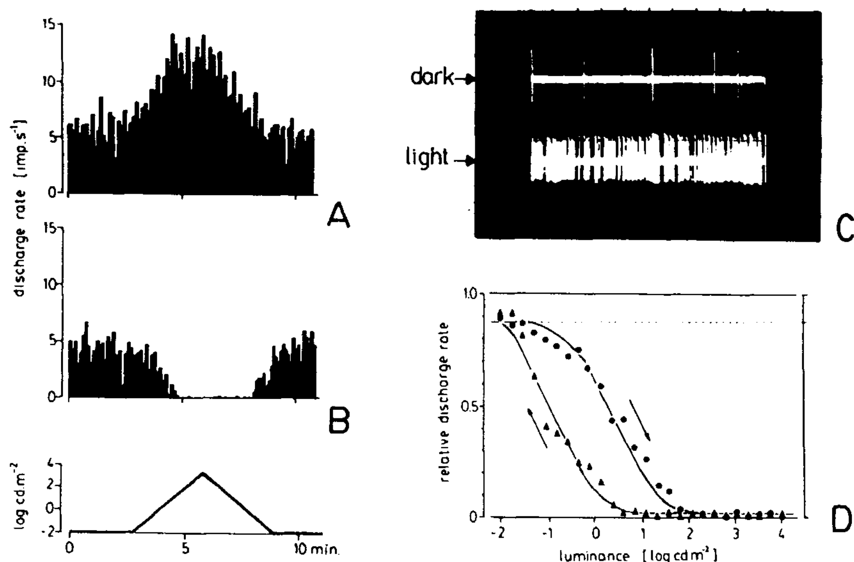

FIGURE 1. Examples of three visually responsive neurons in the rat SCN. Action potentials were recorded extracellularly in the urethane-anesthetized rat. The maintained firing rate is dependent on the level of retinal illumination (*e.g.* the activated cell in C). The responsiveness of two other SCN cells is illustrated in A (activated cell) and B (suppressed cell). Both cells alter their discharge as a smooth function of the exponentially increasing and decreasing ambient luminance, which is indicated underneath the two records in A and B. The normalized discharge rate of the suppressed cell in B is plotted as a function of ambient luminance (D). This neuron exhibits a monotonic intensity-response curve with a threshold around 0.01 cd/m^{-2} and a working range between 0.01 and 100 cd/m^{-2}. The intensity-response function for increasing luminance (filled circles) is similar in curvature but translated towards the right by approximately 1 log unit compared to that for decreasing luminance (filled triangles), illustrating hysteresis.

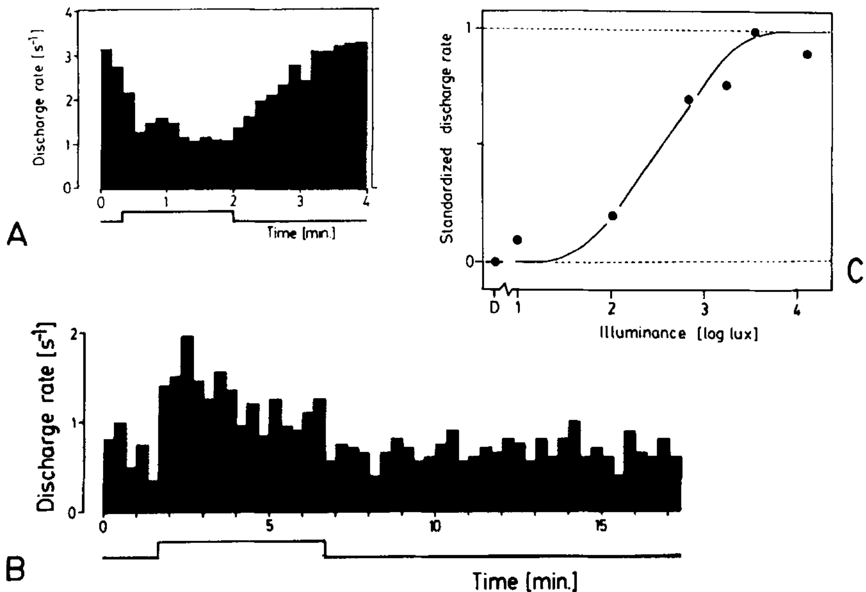

FIGURE 2. Typical examples of light-suppressed (A) and light-activated (B) cells recorded in the SCN of urethane-anesthetized hamsters. The intensity-response relation is plotted for a third activated SCN neuron. For this curve the steady-state discharge rate at different light intensities was standardized by first correcting for the mean dark discharge rate and then normalizing the adjusted firing rates.

intensities, the curves saturate, that is, the discharge rate shows no further change with increasing illumination. In some cells the firing rate at a given light intensity is dependent on the previous adaptation level. In these cases, while gradually increasing the illumination level, different discharge rates are observed at a particular light intensity from those during decreasing illumination (FIGURE 1D). Thus, hysteresis may occur in the intensity-response function. The threshold sensitivity for light varies between as well as within cells. For a given cell the threshold for a light response is often related to the dark discharge rate prior to photic stimulation.[24] Saturation intensities may be similarly variable. If, in addition to the variable intensity-response behavior, the variability of responses as a function of time is considered, the question arises as to what extent these sources of variation may restrict the reliable processing of visual information by the SCN. The average visual response of a large number of SCN cells, however, reveals that together they are capable of acurately representing the level and temporal pattern of illumination.[26] Whether this type of response integration over individual neurons is actually employed by the SCN visual system is presently unknown.

THE FUNCTIONAL IMPORTANCE OF SCN VISUAL PROPERTIES

Electrical recordings in rats, hamsters, and cats have demonstrated that the SCN contain two subpopulations of visually responsive neurons, the activated and the

suppressed cells. Except for the sign of their response, both cell types exhibit similar features. At a low threshold, responses are absent, whereas at high illumination levels the responses saturate. Between these rather ill-defined values each cell has its operational or working range. In functional terms the visual SCN cells are best characterized as luminance units. Within their working range they respond to light by increasing (activation) or decreasing (suppression) their mean discharge rate to a level

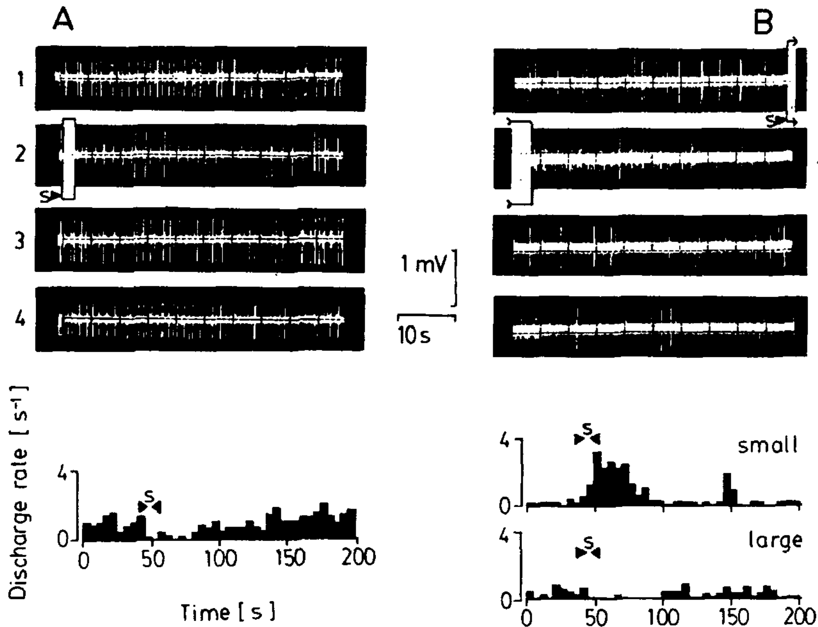

FIGURE 3. Suppression and activation following electrical stimulation of the RHP in an *in vitro* explant of the rat SCN. The explant is continuously perfused with a salt solution[6] containing 1 m*M* calcium. In *A* (subsequent traces 1–4), a continuous oscilloscope record is shown of the activity of two simultaneously recorded SCN cells in one preparation. In response to electrical stimulation of the optic chiasm the cell with the larger action potential is suppressed for approximately 40–80 seconds. The stimulus-artifacts are marked by an *s* (stimulation parameters: 0.1 ms duration, 700 μA pulses at 15 s^{-1}, ipsilateral medial portion of the chiasm). The regularly firing cell with the smaller action potential in A is unaffected by stimulation. The record of the discharge rate of the responsive neuron is shown underneath the oscillograms. In B (1–4), the behavior of two SCN cells in another *in vitro* preparation is illustrated. The cell with the large spike is suppressed, whereas the cell with the small action potential is activated by ipsilateral stimulation of the chiasm (800 μA pulses, parameters otherwise as in A). The activation (small cell) and suppression (large cell) are illustrated separately below the oscillograms.

that, on the average, is in one-to-one correspondence to the external luminance. In other words, a visual SCN cell has a monotonic intensity-response function. Once in the steady state, the luminance-dependent firing rate appears to be maintained for as long as the light is on.[24,26,28] Thus, at any time during sustained illumination, the overall activity level of a visual SCN cell will directly reflect the luminance. Therefore, we refer to such behavior as luminance coding.

This simple notion of luminance coding is not strictly applicable if the behavior of some SCN cells in response to gradual changes in retinal illumination is considered. In contrast to step responses, the intensity-response function for continuous variation in luminance for these cells often shows hysteresis.[26] This indicates that the luminance coding process may be history-dependent. The behavior of a visual SCN cell, then, is determined to some extent by the previously experienced illumination level. The conceptual complication of the hysteresis phenomenon is of minor practical consequence, however. For hysteresis the intensity-response curve is commonly shifted by less than one order of magnitude, whereas the curvature is only slightly affected (FIGURE 1D).

One major function of the visual input to the SCN is to mediate photic entrainment. The process of entrainment is currently understood as a daily adjustment of the phase of the circadian pacemaker by the light-dark cycle. Such phase adjustment is possible due to the fact that photic stimulation can phase shift circadian pacemakers in a phase-dependent manner.[1] Takahashi *et al.*[30] have measured the intensity-response function for phase-shifting behavior of the pacemaker controlling the hamster activity rhythm, that is, the SCN. They report a monotonic curve with a threshold and saturation. This curve can be effectively described by a Michaelis equation with an effective working range of about three log units. These characteristics correspond quite closely to those of our average intensity-response function for light-activated SCN cells in the hamster. An example of an intensity-response function for a single hamster SCN cell is shown in FIGURE 2C. Another common qualitative feature of the phase-shifting and the neuronal intensity-response curves is their high threshold, approximately six orders of magnitude above the absolute sensitivity threshold for rod photoreceptors.[30] These observations for phase-shifting behavior correspond closely to comparable findings of Brainard *et al.*[31] These authors studied the dependence of the degree of nocturnal melatonin suppression on the intensity of the suppressing light pulse. They report an intensity-response function for the hamster that is similar in shape to those for the phase response behavior and the visual response of SCN cells. Furthermore, the curve for melatonin suppression has a narrow working range and a high threshold.

A peculiar finding reported by Takahashi and his coworkers[30] for light-pulse induced phase shifts is the extremely wide range over which a reciprocal relationship between intensity and duration of photic stimulation holds. Within the working range of the intensity-response function and for stimulus durations up to at least 45 minutes, a phase shift of a given magnitude is observed, providing the product of intensity and duration of the light pulse is constant. This reciprocal relationship has a parallel in the behavior of visual SCN neurons. The Michaelis equation describing the intensity-response curve is virtually linear around the inflection point where reciprocity holds. Consequently, for the tonic light responsiveness of SCN cells, the electrical activity integrated over the duration of a light pulse will similarly be constant within this range. It is of considerable functional importance that both visual SCN cells and the circadian pacemaker of the SCN process light on the basis of a photon-counting mechanism. Indeed, the overall response of both systems is dependent on the number of photons presented, whether the rate of photon input is high and the light pulse short or vice versa.

NEURAL MECHANISMS OF LUMINANCE CODING BY THE SCN

Very little is known about the photoreceptor system responsible for phototransduction at the initial stage of the visual input to the SCN. The wavelength sensitivity curve

for phase shifting the hamster activity rhythm resembles the spectral absorption curve for rhodopsin.[30] It is unclear, however, whether rod photoreceptors play a major role in photic entrainment. Neither is it known what contribution the cone photoreceptors have in this process.[11,32] Virtually the only definite information about the retinal organization of the optic SCN afferents that is available concerns the ganglion cells. Both the RHP and the RGSP originate from these retinal output cells.[14,17] The ganglion cells giving rise to the RHP are found throughout the central and peripheral aspects of the retina. They appear to spread their dendritic trees rather widely.[14] This suggests that they may integrate visual information from relatively large regions of the retina. Consistent with this idea is the fact that the visual receptive fields of SCN cells are, in fact, extremely large, often exceeding 40 degrees of arc in diameter.[24] At present it is impossible to determine whether the spread of the RHP ganglion cell dendritic arborization is wide enough to account for spatial integration over such large retinal areas. It is conceivable, on the contrary, that the large receptive field size is a consequence of extensive RHP fiber convergence on individual SCN cells. Besides their size, a special feature of the SCN receptive fields is their lack of antagonistic center-surround organization.[24] Irrespective of the portion of the receptive field that is illuminated, the response is invariably one of activation or suppression depending on the particular type of visual SCN cell observed. The reasons for the homogeneity of receptive field organization remain to be determined. It is possible that those ganglion cells that directly or indirectly project to the SCN lack receptive field organization. Alternatively, these ganglion cells may belong to the rare class of tonic W cells described for the cat.[33] The tonic W cells exhibit luminance coding properties that would make them a suitable component of the luminance channel to the SCN. In the cat, however, tonic W cells are known to have small receptive fields with a distinct center-surround antagonism.[33] Thus, by assuming strong convergence of many overlapping W-cell receptive fields on single SCN neurons, it would be possible to construct large homogenous receptive fields for SCN cells from W-type ganglion cells.

Although most aspects of the retinal mechanisms contributing to luminance coding by the SCN are still unknown, it is clear that the retina is not responsible for the occurrence of the two opposite visual response types in the SCN—activation and suppression. In *in vitro* explants[6,34] of the small portion of the rat hypothalamus (comprising the SCN and part of the optic chiasm and optic nerve), suppression as well as activation can be evoked by electrical stimulation of optic fibers (FIGURE 3). Thus, in the absence of the retina and vLGN, electrical excitation of RHP afferents of the SCN will still result in either a decrease or an increase of SCN cell discharge. The mechanism for this dual response must therefore be present at or beyond the level of the optic synapses on SCN neurons. These *in vitro* experiments also imply that the vLGN input to the SCN is not necessary for the visual reactions of SCN cells. This raises the question of the functional characteristics and contribution of the vLGN projection to the hypothalamus.

THE RETINO-GENICULO-SUPRACHIASMATIC SYSTEM

In the vLGN, visual cells can be recorded with properties similar to those of the light-responsive SCN cells.[13,16,35,36] These vLGN neurons are either tonically activated or suppressed by an increase in ambient light intensity (FIGURE 4A,B). Moreover, their discharge rate is a monotonic function of light intensity (FIGURE 4C), and the cells are characterized by large receptive fields.[36,37] At least a part of these vLGN luminance units project to the SCN, as has been demonstrated in antidromic stimulation

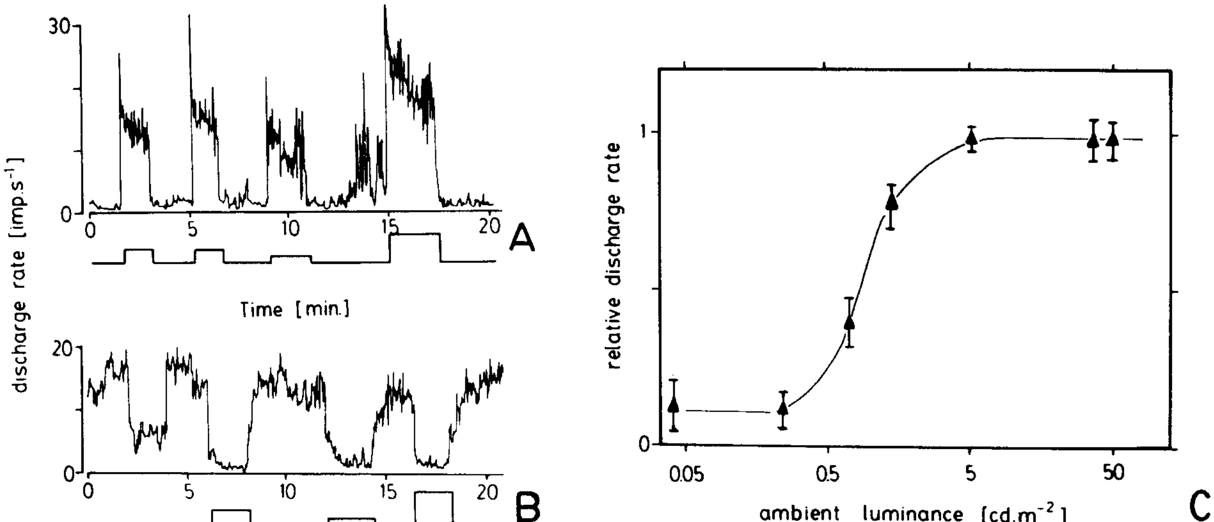

FIGURE 4. Tonic light-activation (A) and light-suppression (B) in two vLGN neurons recorded in the urethane-anesthetized rat. The temporal pattern of stimulation is indicated below the records in A and B. Note the occurrence of irregular oscillations in the dark discharge rate for the activated cell in A after prolonged ($\geq$3 min) dark adaptation. In C the intensity-response function is plotted for a third vLGN cell. For this light-activated cell the steady state discharge rate ($\pm$ SEM) was normalized with respect to the mean saturation discharge rate recorded in this experiment.

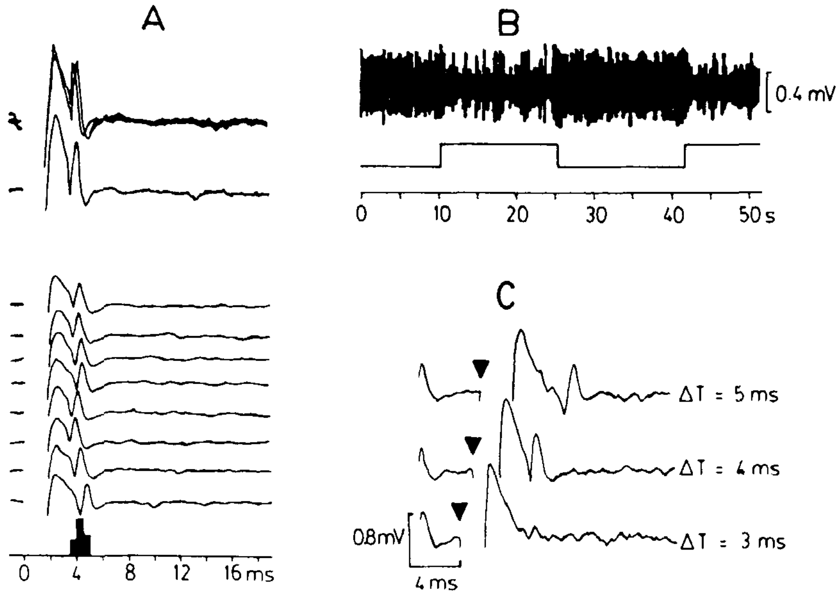

FIGURE 5. Antidromic activation of a light-suppressed vLGN cell in the urethane-anesthetized rat by electrical SCN stimulation. This cell responded tonically to whole-retinal illumination (B: stimulation pattern indicated below the record). For this experiment stimulating electrodes were placed in the ipsilateral SCN, and constant current pulses (300 μA, 0.2 ms) were applied. Each stimulus was followed by an antidromic action potential recorded from the vLGN cell body. The spike arrived in the soma at a constant latency of 4.2 ms as illustrated in the records and latency histogram in A. Following a spontaneous orthodromic spike in the vLGN cell, an electrical stimulus could be triggered after a variable delay T to evoke an antidromic spike. At delays of 3 ms and below, collision occurred consistently between the ortho- and the antidromic spike (C). The collision test indicates that this visually suppressed vLGN cell indeed sends an axon to the SCN.

experiments[13,38] (FIGURE 5). The question arises as to what extent these tonically responding and, possibly, other vLGN cells contribute to the overall visual behavior of the SCN. In a number of studies, the RGSP has been disrupted by transection of the optic tracts,[25] bilateral lesions of the vLGN,[23] or by hypothalamic deafferentation,[8] sparing only the RHP. Under all these conditions the SCN remains visually responsive, and no difference in visual properties of the SCN can be demonstrated, compared to intact animals (FIGURE 6). Thus, it is evident that the RGSP is not necessary for the expression of tonic suppression and activation by SCN cells.

The vLGN can be subdivided on cytoarchitectonic grounds into an internal and an external division.[39-41] Studies in which horseradish peroxidase was used as a retrograde tracer indicate that the vLGN-SCN fibers originate mainly in the dorsal lamina of the internal division of the vLGN.[16] The perikarya are found just ventral to the axons that separate the ventral from the dorsal vLGN.[16] The termination of the vLGN-SCN projection has been described histochemically in the hamster with the aid of avian pancreatic polypeptide (APP)-directed antisera. It was demonstrated that the vLGN-SCN projection and its terminals in the ventro-lateral aspect of the SCN exhibit APP-like immunoreactivity.[19-21] More recently it has become clear that NPY, a

polypeptide that functionally and chemically differs only slightly from APP,[42,43] is the peptide contained in the geniculate SCN terminals.[44]

Recently the functional role of these peptides for the circadian pacemaker of the SCN was examined in hamsters by microinjection of APP or NPY into the suprachiasmatic region.[45,46] In response to local administration of these peptides, phase shifts in the free-running locomotor activity rhythm were observed. Injection advances or delays the phase of the activity rhythm, depending on the phase of the circadian cycle at which it is administered. The phase-shifting behavior in response to APP or NPY injection resembles that observed after dark pulse presentation to a free-running hamster.[47] Interestingly, the phase responses induced by a dark pulse or the polypeptide injection at any given phase of the rhythm are roughly the opposite of the phase shifts evoked by a light pulse presented at that phase.[1,30,47]

The question should be addressed whether the release of endogenous NPY similarly phase shifts the free-running activity rhythm of hamsters. Electrical stimulation of the dorsal internal division of the vLGN, which presumably results in NPY release at the vLGN terminals in the SCN, indeed produces phase-dependent shifts in hamster activity rhythms.[48] These phase shifts are similar to those in response to dark pulses or APP/NPY administration.

In summary, the RGSP supplies the SCN with information that, in principle, is capable of controlling the phase of the circadian pacemaker in the SCN. In view of the similarity of the effects of NPY/APP injection, vLGN stimulation and dark pulses, activation of the RGSP is apparently correlated with the effects of darkness. The RHP is sufficient for entrainment of circadian rhythms as was shown in studies where disruption of the RGSP did not interfere with entrainment.[12,49] It is difficult to assess

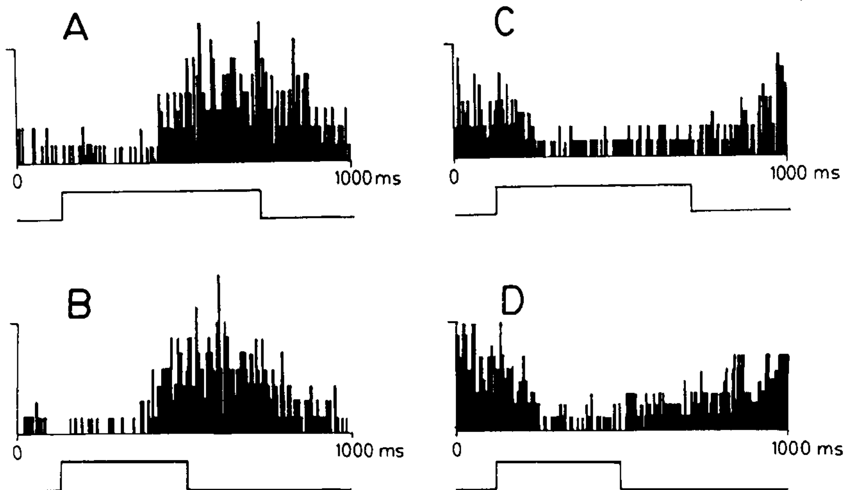

FIGURE 6. Peristimulus time histograms computed for a light-activated (A, B) and a light-suppressed (C, D) SCN cell recorded in urethane-anesthetized, vLGN-lesioned rats. Notwithstanding extensive lateral geniculate lesions, damaging all of the vLGN and portions of the optic tracts, the dorsal LGN and the zona incerta, both SCN cells exhibit sustained responses to visual stimulation. Each histogram represents the average response in a series of 100 stimulus presentations. Note that for these fairly brief flashes the responses outlast the stimulus considerably.

whether the RGSP is likewise sufficient for entrainment because as yet it has been impossible to interrupt the RHP without concurrent damage to the optic tract. Since the neurotransmitter(s) of the RHP are unkown (although acetylcholine has been implicated[50–52]), specific antagonists cannot be used instead of surgical RHP transection. Therefore, the only currently feasible experiment to shed light on this problem is to entrain the activity rhythm of blinded hamsters by periodic circadian stimulation of the vLGN.

CONCLUDING REMARKS

From electrophysiological investigations it became evident that the visual system of the SCN and its optic afferents is specialized for processing luminance information. By contrast, the classical primary visual pathways are much more differentiated towards image and movement processing. The response properties of visual SCN cells are well fit for their putative function of monitoring the overall level of illumination in the course of the 24-hour day. The close parallels among visual SCN cell characteristics, the light-dependent phase-shifting behavior, and melatonin suppression are compelling indications that these functions are indeed mediated by the activated or suppressed neurons of the SCN.

Two features of the way luminance is processed by the SCN in nocturnal rodents stand out. The threshold of response is high (approximately .1–1 lux) compared with the threshold sensitivity of the rod dominated retina ($\ll 10^{-4}$ lux). Furthermore, the working range of visual SCN cells is very narrow. Saturation of response is complete at 1–3 log units above threshold. In their normal habitat animals may experience a luminance range from about 10^{-4} lux (a "dark" night) to as much as 10^5 lux (a "bright" day). During the light-dark transitions at dawn and dusk the environmental luminance moves rather quickly through the operational range of the SCN cells. Thus, due to their high threshold and narrow working range, SCN cells effectively transform the gradual luminance changes throughout the 24-hour day into a square wave process. Conceivably, in this manner the weather-related day-to-day variations in absolute light intensity have only a minor disturbing effect on the precision of photoperiod coding and photic entrainment by the SCN. It would be of interest to determine if a similar mechanism may exist in diurnal species. In principle, diurnal animals are faced with the same tasks as nocturnal species: they monitor the day-night alternation as well as the photoperiod and, since they also synthesize melatonin at night,[7] they may similarly suppress their pineal melatonin production at dawn. Thus, diurnal species might indeed employ luminance coding mechanisms comparable to those described here for the rat and hamster to subserve the visual functions of the SCN.

The visual physiology of the SCN is only a single aspect of our eventual understanding of mammalian circadian timekeeping and photoperiodism. At present the precise organization of this circadian pacemaker is largely unknown. Electrophysiological and neuroanatomical investigations have partly illuminated some aspects of the mechanisms underlying the photic entrainment of the SCN pacemaker. Unfortunately, we lack the criteria by which those SCN neurons that are part of the rhythm generating mechanism can be recognized. As a consequence it is impossible to determine whether visual SCN cells are a separate population of visual input cells to the pacemaker or an integral part of the rhythm generator itself. There is a similar lack of understanding of the neural mechanisms of photoperiodic control of the pineal gland by the SCN. The functional connections between visual SCN cells and the SCN efferents in the multisynaptic pathway to the pineal therefore remain to be uncovered.

The major contributions of electrophysiology to our current understanding of the visual SCN functions are thus the description of luminance coding and the functional properties of the RHP and RGSP as the two main visual pathways to the SCN.

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