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The Visual Input Stage of the Mammalian Circadian Pacemaking System: I. Is There a Clock in the Mammalian Eye?

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Abstract Threads of evidence from recent experimentation in retinal morphology, neurochemistry, electrophysiology, and visual perception point toward rhythmic ocular processes that may be integral components of circadian entrainment in mammals. Components of retinal cell biology (rod outer-segment disk shedding, inner-segment degradation, melatonin and dopamine synthesis, electrophysiological responses) show self-sustaining circadian oscillations whose phase can be controlled by light–dark cycles. A complete phase response curve in visual sensitivity can be generated from light-pulse-induced phase shifting. Following lesions of the suprachiasmatic nuclei, circadian rhythms of visual detectability and rod outer-segment disk shedding persist, even though behavioral activity becomes arrhythmic. We discuss the converging evidence for an ocular circadian timing system in terms of interactions between rhythmic retinal processes and the central suprachiasmatic pacemaker, and propose that retinal phase shifts to light provide a critical input signal.

INTRODUCTION

THE POSSIBILITY OF OCULAR TIMING

This paper arose out of a workshop we organized in 1985 addressing the question: "Is there a clock in the mammalian eye?" Circadian timing of ocular functions has been demonstrated in many invertebrate and some nonmammalian vertebrate species, whereas the possibility of an ocular circadian timing system in mammals is a matter of controversy. In mammals, retinal input of environmental information is critical for the entrainment and phase shifting of circadian rhythms driven by the putative circadian pacemaker in the suprachiasmatic nuclei (SCN). Independent of temporal niche, all mammals show a similar phase response curve (PRC) to light, with a sensitive interval confined between dusk and dawn hours. Because rod photoreceptor disk shedding occurs at dawn across nocturnal and diurnal species (Besharse, 1982; Tabor et al., 1982; Fisher et al., 1983), it may therefore provide a potential phase marker for the PRCs common across temporally adaptive niches. In all-cone or duplex retinae, other photoreceptor mechanisms may subserve this function (Hotz et al., 1990). Thus, elucidation of the mechanisms by which light information is coded and transmitted to the SCN is of obvious importance for circadian physiology. Yet the tradition in circadian research has been to interpret light effects on central rhythmic mechanisms without accounting

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for ocular processing that may modulate input to the SCN, particularly under laboratory conditions used for circadian experimentation. We have attempted to integrate experimental data from different fields—visual system neuroanatomy and physiology, retinal and pineal neurochemistry, psychophysics, and circadian physiology—which, when taken together, lend plausibility to the existence of a mammalian ocular timing system.

CIRCADIAN TERMINOLOGY FOR OCULAR TIMING

"Circadian rhythms" are defined as those ~24-hr cycles that persist in the absence of periodic time cues in constant darkness (DD) or constant light (LL). Under a light–dark (LD) cycle, these rhythms attain a reliable phase position, which can be shifted by changes in timing of the external photic zeitgeber. When a given rhythmic physiological function is isolated, it may prove to be a "pacemaker" or an "oscillator," or it may be "driven" (Pittendrigh and Daan, 1976a,b). A driven rhythm results from a remote rhythmic signal, whereas an oscillator is capable of self-sustained timing; a pacemaker additionally drives oscillations in distal processes. As applied to our proposed ocular rhythmic system, each of these levels of rhythmic function may be represented in the eye. Retinal rhythms may be driven by putative efferents from the SCN or other central nervous system (CNS) sites. If so, SCN lesions should render the retinal functions arrhythmic. Such a retinal driven function could act to prepare the eyes for periodic light signals "expected" by the SCN. Certain retinal oscillator functions may be capable of self-sustained circadian timing without direct input into the SCN, while still serving as a dynamic gate for the amount of light information available to the SCN (Groos, 1982; Groos and Meijer, 1985). In a further elaboration, rhythmic retinal processes may themselves show phase shifts to light, influencing distal phase adjustments in the SCN.

It may appear from this discussion that retinal rhythms are being construed solely as inputs to the SCN, albeit with the added complexity inherent in a coupled oscillator system. One needs also to consider that the putative retinal pacemaker may drive a host of rhythmic processes within the eye itself. These in turn may influence retinal function with or without consequences for central rhythm regulation.

PHOTORECEPTORS IN THE CONTEXT OF CIRCADIAN EXPERIMENTATION

Light reception in the retina results from the capture of incident quanta of radiation by the visual pigments of rods and cones. These integral transmembrane glycoproteins are embedded in visual cell outer-segment phospholipid membranes. Upon light absorption, visual pigments activate a cascade of biochemical reactions that amplify the light signal and transduce it into a neural signal, which is ultimately transmitted to the brain (Kühn, 1984; Stryer, 1986; Baylor, 1987; Fung, 1987; Chabre and Deterre, 1989). The neural signal flows mainly in the radial direction from the photoreceptors to bipolar cells and to ganglion cells, with lateral interactions in the outer and inner plexiform layers and feedback connections within and between retinal layers. The functional architecture and the complex synaptic circuitry of the mammalian retina differ across species, but essentially follow a common principle that enables the retina to code and interpret the visual signal (Kolb and Nelson, 1984).

The basic organization of rods and cones follows a common pattern, with outer segments containing visual pigments and inner segments comprising the cell's metabolic machinery. As derivatives of the CNS, visual cells are not regenerated by mitosis. However, a dynamic renewal of major components is a basic phenomenon in vertebrate and invertebrate eyes. Rods and cones renew their outer segments by intermittent shedding of old disk membranes from their tips ("disk shedding"), in balance with membrane assembly at their base and molecular membrane replacement throughout the entire outer segment (Young, 1976; Bok, 1985). In visual cell inner segments, bulk degradation—visible by electron microscope—involves digestion of cytoplasmic organelles or ground plasma, and is termed "autophagy" (Remé, 1981). Differences between rod and cone function have long been recognized, based on observations that the temporal habitat of various species is correlated with retinal photoreceptor composition (Schultze, 1886). Diurnal animals possess cone-dominated retinae; nocturnal or crepuscular animals, rod-dominated retinae; and species without a clear temporal behavioral niche, duplex retinae. Cone-mediated responses in daylight vision are less sensitive and faster than rod-mediated responses in night vision.

Cones enable the visual system to detect rapid intensity changes, rapid movement of objects, and colors at high light levels, whereas rods are specialized for absorbing photons at low light levels. In nocturnal or crepuscular animals with rod-dominated retinae, rods as mediators of dawn and dusk signals are likely to be of predominant importance for the circadian system. In species with duplex or cone-dominated retinae, there are suppressive interactions of rods on cone thresholds at low light levels (e.g., Frumkes and Eysteinsson, 1988; Denny et al., 1990), which may conceivably enable those species to discretely perceive the slow, gradual dawn and dusk transitions. In all-cone retinae, the phototopic threshold may be close to the scotopic threshold found in all-rod or duplex retinae, which would enable the cones to sense light levels around dawn and dusk periods.

The range of light levels perceived by the human visual system spans 11 log units (Fig. 1), with an absolute psychophysical threshold of 100 light quanta incident on the cornea for rods and 8000–10,000 for foveal cones. The scotopic and photopic thresholds, as well as ranges, differ across species. One of the basic functions of duplex retinae is to adapt to these enormous variations of illuminance (Shapley and Enroth-Cugell, 1984), in contrast to either rod- or cone-dominated retinae. Light and dark adaptation are performed by processes that involve photoreceptor and neural network mechanisms (Shapley and Enroth-Cugell, 1984; Dowling, 1987). These mechanisms are the ones that may be altered by lighting conditions commonly used in circadian rhythm research.

Upon absorption of light quanta, the chromophore is released from the visual pigment molecule, and undergoes a configurational change. This is followed by a reduction; the chromophore is then esterified in the pigment epithelium, reisomerized and oxidized, and delivered to the photoreceptor outer segment to restore the complete visual pigment molecule (Wald, 1968; Bridges et al., 1983; Bernstein and Rando, 1986). Movements of retinoids to and from the outer segment are performed by several transport proteins (Chader et al., 1983; Bok, 1985; Saari, 1990). Periodic darkness or dim light are required after exposure to strong lighting to restore the visual pigment molecule. With light levels as low as 80 lux, a steady state is reached after 1 to 2 hr (with bleaching of more than 90% of visual pigment), and is maintained over 24 hr in the albino rat (Rapp and Williams, 1980). The more rhodopsin bleached by a given light pulse, the slower the rate of its regeneration (Dowling, 1963; Penn

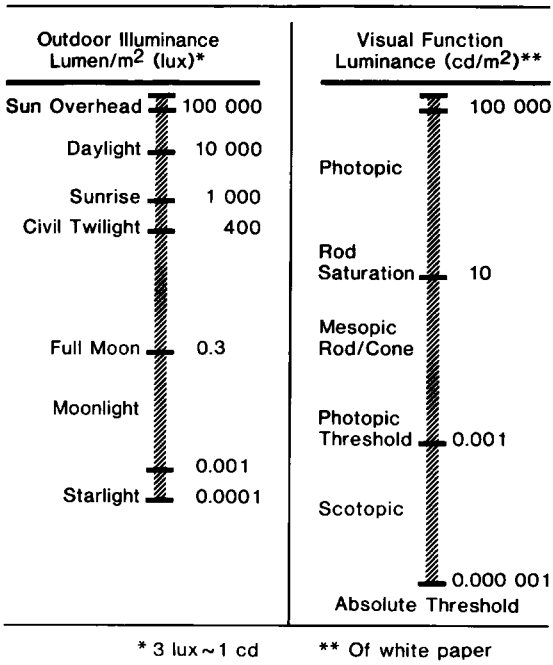


FIGURE 1. Outdoor illuminance and luminance ranges of scotopic and photopic visual function. Illuminance (E; lumen/m^2) is defined as the light level measured on a surface; luminance (L; candela/m^2) represents light emitted from a surface. Retinal illuminance varies with pupil size and is expressed in Trolands ($T = L \times p$). There are scotopic and photopic Trolands, defining the relative luminous efficiency of light as a function of wavelength. In this diagram, light levels are presented in illuminance and luminance, regardless of pupil size and spectral efficiency. The interconversion of candela (L) and lux (E) is derived from $L = \rho (E / \pi)$, with the degree of reflection, $\rho = 0.9-1.0$ (for white paper). (Sources: Goersch, 1987; H. Krüger, personal communication.)

and Williams, 1986). In circadian rhythm experimentation, we must consider whether a constant level of visual pigment is maintained over prolonged intervals, and must identify the limiting light intensity for rhodopsin regeneration. Therefore, LL or prolonged bright light pulses may be deleterious by modifying or even destroying rod structure and function. In cones, light adaptation may prevent the retina from blinding in such conditions, thus avoiding a "saturation catastrophe" (Shapley and Enroth-Cugell, 1984). Conversely, prolonged periods of darkness, as would be experienced in tests of free-running periodicity (τ_{DD}), may serve to degrade or even destroy normal cone function. In both rods and cones, photochemical damage can be induced by lighting regimens that exceed the physiological range of a given species (for review, see Terman et al., 1990).

CIRCADIAN RHYTHMS IN THE MAMMALIAN RETINA

CELLULAR AND MOLECULAR RHYTHMS

In the frog, inner-segment opsin levels show 24-hr variation (Bird et al., 1988), and in toad and fish there is additional evidence for self-sustaining circadian rhythmicity (Korenbrot and

Fernald, 1989). In rat rods, the synthesis of phospholipids follows a circadian rhythm, with elevated activity in inner segments during the day (Dudley et al., 1984). Magnesium-stimulated enzyme activity (MDPNase, a marker for lysosomal enzymes involved in the digestion of rod outer-segment tips) also shows circadian and light-elicited properties, with intense staining before, during, and after the shedding peak (Irons, 1987; Irons and O'Brien, 1987; Irons et al., 1990). Furthermore, in rat rod inner segments, 24-hr rhythmic expression of transducin (a transducing G-protein mediating initial stages in the phototransduction cascade) messenger ribonucleic acid (mRNA) is observed, with low levels at night, increasing prior to light onset, and highest in the morning hours (Fig. 2b). Newly synthesized transducin remains in rod inner segments during the day and is transported to outer segments at night (Fig. 2a), and may be involved in the control of rhythmic photoreceptor sensitivity (Brann and Cohen, 1987).

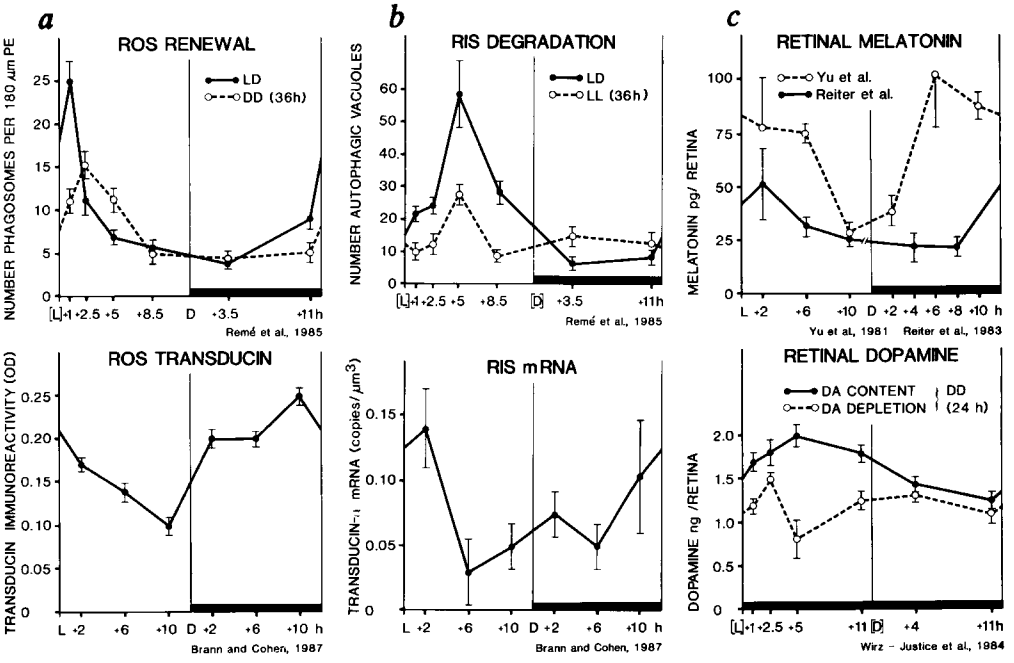


FIGURE 2. DD, LD 12:12, and LL waveforms of rat retinal rhythms. (a) Rod outer-segment (ROS) disk shedding (measured in pigment epithelium, PE) and transducin (optical density, OD) levels. (b) Rod inner-segment (RIS) degradation (autophagy) and transducin mRNA levels. (c) Retinal melatonin levels and dopamine (DA) depletion (as a measure for DA synthetic rate). All curves (mean ± *SD*; $n = 5-10$ animals per time point) are plotted on the time base of the LD entrainment cycle prior to the experiment. The time axes represent hours after lights-on and lights-off, respectively, of the entraining LD cycles before the DD and LL regimens were initiated. The durations of DD and LL, respectively, before the beginning of the experiments are indicated in the individual graphs with DD of 36 and 24 hr (panels a and c), and LL of 36 hr (panel b). [L] and [D], extrapolated times of light and dark onset within LL or DD releases. The illuminance levels for the light phases of the LD cycles, measured on the top of the cages for the experiments analyzing ROS renewal, RIS degradation, and retinal DA depletion, were 25 to 50 lux. Illuminance levels in the remaining experiments were not specified.

DISK-SHEDDING AND AUTOPHAGY RHYTHMS

Rod disk shedding occurs in the early light phase across nocturnal and diurnal animals (Besharse, 1982), and may thus provide a potential phase marker for the similar PRC in nocturnal and diurnal species. Whereas rod rhythms show a consistent pattern, cone rhythms display considerable species variations (e.g., Long et al., 1986). For example, the duplex retina of the rhesus monkey shows a biphasic pattern of cone disk shedding, with peaks in both day and night (Anderson et al., 1980). In the few all-cone retinae investigated to date, disk shedding occurs during the early light phase (e.g., Immel and Fisher, 1985).

Disk shedding exhibits a circadian rhythm in vertebrate species (LaVail, 1976, 1980; Besharse, 1982). The characteristics of mammalian rod circadian disk-shedding rhythms have been elucidated in detail in the albino rat: It is an endogenous rhythm that persists for several cycles with a dampened peak in DD, but is abolished in LL (Fig. 2a). An interval of darkness is required for shedding to occur, the length of which differs across species. Furthermore, the rhythm can be dissociated in the two eyes of the same animal by using monocular occlusion (Teirstein et al., 1980). Low light intensity (~3 lux) is sufficient to phase-shift the rhythm in an LD cycle, though relatively higher levels (~10 lux) are required to inhibit the shedding peak in LL (Goldman, 1982). Under simulated naturalistic dawn-and-dusk LD cycles, disk shedding is triggered at extremely low light levels (0.002 lux) and progresses independently of stimulus intensity (Bush et al., 1990). With relatively bright light pulses given in DD (~100 lux of 30- to 45-min duration), disk shedding can be elicited at any time of the 24-hr cycle, with the magnitude of response showing a phase dependency (Remé et al., 1986, 1990). At a given phase of an LD cycle, disk-shedding responses are intensity-dependent (Remé et al., 1985). For animals maintained on LD cycles of low intensity (3 lux) and then transferred to higher intensities, the disappearance rate of phagosomes from the pigment epithelium is proportional to light intensity, possibly indicating a light dependence of digestive enzyme activity (Baker et al., 1986).

The peak of autophagy (the intracellular digestion of organelles) occurs in the middle of the light phase of the LD cycle, several hours after the disk-shedding peak. Under LL, the rhythm of autophagy persists with a dampened peak, but is rapidly extinguished in DD, indicating that light is essential for the expression of this rhythm (Remé et al., 1985; Fig. 1b). Autophagy may thus be triggered by light-sensitive pigments in rod inner segments. Like disk shedding, autophagy can be elicited in DD by a light pulse at any circadian phase, and the light response is intensity-dependent in an LD cycle (Remé et al., 1986). Thus, the mechanisms of shedding and autophagy appear to depend on darkness and light, respectively, adding local regulatory processes to an endogenous ocular oscillator of unknown locus.

ELECTROPHYSIOLOGICAL AND PSYCHOPHYSICAL RHYTHMS

ELECTRORETINOGRAM, VISUAL EVOKED CORTICAL POTENTIAL, AND ELECTRO-OCULOGRAM

The 24-hr rhythm in the dark-adapted rod electroretinogram (ERG) of normal human subjects shows b-wave sensitivity that is significantly lower 1.5 hr after light onset than at any other time in the LD cycle (Birch et al., 1986). In patients suffering from the inherited retinal degeneration retinitis pigmentosa, a larger than normal reduction of b-wave sensitivity of

the rod ERG has been observed, pointing to a defect in rhythmic photoreceptor renewal (Sandberg et al., 1988). In both albino and pigmented rabbits, a decrease in ERG b-wave amplitude is coupled to the peak of rod disk shedding shortly after light onset (White et al., 1987; White and Hock, 1990). In pigmented rats, ERG sensitivity is lowest 1.5 hr after light onset, when phagosome frequency in the pigment epithelium is highest, indicating that b-wave changes reflect variations in photoreceptor function (Sandberg et al., 1986). However, the reduction in ERG sensitivity is larger (~40%) than would be expected from the shortening of rod outer segments (~11%), indicating that other mechanisms may contribute to rod desensitization, such as lowered transducin levels (Brann and Cohen, 1987). Circadian changes in rabbits' visual evoked cortical potential (VECP) have been measured together with ERG in the same animals (Bobbert and Brandenburg, 1982). The results indicate that VECP variations may result from changes in retinal sensitivity to light.

In normal human subjects, circadian variations contribute between 20% and 50% to the normal variability of the electro-oculogram (Anderson and Purple, 1980).

PSYCHOPHYSICAL SENSITIVITY

Normal human subjects show 24-hr rhythmic variation in their absolute visual threshold (Knoerchen and Hildebrandt, 1976; Bassi and Powers, 1986; T. Roenneberg, personal communication). Studies of circadian oscillation of visual sensitivity have been performed in the rat (Rosenwasser et al., 1979; Terman and Terman, 1985a; Fig. 3). The rhythm of detectability of very dim flashes against DD or dim LL backgrounds probably represents circadian modulation of the absolute threshold for scotopic vision. In contrast to disk shedding, the circadian rhythm of visual sensitivity free-runs without dampening for weeks and even months: Sensitivity reaches a peak during the subjective night and falls rapidly during the early subjective day. The rhythm is self-sustaining, since it persists under constant conditions, can be entrained to skeleton photoperiods, and can be phase-shifted by them. A complete PRC for visual sensitivity has been derived (Terman and Terman, 1985b; Fig. 3c). These rhythmic visual functions appear not to depend on the SCN pacemaker; the rhythm persists in SCN-lesioned animals in the absence of concurrent rhythmicity in feeding behavior (Fig. 3b).

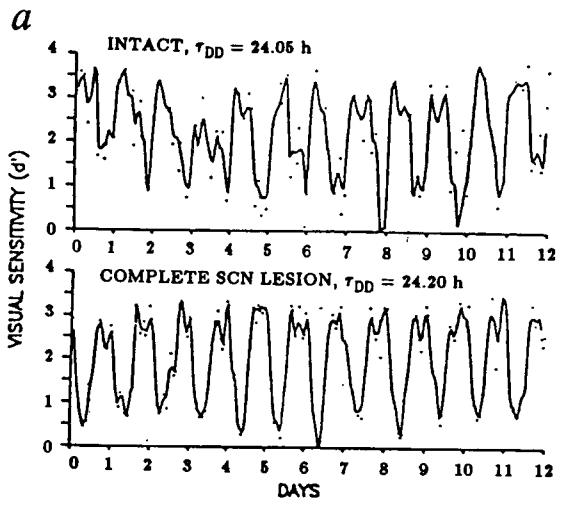
NONRETINAL OCULAR RHYTHMICITY: INTRAOCULAR PRESSURE

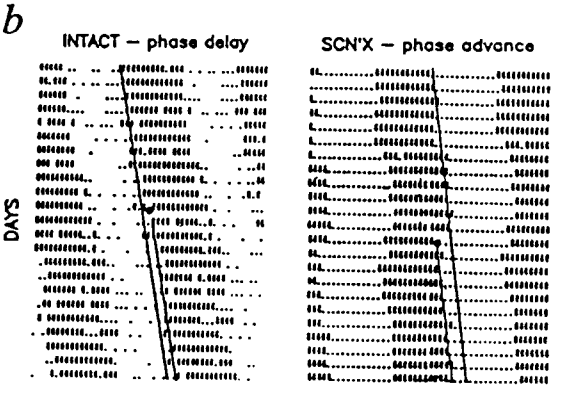
A 24-hr rhythm of intraocular pressure (IOP) has been measured in humans. The pattern is dependent on the methodology, sampling interval, and vigilance state (Drance, 1960; Frampton et al., 1987). In animals the IOP rhythm is entrained to the LD cycle, can be phase-shifted, persists in DD, and is dampened in LL (Bar-Ilan, 1984; Gregory et al., 1985; Rowland et al., 1986). Melatonin may be involved in IOP regulation in both animals and humans (Chiou and McLaughlin, 1984; Quay, 1984).

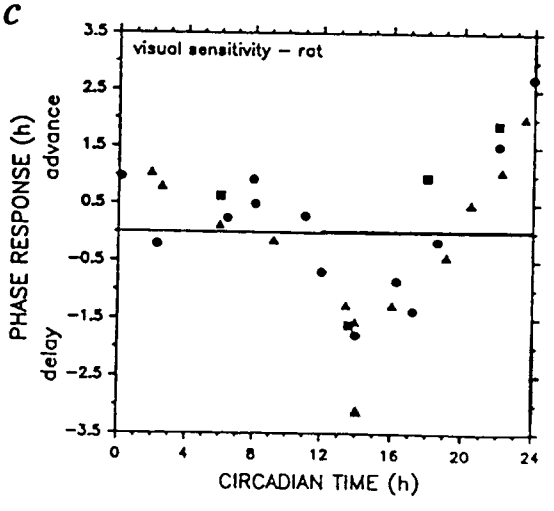
RETINAL RHYTHM REGULATION

EVIDENCE FOR LOCAL REGULATORY MECHANISMS

The possibility of extra-SCN pacemakers has long been discussed (e.g., Rusak, 1989), even though the SCN is considered the classic pacemaker for circadian rhythms (Moore, 1983).







In vertebrate species, there is evidence for local ocular rhythm regulation. Although many studies have been devoted to retinal rhythm regulation (Besharse, 1982), knowledge of the localization, nature, and mediating components of the putative ocular rhythm generator is incomplete. There have been no *in vitro* experiments with the mammalian eye testing the persistence of ocular rhythms under complete isolation from systemic influences. In the rat, manipulation of the endocrine system (LaVail and Ward, 1978; Tamai et al., 1978), superior cervical ganglionectomy (LaVail and Ward, 1978), monocular occlusion, and optic nerve transection (Goldman et al., 1980; Teirstein et al., 1980) have failed to abolish the disk-shedding rhythm. However, the possibility of efferent influences over rhythmic ocular processes cannot be ruled out completely. Teirstein et al. (1980) failed to phase-shift the disk-shedding rhythm to an altered lighting cycle (7-hr phase delay) after optic nerve transection. This raises the possibility of a CNS efferent pathway via the optic nerve that may serve to entrain the rhythm to LD cycles. Bobbert and Brandenburg (1982) lost the circadian rhythm of ERG b-wave amplitude following ganglionectomy, eliminating the main sympathetic innervation of the eye and rhythmic input from the SCN in the rabbit. In each eye of the Japanese quail, an independent, light-entrainable rhythm of retinal melatonin was found, indicating separable circadian pacemakers (Underwood et al., 1988). In *Xenopus laevis*, retinal rhythmicity persists *in vitro* (Besharse and Iuvone, 1983; Flannery and Fisher, 1984). Furthermore, there is evidence in *Rana pipiens* that these retinal rhythms are driven by light and regulated locally (Basinger et al., 1976; Hollyfield and Basinger, 1978).

The possibility still remains that the SCN pacemaker drives mammalian retinal rhythms indirectly, via unknown efferents. A recent disk-shedding experiment makes this seem unlikely, however (Fig. 4). Rats with complete SCN lesions were released into DD following LD 12:12 exposure. The disk-shedding peak was indistinguishable from that of intact controls (M. Terman, C. E. Remé, J. S. Terman, and A. J. Silverman, in preparation), firmly establishing a preliminary result of R. Y. Moore and M. M. LaVail (personal communication).

The concept of local controls over ocular rhythmicity, particularly for rod disk shedding, has rested on the observation of rhythmic continuity following optic nerve transection and the ability of the two eyes to assume contrasting circadian periods and phases (Goldman et al., 1980; Teirstein et al., 1980). Given new doubt that the SCN is responsible for generating these rhythms, the existence of a retinally self-contained pacemaker becomes even more plausible. Such a pacemaker could interact with the SCN, modulating central rhythmic function as well as driving rhythms in the eye itself.

FIGURE 3. Analysis of visual sensitivity rhythms in pigmented rats maintained in DD and trained to detect presence and absence of dim green test flashes in the region of the scotopic absolute threshold. (a) Hourly level of detectability, d', across 12-day samples for animals with and without lesions of the suprachiasmatic nucleus (SCN). The lesioned animal showed an arrhythmic feeding pattern. Curve fits by running median. From Terman and Terman (1985a). Reprinted by permission of the New York Academy of Sciences. (b) Sensitivity rasters before and after a 1-hr bright light pulse (filled dots; 350 lux full-spectrum fluorescent) that elicited phase shifts in both intact and lesioned animals. Large symbols, d' above the daily median. Straight-line fits based on periodogram analysis. (c) Visual phase response curve for three unlesioned rats.

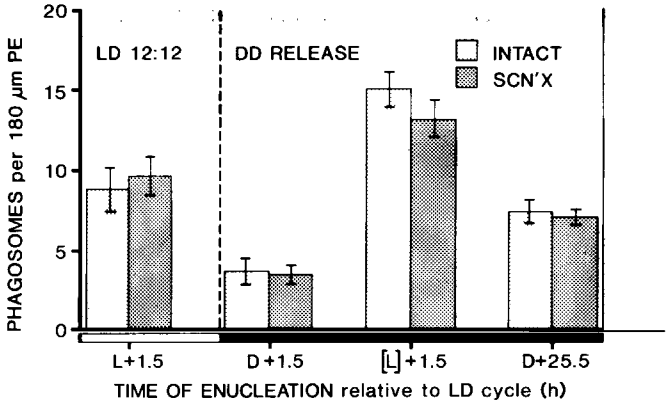


FIGURE 4. Morning–evening pattern of rod outer-segment shedding (mean ± *SEM*) in two groups of albino rats, one with lesions of the SCN leading to behavioral arrhythmicity. Samples were first taken after several weeks of exposure to LD 12:12 (light levels < 50 lux), as well as during the first day of DD release. $n = 4–11$ eyes per condition; not shown, similar results for a group of partially lesioned animals with residual, dampened behavioral rhythms. Phagosomes were quantified in 180 μm of pigment epithelium in a 2- to 3-mm^2 specimen derived from the area around the optic nerve head (M. Terman, C. E. Remé, J. S. Terman, and A. J. Silverman, in preparation). [L], extrapolated time of light onset within DD release. The release into DD results in higher phagosome numbers than recording under LD because darkness "masks" phagosome degradation by slowing it; degradation is dependent on light intensity.

CENTRAL–PERIPHERAL LINKS

In considering the issue of independent circadian retinal function, the question of central–peripheral connections, neuronal or humoral, is crucial. The empirical evidence, unfortunately, is as yet inconclusive.

NEURONAL AFFERENTS AND EFFERENTS

The demonstration of a direct retinohypothalamic tract to the SCN provided the first morphological evidence for a direct pathway by which light reaches the circadian pacemaker in mammals (Moore, 1973). This tract has now been demonstrated in many species, including humans (Sadun et al., 1984). A second visual pathway from the retina to the SCN is via the ventral lateral geniculate nucleus (LGN) (Pickard et al., 1987; for reviews, see Meijer and Rietveld, 1989; Harrington and Rusak, 1989; Zhang and Rusak, 1989). Whereas the pathway from the retina is well documented, there is little evidence for efferents from the CNS to the retina in mammals. Such efferents would have great functional significance, by influencing light perception or playing a role in ocular circadian rhythm regulation, as has been shown for *Limulus* (Barlow et al., 1977; Chamberlain and Barlow, 1984).

Claims for the existence of efferent fibers have been made since the 19th century (e.g., von Monakow, 1889), with continuing debate (e.g., Terubayashi et al., 1983; Dräger et al., 1984; Künzle and Schnyder, 1984; Schnyder and Künzle, 1984; Itaya and Itaya, 1985; for review, see Weidner et al., 1983). The apparent controversy may result from technical difficulties in conclusively demonstrating such elusive anatomical structures. The origin of such fibers has been localized to the medial pretectal area, periaqueductal grey matter, tegmentum, SCN, and tissue beyond the traditional SCN boundaries (Moore, 1983; Rusak, 1989). In the rat, a retinopetal pathway arising in the oculomotor nuclei might constitute a means of cortical control, including parasympathetic pupillary innervation (Hoogland et al.,

1985). Pupillary gating would regulate light input to the retina and thus influence zeitgeber information. In contrast, sympathetic innervation reaches the iris via the superior cervical ganglion. In the Mongolian gerbil, retinopetal fibers in the optic nerve have been demonstrated (Larsen and Möller, 1987). A retino-hypothalamo-retinal loop was postulated, based on evidence of rhythmic photic responses of the visual system in the rabbit (Brandenburg et al., 1981). Indirect evidence for central input to the retina comes from studies of intracranial optic nerve transection; in this situation, the eyes are partially protected against light damage and contain lower levels of steady-state rhodopsin with less photon absorption capacity (Bush and Williams, 1991). Visual pigment levels in light-adapted animals therefore may be regulated via optic nerve efferents. In a similar way, lesions of the tectoretinal pathway decreased retinal dopamine (DA) receptor binding (Plummer et al., 1986).

HUMORAL AFFERENTS AND EFFERENTS

Humoral information is a likely source of efferent input to the eye. Any circulating hormone with circadian periodicity is a potential candidate for transmitting temporal information to the eye, but the blood–retina interface is selective. Hormones that pass the interface may modulate circadian retinal functions, and serve as internal zeitgebers.

DOPAMINE AND γ-AMINOBUTYRIC ACID

Complexities of neurotransmission in the mammalian retina are as great as in the CNS itself. We wish to focus on DA and γ-aminobutyric acid (GABA), those retinal neurotransmitters most studied with respect to circadian rhythmicity and responsivity to light. Only data in mammals are summarized here, although the most extensive information comes from lower vertebrates (for review, see Besharse et al., 1988). DA is found in some types of amacrine and interplexiform cells (Nguyen et al., 1981; Ballesta et al., 1984; Negishi et al., 1985; Frederick et al., 1982). Both D1 and D2 dopaminergic receptor-binding sites have been characterized in a number of mammalian species (see Dubocovich, 1988b). The DA-containing amacrine cells synapse with other amacrine cells, which connect the bipolar and ganglion cells (Masland, 1988). One finds consistent interactions between GABA-ergic and dopaminergic systems in the retina: GABA inhibits dopaminergic activity, whether mediated through interplexiform cells or amacrine cells (Yazulla, 1986). GABA-ergic cells are themselves modulated by benzodiazepine receptors, correspondingly localized on some amacrine cells and on the arborizations in the inner plexiform layer (e.g., Richards et al., 1987).

Light effects are specific for DA in the retina and are not found in other brain areas rich in DA, such as the striatum. Light rapidly stimulates DA synthesis (Da Prada, 1977; Iuvone et al., 1978; Nowak and Zurawska, 1989). This is dose-dependent: The threshold for DA stimulation in albino rats is between 0.5 and 5 lux, with saturation occurring at ~33 lux (Proll et al., 1982). Short-term exposure to LL increases DA synthesis (Iuvone and Neff, 1981) and decreases DA and benzodiazepine receptor binding (Dubocovich et al., 1985; Wirz-Justice et al., 1985; Plummer et al., 1986). One of these studies found a reduction after pretectal lesions similar to that after LL, further suggesting a central projection to the retina (Plummer et al., 1986). Long-term exposure to LL (350–700 lux for 4 months) induces supersensitivity of the DA response to a light pulse. A DA response can still be elicited, even though photoreceptors have degenerated to 4% of their original number (Morgan and Kamp, 1980). Responsivity to light is also maintained in albino rats kept 9.5 weeks in intense LL: Their pineal melatonin can still be suppressed by a light pulse (Reiter and Klein,

1971). Only after extremely long exposure of 6 months to LL are photoreceptors reduced to 2% of baseline, which is insufficient to obtain a DA response to a light pulse (Morgan and Kamp, 1983). A similar loss of responsivity of retinal DA neurons to light has been shown in the RCS rat strain with dystrophic retinae (Frucht et al., 1982). Thus, it appears that remarkably few photoreceptors are required to maintain the light sensitivity of DA neurons.

The converse, adaptation to darkness as measured by decrease in DA synthesis, is also rapid (Proll and Morgan, 1982). Long exposure to DD increases DA and benzodiazepine receptor binding (Biggio et al., 1981; Dubocovich et al., 1985; Wirz-Justice et al., 1985), and induces supersensitivity of DA-stimulated adenylate cyclase activity (Spano et al., 1977). This is similar to that found in early development when rats still have their eyes closed (Da Prada, 1977; Trabucchi et al., 1976). Retinal DA (and GABA) can be stimulated by light only after eye opening (Cohen and Neff, 1982; Morgan and Kamp, 1982; Kamp and Morgan, 1984).

DA synthesis varies over the 24-hr LD cycle (Iuvone et al., 1978; Melamed et al., 1984). One study has shown that the rhythm persists in DD with a peak in the early subjective day, similar to the rhythm of disk shedding (Remé et al., 1984b; Wirz-Justice et al., 1984). An endogenous DA rhythm was not found in a second study (Melamed et al., 1984). Although DA synthesis shows a 24-hr rhythm, DA receptor number, DA-stimulated cyclic adenosine monophosphate, and benzodiazepine receptor binding do not (Spano et al., 1977; Dubocovich et al., 1985; Wirz-Justice et al., 1985). Longer exposure to LL, DD, or psychoactive drugs may be necessary to induce significant modification of retinal receptor binding, very likely reflecting concomitant changes in photoreceptor morphology (Terman et al., 1990).

Pharmacological probes have been a useful tool for elucidating the interactions between light stimulation, DA turnover, and the GABA–benzodiazepine receptor complex. DA agonists, antagonists, synthesis inhibitors, or drugs that stimulate release modify dopaminergic cells in the retina as in other DA-rich brain regions (Da Prada, 1977; Spano et al., 1977; Iuvone and Neff, 1981; Morgan, 1982; Remé et al., 1984a,b). Direct or indirect potentiation of GABA inhibition (by GABA, muscimol, and benzodiazepines) blocks light-evoked activation of retinal DA turnover (Kamp and Morgan, 1980, 1982; Morgan, 1982). GABA disinhibition through GABA antagonists such as picrotoxin or bicuculline potentiates it (Kamp and Morgan, 1981; A. Wirz-Justice, unpublished observations). Furthermore, the pharmacological data suggest that GABA receptors responsible for inhibiting DA are actually located on DA neurons (Kamp and Morgan, 1980). Thus the timing of an inhibitory GABA influence on DA neurons may play an important role in regulating the response of these neurons to light.

The distribution of DA follows that of rods in both bovine and primate retinae, suggesting that DA may be involved in rod neural circuitry (Mariani et al., 1985; Brann and Young, 1986). The circadian rhythm of DA synthetic rate (Wirz-Justice et al., 1984) is parallel to that of disk shedding (Remé et al., 1984b). Furthermore, chronic treatment with the monoamine oxidase inhibitor clorgyline, which increases retinal DA, also dampens the disk-shedding rhythm (Remé et al., 1984b). A strong dampening of the disk-shedding rhythm also occurs with the DA-releasing agent methamphetamine (Remé and Wirz-Justice, 1985). In rabbits, a DA receptor agonist blocks the circadian disk-shedding peak (White et al., 1990).

MELATONIN

The ontogenetic, phylogenetic, morphological, and biochemical similarities of the vertebrate retina and pineal gland as photoreceptive organs have been the subject of a number of recent

reviews (Menaker, 1985; Pang and Allen, 1986; Wiechmann and Hollyfield, 1989; Dubocovich, 1988b). Melatonin synthesis in the retinae of many species, including the human, has been localized to photoreceptors and a subpopulation of bipolar cells (Gern and Ralph, 1979; Wiechmann et al., 1986; Wiechmann and Hollyfield, 1989). Exogenous melatonin enhances circadian disk shedding in the albino rat (White and Fisher, 1989).

However, the pineal in mammals has no photoreceptive and self-sustaining oscillatory capacity. The pineal rhythm of melatonin, with its peak in the dark phase, is driven by the SCN, which in turn is dependent on light input through the retina for entrainment. The reported timing of the retinal melatonin peak is variable (Binkley et al., 1979; Menaker, 1985; Pang and Allen, 1986; Nowak et al., 1989; examples in Fig. 1c). The phase of the retinal melatonin rhythm is not necessarily in concert with that of the pineal: For example, when plasma, pineal, and retinal melatonin rhythms in Djungarian hamsters were measured under natural lighting conditions throughout the year, retinal melatonin showed unimodal, bimodal, or arrhythmic patterns, unlike pineal and plasma melatonin, which followed the photoperiod (Steinlechner and Reiter, 1985).

The "internal zeitgeber" function attributed to pineal melatonin (Armstrong, 1989) may also apply to retinal melatonin (Dubocovich, 1988b). Yet the analogy calls for caution, because even though melatonin in the pineal and melatonin in the retina appear to have common characteristics, the regulatory factors and physiological functions in the two organs may have evolved differently. Two roles have been suggested for melatonin in mammals—as a local neuromodulator and as a hormone. In the pineal, melatonin plays primarily a hormonal role, being synthesized in large amounts and transported to target organs by cardiovascular circulation. In animals with seasonal cycles, its primary action is considered to be on gonadal function via the hypothalamo-hypophyseal-gonadal axis. The presence of specific melatonin-binding sites in the SCN, pars tuberalis, and anterior pituitary, but not in the pineal (Vaněček et al., 1987; Reppert et al., 1988; Williams, 1989), speaks for this role, rather than that of a local neuromodulator in the pineal itself. In contrast, melatonin in the retina most likely plays a primarily local neuromodulatory role within receptor sites on the rods themselves (Dubocovich, 1988b). Under normal physiological conditions, the retina does not take up any considerable amount of melatonin from—nor does it release any melatonin into—the circulation. Studies of local and systemic melatonin levels after pinealectomy, enucleation, or both indicate that in many mammals retinal melatonin does not contribute to circulating levels (Lewy et al., 1980; Tetsuo et al., 1982; Neuwelt and Lewy, 1983; Steinlechner, 1989). This contrasts markedly, for instance, with the situation in the Japanese quail, where the retina is an important source of circulating melatonin (Underwood et al., 1984, 1988). However, there may be a feedback loop between the pineal and retina, since retinal melatonin increases after pinealectomy (Yu et al., 1981; Reiter et al., 1983; Steinlechner, 1989).

DOPAMINE–MELATONIN INTERACTIONS

Recent reviews have provided extensive evidence in both lower vertebrates and mammals that retinal DA transduces the light signal, retinal melatonin the dark signal (Besharse et al., 1988; Dubocovich, 1988b). In mammals, retinal pigmentation is not a crucial factor: There is no difference between albino and pigmented Long–Evans rats in the rate of DA stimulation by light (Morgan and Kamp, 1982), or the nighttime suppression of pineal

melatonin by light (Webb et al., 1985). This is important, because stimulation of disk shedding by a light pulse also shows no difference between pigmented and nonpigmented eyes, as long as the pupil of the pigmented eye is dilated. In addition, retinal damage induced in albino rats by high-intensity illumination, and retinal degeneration in the RCS rat, are both potentiated by melatonin injections and prevented by the DA agonist bromocriptine (Bubenik and Purtill, 1980); the converse, protection from damage by pinealectomy, has also been observed (Rudeen and O'Steen, 1979).

In the frog, retinal melatonin synthetic activity (as measured by the enzyme *N*-acetyltransferase, or NAT) persists *in vitro* in LD and DD, is blocked in LL, and can be phase-shifted; moreover, a calcium-dependent dark-induced increase in NAT activity can be blocked by DA agonists and protein synthesis inhibitors (for review, see Besharse et al., 1988). These studies show that DA inhibits NAT via D2 receptors and adenylate cyclase on photoreceptors, where melatonin biosynthesis is thought to occur. Photoreceptor disk shedding can be activated by melatonin (Besharse and Dunis, 1983). Rhythms persisting in the isolated frog eye cup suggest the presence of a circadian oscillator (Besharse and Iuvone, 1983).

In addition, in lower vertebrates, retinomotor movements such as cone elongation exhibit a daily rhythm in sensitivity to dark exposure or melatonin treatment; melatonin mimics dark by causing cone elongation, whereas DA mimics light by causing cone contraction (Pierce and Besharse, 1985, 1988; Besharse et al., 1988). GABA is also important for the "dark" message, evidenced by the fact that muscimol, a GABA agonist, can, like the DA antagonist spiroperidol, cause significant cone elongation in the morning (Pierce and Besharse, 1988).

Thus, in addition to the selective and opposite modulation of DA and melatonin metabolism by light and dark, there exist direct and pharmacological interactions: In rabbit retina, melatonin inhibits DA release and adenylate cyclase (Dubocovich, 1983); luzindole, the first competitive antagonist of melatonin receptors, prevents this effect (Dubocovich, 1988a). Conversely, treatment of rats and rabbits with a DA receptor agonist inhibits retinal NAT activity (Nowak et al., 1989).

It has been proposed, for lower vertebrates (Besharse et al., 1988) and mammals (Dubocovich, 1988b), that DA–melatonin interactions provide a neurohumoral correlate of the dawn and dusk signal—the "internal zeitgeber" within the retina. DA (functionally modulated by GABA and benzodiazepine receptors) and melatonin (probably synthesized within the photoreceptors) may represent key ingredients of a neurochemical mechanism for retinal circadian rhythm regulation. DA neurons have processes that are widely extended and do not make contact with bipolar or ganglion cells, but only with other amacrine cells. That stimulation of DA synthesis by light is intensity-dependent suggests a function in coding for luminance (Ehinger, 1983), precisely the function required and also carried out by the SCN (Meijer and Rietveld, 1989).

LIGHT AS A PHOTORECEPTOR MODULATOR

SHORT-TERM LIGHT RESPONSES

Light exposure not only elicits the classical photic response followed by graded desensitization, but may also transiently alter the metabolism and functional properties in photoreceptors, with alteration of information processing to the circadian system. Light exposure against a

dim background or darkness can elicit disk shedding and autophagy responses in rods several times within a 24-hr cycle (Remé et al., 1986, 1990). Conceivably, one or several elicited disk-shedding responses reduce sensitivity. For example, the ERG sensitivity is lowest 1.5 hr after light onset, when the phagosome frequency in the pigment epithelium is highest in pigmented rats (Sandberg et al., 1986). A similar correlation of disk shedding and ERG sensitivity has been observed in rabbits (White et al., 1987; White and Hock, 1990). Furthermore, biochemical processes respond to light pulses: Rat retinal inositollipids, whose breakdown products may participate in cell signaling in photoreceptors (Anderson and Brown, 1988) and pigment epithelium (Birkle et al., 1989), increase after a 0.5-hr light pulse (Pfeilschifter et al., 1988). Inositollipid-derived second messengers—ubiquitous in a variety of tissues and present in the retina—may be involved in the regulation of gene expression (Alberts et al., 1989; Berridge and Irvine, 1989). Conceivably, gene expression in photoreceptor cells may thus be modulated via inositollipid derivatives, with light acting as an agonist. In addition, the interphotoreceptor matrix undergoes light-evoked changes (Uehara et al., 1990). In the fish *Haplodromis burtoni*, and the toad *Bufo marinus*, opsin mRNA rises to daytime levels after brief light exposures during the dark phase (Korenbrot and Fernald, 1989). Light pulses that are capable of phase shifting also induce gene expression of the proto-oncogene c-*fos*. This has been demonstrated not only in the SCN (Rusak et al., 1990), but also in the retina (Sagar and Sharp, 1990).

LONG-TERM LIGHT RESPONSES: PHOTOSTASIS

In developing albino rats, visual cells can adapt to different illuminance levels within the range of low-level LD cycles. This phenomenon has been termed "photostasis" by Penn and Williams (1986). Animals raised from birth under LD cycles of different light levels develop rod outer segments of contrasting length and rhodopsin content. An animal born and raised in LD 12:12 with illuminance levels of 3 lux during the light phase, for example, has significantly longer outer segments and higher dark-adapted rhodopsin levels than one born and raised with illuminance levels of 80 lux or 800 lux. Rats from these different lighting conditions absorb the same amount of photons per 24 hr in a given illuminance condition (longer outer segments and higher rhodopsin content leading to higher photon absorption capacity). These observations have also been made in mature albino rats, which, when transferred to LD cycles of different light levels (3, 80, and 800 lux), adjust their rod outer-segment structure and membrane composition, retinal antioxidant level, and ERG output within 2 to 3 weeks (Williams et al., 1988; Penn et al., 1989). The ambient illuminance level has also been shown to determine rod outer-segment phospholipid composition (Penn and Anderson, 1987), which may in turn influence rhodopsin function (e.g., Wiedmann et al., 1988).

Disk shedding may be one of the means by which phototostasis controls photon absorption capacity. However, a given level of rhodopsin does not simply determine visual sensitivity; the ERG b-wave threshold is not directly related to rhodopsin concentration (Dowling, 1987). Rats kept under dim LL with low levels of remaining visual pigment show a rise in ERG b-wave threshold that is disproportionately higher than would be expected merely on the basis of the rods' photon-catching capacity (Rapp and Williams, 1977). Thus, visual sensitivity is regulated by additional biochemical, neuronal, or humoral factors. It should be emphasized that photostasis has recently been observed in the *Limulus* eye (S. Chamberlain, personal

communication) and in albino and pigmented rabbits (M. P. White, personal communication). It will be important to demonstrate the photostatic principle in other mammals. In pigmented eyes, pupillary gating may subserve photostatic regulation within a limited time and illuminance range (a maximally constricted pupil reduces incident light by a factor of ~20).

SUPRACHIASMATIC–OCULAR DIALECTICS

SUPRACHIASMATIC–OCULAR INTERDEPENDENCE

It is tempting to hypothesize that the short-term and long-term light-induced changes of rod cell biology may modify the response of photically responsive neurons in the SCN (Groos and Meijer, 1985; Meijer et al., 1986), such as the phenomenon of hysteresis in the intensity–response curve when stimulus intensity is reduced (Meijer, 1990). This indicates that there is an aftereffect consisting of rod desensitization by increasing light intensity. The response threshold of SCN cells in anesthetized animals is high in rats (0.1–1 lux) and hamsters (1–10 lux), compared to the absolute visual threshold. The working range of these photically responsive cells is narrow, with saturation occurring 1–3 log units above threshold. Light levels above and below this range do not provide information to the SCN. This range is very similar to that for retinal DA stimulation by light (Proll et al., 1982).

Since the photically responsive SCN neurons have a small working range, they are less likely than the retina to adapt to a wide range of environmental lighting conditions. Indeed, their primary role may be this very stability. Furthermore, the absence of a circadian rhythm in responsiveness of visual SCN cells has been a puzzling observation in the search for the physiological basis of the PRC (Meijer, 1990). By contrast, with short-term and long-term photostatic adjustment, the rod characteristics are more likely to provide the substrate of the PRC to light.

OTHER PACEMAKERS IN MAMMALS, OTHER EYES IN INVERTEBRATES

The SCN can be considered the "master pacemaker" in mammals. However, certain circadian functions do persist after SCN lesioning, and this invokes other pacemakers. Although *ad libitum* feeding behavior loses circadian rhythmicity after SCN lesion, rodents successfully anticipate restricted mealtimes when food is made available on a strict daily schedule (Stephan et al., 1979a,b; Boulos et al., 1980; Aschoff et al., 1982). The rhythm of anticipatory activity free-runs for several days after release from food restriction. Pointedly, this system is not coordinated by light input, and there are probably no ocular interactions. The locus of control has yet to be identified.

The possibility that visual sensitivity is governed by an extra-SCN pacemaker is particularly provocative because the eye is an input stage for the SCN. The essence of the current dialectic is that such an oscillator exists in the retina, and is responsible for an initial, ocular processing of light information, even though this does not mean that the retinal oscillator is primary; indeed, circadian rhythms persist in blinded animals. In nonmammalian species, light-sensitive circadian functions of the pineal and retina are well established, and in invertebrates efferent influences are integral to expression of some of these rhythms (Fleissner, 1982; Barlow, 1983). In the model system of the *Bulla* eye, a circadian pacemaker resides among neurons at the base of the retina; each of these neurons is probably a self-sustaining

oscillator (Block et al., 1984). The ocular pacemakers in the two eyes are mutually coupled. Similar principles may apply to the mammalian retina. It is commonly thought that rod synthetic activity (such as inner-segment protein synthesis) and degradation (such as disk shedding) are circadian oscillatory processes. In our scenario, a dynamic interaction of ocular and central rhythmic processing is assumed: A rhythmic retina will modulate photic input to the pacemaker. Thus, in an intact animal, the ocular oscillator is an integral component of the circadian system.

SELF-SUSTAINED OSCILLATORS

For mammals, the criteria for self-sustained oscillation with pacemaker properties have been satisfied only for the SCN: Its intrinsic rhythmicity persists in constant conditions *in vitro*; it persists *in vivo* within a hypothalamic island without neural inputs (Inouye and Kawamura, 1982); it drives a wide range of distal physiological and behavioral rhythms; and fetal SCN implants reinstate rhythmicity in a lesioned animal and transfer circadian period (Meijer and Rietveld, 1989; Rusak, 1989; Vogelbaum and Menaker, 1990). By contrast, studies of the retina have satisfied only some of these criteria. Several retinal rhythms persist under constant conditions (e.g., disk shedding and autophagy, DA and melatonin synthesis, and opsin mRNA synthesis) and therefore can be considered self-sustaining. They may, however, be driven by rhythmic efferent influences that could be neural, hormonal, or thermal, and that could originate from the SCN or from other, unidentified pacemakers.

Arguments against this dependency derive from experiments with SCN-lesioned animals. The visual sensitivity rhythm, as measured psychophysically, shows a complete PRC. After SCN lesioning, which abolishes the behavioral activity rhythm, this sensitivity rhythm persists (Fig. 3), as does the rod outer-segment disk-shedding rhythm (Fig. 4). Ideally, self-sustaining ocular rhythmicity would be demonstrated using *in vitro* measurements (as by the method of Niemeyer [1981] for the perfused mammalian eye; however, the method does not permit investigation of an individual eye throughout a 24-hr cycle). Analogous experiments have long been carried out on eyes of the mollusc (*Bulla bulla*; Block et al., 1984), frog (*Xenopus laevis*; Flannery and Fisher, 1984), and goldfish (*Lepomis cyanellus*; Powers et al., 1990), and these have conclusively demonstrated self-sustaining oscillator characteristics at the levels of neurophysiological and anatomical rhythmicity.

MUTUALLY COUPLED OSCILLATORS, REGULATORY GATES

There is a recent history of controversy about single- versus dual-oscillator models of circadian organization. For the hamster, splitting of the activity pattern under dim LL provides the main evidence that there must be "dawn" and "dusk" oscillators. In the human, experimental manipulations and simulation of the sleep–wake cycle lend strong support to a model wherein a single SCN pacemaker is coupled to a relaxation oscillator, representing a postulated sleep factor solely dependent on prior wakefulness (Borbély, 1982; Daan et al., 1984, 1988).

Potential ocular–SCN interaction involves a related scenario. If the eyes and SCN both have rhythm-generating properties, they would normally be in close synchrony through mutual coupling. The rod outer-segment disk-shedding rhythm might be taken to index the period and phase of the ocular subsystem, while behavioral activity would index that of the SCN. Lesion experiments indicate that ocular rhythmicity is not merely driven by SCN

neuronal efferents. Monocular eye patch experiments demonstrate that the two eyes can uncouple. They are therefore not directly driven by the SCN, although they may be coupled by a common hormonal influence. In the rat, a recently demonstrated population of retinal ganglion cells projecting from one eye to the other may also subserve such a coupling function (Müller and Holländer, 1988). It is not known, however, how closely those rhythms in the eye are related to the ocular rhythm-generating mechanism itself.

Our scenario is derived from the two-process model of sleep regulation, in which a circadian oscillator, C_2, located in the SCN, is coupled to a relaxation oscillator S (for sleep) solely dependent on previous wakefulness; the interaction of the two determines sleep timing and duration. In the eye, we postulate an ocular circadian oscillator, C_1, which is coupled to a relaxation oscillator, R (for retina), solely dependent on prior light exposure (Fig. 5). The interaction between C_1 and R determines retinal sensitivity at a given time of day. Although the nature and locus of the ocular oscillator has not been specified, it is hypothesized to be linked to the photoreceptors. Light-elicited synthetic retinal responses (such as opsin mRNA synthesis) and degradative activity (such as disk shedding) point to a short-term process that can modulate retinal sensitivity. Additional neuronal and neurohumoral processes are likely to be involved. Long-term regulation of light sensitivity may be provided by photostasis. Taken together, the baseline level of the circadian rhythm of visual sensitivity is determined by the retina's history of exposure to light. In this way, the local ocular system (C_1/R) would actively gate light input to the SCN (C_2), as well as provide it with a phase-shifting signal. For example, in a DD free-run, during which rods would be extremely sensitive, a single light pulse is sufficient to phase-shift the circadian system. Under LL conditions of increasing intensity, the phase shift is reduced in magnitude, indicating decreased

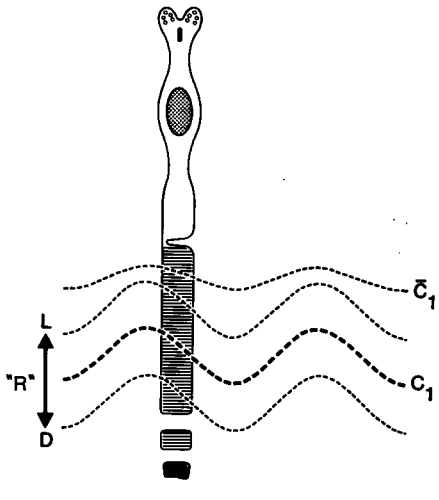


FIGURE 5. Two-process model of retinal rhythmicity. An ocular circadian oscillator (C_1) of unknown locus—but hypothetically residing in the photoreceptors—provides a threshold gate for a relaxation oscillator ("R," for retina, also hypothetically located in the photoreceptors). R is dependent on prior light exposure. Rod outer-segment disk shedding occurs at the intersection of R and C_1. As light levels increase, rods shorten and the C_1 threshold increases. Darkness decreases this threshold. The length, rhodopsin content, and sensitivity of the rod outer segment determine photon absorption capacity, as well as the magnitude of the light signal reaching the second retinal neuron and the SCN. C_1 is construed as mutually coupled with C_2, the circadian pacemaker of the SCN, and R is hypothesized to adjust the magnitude of photic transduction to the small working range of photically responsive neurons in the SCN and LGN. Under conditions of photoreceptor damage by high-intensity light, C_1 may be dampened—or even abolished ($\bar{C}_1$). The photoreceptor is drawn facing downward, because the rising C_1 threshold is intended to parallel the shortening of the outer segment.

retinal sensitivity to light pulses of constant intensity (Nelson and Takahashi, 1990). In this framework, the primary phase-shifting mechanism is ocular, and the SCN phase shift is secondary. This does not mean that the primary oscillatory driver for the organism as a whole is in the eye, however, as is obvious from experiments with blinded animals that show clear and persistent circadian rhythmicity.

The unaltered visual sensitivity and disk-shedding rhythms in SCN lesion experiments support the concept of a local oscillatory process in the mammalian eye, but do not explain it. Although we had long considered the rhythm of disk shedding to be a likely candidate for a "hand of the ocular clock," its characteristics also resemble some aspects of a light-dependent "Process R" interacting with the circadian oscillator C_1. It is tempting to attribute the neurochemical role of light and dark transduction to DA and melatonin, respectively, given that inhibition or stimulation of these factors modifies disk shedding. Whether they can thus be invoked as intrinsic to the C_1 oscillator, or as modifiers of "Process R," is an experimental issue.

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