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EFFERENT CONTROL OF CIRCADIAN RHYTHMS IN THE *LIMULUS* LATERAL EYE

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In many animals the retina and the brain form a two-way communication system. In addition to the retina transmitting visual information to the brain, the brain feeds back signals that modulate the function of the retina. The brain's input to the retina can modify the configuration of ganglion-cell receptive fields (1,2), adapt the retina to changes in ambient illumination (3-8), or control metabolic processes in the retina (9-11). In most of these cases the efferent input to the retina is controlled by a circadian clock located in the brain.

The visual system of the horseshoe crab, *Limulus polyphemus*, provides a clear example of the brain's modulation of retinal function (4). At night a circadian clock in the brain generates neural activity that is transmitted via efferent optic nerve fibers to all major photoreceptor organs of the animal (12). Research in our laboratory has focused mainly on the effects of the clock's input to the lateral compound eyes.

Table I

Circadian Rhythms in the *Limulus* Retina

Retinal Property	Day	Night
Efferent input	absent	present
Gain	low	high
Noise	high	low
Frequency response	fast	slow
Photon catch	low	high
Aperture	constricted	dilated
Acceptance angle	6°	13°
Cell position	proximal	distal
Pigment granules	clustered	dispersed
Membrane turnover	trigger	prime
Lateral inhibition	strong	weak

Table I lists the circadian rhythms we have detected in the *Limulus* lateral eye. The first one, the efferent input, mediates all the others. The efferent input is generated by the clock at dusk, remains high during the night, and stops at dawn (5). No efferent activity is generated during the day. All except one of the retinal changes in Table I are endogenous; they continue unabated when the animal is maintained under constant environmental and photic conditions. The one exception is the metabolic event of membrane turnover, which is primed by efferent input but is triggered by the first light of dawn (9,10). Although membrane turnover is characteristic of all photoreceptors, its precise role in vision is not fully understood. All the remaining circadian changes in Table I

combine to increase visual sensitivity at night.

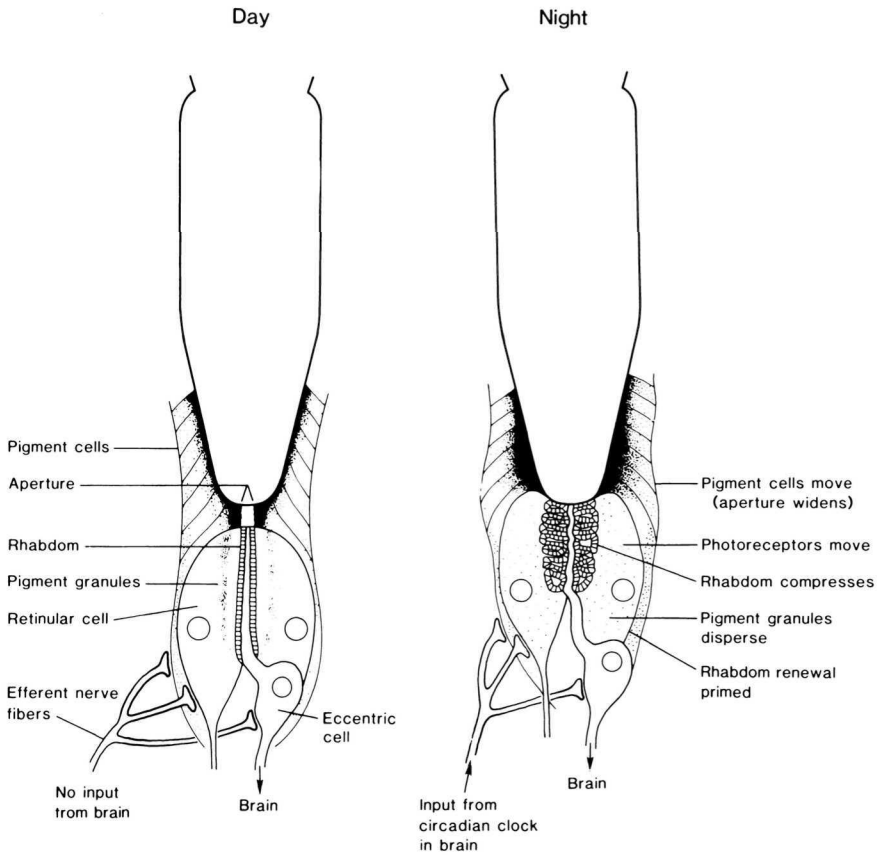

Fig. 1. Circadian changes in the structure of *Limulus* ommatidia. The longitudinal reconstructions are based on micrographs of serial cross sections of dark-adapted ommatidia fixed *in situ* during the day and at night. The reconstruction on the left shows the morphological components of the ommatidium in the daytime state. The schematic efferent nerve terminals are included to show that each cell type receives synaptic input from the circadian clock (38). Taken from refs. 14 and 18.

CIRCADIAN RHYTHM IN RETINAL STRUCTURE

Figure 1 summarizes the structural changes in the retina produced by the circadian clock (13,14). These anatomical reconstructions show that an ommatidium in the lateral eye is composed of 8 to 12 retinular cells tightly clustered around the dendrite of an eccentric cell. Light collected by the corneal lens passes through an aperture formed by surrounding pigment cells and enters the rhodopsin containing rhadom of the retinular cells.

During the day, the aperture (17 μm diameter) restricts the light entering the retinular cells and

small pigment granules are concentrated in the cytoplasm of the retinular cells forming a circular band near the edge of the rhabdom. At night the efferent input moves the pigment cells laterally, increasing the aperture diameter to 60 μm. The efferent input also moves the retinular cells distally within a few microns of the cornea and compresses the rhabdom against the base of the lens, causing deep folds in the rhabdom rays and bends in the distal portion of the eccentric cell dendrite. In addition, the pigment granules in the retinular cells disperse. All structural changes in Fig. 1 continue in complete darkness, following the circadian rhythm of efferent optic nerve activity.

The circadian changes in retinal structure increase the acceptance angle and quantum catch of single ommatidia (14). Measurements were made of the threshold of the optic nerve discharge to brief flashes from an array of fiber-optic light pipes attached to the arm of a vernier protractor located at various angular positions along the anteroposterior axis of the eye. The acceptance angle (width of field of view at half maximum) increased from 6° during the day to 13° at night. Acceptance angles were calculated for both states of the eye utilizing a computer ray tracing program that models the refractive properties of the corneal lens (15,16). The computed angle for the nighttime state closely matches the experimental values of 13°, but that for the daytime state is less than the measured value of 6°. The discrepancy may result from light scatter by inhomogeneties within the optical apparatus of the eye.

The wider field of view at night increases the quantum catch of ommatidia. Computations based on precise measurements of the optical parameters of ommatidia yield an increase in quantum catch of 0.8 log units (17) which is less than the quantum catch increase deduced from physiological measurements as described below. The discrepancy is not understood. The wider field of view at night also reduces spatial resolution. Since the nighttime acceptance angle of 13° is about twice the angle separating the optic axes of adjacent ommatidia, the fields of view of adjacent ommatidia overlap considerably (18).Thus under control of a circadian clock, the *Limulus* eye exchanges daytime acuity for high quantum catch at night.

In sum, five of the properties in Table I--photon catch, aperture, acceptance angle, cell and pigment granule position--exhibit circadian rhythms related to changes in retinal structure.

CIRCADIAN RHYTHM IN RETINAL PHYSIOLOGY

Electroretinogram

Figure 2 gives the electroretinograms (ERGs) recorded over a three-day period from the *Limulus* lateral eye *in situ* while the animal remained in the dark. The animal had been maintained in a natural light-dark cycle before the experiment. On day 1 the amplitude of the ERG began to increase at 3:30 P.M., reached a maximum level at 6 P.M., remained high until 2:30 A.M., and then began to decrease to a low daytime level. This cycle was continued on days 2 and 3 with a period of 24.8 hr. After two weeks in darkness (data not shown), the rhythm had drifted completely out of phase with the solar day. Experiments with other animals show that the endogenous rhythm persists without noticeable attenuation for periods up to one year in darkness (5).

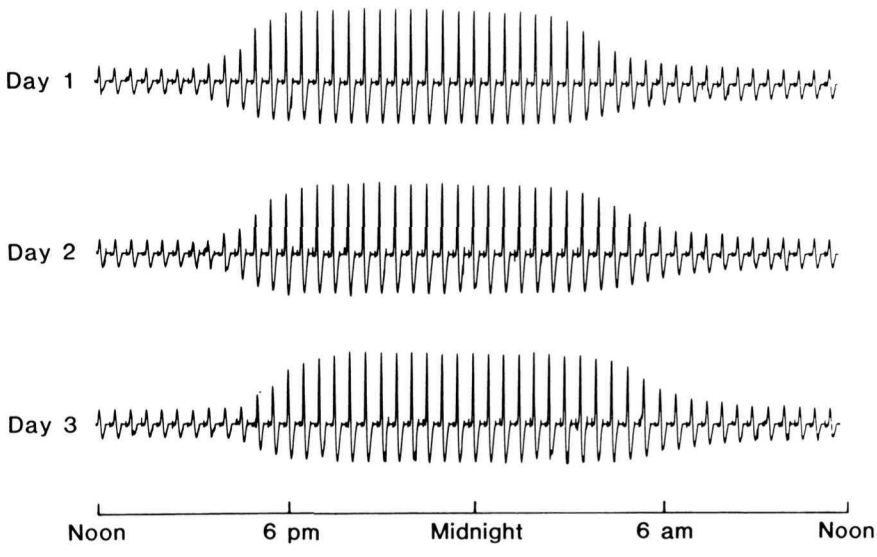

Fig. 2. Circadian rhythm in the amplitude of the ERG of the lateral eye. This continuous three-day chart recording began at noon of day 1 when the recorder was gated on for 700 msec during which time a 100-msec flash was presented to the eye. The sequence was repeated every 30 min for three days with the test flash intensity held constant at 10^6 photons/flash incident on a single ommatidium. The peak-do-peak amplitude during the first night was 210 μV.

The circadian changes in visual sensitivity that correspond to the changes in ERG amplitude in Fig. 2 can be determined from the intensity-response function in Fig. 3. The "day" data were recorded at noon and the "night" data were recorded at midnight. Both sets of data were fitted by the same curve shifted 1.3 log units on the abscissa and 0.1 log unit on the ordinate. A major portion of the increased sensitivity at night to brief flashes causes a lateral shift of the intensitry-response function.

At low levels of illumination (log I = -4 to -7), the amplitude of the ERG is directly proportional to the light intensity and thus we can use changes in response amplitude as a measure of changes in sensitivity. The nighttime increase in ERG amplitude from 3 μV to 60 μV at log I = -5 corresponds to a twenty-fold increase in the sensitivity of the lateral eye. Other experiments have yielded up to 100-fold increases in sensitivity. The lateral shift of the intensity-response function in Fig. 3 is consistent with the idea that the nighttime increase in ERG sensitivity results primarily from structural changes that increase the quantum catch of photoreceptors (see Fig. 1).

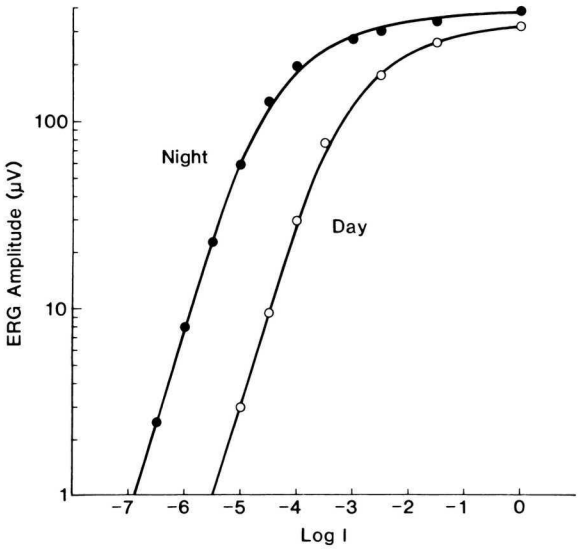

Fig. 3. Intensity-response functions for the ERG at night and during the day. Plotted on a log scale on the ordinate is the ERG amplitude as a function of log light intensity plotted on the abscissa. Data were taken from the experiment in Fig. 2. Both sets of measurements were carried out with the eye in the dark-adapted state. The light intensity on a single ommatidium at log I = 0 was estimated to be about 3×10^{10} photons/flash. Taken from ref. 5.

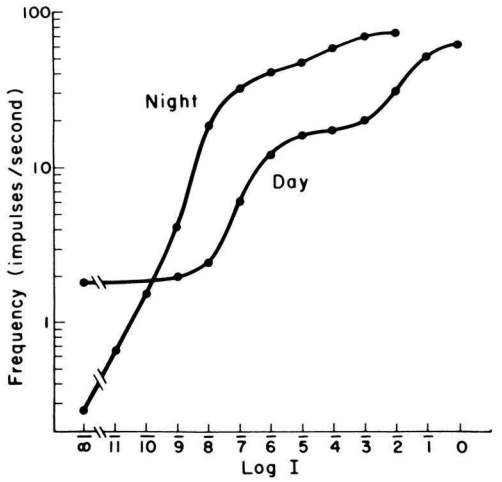

Fig. 4. Intensity-response functions for the optic nerve discharge at night and during the day. The mean firing rate of the single optic nerve fiber during the last 3 seconds of a 6-second flash is plotted on the ordinate as a function of log-light intensity plotted on the abscissa. The animal remained in darkness throughout the experiment and all measurements were made with the retina in the dark-adapted state. The light intensity incident on the single ommatidium at log I = 0 was approximately 10^{12} photons/s from 400 to 650 nm. Taken from ref. 4.

Optic Nerve Response

Figure 4 gives the daytime and nighttime intensity-response functions for the steady-state firing rate of a single optic nerve fiber. The spike discharge was recorded *in situ* without impairing the transmission of efferent activity from the brain to the eye. The recorded ommatidium was optically isolated with a fiber-optic light pipe (19) to minimize any lateral inhibitory influences from neighboring receptors.

During the day, the optic nerve discharge exhibited a high spontaneous rate (around 2 impulses/s), a threshold of about log I = -9, and a graded response over a 9 log-unit range with a distinct plateau at intermediate intensities. These characteristics closely match those recorded from a single fiber *in situ* with the optic nerve cut (20,21). At night the same fiber exhibited a low spontaneous rate (around 0.2 impulses/s), a threshold below log I = -11, and a graded response over at least a 9 log-unit range with no pronounced plateau. These data show that the efferent input from the circadian clock reduces the spontaneous optic nerve discharge and significantly changes the intensity coding characteristics of the optic nerve response.

The intensity-response functions and their circadian changes (Figs. 3 and 4) differ significantly for the ERG and the optic nerve discharge. As indicated above, the lateral shift in the ERG function at night can be attributed to an increase in quantum catch caused by circadian changes in retinal structure (Fig. 1).

However, an increase in quantum catch cannot completely account for the nighttime change in the shape of the optic nerve function. It is apparent that the daytime intensity-response function must be shifted vertically as well as laterally. A vertical shift corresponds to an increase in retinal gain, that is, an increase in the retinal response/absorbed photon. As discussed below (see Fig. 6), the nighttime increase in retinal gain may not be uniform throughout the range of light intensities used in these experiments.

The differences in the shapes of the intensity-response functions in Figs. 3 and 4 are in part related to the differences in the retinal responses being measured. The ERG, as recorded with an AC-coupled amplifier, is a transient potential generated by the simultaneous depolarization of the approximately 10,000 photoreceptors (retinular) cells in the *Limulus* eye in response to a brief flash of light. The optic nerve response in Fig. 4 is the steady-state discharge measured near the end of a long duration flash. It may be more appropriate to compare the characteristics of the ERG response with those of the transient discharge of the optic nerve response occurring at the onset of the light flash. Indeed, the shapes of the intensity-response function of the transient discharge both day and night (data not shown here) closely match those of the ERG shown in Fig. 3.

The decrease in threshold at night for eliciting steady-state optic nerve response in Fig. 4 is about 2 log units, which is similar to the threshold decrease for the ERG responses in Fig. 3. However, the circadian change in the shape of the optic nerve function yields much greater increases in sensitivity for suprathreshold stimuli. For example, the nighttime increase in sensitivity in Fig. 4 for a steady discharge rate of 20 impulses/s is 100,000.

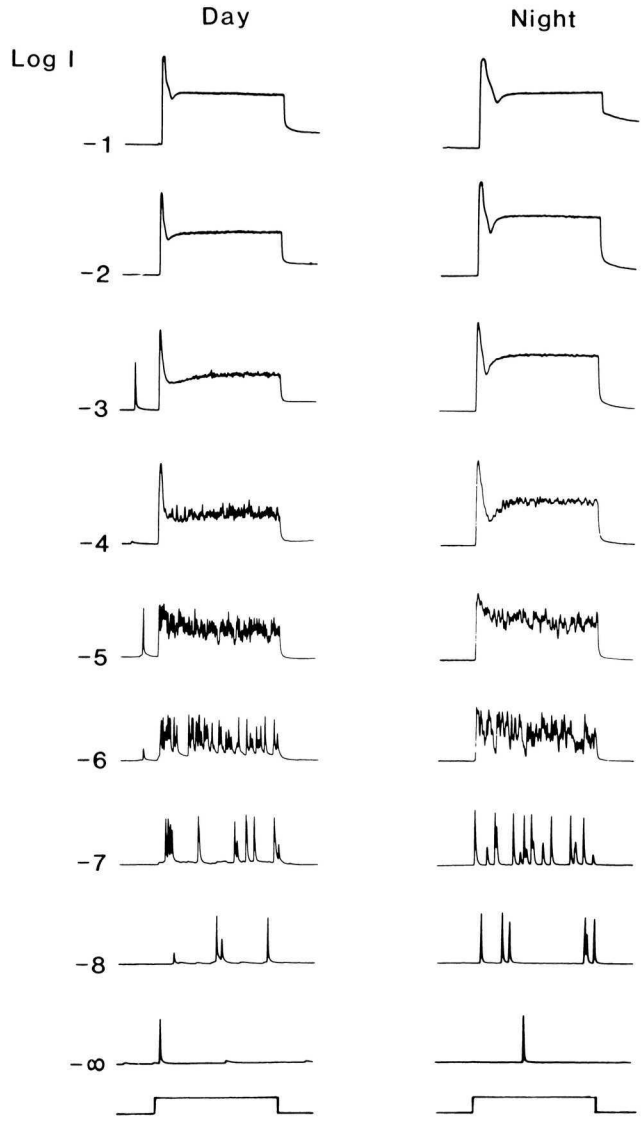

Fig. 5. Photoreceptor potentials recorded with a glass microelectrode from a single dark-adapted retinular cell *in situ* during the day and at night. Note that the daytime responses were occasionally preceded by spontaneously occurring quantum bumps, both SPFs and LPFs. Also, five spontaneous bumps can be detected in the dark trace (log I = -∝) during the day but only one at night. Amplitude of the LPF in the dark trace at night is 32 mV. The efferent input to the retina reduce photoreceptor noise and increases photoreceptor response. Refer to Fig. 4 for the light calibration. Resting potential -58 mV. Flash duration 10 s.

Photoreceptor Response

The brain's input to the retina acts at an early stage in the process of visual excitation (22,23). Figure 5 shows records of the membrane potential of a single, dark-adapted photoreceptor *in situ*. The recording from the same cell was maintained for more than 45 hours while the animal remained in darkness. At each level of illumination the nighttime responses are larger than the daytime responses. All responses at dim levels of illumination (log I = -7 and -8) are comprised of two components: small potential fluctuations, SPFs (≤15 mV) and large potential fluctuations, LPFs (≅ 30 mV). SPFs are the well-known quantum bumps that can be elicited by single photon absorptions in the retinular cell (24). LPFs appear to be regenerative events triggered by SPFs that enable single photon events to fire off nerve impulses in the eccentric cell (25,26). At intermediate light intensities, the LPFs andSPFs begin to merge together, producing a response of fluctuating potentials superimposed on a small constant depolarization. At high intensities, the fluctuations are reduced and the receptor potential is characterized by a large initial transient depolarization which decays to a relatively smooth steady-state response.

If the clock's action on the retina were only to increase the quantum catch at night, then it should be possible to record photoreceptor potentials at night that matched the shape and amplitude of those recorded during the day at higher intensities. Such matches can be found for responses to dim flashes (log I = -8 to -6) but not for intermediate and bright flashes (log I = -5 to -l). In this intensity range no night responses can be found that have the same amplitude and shape of the initial transient depolarization and the same steady-state level of depolarization as daytime responses. Apparently response linearity exists only at low light intensities. This point is further examined with the intensity-response characteristic.

Figure 6 gives the daytime and nighttime intensity-response functions for the steady-state portions of the photoreceptor responses shown in Fig. 5. Comparing the shapes of the intensity-response functions in Figs. 3, 4, and 6 reveals a similarity between those for the steady-state optic nerve firing rate (Fig. 4) and photoreceptor potential (Fig. 6). This is understandable since the ionic currents that give rise to the photoreceptor potential are passively conducted from the retinular cells to the eccentric cell where they form the generator potential for spike initiation. The more pronounced plateau region for optic nerve responses during the day in Fig. 4 may reflect characteristics of the spike firing mechanism. Barlow and Kaplan (25) found that the voltage-to-spike conversion factor for the daytime state was 1.0 impulses/s/mV for generator potentials below 15 mV and increased sharply for potentials above 15-20 mV. Recent measurements confirm this result and show that the conversion factor does not change with time of day (23). As a consequence, the intensity-response functions at levels of illumination that evoke generator potentials above 15 mV have greater slopes for optic nerve responses (Fig. 4) than for photoreceptor responses (Fig. 6).

What cellular mechanisms underlie the nighttime increase in photoreceptor sensitivity? Increases in photon catch can account for up to 100-fold increases in sensitivity. Such increases shift the intensity-response to the left (Fig. 3). What contribution is made by increases in photoreceptor

gain? No change in gain is evident in the amplitude of quantum bumps recorded at night; however small circadian changes have been detected in the shape of the quantum bumps (23). Recordings of optic nerve responses at the onset of efferent activity indicate that the clock's input causes rapid increases in discharge rate at intermediate light intensities without changing those recorded at low light levels (R. Barlow, unpublished observations). This result, together with that discussed earlier showing a lack of superimposition of responses at intermediate intensities, suggests that the clock first increases the gain of photoreceptors at intermediate and high light intensities and later increases quantum catch. As discussed below, the initial effect of the clock's input may be to modulate a voltage-dependent gain in lateral-eye photoreceptors (27) similar to that detected by Pepose and Lisman (28) in ventral photoreceptors.

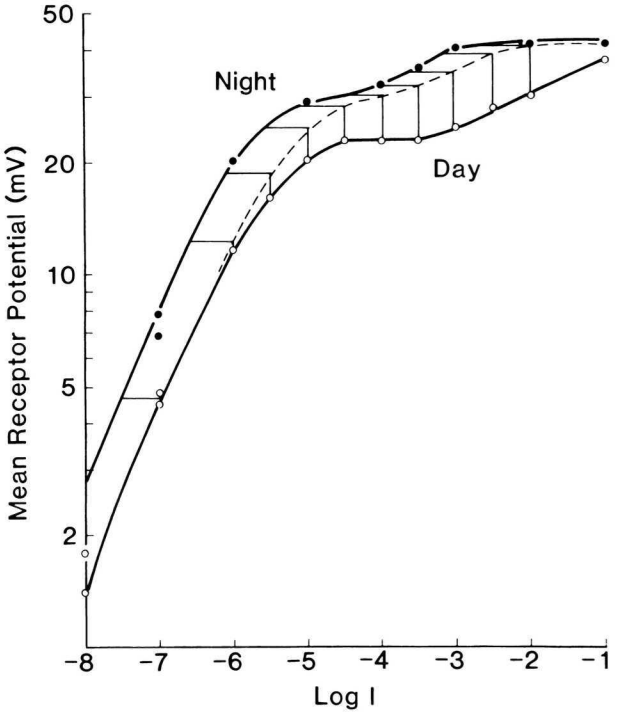

Fig. 6. Intensity-response functions for the photoreceptor potentials shown in Fig. 5. The mean receptor potential for the last 5 seconds of a 10-second flash is plotted on the ordinate as a function of log-light intensity plotted on the abscissa. All measurements were made with the cell in the dark-adapted state. The possible effects of a decrease in voltage-sensitive gain mechanism and an increase in photon catch are indicated by the vertical and horizontal line segments (see text). Taken from ref. 23

Figure 6 models the possible effects of a voltage-sensitive gain mechanism on the intensity-response function. We assume that the nighttime increase in the receptor potential at low

light levels results only from an increase in photon catch causing a left shift of the response function of about 0.6 log units. Shifting the entire nighttime function to the right by 0.6 log units (dashed line) compensates for the change in photon catch. The difference between the dashed line and the daytime response function indicates the possible effects of a voltage-sensitive gain mechanism (vertical line segments).

Voltage-sensitive potassium channels have been detected by Pepose and Lisman (28) in *Limulus* ventral photoreceptors which are physiologically similar to retinular cells of the lateral eye (26). Such voltage-sensitive channels may serve to light adapt photoreceptor cells by counteracting large changes in membrane potential generated by large increases in sodium conductance in bright light. Pepose and Lisman suggest that the potassium channels may act to compress a large range of incident light intensities into a small range of receptor response. Such a light adaptation mechanism may prove useful during the day when ambient intensities cover wide ranges. But at night the ambient intensity is low and response compression may not be necessary. Consistent with our results is the possibility that the efferent input reduces the effectiveness of voltage-sensitive potassium channels in photoreceptors at night and thereby increases their gain. Other ionic channels as well as other cellular mechanisms may also be involved.

EFFERENT OPTIC NERVE ACTIVITY MEDIATES THE CIRCADIAN RHYTHMS IN THE *LIMULUS* RETINA

Circadian rhythms in the structure of the *Limulus* retina (Fig. 1) are abolished by cutting the optic nerve (14). Shocking the distal end of the cut optic nerve to mimic the efferent input converts retinal structure from the daytime to the nighttime state (see Fig. 1 and Table I). We therefore conclude that efferent fibers in the optic nerve mediate the circadian rhythms in the morphology of the lateral eye.

Circadian rhythms in the physiology of the retina are also blocked by cutting the optic nerve and restored by shocking it (4, 5). Specifically, shocking the optic nerve during the day shifts the intensity-response functions in Figs. 3, 4, and 6 to the nighttime state. Thus we can also conclude that efferent fibers mediate the circadian rhythms in retinal physiology.

Figure 7 shows the effect of cutting the optic nerve at night on the membrane potential of an eccentric cell. At 9:30 P.M. the intracellular recording exhibited characteristics of the nighttime state: low noise in the dark and high response to a dim stimulus. At 9:40 P.M. the optic nerve was cut without disturbing the recordings or state of dark adaptation of the retina. By 10:00 P.M. the recording began to exhibit characteristics of the daytime state: spontaneous quantum bumps in the dark and lowered response to dim light. An hour later at 11:00 P.M. the decay of the eye to the daytime state was complete. Note that the high rate of spontaneous bumps in the dark combined with low light sensitivity almost obscured the dim light response.

Figure 8 shows the effect of shocking the optic nerve during the day on the membrane potential of a retinular cell and on the ERG amplitude. The records at 2:30 P.M. are characteristic of the dark-adapted daytime state: frequent quantum bumps in the dark and small response to dim light. At 2:32 P.M. current pulses were delivered to the distal end of the cut optic nerve at the rate of 4/s

for 30s every minute, a regime which simulated the endogenous efferent input to the retina (4). By 4:30 P.M. the photoreceptor potential exhibited all the characteristics of the nighttime state: reduction of dark noise and large amplitude response for both the receptor potential and ERG. Turning off the optic nerve shock at 4:30 P.M. allowed the retina to return to the daytime state (6:30 P.M.) and remain in that state until the recording was lost at 8:45 P.M.

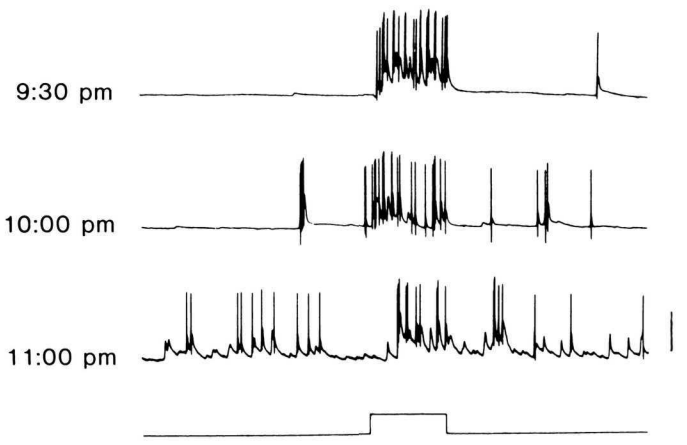

Fig. 7. Effect of cutting the optic nerve on the membrane potential recorded from an eccentric cell *in situ*. After the nerve was cut at 9:40 P.M., the characteristics of the membrane potential began to return to the daytime state. By 11:00 P.M. the cell's properties were indistinguishable from the daytime state (data not shown). Flash duration 4 s. Vertical bar 10 mV. Taken from ref. 23.

OTHER CIRCADIAN RHYTHMS IN THE LATERAL EYE

Three of the circadian rhythms in Table I--frequency response, membrane turnover, and lateral inhibition--have not yet been addressed in this paper. Briefly, the frequency response of the firing rate of single optic nerve fibers peaks at higher frequencies and exhibits a higher cutoff during the day than at night (29). The frequency response characteristics are controlled by the efferent input and are thought to originate in the photoreceptor cell.

The efferent input also controls the daily turnover of the rhabdom membrane in the retinular cells (9,10). The photosensitive structures are broken down and rebuilt at the first light of dawn each day--a process that is complete within 30 minutes of light onset. Blocking the efferent input blocks turnover and mimicking the efferent input restores it. Light triggers the turnover process, but the efferent input from the clock primes the process. Finally, lateral inhibitory interactions exerted among neighboring retinal receptors are also under efferent control (30). The clock's input to the retina reduces the strength of the inhibitory interactions without significantly changing the configuration of the inhibitory field. As a consequence, the Mach-band response patterns generated by step patterns of illumination of the retina are shifted to higher response levels without changing the shape or width of the Mach bands.

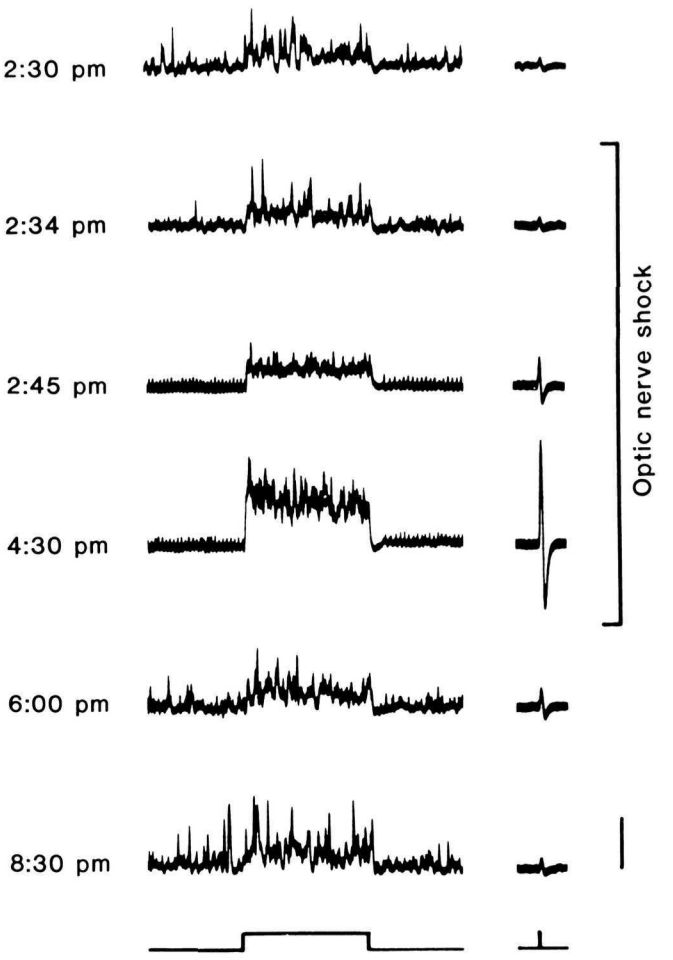

Fig. 8. Effect of optic nerve shock on the membrane potential recorded from a retinular cell *in situ*. At 2:34 P.M. two minutes after shock onset, the photoreceptor potential began to exhibit the characteristics of the nighttime state. By 4:30 P.M. the transfer to the nighttime state was complete as indicated by both the intracellular recording and the ERG. Turning the shock off at 4:30 P.M. allowed the photoreceptor to return to the daytime state. Taken from ref. 22.

In summary, all ten circadian rhythms in Table I are controlled by the efferent input from a clock located in the animal's brain. The multiple physiological and anatomical effects occur without detectable changes in the membrane potential or membrane resistance of retinal cells (22).

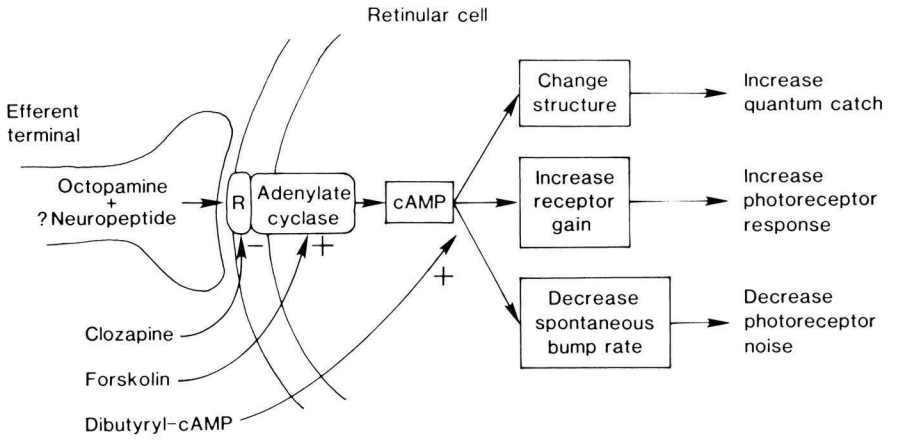

Fig. 9. Proposed scheme for neurochemistry of efferent effects.

NEUROTRANSMISSION OF THE CIRCADIAN RHYTHMS

What neurotransmitter is capable of mediating all the retinal rhythms listed in Table I? A wide variety of candidates has been tested, but only octopamine satisfies all five criteria for a neurotransmitter: synthesis, localization, release (31,32), physiological mimicry, and pharmacological blockade (33,34,35). Although octopamine injected in the eye during the day changes its characteristics toward the nighttime state, the changes were never complete. It is possible that our method of injection does not adequately mimic the endogenous neurotransmitter mechanism or that octopamine does not act alone. Preliminary experiments with extracts from the *Limulus* brain suggest that a second neurotransmitter, a neuropeptide, may also be involved.

Both Forskolin and cAMP analogs increase retinal sensitivity and change retinal structure when injected during the day. Forskolin, which activates adenylate cyclase, is very effective in mimicking the clock's action on the retina. cAMP analogs are less effective. It appears that efferent neurotransmission in the *Limulus* retina may be yet another example of cAMP serving as an intracellular second messenger (36,37).

Figure 9 presents a proposed scheme for the neurochemistry of specific circadian changes in retinular cells. We have not as yet tested the effects of octopamine, cAMP analogs, or Forskolin on the other circadian rhythms listed in Table I.

ACKNOWLEDGEMENTS

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