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CHAPTER 35

Circadian and efferent modulation of visual sensitivity

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Introduction

Animals adapt their visual sensitivity by responding to changes in ambient lighting and, in many cases, anticipating them. Studies by John Dowling, his students and colleagues have contributed significantly toward understanding how light-dependent as well as endogenous circadian and efferent mechanisms modulate the sensitivity of the retina.

Cajal (1892) first identified efferent inputs to the vertebrate retina at the end of the last century. In 1966 Dowling and Cowan showed that the centrifugal fibers entering the bird retina terminate on cell bodies of the inner nuclear layer. Dowling and Ehinger (1975) then showed that a recently detected interretinal cell, the interplexiform cell, carries information from the inner to the outer plexiform layers of fish and primate. Zucker and Dowling (1987) later found that the centrifugal fibers entering the fish retina terminate on the interplexiform cells. With these studies John Dowling and his colleagues uncovered a curious property of the fish visual system: a centrifugal input from the brain terminates on a second centrifugal pathway in the retina. They further showed that the second centrifugal component, the interplexiform cell, contains dopamine, and that dopamine strongly modulates the circuitry of the outer retina (Lasater and Dowling, 1985; Mangel and Dowling, 1985; Dowling, 1991). Centrifugal innervation and dopamine appear to be related in another teleost, the zebrafish where a dominant mutation in zebrafish, *night blindness b*, raises visual thresholds in prolonged darkness, disrupts the centrifugal innervation to the retina, and reduces the number of retinal dopaminergic interplexiform cells (Li and Dowling, 2000a). These studies from John's laboratory have uncovered intriguing properties of the brain's efferent input to the retina in some species, but how they influence visual sensitivity is not clear.

Recently John Dowling and his colleagues turned their attention towards the circadian modulation of visual function. Using a behavioral paradigm, Li and Dowling (1998) found that a circadian clock decreases the visual sensitivity of zebrafish rather than increases it as has been found in most other animals. They then showed that dopamine, which they had already coupled with the centrifugal input to the retina, appears to mediate the effect of the circadian clock on visual sensitivity of the fish retina (Li and Dowling, 2000b). In addition to pioneering studies on light-triggered mechanisms of retinal adaptation, John Dowling and colleagues have provided important insights about how circadian and efferent mechanisms may modulate visual sensitivity. Taken together, their studies underscore the variety of physiological processes that have evolved to modulate the function of the visual system.

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In this chapter I review the range of circadian rhythms detected in various visual systems, focus on a few of them and consider the modulation of retinal sensitivity by efferent signals from the brain. As noted above much has been learned from research on fish, the primary animal model in John Dowling's laboratory. I will present the results of research carried out in my laboratory on two other animal models: an invertebrate, the horseshoe crab *Limulus polyphemus*, and a vertebrate, the Japanese quail *Coturnix coturnix japonica*. I will also mention briefly preliminary results from studies of *Xenopus laevis* and humans.

Circadian rhythms characterize most visual systems

Circadian oscillators are intimately related with the visual systems of most, if not all, animals. Entrained by visual inputs, the oscillators modulate the function of the visual system at the level of the retina and higher pathways. The range of properties that exhibit circadian changes is truly remarkable. Table 1 list those detected in vertebrates and Table 2 gives those found in the well-studied invertebrate, *Limulus* (review of other invertebrates: Barlow et al., 1989). They extend from changes in photoreceptors, the most distal cells in the visual system, to more proximal levels both in the retina and in higher visual centers. A number of species share circadian rhythms such as the daily the synthesis of rhodopsin (toad, fish and mouse) the shedding of rod disc membranes (frogs and rats), and cone disc membranes (chicks and squirrels). Interestingly in *Limulus*, a circadian oscillator controls the priming of the processes that shed rhodopsin-containing membrane (rhabdom) but not the shedding event itself. Important to this chapter is that the synthesis of two ubiquitous neuromodulators, dopamine and melatonin, undergo circadian rhythms in many vertebrate retinas. Most important is that the output of the visual system—behavior—undergoes circadian changes in *Limulus*, fish and mammals. How circadian changes at various levels of the visual system influence behavior is not known.

Where are the circadian oscillators that affect the visual system located? Those that modulate retinal function can be located either in the brain as in *Limulus* (Barlow et al., 1977; Calman and Battelle, 1991) or in the retina itself as in quail (Underwood et al., 1988) and hamster (Tosini and Menaker, 1996). In *Xenopus* circadian oscillators are located in the photoreceptors themselves (Cahill and Besharse, 1993).

Circadian rhythms in the sensitivity of the *Limulus* lateral eye

A clear example of the circadian modulation of the visual system is the horseshoe crab, *Limulus*. At dusk a circadian oscillator in the brain transmits efferent optic-nerve activity to the lateral eyes influencing most every physiological and anatomical property of the retina (Table 2). The endogenous rhythms of the retina combine with mechanisms of light and dark adaptation to increase visual sensitivity by $\sim 10^6$ from day to night nearly compensating for the shift in the intensity of ambient illumination after sunset.

The centrally located clock increases visual sensitivity primarily by acting on the most distal cell of the visual system, the photoreceptor. Efferent optic nerve fibers from the circadian clock terminate on individual photoreceptor cells. At night efferent signals carried by the fibers change the "noise", gain and photon catch of single cells which in turn changes their intensity coding properties. At night a single photoreceptor cell recorded over a two-day period from an unanesthetized *Limulus* in darkness (Fig. 1, left) reveals an increase in its receptor potential evoked by a test flash ("signal") and a decrease in the rate of quantum bumps generated in the absence of light ("noise"). During the day, its "signal" declined and "noise" increased. These circadian changes in activity are transmitted to the second-order eccentric cell of an ommatidium. Their effects on retinal sensitivity can be studied by recording the output of a single optic nerve fiber (Fig. 1, right). First, the intensity–response function of the discharge of a single optic nerve fiber was measured with the ommatidium in its natural daytime state, i.e. adapted to a background intensity equal to that measured in the animal's underwater environment during the day (Log I = − 2). The monotonically shaped intensity–response function (unfilled circles) encoded a range of ~4 log units of light intensity. Then the animal was

Table 1. Circadian rhythms in the vertebrate visual system

	Time	Animal
Anatomy		
Rod: disc shedding	day	rat (LaVail, 1976, Tierstein et al., 1980), *Xenopus*(Pierce and Besharse, 1986)
myoid contraction	night	fish (Levinson and Burnside, 1981)
Cone: disc shedding	night	squirrel (Young, 1967), chick (Young, 1978)
myoid contraction	day	fish (Levinson and Burnside, 1981), *Xenopus* (Pierce and Besharse, 1985)
synaptic ribbon increase	day	fish (Kohler et al., 1990), newt (Wulle et al., 1990)
RPE pigment migration	day	fish (Kohler et al., 1990), *Xenopus* (Pierce and Besharse, 1985)
Horizontal-cell spinule formation	day	fish (Weiler et al., 1988; Douglas and Wagner, 1983)
Corneal epithelium thickness increase	night	quail (Oishi and Matsumoto, 1985), human (Fujita, 1980)
Metabolism		
Rod opsin synthesis	day	toad and fish (Korenbrot and Fernald, 1989), mouse (vonSchantz et al., 1999)
Cone opsin synthesis	night	chick (Pierce et al., 1993; vonSchantz et al., 1999)
Retinal dopamine synthesis	day	rat (Wirz-Justice et al., 1984), fish (Wulle et al., 1990), quail (Manglapus et al., 1999)
Retinal melatonin synthesis	night	*Xenopus* (Cahill and Besharse, 1990), birds (Zawilska and Iuvone, 1992; Underwood et al., 1988; Thomas and Iuvone, 1991; Manglapus et al., 1999), hamster (Tosini and Menaker, 1996)
Retinal tryptophan hydroxylase synthesis	night	*Xenopus* (Green et al., 1995) and chicken (Chong et al., 1998)
Retinal tyrosine hydroxylase activity increase	day	fish (McCormack and Burnside, 1993)
Retinal serotonin NAT activity increase	night	chicken (Hamm and Menaker, 1980), *Xenopus* (Besharse and Iuvone, 1983)
Physiology		
Cone dominance of ERG b-wave	day	quail (Manglapus et al., 1998), pigeon (Barattini et al., 1981)
Rod dominance of cone H-cell response	night	fish (Mangel and Wang, 1996)
ERG b-wave increase	night	rabbit (Brandenburg et al., 1983; Manglapus et al., 1998)
	day	zebrafish (Li and Dowling, 1998), lizard (Fowlkes et al., 1984), *Xenopus* (Barlow et al., 2000)
Electro-oculogram increase	day	human (Anderson and Purple, 1980)
Lateral geniculate nucleus response increase	night	rat (Hanada and Kawamura, 1984)
Visually-evoked cortical potential increase	night	rabbit (Bobbert et al., 1978)
Intraocular pressure increase	night	human (Boyd and McLeold, 1964), rabbit (Katz et al., 1975)
Behavior		
Visual sensitivity increase	night	rat (Rosenwasser et al., 1979; Reme et al., 1991), goldfish (Bassi and Powers, 1987)
	day	zebrafish (Li and Dowling, 1998), human (Bassi and Powers, 1987; Barlow et al., 1997)

dark adapted during the day and the I-R function was remeasured. It acquired a nonmonotonic shape (dashed curve) revealing a second encoding mechanism (Kaplan and Barlow, 1975) that increased sensitivity by ~4 log units to the lower range of light intensities. Dark adapting the eye also caused spontaneous optic nerve spiking (~0.6 ips) in the dark (Log $I = -\infty$). The animal remained in darkness until the clock shifted the eye into its nighttime state and a third I-R function was measured (filled circles). Its monotonic shape "Night" function reveals a remarkable increase in gain (impulses/s/photon) at low light intensities and a decrease in spontaneous spiking activity in the dark (Barlow and Kaplan, 1993). The clock's circadian input combined with dark adaptation to shift the

Table 2. Circadian rhythms in the *Limulus* lateral eye

Retinal property	Day	Night	Reference
Efferent input	absent	present	Barlow et al., 1977; Barlow, 1983
Gain	low	high	Renninger et al., 1984; Barlow et al., 1987
Noise	high	low	Barlow et al., 1977; Kaplan and Barlow, 1980; Barlow et al., 1993
Quantum bumps	short	long	Kaplan et al., 1990
Frequency response	fast	slow	Batra and Barlow, 1990
Dark adaptation	fast	slow	Kass and Berent, 1988
Lateral inhibition	strong	weak	Renninger and Barlow, 1979; Ruta et al., 1999
Cell position	proximal	distal	Barlow and Chamberlain, 1980; Barlow et al., 1980
Pigment granules	clustered	dispersed	Barlow and Chamberlain, 1980
Aperture	constricted	dilated	Chamberlain and Barlow, 1977, 1987
Acceptance angle	6°	13°	Barlow et al., 1980
Photomechanical movements	trigger	prime	Chamberlain and Barlow, 1987
Photon catch	low	high	Barlow et al., 1980
Membrane shedding	trigger	prime	Chamberlain and Barlow, 1979, 1984
Arrestin mRNA level	high	low	Battelle et al., 2000
Intense light effects	protected	labile	Barlow et al., 1989
Visual sensitivity	low	high	Powers and Barlow, 1985; Herzog et al., 1996

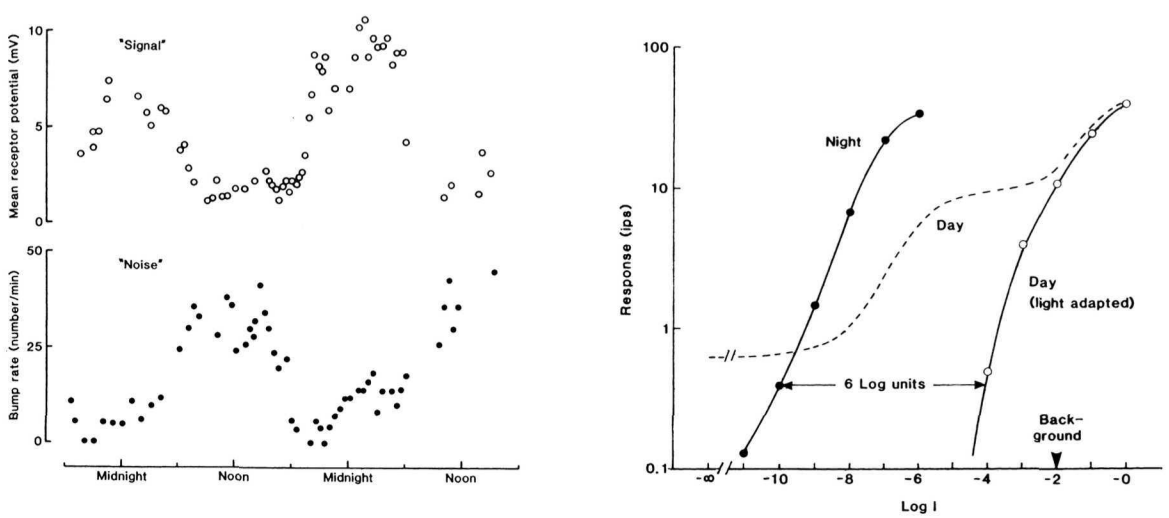

Fig. 1. *Left:* Circadian rhythms in response and noise recorded over a 2-day period from a single *Limulus* photoreceptor cell in situ. Open circles give the mean amplitudes of the receptor potential ("signal") in response to 6-s test flashes. Light intensity incident on the single ommatidium was 10^6 photons/s (400–700 nm). Filled circles give the rates of quantum bumps ("noise") generated spontaneously in darkness. (Barlow et al., 1987). *Right:* Intensity-response functions for a single optic nerve fiber of the *Limulus* lateral eye. The steady-state firing rate is plotted on a log scale on the ordinate as a function of log light intensity plotted on the abscissa. Steady-state rates are the average rates the last 7 s of 10 s flashes. Unfilled circles give light-adapted function (background intensity: Log I = − 2), and dashed curve gives dark-adapted function measured during the day. Filled circles give function measured in darkness at night. Light intensity incident on the single ommatidium at Log I = 0 was 10^{12} photons/s (400–700 nm).

I-R function ~6 log units to the left: an approximate million-fold increase in retinal sensitivity.

Part of the nighttime increase in sensitivity results from a >10-fold increase in photon catch caused by a distal shift in the position of photoreceptor cells and dilation of the aperture that limits the light absorbed by photoreceptors (Table 2). As indicated above part results from an increase in the gain of the photoreceptor response (membrane depolarization/photon; Barlow et al., 1987) which is influenced by a voltage-dependent conductance that repolarizes the photoreceptor membrane during light stimulation

(Pepose and Lisman, 1978). Reducing the efficacy of this membrane mechanism of light adaptation appears to be one way the clock increases photoreceptor gain at night (Barlow et al., 1987). The clock also increases gain by increasing the duration of quantum bumps, the elemental responses to single photons (Kaplan et al., 1990). The temporal change may result from decreased nighttime levels of arrestin, the molecule that deactivates activated rhodopsin (Battelle et al., 2000).

How does the clock reduce "dark noise" in Limulus photoreceptors? Dark noise, which limits visual sensitivity, is a ubiquitous property of both vertebrate and invertebrate photoreceptors. It has been attributed to thermal isomerizations of native rhodopsin (Barlow, 1988), but the Arrhenius energy we measure for dark noise (~27 kcal/mole; Barlow et al., 1993) is far less than that required for isomerization (~45 kcal/mole; Birge, 1990). An alternative explanation is that dark noise results from the thermal isomerization of an unstable form of rhodopsin, one in which the Schiff-base linkage is unprotonated. Theoretical studies indicate that deprotonation lowers the energy barrier for isomerization from ~45 to 23 kcal/mole which is near the Arrhenius energies we measured (Barlow et al., 1993; Birge and Barlow, 1995). Indeed, mutations of rhodopsin that completely or partially deprotonate the Schiff base activate transduction mechanisms in darkness (for example: Sakmar et al., 1989; Robinson et al., 1992). We hypothesize that during the day not all of the large number of rhodopsin molecules (~10^9) within the photoreceptors of a *Limulus* ommatidium are protonated. A small population is unprotonated and can thermally isomerize to produce spontaneous quantum bumps that mimic photon absorption events. We further hypothesize that the circadian clock decreases pH in the vicinity of photoreceptors at night which in turn decreases the small population of unstable rhodopsin molecules and thus reduces dark noise (Barlow et al., 1993). Interestingly, a circadian clock decreases the pH of the fish retina at night that, in turn, may modulate synaptic transmission to suppress cone horizontal cell responses (Mangel, this volume).

The circadian clock's influence on retinal sensitivity can also be assessed by the day-night changes in signal-to-noise (S:N) properties of single photoreceptor cells. At night the S:N properties of the dark-adapted reticular cell recorded in Fig. 1 (left) increased approximately 50-fold. Remarkably signal increased and noise decreased at night. This is not unique to *Limulus*. Somatostatin has the same effect in the rabbit retina: it increases the signal and decreases the noise of ganglion cells (Zalutsky and Miller, 1990). Low concentrations of somatostatin (1 nM) increased the S:N characteristic about 6-fold. Higher concentrations (200 nM) completely suppressed spontaneous activity, yielding infinite sensitivity as measured by S:N properties. This is also the case for *Limulus* where the clock suppresses noise and increases signal in the early evening between 2100 h and 2400 h. Interestingly, this is the time of day when the animals search for mates.

Octopamine is the primary transmitter of the clock's actions on the retina (Battelle et al., 1982; Kass and Barlow, 1984). It acts via the second messenger cAMP to increase the gain and photon catch of photoreceptors but not to decrease their noise (Schneider et al., 1987). As noted above the nighttime decrease in noise appears to require a clock dependent reduction in retinal pH. Octopamine and protons may not be the only mediators of the clock's action. Experiments with retinal slices point to the existence of a third substance (Pelletier et al., 1984) that participates in a "push-pull" mechanism for controlling the circadian changes in retinal structure (Barlow et al., 1989). In this scheme the clock's release of octopamine "pushes" the structure of the retina to the nighttime state increasing photon catch and the acceptance angle (Table 2). The third substance, perhaps a circulating hormone, "pulls" retinal structure back to the daytime state after the cessation of efferent input at dawn. The push-pull actions appear coordinated and interdependent (Chamberlain and Barlow, 1987).

How do the circadian rhythms in retinal sensitivity effect Limulus behavior? The animals use vision to find mates (Barlow et al., 1982). Each spring they migrate to protected beaches from Maine to Mexico, pair off and build nests near the water's edge at high tide (Barlow et al., 1986). We studied their visual performance in the vicinity of underwater mate-like objects and found that they could see them about equally well day and night (Herzog et al., 1996). Their outstanding nighttime vision is consistent with our observation that the circadian increase in retinal

sensitivity at night about compensates for the reduction in ambient lighting after sunset. The circadian changes in visual sensitivity serve an essential function: they enable animals to detect mates at night.

What is the neural code underlying mate detection in Limulus? Using neural mechanisms generally found in more complex retinas, the lateral eye converts the responses of photoreceptor cells into trains of optic nerve impulses and transmits them to the brain and to neighboring retinal receptors to mediate lateral inhibition. The entire ensemble of responses across the array of ~1,000 optic nerve fibers yields a "neural image" that encodes what the animal sees. We examined how the eye encodes natural scenes by using a cell-based model of the eye together with a shell-mounted camera (CrabCam; Passaglia et al., 1998). Computed ensembles of optic nerve activity ("neural images") reveal a robust encoding of moving mate-like objects during the day (Passaglia et al., 1997). At night the neural images are less clear. They are dominated by bursts of spikes apparently triggered by random photon events at the low nighttime light levels (Hitt et al., 2000). How does the brain decipher a reliable signal from such a noisy input? "Slow" synapses at the first synaptic level in the brain (lamina) integrate the optic nerve input with a time constant of ~400 ms. This lowpass temporal filtering suppresses the burstiness of the optic nerve input and enhances the coding of a mate-like object in the neural image but not to daytime levels. Additional lowpass spatial filtering appears necessary although laminar receptive fields have not been mapped with precision. In sum, circadian increases in the sensitivity of the lateral eye in combination with lowpass spatial and temporal filtering of its input to the brain explains in part how *Limulus* can see so well at night.

Circadian rhythms in retinal sensitivity of the Japanese quail

We extended our study of the circadian rhythms in *Limulus* to a vertebrate model, the Japanese quail, because its retina exhibits a circadian modulation of melatonin synthesis (Underwood et al., 1988, 1990) and receives an extensive efferent optic-nerve input from the brain (Uchiyama, 1989). Surprisingly, the efferent and circadian systems in quail are not related as they are in *Limulus*. Rather than mediating circadian rhythms, the efferent optic-nerve input from the quail brain rapidly increases retinal sensitivity regardless of the time of day (Uchiyama and Barlow, 1994). The circadian oscillators that modulate retinal sensitivity in quail are located in the eyes themselves (Manglapus et al., 1998a). The suprachaismatic nucleus and pineal body also contain circadian oscillators. The circadian organization of quail is truly remarkable with four distinct circadian oscillators in the animal's head!

The influence of the ocular circadian oscillators on retinal function was investigated by recording the amplitude of the b-wave of the electroretinogram (ERG) when an animal is maintained in constant darkness (Manglapus et al., 1998a). Under these conditions the b-wave increases during the animal's subjective night and decreases during its subjective day. The latency to the peak of the b-wave decreases with as intensity increases, from ~80 ms to 40 ms, but does not change significantly from day to night. Reflecting postphotoreceptor activity, the corneal positive b-wave provides a convenient measure of retinal sensitivity (Dowling, 1960). The ERG a-wave reflects photoreceptor activity and was isolated by blocking the b-wave with APB producing the PIII component of the ERG. PIII also changes with time of day when an animal is kept in constant darkness. For unknown reasons the day–night changes are generally more robust over the first but not the second day. Entraining animals to a light–dark cycle shifted by 4 h from the solar cycle yielded an endogenous rhythm in the a- and b-waves that was shifted by 4 h. This and the ~24 h period of the endogenous rhythm of the ERG components are two hallmarks of a process controlled by a circadian oscillator.

The circadian rhythm of the ERG b-wave is associated with a shift in the spectral sensitivity of the retina (Fig. 2A). During the day, the sensitivity of the b-wave response is maximal in the range of 550 to 600 nm. At night the sensitivity increases about six fold and its maximum shifts to shorter wavelengths (~500 nm). Greater increases in sensitivity are detected at shorter wavelengths (<470 nm). The nighttime data are well fit with a nomogram for a rod photopigment (λ_{max} = 506 nm)

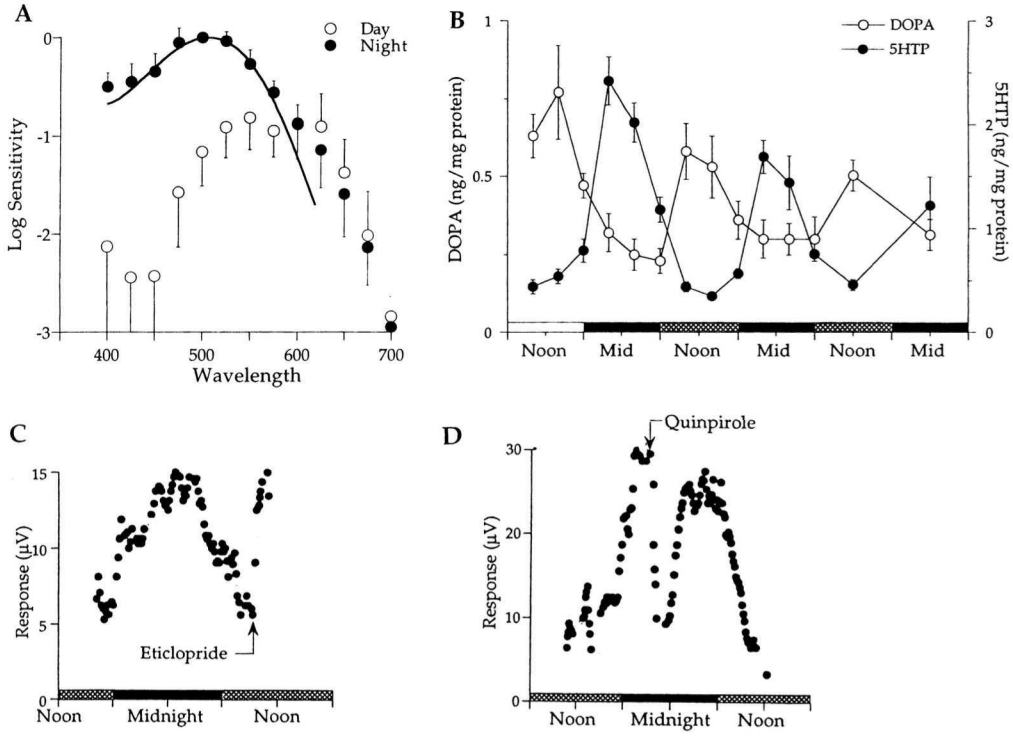

Fig. 2. Circadian rhythms in the Japanese quail retina. (**A**) Spectral sensitivity of the ERG b-wave is high at night (filled circles; λ_{max}~500 nm) and low during the day (unfilled circles; λ_{max} ~550–600 nm). Circadian changes are maximal for short wavelength stimuli. Smooth curve is a monogram for a rod photopigment (λ_{max} = 506 nm) based on microspectrophotometric measurements. (Manglapus et al., 1998) (**B**) Retinal concentrations of DOPA (left y-axis) and 5-HTP (right y-axis) as a function of time. Measurements began every 4 h in cyclic lighting and continued into constant darkness. Noon is the middle of the subjective day, and midnight (Mid) is the middle of the subjective night. (**C**) Amplitude of the ERG b-wave in response to 470 nm flashes. Eticlopride, a dopamine D2 receptor antagonist, injected during the day (0935 h; arrow) rapidly increased the b-wave amplitude to nighttime levels. (**D**) Quinpirole, a dopamine D2 receptor agonist, injected at night (arrow; 2150 h) reduced the b-wave amplitude to low daytime levels. After midnight, the quinpirole effect subsided, and the b-wave amplitude returns to its high nighttime state (Manglapus et al., 1999).

derived from microspectrophotometric measurements. Thus rods dominate retinal sensitivity at night and cones dominate sensitivity during the day. This endogenous day–night change resembles the Purkinje shift of human vision but, unlike the Purkinje shift, it does not require a change in ambient light intensity. The spectral sensitivity of the isolated a-wave (PIII) does not change with time of day. It remains maximal at ~520 nm and may reflect multiple receptor mechanisms. The rhythmic changes in the a- and b-wave amplitudes have periods of ~24 h. They represent a circadian rhythm in the functional organization of the retina: a shift in rod–cone dominance.

In most studies of retinal circadian rhythms the action of clocks is to increase sensitivity at night. The clock in the Japanese quail eye, however, acts to decrease sensitivity during the day. Li and Dowling (1998) reported a similar result in zebrafish. They found that that a circadian oscillator decreases the visual sensitivity of zebrafish during the day rather than increasing it at night.

Dopamine appears to be the neuromodulator of circadian rhythms in the quail retina (Manglapus et al., 1999). The activity of tyrosine hydroxlyase, the rate-limiting enzyme of dopamine synthesis, correlates with the circadian rhythm in retinal sensitivity (Fig. 2B). At night, dopamine levels are low, and the retina is rod dominated; during the day, dopamine levels are high and the retina is cone dominated. Blocking dopamine D2-like receptors during the day with eticlopride increases the

sensitivity of the retina shifting it to the rod-dominated nighttime state (Fig. 2C). Activating dopamine D2-like receptors with quinpirole at night decreases the sensitivity (Fig. 2D) and shifts the retina to the cone-dominated daytime state. Haloperidol, a general blocker of both D1 and D2 receptors, mimics the effects of eticlopride by shifting the retina to the rod-dominated nighttime state. A selective antagonist for D1 dopamine receptors has no effect on retinal sensitivity or rod-cone dominance. Depleting retinal dopamine with 6-OHDA abolishes rhythms in sensitivity and yields a rod-dominated retina regardless of the time of day. Dopamine thus appears to mediate the circadian clock's action on the functional organization of the retina. Increased levels of dopamine during the day appear to block rod signals at the outer retina, allowing only cone signals to be transmitted to the inner retina.

Dopamine also mediates circadian rhythms in retinal physiology and morphology. Mangel reports in this book that dopamine mediates a circadian rhythm in the rod–cone dominance of fish cone horizontal cells via a subclass of D2 receptors termed D4 receptors. Applied at night, it produces cone-like responses typical of those observed during the day. Blocking D4 receptors during the day results in nighttime, rod-dominated responses (Mangel and Wang, 1996). The role of dopamine in the circadian rod-cone shift in fish retina strongly parallels it action in the quail retina. With regard to the circadian modulation of retinal structure, dopamine mediates circadian changes in horizontal spinule formation in fish (Wagner et al., 1992) and causes cone contraction and retinomotor movements in fish (Burnside, this book) and *Xenopus* (Pierce and Besharse, 1985). It is interesting to note that removing dopamine from the fish retina does not inhibit circadian retinomotor movements (Douglas et al., 1992).

Dopamine is a ubiquitous retinal neuromodulator. It not only mediates circadian rhythms in a wide range of species; it exerts both morphological and physiological adaptive effects in most (Dowling, 1991; Besharse and Iuvone, 1992; Witkovsky and Dearry, 1992). Often it appears to adapt retinas for daytime function, that is, serve as a light signal. For example, light releases dopamine in the retinas of *Xenopus* (Witkovsky et al., 1993) and rabbit (Bauer et al., 1980). It can induce light-adaptive cone contraction via a D2 receptor mechanism in *Xenopus* (Pierce and Besharse, 1985) and fish (Burnside, this book) as well as decrease gap junctional coupling between horizontal cells in fish via a cAMP mechanism (Lasater and Dowling, 1985). It appears to uncouple amacrine cells via the same mechanism (Hampson et al., 1994). It modulates rod–cone coupling in *Xenopus*, enhancing cone signals and suppressing rod signals (Witkovsky et al., 1988), and does so via gap junctions (Krizaj and Witkovsky, 1993). It mimics the effects of light on rod–cone coupling in salamader (Yang and Wu, 1989). However, there is evidence that dopamine can increase sensitivity as if to adapt retinas for nighttime function. For example, in an elegant behavioral experiment Lin and Yazulla (1994) showed that dopamine increases brightness perception in fish. Li and Dowling (2000b) provide evidence that dopamine is required for maintaining light sensitivity in zebrafish and its depletion effects rod pathways in the inner retina. They found that abolishing dopaminergic cells with ocular injections of 6-OHDA blocks circadian rhythms and maintains the retina in its sensitive daytime state.

Regarding the site of action of dopamine, its receptors have been found in both the inner and outer plexiform layers of the retina (Kebabian and Calne, 1979). D1 receptors are located on horizontal cells and D2 receptors on both photoreceptors and amacrine cells (see Manglapus et al., 1999; Witkovsky and Dearry, 1992). The detection of D2 receptors in the outer retina is consistent with our observation in quail that dopamine acts at this level to modulate the transmission of rod signals to the inner retina.

Do the dopaminergic mechanisms described above function in the quail retina? We do not yet have an answer, but whatever mechanisms underlie the endogenous rod–cone shift in quail they must be (1) located in the outer plexiform layer because ON bipolar cells (b-waves) and not photoreceptors exhibit a rod–cone shift (Manglapus et al., 1998a); (2) triggered by cone responses because rod signals are not blocked below cone threshold (Manglapus et al., 1998a) and (3) mediated by dopamine via D2 receptors (Manglapus et al., 1999).

Does dopamine act alone in the quail retina? Interestingly, the circadian rhythm of dopamine synthesis is reciprocally related to that of melatonin in the quail retina (Fig. 2B). Also, the expression of

mRNAs encoding two enzymes in the synthesis of melatonin, tryptophan hydroxylase and *N*-acetyltransferase, parallels the circadian rhythm in melatonin synthesis (Manglapus et al., 1998b); however, rhythmic changes in melatonin synthesis by itself does not modulate retinal sensitivity (Manglapus et al., 1998c). Melatonin levels have been linked with retinal function in darkness in at least two studies. In one, Pierce and Besharse (1985) found that melatonin mimics the effects of darkness on cone elongation in *Xenopus*. In the other, Mangel and Wang (1996) found that exogenous melatonin shifts cone horizontal cells to rod dominance in the fish retina in vivo. Inspired by these results, we tested the influence of melatonin on the quail retina following techniques used for dopamine. Although our studies are preliminary in nature, they have yet to show a direct effect of melatonin on either retinal sensitivity or rod-cone dominance (Manglapus et al., 1998a).

However, melatonin may have an indirect role in mediating circadian rhythms in the quail retina. Circadian rhythms in retinal melatonin have been found in a number of animals (see Table 1). Particularly interesting is melatonin's inhibition of dopamine release in rabbit, *Xenopus* and chicken retinas (Dubocovich, 1988; Boatright et al., 1994), and conversely dopamine's inhibition of melatonin release in both *Xenopus* and chicken (Cahill and Besharse, 1992; Zawilska, 1994). These two neuromodulators form a mutual inhibitory or "push-pull" biosynthetic mechanism in chick and *Xenopus*.

Our working hypothesis is that at night melatonin, under direct control of a retinal circadian clock, reduces dopamine levels and shifts the retina to rod dominance and increases its sensitivity. During the day, the clock-controlled melatonin levels decrease and dopamine levels increase to reduce the sensitivity of the retina and prepare it for visual processing during the day. In short, melatonin and dopamine interact at dawn and dusk to change the organization of the retina for optimal function day and night.

Circadian rhythm in the sensitivity of the *Xenopus* retina

Do the circadian rhythms in anatomy and metabolism of the *Xenopus* retina listed in Table 1 influence its sensitivity? To try to answer this question we recorded the ERG of an adult eye while the animal remained in darkness for several days. Although this approach was successful with *Limulus* and quail, it proved difficult with *Xenopus* because of the animal's poor tolerance to anesthesia. In most experiments the animal did not remain stable long to determine whether the ERG amplitude exhibited a circadian rhythm. In the few cases when it stabilized, the b-wave amplitude was lower at night than during the day. Although these results must be considered very preliminary, they suggest that a circadian oscillator either increases retinal sensitivity during the day or depresses it at night. *Limulus* is opposite: a circadian efferent input to the retina at night increases its sensitivity (Fig. 2). Also in quail, if our hypothesis is correct, a circadian increase in retinal melatonin at night inhibits dopamine release, shifting the retina to rod dominance and increasing its sensitivity. How circadian mechanisms may modulate the sensitivity of the *Xenopus* retina is not known, but its higher sensitivity during the day is reminiscent of what Li and Dowling (1998) reported in a behavioral study of the visual sensitivity of zebrafish. Thus circadian increases in sensitivity do not necessarily occur at night in all animals. In some, clocks may modulate visual sensitivity at the times of dawn or dusk when animals often search for prey.

Do circadian rhythms exist in human vision?

Electrophysiological studies have reported diurnal variations in the amplitude of the human ERG (Nozaki et al., 1983) and in its temporal response properties (Hankins et al., 1998). Psychophysical studies have found similar diurnal variations in human scotopic sensitivity (Bassi and Powers, 1986) and in chromatic sensitivity (Roenneberg et al., 1992). Interestingly, blood glucose levels influence human visual sensitivity (McFarland and Forbes, 1940; McFarland et al., 1945) and the hormonal control of glucose homeostasis changes with time of day (Agren et al., 1931; Aschoff, 1979a) with glucose utilization decreasing at night (Van Cauter et al., 1988). Are these daily changes in human vision and metabolism related?

In a preliminary psychophysical study we measured both contrast sensitivity and blood sugar levels of subjects over a period of several days (Barlow et al., 1993). Subjects were exposed to diurnal changes in environmental illumination, but their tested eye was patched at all times except when contrast thresholds were being measured at 2 h intervals using the Quest algorithm (Watson and Pelli, 1983). Subjects slept at night except when being tested. Under these conditions we found that contrast sensitivity decreases as much as four times at night, and the decreases were roughly correlated with decreases in blood glucose levels that naturally occur at night. Ingestion of fixed amount of glucose at night (Trutol) increased blood sugar levels (average increase: 74 ± 7 to 135 ± 14 mg/dl) and elevated contrast sensitivity to normal levels. To further test the influence of blood sugar level on visual sensitivity we reduced it artificially by injecting insulin during the day. Lowering blood glucose from normal levels to the range of 50–60 mg/dl reduced contrast sensitivity ~10-fold. Levels below 50 mg/dl occasionally produced a transient visual scotoma lasting about 5 min and covering about 20° of the central visual field. The reason for this is not known.

The site of glucose action may be the retina. Ames and Gurian (1963) and later Winkler (1981) showed in mammal that glucose and oxygen are necessary for optimal retinal function: low glucose and/or oxygen decreases optic-nerve action potentials within minutes, and glucose perfusion and/or reoxygenation produce rapid and complete recovery. Also the sensitivity of cat eyes as assessed by the ERG b-wave increased when perfused with glucose (Macaluso et al., 1992) and when made hypoxic (Linsenmeier et al., 1983). The retina is not the only glucose dependent part of the visual system. We used functional magnetic resonance imaging (fMRI) to examine higher levels and in initial studies found that physiological changes in blood glucose levels changed the hemodynamic responses of the visual cortex (Barlow et al., 1997). fMRI also revealed significant time-of-day changes in cortical activity.

Effects of metabolism on vision date back to the early days of aviation when pilots flying at altitudes (>18,000 ft) reported darkened visual fields. Related research carried out during World War II showed that both hypoxia and hypoglycemia decreased visual sensitivity, as assessed by dark adaptation and that glucose ingestion could counter the effects of hypoxia on visual sensitivity and visa versa (McFarland and Forbes, 1940; McFarland et al., 1945). Our preliminary studies confirm this earlier work showing that glucose, a major energy source for CNS function, can modulate human contrast sensitivity. We hypothesize that the changes in sensitivity with time of day we detected result from daily changes in blood sugar level. Because our studies were not carried out under constant conditions, the daily changes in sensitivity cannot be considered as evidence for a circadian rhythm in visual sensitivity.

Efferent modulation of retinal sensitivity

Circadian oscillators, metabolism, and adaptation are not the only modulators of retinal sensitivity. As noted at the beginning many animals have evolved centrifugal pathways that can modulate retinal function via efferent signals transmitted either from the brain or from within the retina. Centrifugal pathways from the brain are known to exist in fish, birds and mammals (Uchiyama, 1989) and invertebrates (Barlow et al., 1989). Their functional organization can be classified as either "local" or "global". An example of "global" is the *Limulus* visual system in which a few efferent fibers enter the retina, branch profusely and influence the entire retina. An example of "local" is the retinotopic arrangement of the centrifugal input from the isthmo-optic nucleus (ION) in Japanese quail. It provides the circuitry for modulating the properties of specific regions of the quail retina.

We studied the influence of the centrifugal pathway in quail and found that it can increase the response of ganglion cells without changing the configuration of their receptive fields (Uchiyama and Barlow, 1994). Specifically, stimulating the ION with a brief train of 10 impulses (pulse duration: 100 μs; pulse frequency: 200 Hz) immediately preceding the onset of a 1 s drifting sine wave grating enhanced the response of a ganglion cell >60% (Fig. 3A–C). Both with and without ION input the response was maximal for sine-wave grating with spatial frequencies in the range of 1–2 cycles/deg

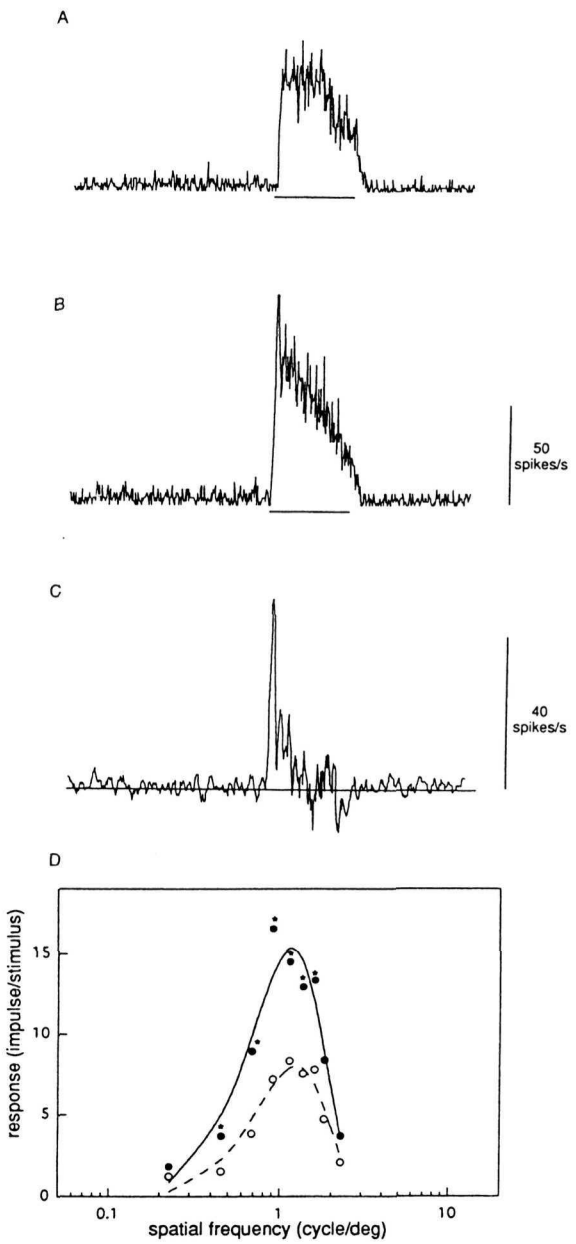

Fig. 3. Efferent input increases the response of a retinal ganglion cell in Japanese quail. (A–C): Histograms of spikes evoked by drifting gratings (horizontal bars) for 1 s without (A) and with (B) stimulation of the ION. The difference in the two histograms (A–B) is plotted in (C) after time averaging. 50 sweeps were averaged for this ON-OFF direction-selective cell. (D): Spatial frequency tuning curves of a retinal ganglion cell with (filled circles) and without (open circles) ION stimulation. Smooth curves were fitted using the DOG. Temporal frequency was maintained at 5 Hz for ON non-direction-selective cell. Asterisks show responses under ION stimulation that are statistically higher ($p < 0.05$) than control responses (Uchiyama and Barlow, 1994).

(Fig. 3D). The data when normalized overlap indicating that the ION input increased response without changing the shape of the spatial frequency tuning curve. We conclude that efferent inputs from the midbrain can enhance retinal responses without affecting the center-surround organization of their receptive fields.

The feedback system in quail is retinotopically organized—retina to tectum to ION to retina—with about 10,000 centrifugal fibers projecting from the ION to the retina in a point-to-point manner. This "local" organization may enable single ION fibers to assist in shifting visual attention in space by changing ganglion cell responses in a specific region of the retina. Such a selective attention mechanism would be consistent with the known role of the optic tectum in orienting behavior (Uchiyama, 1989). It is also reminiscent of the "searchlight hypothesis" proposed for the cortical feedback to the lateral geniculate nucleus (Crick, 1984; Koch, 1987). Although centrifugal fibers innervate the mammalian retina, the most abundant efferent pathway is the cortical feedback to the LGN. Recent studies suggest that the cortical feedback to LGN cells may have a role in the generation of orientation tuning (Murphy et al., 1999), may increase their responses by disinhibition (Wörgötter et al., 1998), may enhance their contrast gain (Przybyszewski et al., 2000) and may operate via metabotropic receptors (McCormack and vonKrosigk, 1992). In sum, there is much more to learn about this massive and intriguing efferent pathway of the mammalian visual system (Crick and Koch, 1998).

The efferent input to the retina of teleost fish from the olfactory bulb terminates on other efferent neurons: the dopaminergic interplexiform cells (DA-IPCs; Zucker and Dowling, 1987). Having a mutual interest in efferent pathways, John Dowling and I attempted to do with the green sunfish retina what my laboratory had done earlier with the *Limulus* eye, namely drive efferent inputs by shocking the optic nerve trunk and monitoring their effect on retinal sensitivity. We used an isolated eyecup preparation but unfortunately could not maintain

its viability, as assessed by the ERG, and thus could not determine the effect of shocking. A more recent study by John and Lei Li revealed a possible role of centrifugal inputs in the regulation of visual sensitivity of zebrafish. They found that a dominant mutation, *night blindness b*, suppresses visual sensitivity, reduces the number of DA-IPCs, and disrupts both the centrifugal input to the retina and the circadian modulation of visual sensitivity, (Li and Dowling, 2000a). Taken together these effects suggest that the centrifugal input excites DA-IPCs which, in turn, raises dopamine levels enhancing the transmission of rod signals to the inner retina which then reduces visual threshold. Other than this possibility the function of the centrifugal input to the fish retina remains unknown.

Conclusions and future perspectives

The ultimate goal of neuroscience is to understand how the brain works. In his book, *The Retina: An Approachable Part of the Brain* (1987) John Dowling suggests that we can gain important information about brain function by analyzing a small piece of brain tissue, the retina. Our challenge then is to understand how the retina works, that is, how its circuitry produces a "neural image" of the visual world.

Analyzing a relatively simple retina may yield important insights about the function of more complex ones. Indeed that of the horseshoe crab, *Limulus*, has proven complex enough to be interesting, yet simple enough to be understood. Using a computational approach we unraveled its coding properties and determined the neural image it sends to the brain about visual stimuli that are behaviorally relevant, namely mates. We were surprised to discover that this retina is not so "simple" after all. A circadian clock increases its sensitivity at night enabling the animal to detect potential mates as well as it does during the day. We have not yet deciphered the eye's neural code for nighttime vision but have uncovered some of the remarkable cellular mechanisms that produce the highly sensitive nighttime state. This is an extremely sophisticated eye that modulates most every property of the retina, to gain sensitivity at night. The challenge is to understand how it efficiently encodes information about potential mates under the photon-limited conditions of the animal's marine habitat at night. The lesson learned as Keffer Hartline noted: "if it's simple, it's not an eye."

This brings us to the vertebrate eye, a far more complex organ than that of *Limulus*. With tens of millions of cells, numerous cell types, dendritic processes and synaptic contacts, the task of deciphering its neural code is indeed taunting. How to meet John's challenge? Is the vertebrate retina truly approachable? Developing a cell-based, realistic computational model as we did for *Limulus* appears unrealistic. A different computational approach is needed, one that by necessity models ensembles of neurons. The danger is that such modeling overlooks details in the neural circuitry and "the truth is in the details". As was the case for *Limulus* insights can come from understanding how the retina adapts or is modulated to function optimally under different conditions. Much has been learned from studies by John Dowling, his colleagues and others about the endogenous mechanisms that adapt the retina to function under various lighting regimes. Also we are gaining a better appreciation of the modulatory influences of efferent inputs and circadian oscillators. But we have yet to put all the pieces together.

Major challenges are to understand how circadian changes at various levels of the visual system influence visually guided behavior, how efferent signals from the brain are triggered, and how do they influence the signals the brain receives from the retina.

Doing so requires a multidisciplinary approach, one that combines the power of molecular biology with that of animal psychophysics as well as the tools of electrophysiology, neuroanatomy and computational neuroscience. Insight about the function of a normal visual system can often be gained by mutating the system and carefully investigating the resulting phenotype with a variety of techniques. Here again John Dowling has pointed the way by establishing an ambitious research program that uses the zebrafish to study the cellular basis of visual function with mutagenic techniques. It is an ideal model system as John and his colleagues have demonstrated. The research is tedious and laborious, but some of the contributions to this book underscore its benefits.

The numerous cellular mechanisms that adapt and modulate retinal function provide important clues about its function. They underscore the retina's critical role as the interface between the brain and the constantly changing visual world. Although we ultimately strive to learn how the brain in all its complexity works, understanding first how the retina in all of its altered states works may prove equally challenging.

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