Vision in Horseshoe Crabs

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Abstract *Limulus* has been a superb animal model for understanding vision in higher animals, including man. Nobel-prize winning research on the lateral eye of *Limulus* by H. K. Hartline revealed fundamental principles of retinal function applicable to all eyes. The function of the *Limulus* lateral eye is now well understood as is its essential role in the animal's mating behavior.

1 Introduction

"For such a large number of problems there will be some animal of choice or a few such animals on which they can be most conveniently studied." August Krogh's "Principle" made in 1929 captured well H. Keffer Hartline's decision several years earlier, to study vision in horseshoe crabs. The same is true of A. V. Hill's comment also made in 1929: "we may often throw light upon function or process in the higher animals...by the choice of a suitable organ...in some animal far removed in evolution." Hartline devoted nearly his entire life studying the remarkable eyes of horseshoe crabs, animals that are truly "far removed in evolution." Close inspection of the animal reveals relatively large eyes that look nothing like our own (Fig. 1). What could they possibly teach us about vision in other animals? Hartline provided the answer: they reveal how eyes provide vision – not just in horseshoe crab but in all animals. His groundbreaking discoveries of the physiological properties of *Limulus* eyes laid the foundation for our current understanding of eye function. For his pioneering work, Hartline shared the Nobel Prize in Medicine or Physiology (Hartline 1969).

Hartline began his wonderful journey in research on the *Limulus* eye in 1926 at the Marine Biological Laboratory (MBL) in Woods Hole, MA (Fig. 2). He had gone there hoping to find an animal with relatively simple eyes. His interest in vision began earlier at Lafayette College, where as an

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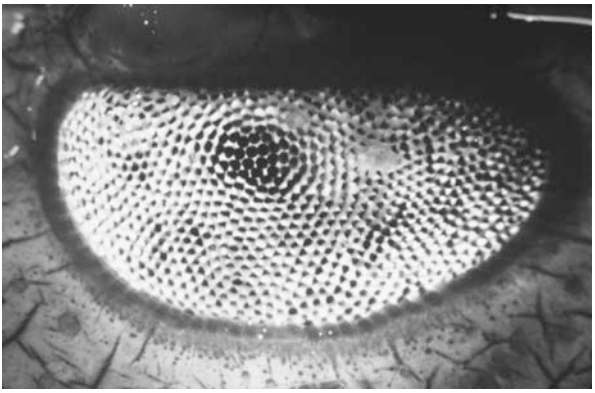

Fig. 1 The compound eye of *Limulus*. A pair of these large eyes, each containing about 1,000 ommatidia (*black disks*), is perched high on each side of the prosoma and provide *Limulus* with wide fields of vision (Herzog and Barlow 1992). The crab can see to not only each side but also ahead, behind, and above. The individual ommatidia are the largest known retinal receptors in the animal kingdom. They are roughly 100 times the size of rods and cones in the human eye

undergraduate he carried out a meticulous study of how pill bugs respond to light. This strictly behavioral study triggered in him a keen interest to understand how light causes changes in an animal's behavior, beginning with action of light on an eye. At the time, he was convinced that the eyes of frogs would be ideal for understanding how light-sensitive cells in the retina begin the process of vision. In earnest, he tried to record nerve signals from frog eyes while a medical student at Johns Hopkins University. But he quickly became frustrated first because the frog's eye proved to be more complex than he imaged and second because he could only study them at night. Daytime was packed with classes and labs – that were of little interest to him and kept him from his frogs. Hartline often joked that Johns Hopkins awarded him a medical degree only if he promised never to touch a patient. After graduating, he questioned whether frog eyes could provide the insight about sight he had hoped for and decided to go to Woods Hole to search for a marine organism that possessed a simpler and more accessible eye.

Hartline always enjoyed telling the story of how he stumbled across a large female horseshoe crab as he strolled along the water's edge on a beach in Woods Hole. He knelt down to look at her eyes and marveled at their size – especially the individual light receptors, the ommatidia (Fig. 1). The receptors were so large that he could see them without a magnifying glass. Numbering about 1,000 in each eye, the individual ommatidia are roughly 100 times the size of rods and cones in the human eye. They are, in fact, among the largest light receptors in the animal kingdom. In awe of their size, Hartline reasoned that if he could see them so easily, he might be able to record their electrical responses to light and understand how they provide vision to the animal.

Hartline's first experiment with the *Limulus* eye was to record a light-evoked electrical signal, termed the electroretinogram (ERG), that he had successfully

Fig. 2 H. Keffer Hartline (1903–1983) sitting on his "think bench" in the woods behind his home near Baltimore

recorded from the human eye. The amplitude of the ERG provides a good measure of retinal sensitivity, and he set about to measure it with a simple cotton wick electrode placed in contact with the cornea of the lateral eye. Because highly sensitive physiological amplifiers did not exist in the late 1920s, he connected the wick electrode to a mechanoelectrical device known as a string galvanometer that proved sensitive enough to record light-induced changes in ERG amplitude (Hartline 1928). While exploring retinal tissue with a wick electrode, Hartline detected brief, tiny electrical events in the optic nerve trunk that he thought might be individual nerve impulses. This possibility excited him, and he managed to locate a vacuum tube – a recent innovation – and built an amplifier that had sufficient sensitivity to detect small nerve signals (Barlow 1986).

In the summer of 1931, Hartline returned to MBL with his colleague, Clarence Graham, and his new highly sensitive vacuum tube amplifier. They found it relatively easy to record masses of electrical impulses even from the tiniest nerve bundles dissected from the optic nerve trunk of *Limulus*, but

impossible to record nerve impulses from a single nerve fiber – which was their goal. On their final day in the laboratory that summer, they succeeded in recording from a single optic nerve fiber when they tested the last *Limulus* in the tank – a large, crusty-shelled adult having dull, scarred eyes – "a miserable specimen" according to Hartline. Stunned at their unexpected, last-minute good fortune, he and Graham furiously set about to learn what they could before packing up the lab to leave the following day.

The outpouring of results from these and subsequent Woods Hole single nerve fiber recordings was enormous, touching on most every aspect of retinal physiology and laying the foundation for all future research. A thorough description of these fundamental contributions together with Hartline's studies using intracellular recording techniques would fill several volumes (Ratliff 1974). There are also numerous studies by others including me who were inspired by Hartline's pioneering work. Reviewing the entire body of work, I complied a "Top 10" list of discoveries and present them here.

1.1 Neural Coding of Light Intensity

In their first recordings from the *Limulus* lateral eye, Hartline and Graham (1932) discovered that the discharge of impulses from single optic nerve fibers increased with light intensity. They found a near linear relationship between the rate of discharge and the logarithm of light intensity similar to that between intensity and brightness in human vision known as the Weber–Fechner Law. They also found that a single nerve fiber with its attached photoreceptor responded over a wide range of intensities that may be as great as 1–1,000,000. Kaplan and I repeated their experiment without excising the eye as they did but leaving it with its blood supply intact in the animal. We were indeed surprised to discover that the eye in vivo has a much greater sensitivity, responding over an intensity range of $1–10^{10}$ (Barlow and Kaplan 1971). Several years later, my laboratory was doubly surprised to find that a circadian clock in the animal's brain further increases lateral eye sensitivity at night (Barlow et al. 1977). Remarkably, a single *Limulus* photoreceptor can signal the brain about individual photons at night and operate under bright sunlight during the day, a range of $1–10^{14}$. Human vision operates over a similar wide range – from the dimmest visible star to the noonday sun – but does so with two types of photoreceptors, rods and cones, and a far more complex retina.

1.2 Spectral Sensitivity

Graham and Hartline (1935) also studied the spectral sensitivity of single photoreceptors and found that their optic nerve response varies with the wavelength of light, peaking in the blue-green region of the spectrum. Years later

Hubbard and Wald (1960) found that the visual pigment extracted from *Limulus* photoreceptors absorbed light in the same region of the spectrum. This spectral match laid the foundation for understanding the cellular mechanisms of color vision of all animals.

1.3 Temporal Summation of Light

Hartline (1934) discovered that the *Limulus* eye functions as an adding machine, summing the influences of individual photons in brief flashes to produce a visual response. The ability of a single photoreceptor to sum the influences of single photons delivered within a short period of time, termed the critical duration, indicates that the photochemical reactions exerted in a photoreceptor by a light flash depend only on energy (intensity × duration). The reciprocal relationship between intensity and duration of brief flashes is known as the Bunsen–Roscoe Law (Hartline 1934). Adherence to it by both humans and horseshoe crabs points to similar photochemical reactions in both human and horseshoe crab eyes.

1.4 Light and Dark Adaptation

Hartline and Graham (1932) found that after the onset of light, the discharge of impulses from a single optic nerve fiber was initially high and then decreased to a lower rate indicating rapid sensory adaptation. After a hiatus of research caused by World War II, Hartline revisited the property of adaptation and with MacDonald (1947) examined both the decrease in sensitivity of the eye caused by light (light adaptation) and the subsequent increase in sensitivity after light offset (dark adaptation). The phenomena of dark and light adaptation are familiar to all who have experienced changes in their vision upon entering a dark movie theater on a sunny day and then after leaving the theater. Before the *Limulus* studies, the ability to adapt visual sensitivity to ambient lighting conditions was well known, but the origin of adaptation, eye vs brain, was not. Hartline and MacDonald (1947) found that light and dark adaptation begin in single photoreceptors of the *Limulus* eye and stated that this was "strong presumptive evidence" for a photoreceptor origin of adaptation in the visual systems of many higher animals, including humans.

The above four "Top 10" discoveries were made from recordings of single optic nerve fibers. These findings convinced Hartline that visual phenomena common to many higher species – as visual adaptation and spectral sensitivity – originated in the retina of this primitive animal. These discoveries were made in the first half of the last century. Studies carried out after 1950 probed the cellular mechanisms underlying optic nerve responses. These later studies were enabled by the advent of glass microelectrodes that have tips tiny enough to penetrate the cell membrane of *Limulus* photoreceptors and record their initial electrical responses to light.

1.5 Photoreceptor Potential

Masters at delicate surgical manipulations, Hartline and Graham succeeded in removing a single photoreceptor unit, an ommatidium, from the eye during their early studies. Using a small electrode, they recorded a minute electrical current, they termed an "action current", that coincided with the generation of impulses in the optic nerve. They suggested that the action current of an ommatidium initiated nerve impulses, but their electrode was too large to probe the inner workings of cells within an ommatidium. Using the new-developed glass microelectrode, Hartline, Wagner, and MacNichol (1952) later succeeded in impaling a single photoreceptor cell, called a retinular cell, and recorded its response to light. They found that a light flash depolarized the transmembrane potential and believed that this photoreceptor potential was "intimately related to the initiation of nerve impulses." Tomita (1956) and MacNichol (1956) then showed that this photoreceptor potential results from an increase in cell membrane conductance and is indeed related to the generation of nerve impulses. These germinal studies in Hartline's laboratory and many others throughout the world led to a detailed understanding of how both invertebrate and vertebrate photoreceptors respond to light.

1.6 Single Photon Detection

Single photoreceptors can respond to the smallest amount of energy: a single photon of light. Hecht et al. (1942) came to this conclusion indirectly from their behavioral study of human visual sensitivity. Yeandle (1958) provided direct physiological evidence for this remarkable result 16 years later when he recorded elemental voltage events from *Limulus* photoreceptors (retinular cells) exposed to very dim light. The discrete voltage events, he called "quantum bumps," increase in frequency as photon flux increases and sum to form the photoreceptor potential that leads to the generation of optic nerve responses as discussed above. A graduate student of Hartline, Alan Adolph (1964), extended this work and reported marked fluctuations in the amplitudes of the discrete quantum bumps. Fred Dodge et al. (1968), also in Hartline's lab, examined the quantum bump amplitudes using techniques of linear systems analysis and found that bump amplitudes decrease as their frequency increases with increasing light intensity, adapting the eye to brighter light. Their "adapting bump" model provided the first comprehensive explanation for light adaptation in the retina, any retina.

1.7 Lateral Inhibition

Hartline's discovery of lateral inhibition in the *Limulus* eye marked a milestone in vision research and is largely the reason he was awarded the Nobel Prize. Interestingly, his discovery was accidental as are many groundbreaking

discoveries. "I turned on the room lights and the optic nerve response decreased" said Hartline, recounting an experiment he had performed on the *Limulus* eye in 1949. "Why should the response decrease when I increase the light intensity?" He had experienced this phenomenon countless times, but had not appreciated its significance. Why he was suddenly alerted to the effect of room light is not clear, but he finally grasped its meaning: illuminating one region of the *Limulus* eye can inhibit the responses of ommatidia in a neighboring region. The concept of lateral inhibition was born (Hartline et al. 1956). It has proven to be a fundamental principle of all visual systems, including that of humans. By enhancing the contrast between light and dark areas in the visual field – a phenomenon known as simultaneous contrast, lateral inhibition influences most everything we see. In 1865, Ernst Mach hypothesized that this ability of human vision could be explained by mutually inhibitory interactions in the retina. Physiological support of Mach's idea waited many years: it was found in a visual system far simpler than our own.

Hartline's discovery of lateral inhibition initiated a remarkable line of research extending to the present day. He and his coworker Ratliff (1957, 1958) found that the optic nerve responses from individual ommatidia could be quantitatively expressed in terms of the algebraic sum of inhibitory influences of neighboring ommatidia. Studying with Hartline as his last graduate student, I extended his work with Ratliff by measuring the receptive fields of lateral inhibition in the eye (Barlow 1969). A fellow graduate student, David Lange, and I detected an essential nonlinearity in the inhibitory interactions (Barlow and Lange 1974) that led to an accurate description of the eye's response to stationary patterns of illumination (Barlow and Quarles, 1975). Ratliff et al. (1967, 1974) analyzed the responses to dynamic pattern of illumination using linear systems analysis. Finally graduate students in my lab, Erik Herzog, Scott Jackson, and Christopher Passaglia, together with Frederick Dodge and I developed a comprehensive cell-based model of the *Limulus* eye that incorporates all known physiological properties of the eye and predicts its response with better than 95% accuracy (Passaglia et al. 1997, 1998). These achievements stand today as the only complete quantitative analysis of neural integration among an ensemble of sensory receptors. The well-known Hartline–Ratliff formulation and its later extension have been the starting point for many treatments of information processing in more complex neural systems. It led to a comprehensive description of the neural code the eye sends to the brain as discussed later in this chapter.

1.8 Circadian Rhythms in Visual Sensitivity

The *Limulus* lateral eye exhibits extraordinary day–night changes in sensitivity. A circadian clock located in the brain transmits efferent optic nerve activity to the eyes at night increasing their sensitivity to light by about 1,000,000 times

over daytime levels (Barlow et al. 1977). This discovery was also accidental. It was made by Stanley Bolanowski, Michael Brachman, and me while recording the lateral-eye ERG during a graduate laboratory exercise at Syracuse University in 1976. As described above, Hartline had recorded the ERG years before, but not at night. We were astonished to see the amplitude of the ERG increase at night and then decrease the following day while the crab was kept in constant darkness. We were doubly astonished to see the day–night rhythm disappear when we severed the optic nerve trunk. Suspicious that the optic nerve trunk may be transmitting efferent activity from the brain, we teased apart the individual fibers of the nerve trunk searching for brain-generated activity. We detected efferent activity in a few fibers but only at night. We recorded the activity and were delighted to find that stimulating the optic nerve with the recorded activity the following day transformed the eye to its highly sensitivity nighttime state: we could play the role of the circadian clock!

The so-called simple eye of this living fossil has evolved remarkably complex, sophisticated mechanisms to increase retinal sensitivity. Table 1 lists the multiple changes in anatomy, physiology, and metabolism that combine to produce the nearly 1,000,000-fold increase in nighttime sensitivity. Circadian rhythms in vision are not unique to *Limulus*; they are widespread among both invertebrates and vertebrates (Barlow et al. 1989, 2001). In most cases, visual sensitivity appears to be under the joint control of a circadian oscillator and light. Why visual systems of some animals need to anticipate changes in light intensity rather than respond directly to them is not known. Interestingly, the large nighttime increase in *Limulus* eye sensitivity nearly compensates for the nighttime decrease in ambient light intensity.

Table 1 Circadian rhythms in the *Limulus* lateral eye

Retinal property	Day	Night
Efferent input	Absent	Present
Gain	Low	High
Noise	High	Low
Quantum bumps	Short	Long
Frequency response	Fast	Slow
Dark adaptation	Fast	Slow
Lateral inhibition	Strong	Weak
Cell position	Proximal	Distal
Screening pigment	Clustered	Dispersed
Aperture	Constructed	Dilated
Acceptance angle	6°	13°
Photomechanical movement	Trigger	Prime
Photon catch	Low	High
Membrane shedding	Trigger	Prime
Intense light effects	Protected	Labile
Visual sensitivity	Low	High

1.9 Horseshoe Crabs Use Vision to Find Mates

Discovery of robust rhythms in *Limulus* eye sensitivity intensified a long-standing question: What does the horseshoe crab use its eyes for? Hartline often joked that he had spent many decades "studying vision in a blind animal." After learning about our discovery of circadian rhythms in *Limulus*, Hartline reminded me that no one had succeeded in uncovering a role for vision in the animal's behavior. Intent on finding one, I spent many dark cold nights diving with *Limulus* at the bottom of Buzzard's Bay near Woods Hole. . . and learning very little. I did learn, however, that crabs turned sharply away from shadows of downwelling moonlight that I cast on their eyes with my underwater clipboard. These shadow responses could be interpreted as predator avoidance behaviors, but it seemed unlikely to me that the retinal circadian rhythms evolved for this purpose. A more plausible explanation was suggested by my MBL colleague Colleen Cavanaugh who noted that *Limulus* often mate at night and they may need sensitive vision to find mates. Their predominant nocturnal migration to shallow waters during the flood tides of full and new moons is well known (Barlow et al. 1986). Upon reaching the water's edge, males seek and clasp onto females who then build nests and deposit eggs. We tested the possible role of vision by offering males cement castings of female shells and other shapes placed in the shallow mating areas. Needless to say, we were delighted to see males swarming around the castings, especially those painted black (Barlow et al. 1982). We were also amazed that the black castings evoked the entire male mating sequence: approach, mounting, and sperm release. In fact the males were so attracted to the castings that they would not leave them as the tide receded, risking dehydration and sea gull attack. We rescued these tenacious, love-struck males detaching them from the castings and returning them to the sea. The great attraction of males to the cement castings of females eliminated a role for chemical cues. These experiments provided the first clear evidence for a role of vision in the animal's behavior – males use vision to find mates!

How well can *Limulus* see? We tested their vision by observing the behavior of males in the vicinity of submerged cement castings using a suspended overhead video camera fitted with an image intensifier for nighttime observations. We found that males detected the castings nearly as well day and night (Powers et al. 1991) with greater sensitivity for higher contrast castings (Herzog et al. 1996). Females avoided the castings as did juveniles (Ridings et al. 2002). We concluded that the large 1,000,000-fold circadian increase in sensitivity of the lateral eyes at night enables the animals to detect potential mates.

How many ommatidia does a male use to see a female? The coarsely faceted lateral eyes provide wide-field vision but with very low resolution. Males may be operating near the optical limit of their lateral eyes by using as few as four ommatidia, about 1% of the eye's receptors, to detect a female at a distance of about 1 m. Sacrificing what little acuity they have to increase their visual sensitivity at night, it is indeed surprising that the animals can see so well in their underwater habitat.

1.10 Neural Code for Vision

What does the eye tell the brain? Forming images of mates with less than 1% of the eye's receptors raises the question of what information the eye sends to the brain when a crab sees a mate underwater. Recording the information transmitted to the brain by the many optic nerve fibers is not feasible. Fortunately, as described above the neural network of the *Limulus* eye has been characterized so thoroughly that its properties can be modeled precisely with a realistic, cell-based model of the eye, one that is capable of computing the entire ensemble of optic nerve responses the eye sends to the brain (Passaglia et al. 1998). With it we analyzed neural coding underlying mate detection by recording the lateral eye's view of its underwater world with a shell-mounted camera (CrabCam, Fig. 3) while simultaneously recording the response of an optic nerve fiber from an ommatidium looking in the same direction as the CrabCam. Upon returning to the laboratory, we played back the videotaped scene to the computational model and calculated the ensemble of optic nerve responses, or "neural images," to the scene. Finding that the response they recorded from the single nerve fiber matched well that computed for the equivalent receptor of the model, we examined the computed neural images for putative neural codes of potential mates. Incredibly, we found that the eye responded vigorously to mate-size objects moving across its visual field, that is, the eye appears "tuned" for detecting horseshoe crabs. We concluded that its spatial and temporal properties are optimized for detecting moving, crab-like objects (Passaglia et al. 1997).

Fig. 3 A mini-video camera, CrabCam, mounted on an adult horseshoe crab records what the right lateral eye sees. A recording chamber mounted anterior to the eye contains a microsuction electrode (black cylinder on right) that records the response of a single optic nerve fiber through a whole drilled in the carapace. A white cap seals the recording chamber. The waterproof electrode and camera simultaneously record a nerve fiber's activity and the eye's underwater view as the crab searches for mates

The lateral eyes of this so-called living fossil are not as primitive as one might expect. They are elegant in design, incorporating many of the integrative mechanisms found in more complex vertebrate eyes. They possess universal excitatory and inhibitory mechanisms that "tune" the eye to transmit robust signals to the brain about mate-like objects. Circadian mechanisms of adaptation enable the eyes to operate over wide ranges of light intensity. Even on the darkest, overcast moonless nights, they can tell the brain about potential mates (Atherton et al. 2000). Under such conditions, *Limulus* can see what we cannot.

2 What Is the Neural Basis of the Crab's Visual Behavior?

The answer to this question would surely rank as the "11th" in our list of Top 10 discoveries from *Limulus* vision research. It remains unanswered but certainly not uninvestigated. Wilska and Hartline (1941) were the first to probe the *Limulus* brain and succeeded in recording responses from neurons in the optic ganglia. They detected cells that responded only to the cessation of illumination, "OFF responses" similar to those recorded from ganglion cells of vertebrate retina and completely unlike the "ON responses" that characterize responses from the *Limulus* eye. Thirty years later Max Snodderly (1971), a student of Hartline, extended their work and found greater complexity with different types of light responses in the two optic ganglia of the brain. He noticed that neurons in the first optic ganglion, the lamina, only responded to light offset, i.e., they were exclusively OFF cells, a finding later confirmed by my student, Christopher Passaglia (1997). In the second optic ganglion, the medulla, Snodderly reported all three types of responses, ON, ON-OFF, and OFF; some having large receptive fields ranging from 25 to 100% of the eye, as confirmed by Passaglia. Using fluorescent dyes that he could inject from an intracellular recording electrode, Passaglia tracked neuronal processes across the medulla and branching into the lamina terminating as far as 2 mm away from the cell body in the medulla. He also found that neurons in the brain integrate the eye's output over periods of 250–500 ms. This temporal integration together with spatial integration from the convergence of optic signals from small regions of the eye onto brain neurons improves the signal-to-noise properties of neural images computed with our cell-based model (see above) for the nighttime state of the eye (Hitt et al. 2000).

The circadian increases in the eye's sensitivity combined with spatial and temporal filtering in the brain can yield detectable visual signals even under very low nighttime levels of illumination. The circadian and neural integrative mechanisms may help explain how *Limulus* can see so well at night, but they do not reveal how the brain processes the information it receives and generates responses to behaviorally relevant visual stimuli. With the same fluorescent dye cell-marking technique used by Passaglia, Kazuo Mori in my lab detected nerve cells that respond well to the contrast, both positive and negative, of mate-size objects that move across the visual field with the approximate speed of a

horseshoe crab (Mori et al. 2007). Moreover Mori found that processes of these cells appear to be anatomically associated with neurons that mediate the motor output of the brain. Although preliminary, these findings lay the foundation for completing the pathway from eye input to brain output.

As noted at the beginning of this chapter, Hartline chose to study "a suitable organ" (A.V. Hill) in "some animal of choice" (A. Krogh) and moved forward the entire field of vision research. He chose the lateral eye of *Limulus* with the hope of understanding how light causes changes in an animal's behavior, an interest inspired by his undergraduate research on pill bugs. How sensory information is coded and decoded to produce a behavioral output is a fundamental question in neuroscience. The relative simplicity of the *Limulus* eye has provided a clear window into the peripheral coding of visual information, but the brain's decoding is not clear. The *Limulus* brain is not simple – no brain is. How it processes the eye's neural code is not completely understood. We must probe deeper into the brain to find how visual inputs control motor outputs. Perhaps then we will know how the animal sees.

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