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DIVERSE CELL TYPES, CIRCUITS, AND MECHANISMS FOR COLOR VISION IN THE VERTEBRATE RETINA

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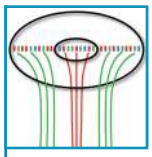


Thoreson WB, Dacey DM. Diverse Cell Types, Circuits, and Mechanisms for Color Vision in the Vertebrate Retina. *Physiol Rev* 99: 1527–1573, 2019. Published May 29, 2019; doi:10.1152/physrev.00027.2018.—Synaptic interactions to extract information about wavelength, and thus color, begin in the vertebrate retina with three classes of light-sensitive cells: rod photoreceptors at low light levels, multiple types of cone photoreceptors that vary in spectral sensitivity, and intrinsically photosensitive ganglion cells that contain the photopigment melanopsin. When isolated from its neighbors, a photoreceptor confounds photon flux with wavelength and so by itself provides no information about color. The retina has evolved elaborate color opponent circuitry for extracting wavelength information by comparing the activities of different photoreceptor types broadly tuned to different parts of the visible spectrum. We review studies concerning the circuit mechanisms mediating opponent interactions in a range of species, from tetrachromatic fish with diverse color opponent cell types to common dichromatic mammals where cone opponency is restricted to a subset of specialized circuits. Distinct among mammals, primates have reinvented trichromatic color vision using novel strategies to incorporate evolution of an additional photopigment gene into the foveal structure and circuitry that supports high-resolution vision. Color vision is absent at scotopic light levels when only rods are active, but rods interact with cone signals to influence color perception at mesopic light levels. Recent evidence suggests melanopsin-mediated signals, which have been identified as a substrate for setting circadian rhythms, may also influence color perception. We consider circuits that may mediate these interactions. While cone opponency is a relatively simple neural computation, it has been implemented in vertebrates by diverse neural mechanisms that are not yet fully understood.

I. INTRODUCTION

The mechanisms that underlie the perception of color have interested scientists since the 17th century (317). Sir Isaac Newton recognized that "The rays, to speak properly, are not coloured. In them there is nothing else than a certain power and disposition to stir up a sensation of this or that colour" (332). We now recognize that "stirring up a sensation" for the perception of color arises from complex neural computations implemented in a multistage process that begins with the distinct spectral tuning properties of cone photoreceptors (26) and then proceeds through the retinal circuitry on to the lateral geniculate nucleus (LGN), the primary visual cortex and, at least in primate, higher order visual areas in neocortex (68). Our understanding of the neural mechanisms for color has evolved together with a growing appreciation for the striking neural complexity of the visual pathways. Nowhere are these revelations more dramatic than in the retina where roughly 100 neural cell types interact to create 40 or more visual pathways, all packaged into a thin neural sheet that transfers signals through two synapses from photoreceptors to ganglion cells whose axons connect the eye to the brain. Over 50 years ago, action potential recordings from neurons in the parvocellular layers of the LGN by Hubel and Wiesel presented a tantalizingly simple picture of how a single visual pathway might be the neural basis for "opponent color theory" (498), the dominant idea in color science at that time. Today we are confronted with a dizzyingly complex array of

pathways and mechanisms that play varied roles in color processing at the retinal level; indeed, new circuitries that may be fundamental to understanding human color vision are still being discovered (506). The motivation for this review is to consider our current understanding of the cell types and circuits of the retina across vertebrate species, from teleost fish like the zebrafish and goldfish, to intensively studied mammals like mouse and rabbit, and to human and non-human primates where certain aspects of color circuitry appear to have been reinvented during primate evolution. Our goal is to determine to what degree mechanisms are shared or diverse across the vertebrates and assess our current understanding of the retinal circuitry involved in the neural processing of color in general.

This review will take us from the roles played by photoreceptors through second- and third-order interneurons that begin the process of comparing photoreceptor signals necessary for wavelength encoding and then move on to the ganglion cells that create multiple parallel pathways for color. We consider opponent interactions among cone photoreceptors with differing spectral sensitivities that serve as the predominant mechanism for extracting color information. Color vision is absent under scotopic conditions when only a single type of photoreceptor cell, rods, is active. However, at higher mesopic light levels where both rods and cones are active, their interactions in the retinal circuitry can influence color perception. Recent studies suggest that the activity of intrinsically photosensitive retinal ganglion cells (ipRGCs) may also influence color perception. We thus also review studies on the mechanisms by which rod photoreceptors and intrinsically photosensitive retinal ganglion cells may interact with cone pathways to impact the perception of color. While certain key features are shared among species, such as cone opponency and the essential role for inhibitory feedback from horizontal cells to photoreceptor cells, it is clear that these features did not evolve from a single neural plan for wavelength-coding circuits that was elaborated from fish to human.

II. ORIGINS OF SPECTRAL SENSITIVITY

A. Photoreceptor Spectral Sensitivity

Spectral sensitivity is determined by a variety of factors including the wavelength sensitivity of light-sensitive chromophores and pigment molecules along with the filtering of incident light by overlying structures such as macular pigments, lens, and photoreceptor oil droplets. The perception of light, and thus color, begins with the absorption of photons by light-sensitive opsins contained in the outer segments of rod and cone photoreceptors. Outer segments are modified cilia that incorporate the various proteins involved in phototransduction. Opsins are G protein-coupled receptors that can covalently bind to light-sensitive chromophore molecules through a Schiff base. The chromophore that is most often used with both vertebrate and invertebrate opsins is 11-*cis*-retinal (210). Absorption of a photon triggers a conformational change from 11-*cis*-retinal to all-*trans*-retinal, straightening out a kink at the 11-*cis* position (200). This induces a conformational change in opsin to initiate a cascade of events that, in vertebrates, involves activation of cGMP-specific phosphodiesterase to cleave cGMP and thereby close cGMP-gated cation channels, resulting in a light-evoked hyperpolarization of the photoreceptor membrane potential. Molecular aspects of the phototransduction cascade are understood in extraordinary detail, as reviewed elsewhere (10, 44, 45, 146, 251, 316, 348).

The amplitude of a photoreceptor's light response is determined by the number of photons absorbed by the light-sensitive chromophore cradled within the opsin protein. The likelihood that a photon will be absorbed depends on the wavelength of that photon along with the spectral absorption properties of both the opsin protein and its chromophore. Different photoreceptor types possess opsins that differ in their spectral absorption properties. While they all absorb photons over a wide range of wavelengths, opsins vary in their peak sensitivity **(FIGURE 1)**. There are five classes of vertebrate opsins: Rh1, Rh2, SWS1, SWS2, and LWS. Rods express only rhodopsin (Rh1). In most birds, reptiles, fish, and amphibians, a cone can possess one of four different cone opsins with peak sensitivity at ultraviolet (UV) (SWS1), short (SWS2), medium (Rh2), or long (LWS) wavelengths. In addition to rod and cone opsins, there is a class of intrinsically photosensitive retinal ganglion cells that possess a different type of opsin, melanopsin, with a peak absorbance midway between that of rods and M cones **(FIGURE 1*C*)**. In the course of evolution, placental mammals lost the SWS2 and Rh2 opsins, so most mammals possess only two cone pigments (SWS1 and LWS). The peak sensitivities of these two pigments vary among species. For example, peak sensitivity of the LWS pigment is in the red range for some animals (e.g., cat) but in the green for others (e.g., mouse). Similarly, peak sensitivity of the SWS1 pigment is in the UV for some animals (e.g., mouse) but in the blue for others (e.g., cat) (213, 283). In addition to S cones with an SWS1 pigment, primates possess two variants of the LWS pigment with one more sensitive to middle wavelengths (M cones) and one more sensitive to longer wavelengths (L cones) **(FIGURE 1)**. When discussing non-mammalian vertebrates, we use the terminology Rh1, Rh2, SWS1, SWS2, and LWS. In keeping with the more commonly used nomenclature for mammals, we refer to mammalian cones that possess the SWS1 pigment as S cones. This includes SWS1 cones such as those in mouse retina that show peak sensitivity in the UV range. In dichromatic mammals, we refer to cones with the LWS pigment as M cones. In primates that have two LWS pigments, we distinguish M and L cones.

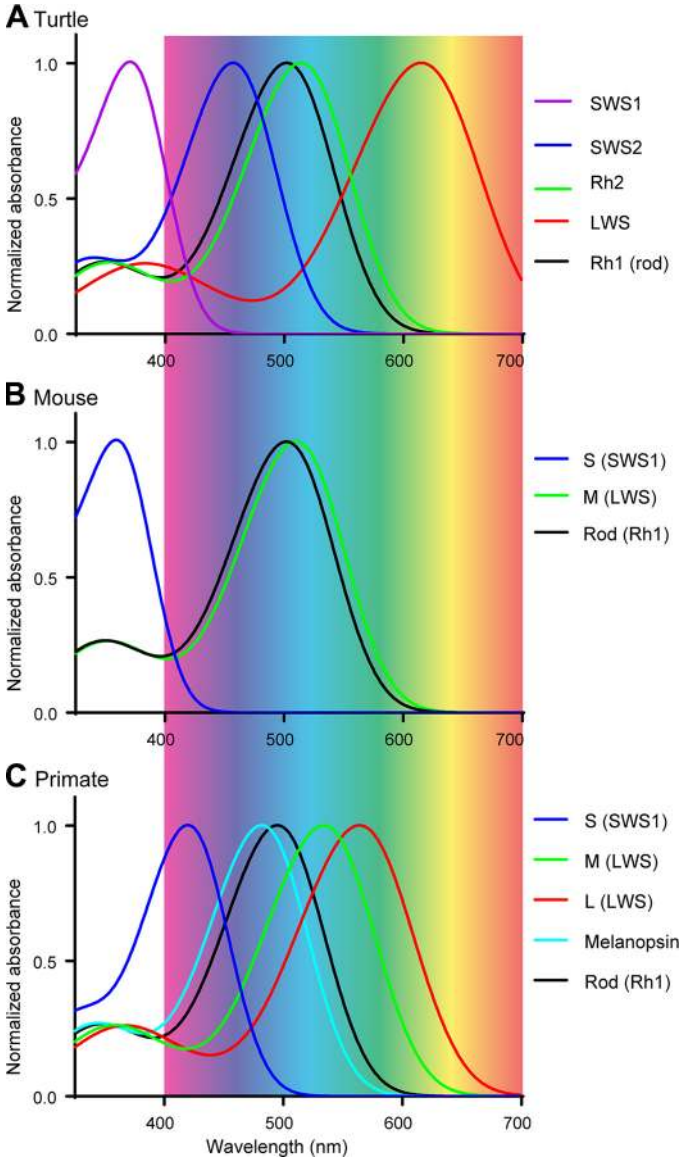


FIGURE 1. Photoreceptor cell spectral sensitivities from turtle (*A*), mouse (*B*), and trichromatic primate (*C*). *A*: pigment absorbance spectra of turtle rods (Rh1 pigment, 502 nm peak absorbance), long wavelength cones (LWS, 615 nm), middle wavelength cones (Rh2, 514 nm), short wavelength cones (SWS2, 457 nm), and ultraviolet (UV) (SWS1, 371 nm) cones. *B*: absorbance spectra of mouse rods (Rh1, 502 nm), S cones (360 nm), and M cones (510 nm). *C*: absorbance spectra of trichromatic primate rods (Rh1, 495 nm), S cones (SWS1, 420 nm), M cones (LWS, 534 nm), and L cones (LWS, 564 nm) as well as melanopsin (482 nm). Absorbance spectra were simulated using A1-based visual pigment nomograms with the peak absorbance values given above (90, 163, 210, 282).

The spectral absorption properties of opsin determine the spectral sensitivity of the light-evoked voltage response of a photoreceptor. The spectral sensitivity of opsin is shaped by a few amino acids near the chromophore binding pocket. Differences in only five amino acids can account for the differences in spectral sensitivity among MWS and LWS opsins in vertebrate species from fish to primate. Differences in only three residues are sufficient to account for differences in spectral sensitivity between primate M and L cones (329, 515, 516). The spectral sensitivity of S cones is also determined by only a few key amino acids (276).

In addition to properties of photon absorption by opsin, spectral sensitivity is also shaped by the identity of the light-sensitive chromophore molecule. The chromophore employed by mammals and many other animals is retinal (vitamin A1 aldehyde). Some non-mammalian vertebrates also use 3-dehydroretinal (vitamin A2 aldehyde) which shifts the absorbance to longer wavelengths (reviewed in Ref. 210). For example, marine fish typically use retinal, whereas freshwater fish use 3-dehydroretinal, either alone or in combination with retinal. Expression of these chromophores in fish can vary with season and other environmental factors (323, 435, 436, 457), shaping spectral sensitivity to meet changing environmental conditions.

Spectral sensitivity is also shaped by the spectral distribution of light reaching the photoreceptors that is in turn shaped by absorbance in overlying tissues including the cornea, lens, and macular pigments. In the human eye, the xanthophyll pigments lutein and zeaxanthin are present in the foveal pit and across the retinal layers in the parafovea giving the macula lutea (Latin for yellow spot) its name. Macular pigment persists after cone death, and its disposition suggests that specialized foveal Müller cells may be repositories for these molecules (151, 269). By preferentially absorbing blue light, these pigments may reduce scatter from blue light to improve foveal acuity and protect cones from damaging short wavelengths in humans (507). While the human lens darkens with age, taking on a yellow-brown color (31, 394), the density of macular pigment tends to diminish with age (236).

The cones of non-mammalian vertebrates and the oviparous mammal platypus (523) have oil droplets in their inner segments that help to focus and filter the light captured by the outer segment (443). While some oil droplets are colorless, others can be green, yellow, orange, or red. Colored oil droplets sharpen spectral tuning at the cost of reducing sensitivity. Narrowing of spectral tuning by oil droplets reduces spectral overlap between cone subtypes. As discussed later, color perception requires comparisons of responses from cones with differing spectral sensitivity and so reducing the spectral overlap among cones with different colored oil droplets can actually reduce the capability for discriminating monochromatic lights (8). However, modeling studies suggest that the narrowing of spectral tuning by oil droplets can improve color discrimination with broadband illumination at high intensities (443, 478).

B. Photopigments and Dimensions of Color Vision

Thomas Young (517) is widely credited with the hypothesis of trichromatic vision, namely, that our perception of color

arises from the activity of three different receptors with different spectral sensitivities. Extended by Maxwell (302) and championed by Helmholtz (184), this became widely known as the Young-Helmholtz trichromatic theory of human color vision. Trichromacy in humans and other primates arises from the presence of three cone types with distinct wavelength sensitivity peaks: L cones (~565 nm), M cones (~535 nm), and S cones (419 nm) **(FIGURE 1*C*)**. As discussed above and reviewed elsewhere (210, 328, 355), most mammals possess S cones with SWS1 pigment and a single type of M cone with LWS pigment and thus appear to be dichromats. Many birds, reptiles, and fishes possess four cone pigments (SWS1, SWS2, Rh2, LWS) and appear to function as tetrachromats (210). However, the number of spectrally distinct photoreceptor types does not necessarily predict the dimensionality of color vision (210). For example, by combining the spectral absorbance of opsins with the filtering properties of different colored oil droplets, turtles have seven spectrally different cone subtypes (282) but nevertheless behave as tetrachromats (8). As we consider later, rhodopsin in rods and melanopsin in intrinsically photosensitive retinal ganglion cells both differ in spectral sensitivity from cone pigments, and absorption by these pigments can impact color perception, but these interactions may not yield genuine tetra- or pentachromatic vision in primates (210).

Among placental mammals, only primates possess a third cone pigment. Old World monkeys and the great apes possess separate M and L pigments that differ in their spectral sensitivities. The M and L pigment genes are located on the X chromosome in a head-to-tail tandem array and likely arose by duplication and divergence from a single ancestral LWS pigment gene (202). With the exception of the genus *Alouatta* (howler monkeys) (211, 214), New World monkeys have only a single polymorphic LWS pigment gene on their X chromosome, but this gene has three alleles that can code for distinct spectral variants (319). A male will express only one of these three LWS pigments and is therefore dichromatic. However, a female may have different alleles on the two X chromosomes and therefore, due to random X chromosome inactivation, can express both allelic forms within the cone array. Thus females that are heterozygous at the X chromosome can be trichromats, whereas females that receive the same allele from both parents will be dichromats. The transition from dichromatic to trichromatic vision can increase the number of discriminable colors (i.e., combinations of hue, saturation, and brightness) from perhaps 10,000 to >1 million (278, 279, 300) and thus provide significant evolutionary advantages (375, 376). In addition to primates, trichromacy has also reemerged in a handful of marsupials that have three cone types (9, 355). In these animals, only two cone pigment genes have been identified, but there are two copies of the rod pigment gene, suggesting that the third cone subtype may possess a modified Rh1 rod pigment (74).

In Old World monkeys, the fact that M and L opsin genes are both on the X chromosome means that males are particularly susceptible to color vision defects if their lone X chromosome possesses an anomalous form of one of the pigments or lacks it entirely. Conversely, females have the potential for normal M and L cone pigments on one X chromosome together with an anomalous pigment on the other. This provides a potential substrate for tetrachromatic vision. In the human population, there are also two normal variants of the L cone pigment, so it is thought that perhaps half of all women have two different L cone pigment genes (328). In a careful study of 24 women who had the genetic potential for tetrachromacy by virtue of having a color anomalous son, only one made color matches consistent with tetrachromacy (219). This suggests that while genuine tetrachromacy among humans may be possible, it is quite rare. The benefits of additional capabilities for color discrimination within the M and L pigment range is minimal since normal trichromats can discriminate wavelengths that differ by as little as 1 nm in the 450–600 nm range (320, 365). On the other hand, the improved discrimination at shorter wavelengths provided by addition of a fourth UV-sensitive pigment, as in many birds and reptiles, offers a more significant selective advantage for tetrachromacy. For a more complete discussion of the genetics of human color vision and color vision defects, we refer the reader to some recent reviews (210, 328).

The observation that in New World monkeys, female members of the same species can be either dichromatic or trichromatic suggests that the retina and brain are capable of using information from three cone types when present. One possibility is that other than a difference in cone opsin expression, the postreceptoral neural wiring of the retinas in both male and female monkeys is identical, and no further changes in the visual system are required to confer trichromatic color vision. A second possibility is that the visual system is fundamentally modified in trichromatic females during early development. To test these ideas, a viral vector was used to introduce the human L cone pigment gene into the retina of a normally dichromatic adult male squirrel monkey expressing only a single M/L gene (289). The authors reported behavioral performance consistent with the acquisition of trichromacy, suggesting that the underlying circuitry present in adult dichromats may be sufficient to use information captured by three cone subtypes for trichromatic discrimination. Similarly, mice genetically engineered to express a human L cone pigment in addition to the endogenous M and S cone pigments showed behavioral changes consistent with additional chromatic sensitivity (215). However, stochastic, cone-to-cone variation in pigment expression would be expected to produce blotchy expression patterns in the cone mosaic, and the differences in apparent luminance between these blotches could potentially be used for discriminating patterns of differing spectral content without the need for genuine trichromatic color

vision (72, 288). The question of whether there may be differences in the postreceptoral retinal organization of dichromatic versus trichromatic members of the same species will be considered in more detail below in the context of primate retinal circuits and color opponent mechanisms.

C. Cone Types and Cone Mosaics

Different species vary in the types and arrangements of their cones (472). While birds, reptiles, fish, and amphibians typically possess four different cone pigments (SWS1, SWS2, Rh2, and LWS), many of these animals have more than four cone subtypes. This is because, in addition to four types of single cones that each express different opsins, many nonmammalian vertebrates have morphologically distinct double cones that contain some of the same pigments. Double cones consist of a large primary member and smaller accessory member with membranes fused to one another; they are not coupled to one another but instead signal independently. The two members of a double cone can possess either the same or different opsins.

Birds have four types of single cones with different cone pigments plus a double cone. Comparisons between behavioral sensitivity and the spectral sensitivity of single and double cones that contain different-colored oil droplets have led to the suggestion that double cones in birds participate in luminance and movement detection but not color vision (157, 174, 344). It has also been suggested that the orientation of double cones may promote detection of polarized light (54, 183). The participation of four spectrally distinct small single cones in color vision allows tetrachromatic color vision in birds (157, 344).

Turtles possess four different cone pigments (282, 341) **(FIGURE 1*A*)** but have seven morphologically distinct cone subtypes: Rh2 (M) pigment in single cones with yellow oil droplets, SWS2 (S) pigment with UV-absorbing oil droplets, SWS1 (UV) pigment with clear oil droplets, two types of single cones with LWS (L) pigment but differently colored oil droplets, and a double cone in which both members possess the LWS pigment but the principal member has an orange oil droplet while the accessory member lacks an oil droplet altogether. Whether these different cone types participate equally in color vision remains unclear.

Opsin expression in fish retina is complicated by an ancestral gene duplication event (155). Zebrafish, like most other fish, therefore have genes coding for eight different cone opsins: two L pigments (LWS-1 and -2), four M pigments (Rh2–1, 2–2, 2–3, and 2–4), an S pigment (SWS-2), and UV pigment (SWS-1) (65, 433). Zebrafish have two types of single cones that possess SWS-1 and SWS-2 pigments, respectively. The primary member of each double cone possesses an LWS pigment, and the shorter accessory member appears to express all four Rh2 pigments (5). The M pigment in a double cone can be of two different varieties (Rh2–1 or 2–2). Adult zebrafish cones are arranged in a regular mosaic that alternates double cones with SWS-1 and SWS-2 single cones **(FIGURE 2*A*)**. This orderly arrangement is preserved throughout the retina, but there are also regional differences in pigment expression among different cone subtypes with a shift from shorter to longer wavelength-preferring versions of both M (from RH2–1 and 2–2 to RH2–3 and 2–4) and L (from LWS-1 to -2) pigments as one moves from center to periphery. Like many other fish, zebrafish cones can also employ chromophores derived from either vitamin A1 (retinal) or A2 (3,4-didehydroretinal), introducing additional spectral differences between cones (126).

It is hypothesized that during evolutionary passage through a nocturnal "knot-hole" early in the Jurassic period (484), mammals lost all but two cone pigments to render them dichromatic (209). The typical dichromatic mammal has only middle (M; Rh2) and short (S; SWS1) wavelength sensitive opsins. S cones are typically distributed more sparsely than M or L cones (355). In mouse retina, in addition to genuine S cones that express only SWS1 opsin (182), M cones can also express SWS1 opsin (7, 386). SWS1 pigment co-expression in M cones varies along a dorsal-ventral gradient with stronger SWS1 pigment expression in ventral retina and weaker expression in dorsal retina **(FIGURE 2*B*)**.

A hallmark of the primate retinal structure is a pitlike depression called the fovea that demarcates the locus of peak visual acuity along with a host of striking anatomical and physiological specializations related to spatial and color vision (368, 369). Within 100 μm of the foveal center, the mosaic is dominated by a high density of L and M cones, whereas rods and S (SWS1) cones are greatly reduced in density (2, 39, 81, 168, 297, 346). In the human retina, rods are completely absent from the foveal center **(FIGURE 2*C*)**. Because L and M cones are morphologically indistinguishable, the foveal cone array appears quite regular. However, the distribution of L and M cones within that regular mosaic is random (26, 192, 388). Moreover, there is considerable interindividual variation in the proportion of M versus L cones **(FIGURE 2*D*)**. However, neither the distribution nor relative number of M versus L cones appears to impact color perception (27, 192, 315, 389). S cones are present in a low-density, regular, nonrandom array, similar to other mammals (80). Rods begin to outnumber cones beyond the central 1 degree (~300 μm from the foveal center) and peak in density at ~3 mm eccentricity where they outnumber cones ~20:1 (345, 346) **(FIGURE 2*C*)**.

D. The Principle of Univariance

The broad spectral tuning properties of photoreceptors illustrated in **FIGURE 1** underlies a fundamental property of the physiology of these cells known as the principle of uni-

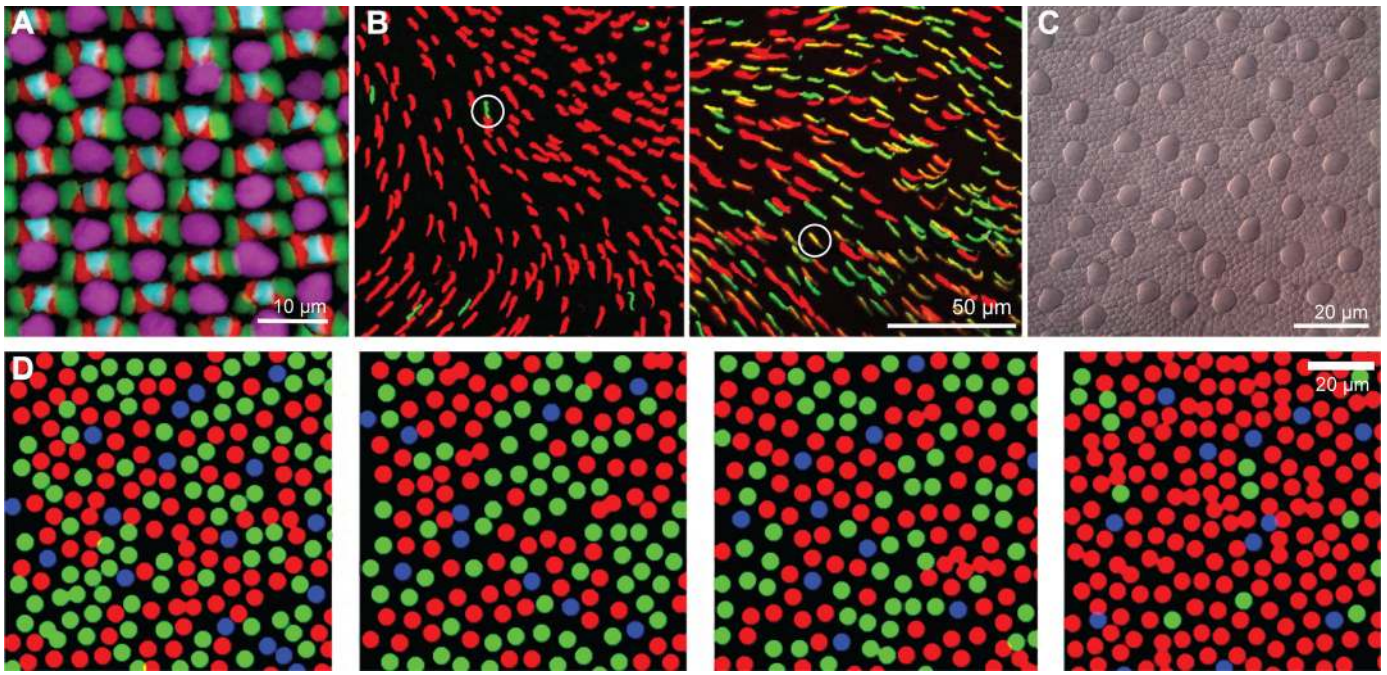


FIGURE 2. Photoreceptor mosaics. *A*: photoreceptor mosaic in zebrafish showing the regular array of double cones alternating with SWS1 and SWS2 single cones. The large primary member of the double cones possesses LWS pigment, and the shorter accessory member possesses Rh2 pigment. This orderly array is maintained across the retina (blue = SWS2 opsin; green = Rh2 opsin; violet = SWS1 opsin; red = LWS opsin) (Image courtesy of R. Wong, unpublished data.) *B*: cones of the mouse in dorsal versus ventral retina. *Left panel*: immunostaining of M (red) and S (green) opsins in dorsal retina where the great majority of cones express only M opsin. An S cone is circled. *Right panel*: in ventral retina, many of the M cones also express S opsin. A cone containing both M and S opsin is circled. [Adapted from Haverkamp et al. (182).] *C*: photoreceptor mosaic in the macaque monkey retina in an unstained preparation from mid-peripheral retina. Plane of focus is on the inner segments; the lower density large cone profiles are irregularly and randomly arranged in a sea of smaller rod profiles. Rods greatly outnumber cones except in the central retina (Dacey, unpublished data). *D*: human cone types identified in the living eye at ~1 degree (~250 μm) from the foveal center by adaptive optics imaging combined with retinal densitometry from 5 human subjects (each panel is from a different subject) (192, 193). L cone (red) and M cone (green) ratio is variable across subjects with some individuals showing an array dominated by M cones (*leftmost panel*) and others by L cones (*rightmost panel*). Note that L and M cones appear to be arranged randomly, while the sparse S cones (blue) form a more regular mosaic. [Adapted from Brainard (26) and Hofer et al. (193), with permission.]

variance which asserts that "the signal from each cone depends only upon the rate at which it is effectively catching quanta, it does not depend upon the associated wavelength" (324). Thus, if photon flux is adjusted to produce the same effective quantal catch for lights of two different wavelengths, then the responses will be indistinguishable. Photocurrents measured in the outer segments of cones obey the principle of univariance (19, 247). In general, this is also true for cone voltage responses measured in the inner segment. **FIGURE 3** illustrates this with recordings from a red-sensitive turtle cone showing that small spots of red (680 nm) and green (550 nm) light evoke identical responses when the intensity of the green light is increased so that the amplitude of the cone light response matches that evoked by red light. With larger spots of light that illuminate the surrounding region of retina, slight deviations from univariance can sometimes be detected due to interactions with neighboring photoreceptors through gap junctions or by negative feedback from horizontal cells (147, 196, 337, 347, 403).

An important consequence of univariance is that the response of a single photoreceptor cannot by itself be used to discriminate between different wavelengths. Wavelength discrimination instead requires comparisons between photoreceptors with differing spectral sensitivities. Comparisons between cones of differing spectral sensitivities begin at the very first synapses in the retina within the outer plexiform layer.

E. Color Opponency

Noting that certain color combinations are theoretically possible but never perceived (e.g., reddish green or bluish yellow), Ewald Hering (186) hypothesized in 1878 that color vision involves processing of opponent pairs of colors (red vs. green, blue vs. yellow, and white vs. black). The hypothesis of color opponency was further refined in the modern era by Jameson and Hurvich (203, 204) who showed that the perception of red could be cancelled by

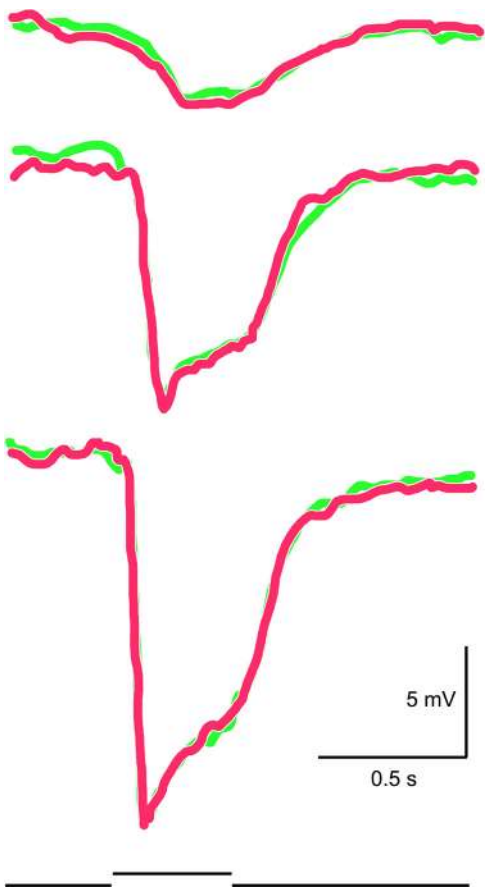


FIGURE 3. Univariant responses of a red-sensitive turtle cone to red (680 nm) and green (550 nm) lights evoked by 0.4-s flashes of 0.2 mm diameter. The intensity of 680-nm light was adjusted to evoke a hyperpolarizing response that matched the amplitude of the response to 500 nm. The matched responses are superimposed.

green and yellow cancelled by blue. They went on to quantify the red/green and blue/yellow spectral response curves of human color vision. Color opponency provides an efficient mechanism for removing redundancies that arise from the overlap in spectral sensitivity among different cone subtypes as well as spectral redundancies that are present in natural images (37, 264). It has been suggested that the evolution of blue/yellow opponency may have also been driven by advantages in detecting circadian changes in the spectral content of skylight (354, 418).

One psychophysical consequence of color opponency is the presence of colored after-images seen after one abruptly switches view from a brightly colored object to a white background. Gazing at a bright red spot will generate a green after-image and vice versa; a yellow spot will produce a blue after-image and vice versa. As considered in detail in the following sections, the retina plays a fundamental role in opponent processing (499, 520). However, it has also long been recognized that the perceptually unique hues of human vision (i.e., hues that cannot be created by mixing lights of different colors) do not lie along the cardinal axes produced by antagonistic interactions between cone types (i.e., cone opponency) that are observed in neurons from the primate retina and LGN. This indicates that retinal processes are by themselves insufficient to account for the opponent balance in hue perception (46, 103, 107, 266, 510). For additional discussion of opponent interactions in color vision, we refer the interested reader to other sources (408, 487).

Because opponent interactions between cone types do not precisely match color opponent interactions in hue perception, we reserve the term *color opponency* for discussion of color perception where the underlying neural basis or locus is unclear. We use the term *cone opponency* when referring to responses in which the underlying cone inputs have been identified and associated with a light response (e.g., midget ganglion cells may show L vs. M cone opponency). We use the more general term *spectral opponency* when discussing the opponent responses of neurons to stimuli that vary in chromaticity but not luminance, but where the cone inputs have not been carefully specified.

Color can be defined as occupying a three-dimensional color space with three principal axes corresponding to the opponent pairs proposed by Hering: red versus green, blue versus yellow, and white versus black. The red/green and blue/yellow axes define the hue or chromaticity, whereas the white/black axis defines luminance. To assess the perception of changes in hue in isolation from changes in luminance, one needs to ensure that the measured response arises only from changes in chromaticity. The visual system is extraordinarily sensitive to small changes in luminance, so this presents a challenging confound to experiments that attempt to define mechanisms involved in processing of chromaticity or pure spectral differences. Building on the principle of univariance, Donner and Rushton (117) developed the method of silent substitution (128) to address this challenge. As illustrated in **FIGURE 3**, the principle of univariance states that we should be able to find an intensity that evokes an identical response in a single cone to two lights that differ in wavelength. If the downstream neuron receives input only from that single cone type, its response to the two different wavelengths should also be the same. However, if there are contributions from a second photoreceptor with a different spectral sensitivity, then the downstream response will show a different response to the two wavelengths. Use of the silent substitution technique to isolate the light-evoked voltage responses of L, M, and S cones in the macaque monkey retina in vitro is illustrated in **FIGURE 4** (347) using three spectrally distinct primary light sources. In this figure, one can see that while steadily illuminating the retina with two wavelengths (e.g., blue and green) to preferentially desensitize two of the three cone subtypes, temporal modulation of a third wavelength (e.g., red) can evoke temporally modulated responses that are only observed in the third cone subtype. This is a valuable technique for distinguishing inputs from specific photore-

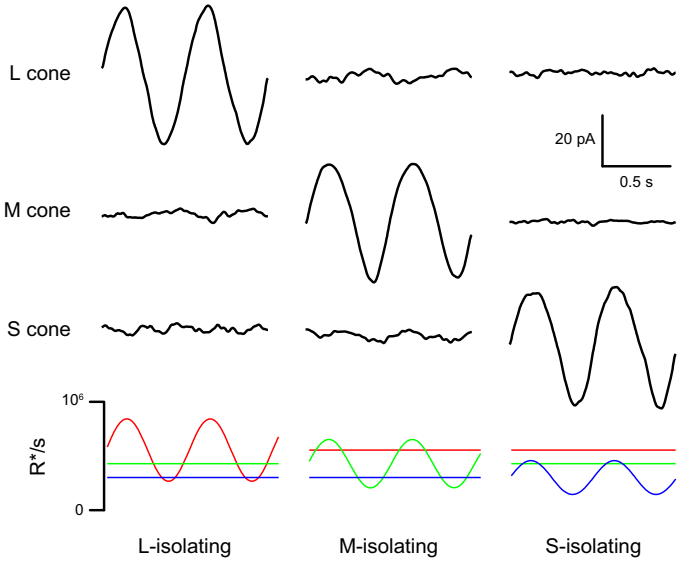


FIGURE 4. Silent substitution method applied to identify L, M, and S cones in the macaque monkey retina. The traces show light-evoked membrane current responses from single L, M, and S cones in the intact retina in response to sinusoidal modulation of stimuli arising from 3 primary lights (75, 347). The colored traces at the bottom show the calculated quantal catch during 2 stimulus cycles (R*/s) for L (red), M (green), and S (blue) cones with each of the 3 primary lights for L, M, and S cone isolating stimulus configurations. This method was used to distinguish the sparse S cones from the majority L and M cones in the overall cone array.

ceptors, although one should note that the steady backgrounds vary for different "silent substitutions" and differences in tonic activity produced by differences in background illumination of "silent" cones might potentially influence retinal circuits. This silent substitution technique has been extended to the use of five spectrally different lights, allowing independent modulation of rods, intrinsically photosensitive retinal ganglion cells, and the three cone subtypes (4, 221, 404).

F. Color Constancy

A primary purpose of color vision is to discriminate objects that differ in the spectral characteristics of surface reflectance. To achieve this, the visual system must not only detect and discriminate different wavelengths but also subtract the spectral characteristics of the illuminant to yield accurate assessments of reflectance. This latter property is known as color constancy. As reviewed in detail elsewhere (144, 408, 487), perfect color constancy is not maintained under all conditions, but the visual system does a remarkably good job of maintaining stable color appearance under widely varying illumination conditions. While higher visual mechanisms also contribute (28, 29, 64, 118), including cortical mechanisms in area V4 (144, 408, 486), psychophysical studies indicate retinal mechanisms have an important role in maintaining color constancy (144). One early mechanism that helps to compensate for changes in the spectral content of the illuminant are the changes in sensitivity of individual cones during light adaptation (29, 64, 336, 477). For example, a shift in the spectral content of the illuminant to longer wavelengths will adapt L cones more strongly than S or M cones. However, this mechanism, termed von Kries adaptation, cannot fully explain color constancy (28, 29, 64, 118). In a further effort to account for color constancy, Edwin Land, inventor of the Polaroid camera (252), developed the "retinex" theory in which the spectral content of the illuminant is calculated by computing sensitivity or "lightness" values for the three different cone types over a wide spatial area. Although details of the implementation differ from those specifically proposed for the retinex theory, one retinal mechanism that can be used to compute the spatially averaged spectral content is lateral inhibition from horizontal and amacrine cells with their large receptive fields. With lateral inhibition, responses collected over a spatially extensive area inhibit local responses collected in the center. As we consider further below, lateral inhibition also results in the formation of center-surround receptive fields in cones, bipolar cells, and retinal ganglion cells and provides a mechanism for subtracting the spatially averaged chromatic and luminance properties from local responses. Inhibitory feedback from horizontal cells to cones has thus been proposed to be an important locus for generating color constancy (225, 392, 463). Within the retina, lateral inhibition from widefield amacrine cells also contributes to spectrally opponent surrounds in some ganglion cells (see below) and may therefore also contribute to color constancy.

III. ANATOMY AND PHYSIOLOGY OF ROD AND CONE SYNAPSES

Before examining specific synaptic circuits involved in early color processing, we summarize a few key points concerning the synaptic physiology and anatomy of photoreceptor, horizontal, and bipolar cells for readers who may not be familiar with these topics. For additional details, we refer the reader to other reviews (306, 377, 400, 522).

The light-evoked voltage responses of rods and cones are transformed at their synaptic terminals into a series of vesicle release events, resulting in a change in glutamate release that alters the membrane potential of second-order horizontal and bipolar cells. Release from rods, cones, and bipolar cells involves a specialized structure known as the synaptic ribbon. Retinal ribbons are platelike protein structures with synaptic vesicles tethered along their surface by fine filaments. Dendrites of horizontal cells and some bipolar cells enter invaginations at the base of the synapses of rods and cones to terminate just beneath the ribbons. Typically, two horizontal cell dendrites flank a single bipolar cell dendrite within the invaginating ribbon synapse. In mammalian retina, the central element is typically an ON bipolar cell that depolarizes to light, whereas OFF bipolar

cells that hyperpolarize to light typically make flat contacts with the cone terminal just outside the synaptic invagination. At the output end, ON bipolar cells typically terminate in the inner half of the inner plexiform layer (IPL), closest to the vitreous, whereas OFF bipolar cells terminate in the outer half of the IPL (135). Cones release glutamate (70) in the dark to act on ionotropic α-amino-3-hydroxy-5-methylisoxazole-propionic acid (AMPA) receptors in horizontal cells (136, 426, 442) and AMPA or kainic acid (KA) receptors in OFF bipolar cells (25, 110, 205, 277, 371, 471). ON bipolar cells utilize a G protein-coupled glutamate receptor, mGluR6, which couples to a second messenger signaling cascade that results in the closing of cation-permeable TRPM1 channels (295, 412). Thus the reduction in glutamate release that accompanies light-evoked hyperpolarization of rods or cones causes a sign-conserving hyperpolarization in OFF bipolar and horizontal cells but a sign-inverting depolarization in ON bipolar cells. In ON bipolar cells of fish retina, this sign-inverting depolarization also involves activation of glutamate transporters that couple to anion channels (165, 166).

IV. CENTER-SURROUND RECEPTIVE FIELD ORGANIZATION AND ITS ROLE IN CONE OPPONENCY

A. Origins of Center-Surround Receptive Fields

It is well established that negative feedback from horizontal cells to cones provides a mechanism for generating antagonistic cone interactions at the very first synaptic step in the visual process and thus plays a critical role in generating cone-opponent signals in the retina. Most horizontal cells have large receptive fields arising from their large dendritic fields and strong gap junction coupling with neighboring horizontal cells. Negative feedback from horizontal cells to cones thus yields a large antagonistic receptive field that surrounds a small excitatory central region in the cone receptive field. This center-surround receptive field arrangement is then transmitted to cone bipolar cells and in turn to ganglion cells. As mentioned earlier, this provides a mechanism for subtracting the mean light levels detected by spatially extensive horizontal cells from the light responses of individual cones in the center of the receptive field. Center-surround receptive fields improve signaling efficiency by removing spatially redundant information about luminance and chromaticity. Furthermore, if the spectral sensitivity of a horizontal cell differs from that of the photoreceptor, inhibitory feedback from horizontal cells provides a mechanism for making spectral comparisons between a particular photoreceptor and its neighbors. Recent studies in which horizontal cells were eliminated or inactivated by genetic means have characterized the impact of horizontal cells on the kinetics and spatial properties of retinal ganglion cells. Pharmacological studies in a number of species suggest a significant role for horizontal cell feedback in generating receptive field surrounds (77, 96, 206, 305, 473), but genetic elimination or inactivation of horizontal cells in mouse retina has shown surprisingly modest effects (62, 120, 426). These latter techniques have not yet been used to analyze contributions of horizontal cells to chromatic processing.

B. Mechanisms of Horizontal Cell to Cone Feedback

Given its fundamental role in retinal processing, it is surprising that the basic biophysical mechanisms by which horizontal cells provide negative feedback to cones remain unsettled. Before explicitly considering its role in cone opponency, we first consider what is known about how horizontal cells communicate with photoreceptors (61, 248, 441). Negative feedback from horizontal cells to cones was first demonstrated by Baylor et al. (18) with the discovery that small spots of light centered on a turtle cone evoked a hyperpolarizing light response, but expanding the spot to illuminate a surrounding region of the retina caused a delayed depolarization of the cone. Moreover, after desensitizing the central cone by steady central illumination, hyperpolarizing neighboring horizontal cells by flashing a bright annulus could evoke purely depolarizing responses in the cone **(FIGURE 5*A*)**. Horizontal cells contain the inhibitory neurotransmitter GABA, and it was originally suggested that the hyperpolarization of horizontal cells by light caused a reduction in GABAergic transmission at a presumed horizontal cell to cone synapse and that this disinhibition was responsible for the depolarizing feedback response of cones (reviewed in Ref. 441). However, while GABA has been shown to modulate the strength of feedback (189, 234, 281, 430, 508), GABA antagonists failed to block negative feedback responses in cones showing that the actions of GABA released from horizontal cells on $GABA_A$ receptors in cones are not the key mechanism. Instead, it was found that horizontal cell feedback alters the voltage dependence and amplitude of the cone calcium current (I_{Ca}) (439, 467, 468). As illustrated in **FIGURE 5*B***, effects of horizontal cell feedback on the cone I_{Ca} produce a negative voltage activation shift and small increase in I_{Ca} amplitude when the surround is illuminated (40, 42, 152, 361, 362, 440, 468). A critical feature of this novel mechanism is that the shift in I_{Ca} may produce small and almost undetectable depolarizing voltage changes in the cone. In cones where the chloride equilibrium potential (E_{Cl}) is sufficiently positive, the depolarizing increase in I_{Ca} can be boosted by activation of Ca^{2+}-activated Cl^- channels (15, 16, 293, 440, 467). Differing contributions from Cl^- channels may provide an explanation for the larger depolarizing surround responses seen in cones from some preparations (e.g., turtle) but not others (41). This unconventional mechanism is consistent with the well-established fact that the

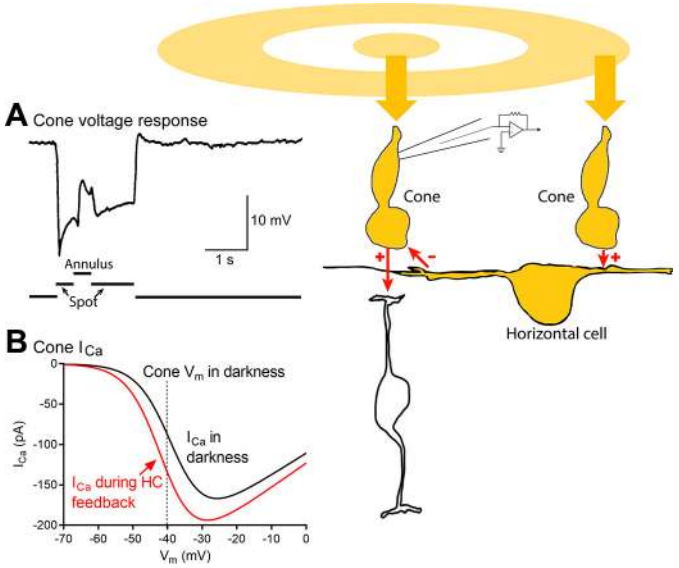


FIGURE 5. Inhibitory feedback from horizontal cells to cones. Schematic diagram shows a central cone with recording pipette that receives inhibitory feedback from a horizontal cell driven by annular illumination of the receptive field surround. *A*: recording from a turtle cone showing that illuminating this cone with a small spot of light evoked a hyperpolarizing response. Subsequent application of an annulus to illuminate the receptive field surround caused the surrounding cones to hyperpolarize, which in turn caused their postsynaptic horizontal cells to hyperpolarize. The resulting change in inhibitory feedback from horizontal cells back to the central cone generated a depolarizing response in that cone [cone response from Burkhardt et al. (42).] *B*: illustration of horizontal cell feedback effects on the cone calcium current (I_{Ca}). The change in inhibitory feedback produced by hyperpolarization of a postsynaptic horizontal cell causes cone I_{Ca} to activate at more negative potentials and increases its peak amplitude, thereby increasing the amplitude of I_{Ca} within the normal physiological range of cone membrane potentials between −40 and −60 mV.

lateral elements formed by horizontal cell dendritic tips in the cone pedicle show a paucity of synaptic vesicles and membrane specializations typical of most synapses. Consistent with horizontal cell feedback acting directly on I_{Ca}, it has recently been shown that in primate S cones, activation of the opponent surround by yellow light evoked inward currents, whereas direct stimulation of the cone with blue light evoked outward photocurrents (347). The surround-evoked inward currents in these S cones arose from a negative shift in I_{Ca} activation and increase in I_{Ca} peak amplitude.

If horizontal cell negative feedback acts to shift the activation range of the cone I_{Ca} directly, then what is the biophysical mechanism for this action? Two mechanisms have been proposed. The first is the ephaptic hypothesis originally formulated by Byzov and Shura-Bura (49). In this hypothesis, extracellular current flowing into horizontal cells may encounter sufficient extracellular resistance within the invaginating cone synapse to generate a voltage drop between the synaptic cleft and more distant extracellular locations. When horizontal cells are relatively depolarized in darkness, the local potential within the cleft should thus be slightly more positive than the surrounding extracellular potential. This effectively increases polarization across the cone membrane, thereby making it more difficult to activate voltage-dependent Ca^{2+} channels in the cone terminal. When horizontal cells hyperpolarize in response to light, current flowing through the cleft and into open cation-permeable channels at the tips of horizontal cell dendrites will cause the local extracellular field potential in the cleft to become more negative. This diminishes polarization of the cone membrane, lowering the threshold for Ca^{2+} channel activation and shifting the current-voltage relationship to more negative potentials. Kamermans et al. (224) suggested that a potential source for ephaptic currents could be hemigap junctions at the tips of horizontal cell dendrites. The best evidence in favor of this idea is that gap junction blockers in goldfish retina and genetic elimination of a particular gap junction protein (Cx55.5) in zebrafish retina reduce horizontal cell to cone feedback (224, 239). However, direct effects of the gap junction inhibitor carbenoxolone on Ca^{2+} channels (469) and effects of connexin elimination on horizontal cell receptive field properties (406) might also contribute to these effects on feedback. Eliminating connexin 57 from mouse horizontal cells did not appear to alter horizontal cell to cone feedback (406). One prediction of an ephaptic mechanism involving continuously open channels such as hemigap junctions is that voltage changes should be virtually instantaneous. While no kinetic differences were observed when comparing horizontal cell and cone light responses evoked by surround illumination (479), when paired whole cell recordings were used to compare feedforward and feedback kinetics directly in individual cones and horizontal cells, feedback currents evoked in cones by hyperpolarizing steps applied to horizontal cells were slower than predicted for an instantaneous ephaptic mechanism. Measurements of electrotonic properties and computer simulations showed that the slow kinetics of feedback observed in these experiments were not due to slow voltage clamp kinetics (491). These data suggest that, similar to GABA (434), while ephaptic voltage changes may modify feedback, they are unlikely to be the primary mechanism.

Another proposed mechanism for feedback involves extracellular pH changes whereby hyperpolarization of horizontal cells leads to extracellular alkalinization within the cone synaptic cleft. This alkalinization diminishes proton inhibition of cone I_{Ca} and also alters the local membrane surface charge profile to shift I_{Ca} activation to more negative potentials (190). It is now generally accepted that pH changes play an essential role in feedback (50, 446, 470, 479, 488). One key finding in favor of this idea is that supplementing bicarbonate-buffered extracellular media with strong buffers such as HEPES blocks horizontal cell to cone feedback (190, 446). A second key finding is the demonstration of pH changes within the cone synaptic cleft using a pH sensor tethered to the extracellular $\alpha_2\delta_4$ subunit of L-type Ca^{2+}

channels that cluster just beneath the synaptic ribbons (488). The specific ionic mechanisms responsible for feedback-induced proton changes remain unclear. Warren et al. (490) found that Na^+/H^+ exchangers are an important source for protons in feedback, but that light-dependent changes in pH are more likely to involve transmembrane flux of pH buffers. Feedback can be abolished by removal of bicarbonate, suggesting this buffer is required for feedback (490). Bicarbonate flux through $GABA_A$ receptor anion channels may contribute to feedback-induced pH changes (281), providing a potential link to studies suggesting a role for GABA (189, 234, 434, 508). Finally, pannexins, a member of the gap junction-forming protein family, are present at tips of horizontal cell dendrites (249), and it has been proposed that a flux of ATP through pannexins may liberate phosphate to act as a pH buffer in feedback (58, 479).

As we discuss later, there is evidence for contributions of horizontal cell feedback to opponency in downstream neurons that takes advantage of the surprisingly selective effects of the pH buffer HEPES to block horizontal cell feedback. A low concentration of cobalt ions (~0.1 mM) has also been found to selectively eliminate horizontal cell to cone feedback without blocking feedforward transmission from cones to horizontal cells and has therefore been used to test for the role of feedback on downstream neurons (131, 392, 439, 473). The mechanism underlying the ability of low cobalt to selectively block feedback remains unclear.

C. Horizontal Cell Feedback to Rods

In addition to contacting cones, horizontal cell dendrites contact the synaptic terminals of rods. Because surround stimulation did not evoke an observable depolarizing response in rods, it was thought for many years that rods did not receive negative feedback from horizontal cells (32, 71, 254, 313). However, as discussed above, the central mechanism for feedback involves a shift in voltage dependence of I_{Ca} that can produce negligible voltage changes in the photoreceptor. As considered further below in section V, mammalian rods make contact only with the axon terminal compartment of B-type horizontal cells (or H1-type in primates). These terminals can act as an electrically isolated unit in the mammalian rod pathway (331). Thus, without reciprocal feedback to rods, the synaptic input from rods would appear to reach a dead-end. When this question was re-examined, it was found that negative feedback from horizontal cells to rods caused changes in the amplitude and voltage dependence of rod I_{Ca} identical to those seen in cones (13, 438). And like feedback to cones, horizontal cell to rod feedback is sensitive to inhibition by HEPES and low concentrations of cobalt (13, 281, 438). As we discuss later in section IX on rod contributions to color vision, feedback to rods from horizontal cells that also receive input from cones offers a potential mechanism for making spectral comparisons between rods and cones.

D. Positive Feedback From Horizontal Cells

In addition to negative feedback, a form of positive feedback from horizontal cells to cones has also been described (208). It was suggested that this mechanism operates more locally at individual synapses, boosting synaptic output from photoreceptors to compensate for the more extensive, global inhibitory influence from horizontal cells. Positive feedback involves Ca^{2+} influx through Ca^{2+}-permeable AMPA receptors in horizontal cell dendrites, but other details of the mechanism are not yet known. Its potential impact on color processing has not been investigated.

V. HORIZONTAL CELLS

A. Horizontal Cell Types and Cone Opponency

Horizontal cells play a central role in generating color opponent interactions in the retina and provide an archetype for spectral circuitry mechanisms. In this section, we consider some key characteristics of horizontal cells in various species. The morphology and physiology of horizontal cells have been characterized in detail across many mammalian and non-mammalian vertebrate species (150, 357). In most quadrupeds, two broad anatomical cell classes have been identified, referred to as A- and B-types. In the B-type, a distinctive axonlike process extends for some distance from the cell body and terminates in a second dendritic arborization, forming two distinct functional compartments in the same cell. The two types of horizontal cells are therefore often referred to as axon-bearing (B-type) and axonless (A-type). Physiologically, the more stereotyped axon-bearing B-type horizontal cell lacks overt cone opponency and is referred to as a luminosity cell (L-type). Axonless A-type cells show greater morphological and physiological diversity than B-type cells and, in some species, show spectral opponency. Spectrally opponent horizontal cells are referred to as chromaticity cells (C-type). Surprisingly, murine (mouse, rat, gerbil, guinea pig) retinas have only a single B-type cell and lack A-type horizontal cells entirely (356, 357); the functional significance of the absence of this cell type in these rodents is not known. In primate retina, the B- and A-types are called H1 and H2 cells, respectively. H1 cells in other species are also axon-bearing cells. Non-mammalian vertebrates also have as many as three other types of horizontal cells classified as H2, H3, or H4 cells. H2-H4 cells in birds and reptiles are typically axonless A-type cells (150, 265, 292). In fish retina, all four types are axon-bearing (66, 273, 495). As we return to later, it is ironic that the nonopponent "luminosity" H1 type plays such a critical role in the appearance of cone opponency in downstream retinal circuits required for the unique "red-green" component of human color vision, whereas the role played by C-type cells in color vision of lower vertebrates remains in question.

Because of the technical difficulty in measuring surrounds in cones themselves, the first view into the origins of cone opponency in the retina began with horizontal cells that pioneering retinal physiologists found easier to record from. Indeed, the discovery of "color opponency" in horizontal cells came at a moment when modern opponent color theory (203) was searching for a physiological correlate. By the late 1950s, two major physiological classes of horizontal cells were recognized (287, 427). L-type horizontal cells hyperpolarized in response to any wavelength across the visible spectrum, whereas C-type cells showed both hyperpolarizing and depolarizing light response that varied with wavelength **(FIGURE 6)**. C-type horizontal cells have since been found widely in non-mammalian vertebrates including fish, reptiles, and amphibians (reviewed in Ref. 454). On the basis of horizontal cell morphology, it is likely that color opponent horizontal cells are also present in birds (143, 292), but recordings from bird horizontal cells have not been reported. In contrast to the striking and diverse spectral opponency found in non-mammalian horizontal cells, neither A- nor B-type cells in mammals show overt color opponent light responses, although anatomically most mammals possess both axon-bearing and axonless morphological types (330, 334, 357, 421). Nevertheless, both horizontal cell types may play a role in the appearance of color opponency in the retinas of common dichromatic mammals and trichromatic primates.

B. Non-mammalian Horizontal Cells and the Cascade Model of Cone Opponency

In this section, we consider the different types of color-opponent horizontal cells in non-mammalian retinas and potential circuits that have been proposed to generate color opponency in these cells. The most common C-type horizontal cell shows biphasic red/green opponent responses. Turtles, frogs, and fish all have a class of C-type cells that hyperpolarize to medium-wavelength green light and depolarize to longer wavelength red light (229, 287, 310, 340, 427, 513) **(FIGURE 6)**. Other types of biphasic C cells have also been described in various preparations based on differences in their neutral points (i.e., the wavelength at which the response flips polarity). Care must be taken in assigning cells with differing neutral points to discrete subtypes since neutral points can vary considerably from cell to cell even among C-type horizontal cells from different retinas of the same species (456). Studies in turtle retina have shown biphasic cells that hyperpolarize to blue light and depolarize to longer wavelengths (6, 148, 342, 455, 521). Four different types of biphasic C-type cells that hyperpolarize at

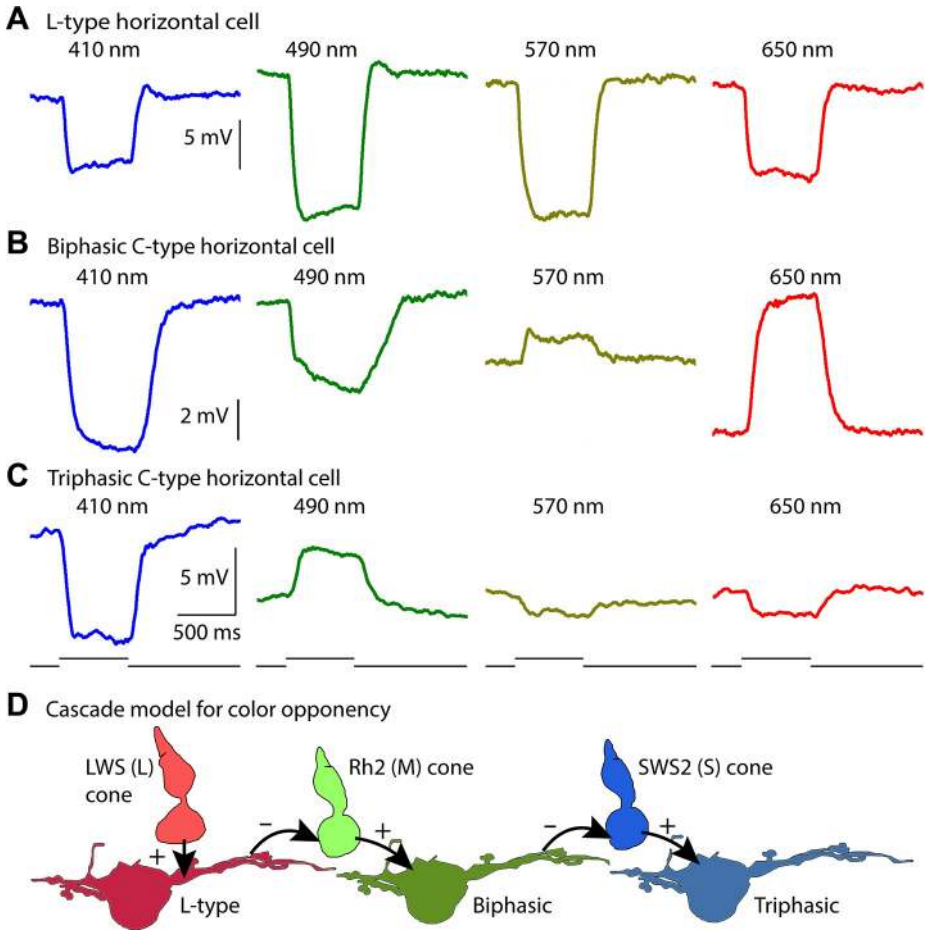


FIGURE 6. Color opponency in horizontal cells. *A*: illustration of the response of an L-type horizontal cell shows that it hyperpolarizes to a wide range of visible wavelengths. *B*: biphasic C-type horizontal cell showing a hyperpolarizing response to 410 and 490 nm light but depolarizing responses to 570 and 650 nm light. *C*: triphasic C-type horizontal cell showing a hyperpolarizing response to 410 nm light, depolarizing response to 490 nm light, and hyperpolarizing responses to 570 and 650 nm light. Examples are from zebrafish retina (66). *D*: schematic illustration of the cascade model for color opponency. In this hypothesis, the responses of LWS (L) cones are predominantly responsible for driving hyperpolarizing responses in L-type horizontal cells. The hyperpolarizing responses of L-type horizontal cells are inverted by inhibitory feedback to Rh2 (M) cones, and the responses of Rh2 cones are then fed forward to biphasic C-cells. This yields hyperpolarizing responses to green light driven by the Rh2 cone light response and depolarizing responses to red light driven by inhibitory feedback from L-type horizontal cells. Inhibitory feedback to SWS2 (S) cones inverts the responses of biphasic horizontal cells to generate depolarizing responses to middle wavelengths and hyperpolarizing responses to longer wavelength light in triphasic C-cells, along with hyperpolarizing responses to blue light generated by the SWS2 cone light response.

shorter wavelengths and depolarize at longer wavelengths have been distinguished in sturgeon retina (162).

In addition to biphasic cells, there are also triphasic **(FIGURE 6)** and tetraphasic cells. Triphasic C cells have been seen in a number of fish species [e.g., carp (445), goldfish (228), zebrafish (66), roach (113), bowfin (159), dace (177)]. There is also one report of triphasic cells in turtle retina that hyperpolarize to short-wavelength blue light, depolarize to intermediate-wavelenght green light, and hyperpolarize again to long-wavelength red light (513). Fish can have tetraphasic horizontal cells that hyperpolarize to red and blue lights but depolarize to green and UV lights (66, 99, 176). Teleost fish have four morphological types of horizontal cells [one rod-dominated (238, 325, 326) and three cone-driven (423, 494)], but at least six spectrally distinct, physiological types of horizontal cells: two monophasic, one biphasic, two triphasic, and one tetraphasic cell (66, 99, 176). This highlights the important point that while morphological distinctions among horizontal cells are useful, the specific cone-type connectivity is more important functionally.

With weak light flashes (<20% of the intensity required to evoke a saturating response), the responses of C-type horizontal cells increase linearly with intensity at any given wavelength (43, 148, 159, 497). Burkhardt and Hassin (43) measured the action spectra of L and M cones directly and compared these with responses of color-opponent horizontal cells in sauger retina. They found that spectral responses of red/green C-type horizontal cells could be fit quite precisely from the simple algebraic difference between L and M cone inputs using only a single free parameter to weight their relative inputs. A similar model using published nomograms of cone absorbance spectra can also predict color opponent responses of biphasic, triphasic, and tetraphasic cells in zebrafish retina (66).

These data indicate that relatively simple linear interactions among cones can account for spectrally opponent responses in C-type horizontal cells. Based on anatomical connectivity, Stell and colleagues (422, 423) proposed that spectrally opponent responses of H2 and H3 horizontal cells in goldfish might arise from a simple cascade of synaptic connections between cell types **(FIGURE 6*D*)**. Studies of Golgi-stained goldfish retina indicated that L-type H1 horizontal cells contact all types of cones, red-green opponent H2 horizontal cells appeared to contact only green-sensitive Rh2 (M) and blue-sensitive SWS2 (S) cones, and triphasic H3 cells selectively contact SWS2 cones. Similar connectivity patterns were observed in roach fish retina (113, 119). Although H1 cells receive input from multiple different cone types, Stell et al. (422) suggested that the hyperpolarizing responses of these cells would be dominated by LWS (L) cone inputs and the hyperpolarizing responses of H2 cells would be dominated by input from Rh2 cones. This led to the cascade hypothesis that the depolarizing responses of color-opponent H2 cells arose from a sign inversion at the feedback synapse from H1 cells back onto M cones that was then fed forward at a sign-conserving synapse onto the H2 cells **(FIGURE 6*D*)**. To account for triphasic responses, they proposed a further cascade of connections in which biphasic H2 cells provided inhibitory feedback to SWS2 cones. The sign-conserving feedforward input from SWS2 cones to H3 cells was predicted to yield hyperpolarizing responses to blue light, whereas inhibitory feedback from biphasic H2 cells to S cones that was then fed forward to H3 cells was responsible for producing depolarizing responses to green light and hyperpolarizing responses to red light.

While this cascade of feedback signals can explain many properties of C-type horizontal cells, it became evident that there are also data inconsistent with this simple model. One concern is that if feedback from horizontal cells is responsible for red-sensitive depolarizing responses but not hyperpolarizing responses to green light, then responses to red light should be evoked more efficiently by large-diameter stimuli than responses to green light. However, while there is no clear effect of stimulus diameter on color opponency (41), comparisons between wavelengths are complicated by the fact that horizontal cell receptive field diameter can also vary with test flash intensity (454, 455). Furthermore, in turtle retina, the L-type horizontal cells that mediate feedback from red-sensitive to green-sensitive cones possess small receptive fields (333). A second concern that has been raised is the small amplitude or absence of depolarizing responses to red light in M cones (41). However, as discussed above, it has become clear that horizontal cell to cone feedback involves mechanisms that can adjust the strength of cone I_{Ca} and thus M cone output without necessarily producing strong depolarizing responses in the cone.

A third, more serious concern is that the cascade model assumes that responses of red-green opponent C-type cells to green light pass through only a single synapse (from M cones to red/green opponent horizontal cells), whereas depolarizing responses to red light must pass through three synapses (L cones to L-type horizontal cells to M cones to red/green horizontal cells). Thus, even if feedback synapses employ instantaneous ephaptic mechanisms, the extra feedforward synapse should introduce a longer latency to depolarizing responses evoked by red light. However, contrary to these predictions, depolarizing responses to red light in biphasic horizontal cells show shorter latencies than hyperpolarizing responses to green light (148, 159, 199, 497).

Other findings raised further questions about the cascade model. Unlike goldfish retina, Wagner et al. (482) did not find evidence for selective contacts between H3 cells and S cones in carp retina as required by the original cascade model. Kraaij et al. (246) measured the spectral sensitivity

of inward feedback currents evoked in goldfish cones by light-evoked hyperpolarization of horizontal cells and found that cone feedback currents showed a broader spectral sensitivity than expected if horizontal cells received the selective cone inputs predicted by the cascade model. Furthermore, they did not observe any evidence for color opponent signals in the feedback responses of S cones as predicted for the generation of triphasic C-cell responses. To explain these results, Kamermans and co-workers (225, 227) developed a model that did not require the highly selective contacts required by the cascade model, but instead incorporated feedforward and feedback contacts among multiple cell types, weighting these contacts by the measured spectral sensitivity of horizontal cells and cone feedback currents. This model successfully predicted color opponent responses in horizontal cells and, because it does not require a cascade of synaptic interactions to generate responses to red light, eliminated the conundrum that responses to red light do not show slower kinetics than responses to shorter wavelengths.

The original cascade model and refinement by Kamermans and co-workers (225, 227) both assume a central role for horizontal cell to cone feedback in generating color opponency. Consistent with this, selectively blocking horizontal cell to cone feedback with HEPES or low concentrations of cobalt inhibited depolarizing responses to long wavelength light of biphasic C-type horizontal cells but not hyperpolarizing responses to shorter wavelengths (131, 132, 473). Furthermore, feedback-induced calcium spikes in green-sensitive cones promoted by the application of strontium were accompanied by the appearance of spikes in the depolarizing responses to long wavelength light in biphasic horizontal cells (363). In triphasic cells, hyperpolarizing responses to short wavelength light that are thought to be mediated by direct feedforward inputs from S cones are spared by HEPES, but depolarizing responses to intermediate wavelengths and hyperpolarizing responses to long wavelengths, which are both thought to require feedback, are inhibited (228). Blocking connexin hemichannels with carbenoxolone or genetic elimination of connexins also reduce depolarizing responses of biphasic C cells (224, 239).

One potential alternative mechanism for generating depolarizing responses in color-opponent horizontal cells that does not require horizontal cell to cone feedback would be the presence of direct sign-inverting synapses from cones to C-type horizontal cells (357). Consistent with such a possibility, biphasic red-green opponent horizontal cells in turtle retina receive one-third of their inputs directly from red-sensitive cones (342). Closure of cation channels by activation of metabotropic mGluR6 glutamate receptors produces a sign inversion at the cone to ON bipolar cell synapse. However, unlike depolarizing responses of ON bipolar cells, depolarizing responses of biphasic C-type horizontal cells are not inhibited by the mGluR6 agonist L-AP4 (425), but are instead blocked by agonists and antagonists for ionotropic glutamate receptors (308, 425, 454, 468, 502). Depolarizing responses of ON bipolar cells in fish retina can also be achieved by the activity of chloride channels coupled to glutamate transporters (165, 166). However, for this mechanism to produce depolarizing responses in C-type horizontal cells, these cells would need to possess glutamate transporters and show values for E_{Cl} that are more negative than the membrane potential. While EAAT3 transporters have been found in horizontal cells from rat retina (372, 402), this transporter subtype shows little chloride conductance (480), and glutamate transporters appear to be absent from horizontal cells of most other species including goldfish and turtle (402, 461). Furthermore, horizontal cells possess Na^+-K^+-$2Cl^-$ (NKCC) cotransporters that accumulate chloride within cells (116) and exhibit values for E_{Cl} above their resting potential (309). It is therefore unlikely that glutamate transporters on horizontal cell dendrites are responsible for the depolarizing responses of C-type horizontal cells.

In sum, the responses of C-type horizontal involve relatively simple, linear interactions with cones. Hyperpolarizing responses to green light in biphasic cells and to shorter wavelengths in triphasic cells appear to reflect direct inputs from cones. Depolarizing responses of biphasic and triphasic C-type cells as well as the hyperpolarizing responses to long wavelengths in triphasic C-type cells appear to arise from mechanisms involving inhibitory feedback from horizontal cells to cones. These responses can be explained by appropriately weighted interactions among different cone subtypes (227) without requiring the highly selective cone wiring of the original cascade model (422).

Finally, before turning to mammalian horizontal cells, let us consider the role for color opponency in C-type horizontal cells of non-mammalian vertebrates. One possibility is that spectral opponency in C-type horizontal cells may contribute to generating spectral opponency in bipolar cell surrounds. However, as we discuss later in the section on bipolar cells (see sect. VI*A*), there are data that argue the contrary. Alternatively, spectral opponency in horizontal cells may simply narrow the spectral sensitivity of bipolar cell surrounds to improve spectral coding, akin to the effects of oil droplets (66). Finally, it has also been suggested that color opponency in horizontal cells may be less important for color vision than for adjusting receptive field size to optimize spatial vision with changes in spectral content under different ecological conditions (226).

C. Mammalian Horizontal Cells: A-Type Cells and S Cone Connectivity

The diverse morphology and cone type connectivity of A-type cells in mammalian retina defies easy categorization (150, 357). In the dichromatic cat and rabbit, A-type hori-

zontal cells contact both S and M cones without preference and show luminosity-type responses similar to B-type horizontal cells. However, in two other species, the horse and ground squirrel, A-type horizontal cells connect exclusively to S cones. Since all of these mammals are dichromats, a functional explanation for this striking species difference remains unclear. Perhaps even more striking than the surprising pattern in the horse and ground squirrel, mice and other murine species lack A-type horizontal cells altogether (356, 357), confounding any simple rationale for this cell type's variability based on either phylogeny or visual specialization. Among dichromatic mammals, a specific role for A-type horizontal cells in S versus M cone opponency in ganglion cells has not been determined (294, 311).

The A-type counterpart in the primate retina, the H2 horizontal cell, receives preferential input from the low-density S cones and makes relatively sparse connections with the higher density L and M cones. The primate H2 cell also gives rise to a distinctive meandering process that receives input predominantly but not exclusively from S cones, mirroring the cell's somato-dendritic connection pattern (1, 59). As noted earlier, S cones in macaque monkey have been shown to display a surround mediated by negative feedback from horizontal cells receiving input from both L and M cones, providing a locus for S versus L+M cone opponency in the S cone itself. Since the H1 or B-type horizontal cell in primate avoids contact with S cones (see below), H2 cells appear to be the source of the L+M feedback signal and cone opponency in the S cone receptive field **(FIGURE 7)**. The S cone light response in the dichromatic mouse has been characterized by suction recordings from the outer segment (335), but whether these cones show an M cone opponent surround remains to be determined.

Although cone GABA receptors do not appear to be essential for horizontal cell to cone feedback, both A- and B-type horizontal cells possess the machinery needed for GABA release (170) including the SNARE protein syntaxin 4 (188, 370). Based in part on the presence of syntaxin 4 beneath S cones, it has been speculated that inhibitory GABAergic feedforward inputs from S cone-dominated H2 cells to S cone ON bipolar cells might provide an alternate pathway for generating L+M cone OFF surrounds in S cone ON bipolar cells (and in turn the S ON/L+M OFF bistratified ganglion cells that receive input from these bipolar cells) (327, 370). However, this scenario seems to be precluded by the finding that application of GABA receptor antagonists has no effect on S versus L+M opponency in small bistratified ganglion cells (75).

D. Mammalian Horizontal Cells: B-Type Cells and Luminance

In contrast to A-type cells, the B-type axon-bearing horizontal cells in mammals are more stereotyped in their photoreceptor connectivity and display two functionally and anatomically distinct compartments. The somato-dendritic tree contacts cone pedicles, whereas the axonal arborization that arises from an axonlike process of variable length contacts rod spherules exclusively. These two compartments each form separate gap junction-coupled networks (349). The functional significance of this unusual morphology and whether it might play some role in rod-cone inter-

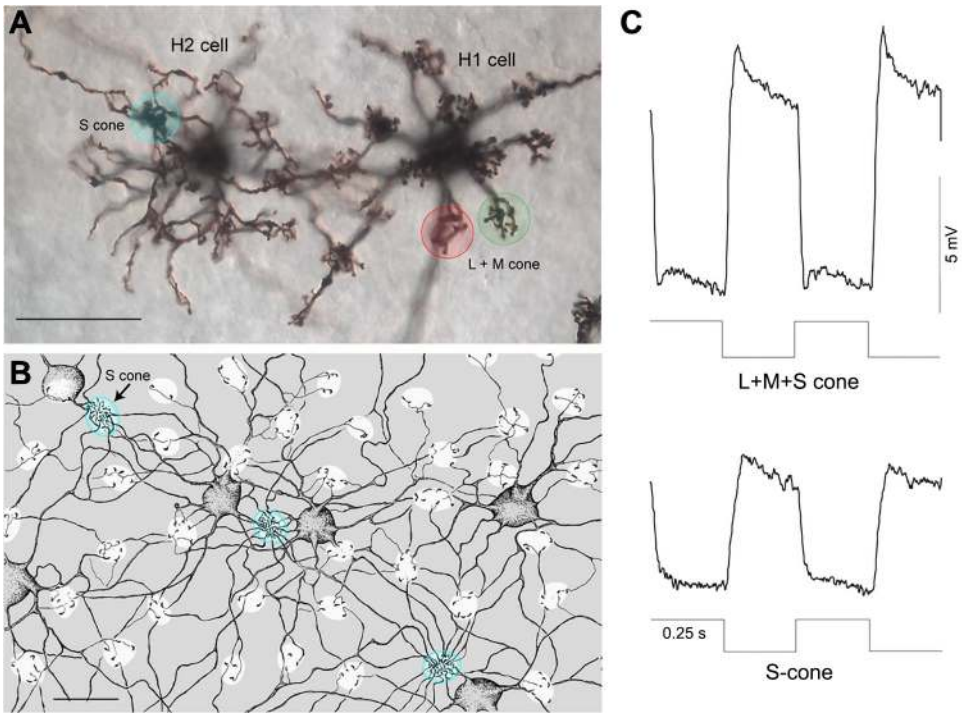


FIGURE 7. Morphology and cone connectivity of horizontal cell types in the primate retina. *A*: somato-dendritic morphology of H1 and H2 horizontal cell types revealed in Golgi-stained retina from macaque monkey. H1 cells make dense contacts with L and M cones (red and green circle insets) but avoid contact with S cones; conversely, H2 cells make dense contacts with S cones (blue circle inset) but only sparse contacts with L and M cones. *B*: camera lucida tracing of the network of cone connections in H2 cells filled with Neurobiotin, which passes through H2-H2 cell gap junctions. Note the sparse contact with the majority (M/L) cones and dense contacts with three presumed S cones in this field. *C*: H2 cells hyperpolarize in response to stimuli across the visible spectrum and lack cone opponency. *Top trace* shows an H2 cell voltage response evoked by combined stimulation of L, M, and S cones; *bottom trace* shows the response to an S cone isolating stimulus. [Adapted from Dacey et al. (91).]

actions in vision is not entirely clear. The early physiological recordings from B-type cells in cat and rabbit retina suggested that rod and cone inputs were restricted to separate anatomical compartments leading to the hypothesis that the long axonlike process served to restrict electrotonic spread of light evoked synaptic currents between the two dendritic structures (24, 331). In carp retina, a similarly distal axon terminal compartment does not appear to make any contact whatsoever with photoreceptors but nevertheless displays large light-evoked responses, suggesting that signals can readily traverse the thin axon that connects the soma to the axon terminal (495, 527). When rod-cone coupling was eliminated from mouse retina by deletion of connexin 36 (Cx36), cone signals were observed in the exclusively rod-connected axon terminal of B-type horizontal cells, indicating that the axon transmits the cone-driven response from soma to axon terminal (447). This provides a potential pathway for cone signals to influence rod responses. As addressed later when discussing possible rod pathways for influencing color vision (see sect. IX*D*), there is conflicting evidence about whether rod signals can travel through mouse B-type horizontal cells in the other direction, from axon terminal to soma (428, 447).

In contrast to what is known for other nonprimate mammals, the primate B-type or H1 cell contacts L and M cones indiscriminately but largely or completely avoids S cones **(FIGURE 7)**. The connectivity pattern in H1 cells is reflected by a lack of response to stimuli that selectively modulate S cone light responses (88) and a spectral sensitivity that reflects the sum of local L and M cone inputs in the overlying mosaic (86, 106, 112, 466). The absence of S cone responses in H1 horizontal cells suggests that these cells cannot provide a route by which S cone signals might feed back and contribute to the surrounds of L and M cones. Consistent with this picture, the two major ganglion cell types in primate retina, the LGN-projecting midget and parasol ganglion cells, receive mixed L and M cone inputs with no evidence of S cone input to their surrounds. Indeed, parasol ganglion cells show an overall spectral tuning that closely matches the human spectral luminosity function (259), which is modeled as the sum of L and M cone spectral sensitivities, without a contribution from S cones (268).

It is worth noting that, despite the lack of cone opponency in horizontal cells of the trichromatic primate retina, the differences in S, M, and L cone inputs to H1 and H2 horizontal cells are consistent with the fundamental cone opponent interactions that determine the "cardinal axes" of chromatic processing in the primate (107). Thus the absence of an S cone contribution to the H1 cell and the resultant receptive field surround of midget and parasol ganglion cells aligns with the L versus M, "red-green" and L+M, "achromatic" cardinal axes whereby S cone signals are excluded. In contrast, the dominant contribution of S cones to the H2 cells aligns with the S versus L+M axis where the S cone signal is critical.

VI. BIPOLAR CELLS

A. Color Opponent Bipolar Cells in Non-mammalian Vertebrates

Spectral opponency is present in non-mammalian bipolar cells where it has been linked to the antagonistic center-surround receptive field structure that appears clearly at the bipolar cell level of the retinal circuit (441). However, as we consider in this section, the cone-opponent interactions responsible for these opponent interactions can be complex and involve a number of distinct neural mechanisms.

A first complexity is that cone opponency in non-mammalian bipolar cells appears in two distinctive forms related to center-surround organization: single opponent cells typically show spectral antagonism between center and surround. In contrast, more complex double opponent cells show spectral antagonism separately in both center and surround. For example, in goldfish retina, two types of single opponent bipolar cells were observed in which cells either hyperpolarized or depolarized to long wavelengths in the center of the receptive field but also showed a broadly tuned receptive field surround that responded with opposite polarity to the center response (220, 230, 312). Similar cells have been seen in carp (409) and turtle retina (6, 180, 464, 513). In addition, single opponent bipolar cells can show opponency restricted to either center or surround. Thus OFF center monophasic cells in turtle show a spectrally broad center but spectral opponency in the surround (red OFF vs. blue/green ON antagonism in the surround) (6).

In contrast to single opponent cells, most of the double opponent cells in carp retina show a center that is depolarized by certain wavelengths (e.g., red) and hyperpolarized by others (e.g., green), whereas the receptive field surround shows the inverse arrangement (e.g., hyperpolarized by red and depolarized by green light) (231, 232, 312, 409). A few ON and OFF bipolar cells in carp retina show triphasic responses to center stimulation but biphasic responses to surround stimulation (409). These triphasic cells respond with the same polarity at short and long wavelengths but with the opposite polarity at medium wavelengths and thus show two neutral points (~500 and 600 nm). Dace retina has similar cell types (177). In the less studied turtle retina, double opponent or triphasic bipolar cells have not been reported (6, 180, 464, 513).

The ability of small centered spots of light to activate color opponent responses in the receptive field centers of bipolar cells in carp and turtle retina (6, 180, 409, 464, 513) suggests that center opponent responses of these cells could

potentially arise by direct inputs from different cone types to generate both hyperpolarizing (OFF center) and depolarizing (ON center) responses rather than by negative feedback from horizontal or amacrine cells. While we argued above that it is unlikely to be the mechanism for generating depolarizing responses in C-type horizontal cells, there is better evidence for such a mechanism in bipolar cells. Consistent with this possibility, the dendrites of a red ON/green OFF center bipolar cell in turtle retina form invaginating central elements at triadic ribbon synapses with LWS cones (occupying the typical position for sign-inverting ON bipolar cells) but contact Rh2 (M) cone pedicles at flat contacts outside the invagination (occupying the typical position for sign-conserving OFF bipolar cells) (180). In addition, red/green color opponent bipolar cells in turtle retina are bistratified with processes terminating in both the ON and OFF sublaminae of the inner plexiform layer (180). This led Haverkamp et al. (180) to hypothesize that depolarizing center responses of red/green bipolar cells to red light involved contacts from red-sensitive cones onto sign-inverting mGluR6 receptors, whereas hyperpolarizing center responses to green light in these same cells involved contacts from green-sensitive cones onto AMPA/KA receptors. However, these purely anatomical findings should be interpreted cautiously since ON bipolar cells can also sometimes form flat contacts some distance from the ribbon (52, 450, 451). In tiger salamander, OFF bipolar cells form the central invaginating element in the synaptic triad more often than ON bipolar cells (253).

Physiological evidence for separate ON and OFF inputs has been observed in giant *Danio* retina in which depolarizing responses of color opponent bipolar cells to red or green light were selectively inhibited by a glutamate transport inhibitor threo-β-benzyloxyaspartate (TBOA), whereas hyperpolarizing responses were selectively inhibited by an AMPA/KA antagonist (503). The mGluR6 agonist L-AP4 failed to inhibit light responses in these cells (503). This suggests that in fish, chloride currents associated with glutamate transporter activity may be responsible for depolarizing center responses and AMPA/KA receptors for hyperpolarizing responses. In ON bipolar cells, the use of glutamate transporters to generate depolarizing responses appears confined to fish, so if the depolarizing responses of red/green opponent bipolar cells in turtle retinas arise from direct cone inputs, they are more likely to be mediated by mGluR6, although this has not yet been tested.

In double opponent bipolar cells of fish retina, it has been proposed that opponent responses in the surround might arise from inhibitory feedback by red/green biphasic C-type horizontal cells back onto cones (454). However, the absence of spectral opponency in feedback currents of goldfish cones (246) argues against horizontal cell feedback to cones as being the primary mechanism for generating opponency in the surround. Moreover, inhibitory feedback from this class of C-type horizontal cells should give rise to triphasic or tetraphasic bipolar cell surrounds, and this has not been observed.

Another less studied pathway by which circuitry of the outer retina might implement cone antagonistic interactions is a feedforward inhibitory synapse from horizontal cells to the dendrites of cone bipolar cells. Unlike feedback to cones, feedforward inhibition is likely to be GABAergic (441). If GABAergic feedforward inhibition from color-opponent horizontal cells to bipolar cells is involved in generating double opponent responses, then GABA agonists and antagonists should inhibit color opponent responses in the receptive field surround. However, rather than selectively inhibiting only surround-mediated responses, GABA inhibits both depolarizing and hyperpolarizing responses of color opponent bipolar cells in fish retina (532). Effects of GABA antagonists on these responses have not been tested.

Another mechanism that could potentially contribute to color opponency in the surround is lateral inhibition from amacrine cells to bipolar cells or ganglion cells (69, 145, 206, 410, 529). Surrounds in bipolar cell and ganglion cells typically weaken during dark adaptation (441). Ichinose and Lukasiewicz (206) found that inhibiting horizontal cell feedback with low concentrations of cobalt reduced ganglion cell surrounds at high light levels, whereas inhibiting amacrine cell feedback with $GABA_c$ antagonists reduced surrounds at low light levels. They suggested that horizontal cell feedback plays a stronger role in shaping properties of the surround under bright illumination, whereas amacrine cells play a bigger role under dim illumination. The contributions of amacrine cells to color opponent surrounds of bipolar cells have not been investigated directly, but as we discuss later, amacrine cell inhibition contributes to the surrounds of some types of blue-yellow opponent retinal ganglion cells in mammalian retina.

In summary, sign-inverting feedforward synapses from cones, inhibitory feedback from horizontal cells to cones, inhibitory feedforward inputs from horizontal cells to bipolar cells, and inhibitory feedback from amacrine cells to bipolar cells have all been proposed as possible mechanisms by which spectral opponency might arise in color opponent bipolar cells of non-mammalian retina. The same mechanisms are unlikely to be employed in all species. For example, the role of glutamate transporters in generating depolarizing light responses in bipolar cells appears unique to fish. We are thus left with a number of uncertainties concerning the mechanisms that might be responsible for generating color opponent responses in the centers and surrounds of different bipolar cells in various non-mammalian species.

B. Limited Cone-Specific Connectivity in Mammalian Bipolar Cells

In contrast to non-mammals, the circuitry related to color opponency in mammalian bipolar cells appears relatively simple and limited in distribution. Thus a fish retina may display at least 20 bipolar cell types, some of which show double spectral opponency, along with complex patterns of cone connectivity and axon terminals that can be bistratified or tristratified. In contrast, mammals show about half the number of types and, aside from a possible bistratified bipolar cell in human retina (244), primarily show nonselective cone connectivity and monostratified axonal arborizations.

Intracellular recordings to characterize the light-driven responses of mammalian bipolar cells have proven more difficult than for non-mammalian retina, so the basic center-surround receptive field structure of this cell class was only confirmed relatively recently (91), and although an S cone selective cone bipolar cell appears to be common across mammals (53, 182, 240), true cone opponency, while inferred, has not been directly demonstrated in these cells. Indeed only a few instances of spectral opponency in bipolar cells have been noted from very limited data in the primate retina (84).

In contrast to the limited information from physiological recordings, the morphology of cone bipolar cells in both primates and non-primate mammals have been characterized in detail. Thirteen and 14 types are now recognized in mouse and ground squirrel, respectively (30, 129, 145, 275, 493), and 12 types in primate (218, 371, 450, 451). Recent results using high-resolution optical measurements of glutamate release by bipolar cell axon terminals has provided a new window into the overall physiology of mammalian bipolar cells correlated with each of the known anatomical types and appears to confirm the general lack of spectral opponency for mouse bipolar cell types (145). Recall that in dichromatic mouse retina, M cones coexpress both S and M opsins in ventral retina, so opponent S versus M signals are thought to be absent from this part of the retina. Most bipolar cells contact both S and M cone types, but there is a single OFF bipolar that selectively contacts M cones (type 1) and a single ON type that selectively contacts S cones (type 9). These two cone type-selective bipolar cells may provide the basis for dichromatic color vision in the dorsal retina of this species, although, as mentioned above, overt spectral opponency has not yet been recorded from either type (30, 182). However, this relatively simplistic view of the mouse inner retinal circuitry should be considered with caution since a recently identified S ON/M OFF cone opponent type of ganglion cell in the mouse receives input from at least three other ON cone bipolar types in addition to the type 9 S cone selective bipolar and does not receive input from the OFF type 1, M cone-selective bipolar (419).

In the ground squirrel, elegant paired recordings identified both an ON bipolar cell that is selectively connected to S cones and multiple OFF bipolar cells that avoided S cone input and were instead selectively connected to M cones (270). As will be considered below, it is the S cone related bipolar cell and its inner retinal circuitry in ground squirrel that is linked to color opponency at the ganglion cell level (407).

C. Bipolar Cell Types and Chromatic Circuits in the Primate

In the trichromatic primate, there is a clear separation between the dedicated S cone circuitry involved in blue-yellow opponency and the L versus M cone circuitry involved in red-green opponency. This distinction first appears clearly at the bipolar cell level and has been inferred from detailed characterization of the cone synaptic connectivity patterns for bipolar cells in macaque monkey retina using electron microscopic reconstruction methods.

1. S ON, S OFF bipolar asymmetry

The primate retina contains an S cone-selective ON-bipolar cell that forms all of the invaginating central elements at the S cone pedicle (93, 187). These bipolar cells have not been characterized physiologically, but since they make synapses in the "ON" sublamina of the inner plexiform layer with a ganglion cell which shows an S cone-mediated "blue ON" light response (53, 87, 240, 451) that is abolished by pharmacologically attenuating ON pathway transmission (75, 142), it is evident that these bipolar cells must be S ON center cells. Less direct evidence suggests strongly that these S ON center bipolar cells likely display an L+M cone OFF surround. First, H2 horizontal cells target S cones preferentially but also make sparse contacts with L and M cones (59, 88, 158) providing a basis for L and M cone negative feedback to S cones. Second, S cones themselves show cone opponent surrounds from L and M cone feedback, again presumably due to H2 cell lateral connections (347).

Primate S cones also synapse with a selective presumed OFF midget bipolar pathway that has been little studied but would be an important component in understanding the origins of human color vision (424). It is well established that in the macaque monkey retina each S cone receives dense and selective flat contacts from a single midget bipolar cell (93, 240) and, by the same argument made for the S ON bipolar cell, these S cone selective flat midget bipolar cells would be expected to show an S OFF center and L+M ON surround. These midget bipolar cells provide selective output to OFF midget ganglion cells in the inner plexiform layer and thus presumably provide the origin for an S OFF opponent pathway (93, 240). Both the S ON and S OFF opponent pathways in the primate are considered further when we discuss ganglion cells.

2. Midget bipolar cells and L versus M cone opponency

From recordings made in the macaque monkey LGN, Wiesel and Hubel (498) were the first to suggest that a circuit must exist in the primate retina to create the cone opponency required for the red-green and blue-yellow axes of color vision characteristic of Old World primates including humans **(FIGURE 8)**. In principle, wiring one cone type to a center mechanism and the opposing cone type to an inhibitory mechanism via horizontal cell negative feedback or amacrine cell lateral inhibition would nicely address this apparently simple problem as Wiesel and Hubel suggested. However, at present, there is little evidence that such selective circuitry is present for L and M cones, although data from many physiological studies have inferred cone type-specific inhibitory pathways (for review, see Ref. 79). At the same time it is well established that in the foveal center, each L and M cone forms a private output to a single invaginating (presumed ON center) and flat (presumed OFF center) midget bipolar cell. By this restricted connection to a single cone, each midget bipolar cell would show a receptive field center response strongly dominated by either an L or M cone. Since L and M cones are densely and nonspecifically contacted by H1 luminosity-type horizontal cells that sum L and M cone inputs (89, 91), it would be expected that the surrounds of these bipolar cells would show a mixed L+M response. Midget bipolar cells provide selective output to midget ganglion cells, which can show L versus M cone opponency and have been implicated as a major visual pathway for color vision in the primate. We will consider the midget pathway connectivity and L versus M cone opponency further below in the context of the midget ganglion cells where there is a long history of physiological studies.

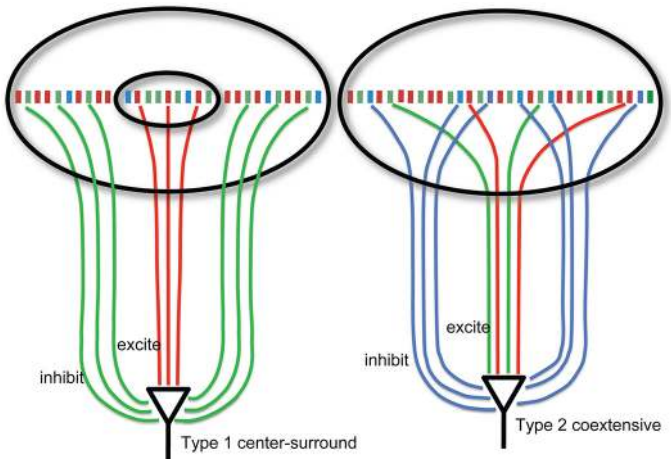


FIGURE 8. An early conception of color opponent circuitry suggested by Wiesel and Hubel (498) based on extracellular recordings made in the primate lateral geniculate nucleus. *Left*: type 1 cells with clear antagonistic center-surround receptive field organization were envisioned to draw inputs from distinct cone types (in this diagram, L cones to the excitatory center and M cones to the antagonistic surround). Depending on stimulus configuration, these cells could transmit both achromatic spatial or chromatic signals. This type of pathway was subsequently linked to the midget ganglion cells, and our current understanding of the circuitry of this pathway is discussed further in this review. *Right*: type 2 cells lacked clear center-surround organization and instead showed antagonistic cone inputs to the receptive field (in this schema L+M cones vs. S cones) that are spatially coextensive. Type 2 cells were envisioned to play a specialized role in pure color-coding. This type of pathway has subsequently been associated with S cone signaling in the primate small bistratified ganglion cell type. Current understanding of the diversity of S cone circuitry in mammalian retina is discussed further in the text.

In sum, if we consider both horizontal cells and the diverse bipolar cell types of mammals together, it is clear that mammals, with the exceptions of the distinctive S cone bipolar cell and the unique private line connection of the primate midget bipolar cell, lack the cone type selective connectivity and multiple complex opponent circuits that are apparent in various non-mammalian vertebrates. This picture holds true even for the trichromatic primate retina where we argue below that the circuitry that initiates the red-green and blue-yellow axes of color vision acquires spectral opponent properties without recourse to complex outer retinal circuitry.

VII. COLOR OPPONENT AMACRINE CELLS

Amacrine cells comprise the most anatomically diverse cell class of the retina with estimates now approaching 40 distinct types (244, 245, 286, 462). In contrast, the functional diversity of these myriad cell types has been relatively understudied and, compared with the more experimentally tractable horizontal cells, there are many fewer reports on color opponent amacrine cells or amacrine cell circuits that might be linked to cone opponency. Kaneko (230) identified sustained amacrine cells that hyperpolarize to red light and depolarize to green light in goldfish. Subsequent investigators identified additional subtypes in carp and goldfish retina including red ON/green OFF, blue ON/yellow OFF, and yellow ON/blue OFF (114, 312). In zebrafish retina, a triphasic amacrine cell was also observed (444).

In turtle retina, Ammerüller et al. (6) identified five anatomic types of amacrine cells showing three different types of color opponency (3 red OFF/blue ON center, 1 red OFF/green ON center, and 1 double opponent cell with red ON versus blue OFF center with an opponent surround). When responses to UV light were later examined, additional subtypes emerged showing yellow ON/blue OFF and blue/green/red ON versus UV OFF (384). The presence of similar spectral signatures in anatomically different subtypes suggests that they inherit responses from similar color opponent bipolar cells (179). New amacrine cell spectral subtypes also emerge that were not seen among bipolar cells, suggesting that further processing occurs in the inner plexiform layer.

In mammalian retina, characterization of amacrine cell physiology has focused principally on the starburst and AII amacrine cells, both of which lack color opponency. In primates, the few amacrine cells whose light responses have been characterized with regard to S, L, or M cone inputs also lack color opponency (84). In this context, we also note that application of GABA and glycine receptor antagonists to block inner retinal synaptic inhibition mediated by amacrine cells has little or no effect on cone opponency in the two major classes of cone opponent ganglion cells in the primate, L versus M cone opponent midget cells and S versus L+M opponent small bistratified cells (75, 77), thus precluding a primary role for amacrine cells in cone opponent circuitry.

VIII. COLOR OPPONENT RETINAL GANGLION CELLS

A. Color Opponent Retinal Ganglion Cells in Non-mammalian Vertebrates

Hartline (175) established that visual signals are carried from the retina via multiple different types of retinal ganglion cells. Early investigators identified a number of different types of color opponent retinal ganglion cells in species from fish to primate (98, 101, 160, 201, 312, 481, 501). In turtle retina where only two spectrally opponent bipolar cell types have been found, 12 different types of color-opponent ganglion cells have been identified, including double opponent cells (6, 179, 180, 290, 384). In fish, double opponent retinal ganglion cells can be further subclassified into both linear (X-like) and nonlinear (Y-like) subtypes (23, 460). Thus, in non-mammalian retinas, there appears to be a rich diversity of color-related cell types at the ganglion cell level that expand the capabilities found in bipolar cells. However, the anatomical origins, detailed circuitry, and related physiological properties of these types remain to be studied in detail.

B. Color Opponent Retinal Ganglion Cells in Non-primate Mammals

As considered above for bipolar cells, the vast majority of ganglion cells in dichromatic mammals lack spectral opponency (14, 514). The few ganglion cells that show opponency are related to S cone circuitry (294, 311, 314, 419). As we describe below, a variety of pathways for processing S versus M cone signals have been identified among different mammals.

The cellular mosaics and circuitry for both S ON/M OFF and M ON/S OFF ganglion cell types have been characterized in ground squirrel retina using multielectrode array recordings (407). ON inputs for S ON and M ON cell types were eliminated by combined bath application of the mGluR6 receptor antagonist LY341495 and agonist L-AP4 (407), suggesting they both arise from ON bipolar cells that receive relatively pure inputs from S and M cones, respectively (270). In addition, as illustrated in **FIGURE 9**, S OFF responses were blocked by the mGluR6 agonist/antagonist combination and by the glycine receptor antagonist strychnine, but not by the GABA receptor antagonist picrotoxin. This suggested that S OFF responses in M ON/S OFF ganglion cells arise from S cone inputs into S ON bipolar cells that synapse onto glycinergic amacrine cells which in turn make sign-inverting synapses onto either M ON bipolar cells or M ON ganglion cells. This hypothesis was substantiated by discovery of a blue-sensitive, glycinergic amacrine cell that can act as an intermediary between S ON bipolar cells and M ON retinal ganglion cells (63) **(FIGURE 9)**. In contrast to S OFF responses, M OFF inputs are resistant to ON pathway blockade and strychnine (407) and show longer latency than ON responses. These results suggest that M OFF responses may arise from inhibitory feedback to S cones by horizontal cells that receive strong M cone inputs (407), although this model was not tested by pharmacological blockade of horizontal cell feedback with HEPES.

In rabbit retina, an S ON/M OFF and two types of M ON/S OFF ganglion cells have been identified. S ON/M OFF cells are monostratified with dendrites terminating only in the ON sublamina of the inner plexiform layer, suggesting they receive input solely from ON-type bipolar cells. Consistent with this, blocking ON bipolar cells with L-AP4 eliminated both S ON and M OFF components. Inhibiting horizontal cell to cone feedback with HEPES also eliminated M OFF responses. Together, these results suggest that S ON inputs into these cells are conveyed through S ON bipolar cells, whereas M OFF responses originate with feedback from horizontal cells to S cones and are then transmitted to S ON bipolar cells (311). This circuit appears similar to that employed by S ON/M OFF ganglion cells in ground squirrel as described above. While A-type horizontal cells contact both S and M cones, the latter are more plentiful, providing a substrate for opponent M OFF responses in the receptive field surround (171).

Among the two types of M ON/S OFF ganglion cells in rabbit retina, the first is a monostratified cell with dendrites in the ON sublamina, utilizing circuitry much like that described above for M ON/S OFF cells from ground squirrel retina. Both ON and OFF responses of this cell type in rabbit were blocked by L-AP4, and S OFF responses were also blocked by strychnine, suggesting a sign-inverting amacrine cell generates S OFF responses (311).

The second M ON/S OFF ganglion cell in rabbit retina is a bistratified cell. In this cell, S OFF responses persisted in L-AP4 as well as with GABA and glycine antagonists, suggesting they arise by direct inputs from an S OFF bipolar cell. M ON responses persisted in L-AP4 but were attenu-

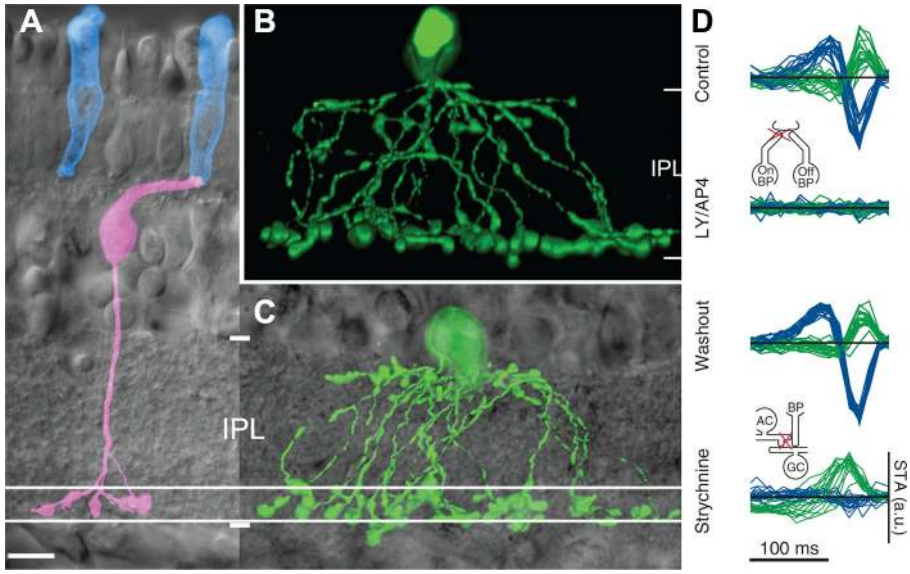


FIGURE 9. S cone circuitry in dichromatic, nonprimate mammals utilizes inner retinal inhibitory pathways to achieve spectral opponency in the OFF pathway. *A*: in the retina of a cone dominant ground squirrel, an S cone (blue) contacts an S cone ON bipolar cell (magenta) whose dendrites terminate in the inner, more vitreal half of the inner plexiform layer (IPL). The S cone signal is transmitted from S cone bipolar cells via glycinergic synapses to S cone amacrine cells (green; *B* and *C*). *D*: superimposed time courses of S (blue lines) and M (green lines) cone inputs to S OFF/M ON ganglion cells recorded simultaneously using a multielectrode recording array in the retina of a ground squirrel. When cone inputs into ON bipolar cells were attenuated with a combination of 50 μM L-AP4 and 75 μM LY341495 (LY/AP4), both S OFF and M ON responses were abolished. When glycinergic inputs from amacrine cells to ganglion cells were attenuated by application of 100 μM strychnine, the S OFF signals but not M ON signals were abolished, confirming the requirement for an inhibitory sign-reversing amacrine cell as the basis for S OFF opponency in this species. [Adapted from Chen and Li (63) and Sher and DeVries (407), with permission.]

ated by HEPES, suggesting that they reflect negative feedback from horizontal cells to S cones that is then relayed to S OFF bipolar cells. This mechanism requires the presence of S cone OFF bipolar cells in rabbit retina. While S cone OFF bipolar cells have not been observed in many recordings from ground squirrel retina (270), there is anatomical evidence for an S cone OFF bipolar cell in rabbit retina, so this may reflect a species difference (280). This mechanism further assumes that the presence of dendrites in the ON sublamina of this bistratified M ON/S OFF cell are not a reliable marker for ON-type cells. There is precedence in mouse retina for a bistratified ganglion cell that receives inputs only from one type of bipolar cell, albeit ON type (197, 390).

Guinea pig retinas also have S ON/M OFF cells and a single type of M ON/S OFF ganglion cell. In guinea pig, both cells are monostratified with dendrites only in the ON sublamina, suggesting that they receive inputs solely from ON bipolar cells (514) and may therefore employ similar mechanisms to those suggested above for ground squirrel retina and for monostratified cells in rabbit retina.

Responses from a small sample (n = 3) of M ON/S OFF cells have been described in a dichromatic wallaby retina (185). S OFF responses were delayed with respect to M ON responses consistent with the idea that S OFF signals are conveyed indirectly to the M ON ganglion cells, perhaps via the intermediary amacrine cells described for rabbit and ground squirrel.

In mouse retina, only ~2% of ganglion cells show S ON/M OFF color opponency (124, 125). These cells include recently described monostratified M5 cells that show weak expression of the novel photopigment melanopsin (419). In M5 cells, the center response appears to arise primarily from inputs by type 9 S ON bipolar cells and the surround from spiking GABAergic amacrine cells (419). Blocking horizontal cell feedback reduced the surround of these cells but did not fully eliminate it. This differs from S ON/M OFF cells in rabbit retina described above where the M OFF surround is not sensitive to blockade of inhibition and instead appears to arise from horizontal cell feedback to cones (311). We return to discuss the circuitry of M5 cells further in section X on melanopsin.

In the transitional zone of mouse central retina where many M cones show strong coexpression of both S and M opsins, large alpha-type ganglion cells also show spectrally opponent responses consisting of either S ON with opponent M OFF surround or M ON with opponent S OFF surround (60). A combination of $GABA_A$ and $GABA_C$ blockers or use of tetrodotoxin (TTX) eliminated opponency in these cells, suggesting involvement of spiking, GABAergic amacrine

cells. The size of opponent surrounds suggests that these GABAergic amacrine cells have large receptive fields. As discussed further in section IX on rod inputs, mice also have a population of color opponent retinal ganglion cells that show S OFF responses to the center and medium-wavelength responses to the surround which may arise from rods (216).

In summary, dichromatic mammals employ a variety of different mechanisms for encoding S versus M cone signals. Many species have S OFF/M ON cells where the M ON input is provided by M ON bipolar cells and the S OFF input is provided by S ON bipolar cells that contact intermediary amacrine cells that in turn inhibit inputs from M ON bipolar cells. Most species also have S ON/M OFF cells where the ON input is provided by S ON bipolar cells and the OFF input is provided by inhibitory feedback from horizontal cells to S cones. Mouse retina appears to differ in that the OFF input to S ON/M OFF ganglion cells is provided by inhibitory amacrine cells rather than horizontal cells. Rabbits also possess a bistratified M ON/S OFF ganglion cell that may receive direct inputs from S OFF bipolar cells, but this circuit remains to be verified more directly.

C. Color Opponency in Primate Ganglion Cells

The discovery of spectral opponency in the LGN of primates laid the foundation for later work addressing its underlying mechanistic origins in the retina. Spectral opponency was first recorded in the macaque LGN at about the same time that opponency was found in horizontal cells of the fish retina and contributed to the general experimental support for opponent color theory in human vision (102, 104, 105, 108, 109). Subsequent psychophysical identification of distinct S versus L+M "blue-yellow" and L versus M "red-green" axes in color space (250) more formally established a second, cone-opponent stage of color processing. This result in turn provided the experimental framework for using the identical cone-type specific stimulus space in recordings from the primate parvocellular LGN (107) and led to the identification of ON and OFF pathways associated with both the S versus L+M and the L versus M axes (262, 458, 459). Both were traced to the small receptive fields of the parvocellular layers, implicating the parvocellular-projecting midget ganglion cells of the retina (233, 379). However, an alternative hypothesis suggested two morphologically separate and parallel circuitries, a primordial mammalian S cone pathway involving the newly discovered "blue-cone" bipolar cell (291) and the well-established private line midget circuit that exploited the recent origin of L and M cones in the trichromatic primate lineage (318). This hypothesis has found experimental support but unexpected retinal mechanisms have also been discovered. Our current understanding of the retinal ganglion cells and circuits linked to these two chromatic subsystems in the primate is considered in turn below.

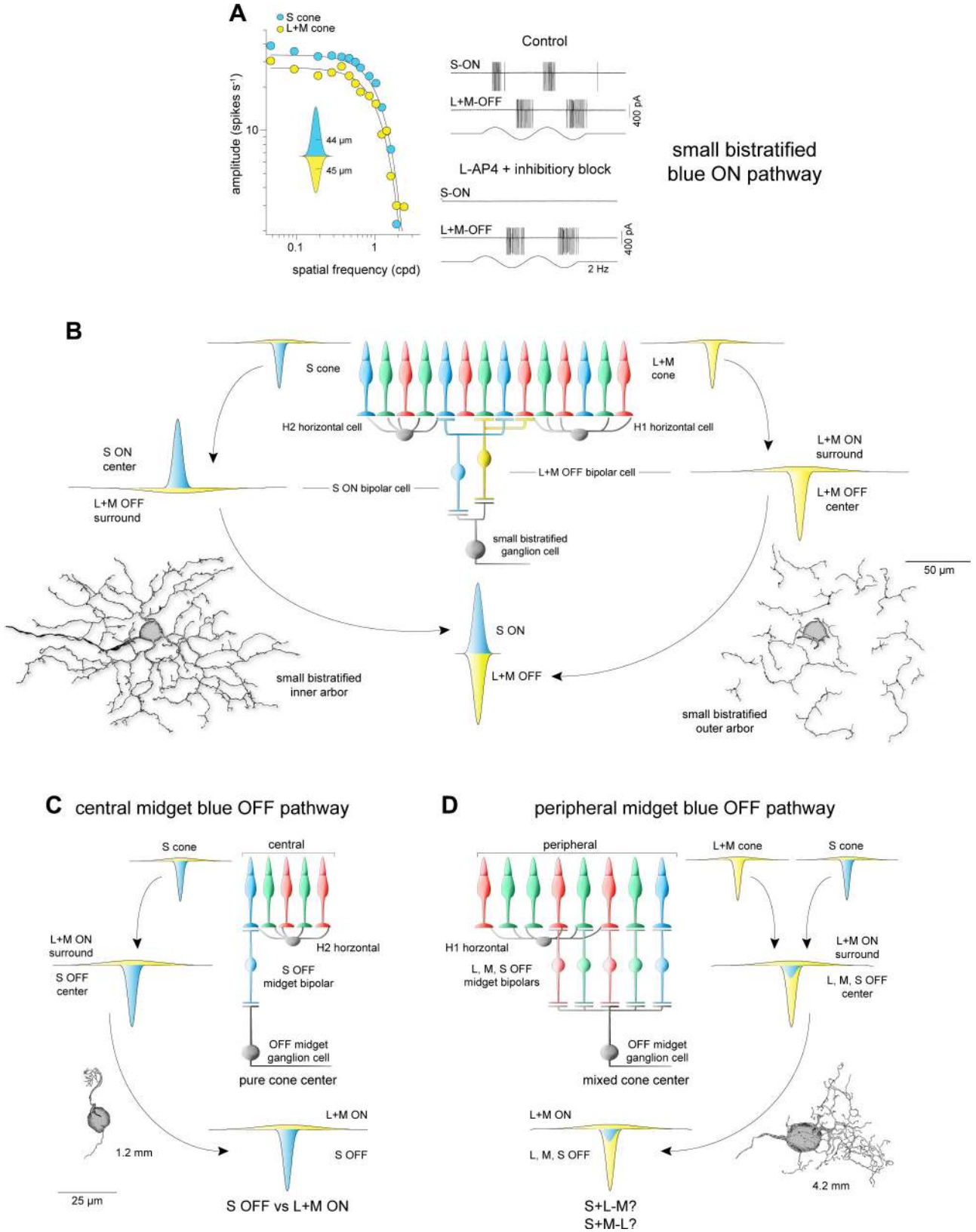
1. S ON/L+M OFF small bistratified ganglion cell

As described in the earlier section on bipolar cells (see sect. VI*B1*), the primate S cone is presynaptic to both ON and OFF pathways that are linked to anatomically distinct inner retinal circuits (85). The S cone-selective ON bipolar cell forms an axon terminal near the inner, vitreal border of the inner plexiform layer where it makes synapses with inner tier dendrites of a small bistratified ganglion cell that has thus far been observed only in primate retina (53, 82, 87, 154). These small bistratified ganglion cells show S ON/L+M OFF cone opponent light responses **(FIGURE 10*A*)**. While the S ON response presumably arises from direct excitatory synaptic inputs by S cone ON bipolar cells, the origin of the L+M OFF component has been more difficult to clearly identify. The outer tier dendrites receive sparse input from a diffuse OFF cone bipolar with nonselective input from L and M cones (153, 358), providing an obvious synaptic pathway for an L+M OFF response. So it was surprising when it was reported that the mGluR6 receptor agonist L-AP4 abolished both S ON and L+M OFF responses (53, 142). However, in other recordings from small bistratified ganglion cells, application of L-AP4 selectively attenuated S ON responses (75), whereas L+M OFF inputs were preserved **(FIGURE 10*A*)**. Moreover, whole cell voltage clamp recordings revealed that the L+M OFF-evoked synaptic current showed a reversal potential of 0 mV consistent with direct glutamatergic inputs from OFF bipolar cells (76, 85). Furthermore, blocking synaptic inhibition with the glycine antagonist strychnine or the $GABA_{A/C}$ antagonist picrotoxin did not affect the chromatic balance in these cells (75). The reduction in L+M OFF responses by L-AP4 observed in extracellular recordings by Field et al. (142) could be caused by the hyperpolarizing effects of L-AP4 on ON-type bipolar cells that would be expected to reduce excitability of postsynaptic ON/OFF ganglion cells. Inhibitory surrounds arising from horizontal cell feedback also provide input into the small bistratified ganglion cell, but the surrounds of ON and OFF bipolar cells appear to cancel one another, producing co-extensive M and S cone receptive fields (85) **(FIGURE 10*B*)**.

In addition to the small bistratified ganglion cell, a second bistratified cell with a larger dendritic field also projects to the LGN in both macaque and human retina (92, 359). A small number of recordings from these cells reveal a similar S ON versus L+M OFF light response (90), but details of the receptive field organization and underlying circuitry remain unexplored. Monostratified S ON cells akin to the S ON/ M OFF cells in ground squirrel and rabbit retina have not been observed in primate retina.

At low scotopic levels, rod signals are carried exclusively by a single type of rod ON bipolar cell without involvement of

OFF bipolar cells. Loss of mGluR6 from ON bipolar cells therefore causes congenital stationary night blindness (CSNB) (524) and, along with this, causes loss of sensitivity in ON-type cone bipolar cells, presumably including S ON bipolar cells (437). In CSNB patients, blue/yellow perception is impaired in the periphery, but despite impaired transmission by S ON bipolar cells, blue/yellow perception appears relatively normal in central retina (437). This has



prompted the suggestion that S ON bipolar cells are not involved in blue/yellow color vision (327). However, there are also no obvious deficits in the perception of ON versus OFF luminance contrast in CSNB patients (121), suggesting that cone-driven OFF bipolar cell inputs can carry sufficient information about light increments and decrements to compensate for the loss of ON bipolar cell inputs at higher light levels. Similarly, information carried by S OFF bipolar cells may be sufficient to compensate for loss of input from S ON bipolar cells in the ultimate perception of color. Indeed, this conclusion was reached in a much earlier study in which L-AP4 was injected into the eye of a macaque monkey to attenuate ON pathway signals, including those arising from S cones (411). The results showed that psychophysically measured spectral sensitivity to S cone stimulation was relatively unaffected leading to the conclusion the S OFF pathways provide a sufficient S cone signal. In the next section, we discuss evidence for S OFF cells in primate retina.

2. S OFF midget ganglion cell

The S ON bipolar cell provides virtually the entire ON pathway output for S cones. S cones therefore lack the private-line connection with an ON midget bipolar cell (and in turn ON midget ganglion cell) that is found for all L and M cones. Thus the S ON bipolar, especially in central retina where many of the S cone to ON bipolar connections are one-to-one, in essence replaces the ON midget bipolar cell circuit (451) **(FIGURE 11, *A–F*)**. The major OFF bipolar cell connection to the S cone was shown to originate from a flat midget bipolar by serial electron microscopic (EM) reconstruction (240), which in turn forms a private line connection as expected for an OFF midget ganglion cell. This result was questioned however when it was subsequently shown in the retina of marmosets that the S cone lacked connectivity to OFF midget bipolar cells when combining immunohistochemical markers for S cones and flat midget bipolar cells (263). The recent development of powerful new EM reconstruction methods has allowed this question to be revisited, with complete reconstructions of the S cone output to ON and OFF bipolar cells confirming the original observation of a private line S OFF midget bipolar and its midget ganglion cell partner (96) **(FIGURE 11, *A–H*)**. Indeed, these reconstructions show that every S cone receives the majority of its noninvaginating contacts from an OFF-midget bipolar, which in turn synapses exclusively with a single OFF midget ganglion cell, suggesting strongly that the midget pathway is the major OFF counterpart of the S ON pathway **(FIGURE 11, *C*, *G*, AND *H*)**. This arrangement represents a striking asymmetry in the post-receptoral S cone ON and OFF circuitry **(FIGURE 10, *B* AND *C*)**. This asymmetry was first observed indirectly in the relative encounter rate of S cone ON versus OFF responses at both the retinal and LGN level where S OFF responses were recorded with much less frequency (100, 107, 458). It might appear surprising, given the relatively high density of cells in the midget pathway, that the S OFF midget ganglion cell would be encountered so rarely. However, the small percentage (3%) of cells that show an S OFF response in a large sample of parvocellular LGN cells (458) is consistent with the finding that S cones comprise only a small percentage of the total cone population (7%, but as low as 2% in the central retina; **FIGURE 11*E***). A second factor that would have an impact on observing S OFF signals is related to the way in which the midget circuit changes with increasing distance from the foveal center. Across most of the retina, midget *bipolar* cells maintain their private line single cone connectivity (169, 307). However, unlike bipolar cells, midget *ganglion* cell dendritic trees enlarge and draw input from increasing numbers of cones with increasing distance from the foveal center (48, 79, 83, 137, 505). The expected consequence of this anatomy is that OFF center midget ganglion cells would presumably combine input from S, L, and M cones, with the low-density S cones providing the weakest input outside of central retina **(FIGURE 10*D*)**. This expectation has been confirmed anatomically by electron microscopic reconstruction (450) and physiologically by high-density multielectrode array recordings to characterize cone input weights to hundreds of ganglion cells in the far retinal periphery (137). It is also consistent with the finding that loss of S ON bipolar cells in CSNB patients has a much greater effect on blue/yellow perception in the periphery than in the central visual field (437).

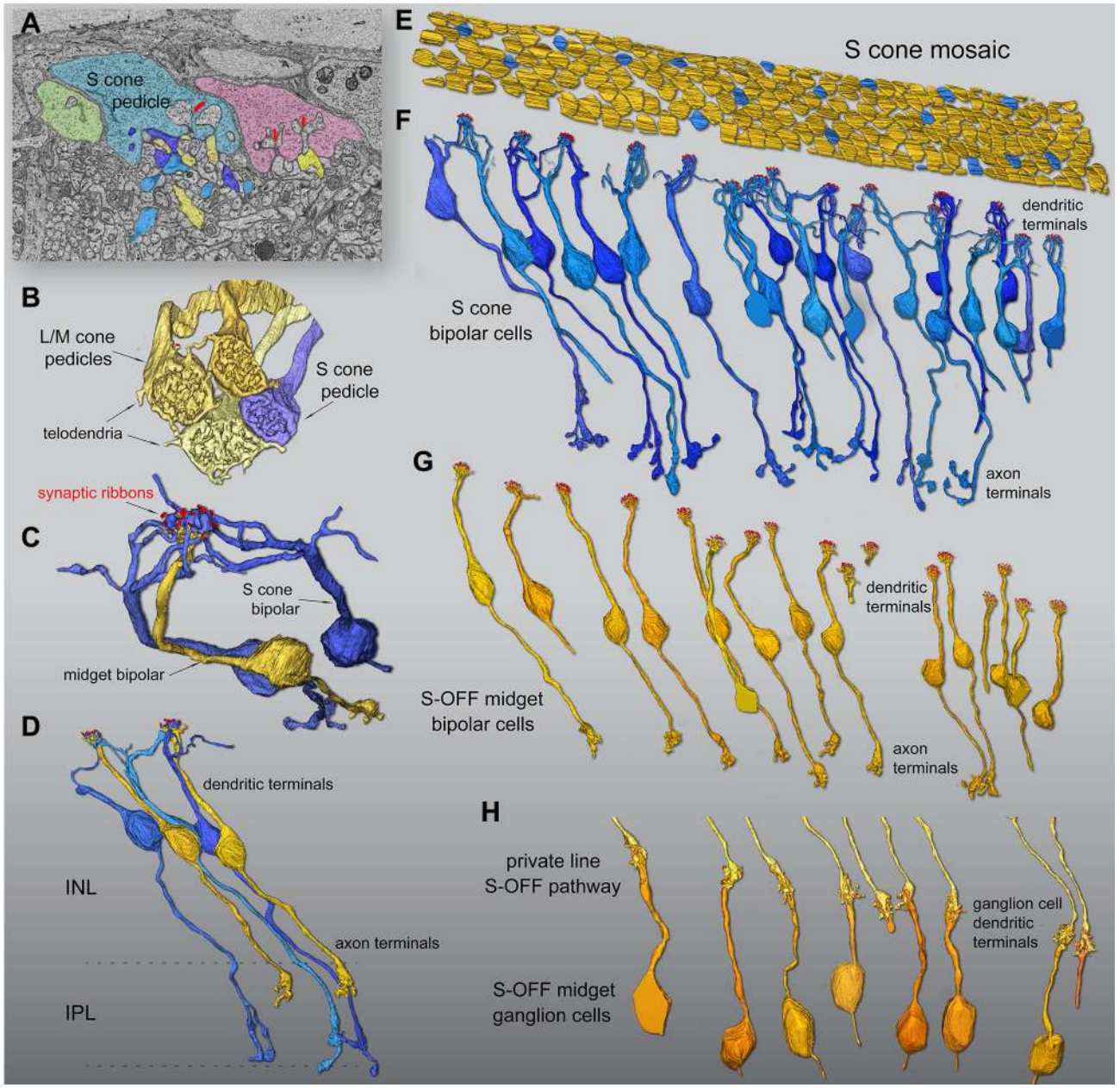
S OFF midget ganglion cells from central retina where the private line connection prevails have not been characterized physiologically. However, these cells would be expected to have an L+M surround arising by negative feedback from the S cone connecting H2 horizontal cells as has been shown

FIGURE 10. Asymmetry in the circuitry for ON versus OFF S cone-based opponency in the primate retina. *A*: *left panel* plots spatial tuning (response amplitude as a function of spatial frequency) of S ON and L+M OFF responses from a macaque blue ON small bistratified ganglion cell. Overlap of the spatial tuning plots shows the spatially coextensive S ON and L+M OFF fields. Gaussian fits to the data are illustrated by the inset profiles with Gaussian radii indicated. *Right panel*: *top*, spike discharge to sine-modulated S versus L+M stimuli. *Bottom*, L+M response is preserved after attenuation of the ON pathway and inhibitory transmission. *B*: circuitry for the small bistratified cell. S ON and L+M OFF responses arise from parallel ON and OFF pathway excitatory inputs to the bistratified ganglion cell dendritic tree. ON and OFF L+M surrounds arising from H1 and H2 cell feedback to cones appear to largely cancel at the ganglion cell level. *C*: in contrast to the small bistratified cell, the S OFF pathway originates in the midget circuit with a private-line OFF midget bipolar cell connected to each S cone in central retina and an L+M ON surround provided by H2 horizontal cell feedback to S cones. *D*: in the retinal periphery, OFF ganglion midget cells receive convergent input from S, L, and M cones, eliciting a weaker S cone contribution to the receptive field and more complex chromatic tuning (see text for discussion and references).

directly for S cones (347) **(FIGURE 10*C*)**. Beyond central retina, the impact of mixing S, L, and M cone inputs on the spectral tuning of S OFF midget cells is less clear, but it would predict that these cells might show sensitivity that does not lie strictly along the S versus L+M cardinal axis **(FIGURE 10*D*)**. In a recent study designed to test this idea directly, OFF midget ganglion cells were recorded in the near retinal periphery, and chromatic stimuli were modulated around a color circle in L+M versus S cone opponent space (506). The results showed that all ON midget cells and the majority of OFF midgets lacked a measurable S cone input. However, ~10% of the OFF midgets cells displayed an S cone input that shifted chromatic tuning off of the L versus M cardinal axis. As will be considered in more detail below, these results were well predicted by a nonselective wiring model for the cone inputs to the midget ganglion cell receptive field.

3. Other S OFF pathways

Ganglion cells in macaque retina that contain the photopigment, melanopsin, and thus show inherent photosensitivity, can also show S OFF/L+M ON opponent light responses (89). These cells will be considered later in this review in the context of the unique role that melanopsin might play in color circuitry (see sect. X*A*). Beyond these cells, none of the other non-midget ganglion cell types in primate retina that have so far been identified shows an S OFF response component. However, it should be noted that at the level of the LGN, a population of cells with large receptive fields and



other response properties that appear inconsistent with an origin in the midget pathway shows S OFF responses along with complex chromatic tuning that may not fall along the L versus M or S versus LM cardinal axes (298, 429, 431, 432). The retinal origin(s) of these possibly non-midget S OFF LGN relay cells remains to be clarified.

4. Midget L versus M "red-green" opponent circuit

The midget-parvocellular pathway has been intensively studied both anatomically and physiologically. It is well established as the origin of L versus M cone opponent signals required for the red-green dimension of color vision in trichromatic primates (for reviews, see Refs. 79, 233, 258, 413). Nevertheless, the overall role of the midget pathway in visual processing and the underlying retinal circuitry for L versus M cone opponency has remained controversial (79, 258, 505). In the central, macular region of the retina, midget ganglion cells form a "private-line" circuit in which ON and OFF midget bipolar cells contact a single L or M cone and in turn provide synaptic output to only a single ON or OFF midget ganglion cell partner, establishing a clear anatomical basis for an L or M cone pure receptive field center. In the instance of such a private-line pathway, L versus M cone opponency would hinge on the opposing circuits that create surround antagonism. A number of studies have provided evidence that the midget ganglion cell or its LGN parvocellular relay cell counterpart may show a surround that can be derived nearly or completely from the opposing cone type (i.e., L center/M surround or vice versa) (257, 260, 299, 378, 379). At the same time, the likely basis for surround circuitry fails to support this apparent L and M cone-specific wiring. As discussed in detail above, H1 horizontal cells connect indiscriminately to both L and M cones and show the expected broad spectral tuning (86, 88, 95, 112, 492). Amacrine cell connectivity within the foveal midget circuit appears similarly cone nonselective (51).

However, it has also been long recognized that selective wiring for cone type purity in the surround, while appealing, may not be required for L versus M cone opponency in the midget circuit. Thus, given the cone-pure center of the midget private-line pathway, a mixed cone surround would also provide an L versus M cone opponent signal without the need for L and M cone selective wiring (267). Recently, the question of the origin of the opponent surround in the midget circuit was addressed directly by combining voltage-clamp recordings of L or M cone evoked synaptic currents with pharmacology to dissect the midget circuit (77). There were two main results that clearly implicated cone-indiscriminate horizontal cell negative feedback as the basis for the midget surround. First, voltage-clamp recordings from midget ganglion cells showed that both the L and M cone antagonistic postsynaptic currents were excitatory and therefore originated at the bipolar cell level; thus the midget cone bipolar cell already shows L versus M cone opponency. Second, attenuation of all GABAergic and glycinergic synaptic inhibition had no effect on L versus M opponency, indicating that the antagonistic surround does not originate via a conventional, presynaptic inhibitory pathway in either the outer or inner retina. However, surround antagonism and cone opponency were abolished by buffering the bath with HEPES, further supporting the conclusion that the surround arises by negative feedback from H1 horizontal cells to L and M cones and that H1 cell feedback arises by an unconventional mechanism involving protons and pH (78, 96, 305).

The mixed cone surround hypothesis also fits with the known anatomical changes in the midget circuit that accompany increasing distance from the foveal center. As noted above, with increasing distance from the foveal center, the private-line midget circuit breaks down as the ganglion cell dendritic tree gradually enlarges and draws input from an increasing number of midget bipolar cells, resulting

FIGURE 11. Serial block-face scanning electron microscopy confirms an S OFF midget pathway in the macaque monkey retina. *A*: image of a single vertical section at the level of the cone pedicles obtained 400 μm from the foveal center illustrates the reconstruction process. An S cone pedicle (light blue fill) is flanked by neighboring L and M cone pedicles (light green and red fill). The smaller painted profiles extending toward the S cone pedicle base are S ON bipolar (dark blue) and flat-OFF midget bipolar cell (yellow) dendritic branches (synaptic ribbons, red). *B*: reconstruction of 4 cone pedicles (3 L/M cones, yellow; and 1 S cone, blue) rotated to view their synaptic faces. S cone pedicles were identified by their smaller size and the absence of the telodendria (arrows) that interconnect L and M cones. S cone identity was further confirmed by their unique and exclusive synaptic connection to the morphologically distinct S cone bipolar cell (as shown in *C*, *D*, and *F*). *C*: reconstructed S cone pedicle showing its synaptic ribbons (red) and postsynaptic dendritic contacts with an OFF midget bipolar (yellow) and two S ON bipolar cells (dark blue). Note that the S ON bipolar cell dendrites form multiple branches which extend for some distance laterally to converge on the S cone pedicle; in contrast, the OFF midget bipolar extends a single thick dendrite to the pedicle surface where it divides profusely into many small flat contacts with the pedicle base. *D*: vertical view of two S cone ribbon clusters (red ribbons; pedicle transparent) synapsing with 3 S cone ON bipolar and two OFF midget bipolar cells illustrates the morphology and relative depth of stratification of the axon terminals in the inner plexiform layer (IPL). S ON bipolar cells terminate close to the inner border, and OFF midget bipolar cells terminate near the outer border of the IPL. *E*: outlines of 185 cone pedicles reconstructed in a patch of the cone mosaic in which 17 regularly spaced pedicles (~9%; blue) were found to be S cones; the majority L/M cones are shown in yellow. *F*: each of the S cones made synaptic contact with invaginating central elements that arose exclusively from a homogeneous population of 26 S cone bipolar cells (~1.5 S ON bipolar cells/S cone). *G*: each of the 17 S cones also received dense flat contacts from an OFF midget bipolar cell; as expected, there was a single OFF-midget bipolar dedicated to each S cone. Nine of these OFF-midget bipolar cells were completely contained within the volume and reconstructed to their axon terminals. *H*: each of these 9 OFF midget bipolar cells synapsed exclusively with a single OFF-midget ganglion cell confirming a "private line" synaptic pathway from S cone to ganglion cell. [All data shown in the figure from Dacey et al. (93).]

in the convergence of multiple L and M cone inputs to the receptive field center (48, 83, 222, 296, 505) **(FIGURE 12*A*)**. The original mixed surround hypothesis predicted that if L and M cones were incapable of selective wiring, then outside of the macular region, L versus M cone opponency would progressively deteriorate to some unknown degree in the visual periphery. Thus the recent finding that some midget ganglion cells show robust red-green opponency in the retinal periphery appeared to support cone selectivity, or at least biased connectivity, in the receptive field center (48, 299, 414) and appeared inconsistent with previous models that predicted relatively steep declines in opponency with increasing distance from the fovea (321, 322). A recent study modeled the midget ganglion cell receptive field as

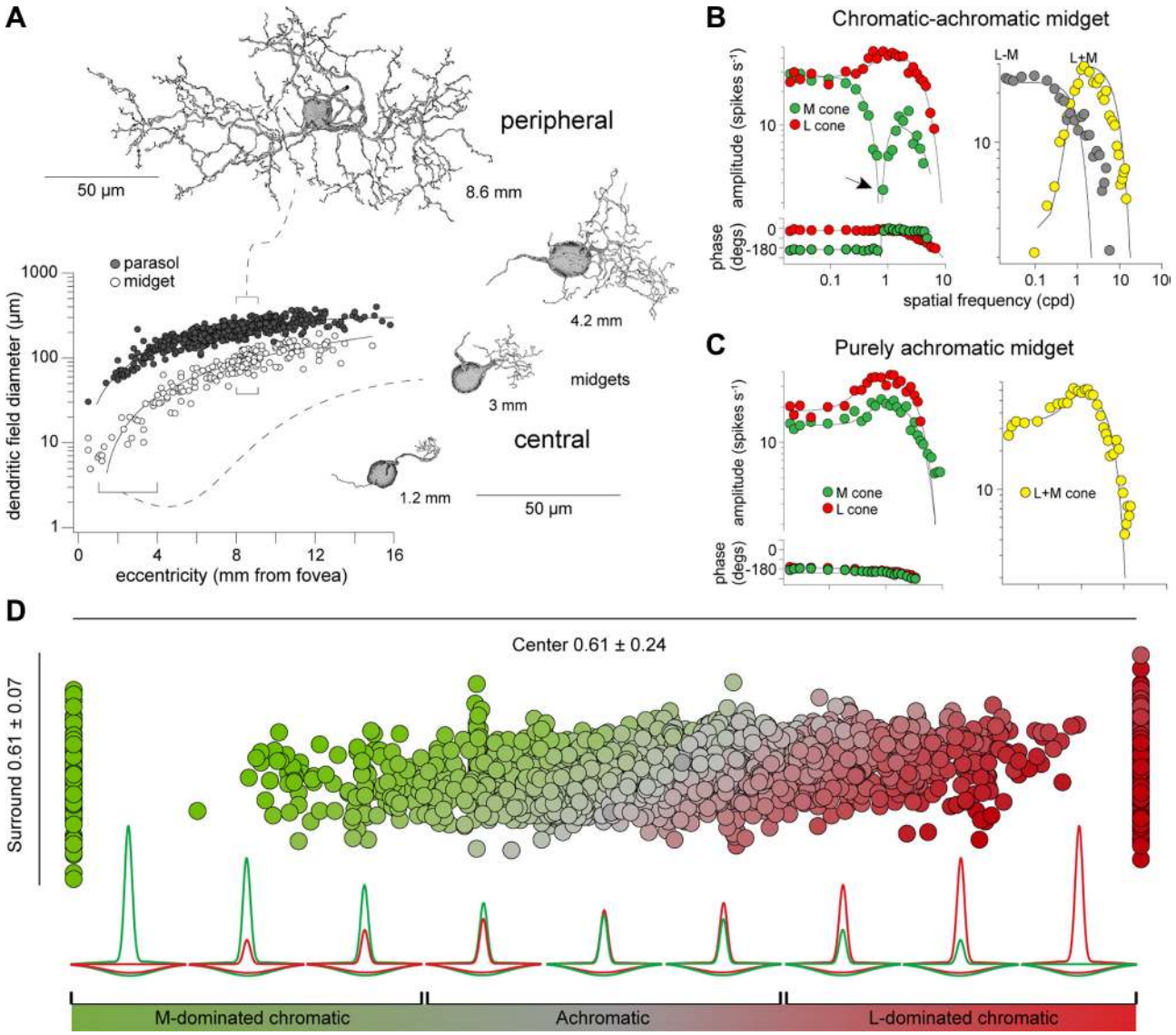


FIGURE 12. In the primate retina, red-green color opponency piggybacks on the achromatic midget pathway. *A*: midget ganglion cells in the central retina draw input from individual L or M cones. The dendritic trees of midget ganglion cells enlarge with increasing distance from the fovea to draw combined inputs from an increasing number of L and M cones. *B*: physiologically, midget ganglion cells show both red-green opponent (L vs. M) chromatic and achromatic (L+M) light responses, depending on stimulus spatial frequency and the relative weighting of L and M cone inputs to the receptive field center versus the antagonistic surround. This example from an L ON cell shows bandpass characteristics to L cone stimuli but a notch and accompanying phase reversal in the frequency response when using M cone stimuli. At low spatial frequencies, M cone inputs are dominated by inhibitory feedback from horizontal cells that receive input from both M and L cones. At high spatial frequencies, M cone inputs are dominated by excitatory inputs from single cones that are in phase with the excitatory inputs from L cones. *C*: in instances where L and M cone weighting is similar in the center and surround, midget cells show purely achromatic responses with similar bandpass frequency characteristics using both M and L cone-isolating stimuli. *D*: center versus surround L and M cone weights sampled randomly from the cone mosaic in a model of the midget receptive field (2,154 model receptive fields at a range of retinal locations) can explain variation in L versus M opponency in the midget cell population (see Ref. 505 for details).

sampling nonselectively from a realistic cone mosaic **(FIGURE 12, *B–D*)** and may have resolved some of the apparent discrepancies in these studies (505). It was found that while opponency gradually diminished in frequency with increasing eccentricity, a substantial number of opponent cells were maintained at all eccentricities. A key insight from this work was that at any given retinal location midget cells varied widely from strongly opponent to completely achromatic **(FIGURE 12, *B* AND *C*)**, but while local cell-to-cell variability was high there was also a systematic decrease in the overall chromatic sensitivity for the cell population with increasing distance from the fovea. These physiological and modeling data are also consistent with recent results from psychophysical measurements of the gradual decline in red-green chromatic sensitivity across the visual field (173). Thus the nonselective connection hypothesis is parsimonious and can account for both the maintenance of substantial red-green opponency in a subset of midget ganglion cells, as well as the gradual decline in this property in the visual periphery.

From the perspective of Hubel and Wiesel's early and simple conception **(FIGURE 8)** it might appear counterintuitive that a completely nonselective wiring diagram, without recourse to conventional synaptic inhibition, can produce robust L versus M cone antagonism and ultimately the richness of human trichromatic color vision. However, the model is consistent with current views of the molecular genetic and evolutionary origin of the L and M cones in primates. First, the gene duplication event that gave rise to spectrally distinct L and M cone opsins occurred recently in primate evolution, after the division of New and Old World monkeys ~30–40 million years ago. Second, a stochastic model explains segregated expression of L and M opsin in individual cones together with their random distribution in the overall cone mosaic (212, 241, 489). These two features have led to the hypothesis that L and M cones are not recognized as distinct circuit elements (in contrast to S cones) and thus are incapable of forming a cone-type specific wiring pattern.

The stochastic hypothesis also fits with the primacy of the midget circuit in the evolution of achromatic spatial vision in the primate. It is well established that foveal cone spacing sets the limit on human spatial resolution (191, 391). The private-line midget circuit preserves the acuity afforded by the foveal cone mosaic and likely evolved for this purpose in conjunction with the basic foveal structure unique to primates, well before the gene duplication that gave rise to L and M cone opsins. In this regard it is important to emphasize that a foveal private-line midget circuit is also present in dichromatic New World monkeys (223). Thus midget ganglion cells display achromatic, nonopponent physiology at spatial grains that are optimized for the receptive field center, and this pathway can be considered the visual channel that sets the limit on achromatic acuity. It appears then that red-green color opponency has exploited this fundamental high-resolution circuit to confer a second response dimension when center-surround antagonism is engaged and, most strikingly, without the need to construct a new and highly complex circuit (296, 505).

The principle of univariance considered near the beginning of this review suggests that single cones should be effectively color-blind and that retinal circuits are required to compare the signals across spectrally distinct cone types to encode wavelength. Recently, it has become technically possible to test the hypothesis that cones might nevertheless provide "labeled lines" for color perception. With the use of high-resolution adaptive optics methods, it is possible to determine the percept associated with stimulating single L or M cones in the living human eye (193, 393). Stimulating identified L and M cones produced percepts of red, green, and white with considerably variability from cone to cone. This has led to the suggestion that chromatic and achromatic signals may be processed by distinct populations of midget bipolar cells (327). However, if output from a subset of cones was reserved exclusively for chromatic vision, this would degrade achromatic acuity and, as mentioned above, acuity at the foveal center closely follows the Nyquist limit predicted from cone-to-cone spacing (391). An alternate idea is that the brain might learn a map of the cone mosaic through experience (26, 396). While the likelihood of reporting green or red following single cone stimulation was not significantly enhanced in cones that were immediately surrounded by cones of a different spectral sensitivity (393), the threshold for single cone detection of a colored light stimulus was elevated by use of an adapting light of the opposite color when the cone was surrounded by cones of the opposite spectral sensitivity (453). After eliminating cone coupling and light scatter, the authors concluded that the most likely explanation for this latter effect was inhibitory feedback from horizontal cells.

In summary, like dichromatic mammals, trichromatic primates employ specialized circuits for processing S cone signals. The best characterized is a bistratified ganglion cell that receives direct inputs from S cone ON bipolar cells and diffuse OFF cone bipolar cells that contact both L and M cones. Interestingly, primates appear to lack the monostratified S ON/M OFF ganglion cells found in dichromatic mammals. Anatomical contacts between S cones and midget OFF bipolar cells suggest a pathway by which S cone signals might be conveyed to S OFF/M ON ganglion cells in primates. To use the spectral information provided by reacquisition of a third cone pigment, for processing of M and L cone inputs, Old World primates adapted existing foveal circuitry that originally evolved for high achromatic visual acuity. In this circuit, L versus M color opponency was achieved by comparing responses of individual L or M cones to the summed inputs from many neighboring cones provided by inhibitory feedback from horizontal cells.

IX. ROD CONTRIBUTIONS TO COLOR VISION

A. Rod Signal Contributions to Spectral Coding in Non-mammals

The principle of univariance explains the monochromatic world that we experience under dim light conditions when only rod photoreceptors are active. However, unlike us, amphibians have two types of rods that differ in spectral sensitivity, and behavioral tests show that frogs can distinguish blue from green light under scotopic conditions, suggesting opponent interactions between these two rods (518). "Red" rods use rhodopsin, whereas "green" rods use a modified cone SWS2 opsin (242). Nevertheless, due to a similar outer segment structure and use of rod transducin, both rods show similar high sensitivity (285, 518).

In addition to evidence for rod-rod interactions, amphibians show a variety of rod-cone opponent interactions at higher light levels. Thalamic recordings from *Rana pipiens* show opponent responses to bright lights in which SWS2 rods appear to provide the dominant depolarizing ON inputs, whereas cones provide OFF inputs (235). On the other hand, in color opponent bipolar cells of *Xenopus* retina, SWS2 rods contribute to hyperpolarizing responses in opposition to depolarizing inputs from long wavelength cones (512). Dim flashes further revealed depolarizing inputs to these same cells from Rh1 rods, suggesting they sum with long wavelength cones. Rod inputs can also sum with long wavelength cone inputs in color opponent retinal ganglion cells of goldfish retina (374). Color-opponent ganglion cells in *Xenopus* showed spectral properties similar to those exhibited by their presynaptic bipolar cells. Mudpuppies possess color-opponent horizontal cells that show depolarizing responses to dim blue light that appear to arise from rod inputs and hyperpolarizing responses to bright red light arising from cone inputs (237). A second type of horizontal cell from mudpuppy revealed color opponency only under light-adapted conditions. Under these conditions, spectral sensitivity measurements indicated that the hyperpolarizing responses arose from rod inputs, whereas the depolarizing responses to red light arose from cone inputs (134).

Amphibians thus employ a variety of different retinal mechanisms for comparing responses of Rh1 rods with SWS2 rods and with cones. With only one type of rod, mammals are incapable of rod-rod interactions and, as we shall see below, while there is evidence for opponent interactions between rods and cones in mouse retina, the evidence for rod-cone opponency in primate retina is less compelling.

B. Rod Pathways in Mammalian Retina

There is a long history of psychophysical results in human vision showing that signals originating in rod photoreceptors can influence color vision (38, 303, 304, 525). Genuine spectral discrimination is absent under scotopic illumination, although some color percepts remain even under conditions when only rods are active. These percepts appear to be due to higher level cognitive activity that infers colors from monochromatic inputs based on previous experience in the natural world (364, 525). However, as cones become active at mesopic intensity levels, interactions between rods and cones can influence brightness, hue, and saturation. As we discuss below, a number of different pathways convey rod signals through the mammalian retina, offering multiple pathways for the convergence of rod and cone signals at mesopic light levels within the retinal circuitry.

Before delving into specific mechanisms for rod-cone interactions in the mammalian retina that might be involved in color vision, we begin by considering the various pathways by which rod signals are conveyed through the retina. The convergence of rod and cone inputs and other aspects of rod signaling are reviewed further elsewhere (133, 140, 141, 167).

The primary rod pathway in mammalian retina involves contacts between rods and depolarizing ON-type rod bipolar cells (reviewed in Ref. 141). Rod ON bipolar cells synapse onto specialized AII amacrine cells that make gap junctions with the synaptic terminals of ON cone bipolar cells, allowing rod signals to piggyback onto cone pathways. In parallel, AII amacrine cells also make inhibitory glycinergic contacts onto OFF bipolar cells, inverting the rod signal and allowing it to flow into the OFF pathway. In this way, a single ON-type rod bipolar cell can drive both ON and OFF responses in retinal ganglion cells. Rods and rod bipolar cells are capable of sensing single photon events and are thought to be the primary pathway by which signals at low scotopic intensities are transmitted through the retina (20, 139, 195, 383, 395, 476). Adaptation of mammals to a nocturnal lifestyle may be one of the evolutionary driving forces for development of this specialized rod circuit which appears to be present only in mammals (509). Traditionally, rod bipolar cells were thought to receive input exclusively from rods. However, recent studies indicate that as many as 40% of rod bipolar cells receive some cone inputs and as many as 50% of cones contact rod bipolar cells (351, 353).

The second major pathway involves electrotonic signal transfer through gap junctions between rods and the telodendria of cones (111, 243, 373, 448). S cones couple to rods (339), and rod-cone coupling is found in 90% of primate M and L cones (195, 339). Rod-cone coupling in mammals can be strong [e.g., 32 rods to each cone in mouse (449)] and can contribute to rod signals in mammalian horizontal cells that exclusively contact cones (94, 95, 420, 465). This pathway contributes to transmission of rod signals at higher intensities than the primary rod bipolar cell

pathway (476). The strength of rod-cone coupling varies in a circadian manner, strengthening at night and weakening during daytime (382).

Weak cone-cone coupling among M and L cones in primate retina reduces spectral differences between these cells (196), but this effect is minimized by the patchy distribution of M and L cones in primate retina (198). S cones do not couple to M cones in ground squirrel retina (271), nor do they couple to M and L cones in primate retina (196, 339).

Rod-rod coupling is very weak in mammals; some rods are not coupled at all to one another while most couple to only a few neighbors (195, 449). In non-mammalian vertebrates, rod-rod coupling is much stronger than rod-cone or cone-cone coupling (11, 12, 71, 496).

The third pathway involves direct contacts between rods and OFF bipolar cells. In most non-mammalian species, bipolar cells receive inputs from both rods and cones, although some bipolar cells are more rod-dominated and some more cone-dominated. In mammals, it was long thought that rods did not contact OFF bipolar cells. However, it is now clear that at least three types of OFF bipolar cell can make contacts with rods along with their more numerous contacts with cones (149, 181, 272, 301, 415, 449, 452). The strength of this tertiary pathway can vary among species (367). Unlike the primary rod bipolar cell pathway that operates more strongly at scotopic light levels, this pathway appears to contribute more strongly at mesopic intensities (352).

A fourth pathway has been proposed whereby rods may directly contact cone-driven ON bipolar cells (35, 73, 351, 353). The gap junctions that connect rods to cones and AII amacrine cells to ON cone bipolar cells both utilize Cx36, so its elimination should abolish both the primary rod bipolar and secondary rod-cone pathways. However, rod-driven ON responses were still observed in cone ON bipolar cells, retinal ganglion cells, and LGN in mice after Cx36 was eliminated, suggesting the presence of direct rod inputs into cone ON bipolar cells (35, 351). The finding that L-AP4 blocks residual ON responses in Cx36 knockout mice supports this conclusion (73). Direct rod inputs into cone-driven ON bipolar cells span scotopic to mesopic intensities (73, 351).

C. Rod/Cone Interactions in Mammalian Retina

The convergence of rod and cone signals through these four pathways can modulate the activity of retinal ganglion cells. Although rods are largely absent from the very center of the primate fovea, most retinal ganglion cells, including midget ganglion cells in the parafovea where rods peak in density, receive both rod and cone inputs (56, 75, 138, 161, 261, 474, 475). In parasol ganglion cells, rod inputs sum linearly with M and L cone inputs to influence contrast sensitivity (56).

In addition to summation of rod and cone inputs, suppressive rod-cone interactions have also been observed, both psychophysically and in recordings from horizontal cells and retinal ganglion cells. The activity of dark-adapted rods can have a suppressive effect on cone-driven responses that diminishes with light (130, 156, 360, 385). From studies in mudpuppy, it was proposed that this suppressive effect derived from feedback inhibition to cones by horizontal cells that receive rod input. When rods hyperpolarize to light, this relieves the tonic feedback inhibition of cones (130). In mammals, such a mechanism would require that rod signals enter the cone-dominated soma of horizontal cells, either by passing through gap junctions to cones or by traveling through the thin axon that connects the rod-driven axon terminal to the cone-driven soma of B-type horizontal cells (428).

D. Rod/Cone Interactions That Might Influence Color Vision

The retention of color vision at scotopic intensities in human S cone monochromats has suggested the possibility of opponent interactions between rods and S cones (381). A direct example of such a chromatic rod-cone interaction was recently shown for a ganglion cell in the mouse retina known as the JAMB cell. In JAMB cells, UV-sensitive S cones drive an OFF response in the center and rods drive an ON response in the surround (216). The center OFF response to UV light is resistant to GABA/glycine inhibitors or L-AP4, suggesting it is due to direct inputs from S cones to OFF-type bipolar cells. S cones also drive inhibitory synaptic currents in the receptive field center of JAMB cells via ON bipolar cells and intermediary GABAergic amacrine cells. The inhibitory green surround responses were resistant to GABA/glycine inhibitors and L-AP4 but reduced by HEPES, suggesting that they involve inhibitory feedback from rod signals in horizontal cells to S cones. As mentioned with regard to rod-cone suppressive interactions, rod signals might arise in B-type horizontal cells by rod-cone coupling or by travel within horizontal cells from the rod-dominated axon terminal to the cone-dominated soma (428). A homologous cell type to the JAMB cell does not appear to be present in primates and, to date, there is no evidence from primate retinal ganglion cells for opponent interactions between rods and S cones or rods and M or L cones.

Rather than the opponent interactions between S cones and rods suggested by studies of S cone monochromats, psychophysical studies in humans generally suggest that rod activity enhances the perception of blue relative to yellow (38). Recordings from small bistratified S ON ganglion cells in primate retina also show that rod inputs can sum with those

of S cone inputs, providing one possible pathway for these perceptual effects (75, 138).

In addition to altering the blue/yellow balance, rod inputs can enhance the perception of green relative to red, suggesting that rod signals sum with M cone signals in opposition to L cones (38, 57). While opponent interactions between L and M cones versus rods have not been seen in recordings from retinal neurons of primates, the possibility of such opponent interactions in another species is supported by the presence of color vision in seals that lack S cones and are thus M cone monochromats (343).

One mechanism that could potentially generate opponent interactions between rods and M or L cones is negative feedback from horizontal cells to cones and rods. As discussed, mammalian rods exclusively contact the axon terminal of B-type horizontal cells while the somatic compartment contacts only cones. In mouse retinas that have only B-type horizontal cells, Trümpler et al. (447) detected cone signals in horizontal cell axon terminals after rod-cone coupling was genetically eliminated, showing that rod signals can travel through the narrow axon connecting these two compartments, at least in one direction (447). Inhibitory feedback to rods from horizontal cell axon terminals that receive cone input in this way would provide a substrate for making spectral comparisons between rods and cones. Consistent with such interactions, Szikra et al. (428) found that when cones were stimulated with large-diameter, bright flashes, they observed small depolarizing responses in mouse rods that could be inhibited by use of HEPES to inhibit horizontal cell feedback.

While they found that rod signals could travel from soma to axon terminal, Trümpler et al. (447) failed to obtain recordings of light responses in horizontal cell somas from mice that lacked both rod-cone coupling and functional cones, leading them to conclude that rod signals were not capable of traveling the other direction from axon terminal to soma. In contrast, Szikra et al. (428) detected depolarizing responses in cones when using light flashes that should only stimulate rods and concluded that rod signals can be transmitted from axon terminal to soma and then inverted during horizontal cell to cone feedback. They argued that these rod-driven responses did not arise from rod-cone coupling. The responses illustrated by Szikra et al. (428) are similar in size (<2 mV) and waveform to intraretinal electroretinograms (33), raising a concern about possible contributions from extracellular field potentials. On the other hand, the negative results of Trümpler et al. (447) are based on the failure to obtain recordings from the somata of double knockout mice, and such a failure might be due to a variety of factors. There are a couple of other possible explanations for these discrepant observations. For example, just as an occasional cone makes contact with a rod bipolar cell, it is possible that an occasional dendrite extending from the soma of a B-type horizontal cell might directly contact a rod. Reconstructing the entire dendritic tree of a horizontal cell could test such a possibility. Electrical separation of the horizontal cell body from its axon terminal compartment depends critically on the shunting effect of each compartment. Glutamate release from photoreceptors diminishes and horizontal cells become less strongly coupled under bright illumination (511, 528). By increasing horizontal cell input resistance, these effects could promote signal transfer between compartments. Transmission of rod signals from the axon terminal to soma in B-type horizontal cells has been proposed as a possible mechanism to account for a number of different rod-cone interactions, so further experiments to address this question would be useful.

In summary, while mammalian rod circuitry has been characterized in detail, the specific retinal circuits that contribute to rod influences on human color vision remain to be fully clarified. The finding that rods and S cones both provide inputs into small bistratified S ON ganglion cells in primate retina (75, 138) may contribute to the ability of rod activity to enhance the perception of blue relative to yellow (38). The mechanism by which rod signals might sum with M cone signals in opposition to L cone signals in primate retina is unclear (38, 57). Recall that in primate retina, B-type horizontal cells make indiscriminate contact with M and L cones. Negative feedback to rods from axon terminal compartments that receive mixed M + L cone inputs or negative feedback to a mixture of M and L cones from rod inputs arriving in the horizontal cell soma would both provide mechanisms for rod versus M+L cone opponency, but neither of these mechanisms would produce selective summation of M cone signals with rod signals. As mentioned earlier, rods can couple directly to M and L cones, but there does not appear to be any difference in the strength of coupling between the two cone subtypes (195). There are numerous circuits by which rod and cone bipolar cells can inhibit one another via amacrine cell interactions in the inner retina (122, 255) but, as argued above, it does not appear that M and L cones are recognized as distinct circuit elements in the early retinal circuitry. Thus the site of summation between rod and M cone signals remains unclear.

X. MELANOPSIN-EXPRESSING RETINAL GANGLION CELLS

A. Melanopsin-Expressing Retinal Ganglion Cells and Cone Opponent Circuitry

In addition to rod and cone photoreceptors, the mammalian retina possesses a morphologically distinct group of ganglion cells that contain the opsin-based photopigment melanopsin and are thereby capable of intrinsic responses to light. The morphology, physiology, and function of these unique cells have been reviewed in depth (256, 387, 398,

399). Key roles for melanopsin-expressing ganglion cells are to provide signals for absolute retinal irradiance required to set the phase of the circadian rhythm which involves projections to the suprachiasmatic nucleus and to contribute to driving the pupillary light reflex which involves projections to the pretectum. As we discuss below, there is also growing evidence that these cells can influence conscious visual perception and may contribute to cone-opponent circuits.

Melanopsin in the dendritic membrane of these ganglion cells appears to couple through the G protein G_q to activate phospholipase C, resulting in the opening of TRPC channels, much like the signaling pathway used by rhabdomeric photoreceptors of invertebrates (67, 164, 207, 350). The spectral sensitivity of melanopsin differs from rod and cone opsins, with absorption peaking in the blue range near 480 nm (see **FIGURE 1*B***) (22, 89, 178, 284), falling between that of human S cone (with a peak absorbance of ~420 nm) and M cone pigments (~535 nm), and differing slightly from rhodopsin which peaks near 495 nm (34, 483) **(FIGURE 2*C*)**. Melanopsin-driven light responses show extremely slow kinetics and minimal light adaptation, allowing them to serve as photon-counters with a very long integration time. However, like other ganglion cells, melanopsin-expressing cells also receive synaptic input from rods and cones, raising the question of whether the spectrally distinct melanopsin-based response could interact with rod and/or cone inputs and contribute to color opponency (89, 504).

The melanopsin-driven response appears to enhance the perception of brightness in humans (36) and generate conscious visual percepts (194, 416, 519, 526). The color balance needed to produce unique white can also be influenced by melanopsin activation, suggesting that melanopsin contributes to color perception (55). In both primate and non-primate mammals, two ganglion cell populations express melanopsin at a high level and deploy a loose plexus of photosensitive dendrites at the inner and outer borders of the inner plexiform layer. In the rodent, these are referred to as M1 and M2 cells (21). In the primate retina, these ganglion cells project to the LGN along with projections to the pretectum and suprachiasmatic nucleus (172). They also receive both rod and cone input and show S OFF versus L+M ON type of cone opponency. These results suggest that cone-driven responses of these cells could play a fundamental role in aspects of conscious visual perception including color vision mediated by the geniculostriate pathway (89). Consistent with properties of these cells, psychophysical studies suggest that melanopsin signals add with L and M cone inputs in opposition to S cone inputs (526). The impact of melanopsin on the pupillary reflex is also consistent with contributions from an opponent circuit in which melanopsin sums with L and M cones in opposition to S cones (17, 417). A recent psychophysical study using silent substitution techniques to study color vision suggests that melanopsin may add with M cones in opposition to L cones (55). As discussed earlier, evidence suggests that L and M cones are not recognized as distinct circuit elements early in the retina, so the processing of melanopsin plus L cone pigments in opposition to M cone pigments does not match the simple S OFF versus L+M ON responses found for melanopsin-containing ganglion cells in macaque retina.

Among non-primate mammals, there is no evidence for cone opponency in the two major melanopsin-containing ganglion cell populations (M1 and M2). M3 cells do not appear to form a separate functional population and may represent a variant of the M1 and M2 types (21, 274). Two additional ganglion cell types have been described that show weak melanopsin expression levels. M4 cells project to the LGN, correspond to the anatomical ON alpha ganglion cell type, and lack color opponency (127, 397). A significant fraction of neurons in the mouse LGN respond to selective modulation of melanopsin independent of other photopigments (97); it is possible that ON-alpha cells contribute to this signal in the mouse LGN though direct evidence is lacking. There is no evidence that the alpha cell correlate in the primate, the LGN-projecting parasol cell, expresses melanopsin.

The final melanopsin-expressing ganglion cell type, termed the M5 cell in mouse, shows a cone-opponent S ON center response and M OFF surround response (419). As discussed earlier when considering S cone circuits, the center response of the M5 cell involves direct ON inputs from S cones through S cone selective type 9 ON bipolar cells. Inhibiting horizontal cell feedback with HEPES diminished M OFF responses in the surround but did not entirely eliminate opponency. Instead, blocking inputs from spiking GABAergic amacrine cells with $GABA_A$ and $GABA_C$ antagonists or with TTX fully eliminated opponency. Blocking ON bipolar cell inputs with L-AP4 also eliminated M OFF responses. From these results, the authors concluded that while horizontal cell to cone feedback helps to shape the surround, the major pathway for opponent OFF responses involves a sign-reversing amacrine cell synapse in the inner plexiform layer. How the very weak melanopsin response in this cell type might interact with cone-opponent responses and the role that this ganglion cell type might play in mouse color vision remains unclear. However, it has recently been reported that some neurons in the mouse suprachiasmatic nucleus that regulate circadian rhythms show evidence for opponent processing of short and long wavelengths, with both S ON/M OFF and S OFF/M ON cells (485). S ON cells were also shown to receive ON inputs from melanopsin; effects of melanopsin activity on S OFF cells were less consistent. Cone opponent M5 cells project to the mouse LGN, but there is no evidence that these cells also project to the suprachiasmatic nucleus; overall, these results remain difficult to interpret. We note that there is no evidence for mel-

anopsin expression in the S ON/L+M OFF small bistratified ganglion cell type in primate retina.

B. Other Pathways by Which Melanopsin Might Influence Color-Related Circuits

There are multiple pathways by which melanopsin-driven activity can be transmitted back into the retinal circuitry. Melanopsin-containing ganglion cells make gap junctions with many amacrine cells (274, 380). In addition, a subset of M1 ganglion cell types in both mouse and primate give rise to intrinsic axon collaterals within the retina (217) that form glutamatergic synapses onto dopaminergic amacrine cells (530, 531, 533) and can thereby modulate dopamine's role in light adaption (366). This modulation can have widespread influences since dopamine acts on virtually every neuron in the retina, serving as a circadian neuromodulator to shift the retinal circuitry from rod- to cone-driven vision (500).

Melanopsin immunoreactivity has been reported in a handful of peripheral cones (0.11–0.55% of cones) from human and mouse retina (115). Melanopsin-positive cells labeled in the Opn4-cre mouse line also include cone photoreceptors, but this may reflect off-target effects of the transgene (123). mRNA expression profiling data do not show evidence for significant Opn4 expression in mouse cones (47), and photocurrents measured in cone outer segments show spectral sensitivities that match cone opsin absorbance (247, 335, 338, 401).

The many pathways by which melanopsin activity might influence color and other aspects of conscious visual perception may account for the range of psychophysical results regarding melanopsin impacts on vision. While there is currently significant interest in this novel mechanism, it is worth noting that the influence of melanopsin activity on color vision is likely to be quite subtle since observers do not report any obvious differences in images shown on five-primary visual displays that differ only in the degree of melanopsin activation (3).

XI. CONCLUSIONS AND FUTURE DIRECTIONS

A few themes stand out when our current knowledge of the retinal mechanisms involved in color vision is considered broadly in both mammals and non-mammalian vertebrates. First, given photoreceptor univariance, cone opponent interactions–the first indication of wavelength encoding–are a dominant and highly complex feature of many retinal neurons in non-mammalian vertebrates. These animals show complex triphasic and occasionally tetraphasic spectral opponency along with double opponent center-surround receptive fields in the responses of second-order horizontal and bipolar cells. In addition, some non-mammalian retinas link the rod transduction pathway with multiple opsins to get around the limitation of univariance and create a unique "rod-based" spectral opponency. In contrast, in both dichromatic mammals and trichromatic primates, most retinal neurons lack cone opponent signals. Indeed, the extremely complex cone opponency that has been the subject of intensive study in horizontal cells of teleosts is totally lacking in horizontal cells of mammals. In the general mammalian plan, opponent signals in bipolar cells and ganglion cells appear restricted to a few circuits linked to S cones. Even in the trichromatic primate visual system, it is striking that double-opponent L versus M cone receptive field structures do not appear until the level of primary visual cortex and even there they are rarely encountered (405).

A second theme is the re-acquisition of complex trichromatic color vision in primates, including humans. Primates employ the same basic retinal architecture as dichromatic mammals including some of the specialized circuitry related to S cones, such as the S cone selective ON cone bipolar cell type. To circumvent limitations imposed by the existing retinal circuitry, L versus M cone opponency arose by "piggy-backing" on the specialized foveal private-line midget circuit that evolved to provide the high achromatic visual acuity characteristic of primate vision. The result is acquisition of a "red-green" chromatic dimension without the need to reinvent the highly complex and cone-type specific circuitry that we find in non-mammalian retina.

Finally, we see emerging evidence for more subtle influences on color vision in mammals at the retinal level that extend beyond the requirement for simple cone opponent interactions. Rod photoreceptors, the heavy lifters for achromatic spatial vision at low light levels, can interact with cone circuits via diverse synaptic pathways that are only beginning to be understood. And more surprising is the finding that the recently discovered opsin melanopsin, resident in the dendritic network of certain ganglion cells, not only provides the retinal mechanism for setting the circadian clock but also appears to interact with cone signaling pathways and thereby influence human color perception.

The studies summarized in this review reveal diverse retinal mechanisms and potential pathways for the first steps towards color vision. New questions have emerged, but a number of old questions also remain unanswered. While cone opponency in non-mammalian horizontal cells has been well characterized, it is striking that many aspects of this circuit and how it contributes to color vision remain unclear. For example, does feedforward inhibition from horizontal cells to bipolar cell dendrites shape color opponent surrounds of non-mammalian bipolar cells? Similarly, while evidence has accrued that negative feedback from horizontal cells to rods and cones is mediated by changes in extracellular pH, the critical mechanism by which horizon-

tal cell membrane potential regulates pH remains unidentified. Do horizontal cells only contribute to generating opponent surrounds in bipolar cells or do they perform other functions related to color perception? Does horizontal cell to rod feedback contribute to center-surround receptive fields or to rod-cone opponency?

Beyond the horizontal cells, it remains unclear how cone opponent responses are generated in the receptive field centers of spectrally opponent bipolar and ganglion cells in non-mammals. In mammalian retina, apparent S OFF and S ON center bipolar cells connect to their ganglion cell counterparts, but the physiology of these key cone bipolar cell types remains to be studied. In the trichromatic primate retina, the unique and intensively studied midget circuit clearly contributes the critical L versus M cone signal to the "red-green" visual channel, but the specific locus at which S cone signals sum with this pathway is unclear. Moreover, understanding how the visual cortex extracts both chromatic and achromatic information from the midget-parvocellular pathway remains an important goal. In human vision, rod inputs apparently sum with M cone inputs in opposition to L cone inputs. However, M and L cones do not appear to be recognized as distinct circuit elements early in the retina, so the site of these interactions remains unclear. Similarly, emerging evidence suggests that the melanopsin-based light response, although extremely sluggish, can influence human color perception, but again, the site for these interactions remains unknown.

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