Published in final edited form as:
Prog Retin Eye Res. 2012 September ; 31(5): 407–441. doi:10.1016/j.preteyeres.2012.04.003.

Lateral interactions in the outer retina

Wallace B. Thoreson[1,*] and **Stuart C. Mangel**[2,*]

[1]Departments of Ophthalmology & Visual Sciences and Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198 USA

[2]Department of Neuroscience, The Ohio State University College of Medicine, Columbus, OH 43210 USA

Abstract

Lateral interactions in the outer retina, particularly negative feedback from horizontal cells to cones and direct feed-forward input from horizontal cells to bipolar cells, play a number of important roles in early visual processing, such as generating center-surround receptive fields that enhance spatial discrimination. These circuits may also contribute to post-receptoral light adaptation and the generation of color opponency. In this review, we examine the contributions of horizontal cell feedback and feed-forward pathways to early visual processing. We begin by reviewing the properties of bipolar cell receptive fields, especially with respect to modulation of the bipolar receptive field surround by the ambient light level and to the contribution of horizontal cells to the surround. We then review evidence for and against three proposed mechanisms for negative feedback from horizontal cells to cones: 1) GABA release by horizontal cells, 2) ephaptic modulation of the cone pedicle membrane potential generated by currents flowing through hemigap junctions in horizontal cell dendrites, and 3) modulation of cone calcium currents (I_{Ca}) by changes in synaptic cleft proton levels. We also consider evidence for the presence of direct horizontal cell feed-forward input to bipolar cells and discuss a possible role for GABA at this synapse. We summarize proposed functions of horizontal cell feedback and feed-forward pathways. Finally, we examine the mechanisms and functions of two other forms of lateral interaction in the outer retina: negative feedback from horizontal cells to rods and positive feedback from horizontal cells to cones.

Keywords

lateral inhibition; receptive field surround; bipolar cell; cone photoreceptor; rod photoreceptor; horizontal cell; feedback inhibition; feed-forward signaling; ambient illumination

1. Introduction

H. K. Hartline received the Nobel Prize in Physiology or Medicine in 1967 partly for the discovery of antagonistic connections between neighboring photoreceptors in the horseshoe

Addresses for Correspondence: Wallace B. Thoreson, Department of Ophthalmology and Visual Sciences, University of Nebraska Medical Center, 4050 Durham Research Center, Omaha, NE 68198-5840 U.S.A., Phone: 402-559-2019, Fax: 402-559-5368, wbthores@unmc.edu and Stuart C. Mangel, Ph.D., Department of Neuroscience, Ohio State University College of Medicine, 333 W. 10th Avenue, Columbus, OH 43210 U.S.A., Phone: 614-292-5753, Fax: 614-292-5773, mangel.1@osu.edu.
*Both authors contributed equally.

crab, *Limulus* (Hartline et al., 1956; Hartline and Ratliff, 1957). He and his colleagues found that the light-evoked activity of a single photoreceptor is inhibited by the responses of surrounding photoreceptor cells. This lateral inhibition creates a center-surround organization to the receptive field whereby light falling on the center excites the cell and light falling on surrounding regions inhibits the cell. Lateral or surround inhibition improves spatial discrimination and the detection of edges and generates the psychophysical phenomenon known as Mach bands (Ratliff and Hartline, 1959; Ratliff, 1965). Mach bands, which are named for Ernest Mach who studied them in the 1880s, are bright and dark bands that are seen at the light and dark edges, respectively, of contrast gradients whose physical energy does not contain the perceived bands. Explanations for these and similar perceived edge effects have interested scientists for centuries. For example, Galileo recognized that Mach bands visible at the borders of the lunar disc represented perceptual effects that were not intrinsic properties of the moon's surface (Piccolino and Wade, 2008).

In mammalian and non-mammalian retinas, both bipolar cells, which are post-synaptic to cone photoreceptor cells, and ganglion cells, which are post-synaptic to bipolar cells, exhibit an antagonistic center-surround receptive field organization (Kuffler, 1953; Barlow, 1953; Werblin and Dowling, 1969; Dacheux and Miller, 1981). Baylor et al. (1971) discovered that the light responses of cones also exhibit a center-surround receptive field organization. Furthermore, they reported evidence that the receptive field surround of cones is produced by inhibitory feedback from horizontal cells.

Although the presence of center-surround receptive fields in bipolar cells and cones and the existence of negative feedback from horizontal cells to cones have been known for many years, the contributions of these and other circuits in the outer retina to visual processing and the mechanisms by which they operate are still not fully understood. In this review, we summarize an array of studies on the functions and mechanisms of lateral signaling in the outer retina. Because the light/dark adaptive state modulates visual processing, spatial discrimination, and the center-surround receptive field organization of retinal neurons, our approach is to consider outer retina signaling with respect to the level of ambient or background illumination. In Section 2, we examine properties of the receptive field surround in retinal neurons with a particular focus on bipolar cells. In Section 3, we then consider three proposed mechanisms for negative feedback from horizontal cells to cones: 1) GABA release by horizontal cells, 2) ephaptic modulation of the cone pedicle membrane potential generated by currents flowing through hemigap junctions in horizontal cell dendrites, and 3) modulation of cone calcium currents (I_{Ca}) by changes in synaptic cleft proton levels. In addition to negative feedback from horizontal cells to cones, in Section 4 we consider the mechanisms and functions of direct feed-forward input from horizontal cells to bipolar cells and evaluate the evidence for a role for GABA in this synapse. In addition to considering possible underlying mechanisms, in section 5 we examine various proposed functions of horizontal cell to cone feedback and direct horizontal cell input to bipolar cells including evidence for and against a role for these pathways in the generation of center-surround and color opponent receptive fields in bipolar and ganglion cells. Finally, in section 6 we discuss two other forms of lateral interaction in the outer retina: negative feedback from horizontal cells to rods and positive feedback from horizontal cells to cones. There are a number of previous reviews on lateral signaling in the outer retina and horizontal cell to cone feedback that the reader may find of interest (Wu, 1992; Piccolino, 1995; Perlman and Normann, 1998; Kamermans and Spekreijse, 1999; Burkhardt, 1993, 2011; Barnes, 2003; Twig et al., 2003; Kamermans and Fahrenfort, 2004; Fahrenfort et al., 2005).

2. Outer Retina Signaling-Fundamental Features

2.1. Center-surround receptive field organization of bipolar cells: spatial and temporal characteristics

To understand the mechanisms that produce the receptive field surround in the outer plexiform layer, the first synaptic layer in the retina, it makes sense to start with the output neurons of the outer retina, the bipolar cells. Accordingly, before discussing how horizontal cell feedback to cones and direct horizontal cell input to bipolar cells influence the receptive field surround of bipolar cells, we first summarize the fundamental features of the center-surround receptive field organization of bipolar cells, and based on these characteristics, we then outline some requirements for a mechanistic explanation of the bipolar cell surround.

The light responses of individual ganglion cells have been extensively studied electrophysiologically both *in vivo* and using *in vitro* retina preparations (e.g., whole-mounted intact retina and retinal slices). However, the light responses of individual bipolar cells cannot be studied *in vivo* for technical reasons and have thus only been studied using *in vitro* retina preparations. For studies on the properties of bipolar cell receptive fields described below, we focus on experimental observations of bipolar cell light responses obtained from whole-mounted *in vitro* retinas using intracellular, fine-tipped microelectrode recordings. We do so for two reasons: 1) slicing the retina physically eliminates neural connections, especially those involving lateral interactions, and limits neural and neurotransmitter interactions and 2) recordings with fine-tipped, intracellular microelectrodes preserve the intracellular milieu of neurons to a greater extent than recordings with much larger-tipped, whole-cell patch pipettes.

Under these recording conditions, the light responses of cone-driven bipolar cells in intact mammalian and non-mammalian retinas consistently exhibit an antagonistic center-surround receptive field organization (Werblin and Dowling, 1969; Kaneko, 1970, 1973; Schwartz, 1974; Yazulla, 1976; Dacheux and Miller, 1981; Naka, 1982; Stone and Schutte, 1991; Dacey et al., 2000; Fahey and Burkhardt, 2001, 2003). As shown in Fig. 1A–B, in the presence of maintained photopic background illumination, OFF-center cone-driven bipolar cells in monkey retina hyperpolarize in response to a small spot centered on the receptive field, but depolarize to a larger spot that stimulates both the receptive field center and surround (Dacey et al., 2000). ON-center cone-driven bipolar cells in fully light-adapted (photopic) monkey retina also exhibit a similar center-surround receptive field organization, except that center stimulation depolarizes the ON-center cell and a combination of center and surround stimulation hyperpolarizes it (Fig. 1C; Dacey et al., 2000).

The receptive field surround has two characteristic features, as shown in Fig. 1. When an annulus or ring of light is flashed so that only the surround is stimulated, the response to surround stimulation by itself (i.e., in the absence of center stimulation) is opposite in polarity to the response that occurs to center stimulation alone (Figs. 1D, E). We term this type of surround response “surround activation”. It has been previously called “surround excitation” and “surround responsiveness” (Donner and Gronholm, 1984; Mangel, 1991). In addition to surround activation revealed by annular illumination, simultaneous stimulation of the receptive field center and surround with a large spot of light shows that surround illumination also reduces the amplitude of the center response. The decrease in center response amplitude due to simultaneous surround stimulation is termed “surround antagonism” here. Surround antagonism, which has also been referred to as “surround inhibition” and” surround suppression” (Werblin and Dowling, 1969; Kaneko, 1970; Donner and Gronholm, 1984; Mangel, 1991; Troy and Shou, 2002; Burkhardt, 2001, 2011), is illustrated in Figure 1F which shows that the response of a fully light-adapted (photopic)

monkey OFF-center cone-driven bipolar cell decreases in amplitude when the diameter of the centered spot stimulus increases in size.

Surround antagonism is a fundamental feature of the center-surround receptive field of vertebrate bipolar cells and has been consistently observed when intracellular, fine-tipped microelectrode recording is used in intact retinas (e.g., amphibian - Werblin and Dowling, 1969; Stone and Schutte, 1991; Fahey and Burkhardt, 2001, 2003; Zhang and Wu, 2009; fish - Kaneko, 1970, 1973; Naka, 1982; turtle - Schwartz, 1974; Yazulla, 1976; rabbit - Dacheux and Miller, 1981; monkey - Dacey et al., 2000). Center-surround antagonism has also been consistently observed in ganglion cells using *in vivo* recordings from mammalian retinas (Kuffler, 1953; Barlow et al., 1957; Hubel and Wiesel, 1960; Rodieck and Stone, 1965; Enroth-Cugell and Robson, 1966; Michael, 1968; Weinstein et al., 1971; Maffei et al., 1971; Enroth-Cugell and Lennie, 1975; Hammond, 1975; Enroth-Cugell et al., 1975, 1983; Chan et al., 1992; Troy et al., 1993, 1999; Levick, 1996; Muller and Dacheux, 1997; Kaplan and Benardete, 2001; Troy and Shou, 2002) and using *in vivo* and *in vitro* recordings from non-mammalian retinas (Barlow, 1953; Wagner et al., 1960; Daw, 1968; Naka and Nye, 1971; Donner, 1981). In contrast to the consistent observations of center-surround antagonism, surround activation of vertebrate bipolar and ganglion cells has not always been observed, a finding that will be discussed in Sections 2.2 and 2.3 below.

Quantitative measurements have revealed that the receptive field surround of light-adapted, cone-driven bipolar cells has similar spatial and temporal characteristics in mammalian and non-mammalian retinas. Using stimuli that were either brighter than the background (i.e., positive contrast) or dimmer than background (i.e., negative contrast), and adjusted spatially to produce optimum center and surround responses, cone-driven bipolar cell light responses of the same polarity (i.e., depolarization or hyperpolarization) are similar in waveform and amplitude irrespective of whether they are elicited by center or surround stimulation. This is true in both amphibian (Stone and Schutte, 1991; Fahey and Burkhardt, 2003; Burkhardt et al., 2011) and monkey (Dacey et al., 2000) retinas. For example, depolarizing responses of ON-center bipolar cells to positive contrast in the receptive field center and negative contrast in the surround are similar to one another. Depolarizing responses of OFF-center bipolar cells to positive contrast in the surround and negative contrast in the center are also similar to one another. When surround strength is measured relative to center strength by the responses of light-adapted cone-driven bipolar cells to centered spots vs. concentric annular stimuli, the strength of surround activation is approximately equal to center strength (range of surround response size/center response size: 0.50 – 1.55) in both tiger salamander (Fahey and Burkhardt, 2003) and monkey (Dacey et al., 2000) retinas. However, when the strength of surround antagonism is quantified as the decrease in center response produced by simultaneous surround stimulation, it is typically found to range between 0.2 and 0.6 (e.g., Fahey and Burkhardt, 2003). These observations are consistent with the hypothesis that surround antagonism and surround activation may involve different mechanisms. The exact spatial dimensions of the center and surround components of the bipolar cell receptive field and the ratio of center size/surround size vary with the level of ambient illumination (see Section 2.2), the stage of development (Section 2.3), eccentricity, bipolar cell subtype, and species.

In the temporal domain, the latency of responses of ON-center bipolar cells in non-mammalian retinas to centered spot stimuli has typically been observed to be about 30 ms longer than that of OFF-center bipolar cells, a finding that is consistent with the presence of a G-protein second messenger cascade in the light response pathway of ON-center, but not OFF-center, bipolar cells (Copenhagen, 2004; Burkhardt et al., 2007; Burkhardt, 2011). The latency of the surround response of light-adapted ON-center and OFF-center cone-driven bipolar cells in non-mammalian retinas is 30–50 ms longer than that of the center response

(Stone and Schutte, 1991; Fahey and Burkhardt, 2003). A similar long delay in the surround responses of bipolar cells has also been observed with respect to surround antagonism: surround illumination is most effective in reducing the size of the center response when it precedes center illumination by approximately 50 ms (Fahey and Burkhardt, 2003). The surround responses of ganglion cells are also delayed compared to center responses (Nye and Naka, 1971; Popel and Eckhorn, 1981; Frishman et al., 1987; Troy and Shou, 2002). In addition, the ganglion cell surround responds over a wider temporal frequency range than the center mechanism and therefore the surround resolves higher temporal frequencies than the center (Troy and Shou, 2002). In general, the wider the spatial field of a retinal mechanism, the better its temporal resolution.

It is perhaps important to note here that, in addition to the classic antagonistic center-surround receptive field first described by Kuffler (1953), ganglion cells exhibit other surround mechanisms that may be produced in the inner retina. Specifically, in addition to an antagonistic surround response that 1) originates in the outer retina, 2) is strongest following prolonged light adaptation (see Section 2.2), and 3) is relatively sustained (Kuffler, 1953; Barlow and Levick, 1969; Werblin and Dowling, 1969; Hammond, 1975; Thibos and Werblin, 1978a; Dacey et al., 2000; Fahey and Burkhardt, 2003), ganglion cells have been reported to have a change-sensitive or transient surround that originates in the inner plexiform layer (Werblin, 1972; Werblin and Copenhagen, 1974; Thibos and Werblin, 1978b; Cook and McReynolds, 1998) and a disinhibitory surround which originates in the inner plexiform layer that is larger in size than the classic antagonistic surround (Ikeda and Wright, 1972; Li et al., 1992; Shou et al., 2000; Troy and Shou, 2002). Bipolar cells may also have a surround mechanism in addition to the classic surround response that is antagonistic to the center. In addition to synaptic inputs from horizontal cells to cones and from horizontal cells to bipolar cells, there is evidence that the receptive field surrounds of bipolar cells are shaped in part by inner retinal circuits in the form of amacrine cell input to bipolar cell synaptic terminals (Lukasiewicz, 2005; Zhang and Wu, 2009).

2.2. Modulation of the receptive field surround by ambient light levels

Although light-adapted bipolar and ganglion cells exhibit a robust receptive field surround, dark adaptation greatly reduces and perhaps eliminates, the surround in both bipolar and ganglion cells. Although this phenomenon has been studied more extensively in ganglion cells (cat - Barlow et al., 1957; Barlow and Levick, 1969; Enroth-Cugell and Lennie, 1975; Hammond, 1975; Chan et al., 1992; Troy et al., 1993, 1999; rabbit – Masland and Ames, 1976; Jensen, 1991; Muller and Dacheux, 1997; amphibian – Donner, 1981; fish – Raynauld et al., 1979), strong evidence supports the view that the strength of the bipolar cell surround decreases as the intensity of background illumination declines. From the first study that examined the dependence of the center-surround receptive field organization of ganglion cells on ambient light level (Barlow et al., 1957), it has been widely observed that at low ambient light levels surround antagonism is greatly reduced while center size and strength are increased (see Fig. 2 here). There is minor disagreement concerning whether surround antagonism in ganglion cells is completely absent (Barlow et al., 1957; Rodieck and Stone, 1965; Maffei et al., 1971; Masland and Ames, 1976; Peichl and Wassle, 1983; Jensen, 1991; Muller and Dacheux, 1997) or merely greatly reduced (Enroth-Cugell and Lennie, 1975; Barlow and Levick, 1976; Donner, 1981; Chan et al., 1992; Troy et al., 1993, 1999) following a maintained decrease in ambient illumination from photopic or mesopic levels to mid-scotopic levels. In addition, ganglion cell surround activation requires a higher level of maintained background illumination than surround antagonism (Barlow and Levick, 1969; Hammond, 1975). Decreasing the level of ambient illumination increases the latencies of both center and surround responses, but the latency of the surround response increases to a greater extent (Cleland and Enroth-Cugell, 1970; Enroth-Cugell and Lennie, 1975; Troy et

al., 1993, 1999), thus weakening the effectiveness of surround antagonism. The greatly diminished ganglion cell surround following dark adaptation also does not result from the shift from cone to rod pathway signaling (Barlow et al., 1957; Chan et al., 1992). In addition, diminished ganglion cell surrounds appear to involve a time-dependent process, requiring tens of minutes to complete, especially following a prolonged (~ 30 min) bleach (Barlow et al., 1957; Barlow and Levick, 1969; Hammond, 1975; Donner, 1981). In other words, when the retina has been initially fully light-adapted, the decrease in surround strength following subsequent complete dark adaptation--and when the retina has been initially fully dark-adapted, the increase in surround strength following a sudden increase to a photopic level of ambient illumination--may both take ~ 20–30 minutes to completely unfold. Of course, the ambient light level normally changes gradually during the course of day and night, and there is consistent evidence for an accompanying change in surround strength in response to the gradual change in the intensity of ambient illumination that requires minutes, rather than tens of minutes, to reach a steady state (Barlow and Levick, 1969; Hammond, 1975; Donner, 1981; Chan et al., 1992; Levick, 1996; Troy and Shou, 2002).

The effects of light and dark adaptation on bipolar cell surrounds have not yet been fully documented in part due to the difficulty of maintaining stable long-term, fine-tipped intracellular recordings of bipolar cells in intact retinas. However, since the initial report that the bipolar surround depends on the presence of light adaptation (Werblin, 1970), published evidence strongly suggests that the bipolar cell surround is strongest following a prolonged increase in the ambient light level and substantially weaker following a prolonged decrease in the ambient light level. A comparison of the published results of the Burkhardt and Wu labs on the surround light responses of tiger salamander bipolar cells illustrates the dependency of surround strength on the extent of light/dark adaptation. As noted above, in the presence of background illumination at an intensity (20 cd/m^2) at which bipolar cells are cone-driven, Fahey and Burkhardt (2003) reported that, for all subtypes, most bipolar cells produced responses to surround stimulation by itself (i.e., in the absence of center stimulation) and that surround response strength was approximately equal to center response strength (see Fig. 3). Similarly, as noted in Section 2.1, in the presence of prolonged photopic background illumination (intensity = 200 cd/m^2), monkey bipolar cells exhibit similar surround responses and surround strength (Dacey et al., 2000). Fahey and Burkhardt (2003) further reported that surround antagonism was somewhat weaker when the mean intensity of the background was lowered from 20 cd/m^2 to 0.2 cd/m^2, an intensity at which bipolar cells remain cone-driven. Interestingly, the resting membrane potential and light responsiveness of cone-driven ON- and OFF-center bipolar cells are also regulated by light/dark adaptive processes so that the cells remain light responsive over a large range of background illumination levels (Werblin, 1970; Fahey and Burkhardt, 2001). For example, as the maintained background illumination is increased from 0.1 to 1,000 cd/m^2, the incremental sensitivity of tiger salamander bipolar cells changes by ~4 orders of magnitude but the resting membrane potential of the cells changes by a relatively small amount (i.e., ON-center cells depolarize by ~12 mV and OFF-center cells hyperpolarize by ~18 mV) and the maximum light responsiveness of both cell types remains the same (Fahey and Burkhardt, 2001).

In contrast to studies on tiger salamander bipolar cells under photopic conditions, Zhang and Wu (2009) investigated tiger salamander bipolar cells under “nominally dark-adapted” conditions (i.e., retinas were prepared and maintained in the dark, but stationary spot and annular stimuli of various intensities and moving bar stimuli were used to assess center and surround responses). They reported that four bipolar cell subtypes (2 ON-subtypes and 2 OFF-subtypes) exhibited surround antagonism but not surround activation, and that two other bipolar cell subtypes (1 ON-subtype and 1 OFF-subtype) exhibited surround

antagonism and responses to annuli that suggested the presence of weak surround activation (see Fig. 4). Moreover, Zhang and Wu (2009) also reported that across the entire population of bipolar cells they studied, surround strength was stronger for cells that were more cone-driven and weaker for cells that were more rod-driven. Fahey and Burkhardt (2003) also reported that bipolar cell surround responses could be evoked under nominally dark-adapted conditions if one used bright stimuli that evoked cone-driven responses. These results in nominally dark-adapted retinas are not surprising because extensive ganglion cell recordings have indicated that surround antagonism is present when the ambient illumination is in the mesopic range, but becomes noticeably weaker when retinas are maintained in scotopic background illumination (Barlow et al., 1957; Chan et al., 1992; Troy and Shou, 2002). Hare and Owen (1992) reported that tiger salamander bipolar cells retained center-surround antagonism under maintained upper scotopic background illumination. Thus, one might expect to observe reduced bipolar cell surround strength after the ambient illumination and test stimuli have been maintained in the scotopic range for approximately 20–30 minutes. Taken together, comparison of the results of Fahey and Burkhardt (2003) and Zhang and Wu (2009) suggests that bipolar cell surround antagonism and surround activation are stronger under light-adapted, compared to dark-adapted, conditions, and that the presence of surround activation, which indicates the presence of a stronger surround response compared to surround antagonism, may require a higher maintained background intensity than surround antagonism. Measurements of ganglion cell receptive fields from cat retina *in vivo* indicate that the presence of surround activation requires a higher maintained background illumination level than surround antagonism (e.g., Barlow and Levick, 1969; Hammond, 1975). Additional experiments that investigate bipolar cell receptive field surround responses under maintained background illumination conditions at scotopic, mesopic and photopic levels are needed to directly demonstrate whether this is so.

2.3. Modulation of the receptive field surround during development

In this section, we briefly discuss the development of the receptive field surround in mammalian retinas. Readers interested in other aspects of retinal development, such as cell genesis and differentiation, cell migration, cell connectivity, synaptic layer formation, and retinal waves, are invited to consider a number of excellent recent reviews (e.g., Mumm et al., 2005; Huberman et al., 2008; Tian, 2008).

In the mammalian retina, light-evoked responses appear first in photoreceptor cells, bipolar cells and ganglion cells, the vertical pathway through the retina. Electrophysiological single cell developmental studies have been performed primarily on the retinas of rabbits and cats. In the rabbit, photoreceptor light-evoked activity can be observed at six days of age as a small cornea-negative potential (PIII) in the electroretinogram (Masland, 1977). Ganglion cells produce spontaneous bursting but not light-evoked responses at birth and begin to generate weak light responses at eight days of age (Masland, 1977). At that age, the light responses adapt quickly to repeated stimulation and many ganglion cells are still unresponsive to light stimulation.

Interestingly, by ten days of age, which is when eye opening occurs in rabbits, approximately 60% of the ganglion cells responded to light, but the great majority of light-responsive cells had no discernible surround (and a relatively large center) or exhibited surround antagonism without surround activation (Masland, 1977). By twenty days of age, rabbit ganglion cells become more adult-like with approximately 60% exhibiting both surround antagonism and surround activation. In this study, the retinas were maintained in a “weakly light-adapted state” throughout the experiments and the effects of light/dark adaptation on surround strength and size were not studied developmentally (Masland, 1977). Both *in vivo* and *in vitro* studies of the development of the center-surround receptive field organization of cat and mouse ganglion cells and cat lateral geniculate nucleus neurons

under maintained light-adapted (i.e., mid-mesopic to photopic range) background illumination conditions have yielded qualitatively similar results as those on rabbit ganglion cells (Bowe-Anders et al., 1975; Masland, 1977) in that center responses appear first, followed by surround antagonism, and finally by surround activation (Hamasaki and Flynn, 1977; Rusoff and Dubin, 1977; Daniels et al., 1978; Tootle, 1993; Koehler et al., 2011).

There has been only one published paper documenting the development of bipolar and horizontal cell light responses in the mammal. In experiments performed on nominally dark-adapted rabbit retinas, Dacheux and Miller (1981) reported that putative depolarizing (ON) and hyperpolarizing (OFF) bipolar cells exhibited qualitatively similar development of their receptive field properties as that displayed by rabbit ON- and OFF-ganglion cells. At 8–10 days of age, bipolar cells had light responses with relatively large centers and no discernible surrounds. At 13–15 days of age, evidence of surround antagonism, but not surround activation was observed for some of the cells. Specifically, although annular stimulation alone did not produce a response opposite in polarity to that of the center (i.e., surround activation), annular stimulation in the presence of center stimulation did evoke a small response opposite in polarity to that of the center (i.e., surround antagonism). No evidence of bipolar cell surround activation at later developmental ages was included in this paper. Generally speaking, rabbit horizontal cell light responses were found to mature along a similar time course as that of the bipolar cell surround, although B-type horizontal cells reached an adult level with respect to their intensity-response amplitude function about a week earlier than A-type horizontal cells (Dacheux and Miller, 1981).

Taken together, these results suggest that distinct developmental mechanisms mediate maturation of the center, surround antagonism, and surround activation components of bipolar and ganglion cell receptive fields. Additional studies that examine the development of bipolar cell surround antagonism and surround activation under maintained light-adapted (e.g., low photopic) and dark-adapted (e.g., high scotopic) background illumination conditions are needed to uncover the circuits and synaptic mechanisms that mediate the receptive field surround both during development and in the adult.

2.4. Horizontal cells contribute to bipolar cell surround antagonism and surround activation

When it was discovered more than 40 years ago that 1) horizontal cell dendrites, which are post-synaptic to cone terminals, are in close proximity to bipolar cell dendrites (Dowling and Boycott, 1966; Dowling, 1970; Kolb, 1970; Lasansky, 1971; Gray and Pease, 1971), 2) bipolar cells exhibit a center-surround receptive field organization (Werblin and Dowling, 1969; Kaneko, 1970), and 3) the horizontal cell receptive field is similar in size to that of the bipolar cell surround (Werblin and Dowling, 1969; Kaneko, 1970), it was proposed that horizontal cells contribute to the bipolar cell surround (Werblin and Dowling, 1969; Kaneko, 1970). Perhaps the most direct evidence in favor of this view comes from experiments involving simultaneous electrical recording of nearby horizontal cell-ganglion cell pairs in mammalian and non-mammalian retinas (Maksimova, 1969; Naka and Nye, 1971; Naka and Witkovsky, 1972; Mangel, 1991) and nearby horizontal cell-bipolar cell pairs in non-mammalian retinas (Marchiafava, 1978; Toyoda and Tonosaki, 1978; Toyoda and Kujiraoka, 1982; Naka, 1982; Sakuranaga and Naka, 1985). In these experiments, polarization of horizontal cells by intracellular current injection has consistently shown that hyperpolarizing a horizontal cell produces a hyperpolarization in nearby ON-center bipolar cells and ON-center ganglion cells, but produces a depolarization in nearby OFF-center bipolar cells and OFF-center ganglion cells (see Fig. 5). Conversely, depolarizing a horizontal cell depolarizes nearby ON-center bipolar cells and ON-center ganglion cells, but hyperpolarizes nearby OFF-center bipolar cells and OFF-center ganglion cells (see Fig. 5). Thus, artificially hyperpolarizing horizontal cells to simulate the hyperpolarizing responses

of horizontal cells (both luminosity- and chromaticity-type) to full-field (diffuse) white light stimuli, produces responses in bipolar and ganglion cells that are the same polarity as their surround responses (Toyoda and Kujiraoka, 1982). These data are therefore consistent with the view that horizontal cells contribute to surround activation in both bipolar and ganglion cells. Moreover, artificially hyperpolarizing horizontal cells reduces the responses of ganglion cells to centered spot stimuli (see Fig. 6), a finding which suggests that horizontal cells contribute to surround antagonism. Additional evidence that is consistent with a role for horizontal cells in the generation of the surround under light-adapted conditions is the finding that under maintained mesopic background illumination conditions, rabbit ganglion cells voltage-clamped at the chloride reversal potential to reveal the excitatory signal from bipolar cells exhibit strong surround antagonism (Flores-Herr et al., 2001; see Fig. 11 here). Furthermore, as the intensity of background illumination increases, the gap junctions between horizontal cells become increasingly uncoupled (Ribelayga and Mangel, 2003, 2010; but see Xin and Bloomfield, 1999), thereby decreasing the horizontal cell receptive field size. This decrease in horizontal cell receptive field size parallels the decrease in the size of the ganglion cell receptive field surround that has been observed when background illumination increases (Barlow et al., 1957; Troy et al., 1993, 1999), providing further support for the idea that horizontal cells contribute to the receptive field surrounds of bipolar cells and ganglion cells. The contributions of horizontal cells to the receptive field surrounds of bipolar and ganglion cells are thought to involve both feedback from horizontal cells to cones and direct feed-forward input from horizontal cells to bipolar cells. We consider these two pathways separately in sections 3 and 4 of this review.

Because the strength of the bipolar cell surround is strongest when the ambient light level is in the mid-mesopic to photopic range and weakest when the ambient light level is in the scotopic range (see Section 2.2), the horizontal cell contribution to the bipolar cell surround should be strongest following prolonged (~ 20–30 min) light adaptation and weakest following prolonged dark adaptation in the scotopic range. However, the difference in the horizontal cell contribution to the bipolar cell surround under maintained bright light-adapted compared to dark-adapted conditions may not arise from the horizontal cells themselves. Consistent evidence from a variety of species has shown that following dark adaptation, maintained photopic background (full-field) illumination hyperpolarizes horizontal cells by 30–40 mV for several minutes so that their light responses are saturated. However, if the photopic background illumination is continuously maintained, the membrane potential of horizontal cells slowly recovers in 20–30 minutes to the initial more positive dark-adapted level and the cells become light responsive again but to light stimuli of higher intensities (skate: Dowling and Ripps, 1971; fish: Ruddock and Svaetichin, 1975; Wang and Mangel, 1996; tiger salamander: Yang et al., 1999). As a result, following both prolonged light and dark adaptation, horizontal cells in mammalian and non-mammalian retinas are depolarized (approx. −35 mV) at rest and hyperpolarize to brief light flashes brighter than the background illumination (skate: Dowling and Ripps, 1971; fish: Ruddock and Svaetichin, 1975; Malchow and Yazulla, 1988; Wang and Mangel, 1996; tiger salamander: Yang et al., 1999; rabbit: Mangel, 1991; Ribelayga and Mangel, 2010; monkey: Zhang et al., 2011). In addition, as noted in Section 2.2, the resting membrane potential and light responsiveness of cone-driven ON- and OFF-center bipolar cells are also regulated by light/dark adaptive processes so that the cells remain light responsive from mesopic to photopic background illumination levels (Werblin, 1970; Dacey et al., 2000; Fahey and Burkhardt, 2001). Although the adaptive mechanisms that underlie the dependency of bipolar cell surround strength and bipolar and horizontal cell resting membrane potentials and light responsiveness on the background light level remain unknown, these findings suggest that the light/dark adaptive state of the retina alters the effect of horizontal cell light responses on bipolar cell surrounds. Moreover, if the minimal bipolar cell surround following prolonged dark adaptation in the scotopic range is the basal or resting state of

horizontal cell to bipolar cell (and/or horizontal cell to cone to bipolar cell) communication, then the retinal processes initiated by prolonged light adaptation represent the primary means by which the bipolar surround is generated.

2.5. Fundamental features of the bipolar cell receptive field surround

Although the receptive field surround of vertebrate ganglion cells was first discovered almost 60 years ago (Kuffler, 1953) and identified in bipolar cells more than 40 years ago (Werblin and Dowling, 1969; Kaneko, 1970), the cellular mechanisms and neural circuitry that generate the bipolar cell surround remain unclear and controversial. A mechanistic understanding of the receptive field surround should account for its fundamental functional characteristics. Accordingly, this section of our review has described some of the basic features of the receptive field surround of bipolar and ganglion cells that have been consistently observed. These include:

1. The receptive fields of bipolar and ganglion cells exhibit both surround activation (i.e., a response of opposite polarity to the center response when only the surround is stimulated) and surround antagonism (i.e., stimulation of the surround reduces the center response) when background illumination conditions have been maintained in the mid-mesopic to photopic range for ~ 20–30 minutes (or until a steady state surround response has been reached).
2. Under maintained (~ 20–30 min) mid-mesopic to photopic background illumination conditions, cone-driven bipolar cell light responses of the same polarity (i.e., depolarization or hyperpolarization) are similar in waveform and amplitude irrespective of whether they are elicited by center or surround stimulation, that is, center and surround strength are similar.
3. Under maintained (~ 20–30 min) mid-mesopic to photopic background illumination conditions, the latency of the cone-driven bipolar cell surround light response is greater than the latency of the center response.
4. The strength of bipolar and ganglion cell surrounds is greater and the latency of bipolar and ganglion cell surrounds is shorter under maintained light-adapted (i.e., mid-mesopic to photopic) conditions, compared to maintained dark-adapted (i.e., scotopic) conditions.
5. Bipolar and ganglion cell surround activation require a higher level of maintained background illumination than surround antagonism.
6. Cone-driven ON-center and OFF-center bipolar cells and horizontal cells remain responsive to light stimuli brighter and dimmer than the ambient illumination as the level of the ambient illumination gradually changes from mesopic to photopic and back again over the course of the day.
7. Bipolar and ganglion cells in mammalian retinas exhibit center responses, but not a receptive field surround at one week of age. Surrounds are first observed at the end of the second postnatal week, at which time they are weakly antagonistic to the center, but do not yet exhibit surround activation. Surround strength then increases in the next several weeks, reaching adult levels by approximately 1–2 months of age. Surround antagonism reaches an adult level before surround activation.
8. Horizontal cells contribute to bipolar and ganglion cell surround activation and surround antagonism. Although horizontal cells are depolarized at rest and hyperpolarize to brief light flashes brighter than the background illumination following both prolonged light and dark adaptation, changes in the light/dark

adaptive state of the retina alter the effect of these horizontal cell light responses on the bipolar cell surround.

A mechanistic understanding of the bipolar cell receptive field surround should be able to provide the physiological, anatomical and neurochemical bases for horizontal cell contributions to both surround activation and surround antagonism, explain how prolonged (~ 20–30 min) light adaptation enhances both surround activation and surround antagonism, and account for the longer latency of surround light responses compared to center light responses. In addition, a complete mechanistic understanding of the bipolar cell surround should be able to explicate the retinal processes that change during prolonged dark adaptation at the scotopic level, so that the bipolar cell surround becomes minimal with a significantly longer latency. Finally, the developmental processes in the mammalian retina that are initiated during the second postnatal week and produce the bipolar cell receptive field surround should be delineated.

We note that a straightforward approach to investigate the endogenous cellular mechanisms that underlie the bipolar cell surround in the adult retina is to block specific hypothesized mechanistic components (e.g., with selective neurotransmitter receptor antagonists) following prolonged light adaptation in the mid-mesopic to photopic range. However, relatively few studies have examined the dependency of the receptive field surround of bipolar cells and cones on the background light level and even fewer studies have investigated the mechanisms that underlie the surrounds of bipolar cells and cones under maintained mid-mesopic to photopic background illumination. Clearly, more experimental study of these cells is needed under different levels of background illumination.

In addition, the fundamental functional characteristics of the bipolar cell surround described in this section suggest some limitations in the mechanisms that underlie the bipolar surround. A relative increase in glutamate release from cones caused by surround illumination applied in the presence of a centered spot can account for bipolar cell surround antagonism. However, if bipolar cell surround activation is due to feedback from horizontal cells to cones, then annular illumination by itself, which produces a bipolar cell response of opposite polarity to that produced by center illumination alone (Kaneko, 1970; Yazulla, 1976; Stone and Schutte, 1991; Dacey et al., 2000; Fahey and Burkhardt, 2003), should depolarize cones to a level more positive than their resting membrane potential. When cones are recorded using intracellular, fine-tipped microelectrodes under light-adapted conditions, turtle cones exhibit purely depolarizing responses to annular illumination (O'Bryan, 1973) but cones of many other species often do not (Fain, 1975; Lasater, 1982; Naka, 1982; Fahey and Burkhardt, 2003). Goldfish and monkey cones can produce depolarizing surround responses but only when they are dialyzed with 33–50 mM [Cl^-] through the whole-cell recording pipette (Kraaij et al., 2000; Verweij et al., 2003; Packer et al., 2010), so that E_{Cl} is more positive than the resting membrane potential. The reasons for this are considered in Section 3.1, but it suggests that surround activation in bipolar cells could potentially arise from depolarizing horizontal cell feedback responses of cones but only if E_{Cl} is more positive than the cone resting potential. As considered below in more detail, other alternative explanations for surround activation include the actions of horizontal cell feedback on cone I_{Ca} or the direct actions of horizontal cells onto bipolar cells.

In addition, evidence suggests that horizontal cell feedback to cones varies with the level of background illumination. Unidirectional transient rod to cone sign-inverting current, which is mediated by sign-inverting feedback from horizontal cells to cones, is reduced by light stimulation (Attwell et al., 1983). This raises the interesting possibility that horizontal cell feedback to cones may be driven by rod excitation of horizontal cells when background illumination remains in the scotopic to mid-mesopic range. As the ambient illumination level reaches the mid-mesopic to photopic range, rods become saturated and the input to

horizontal cells is provided only by cones. Additional experiments are needed to characterize changes in feedback from horizontal cells as the intensity of the maintained background illumination gradually changes, but it is possible that horizontal cell feedback to cones predominates under maintained scotopic to mid-mesopic background illumination conditions, whereas direct horizontal cell feed-forward input to bipolar cell surrounds contributes to a greater extent under maintained mid-mesopic to photopic conditions.

As noted in Section 2.1, many of the apparently contradictory findings concerning outer retina signaling and the effects of ligands on that signaling may have occurred because the studies were performed using different electrical recording conditions. For example, some studies were performed on intact retina preparations using extracellular microelectrode recording or the minimally invasive method of intracellular fine-tipped microelectrode recording, while other studies were performed with sliced retinas in which neural connections and signaling were compromised or by using whole-cell patch-clamp recording in which the intracellular milieu of recorded neurons was altered. Ideally, one should use models of retinal function that approximate the natural visual environment as much as possible and disrupt neuronal function as little as possible.

In addition, other apparently contradictory findings may have been obtained due to differences in the illumination conditions that were used in the retinal studies. As discussed in detail in Section 2.2, the strength of the receptive field surround, including surround antagonism and surround activation, depends on both the intensity and duration of the background illumination. Furthermore, the intensity of the ambient illumination gradually changes during the course of day and night, and it has been consistently observed that surround strength gradually increases and decreases in response to gradual increases and decreases, respectively, in the intensity of the ambient illumination (Barlow and Levick, 1969; Hammond, 1975; Donner, 1981; Chan et al., 1992; Troy and Shou, 2002). In addition, local contrast (i.e., the difference in intensity between specific light and dark regions of a visual scene) in natural images tends to be less than 10% above and below the intensity of the ambient illumination (Srinivasan et al., 1982; Sakai and Naka, 1988; Sterling and Demb, 2004; Burkhardt et al., 2006). It is possible that experimental use of larger changes in contrast or sudden large increases or decreases in the intensity of background illumination may produce atypical light responses that do not usually occur under more natural illumination conditions. The possibility of circadian influences should also be considered. For example, when retina experiments are performed in the late afternoon or evening under dark-adapted conditions, the circadian (24-h) clock in the retina will have partially increased the rod-cone gap junctional conductance (Ribelayga et al., 2008; Ribelayga and Mangel, 2010) and this may change signaling in the outer retina in unexpected ways.

These considerations suggest that the ideal approach to investigate whether a specific neurotransmitter receptor type contributes to the bipolar cell surround would be to test the effect of selectively blocking the receptor under different levels (e.g., low photopic vs. low mesopic) of background illumination maintained for ~ 20–30 minutes (or until a steady state surround response is achieved), using test stimuli ≤ 10% in intensity above and below the level of mean illumination. Experimental limitations, particularly the ability to record from cells for a long time, can make it difficult to achieve these ideal conditions, but it is worth recognizing that rapid increases in the level of background illumination by more than 1 log unit (e.g., from scotopic to low photopic) or test stimuli that are 30% in intensity above and below that of the mean background illumination are not usually encountered under normal physiological conditions.

3. Negative feedback from horizontal cells to cones

3.1. Mechanisms

By comparing responses of cones to large and small diameter light flashes, Baylor et al. (1971) discovered the presence of antagonistic interactions between neighboring cones. Large spots produced the same peak hyperpolarization in a turtle cone as small spots, but the hyperpolarizing peak response to a large spot was followed by a delayed depolarization (Fig. 7). The latency of the depolarizing cone response was similar to the latency of horizontal cell light responses and large diameter light flashes are more effective at stimulating hyperpolarizing light responses of horizontal cells than small spots. These observations suggested that the depolarizing response of cones evoked by surround illumination was due to antagonistic synaptic inputs from horizontal cells. This hypothesis was confirmed by injecting current into a horizontal cell while recording from a nearby cone. Injecting hyperpolarizing current into a horizontal cell produced a depolarization in nearby cones showing that there is a sign-inverting synaptic connection from horizontal cells onto cones (Baylor et al., 1971). Consistent with this hypothesis, blocking horizontal cell light responses with glutamate agonists, glutamate antagonists, or other drugs blocked depolarizing surround responses in cones and rod-like *Gekko* photoreceptors (Cervetto and MacNichol, 1972; Pinto and Pak, 1974; Kleinschmidt and Dowling, 1975; Piccolino and Gerschenfeld, 1977; Gerschenfeld and Piccolino, 1980; Thoreson and Burkhardt, 1990).

O'Bryan (1973) investigated surround antagonism in cones using a protocol designed to isolate depolarizing surround responses. The center of the receptive field was steadily illuminated with a small spot in order to reduce the cone's sensitivity and thus eliminate the light-evoked hyperpolarization that might be evoked by light scattered onto the receptive field center. An annulus was then flashed onto the receptive field surround to evoke a purely depolarizing surround response. Use of this stimulus protocol revealed that the cone's surround response consisted of both transient and sustained depolarizing components. Input resistance measurements revealed a sustained conductance increase during surround illumination but the reversal potential for the surround response could not be measured suggesting contributions from two conductance changes of opposite sign.

Fuortes et al. (1973) isolated depolarizing surround responses of cones in a slightly different way. Taking advantage of the sensitivity of horizontal cells to red light, the authors examined the depolarizing responses of green-sensitive cones evoked by illuminating the surround with red light. In agreement with O'Bryan (1973), they found that the depolarizing surround responses contained both transient and sustained depolarizing components. Piccolino and Gerschenfeld (1978, 1980) showed that spike-like depolarizing responses of cones could be evoked by surround illumination. These spikes were facilitated by the divalent cations Sr^{2+} and Ba^{2+} and blocked by Co^{2+} or the Ca^{2+} channel blocker D600 indicating that they were Ca^{2+}-dependent action potentials (Piccolino and Gerschenfeld, 1978, 1980; Gerschenfeld et al, 1980; Neyton et al., 1981). Burkhardt et al. (1988) showed evidence for three components in the surround responses of turtle cones: 1) an initial graded depolarization, 2) spikes, and 3) long regenerative events that lasted for many seconds and were termed "prolonged depolarizations." Subsequent work showed that prolonged depolarizations are triggered by the regenerative activation of L-type Ca^{2+} channels and exhibit a long-lasting plateau phase maintained by the activation of Ca^{2+}-activated Cl^{-} channels (Thoreson and Burkhardt, 1991; Barnes and Deschenes 1992). Prolonged depolarizing responses with similar waveforms have been observed in cones and rods from a number of species (turtle cones: Burkhardt et al., 1988; Cervetto and Piccolino, 1982; salamander cones: Lasansky, 1981; toad rods: Burkhardt et al., 1991; mouse rods: Babai and Thoreson, 2009).

Evidence for negative feedback from horizontal cells to cones can also be seen in the responses of turtle and fish horizontal cells. Stimulating the surround with annular illumination in the presence of a steady central spot can evoke depolarizing responses in small field horizontal cells (Piccolino et al., 1981). Such depolarizing responses cannot be readily explained by feedforward inputs from photoreceptors but appear to require negative feedback (Piccolino, 1995). In non-color opponent (luminosity (L)-type) horizontal cells, light flashes evoke a membrane hyperpolarization that is often followed by a depolarizing rollback in the membrane potential. This rollback can be partly due to the depolarizing recovery of membrane potential that accompanies light adaptation in cones. However, the finding that the rollback is more pronounced with the use of large diameter and annular flashes suggests that it also reflects negative feedback interactions with cones (Piccolino, 1995). Depolarizing responses of color-opponent horizontal cells are also thought to be due, at least in part, to negative feedback from luminosity-type horizontal cells onto cones (Burkhardt, 1993; Piccolino, 1995; Twig et al., 2003). Evidence for the role of horizontal cell feedback in generating color opponent responses is addressed later in section 5.4 when we consider possible functions of lateral interactions.

Horizontal cell dendrites flank more centrally positioned bipolar cell dendrites in the invaginating cone synapse (Dowling and Boycott, 1966; Dowling, 1970; Kolb, 1970; Lasansky, 1972; Gray and Pease, 1971; Kolb and Jones, 1984). Consistent with the possibility of chemical synapses from horizontal cells, SNARE proteins and other presynaptic proteins can be found in horizontal cell dendrites (Lee and Brecha, 2010; Hirano et al., 2005, 2007, 2011; Sherry et al., 2006). However, ultrastructural evidence for synaptic contacts between horizontal cells and cones is scant. Freeze fracture analysis failed to reveal intramembrane particles in the cone pedicle characteristic of post-synaptic membranes (Schaeffer et al., 1982) and conventional electron micrographs show very few synaptic vesicles in horizontal cell dendrites (Dowling and Boycott, 1966; Gray and Pease, 1971; Lasansky, 1971; Kolb, 1974; Kolb and Jones, 1984). However, conventional synaptic contacts between horizontal cells and rods, which have been observed in human retina (Linberg and Fisher, 1988), could potentially subserve feedback interactions between horizontal cells and rods (Thoreson et al., 2008; Babai et al., 2009). Conventional synaptic contacts between horizontal cells and bipolar cells have also been observed (Dowling et al., 1966).

In fish retina, it has been suggested that feedback occurs at spine-like projections from horizontal cell dendrites known as spinules (Raynauld et al., 1979; Wagner, 1980; Weiler and Wagner, 1984; Djamgoz et al., 1988; Djamgoz and Kolb, 1993; Wagner and Djamgoz, 1993). Spinules form during prolonged light adaptation and retract after prolonged dark adaptation. Following spinule retraction, color opponent responses of ganglion cells (Raynauld et al., 1979) and horizontal cells (Weiler and Wagner, 1984) are abolished and responses of luminosity horizontal cells to high temporal frequency stimulation are diminished (Djamgoz et al., 1988). These effects are consistent with elimination of horizontal cell to cone feedback (Wagner and Djamgoz, 1993). The evidence that physical retraction of horizontal cell spinules from cone pedicles diminishes feedback effects is consistent with both unconventional (e.g., ephaptic interactions considered in section 3.1.2) and conventional synaptic interactions between horizontal cells and cones. However, spinule retraction is seen only in fish retina (Wagner, 1980). In catfish retina, horizontal cells also appear to make conventional synaptic contacts with fine telodendria extending from the cone pedicle (Sakai and Naka, 1986).

Many of the early studies on horizontal cell to cone feedback were performed on turtle cones but depolarizing responses to surround illumination have also been observed in cones of other species including walleye (Burkhardt, 1977; Burkhardt and Hassin, 1978), carp

(Murakami et al., 1982), catfish (Lasater, 1982), goldfish (Verweij et al., 1996), tiger salamander (Lasansky and Vallerga, 1975; Lasansky, 1981; Skrzypek and Werblin, 1983; Wu, 1991), and macaque (Verweij et al., 2003; Packer et al., 2010). Depolarizing surround responses have also been observed in rod-like *Gekko* photoreceptors (Pinto and Pak, 1974). However, as described in Section 2.5 and below in this section, cone depolarizing surround responses appear dependent on artificially increasing the $[Cl^-]_i$ of cones, so that E_{Cl} is more positive than the resting membrane potential. Although depolarizing surround responses have occasionally been observed in salamander and fish cones, they are often absent from the responses of cones in these species (e.g., Hare and Owen, 1996; Kraaij et al., 2000; Fahey and Burkhardt, 2003). Nevertheless, while the feedback depolarization may not always be visible in cones, the presumed post-synaptic consequences of horizontal cell to cone feedback--which includes depolarizing responses of C-type horizontal cells, a delayed depolarizing rollback in the light responses of L-type horizontal cells, and surround antagonism in bipolar cells--are consistently observed in second-order neurons of these animals.

Verweij et al. (1996) made an interesting discovery that may help to explain why negative feedback to cones has robust consequences on bipolar and horizontal cells. They found that when horizontal cells hyperpolarized to light, cone I_{Ca} was activated at more negative potentials (i.e., I_{Ca} shifts leftward on a current/voltage plot, Fig. 8). This result was confirmed by Hirasawa and Kaneko (2003) in newt retina. Cones have a resting potential of −35 to −40 mV and hyperpolarize in response to brief light stimuli that are more intense than the background illumination. A negative shift in activation will therefore enhance I_{Ca} at potentials throughout the physiological voltage range (i.e., more negative than −35 mV; Fig. 8). Increasing I_{Ca} in this range of membrane potentials will increase Ca^{2+} influx and thus increase glutamate release from cones. The feedback-induced increase in glutamate release helps to restore synaptic output diminished by light-evoked hyerpolarization of the cone. Hyperpolarizing cones by current injection or intense illumination can reduce feedback effects in cones (Piccolino, 1995), perhaps because hyperpolarization reduces Ca^{2+} channel activity and thereby reduces the influence of feedback on I_{Ca}. The ability of horizontal cell hyperpolarization to reduce the threshold for activation of I_{Ca} may also explain the ability of feedback to stimulate Ca^{2+}-dependent regenerative events (Piccolino and Gerschenfeld, 1978, 1980; Maricq and Korenbrot, 1988; Burkhardt et al., 1988; Thoreson and Burkhardt, 1991; Barnes and Deschenes, 1992). In addition, increased Ca^{2+} influx into cones will activate Ca^{2+}-activated chloride channels. E_{Cl} in cones is typically close to the dark resting potential (Thoreson and Bryson, 2004) and so activation of Ca^{2+}-activated chloride channels often produces little change in membrane potential in cones. However, if a cone exhibits a value for E_{Cl} that is more positive than the cone's resting membrane potential, then activation of Ca^{2+}-activated chloride channels will cause the membrane to depolarize. It has been observed that goldfish and monkey cones exhibit depolarizing surround responses only when they are dialyzed with 33–50 mM $[Cl^-]$ through the whole-cell recording pipette to make E_{Cl} more positive than the resting membrane potential (Kraaij et al., 2000; Verweij et al., 2003; Packer et al., 2010). In addition, it has been reported that tiger salamander cones exhibit depolarizing surround responses (and hyperpolarizing center responses) when fine-tipped, intracellular recording micropipettes are filled with 2M potassium chloride, but that the cones hyperpolarize to both center and surround stimuli when the pipettes are filled with 2 M potassium acetate (Lasansky, 1981), suggesting that chloride leaking from the pipettes greatly enhances surround responses (i.e., produces surround-evoked depolarizations) by making E_{Cl} more positive than the resting membrane potential. The finding that the depolarizing potentials evoked by surround illumination are influenced by E_{Cl} in cones also suggests that the secondary activation of calcium-activated chloride channels is largely responsible for the depolarizing surround-evoked potentials that are sometimes seen in cones from various species (Kraaij et al., 2000; Verweij et al., 2003). The less pronounced

surround-evoked depolarization in cones from other species may be due to a more negative value for E_{Cl} in these cells (Kraaij et al., 2000; Verweij et al., 2003). Given that 1) bipolar cell surround activation is strongest during maintained mid-mesopic to photopic background illumination and 2) surround illumination depolarizes cones when their E_{Cl} is more positive than their resting membrane potential, it is possible that a maintained increase in the background illumination to the mid-mesopic to photopic level induces a positive shift in the cone E_{Cl} so that horizontal cell feedback to cones mediates cone depolarizing responses to surround illumination and bipolar cell surround activation.

The finding that negative feedback from horizontal cells causes a shift in the voltage-dependence of I_{Ca} may explain how feedback can modulate Ca^{2+}-dependent release of glutamate from cones and produce robust consequences in second-order cells (e.g., surround antagonism of bipolar cells) with little or no depolarization of the cone membrane (Kraaij et al., 2000). However, the issue is whether a light adaptive change in glutamate release from cones under maintained mid-mesopic to photopic background illumination can account for bipolar cell surround activation (i.e., a response to surround stimulation alone that is opposite in polarity to that produced by center stimulation alone) and for bipolar cell center and surround responses that are similar in waveform and amplitude (Yazulla, 1976; Stone and Schutte, 1991; Dacey et al., 2000; Fahey and Burkhardt, 2003; see Sections 2.1 and 2.5 here). As noted in Section 2.5, although modulation of Ca^{2+}-dependent release of glutamate from cones during a hyperpolarizing light response cannot easily account for bipolar cell surround responses that are of opposite polarity compared to bipolar cell center responses, it seems theoretically possible that maintained light adaptation produces a sustained negative shift of the cone resting membrane potential and a sustained decrease in glutamate release from cones relative to their dark release rate. Under this light-adapted state, negative feedback from horizontal cells could shift I_{Ca} leftward and increase glutamate release without producing a depolarization of the cone. Such an increase in glutamate release above the basal, light-adapted rate of glutamate release could evoke opposite polarity bipolar cell responses during surround-only stimulation. Moreover, because bipolar cell surround strength is greater under maintained light-adapted, compared to dark-adapted conditions, negative feedback from horizontal cells should shift I_{Ca} leftward to a greater extent following light adaptation than following dark adaptation. However, it is not clear why a light-adapted cone can hyperpolarize to center stimulation more intense than the background light level (i.e., a stimulus of positive contrast), but not depolarize to surround illumination alone (via a feedback signal from horizontal cells) or to center stimulation less intense than the background illumination (i.e., a stimulus of negative contrast). As noted in Section 2.1 (see Fig. 3 here), Fahey and Burkhardt (2003) observed that under maintained photopic illumination cone-driven bipolar cell light responses of the same polarity (i.e., depolarization or hyperpolarization) are similar in waveform and amplitude irrespective of whether they are elicited by center or surround stimulation (e.g., bipolar cell responses to positive contrast center stimuli and negative contrast surround stimuli are similar in waveform and amplitude). Under maintained mid-mesopic to photopic illumination conditions, measurements of cone responses to center-only and surround-only stimulation using fine-tipped micropipettes and measurements of cone I_{Ca} are needed to clarify the contribution of cones to bipolar cell surround activation and to determine whether surround stimulation in the absence of center stimulation strongly shifts I_{Ca} leftward without altering the membrane potential of cones. In addition, these measurements should also be performed under maintained scotopic illumination conditions to determine whether surround-only stimulation shifts I_{Ca} to a lesser extent following dark adaptation than following light adaptation.

Three main mechanisms have been proposed to explain negative feedback from horizontal cells onto cones: 1) a reduction in GABA release from horizontal cells (GABA disinhibition), 2) ephaptic modulation of cone membrane potential by currents flowing

through hemigap junctions in horizontal cell dendrites, and 3) proton modulation of cone I_{Ca}. We consider evidence for and against these mechanisms below.

3.1.1 The role for GABA in horizontal cell feedback—Immunohistochemical studies have shown that non-mammalian horizontal cells typically possess high levels of GABA, the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD), and the GABA degradatory enzyme GABA transaminase (Lam et al., 1978; Lam and Ayoub, 1983; Lasater and Lam, 1984; Mosinger et al., 1986; Agardh et al., 1987; Kalloniatis and Fletcher, 1993; Connaughton et al., 1999; Deng et al., 2001; Bennis et al., 2003; Klooster et al., 2004; Zhang et al., 2006). GAD and GABA can also be found in horizontal cells of many mammalian retinas including cat, rabbit, and monkey (Lin et al., 1983; Brandon, 1985; Mosinger et al., 1986; Osborne et al., 1986; Agardh et al., 1987; Mosinger and Yazulla, 1987; Chun and Wassle, 1989; Pourcho and Owczarzak, 1989; Vardi et al.,1994; Kalloniatis et al., 1996; Johnson and Vardi, 1998; Marc et al., 1998; Dkhissi et al., 2001). However, most studies on rodent retina find that GABA and GAD are present only during a transient period early in development (Agardh et al., 1986; Fletcher and Kalloniatis, 1997; Schnitzer and Rusoff, 1984; Schubert et al., 2010; Versaux-Botteri et al., 1989; Yamasaki et al., 1999; Osborne et al., 1986; Loeliger and Rees, 2005; but see Guo et al., 2010). The low levels of GABA in horizontal cells of adult rodents may be related to the fact that they lack plasma membrane GABA transporters (Guo et al., 2009, 2010). Higher GABA levels are found in retinas from adult mice fixed by cardioperfusion rather than fixation of isolated retinas (Deniz et al., 2011) perhaps because, without plasma membrane GABA uptake mechanisms, horizontal cells cannot rapidly replenish GABA lost during the fixation of isolated retinas. Lacking plasma membrane transport mechanisms, all of the GABA in rodent horizontal cells presumably comes from synthetic pathways. Although plasma membrane transport mechanisms may be absent, vesicular GABA transporters are present in mammalian retina, consistent with the ability of horizontal cells to release GABA by a conventional synaptic mechanism (Haverkamp et al., 2000; Cueva et al., 2002; Jellali et al., 2002; Johnson et al., 2003; Guo et al., 2009, 2010).

Some studies have shown receptor-binding and immunohistochemical evidence for ionotropic $GABA_a$ and $GABA_c$ receptors on cone terminals (Yazulla et al., 1989; Hughes et al., 1991; Yang et al., 1992; Vardi et al., 1992; Lin and Yazulla, 1994; Mitchell et al., 1999; Wang et al., 2000; Klooster et al., 2004; Picaud et al., 1998; Pattnaik et al., 2000) but others have failed to show labeling (see Wassle et al., 1998). There is also physiological evidence for ionotropic GABA receptors in mammalian (but not primate; Verweij et al., 2003) and non-mammalian cones (Kaneko and Tachibana, 1986a,b; Wu, 1986; Picaud et al., 1998; Pattnaik et al., 2000; Tatsukawa et al., 2005; Liu et al., 2006). The finding that GABA evokes $GABA_A$ receptor-mediated currents in isolated turtle cones (Kaneko and Tachibana, 1986a) suggests the possibility that GABA feedback from horizontal cells to cones may function under some physiological conditions. There is also physiological and immunohistochemical evidence for $GABA_b$ receptors on bullfrog cones (Liu et al., 2005).

Horizontal cells can release GABA upon depolarization. In non-mammalian retinas, this release is only partly calcium-dependent (Schwartz, 1982; Lasater and Lam, 1984; Yazulla and Kleinschmidt, 1983; Ayoub and Lam, 1984, 1985; Cunningham and Neal, 1985). The calcium-independent release mechanism appears to involve the efflux of GABA by a transporter mechanism (reviewed by Schwartz, 2002). Mammalian horizontal cells do not appear to possess plasma membrane GABA transporters suggesting that plasma membrane transporters do not contribute to release in mammals (Guo et al., 2010). The presence of SNARE proteins, vesicular GABA transporters, and other presynaptic proteins in horizontal cell dendrites supports the idea that the calcium-dependent component of release involves

conventional vesicular release mechanisms (Lee and Brecha, 2010; Hirano et al., 2005, 2007; Sherry et al., 2006).

In addition to examining cone responses, the effects of horizontal cell to cone feedback can also be assessed post-synaptically in horizontal and bipolar cells. However, horizontal cells and bipolar cells possess GABA receptors (reviewed by Yang, 2004) and this can complicate the interpretation of effects of exogenously applied GABA agonists and antagonists. Nevertheless, consistent with a role for GABA in feedback, flashing an annulus in the presence of a small centered spot of light evokes predominately depolarizing responses in horizontal cells with small receptive fields (Piccolino et al., 1981) and these responses can be inhibited by GABA (Stone and Witkovsky, 1987). The depolarizing responses of color-opponent horizontal cells that appear to result from horizontal cell to cone feedback can be inhibited by bicuculline, picrotoxin, and GABA in some fish species (Djamgoz and Ruddock, 1979; Murakami et al., 1982). However, these GABAergic agents inhibited depolarizing responses in only a minority of color-opponent horizontal cells in the turtle retina (Perlman and Normann, 1990).

When considering bipolar cell responses, it is even more difficult to separate effects of GABA agonists and antagonists on bipolar cells, horizontal cells, or cones. However, the finding that GABA, $GABA_a$ antagonist bicuculline, $GABA_{a/c}$ antagonist picrotoxin, $GABA_c$ antagonist cis-4-aminocrotonic acid, $GABA_b$ antagonist phaclofen, and $GABA_b$ agonist baclofen separately or in various combinations did not block receptive field surrounds in salamander bipolar cells under scotopic illumination conditions argues against a role for GABA in horizontal cell to cone feedback (Hare and Owen, 1996). GABA antagonists also failed to block surrounds in ganglion cells of the primate retina driven by inputs from L (long wavelength-sensitive) and M (middle wavelength-sensitive) cones (Crook et al., 2009, 2011).

More direct tests of a role for GABA in horizontal cell to cone feedback were performed by studying cone responses to surround illumination. GABA, GABA agonist muscimol, $GABA_a$ antagonist bicuculline, $GABA_{a/c}$ antagonist picrotoxin, and $GABA_b$ antagonist phaclofen all failed to block depolarizing responses of turtle cones evoked by surround illumination (Thoreson and Burkhardt, 1990). $GABA_a$, $GABA_b$, and $GABA_c$ antagonists also failed to block surround-mediated changes in goldfish cones (Verweij et al., 1996) and the $GABA_{a/c}$ antagonist picrotoxin did not block surround responses in primate cones (Verweij et al., 2003). Furthermore, the value for E_{Cl} in salamander cones is ca. −37 mV, which is more positive than the typical membrane potential of a light-adapted cone, suggesting that a light-evoked reduction in GABA release from horizontal cells should cause a hyperpolarization, not a depolarization (Thoreson and Bryson, 2004). Wu (1991) studied depolarizing light responses evoked in salamander cones that had lost their outer segments and were therefore insensitive to light. In contrast with other studies on GABAergic effects, Wu (1991) found that depolarizing responses presumably mediated by horizontal cell to cone feedback were partially inhibited by bicuculline. Tatsukawa et al. (2005) showed that GABA antagonists normally produced little effect on turtle cones, but GABAergic feedback effects could be revealed after potentiating $GABA_a$ receptors with pentobarbital. The authors concluded that GABA levels in the cone synaptic cleft were normally too low for changes in horizontal cell release to exert significant effects. Thus, perhaps the greater efficacy of bicuculline found by Wu (1991) is due to an elevation of GABA levels under these particular experimental conditions, suggesting that GABA may play a role in feedback under certain illumination conditions. However, GABAergic effects on cone membrane potential cannot easily explain the changes in I_{Ca} voltage-dependence that accompany negative feedback to horizontal cells.

3.1.2 Ephaptic modulation of the cone pedicle membrane potential—By injecting current into cones, Byzov and Cervetto (1977) noted non-linearities in the current/voltage relationship that were modulated by light. This led to the proposal that horizontal cell to cone feedback modulated the cone's current/voltage relationship (Byzov, 1979). Voltage-dependent effects of horizontal cell feedback on cones were also noted by other investigators (O'Bryan, 1973; Skrzypek and Werblin, 1983; Wu, 1991). To account for these voltage-dependent effects, Byzov (1977, 1979; Byzov and Shura-Bura, 1986) proposed the hypothesis that feedback did not involve a conventional chemical synapse, but resulted from an ephaptic mechanism in which current flow within the confines of the invaginating cone synapse produced membrane voltage changes that were localized to the cone terminal. The term "ephaptic" was coined by Arvanitaki (1942) to describe the influence of currents flowing through the extracellular space on neighboring neurons. In most parts of the nervous system, ephaptic effects are thought to be minimal because of the relatively large volume and low resistance of the extracellular space (Barr and Plonsey, 1992). However, there are exceptions to this rule (Jefferys, 1995) such as insect photoreceptors where large extracellular potentials have been shown to modulate synaptic output (Weckstrom and Laughlin, 2010). The invaginating cone photoreceptor synapse may represent another exception to this general rule and, as discussed below, the ephaptic mechanism proposed by Byzov and colleagues can account for many of the properties of feedback.

As described earlier, the light-evoked hyperpolarization of the horizontal cell membrane causes I_{Ca} to shift in a negative (leftward) direction along the voltage axis (Verweij et al., 1996). One mechanism that can produce such a shift in I_{Ca} along the voltage axis is ephaptic modulation of the local membrane potential in the cone terminal (Byzov and Shura-Bura, 1986). When the horizontal cell hyperpolarizes, the flow of current into the horizontal cell requires that an equal amount of extracellular current must flow through the extracellular space into the invaginating synapse (Fig. 9). Assuming a finite extracellular resistance in the synaptic cleft, this current flow will produce a small voltage drop making the interior of the cleft slightly more negative than the surrounding extracellular space. This small negative change in extracellular voltage is equivalent to a small membrane depolarization and this shifts the I_{Ca} activation curve to more negative potentials, lowering the threshold for I_{Ca} activation.

In addition to a shift of cone I_{Ca} activation to more negative potentials, horizontal cell hyperpolarization typically increases the peak amplitude of I_{Ca} (Fig. 8) (Verweij et al., 1996; Hirasawa and Kaneko, 2003; Cadetti and Thoreson, 2006; Thoreson et al., 2008; Packer et al., 2010). Although ephaptic modulation of the local potential in the cone terminal can produce a shift in the voltage-dependence of I_{Ca}, it cannot readily explain this observed change in the peak amplitude of I_{Ca}.

Kamermans et al. (2001) hypothesized that the source of ephaptic current at the cone synapse involves current flow through hemigap junctions in the tips of horizontal cell dendrites. In support of this hypothesis is immunohistochemical evidence for the connexin, Cx26, at the tips of horizontal cell dendrites in fish (Kamermans et al., 2001; Janssen-Bienhold et al., 2001) and turtle (Pottek et al., 2003) retina. Connexin 55.5 and pannexin1 have also been observed on horizontal cell dendrites at cone synapses in zebrafish retina (Shields et al., 2007; Prochnow et al., 2009). Mammalian horizontal cells do not possess Cx26 (Deans and Paul, 2001) but instead possess Cx50 and Cx57 (Massey et al., 2003) and studies in mammalian retina have not shown connexins within the invaginating photoreceptor synapse (Puller et al., 2009). Knockout of connexin 57 in mouse retina did not appear to diminish the horizontal cell rollback which is often used as a measure of the strength of horizontal cell to cone feedback (Shelley et al., 2006). Many connexins close

when not coupled to another gap junction (Hoang et al., 2010), but Cx26 hemigap junctions can, at least in some species, remain open under physiological conditions (Ripps et al., 2004; but see Gonzalez et al., 2006).

A second piece of evidence for a role for hemigap junctions in feedback was the finding that a gap junction blocker, carbenoxolone, inhibited horizontal cell to cone feedback in goldfish and primate cones (Kamermans et al., 2001; Verweij et al., 2003). Carbenoxolone also blocked post-synaptic effects of feedback on horizontal cells including the depolarizing rollback in luminosity (L)-type horizontal cells and the depolarizing response to red light in C-type horizontal cells (Kamermans et al., 2001). However, interpretation of these effects is complicated by the fact that carbenoxolone also inhibited hyperpolarizing light responses of L-type horizontal cells (Kamermans et al., 2001), perhaps by inhibiting presynaptic I_{Ca} (Vessey et al., 2004). Inhibiting horizontal cell light responses necessarily inhibits horizontal cell to cone feedback, but Kamermans et al. (2001) found that the effect of carbenoxolone on horizontal cells was slightly delayed relative to the reduction in feedback.

Thoreson and Burkhardt (1990) discovered that a low concentration of cobalt (0.1 mM) selectively blocked depolarizing feedback responses in turtle cones without blocking hyperpolarizing light responses of horizontal cells. Low concentrations of cobalt were also found to block horizontal cell to cone feedback in primate and goldfish cones (Verweij et al., 2003; Fahrenfort et al., 2004) and reduce antagonistic surrounds in bipolar, amacrine, and ganglion cells as well as the depolarizing responses of color-opponent horizontal cells (Vigh and Witkovsky, 1999). Low cobalt blocks Cx26 hemigap junctions suggesting a possible mechanism for this selective blockade of feedback (Fahrenfort et al., 2004). However, cobalt might also block feedback in other ways. For example, low concentrations of cobalt can block GABA receptors (Kaneko and Tachibana, 1986b) and cause changes in membrane surface charge that lead to a positive shift in I_{Ca} activation (Piccolino et al., 1999).

For an ephaptic mechanism to produce a significant shift in the voltage (i.e., 10 mV) of the cone presynaptic membrane without interfering with the ability of horizontal cells to produce a 40 mV hyperpolarization to bright light, the resistance of the extracellular space within the cone synaptic cleft must be much greater than that of a typical extracellular space (such as outside of the cone synaptic cleft) but less than 100 MΩ, and the resistance of the hemichannels in horizontal cell dendrites must be as low as 300 MΩ, i.e. ~3-times larger than the resistance of the extracellular space within the cone synaptic cleft (Kamermans et al., 2001; Fahrenfort et al., 2005, 2009; Dmitriev and Mangel, 2006). However, using a quantitative model that simulated horizontal cell feedback at the cone pedicle to assess the ephaptic hypothesis, Dmitriev and Mangel (2006) concluded that the hemichannel resistance in horizontal cell dendritic tips exceeds 15,000 M-ohms, so that the ratio of the resistance of the hemichannels to that of the extracellular space is larger than 150:1, resulting in a negligible feedback potential (i.e., < 0.2 mV) when reasonable values for the input resistance of horizontal cells (i.e., between 50 and 300 MΩ – see Tachibana, 1981) were used. Lowering the input resistance to less than 50 MΩ increased the feedback potential, but a feedback potential of 10 mV could only be produced by the model if the horizontal cell input resistance was lowered to an improbably low value of 2 MΩ.

Because the ephaptic mechanism is highly dependent on the presence of an extracellular space resistance that is much greater than the typical extracellular resistance, the effects of extracellular currents generated by different horizontal cell dendrites on a cone presynaptic membrane voltage will sum together only if the dendrites are located within the same cone invagination where they share the same extracellular resistance. In most vertebrate species, two horizontal cell dendrites are observed within the same invagination of a cone pedicle (Dowling, 2012). However, horizontal cell dendrites typically contact many cones – e.g.,

each goldfish horizontal cell contacts ~20 cones (Stell and Lightfoot, 1975) – so that generally speaking the dendrites of a single horizontal cell contact many cones and the extracellular currents generated by the dendrites do not sum together. Because of these considerations, Dmitriev and Mangel (2006) treated the extracellular space resistances within the cone invaginations and the horizontal cell dendritic resistances of the 20 dendrites of a single horizontal cell as acting in parallel with their counterparts at the 20 different cone invaginations contacted by the dendrites of the horizontal cell. As a result, each of the 20 horizontal cell dendritic tips contained 1/20 of the total dendritic conductance, so that the horizontal cell dendritic resistance exceeded 15,000 MΩ and the effect of ephaptic feedback on the cone presynaptic membrane was divided by the number of cone invaginations. A concern with a recent model of ephaptic feedback is that the extracellular space resistances within the cone invaginations and the horizontal cell dendritic resistances of the 20 dendrites of a single horizontal cell were not treated as acting in parallel with their counterparts at the 20 different cone invaginations contacted by the dendrites of the horizontal cell (Fahrenfort et al., 2009). This approach yields a very low hemichannel resistance that is only ~3-times larger than the resistance of the extracellular space within the cone synaptic cleft.

In addition to a concern about the impact of ephaptic feedback on the cone presynaptic membrane potential, Dmitriev and Mangel (2006) point out that, because the conductance of glutamate receptors is much greater than that of hemigap junctions, most of the current is likely to enter horizontal cell dendrites through open glutamate receptors. When glutamate release from cones diminishes in light, these channels will close and the ephaptic potential should decrease, not increase. This result implies that ephaptic interactions should produce positive, not negative, feedback from horizontal cells to cones (Dmitriev and Mangel, 2006). Since a decrease in ephaptic potential in light would cause a positive activation shift in cone I_{Ca}, this would further diminish glutamate release and establish a positive feedback loop. If such positive feedback operates at the cone synapse, then there should be a positive shift in I_{Ca} when horizontal cells are hyperpolarized by light. However, this has never been reported (Verweij et al., 1996; Hirasawa and Kaneko, 2003). As discussed later, there is evidence for a positive feedback mechanism coupling horizontal cells to cones but it appears to involve Ca^{2+}-dependent release of a retrograde messenger from horizontal cells (Jackman et al., 2011). Kamermans et al. (2001) initially suggested that current flow through glutamate receptor channels located on horizontal cell dendrites might contribute to ephaptic voltage changes during feedback. Although a subsequent study concluded that glutamate receptors contribute little to feedback, perhaps because of their relatively diffuse distribution within and outside of the synaptic cleft (Fahrenfort et al., 2005), a more recent computational analysis suggested that glutamate-gated channels provide ~ 40% of the feedback mechanism (Fahrenfort et al., 2009).

Due to the requirement for a finite resistance in the extracellular space of the invaginating cone synaptic cleft, one potential concern about an ephaptic feedback mechanism is that it should be incapable of modulating the membrane potential of the cone presynaptic terminal outside of the invaginating cone synaptic cleft where the extracellular resistance is low. In mammalian retina, most OFF-bipolar cell dendrites contact cones at basal contacts outside of the invagination (Kolb, 1970), although there is evidence that the dendrites of at least one OFF-bipolar cell subtype can enter the cone invagination (McGuire et al., 1984; DeVries et al., 2006). In salamander retina, ON-bipolar cell dendrites make the majority of basal contacts (Lasansky, 1978). Because an ephaptic feedback mechanism would not be expected to modulate glutamate release from cones mediated by Ca^{2+} channels at basal contacts, this raises the concern that it might not be capable of mediating surrounds of mammalian OFF-bipolar cell or salamander ON bipolar cells. However, recent evidence suggests that glutamate release from cones occurs largely, if not wholly, at the ribbon (Snellman et al., 2011) and that glutamate released at ribbon synapses can diffuse approximately 500–950 nm

to glutamate receptors on OFF-bipolar cell dendrites at basal contacts (Morigiwa and Vardi, 1999; Wilson, 2004; DeVries et al., 2006).

Recently, it has been reported that zebrafish retinas lacking connexin 55.5 exhibit a number of changes consistent with diminished horizontal cell to cone feedback (Klaassen et al., 2011). These effects include reduced rollback in luminosity-type horizontal cells, reduced depolarizing responses in color opponent horizontal cells, and a reduction in small cone membrane current changes produced by illumination of the receptive field surround. A small leftward shift in cone I_{Ca} was produced by hyperpolarizing horizontal cells in control fish by bath application of a glutamate antagonist, DNQX, and this shift was diminished in fish lacking Cx55.5. The rightward shift in cone I_{Ca} caused by depolarizing horizontal cells with kainate was not reduced in knockout animals. The authors suggest that the incomplete loss of feedback effects may reflect contributions from pannexin (Prochnow et al., 2009), other connexins (e.g., connexin 52.9), or other mechanisms.

In summary, ephaptic modulation of the cone pedicle membrane potential can explain many features of horizontal cell to cone feedback, such as how changes in the horizontal cell membrane potential can shift the voltage dependence of cone I_{Ca} and thereby influence glutamate release from cones. However, it is not clear how ephaptic modulation of the cone pedicle membrane potential can alter the peak amplitude of cone I_{Ca}. Hemigap junctions found at the tips of horizontal cell dendrites in fish and turtle retina have been proposed to be a source for ephaptic current flow into the invaginating cone synapse. In support of this idea, a non-selective gap junction blocker, carbenoxolone, appears to reduce feedback during the period before horizontal cell responses are completely blocked (Kamermans et al., 2001). Furthermore, zebrafish lacking connexin 55.5 hemigap junctions show diminished feedback effects (Klaassen et al., 2011). However, a quantitative analysis of the ephaptic hypothesis (Dmitriev and Mangel, 2006) suggests that it is unlikely that an ephaptic mechanism mediates feedback because the necessity of preserving adequate cone to horizontal cell signal transfer limits the extracellular space and the horizontal cell dendrite resistances to values at which the effectiveness of electrical feedback on the cone presynaptic membrane is negligible.

3.1.3. The role for protons in negative feedback from horizontal cells to cones

3.1.3.1. Evidence for a contribution of protons to negative feedback from horizontal cells: In their studies on horizontal cell to cone feedback, Gerschenfeld et al. (1980) found that hyperpolarization of horizontal cells caused an increase in the calcium conductance of cones. They suggested that a neuromodulatory substance might regulate I_{Ca}. One potential neuromodulator is pH (Barnes and Bui, 1991; Kleinschmidt, 1991; Barnes et al., 1993; Harsanyi and Mangel, 1993) and Hirasawa and Kaneko (2003) found evidence that changes in horizontal cell membrane potential can alter the concentration of synaptic cleft protons and thereby modulate cone I_{Ca}. Protons can act on I_{Ca} by at least two mechanisms: 1) changes in the voltage dependence of Ca^{2+} channels caused by alterations in membrane surface charge and 2) changes in current amplitude caused by protonation of residues in the pore (Barnes and Bui, 1991; Barnes et al., 1993; Harsanyi and Mangel, 1993; Chen et al., 1996).

It is useful to review the effects of membrane surface charge on the activation of voltage-dependent ion channels. As described by Hille (2001), phospholipid head groups impart a negative charge to the membrane surface that is typically neutralized by cationic counter-ions including divalent cations and protons (see also Piccolino et al., 1999). In the absence of extracellular cations, the extracellular potential of the electrical field drops precipitously in the final few angstroms approaching the negatively charged membrane surface. Because this potential drop occurs outside the membrane, the potential drop sensed by trans-

membrane ion channels is only a portion of the total drop from outside to inside the cell. By reducing the trans-membrane voltage drop sensed by Ca^{2+} channels, a smaller membrane depolarization is needed to stimulate channel opening in the absence of surface charge screening by cations. By exposing negative surface charges, a reduction in extracellular protons lowers the threshold for activation, allowing I_{Ca} to activate at more negative potentials. Conversely, acidification increases positive charge on the membrane surface and elevates I_{Ca} threshold, shifting the voltage-dependence of activation to more positive values. Effects of protons on surface charge can be observed even in the presence of divalent cations suggesting that protons and divalent cations act at partially independent binding sites (Kwan and Kass, 1993).

Hirasawa and Kaneko (2003) proposed that hyperpolarization of the horizontal cell membrane potential may alkalinize the synaptic cleft and thereby shift I_{Ca} activation to more negative potentials by reducing the surface charge shielding effects of protons. Alkalinization would also be predicted to enhance the peak amplitude of I_{Ca} by reducing the inhibitory effects of protons on permeation through the Ca^{2+} channel pore. To test this hypothesis, Hirasawa and Kaneko (2003) voltage clamped a cone in the newt retinal slice and flashed a light onto the receptive field surround in the presence of a central small spot of light. Consistent with Verweij et al. (1996), they found that surround illumination caused a 2.55 mV negative shift in the voltage-dependence of I_{Ca}. This shift was accompanied by an increase in the peak amplitude of I_{Ca}. To mimic effects of ephaptic modulation, Hirasawa and Kaneko (2003) applied a small 2 mV depolarizing step to the cone. This small depolarization replicated the negative activation shift in I_{Ca} produced by surround illumination but did not cause an enhancement of the peak amplitude of I_{Ca}. The inability of this small depolarization to replicate the increase in I_{Ca} evoked by surround illumination argues against an ephaptic mechanism. In further support of the hypothesis that protons contribute to horizontal cell to cone feedback, blocking pH changes by addition of the pH buffer HEPES reduced changes in I_{Ca} stimulated by surround illumination. Aminosulfonates including HEPES have been shown to block gap junctions (Bevans and Harris, 1999—although not in carp horizontal cells, Yamamoto et al., 2008). Hirasawa and Kaneko (2003) therefore also tested Tris, which lacks an aminosulfonate moiety and does not block gap junctions (Bevans and Harris, 1999). They found that Tris also blocked surround-induced modulation of I_{Ca}. In addition to using light to modulate horizontal cell membrane potential, these authors chemically modulated horizontal cells by application of the glutamate receptor agonist kainate or antagonist CNQX. Kainate depolarized horizontal cells and caused a positive shift in I_{Ca} activation. Conversely, CNQX hyperpolarized horizontal cells and caused a negative shift in I_{Ca} activation similar to the effects of light. Like the modulation of I_{Ca} by surround illumination, these effects were blocked by HEPES.

The blocking effects of pH buffers on horizontal cell to cone feedback have been confirmed by a number of other investigators. In both mammalian and non-mammalian horizontal cells, HEPES abolished the depolarizing rollback in horizontal cell light responses that is generally attributed to a reduction in cone transmitter release due to horizontal cell to cone feedback (Vessey et al., 2005; Davenport et al., 2008). The pH buffer Tris also reduced this rollback (Vessey et al., 2005). Trenholm and Baldridge (2010) showed that the rollback was reduced only by aminosulfonate buffers that have a pKa value near 7.5 indicating that the blocking effect is not a result of the aminosulfonate moiety *per se*. Downstream effects of feedback are also blocked by HEPES including the antagonistic surround of parasol ganglion cells (Davenport et al., 2008) and color opponent surrounds in midget ganglion cells (Crook et al., 2011).

To confirm that shifts in the voltage-dependence of I_{Ca} caused appropriate changes in intracellular Ca^{2+} levels, Vessey et al. (2005) measured intraterminal Ca^{2+} changes in cone

photoreceptors in the zebrafish retina while manipulating the horizontal cell membrane potential with kainate and CNQX. They bath applied 15–30 mM K^+ to depolarize cones to membrane potentials in a range below the peak of I_{Ca} that should be particularly sensitive to changes in I_{Ca} current/voltage relationship. As expected for a negative shift in I_{Ca}, hyperpolarizing horizontal cells with CNQX enhanced Ca^{2+} increases evoked by bath application of high K^+. Conversely, depolarizing horizontal cells with kainate caused a reduction in high K^+-evoked Ca^{2+} increases. These effects were blocked by increasing the strength of pH buffering.

Cadetti and Thoreson (2006) examined the effects of changes in horizontal cell membrane potential on cone I_{Ca} by directly manipulating voltage-clamped horizontal cells while measuring I_{Ca} in simultaneously voltage clamped cones. Directly hyperpolarizing horizontal cells in synaptically-coupled pairs caused a negative shift in voltage-dependence of cone I_{Ca} and increased its peak amplitude. Conversely, depolarizing horizontal cells caused a positive shift and decreased I_{Ca} amplitude. These effects were blocked by increasing pH buffering with 10 mM HEPES. By contrast, the gap junction blocker carbenoxolone did not significantly reduce effects of horizontal cell voltage changes on cone I_{Ca}. In addition to blocking the modulation of cone I_{Ca} by horizontal cell membrane potential, HEPES also caused a negative shift in V_{50} (Cadetti and Thoreson, 2006) consistent with other studies (described in the next section) suggesting that even when the pH of the HEPES superfusate is matched to the bicarbonate-buffered superfusate pH of 7.4, application of HEPES causes a net alkalinization within the retina (Oakley and Wen, 1989; Dmitriev and Mangel, 2000, 2001, 2004). Such an alkalinization also predicts that HEPES should increase the amplitude of I_{Ca} to that observed when the horizontal cell is held at −90 mV. However, for reasons that remain unclear, HEPES diminished I_{Ca} to the amplitude observed when the horizontal cell was held at more depolarized potentials (Cadetti and Thoreson, 2006).

3.1.3.2. Measurements of extracellular pH changes and pH buffer effects: Both extracellular and intracellular pH changes can modulate gap junctional conductances (Trexler et al., 1999). Because HEPES can produce an intracellular acidification of horizontal cells (Fahrenfort et al., 2009; Trenholm and Baldridge, 2010), it has been suggested that the blocking effect of HEPES may reflect a block of hemigap junctions caused by intracellular acidification (Fahrenfort et al., 2009). However, acidification of horizontal cells is also produced by pH buffers that do not block feedback (Trenholm and Baldridge, 2010). This argues that buffer effects cannot be explained by changes in intracellular pH.

The sensitivity of hemigap junctions to extracellular pH (Trexler et al., 1999) may offer other ways to reconcile the proton and ephaptic hypotheses. For example, if hyperpolarization of the horizontal cell causes alkalinization of the cleft, then this should enhance the hemigap junction conductance which could increase ephaptic current flow into horizontal cell dendrites. Blocking pH changes with HEPES would diminish such a change in ephaptic current and could thus reduce feedback effects at the cone pedicle.

Although enhanced pH buffering has been consistently shown to block horizontal cell to cone feedback, a difficulty with a proton-mediated mechanism of horizontal cell feedback to cones is that measurements of extracellular pH made using H^+-selective microelectrodes have found that light stimulation alters the extracellular pH of the outer retina of frogs, fish, rabbits and cats by only ~ 0.04 pH units (Borgula et al., 1989; Oakley and Wen, 1989; Yamamoto et al., 1992; Dmitriev and Mangel, 2000, 2001). This contrasts with the much larger pH changes predicted by the proton hypothesis. Studies of isolated salamander cones showed that the voltage-dependence of cone I_{Ca} shifts by ~1 mV per 0.1 pH unit (Barnes and Bui, 1991). Therefore, the finding that I_{Ca} shifts by 2.55 to 7.5 mV during surround

illumination (Verweij et al., 1996; Hirasawa and Kaneko, 2003) suggests that a light-evoked increase in extracellular pH of ~0.25 to 0.75 units would be needed to produce the observed negative shift in I_{Ca} (Vessey et al., 2005). In addition to discrepancies about the size of the pH change, light stimulation increases extracellular pH in some species, but decreases it in others. Moreover, light-induced changes in pH have a much slower time course—on the order of tens of seconds to minutes (Borgula et al., 1989; Oakley and Wen, 1989; Yamamoto et al., 1992; Dmitriev and Mangel, 2000, 2001) -- than the response delay (30–50 ms) of the bipolar surround relative to that of the bipolar center (Stone and Schutte, 1991; Fahey and Burkhardt, 2003) or the delay of the cone depolarization compared to the initial hyperpolarization when a large spot is flashed (Baylor et al., 1971).

It might be argued that measurements of extracellular pH in the outer retina under-report the amplitude of light-evoked changes in extracellular pH that occur within the invaginating cone synaptic cleft. The pH within the invaginating synaptic cleft may differ at least transiently from the pH of the surrounding extracellular space. For example, there is evidence that the release of protons accompanying a burst of synaptic vesicle release from cones may briefly acidify the extracellular space within the synaptic cleft (DeVries, 2001). However, protons (and other ions such as sodium and calcium) appear to diffuse freely throughout the extracellular space and localized pH changes are therefore likely to dissipate rapidly. There is no physiological or morphological evidence for the restricted diffusion of protons or other ions within the extracellular space of the synaptic cleft. For example, there are no tight junctions at the entrance to the cleft and, if glutamate released at ribbon synapses within the invaginating cone synaptic cleft can diffuse freely ~500–950 nm to glutamate receptors on bipolar cell dendrites at basal contacts outside the invagination (Morigiwa and Vardi, 1999; Wilson, 2004; DeVries et al., 2006; Snellman et al., 2011) (see Section 3.1.2 above), then one would expect that protons should also be able to diffuse freely out of the cleft.

In addition to the difficulty of maintaining a pH gradient within the cleft, there is also no clear evidence that depolarization of horizontal cells can acidify the extracellular space, as required by the proton hypothesis. Using a small pH-sensitive microelectrode, membrane depolarization was found to alkalinize, not acidify, the extracellular medium surrounding isolated skate horizontal cells (Molina et al., 2004; Kreitzer et al., 2007). When measured with a lipophilic pH-sensitive dye, 5-hexadecanoylaminofluorescein, depolarization appeared to stimulate extracellular acidification of isolated horizontal cells (Jouhou et al., 2007; Trenholm and Baldridge, 2010). However, there is recent evidence that this dye may enter the cell and actually report intracellular pH levels (Jacoby et al., 2011) and there is a consensus that depolarization with glutamate causes an intracellular acidification of horizontal cells (Dixon et al., 1993; Trenholm and Baldridge, 2010).

Addition of HEPES to a bicarbonate-buffered Ringer's solution causes a reduction in the depolarizing rollback of horizontal cell light responses consistent with a reduction in negative feedback to cones (Vessey et al., 2005; Davenport et al., 2008; Trenholm and Baldridge, 2010). However, an under-appreciated effect of enhanced pH buffering with HEPES or other exogenous buffers is that the addition of such buffers can increase the extracellular pH throughout the retina, thereby altering horizontal cell feedback to cones. This effect arises from the consistent finding that the extracellular pH of the retina is 0.2–0.3 pH units lower than the pH of the bicarbonate-buffered superfusate (Oakley and Wen, 1989; Dmitriev and Mangel, 2000, 2001, 2004), a difference that is likely due to the metabolic activity of the tissue. Therefore, addition of a pH buffer such as HEPES to the superfusate, adjusted so that the superfusate pH does not change, will actually produce an alkalinization within the retina. Thus, at least some, and perhaps many, of the effects of exogenous pH buffers in the retina literature may have occurred not from blocking endogenous changes in

pH but because the addition of pH buffers increased the extracellular pH. One can control for this complication by monitoring extracellular pH in the outer retina to ascertain the appropriate amount to lower the pH of the Ringer when a specific buffer is added, so that the extracellular pH does not change when the buffer-containing Ringer is applied to the retina.

In addition to buffer-induced changes in pH, switching entirely from bicarbonate-buffered to HEPES-buffered Ringer's can have profound effects on horizontal cells and other cells in the outer and inner retina. In the nominally dark-adapted outer retina of tiger salamander, use of HEPES without bicarbonate has been shown to have significant effects on the responses and electrical properties of rods, bipolar cells and horizontal cells (Hare and Owen, 1998). After switching from a bicarbonate-buffered Ringer's to a HEPES-buffered Ringer's at the same pH, the dark resting potential of horizontal cells became more positive by approximately 30 mV, increasing the amplitude of their responses to saturating light flashes by a similar amount. In addition, the switch to HEPES shifted the balance of rod and cone inputs into the horizontal cells to favor cone input, and also increased the length constant of the horizontal cell network, suggesting an increase in horizontal cell gap junctional coupling. In the nominally dark-adapted outer retina of rabbit, switching from a bicarbonate-buffered Ringer's to a completely HEPES-buffered Ringer's at the same pH abolished the light responses of A-type horizontal cells in a reversible manner (Hanitzsch and Kuppers, 2001). Such dramatic changes are not seen when bicarbonate remains present during supplementation with HEPES, but they highlight the potential for non-specific effects due to changes in pH buffering.

The adaptive state of the retina can also have a strong influence on retinal pH. Using pH-selective microelectrodes to monitor extracellular pH in intact fish and rabbit retinas, Dmitriev and Mangel (Dmitriev and Mangel, 2000, 2001, 2004) have documented that the circadian clock in the retina lowers the extracellular pH at night, compared to the day, by 0.1 pH units in fish and 0.15 pH units in rabbit. The day/night difference in pH was greatest in the outer retina and more than 5-fold greater than light-evoked changes in pH measured with an extracellular pH electrode. Moreover, a day/night difference in light-evoked changes in extracellular pH was not observed. The decrease in extracellular pH lasted for hours throughout the night and likely represents a sustained increase in acid production due to a tonic increase in energy metabolism (both goldfish and rabbit retinas are rod-dominated). The finding of a higher concentration of extracellular protons in the outer retina at night in the dark appears inconsistent with the idea that the pH of the synaptic cleft mediates the surround because bipolar cell surround strength is greatest in the day under light-adapted conditions. In fact, Dmitriev and Mangel (2000) found that a decrease in superfusate pH by 0.2 pH units during the day, which lowered the extracellular pH in the outer retina of the fish by 0.1 pH units, decreased the size of horizontal cell light responses by 50%. During the night compared to the day, the circadian clock in the fish retina decreases the size of horizontal cell light responses (Wang and Mangel, 1996), and as noted above, lowers the extracellular pH of the outer retina by 0.1 pH units (Dmitriev and Mangel, 2000). Thus, independent of other effects, the circadian-induced decrease in extracellular pH at night may reduce the size of horizontal cell light responses at night in part by producing a sustained shift in the voltage dependence of cone I_{Ca} to more positive potentials, thereby attenuating glutamate release from cones (Barnes and Bui, 1991; Barnes et al., 1993). Conversely, the circadian-induced increase in extracellular pH during daytime may produce a sustained shift in cone I_{Ca} to more negative potentials, thereby increasing glutamate release.

3.1.3.3. Possible mechanisms for pH changes in the cone synaptic cleft: The mechanisms by which horizontal cell membrane potential changes might alter pH are unclear. Chloride/bicarbonate and sodium/hydrogen exchange mechanisms appear to be the main ways by which intracellular pH is regulated in both photoreceptors (Saarikoski et al., 1997;

Kalamkarov et al., 1996) and horizontal cells (Haugh-Scheidt and Ripps, 1998; Molina et al., 2004). Cones and horizontal cells also possess plasma membrane Ca^{2+}-ATPases (PMCA) that can exchange extracellular Ca^{2+} for intracellular protons (Morgans et al., 1998; Molina et al., 2004; Kreitzer et al., 2007). PMCA activity therefore tends to alkalinize, not acidify, the cleft in darkness when horizontal cells and cones are depolarized (Molina et al., 2004; Kreitzer al., 2007; Makani and Chesler, 2010).

ATP hydrolysis generates protons that help to make the cytosol of most cells including cones and horizontal cells more acidic than the extracellular environment (intracellular pH 7.1–7.3; Saarikoski et al., 1997; Krizaj et al., 2011; Haugh-Scheidt and Ripps, 1998). Protons generated by the continual hydrolysis of ATP needed to fuel ATPase activity in darkness (Okawa et al., 2008; Linton et al., 2010) may be exported into the extracellular space of the synaptic cleft by sodium-hydrogen exchange. Accelerated ATP hydrolysis may contribute to the intracellular acidification of horizontal cells stimulated by depolarization (Dixon et al., 1993; Trenholm and Baldridge, 2010). Conversely, hyperpolarization of horizontal cells would be expected to cause a diminished production of protons, presumably resulting in a diminished proton efflux.

Another potential source of synaptic cleft protons is the vesicular ATPase in synaptic vesicles. In glutamatergic vesicles, very few of the protons are free (1/80 vesicles); many more (500/glutamatergic vesicle) are protonated to carboxyl side chains of glutamate at the vesicular pH of ~5.7 (Miesenbock et al., 1998; DeVries, 2001). However, effects of synaptic vesicle release on presynaptic I_{Ca} suggest that many of these protons dissociate from glutamate anions following their release into the more alkaline environment of the cleft (DeVries, 2001; Palmer et al., 2003). Thus, tonic release of glutamatergic vesicles by cones or release of GABAergic vesicles by horizontal cells might provide a source of synaptic cleft protons. Protons might also be pumped out of cones or horizontal cells by outward-facing vesicular ATPases that remain in the plasma membrane after vesicle fusion (Zhang et al., 2010). Consistent with a role for these pumps in pH regulation, Jouhou et al. (2007) found that the acidification of isolated horizontal cells measured with the membrane-bound dye, 5-hexadecanoylaminofluorescein, was blocked by inhibition of the vesicular ATPase.

A third potential source of synaptic cleft protons is extracellular carbonic anhydrase. Extracellular carbonic anhydrase catalyzes the conversion of CO_2 and water to protons and bicarbonate. The resulting production of free acids mediates fizzy taste sensations associated with carbonated beverages (Chandrashekar et al., 2010). Extracellular carbonic anhydrase XIV has been localized to cone terminals by immunohistochemistry (Fahrenfort et al., 2009) and carbonic anhydrase inhibitors block horizontal cell feedback effects on both I_{Ca} (Fahrenfort et al., 2009) and intracellular Ca^{2+} changes in cone terminals (Vessey et al., 2005). Thus, perhaps protons could be generated by extracellular carbonic anhydrase activity in the synaptic cleft.

In addition to the possibility that hyperpolarization of horizontal cells might cause a decline in the production of intracellular protons, another way in which horizontal cell hyperpolarization might alkalinize the synaptic cleft would be to stimulate an influx of protons into horizontal cells. Although the molecular identity is unclear, horizontal cells possess an amiloride-sensitive cation current that might mediate such an influx (Vessey et al., 2005; Jonz and Barnes, 2007). Amiloride can inhibit sodium-hydrogen exchangers as well as many different cation channels including ENaC channels, acid-sensing ion (ASIC) channels, and TRP channels. There is evidence for proton-permeable ENaC channels (Brockway et al., 2002) and ASIC1a channels in horizontal cells (Ettaiche et al., 2006).

In summary, pH changes in the synaptic cleft can replicate effects of horizontal cell feedback on both the voltage-dependence and peak amplitude of cone I_{Ca} (Hirasawa and Kaneko, 2003; Cadetti and Thoreson, 2006). Furthermore, exogenous pH buffers block horizontal cell to cone feedback. These effects are not caused by a blockade of hemigap junctions by the aminosulfonate moiety on HEPES or intracellular acidification of horizontal cells (Trenholm and Baldridge, 2010). However, a number of concerns about the proton hypothesis of horizontal cell feedback to cones remain. First, some, and perhaps many, of the reported effects of exogenous pH buffers may have resulted not from blocking endogenous changes in pH but because the addition of pH buffers increased the extracellular pH. Second, the finding that extracellular proton levels are higher in the outer retina at night in the dark than in the day represents a challenge to the idea that proton-mediated horizontal cell feedback to cones underlies the bipolar cell surround, which is strongest under maintained light-adapted conditions during the day. Third, light-induced changes in extracellular pH in the outer retina are significantly smaller and slower, and in some cases of opposite polarity, than predicted by the proton hypothesis. Fourth, the proton hypothesis lacks a compelling mechanistic explanation for how changes in horizontal cell membrane potential can alter cleft pH.

3. Direct horizontal cell feed-forward input to bipolar cells

4.1. Evidence of direct horizontal cell input to bipolar cells

Although horizontal cell feedback input to cones has been extensively studied (see Section 3), the possibility of direct horizontal cell feed-forward input to bipolar cells has received much less attention. Both anatomical and physiological evidence suggest that horizontal cells provide direct synaptic input to bipolar cells. Horizontal cell dendrites flank more centrally positioned bipolar cell dendrites in the invaginating cone synaptic terminal (Missotten, 1965; Dowling et al., 1966; Dowling and Boycott, 1966; Dowling and Werblin, 1969; Dowling, 1970; Kolb, 1970; Lasansky, 1971, 1973; Gray and Pease, 1971; Kolb and Jones, 1984; Marshak and Dowling, 1987). Moreover, at the ultrastructural level conventional chemical synaptic contacts between horizontal cells and bipolar cells have been observed frequently in non-mammalian retinas (Dowling et al., 1966; Dowling, 1968; Dowling and Werblin, 1969; Naka, 1976; Kolb and Jones, 1984; Sakai and Naka, 1986; Marshak and Dowling, 1987), and less frequently in mammalian retinas (but see Dowling et al., 1966; Fisher and Boycott, 1974; Kolb, 1977; Marshak and Dowling, 1987; Linberg and Fisher, 1988). As described in Section 3.1.1, consistent with the possibility of chemical synapses from horizontal cells to bipolar cells, SNARE proteins and other presynaptic proteins can be found in horizontal cell dendrites (Hirano et al., 2005, 2007; Sherry et al., 2006; Lee and Brecha, 2010). There is, however, no physiological or anatomical evidence for feedback from bipolar cells to horizontal cells or photoreceptors.

Although it is clear that horizontal cells contribute to the receptive field surround of bipolar cells (see Section 2.4 here), it has been difficult to obtain clear physiological evidence that horizontal cells signal directly to bipolar cells due in large part to the presence of horizontal cell input to cones. In roughly half of salamander bipolar cells, light responses evoked by sinusoidal modulation of center and surround could be superimposed on one another by simply scaling and shifting the inverted responses (Burkhardt et al., 2011). This suggests that surrounds are generated by a mechanism involving a simple delay and inversion consistent with feedback from horizontal cells to cones. In the other half of bipolar cells, superposition of center and surround responses could only be obtained with small amplitude modulation but not large amplitude sinusoids, consistent with separate inputs into bipolar cells from cones and horizontal cells under these conditions (Burkhardt et al., 2011). However, the clearest evidence of direct horizontal cell input to bipolar cells has been obtained by the use of APB (L-2-amino-phosphonbutyric acid or L-AP4), a glutamate

analogue. Because APB acts as a selective agonist at the mGluR6 receptors on ON-bipolar cell dendrites, it can be used to selectively block signaling from cones and rods to ON-bipolar cells (Slaughter and Miller, 1981; Shiells et al., 1981). In these experiments, APB was applied while the center and surround light responses of bipolar cells were monitored. If APB blocked both center and surround light responses, this result would suggest that surround responses are signaled via horizontal cell feedback to cones. If APB blocked the center, but not the surround responses of ON-bipolar cells, this would suggest that surround responses are not mediated by feedback input to cones. In tiger salamander retina, bath application of APB has been reported to block about a third of the surround response of ON-bipolar cells when bipolar cells are rod-driven (Hare and Owen, 1992) or when they receive mixed rod-cone input (Yang and Wu, 1991). Under illumination conditions in which tiger salamander ON-bipolar cells were purely cone-driven, APB had no effect on surround responses in about a third of the cells, a partial block of the surround responses in another third of the cells, and a more complete block of surround light responses in the remaining third of the cells (Fahey and Burkhardt, 2003). These findings suggest that when the ambient light level is in the mesopic to photopic range and bipolar cell surround light responses are strongest, direct horizontal cell input to ON-bipolar cells provides all or a substantial component of the surround to approximately two-thirds of the cells. Experiments with CPPG, an mGluR6 receptor antagonist (Awatramani and Slaughter, 2000; Snellman and Nawy, 2004), yielded similar results (Fahey and Burkhardt, 2003).

The effects of APB on the surround light responses of mammalian ON-bipolar cells have not been investigated to date. However, by examining the effects of intracellular current injection into horizontal cells on the extracellularly recorded spike activity of ganglion cells in light-adapted (mesopic range) rabbit retina, Mangel (1991) found that APB blocked the effects of horizontal cell polarizations on ON-, but not OFF-, ganglion cells. This APB result is consistent with the view that horizontal cells provide bipolar cell surround responses primarily via a feedback pathway onto cones, but it does not conclusively eliminate the possibility that rabbit horizontal cells may also signal directly to ON-bipolar cells. As noted in Mangel (1991), “if APB hyperpolarizes ON-centre bipolar cells well below the threshold potential for the release of bipolar cell transmitter onto ON-centre ganglion cells, then horizontal cell polarizations might not be able to depolarize ON-centre bipolar cells sufficiently to cause ganglion cell spiking, even if the horizontal cell to bipolar cell connection is direct (p. 230).” One way to test this possibility would be to determine whether the mGluR6 antagonist CPPG, which depolarizes ON-bipolar cells (Snellman and Nawy, 2004) and thus should not produce a hyperpolarizing block of transmitter release from ON-center bipolar cells, also eliminates or reduces the effects of horizontal cell polarizations on the spike activity of nearby ON-center ganglion cells.

4.2. The role of GABA in direct signaling from horizontal cells to bipolar cells

As described in Section 2.4, artificially depolarizing horizontal cells depolarizes nearby ON-center bipolar cells and hyperpolarizes nearby OFF-center bipolar cells (Marchiafava, 1978; Toyoda and Tonosaki, 1978; Toyoda and Kujiraoka, 1982; Naka, 1982). In other words, if horizontal cells provide direct synaptic input to bipolar cells, the input from horizontal cells is sign-conserving to ON-center bipolar cells and sign-inverting to OFF-center bipolar cells. The polarity of responses evoked by current injection into horizontal cells is consistent with the finding that surround illumination evokes hyperpolarizing responses in both horizontal cells and ON-center bipolar cells and depolarizing responses in OFF-center bipolar cells. Following prolonged background illumination in the mid-mesopic to photopic range, mammalian and non-mammalian horizontal cells are depolarized at rest and hyperpolarize to brief light flashes that are brighter than the background illumination (e.g., Dowling and Ripps, 1971; Ruddock and Svaetichin, 1975; Malchow and Yazulla, 1988; Mangel, 1991;

Lankheet et al., 1993; Wang and Mangel, 1996; Yang et al., 1999; Zhang et al., 2011). Thus, fully light-adapted horizontal cells could tonically release a substance (e.g., GABA) that depolarizes ON-center bipolar cells and hyperpolarizes OFF-center bipolar cells. The surround responses of ON-center and OFF-center cone-driven bipolar cells would thus result from the decrease in release of this substance from horizontal cells when they hyperpolarize to brief surround stimulation.

How could the release of GABA (or any other transmitter substance) from horizontal cells mediate opposite polarity surround light responses in ON-center and OFF-center bipolar cells? The dendrites of ON-center and OFF-center cone bipolar cells express the same type of $GABA_A$ receptor (Greferath et al., 1994; Vardi and Sterling, 1994; Wassle et al., 1998; Shields et al., 2000), but the effect of $GABA_A$ receptor activation, which opens chloride channels, depends on the chloride equilibrium potential (E_{Cl}) which in turn depends on the activity of the chloride co-transporters, Na-K-2Cl (NKCC) and K-Cl (KCC). These chloride co-transporters regulate intracellular chloride levels (Fig. 10) and thereby regulate the polarity of the response to $GABA_A$ receptor activation (Russell, 2000; Payne et al., 2003; Gamba, 2005; Blaesse et al., 2009; Wright et al., 2011). When NKCC is active, it uses the sodium gradient to accumulate chloride. Increases in intracellular chloride shift E_{Cl} to more positive potentials. If E_{Cl} is more positive than the resting membrane potential, then $GABA_A$ receptor activation will cause an efflux of chloride and membrane depolarization (Russell, 2000; Payne et al., 2003; Gamba, 2005; Blaesse et al., 2009; Wright et al., 2011). Conversely, KCC uses the potassium gradient to extrude chloride. If intracellular chloride is decreased so that E_{Cl} is more negative than the resting potential, then $GABA_A$ receptor activation results in an influx of chloride and membrane hyperpolarization.

Experimental results generally support the idea that the E_{Cl} of ON-center bipolar cell dendrites is more positive than the resting membrane potential and the E_{Cl} of OFF-center bipolar cell dendrites is more negative than the resting potential. Miller and Dacheux (1976) found that bipolar cell surrounds in the mudpuppy retina were reduced when the level of extracellular chloride was decreased, and using chloride-sensitive microelectrodes to measure intracellular chloride, Miller and Dacheux (1983) reported that the E_{Cl} of ON-bipolar cells in the mudpuppy retina was more positive than the resting membrane potential. It has also been shown that ON-center cone bipolar cell dendrites express NKCC and OFF-center cone bipolar cell dendrites express the KCC subtype, KCC2 (Vardi et al., 2000; Vu et al., 2000), findings that are consistent with the idea that the E_{Cl} of ON-center bipolar cell dendrites is more positive than the resting membrane potential and the E_{Cl} of OFF-center bipolar cell dendrites is more negative than the resting potential. Using ratiometric two-photon imaging of Clomeleon, a fluorescent chloride indicator transgenetically expressed in mouse type 7 and type 9 ON-cone bipolar cells, Duebel et al. (2006) observed that the $[Cl^-]_i$ was approximately 20 mM higher in the dendrites than in the soma of type 9 ON-cone bipolar cells. This somatodendritic chloride gradient could permit sufficient net chloride efflux from dendrites upon $GABA_A$ receptor activation to produce a depolarization. In addition, inhibitors of chloride cotransport reduced the somatodendritic chloride gradient of type 9 ON-cone bipolar cells. In type 7 ON-cone bipolar cells, $[Cl^-]_i$ was only slightly higher (~4 mM) in dendrites compared to the soma; this somatodendritic chloride gradient is probably not sufficient to produce a depolarization upon $GABA_A$ receptor activation. Using gramicidin perforated patch-clamp recordings that do not appreciably alter intracellular chloride, Billups and Attwell (2002) observed slightly elevated $[Cl^-]_i$ levels in dendrites of rat ON-bipolar cells, but concluded that these levels were not sufficient to produce GABA-mediated depolarization. Satoh et al. (2001) found using gramicidin perforated patch-clamp recordings that GABA hyperpolarized mouse cone bipolar cells but depolarized rod bipolar cells.

How can these apparently conflicting measurements of $[Cl^-]_i$ gradients in rodent bipolar cells be reconciled? Taken together, these studies seem to suggest that the $[Cl^-]_i$ in the dendrites of one type of mouse ON-cone bipolar cell and of rod bipolar cells, which both express NKCC (Vardi et al., 2000; Vu et al., 2000), may exceed somatic $[Cl^-]_i$ by ~ 20 mM (Satoh et al., 2001; Varela et al., 2005; Duebel et al., 2006). However, electrical and $[Cl^-]_i$ measurements also suggest that the $[Cl^-]_i$ in the dendrites of other mouse ON-cone bipolar cell types (Satoh et al., 2001; Duebel et al., 2006) and in rat ON bipolar cells (Billups and Attwell, 2002) is similar to that in their somata, a finding that seems at odds with NKCC activity in the dendrites of many ON-cone bipolar cell types. It is possible, however, that the absence of high $[Cl^-]_i$ in some ON-cone bipolar cell types may be due to low NKCC activity resulting from 1) the use of a low, non-physiological (room) temperature during *in vitro* experiments (Satoh et al., 2001; Billups and Attwell, 2002; Varela et al., 2005; Duebel et al., 2006) since NKCC activity in mammalian cells is significantly reduced at room temperature, 2) performance of the studies under dark-adapted conditions (Satoh et al., 2001; Billups and Attwell, 2002; Varela et al., 2005; Duebel et al., 2006), rather than light-adapted conditions when bipolar cell surrounds are strongest (Dacey et al., 2000; Fahey and Burkhardt, 2003; see Section 2.2), and/or 3) slicing of the retinas (Satoh et al., 2001; Billups and Attwell, 2002; Varela et al., 2005) which can physically eliminate neural connections and limit neural and neurotransmitter interactions (see Section 2.1).

In addition to expression of the chloride cotransporters, NKCC and KCC2 (Vardi et al., 2000; Vu et al., 2000), immunocytochemical studies have consistently found that the dendrites of bipolar cells in mammalian and non-mammalian retinas express $GABA_A$ receptor α_1, $\beta_{2/3}$, and γ_2 subunits and the $GABA_C$ receptor ρ subunit (Greferath et al., 1994, 1995; Vardi and Sterling, 1994; Wassle et al., 1998; Haverkamp et al., 2000). The $GABA_C$ receptor ρ subunit may be expressed at different synapses than $GABA_A$ receptor subunits (Koulen et al., 1998). $GABA_A$ receptor subunits were expressed in a specific region of cone bipolar cell dendrites adjacent to horizontal cell dendrites in rabbits, mice, monkey and human retinas (Greferath et al., 1994; Vardi and Sterling, 1994; Haverkamp et al., 2000). The close spatial proximity of $GABA_A$ receptor subunits on cone bipolar cell dendrites with the vesicular GABA transporter on horizontal cell dendrites (Haverkamp et al., 2000), a likely GABA release site, is consistent with the suggestion that horizontal cells signal directly to bipolar cells through the release of GABA and the activation of $GABA_A$ receptors. As described in detail in Section 3.1.1, substantial evidence has accumulated from immunocytochemical and physiological studies in mammalian and non-mammalian retinas that horizontal cells have the means to release GABA when they are depolarized.

As discussed above, there are a number of observations which suggest that activation of $GABA_A$ receptors on cone bipolar cell dendrites may mediate the opposite polarity, surround light responses of ON-center and OFF-center cone bipolar cells: 1) horizontal cells have the synaptic machinery to release GABA, 2) depolarized horizontal cells can release GABA, 3) cone (and rod) bipolar cell dendrites express $GABA_A$ (and $GABA_C$) receptors, 4) ON-center cone bipolar cell dendrites express NKCC and OFF-center cone bipolar cell dendrites express KCC2, 5) the somatodendritic $[Cl^-]_i$ gradient in mouse type 9 ON-cone bipolar cells is sufficiently large to evoke a net chloride efflux following $GABA_A$ receptor activation and thereby produce membrane depolarization, and 6) bipolar cell dendrites respond to the exogenous application of GABA (Qian et al., 1997; Wassle et al., 1998; Kaneda et al., 2000; Shields et al., 2000; Du and Yang, 2000). A direct test of the hypothesis that activation of $GABA_A$ receptors on cone bipolar cell dendrites mediates cone bipolar cell surrounds would be to determine whether $GABA_A$ antagonists affect cone-driven bipolar cell surrounds under maintained light-adapted conditions, but this has not yet been done. In mixed rod-cone bipolar cells from salamander retina maintained under mid to high scotopic illumination conditions, Hare and Owen (1996) found that bath application of GABA,

various $GABA_{A/B/C}$ antagonists, glycine, and the glycine antagonist strychnine had no effect on surround light responses. Interestingly, application of the GABA analogue D-aminovaleric acid, in conjunction with picrotoxin, a $GABA_{A/C}$ antagonist, blocked the surround responses of both ON-center and OFF-center rod-driven bipolar cells, but had no effect on horizontal cell responses or the center responses of bipolar cells, suggesting that a novel receptor sensitive to D-aminovaleric acid and picrotoxin may be involved under mid to high scotopic illumination conditions. In contrast to this study performed under scotopic conditions, Stone and Schutte (1991) studied bipolar cells from *Xenopus* retina under illumination condi tions in which these cells were purely cone-driven. They found that the hyperpolarizing surround response of ON-center bipolar cells and hyperpolarizing center response of OFF-center bipolar cells were both reduced by 80–90% by bath application of GABA, but the depolarizing surround response of OFF-center bipolar cells and the depolarizing center response of ON-center bipolar cells were only reduced 0–10 % by GABA (Stone and Schutte, 1991). On the other hand, glycine eliminated the surround responses of ON-center and OFF-center cone-driven bipolar cells and slightly reduced the center responses. Although these results are consistent with the idea that GABA (and glycine) may contribute in part to the surround responses of cone-driven bipolar cells, bath application of endogenous agonists can activate non-saturated GABA (and glycine) receptors throughout the retina, thereby complicating interpretation of the results.

Although the effects of $GABA_A$ antagonists on cone-driven bipolar cell surrounds have not been examined, a number of investigations have tested the effects of $GABA_A$ (and $GABA_C$) antagonists on the center-surround receptive field organization of ganglion cells. However, one must exercise caution in interpreting the effects of $GABA_A$ (and $GABA_C$) antagonists on ganglion cell surround responses due to uncertainty concerning the outer and inner retinal sites of their actions and the strong possibility that they block GABA receptors at many retinal locations. In support of this cautionary note, ganglion cell studies have produced apparently conflicting results, even when one takes into account the level of ambient illumination under which the retinas were maintained. For example, when ganglion cells have been studied under mesopic conditions, all of the studies reported that bicuculline, a $GABA_A$ receptor antagonist, and picrotoxin reduced ganglion cell surrounds, but the specific ganglion cell types that were affected varied. Using *in vivo* rabbit retina, picrotoxin shifted the center-surround balance of most ganglion cell types to more center-dominated responses and eliminated the surround in ON-center sustained cells (Caldwell and Daw, 1978). In contrast, Flores-Herr et al. (2001) found that picrotoxinin, the active component of picrotoxin, strongly reduced surround antagonism in ON-center and OFF-center sustained and transient rabbit ganglion cells (Fig. 11). Saito (1983) reported that bicuculline strongly reduced the surround of cat ON-center transient (Y-type) ganglion cells, but had no effect on ON-center sustained (X-type) ganglion cells, and reduced both center and surround responses of OFF-center transient and sustained cells. When ganglion cells have been studied under photopic conditions, picrotoxin has been reported to have little or no effect on ganglion cell surround responses (cat: Frishman and Linsenmeier, 1982; monkey: McMahon et al., 2004), but bicuculline was found to strongly reduce surround responses of cat ON-center sustained and transient ganglion cells, but had no effect on OFF-center sustained and transient cells (Ikeda and Sheardown, 1983). It seems likely that differences in the experimental conditions, such as the electrical recording and light stimulation conditions, the intensity and duration of the background illumination, the time of day, and the experimental preparation itself (i.e., *in vitro* vs. *in vivo*; species) may account for many of these apparently conflicting findings. It is also possible that the inner and outer retinas may produce different types of surround that can be measured at the ganglion cell level. As mentioned in section 2.1, in addition to an antagonistic, relatively sustained surround response that originates in the outer retina and is strongest following prolonged light adaptation (Kuffler, 1953; Barlow and Levick, 1969; Werblin and Dowling, 1969;

Hammond, 1975; Thibos and Werblin, 1978a; Dacey et al., 2000; Fahey and Burkhardt, 2003), ganglion cells have a change-sensitive or transient surround that originates in the inner plexiform layer (Werblin, 1972; Werblin and Copenhagen, 1974; Thibos and Werblin, 1978b; Cook and McReynolds, 1998) and a disinhibitory surround which originates in the inner plexiform layer that is larger in size than the classic antagonistic surround (Ikeda and Wright, 1972; Li et al., 1992; Shou et al., 2000; Troy and Shou, 2002). Moreover, evidence suggests that these different surrounds are mediated by different pathways and transmitters (Cook and McReynolds, 1998; Lukasiewicz, 2005; Zhang and Wu, 2009). Finally, many commonly used $GABA_A$ antagonists, when employed at concentrations that fully block $GABA_A$ receptors (e.g., picrotoxin (100 μM), bicuculline (100 μM), gabazine (SR95531; 20 μM)), can also significantly inhibit glycine receptor-mediated currents of ganglion and amacrine cells in the retina (Han et al., 2005; Li and Slaughter, 2007), suggesting the possibility that some of the reported effects of these drugs on ganglion cell surround responses may have resulted in part from blocking endogenous glycine receptors. In support of the possibility that glycine receptors contribute to ganglion cell surround responses are the findings that strychnine reduced the surround responses of 1) cat ON-center sustained (X-type) ganglion cells under mesopic conditions (Saito, 1983) and 2) cat OFF-center sustained (X-type) and transient (Y-type) ganglion cells under photopic conditions (Ikeda and Sheardown, 1983). In contrast to less selective $GABA_A$ antagonists such as bicuculline and picrotoxin, gabazine is about two orders of magnitude more potent at blocking $GABA_A$ than glycine receptors and can readily discriminate between these receptors if used at a concentration (5 μM) that fully blocks $GABA_A$ receptors but has negligible effects on glycine receptors (Li and Slaughter, 2007). In contrast to the commonly used $GABA_A$ antagonists, the $GABA_C$ antagonists TPMPA and I4AA are ineffective at blocking glycine receptors.

Probably the most convincing evidence in support of the idea that $GABA_A$ receptors mediate generation of the surround in the outer retina under light-adapted conditions was provided by a ganglion cell study that utilized a technique to distinguish outer from inner retina activity (Flores-Herr et al., 2001). Under maintained mesopic background illumination conditions, rabbit ganglion cells were voltage-clamped at the chloride reversal potential to reveal the excitatory signal arriving from bipolar cells or at the Na/K reversal potential to reveal the presence of direct GABA inhibition to ganglion cells. When ON-center and OFF-center ganglion cells were voltage-clamped at the chloride reversal potential, the cells exhibited strong surround antagonism that was almost completely blocked by picrotoxinin (Fig. 11), a finding that strongly suggests that $GABA_{A/C}$ receptors contribute significantly to bipolar cell surround antagonism under mesopic background illumination conditions. Moreover, picrotoxinin, not only greatly reduced surround antagonism (Fig. 11B–D), but also converted the phasic light responses of OFF-center transient ganglion cells into more sustained responses, suggesting that GABA signals in the outer retina under mesopic illumination conditions transform tonic responses into phasic responses. When ganglion cells were voltage-clamped at 0 mV, the reversal potential for non-specific cation currents, picrotoxinin blocked their surround responses, a result that suggests that direct GABA inhibition to rabbit ganglion cells also contributes to surround antagonism. Although the findings of Flores-Herr et al. (2001) strongly suggest that $GABA_{A/C}$ receptors contribute significantly to bipolar cell surround antagonism under mesopic background illumination conditions, it would clearly be worthwhile to perform similar experiments at photopic and scotopic background illumination conditions utilizing gabazine (5 μM) and TPMPA (50 μM) at concentrations at which they selectively block $GABA_A$ and $GABA_C$ receptors, respectively.

It is perhaps important to note that previous evidence that has been viewed as suggesting that horizontal cells contribute to bipolar cell surrounds via feedback to cones is also

consistent with direct horizontal cell signaling to bipolar cells via GABA-gated chloride channels. For example, several labs have reported that strong central illumination can suppress the antagonistic surround responses evoked in ON-center and OFF-center bipolar cells by peripheral illumination (Schwartz, 1974; Lasansky, 1980; Skrzypek and Werblin, 1983). If the E_{Cl} is more positive than the resting membrane potential in ON-center bipolar cells and more negative than the resting membrane potential in OFF-center bipolar cells (see Fig. 10 here and associated text), then central illumination will polarize the bipolar cells in the direction of E_{Cl} for the surround input, thus reducing the effect of direct horizontal cell input.

5. Functions of horizontal cell feedback and feed-forward pathways

Based on studies of human vision and retinal processing, it is well established that retinal circuits are tuned for maximum spatial acuity during the day under light-adapted conditions and for maximum sensitivity to large dim objects at night in the dark (Warrant, 1999; Reeves, 2004; Ribelayga et al., 2008). Although it has been clear for several decades that cone pathway function in the day mediates spatial acuity and rod pathway function at night mediates visual sensitivity to dim light, the retinal pathways and mechanisms that perform these functions and the adaptive processes that switch them back and forth as the visual environment slowly changes over the course of the day and night are still unresolved. Below, we describe current ideas of how the receptive field surround enhances spatial acuity under light-adapted conditions during the day. In addition, we consider other functions that have been ascribed to feedback from horizontal cells to cones and to horizontal cell feed-forward input to bipolar cells including temporal filtering, light adaptation, color opponency, and color constancy (Burkhardt, 1993; VanLeeuwen et al., 2007).

5.1. Function of the receptive field surround

Foremost among the putative functions of horizontal cell to cone feedback and feed-forward input from horizontal cells to bipolar cells is that they may contribute to the formation of center-surround receptive field antagonism in bipolar and ganglion cells and enhance the spatial discrimination ability of the cells. The presence of antagonistic center-surround receptive fields can enhance the ability of ganglion cells to inform the central visual system about whether local regions of the visual scene are brighter or darker than the background. It has been proposed that the ability of bipolar and ganglion cells to report fine spatial details about the visual environment results from subtraction of the surround signal (which pools visual information from a relatively wide area) from the center signal (which responds to local illumination) (Ratliff and Hartline, 1959; Marr, 1982; Srinivasan et al., 1982; Tsukamoto et al., 1990; Atick and Redlich, 1990). In other words, according to this hypothesis, the function of the antagonistic surround is to provide a prediction of the mean luminance that is then subtracted from the output of bipolar cells, thus enhancing the signal of local contrast.

A second proposal concerning surround function utilizes the above idea of spatial pooling by the surround, and also incorporates a theory first proposed by Barlow (1961) concerning visual system processing. According to Barlow (1961, 1989), the spiking of optic nerve fibers that comprises the output of the retina has a limited capacity and so there is an evolutionary advantage for the retina to utilize fewer spikes to communicate redundant information. Because there is redundancy in natural visual scenes due to spatial and temporal correlations arising from the presence of objects and of background regions of constant luminance, it has been proposed that the antagonistic center-surround receptive field reduces spatial correlations in the messages carried by ganglion cells (and bipolar cells) that have nearby overlapping receptive fields (Atick and Redlich, 1992) and reduces temporal correlations between the spikes of single ganglion cells (Dong and Atick, 1995).

This model predicts the presence of antagonistic center-surround receptive fields as well as modulation of the surround by the ambient light level. Moreover, recent electrophysiological evidence suggests that the retina improves the efficiency of information coding in response to the natural visual environment. Specifically, the spatial and temporal characteristics of the center-surround receptive field, including that the surround is delayed relative to the center, reduce both low spatial and temporal frequencies in the ganglion cell spike train, decreasing information from the visual environment that varies little over space and time (Frishman et al., 1987; Dan et al., 1996; Tokutake and Freed, 2008).

As reviewed in section 2.4, a key role for horizontal cells in establishing antagonistic surrounds was provided by experiments showing that electrical stimulation of horizontal cells evoked opposite polarity responses in nearby bipolar and ganglion cells (Naka and Nye, 1971; Marchiafava, 1978; Toyoda and Tonosaki, 1978; Toyoda and Kujiraoka, 1982; Naka, 1982; Sakuranaga and Naka, 1985; Mangel, 1991). Although these experiments did not distinguish between feedback from horizontal cells onto cones and direct horizontal cell input to bipolar cells, pharmacological evidence suggests that feedback to cones helps to establish antagonistic surrounds in bipolar and ganglion cells. Horizontal cell to cone feedback can be inhibited by bath application of submillimolar concentrations of cobalt (Thoreson and Burkhardt, 1990). Application of low cobalt also inhibited responses evoked by stimulation of the receptive field surround in bipolar and ganglion cells from turtle retina (Vigh and Witkovsky, 1999), salamander ganglion cells (Ichinose and Lukasiewicz, 2005), and parasol ganglion cells of monkey retina (McMahon et al., 2004). As discussed earlier, pharmacological inhibition of horizontal cell to cone feedback can also be achieved by bath application of the pH buffer HEPES (Hirasawa and Kaneko, 2003) and HEPES inhibits receptive field surrounds in midget and parasol ganglion cells from primate retina (Davenport et al., 2008; Crook et al., 2011). Consistent with a role for horizontal cell to cone feedback in contrast perception, diminished horizontal cell to cone feedback effects in fish lacking connexin 55.5 were accompanied by diminished contrast sensitivity measured with an optokinetic assay (Klaassen et al., 2011). As discussed in Section 4.1, use of the glutamate analogue APB, which selectively blocks photoreceptor cell input to ON-center bipolar cells (Slaughter and Miller, 1981), has shown that direct horizontal cell input to ON-center bipolar cells can also contribute to both surround antagonism and surround activation (Yang and Wu, 1991; Hare and Owen, 1992), especially when bipolar cells are purely cone-driven (Fahey and Burkhardt, 2003). These data suggest roles for horizontal cell to cone feedback and direct horizontal cell feed-forward input to bipolar cells in the formation of bipolar cell surrounds.

5.2 Temporal frequency characteristics

Horizontal cell feedback and feed-forward interactions may also shape the temporal frequency characteristics of bipolar cells. As discussed in Section 2.1, under maintained light-adapted conditions in the mid-mesopic to photopic range, cone-driven bipolar cell light responses of the same polarity (i.e., depolarization or hyperpolarization) are similar in waveform and amplitude irrespective of whether they are elicited by center or surround stimulation. However, under these light-adapted conditions, the latency of the cone-driven bipolar cell surround light response is approximately 50 ms slower than the latency of the center response. As the maintained ambient light level increases from the mesopic to the photopic range, the similarity in waveform and amplitude evoked by center and surround stimulation may account in part for the decrease in the tonic component of bipolar cell light responses, and the latency difference of the center and surround may contribute to the increase in the phasic component of bipolar cell light responses.

The delay observed in the depolarizing feedback responses of turtle cones (Baylor et al., 1971, see Fig. 8) suggested that some of the delay in the surround response may originate

with horizontal cell feedback to cones. Surprisingly, careful measurements of feedback-induced changes in cone I_{Ca} showed no discernible delay in the initiation of feedback effects (Kamermans et al., 2001). The absence of a significant delay in the initiation of feedback could account for the observation that horizontal cell to cone feedback produces minimal temporal filtering of horizontal cell light responses (Tranchina et al. 1983). This lack of a delay is also consistent with a non-synaptic (e.g., ephaptic) mechanism for horizontal cell feedback. It is generally desirable to have short delays in negative feedback loops because this allows circuits to settle rapidly into a new steady state; long delays can permit oscillations and instabilities. However, it also important to note that although feedback effects on I_{Ca} were initiated with little or no delay, the peak effect of feedback on I_{Ca} was nevertheless attained after the peak of the center light response (Kamermans et al., 2001), consistent with observations of feedback-induced changes in cone membrane potential by Baylor et al. (1971) and many other investigators.

5.3 Light adaptation

Horizontal cell to cone feedback can also contribute to light adaptation. In turtle cones, illumination of the receptive field surround causes a depolarizing rollback that counters the desensitizing hyperpolarization induced by light. By increasing the cone's operating range, this depolarization can restore the sensitivity to incremental light flashes (Burkhardt, 1995). In addition to effects on cone membrane potential, horizontal cell feedback can contribute to post-receptoral adaptation by adjusting the strength of cone synaptic output. Recall that light-evoked hyperpolarization of horizontal cells causes a negative shift in the current-voltage relationship for cone I_{Ca} (Fig. 8). This shift increases I_{Ca} at membrane potentials within the normal physiological voltage range and thereby increases the release of glutamate. The increase in release restores the operating range over which light can modulate synaptic output. These adjustments in release are dynamic: as horizontal cells hyperpolarize to brief light flashes, the strength of feedback from horizontal cells changes. This effect, which has been termed lateral gain control, produces an increase in the center responses of post-synaptic neurons (VanLeeuwen et al., 2009). This enhancement of cone synaptic output caused by horizontal cell hyperpolarization may explain the enhancement of horizontal cell responses to small spots applied in the presence of weak background illumination (Pflug et al., 1990; Nelson et al., 1990). The enhancement of cone synaptic output due to lateral gain control is likely to diminish with maintained background illumination as both cones and horizontal cells depolarize.

5.4 Color opponency and color constancy

Another proposed role for horizontal cell to cone feedback involves the generation of color-opponency in the retina. Color opponency was originally proposed by Ewald Hering and is the idea that color is processed in opponent pairs (red/green, blue/yellow, and black/white) (Hering, 1878; Hurvich and Jameson, 1957). Color opponent responses emerge very early in the visual system. For example, although mammals appear to lack color-opponent horizontal cells, the existence of this cell type in non-mammalian vertebrates has been extensively documented (see review by Twig et al., 2003). Moreover, clear evidence indicates that the color opponent light responses of fish horizontal cells are strongest following prolonged background illumination and absent following prolonged dark adaptation (Djamgoz et al., 1988; Yang et al., 1994). In fish retina, biphasic color-opponent horizontal cells which hyperpolarize to green light and depolarize to red light receive synaptic inputs directly from green-sensitive but not red-sensitive cones (Stell et al., 1975; Witkovsky et al., 1979). Triphasic horizontal cells in fish retina, which hyperpolarize to blue and red light but depolarize to green light, appear to be contacted only by blue-sensitive cones (Stell et al., 1975; Stell and Lightfoot, 1975). This selective arrangement of contacts is not present in turtle retina where Ohtsuka and Kouyama (1985, 1986) found that many red-sensitive cones

directly contact both biphasic and triphasic horizontal cells. However, observations in teleost fish retina have led to the hypothesis that depolarizing responses of biphasic and triphasic horizontal cells to red light, as well as the hyperpolarizing responses of triphasic horizontal cells to green light, are due to negative feedback from horizontal cells onto cones. In support of this hypothesis, annular illumination with red light can evoke depolarizing responses in green-sensitive cones (Fuortes et al., 1973). Similarly, blue-yellow opponent responses have also been observed in primate S cones (Packer et al., 2010). In these cells, centered spots of blue light evoked outward currents arising from phototransduction in S cone outer segments whereas illumination of the receptive field surround with yellow light that preferentially stimulates L and M cones evoked inward currents arising from a negative shift in the current/voltage relationship of I_{Ca} (Packer et al., 2010). Supporting the hypothesis that these opponent responses in S cones are due to horizontal cell feedback, the inward currents evoked by surround illumination were abolished by blockade of horizontal cell light responses with glutamate receptor antagonists (Packer et al., 2010). Further evidence that horizontal cell to cone feedback contributes to depolarizing responses of color opponent horizontal cells comes from experiments in which the injection of hyperpolarizing current into luminosity (non-color opponent) horizontal cells was found to evoke depolarizing responses in nearby color-opponent horizontal cells (Toyoda and Fujimoto, 1983). In addition, selective pharmacological inhibition of cone feedback with HEPES or a low concentration of cobalt selectively inhibits depolarizing responses, but not hyperpolarizing responses, of color-opponent horizontal cells (Vigh and Witkovsky, 1999; Fahrenfort et al., 2009).

Although the evidence summarized above indicates that horizontal cell to cone feedback is important for the generation of depolarizing responses in biphasic color-opponent horizontal cells, there is also evidence that other mechanisms may contribute (reviewed by Burkhardt, 1993). One argument marshaled against a role for feedback is that depolarizing responses to red light are not consistently observed in green-sensitive cones. However, this does not necessarily argue against a role for feedback but may simply reflect the fact that the modulation of cone I_{Ca} by horizontal cell feedback can alter synaptic release without necessarily generating large depolarizing responses in cones (see Section 3.1). Another argument against a role for feedback in generating the depolarizing responses of biphasic color-opponent horizontal cells to red light is that the latency to these responses should be equal to or shorter than the latency of hyperpolarizing responses to green light. While this appears to be true for goldfish retina (Kamermans et al., 2001), the latencies of depolarizing responses are shorter than those of hyperpolarizing responses in color-opponent horizontal cells from carp, turtle and bowfin retina (Fuortes and Simon, 1974; Wheeler and Naka, 1977; Gottesman and Burkhardt, 1987; Asi and Perlman, 1998). A third argument for contributions from other mechanisms comes from receptive field measurements. Luminosity-type horizontal cells have large receptive fields when gap junctional coupling is strong under maintained scotopic, but not photopic, background illumination, and so the effects of horizontal cell feedback increase as the diameter of a light flash is expanded (Baylor et al., 1971; Burkhardt 1977; Packer et al., 2010) under scotopic conditions. However, expanding the stimulus diameter does not appreciably enhance the depolarizing responses of color-opponent horizontal cells in various species (e.g., Norton et al., 1968; Saito et al., 1974; Lamb, 1976; Teranishi et al., 1982; Burkhardt and Hassin, 1978; Gottesman and Burkhardt, 1987; Stone et al., 1990). These results suggest that although horizontal cell feedback may be important for the generation of color opponent responses in horizontal cells, other mechanisms are also likely to be involved.

In addition to color-opponent horizontal cells, non-mammalian vertebrates also possess color-opponent bipolar cells (Kaneko, 1973; Yazulla, 1976; Mitari et al., 1978; Kaneko and Tachibana, 1981; Ammermuller et al., 1995; Ventura et al., 1999; Shimbo et al., 2000;

Wong and Dowling, 2005). They have not been as thoroughly investigated as color opponent horizontal cells, but the pattern of anatomical connections to these cells has led to the suggestion that horizontal cell feedback to cones may also contribute to the generation of color opponency in bipolar cells (Stell, 1983).

In primate retina, there is evidence that the opponent surrounds in red-green opponent midget ganglion cells arise from horizontal cell to cone feedback in the outer retina (Crook et al., 2011). In midget ganglion cells, the center of the receptive field is created by inputs from a single midget bipolar cell which contacts an individual M or L cone. Although the wiring responsible for color opponency in these cells remains controversial (Solomon and Lennie, 2007; Lee et al., 2010), analysis of the conductances underlying the light responses of midget ganglion cells suggests that color opponency arises presynaptically in midget bipolar cells (Crook et al., 2011). Furthermore, blockade of horizontal feedback to cones with HEPES abolished color opponent surrounds in midget ganglion cells (Crook et al., 2011). One testable prediction of the hypothesis that negative feedback from horizontal cells to cones is responsible for opponent surrounds in midget ganglion cells is that midget bipolar cells should also exhibit color opponency.

Blue-yellow opponency in mammalian retina involves a specialized S cone bipolar cell which carries blue ON signals to blue ON ganglion cells (Solomon and Lennie, 2007; Lee et al., 2010; Puller and Haverkamp, 2011). There are two suggestions for the origins of opponent OFF yellow signals in these ganglion cells. The presence of antagonistic yellow surrounds in both S cones (Packer et al., 2007) and blue ON ganglion cells (Field et al., 2007) has led to the proposal that opponent surrounds arise from horizontal cell feedback onto S cone terminals. However, other experiments have found that blue ON signals and yellow OFF signals are spatially coextensive in blue ON ganglion cells, leading to the suggestion that opponent yellow OFF signals derive from inputs of OFF bipolar cells that receive mixed M and L cone inputs (Crook et al., 2009). In this study, the authors postulated that the inhibitory surrounds in M and L cones may cancel the inhibitory surrounds of S cones when these inputs are summed at the level of the ganglion cell (Crook et al., 2009).

Color constancy may also have its origins in horizontal cell to cone feedback (VanLeeuwen et al., 2007). Color constancy is the ability of colors to appear fairly constant despite large changes in the spectral composition of incident illumination. Although cortical mechanisms also contribute (Ruttiger et al., 1999; Conway, 2009; Hurlbert and Wolf, 2004), color constancy involves contributions from retinal neurons (Poppel, 1986). The maintenance of color constancy operates over a large spatial scale and occurs too rapidly to be explained entirely by adaptation within cones themselves (Rinner and Gegenfurtner, 2002). VanLeeuwen et al. (2007) therefore proposed that subtraction of spectrally mixed cone inputs via horizontal cell to cone feedback may be a key early step in maintaining color constancy.

Many of the functions described above result from the ability of horizontal cell feedback onto cones to subtract mean light levels from local changes in intensity. The different functions reflect operation of this feedback circuit in different domains: spatial, temporal and chromatic. In the spatial domain, horizontal cell to cone feedback leads to the formation of center-surround receptive fields and enhancement of local contrast changes. In the temporal domain, the ongoing subtraction of mean luminance allows the synapse to adjust its output to continually changing light levels. And in the chromatic domain, continual subtraction of the changing spectral balance of cone inputs into horizontal cells may contribute to color constancy.

6. Other types of lateral interaction in the outer plexiform layer

6.1 Negative feedback from horizontal cells to rods

Early studies concluded that horizontal cells do not provide feedback to rods, largely because illumination of the receptive field surround with an annulus or large spot failed to evoke a depolarizing response in rods (Brown and Pinto, 1974; Copenhagen and Owen, 1976; Lasansky, 1986). However, as discussed in Section 3.1, feedback effects on I_{Ca} can often produce little or no detectable membrane potential change in cones. In addition, many of these experiments were done in amphibian rods that were extensively coupled to one another by gap junctions. This creates large receptive fields that overlap extensively with horizontal cell receptive fields (Copenhagen and Owen, 1976; Attwell et al., 1984; Zhang and Wu, 2005) and can obscure feedback interactions.

Results from Normann and Pochobradsky (1976) suggested the possibility of horizontal cell to rod feedback. They found that wide-field illumination stimulated delayed oscillations in the rod membrane potential which, like horizontal cell light responses, were abolished by application of aspartate. In addition, axon terminals of B-type horizontal cells from mammalian retina make synaptic contacts exclusively with rods (Hirano et al., 2005; Pan and Massey, 2007). If B-type horizontal cells do not provide feedback to rods, then this would appear to be a dead-end circuit.

Thoreson et al. (2008) re-examined the question of whether horizontal cells provide feedback to rods by obtaining whole cell recordings simultaneously from synaptically-coupled rods and horizontal cells. They found that the effects of changing horizontal cell membrane potential on rod I_{Ca} were nearly identical to horizontal cell effects on cone I_{Ca}. Hyperpolarization of horizontal cells increased the amplitude of rod I_{Ca} and caused it to activate at more negative potentials; depolarizing horizontal cells decreased the amplitude of rod I_{Ca} and caused it to activate at more positive potentials. In both mouse and salamander retina, these effects on I_{Ca} and corresponding effects on intraterminal Ca^{2+}levels were also observed when horizontal cell membrane potential was manipulated chemically with glutamate agonists or antagonists (Babai and Thoreson, 2009). Furthermore, hyperpolarizing horizontal cells with light also caused a negative shift in I_{Ca} from rods lacking outer segments and this effect could be blocked with glutamate antagonists(Thoreson et al., 2008). Like horizontal cell to cone feedback, all of these effects were blocked by increased pH buffering with HEPES suggesting that a similar mechanism is responsible for horizontal cell feedback to both rods and cones(Thoreson et al., 2008; Babai and Thoreson, 2009). It is also worth noting that horizontal cell dendrites enter a deep invagination in the rod terminal (Dowling, 2012), which, like the cone synapse, could potentially support an ephaptic mechanism. The discovery of horizontal cell feedback to mouse rods and the finding that it utilizes similar mechanisms as horizontal cell to cone feedback raises the possibility that mouse genetic models could be used to analyze feedback mechanisms.

The functions of horizontal cell to rod feedback have not been investigated directly but some possibilities are suggested by proposed functions for horizontal cell to cone feedback. As in cones, horizontal cell to rod feedback may enhance local contrast and contribute to post-receptoral light adaptation by subtracting the average level of surrounding illumination (Burkhardt, 1995; Lipin et al., 2010). Feedback to rods might also contribute to the formation of center-surround receptive fields. As discussed earlier, although substantially weaker than those observed in light-adapted retina, retinal ganglion cells can exhibit surrounds under scotopic conditions. In amphibian retina, bipolar cells can also exhibit a center-surround organization when illuminated with light levels that should stimulate only rods (Hare and Owen, 1990). In mammalian retina, rod-driven AII amacrine cells exhibit a center-surround organization but surround responses are not evident in rod bipolar cells

(Bloomfield and Xin, 2000) suggesting that the center-surround organization in AII amacrine cells may arise from interactions in the inner plexiform layer. On the other hand, the noisy response waveforms of rod bipolar cells may simply make it difficult to see weak surround responses in these cells. It is also possible that rod-driven surrounds may only be evident at higher scotopic levels when rod signals may pass through rod-driven OFF bipolar cells (Li et al., 2004; Mataruga et al., 2007). One test of the hypothesis that horizontal cell to rod feedback contributes to formation of receptive field surrounds in the mammalian retina would be to examine whether rod-mediated surrounds in ganglion cells or AII amacrine cells can be blocked by HEPES.

Horizontal cell to cone feedback has been proposed to enhance temporal frequency response characteristics (Burkhardt, 1993). By making post-synaptic responses more transient, feedback-mediated increases in synaptic transmission from rods might also improve the ability of bipolar cells to follow flickering stimuli under dim light conditions.

As discussed in Section 5.4, horizontal cell feedback to cones may contribute to color opponency. Many non-mammalian horizontal cells contact both rods and cones (Fain, 1975; Toyoda et al., 1978; Leeper and Copenhagen, 1979; Hanani and Vallerga, 1980; Wu, 2010) suggesting that horizontal cell feedback to rods might be able to generate color opponent interactions in the rod pathway. Consistent with this possibility, rod/cone-opponency appears to contribute to color opponent responses in mudpuppy horizontal cells (Kim and Miller, 1992). Rod and cone contacts are more strongly segregated in horizontal cells from mammals than amphibians. For example, A-type horizontal cells and the somas of B-type horizontal cells are contacted only by cones whereas the dendrites of B-type horizontal cells are contacted only by rods (Pan and Massey, 2007; Trumpler et al., 2008). But despite this segregation of inputs, the properties of the light responses of the somatic and dendritic compartments of B-type horizontal cells suggest that they both receive a mixture of rod and cone inputs (Trumpler et al., 2008). Thus, akin to the mixing of M and L cones inputs into horizontal cells in the creation of color-opponent surrounds in midget ganglion cells (Crook et al., 2011), negative feedback of a mixture of rod and cone signals onto individual rod or cone terminals has the potential to create spectral opponency under mesopic conditions.

6.2. Positive feedback from horizontal cells to cones

In addition to negative feedback from horizontal cells to cones, there is recent evidence for a positive feedback mechanism linking horizontal cells to cones (Jackman et al., 2011). Negative feedback interactions predict that depolarization of horizontal cells should decrease cone I_{Ca} and thus diminish glutamate release. However, Jackman et al. (2011) found that activation of AMPA receptors in horizontal cells from a variety of species accelerated synaptic release from cones measured with the activity-dependent dye, FM1–43. Laser ablation of horizontal cells abolished this AMPA-stimulated release of glutamate from cones indicating that horizontal cells are required for this effect.

The mechanism by which activation of AMPA receptors in horizontal cells accelerates glutamate release from cones is not yet fully understood. Localized release of caged AMPA using a two-photon microscope caused a very localized increase in intracellular Ca^{2+} levels in horizontal cell dendrites suggesting that this positive feedback mechanism involves horizontal cell Ca^{2+} increases. Inhibiting Ca^{2+} permeable AMPA receptors with philanthotoxin reduced the AMPA-stimulated acceleration of glutamate release from cones suggesting that Ca^{2+}-permeable AMPA receptors on horizontal cell dendrites are responsible for this local elevation of Ca^{2+}. Elevation of Ca^{2+} within horizontal cells by flash photolysis of caged Ca^{2+} increased the rate of vesicle release from presynaptic cones, assessed by measurements of quantal miniature excitatory post-synaptic currents measured in the horizontal cell. Increased release of vesicles from cones presumably requires an

increase in intracellular Ca^{2+} within the cone terminal. However, the stimulation of release from cones does not involve Ca^{2+} entry though L-type Ca^{2+} channels since it occurs in the presence of dihydropyridine antagonists. Ca^{2+} can also enter cones through non-selective cation currents such as cGMP-gated cation channels and store-operated channels (Rieke and Schwartz, 1994; Savchenko et al., 1997; Szikra et al., 2009) but it is not yet clear if these channels are the recipients of positive feedback from horizontal cells. The nature of the retrograde signal from horizontal cells is also unclear. In addition to releasing GABA, horizontal cells may release nitric oxide and endogenous cannabinoids (Savchenko et al., 1997; Blom et al., 2009; Cao and Eldred, 2001; Haberecht et al., 1998; Yazulla, 2008). However, AMPA-stimulated glutamate release was not inhibited by GABA antagonists, nitric oxide donors, or by the endogenous cannabinoid, anandamide (Jackman et al., 2011).

AMPA-stimulated glutamate release from cones was slightly accentuated by blocking negative feedback with HEPES, consistent with an ongoing balance between negative and positive feedback mechanisms (Jackman et al., 2011). Negative feedback involves changes in horizontal cell membrane potential that can spread through gap junctions into neighboring horizontal cells. By contrast, positive feedback may involve localized changes in intracellular Ca^{2+} and thus may operate on a more local scale than negative feedback. As discussed in Section 5.1, negative feedback enhances the detection of contrast changes by removing the spatially averaged light intensity falling over a large area of retina. However, in doing so, negative feedback from horizontal cells also limits the overall rate of release by cones. Since light intensity is encoded in the rate of vesicle release, limiting the rate of release will necessarily limit the rate of information transfer across the synapse. The boost in release provided by positive feedback may be a way for cones to counter this limitation on a local scale.

7. Summary and future directions

By establishing circuits that permit the subtraction of spatially-averaged light levels from local changes in illumination, feedback from horizontal cells to cones and direct horizontal cell input to bipolar cells serve a number of important functions in early visual processing. We began this review in Section 2 by describing the fundamental characteristics of the receptive field surround of bipolar cells, the output neurons of the outer retina. We took this approach because a mechanistic understanding of the bipolar cell receptive field surround should be able to account for its fundamental functional properties and features. Using this functional approach, we then examined evidence concerning the mechanisms that underlie horizontal cell feedback to cones (Section 3), direct horizontal cell feed-forward input to bipolar cells (Section 4), and other less studied forms of lateral interactions in the outer retina (Section 6). In this final section, we summarize our observations on the lateral neural circuits and mechanisms of the outer retina to focus on what is known and provide suggestions for future experimentation that can help to clarify our understanding of lateral pathways in the outer retina.

The circuitry and mechanisms that generate the bipolar cell receptive field surround are not clear and remain controversial, but several fundamental characteristics of the bipolar surround were nonetheless identified in Section 2. First, when background illumination is maintained in the mid-mesopic to photopic range for ~ 20–30 minutes (or until a steady state surround response is achieved), 1) bipolar cells exhibit both surround activation (i.e., a response of opposite polarity, but equal strength, to the center response when only the surround is stimulated by light) and surround antagonism (i.e., stimulation of the surround reduces the amplitude of the center response), 2) the latency of the bipolar cell surround response is greater than that of the center response, and 3) horizontal cells contribute to both surround activation and surround antagonism. Second, a prolonged (~ 20–30 min) reduction

in the intensity of background illumination to scotopic levels produces a minimal surround response with significantly longer latency than that observed after prolonged light adaptation. Finally, bipolar and ganglion cells in mammalian retinas exhibit center but not surround responses at one week of age. Surrounds are first observed at the end of the second postnatal week, at which time they are weakly antagonistic to the center, but do not exhibit surround activation. Surround strength then increases in the next several weeks, reaching adult levels by approximately 1–2 months of age. Surround antagonism reaches an adult level before surround activation.

In section 3, we summarized evidence that antagonistic receptive field surrounds in bipolar cells and ganglion cells involve negative feedback from horizontal cells to cones. However, although negative feedback can account for diminished responsiveness of cells to center stimulation when the receptive field surround is also illuminated (i.e., surround antagonism), it cannot readily explain the generation of opposite polarity responses to illumination of the surround alone (i.e., surround activation). As discussed in section 4.1, surround activation may instead result from direct feed-forward input from horizontal cells to bipolar cells. Other neural pathways, such as inner retinal amacrine cell input to bipolar cell terminals, may also contribute to surround activation. In addition, the recent reports that fish horizontal cells and cones express the photopigment melanopsin (Jenkins et al., 2003; Cheng et al., 2009; Davies et al., 2011) suggest the possibility that a melanopsin-initiated intrinsic response to bright ambient illumination may provide additional means by which horizontal cells and cones contribute to bipolar cell surrounds in fish.

The surround strength of bipolar and ganglion cells gradually increases and decreases as the ambient light level slowly increases and decreases over the course of the day. Therefore, the horizontal cell contribution to the bipolar cell surround should be strongest when the ambient light level is greatest and weakest when the ambient illumination is lowest. However, the difference in the horizontal cell contribution to the bipolar cell surround under maintained bright light-adapted, compared to dark-adapted, conditions may not arise from the horizontal cells themselves. Following both prolonged light and dark adaptation, horizontal cells maintain a depolarized membrane potential (~−35 mV) at rest and hyperpolarize to brief light flashes brighter than the background illumination (skate: Dowling and Ripps, 1971; fish: Ruddock and Svaetichin, 1975; Wang and Mangel, 1996; tiger salamander: Yang et al., 1999; rabbit: Mangel, 1991; Ribelayga and Mangel, 2010; monkey: Zhang et al., 2011). These findings thus suggest that the light/dark adaptive state of the retina alters the effect of horizontal cell light responses on bipolar cell surrounds. Moreover, if the minimal bipolar cell surround following prolonged dark adaptation in the scotopic range is the basal or resting state of horizontal cell to bipolar cell (and/or horizontal cell to cone to bipolar cell) communication, then these findings suggest that the retinal processes initiated by prolonged light adaptation represent the primary means by which the bipolar surround is generated.

The synaptic processes and neural pathways that are modulated by gradual changes in the ambient light level so that horizontal cells remain depolarized and light sensitive following both maintained light and dark adaptation are not clear. It is also not clear how the bipolar surround is strengthened following maintained light adaptation and weakened following maintained dark adaptation. Does the light adaptive-induced increase in the strength of the bipolar surround reflect an increase in negative feedback from horizontal cells to cones, a strengthening of direct horizontal cell feed-forward input to bipolar cells or some other mechanism? It would be useful to compare how negative feedback from horizontal cells to cones and direct horizontal cell input to bipolar cells are modulated by prolonged changes in mean luminance. The mechanisms by which feedback to cones and feed-forward signaling to bipolar cells can be altered by a maintained change in the intensity of background

illumination also need to be addressed. In addition, the relative contributions of different circuits to the structure of receptive fields in different classes of bipolar and ganglion cells and their regulation during development and by the gradually changing level of ambient illumination during the day remain significant unanswered questions.

Despite decades of study, the mechanisms by which negative feedback from horizontal cells can adjust the strength of rod and cone output are still not understood. Although GABA has sometimes been observed to modulate effects of feedback (Wu, 1991; Tatsukawa et al., 2005), most studies of negative feedback to cones have not found evidence that GABA receptor activation is involved. There is more convincing evidence that GABA release from horizontal cells may mediate direct feed-forward effects onto bipolar cells, but additional experiments (e.g., using GABA antagonists) under conditions of controlled and prolonged background illumination are needed to clarify this mechanism.

The major effect of negative feedback from horizontal cells onto cones is to alter the voltage-dependence and amplitude of cone I_{Ca} (Verweij et al., 1996). Light-evoked hyperpolarization of horizontal cells promotes a negative shift in the current/voltage relationship of I_{Ca} and increases the peak amplitude of I_{Ca}. Key pieces of evidence favoring a role for pH in horizontal cell feedback are that these effects on I_{Ca} can be replicated by alkalinization of the synaptic cleft and that buffering of cleft pH blocks feedback (Hirasawa and Kaneko, 2003). However, the mechanism(s) by which synaptic cleft proton levels might be modulated by horizontal cell membrane potential have not yet been established. In addition, the finding that the extracellular pH of the outer retina is lower at night in the dark, than in the day due to the action of the retinal circadian clock (Dmitriev and Mangel, 2000, 2001, 2004), represents a challenge to the idea that proton-mediated horizontal cell feedback to cones underlies the bipolar cell surround, which is strongest under maintained light-adapted conditions during the day.

The major competing hypothesis to explain negative feedback from horizontal cells onto cones and rods is that current flowing through hemigap junctions in horizontal cell dendrites produces a highly localized ephaptic change in the membrane voltage at the cone pedicle (Byzov and Shura-Bura, 1986; Kamermans et al., 2001). Evidence in favor of the ephaptic hypothesis comes from a recent study in which fish lacking Cx55.5 hemigap junctions exhibited diminished effects of horizontal cell to cone feedback (Klaassen et al., 2011). While ephaptic modulation of the cone pedicle membrane can account for a shift in the voltage-dependence of I_{Ca}, it cannot readily explain how changes in horizontal cell membrane potential alter the peak amplitude of cone I_{Ca} (Verweij et al., 1996; Hirasawa and Kaneko, 2003; Cadetti and Thoreson, 2006). Perhaps these apparently disparate findings on the mechanisms of feedback can be reconciled within a single common mechanism (e.g., incorporating pH sensitivity of hemigap junctions). Alternatively, multiple different mechanisms may contribute to negative feedback from horizontal cells to cones, much like the multiple mechanisms that may contribute to formation of bipolar cell surrounds (Lukasiewicz, 2005; Zhang and Wu, 2009).

In addition to negative feedback interactions with cones and feed-forward interactions with bipolar cells, horizontal cells also provide negative feedback to rods. Feedback to rods appears to operate by similar mechanisms as negative feedback to cones and, like feedback to cones, the underlying mechanisms remain unexplained. In addition, the contributions of horizontal cell feedback to rods in visual processing have not yet been examined. For example, it remains unclear whether horizontal cell to rod feedback contributes to the formation of antagonistic surrounds in bipolar and ganglion cells.

Positive feedback interactions between horizontal cells and cones have recently been discovered (Jackman et al., 2011). This positive feedback appears to be driven by the activation of calcium-permeable AMPA receptors in horizontal cell dendrites which trigger release of a retrograde messenger that can increase synaptic release from cones. The identity of this retrograde messenger and the mechanism by which it stimulates synaptic release from cones has not yet been established. In addition, the functional impact of this circuit on visual processing has not yet been fully explored.

Negative feedback from horizontal cells and direct horizontal cell feed-forward input to bipolar cells are critical for a number of important functions in early visual processing, particularly the creation of center-surround receptive fields that enhance spatial discrimination and the generation of color opponent interactions. In addition, by adjusting synaptic output to changes in the overall intensity and spectral balance of illumination, lateral signaling can also contribute to light adaptation and color constancy, respectively. Together with an understanding of the underlying mechanisms, determining how the light/dark adaptive state regulates the contributions of horizontal cell feedback to cones and direct horizontal cell input to bipolar cells in the generation of center-surround antagonism, surround activation, color opponency, post-receptoral adaptation, and color constancy remain important questions for future studies.

Acknowledgments

We thank Andrey Dmitriev for helpful comments on portions of the manuscript. This research was supported by grants from Research to Prevent Blindness (WBT) and the NIH (EY10542 (WBT); EY014235 (SCM); EY005102 (SCM)).

References

Agardh E, Bruun A, Ehinger B, Storm-Mathisen J. GABA immunoreactivity in the retina. Invest Ophthalmol Vis Sci. 1986; 27:674–678. [PubMed: 3700017]

Agardh E, Ehinger B, Wu JY. GABA and GAD-like immunoreactivity in the primate retina. Histochem. 1987; 86:485–490.

Ammermüller J, Muller JF, Kolb H. The organization of the turtle inner retina. II Analysis of color-coded and directionally selective cells. J Comp Neurol. 1995; 358:35–62. [PubMed: 7560276]

Arvanitaki A. Effects evoked in an axon by activity of a contiguous one. J Neurophysiol. 1942; 5:89–108.

Asi H, Perlman I. Neural interactions between cone photoreceptors and horizontal cells in the turtle (Mauremys caspica) retina. Vis Neurosci. 1998; 15:1–13. [PubMed: 9456500]

Atick JJ, Redlich AN. Towards a theory of early visual processing. Neural Comput. 1990; 2:308–320.

Atick JJ, Redlich AN. What does the retina know about natural scenes? Neural Comput. 1992; 4:196–210.

Attwell D, Werblin FS, Wilson M, Wu SM. A sign-reversing pathway from rods to double and single cones in the retina of the tiger salamander. J Physiol. 1983; 336:313–333. [PubMed: 6308225]

Attwell D, Wilson M, Wu SM. A quantitative analysis of interactions between photoreceptors in the salamander (*Ambystoma*) retina. J Physiol. 1984; 352:703–737. [PubMed: 6747904]

Awatramani GB, Slaughter MM. Origin of transient and sustained responses in ganglion cells of the retina. J Neurosci. 2000; 20:7087–7095. [PubMed: 10995856]

Ayoub GS, Lam DM. The release of gamma-aminobutyric acid from horizontal cells of the goldfish (*Carassius auratus*) retina. J Physiol. 1984; 355:191–214. [PubMed: 6387085]

Ayoub GS, Lam DM. The content and release of endogenous GABA in isolated horizontal cells of the goldfish retina. Vision Res. 1985; 25:1187–1193. [PubMed: 4071997]

Babai N, Thoreson WB. Horizontal cell feedback regulates calcium currents and intracellular calcium levels in rod photoreceptors of salamander and mouse retina. J Physiol. 2009; 587:2353–2364. [PubMed: 19332495]

Barlow HB. Summation and inhibition in the frog's retina. J Physiol. 1953; 119:69–88. [PubMed: 13035718]

Barlow, HB. Possible principles underlying the transformation of sensory messages. In: Rosenblith, WA., editor. Sensory Communication. MIT Press; Cambridge, MA: 1961. p. 217-234.

Barlow HB. Unsupervised learning. Neural Computation. 1989; 1:295–311.

Barlow HB, Levick WR. Changes in the maintained discharge with adaptation level in the cat retina. J Physiol. 1969; 202:699–718. [PubMed: 5789945]

Barlow HB, Levick WR. Threshold setting by the surround of cat retinal ganglion cells. J Physiol. 1976; 259:737–757. [PubMed: 957261]

Barlow HB, FitzHugh R, Kuffler SW. Change of organization in the receptive fields of the cat's retina during dark adaptation. J Physiol. 1957; 137:338–354. [PubMed: 13463771]

Barnes S. Center-surround antagonism mediated by proton signaling at the cone photoreceptor synapse. J Gen Physiol. 2003; 122:653–656. [PubMed: 14610023]

Barnes S, Bui Q. Modulation of calcium-activated chloride current via pH-induced changes of calcium channel properties in cone photoreceptors. J Neurosci. 1991; 11:4015–4023. [PubMed: 1660538]

Barnes S, Deschênes MC. Contribution of Ca and Ca-activated Cl channels to regenerative depolarization and membrane bistability of cone photoreceptors. J Neurophysiol. 1992; 68:745–755. [PubMed: 1331354]

Barnes S, Merchant V, Mahmud F. Modulation of transmission gain by protons at the photoreceptor output synapse. Proc Natl Acad Sci USA. 1993; 90:10081–10085. [PubMed: 7694280]

Barr RC, Plonsey R. Electrophysiological interaction through interstitial space between adjacent unmyelinated parallel fibers. Biophys J. 1992; 61:1164–1175. [PubMed: 1600078]

Barrow AJ, Wu SM. Low-conductance HCN1 ion channels augment the frequency response of rod and cone photoreceptors. J Neurosci. 2009; 29:5841–5853. [PubMed: 19420251]

Baylor DA, Fuortes MG, O'Bryan PM. Receptive fields of cones in the retina of the turtle. J Physiol. 1971; 214:265–294. [PubMed: 5579638]

Bennis M, Versaux-Botteri C, Repérant J, Armengol JA, Ward R. Gamma-aminobutyric acid-synthesizing cells in the retina of the chameleon *Chamaeleo chameleon*. J Neurosci Res. 2003; 73:410–415. [PubMed: 12868074]

Bevans CG, Harris AL. Regulation of connexin channels by pH. Direct action of the protonated form of taurine and other aminosulfonates. J Biol Chem. 1999; 274:3711–3719. [PubMed: 9920923]

Billups D, Attwell D. Control of intracellular chloride concentration and GABA response polarity in rat retinal ON bipolar cells. J Physiol. 2002; 545:183–198. [PubMed: 12433959]

Blaesse P, Airaksinen MS, Rivera C, Kaila K. Cation-chloride cotransporters and neuronal function. Neuron. 2009; 61:820–838. [PubMed: 19323993]

Blom JJ, Blute TA, Eldred WD. Functional localization of the nitric oxide/cGMP pathway in the salamander retina. Vis Neurosci. 2009; 26:275–286. [PubMed: 19602301]

Bloomfield SA, Xin D. Surround inhibition of mammalian AII amacrine cells is generated in the proximal retina. J Physiol. 2000; 523:771–783. [PubMed: 10718754]

Borgula GA, Karwoski CJ, Steinberg RH. Light-evoked changes in extracellular pH in frog retina. Vision Res. 1989; 29:1069–1077. [PubMed: 2617854]

Bowe-Anders C, Miller RF, Dacheux RF. Developmental characteristics of receptive organization in the isolated retina eyecup of the rabbit. Brain Res. 1975; 87:61–65. [PubMed: 1120256]

Brandon C. Retinal GABA neurons: localization in vertebrate species using an antiserum to rabbit brain glutamate decarboxylase. Brain Res. 1985; 344:286–295. [PubMed: 2994837]

Brockway LM, Zhou ZH, Bubien JK, Jovov B, Benos DJ, Keyser KT. Rabbit retinal neurons and glia express a variety of ENaC/DEG subunits. Am J Physiol Cell Physiol. 2002; 283:C126–C134. [PubMed: 12055080]

Brown JE, Pinto LH. Ionic mechanism for the photoreceptor potential of the retina of *Bufo marinus*. J Physiol. 1974; 236:575–591. [PubMed: 4207130]

Burkhardt DA. Responses and receptive-field organization of cones in perch retinas. J Neurophysiol. 1977; 40:53–62. [PubMed: 833628]

Burkhardt DA. Synaptic feedback, depolarization, and color opponency in cone photoreceptors. Vis Neurosci. 1993; 10:981–989. [PubMed: 8257672]

Burkhardt DA. The influence of center-surround antagonism on light adaptation in cones in the retina of the turtle. Vis Neurosci. 1995; 12:877–885. [PubMed: 8924411]

Burkhardt DA. Light adaptation and contrast in the outer retina. Prog Brain Res. 2001; 131:407–418. [PubMed: 11420959]

Burkhardt DA. Contrast processing by ON and OFF bipolar cells. Vis Neurosci. 2011; 28:69–75. [PubMed: 21092350]

Burkhardt DA, Bartoletti TM, Thoreson WB. Center/surround organization of retinal bipolar cells: high correlation of fundamental responses of center and surround to sinusoidal contrasts. Vis Neurosci. 2011; 28:183–192. [PubMed: 21439110]

Burkhardt DA, Fahey PK, Sikora MA. Natural images and contrast encoding in bipolar cells in the retina of the land- and aquatic-phase tiger salamander. Vis Neurosci. 2006; 23:35–47. [PubMed: 16597349]

Burkhardt DA, Fahey PK, Sikora MA. Retinal bipolar cells: temporal filtering of signals from cone photoreceptors. Vis Neurosci. 2007; 24:765–774. [PubMed: 18093365]

Burkhardt DA, Gottesman J, Thoreson WB. Prolonged depolarization in turtle cones evoked by current injection and stimulation of the receptive field surround. J Physiol. 1988; 407:329–348. [PubMed: 3256619]

Burkhardt DA, Hassin G. Influences of cones upon chromatic- and luminosity-type horizontal cells in pikeperch retinas. J Physiol. 1978; 281:125–137. [PubMed: 702361]

Burkhardt DA, Zhang SQ, Gottesman J. Prolonged depolarization in rods *in situ*. Vis Neurosci. 1991; 6:607–614. [PubMed: 1909172]

Byzov AL. Origin of non-linearity of voltage--current relationships of turtle cones. Vision Res. 1979; 19:469–477. [PubMed: 483576]

Byzov AL. Model for the feedback mechanism between horizontal cells and photoreceptors of vertebrate retinas. Neirofiziologiia. 1977; 9:86–94. [PubMed: 840332]

Byzov AL, Cervetto L. Effects of applied currents on turtle cones in darkness and during the photoresponse. J Physiol. 1977; 265:85–102. [PubMed: 850195]

Byzov AL, Shura-Bura TM. Electrical feedback mechanism in the processing of signals in the outer plexiform layer of the retina. Vision Res. 1986; 26:33–44. [PubMed: 3012877]

Cadetti L, Thoreson WB. Feedback effects of horizontal cell membrane potential on cone calcium currents studied with simultaneous recordings. J Neurophysiol. 2006; 95:1992–1995. [PubMed: 16371457]

Caldwell JH, Daw NW. Effects of picrotoxin and strychnine on rabbit retinal ganglion cells: changes in centre surround receptive fields. J Physiol. 1978; 276:299–310. [PubMed: 650452]

Cao L, Eldred WD. Subcellular localization of neuronal nitric oxide synthase in turtle retina: electron immunocytochemistry. Vis Neurosci. 2001; 18:949–960. [PubMed: 12020086]

Cervetto L, MacNichol EF Jr. Inactivation of horizontal cells in turtle retina by glutamate and aspartate. Science. 1972; 178:767–768. [PubMed: 5082843]

Cervetto L, Piccolino M. Processing of visual signals in vertebrate photoreceptors. Arch Ital Biol. 1982; 120:242–270. [PubMed: 6291477]

Chan LH, Freeman AW, Cleland BG. The rod–cone shift and its effect on ganglion cells in the cat's retina. Vision Res. 1992; 32:2209–2219. [PubMed: 1287998]

Chandrashekar J, Yarmolinsky D, von Buchholtz L, Oka Y, Sly W, Ryba NJ, Zuker CS. The taste of carbonation. Science. 2009; 326:443–445. [PubMed: 19833970]

Chen XH, Bezprozvanny I, Tsien RW. Molecular basis of proton block of L-type Ca^{2+} channels. J Gen Physiol. 1996; 108:363–374. [PubMed: 8923262]

Cheng N, Tsunenari T, Yau KW. Intrinsic light response of retinal horizontal cells of teleosts. Nature. 2009; 460:899–903. [PubMed: 19633653]

Chun MH, Wassle H. GABA-like immunoreactivity in the cat retina: electron microscopy. J Comp Neurol. 1989; 279:55–67. [PubMed: 2913061]

Cleland BG, Enroth-Cugell C. Quantitative aspects of gain and latency in the cat retina. J Physiol. 1970; 206:73–91. [PubMed: 5498461]

Connaughton VP, Behar TN, Liu WL, Massey SC. Immunocytochemical localization of excitatory and inhibitory neurotransmitters in the zebrafish retina. Vis Neurosci. 1999; 16:483–490. [PubMed: 10349969]

Conway BR. Color vision, cones, andcolor-coding in the cortex. Neuroscientist. 2009; 15:274–290. [PubMed: 19436076]

Cook PB, McReynolds JS. Lateral inhibition in the inner retina is important for spatial tuning of ganglion cells. Nat Neurosci. 1998; 1:714–719. [PubMed: 10196588]

Copenhagen, DR. Excitation in the retina: the flow, filtering, and molecules of visual signaling in the glutamatergic pathways from photoreceptors to ganglion cells. In: Chalupa, LM.; Werner, JS., editors. The Visual Neurosciences. MIT Press; Cambridge, MA: 2004. p. 320-333.

Copenhagen DR, Owen WG. Functional characteristics of lateral interactions between rods in the retina of the snapping turtle. J Physiol. 1976; 259:251–282. [PubMed: 986460]

Crook JD, Davenport CM, Peterson BB, Packer OS, Detwiler PB, Dacey DM. Parallel ON and OFF cone bipolar inputs establish spatially coextensive receptive field structure of blue-yellow ganglion cells in primate retina. J Neurosci. 2009; 29:8372–8387. [PubMed: 19571128]

Crook JD, Manookin MB, Packer OS, Dacey DM. Horizontal cell feedback without cone type-selective inhibition mediates “red-green” color opponency in midget ganglion cells of the primate retina. J Neurosci. 2011; 31:1762–1772. [PubMed: 21289186]

Cunningham JR, Neal MJ. Effect of excitatory amino acids on gamma-aminobutyric acid release from frog horizontal cells. J Physiol. 1985; 362:51–67. [PubMed: 3874955]

Cueva JG, Haverkamp S, Reimer RJ, Edwards R, Wassle H, Brecha NC. Vesicular gamma-aminobutyric acid transporter expression in amacrine and horizontal cells. J Comp Neurol. 2002; 445:227–237. [PubMed: 11920703]

Dacey D, Packer OS, Diller L, Brainard D, Peterson B, Lee B. Center surround receptive field structure of cone bipolar cells in primate retina. Vision Res. 2000; 40:1801–1811. [PubMed: 10837827]

Dacheux RF, Miller RF. An intracellular electrophysiological study of the ontogeny of functional synapses in the rabbit retina. I Receptors, horizontal, and bipolar cells. J Comp Neurol. 1981; 198:307–326. [PubMed: 7240448]

Dan Y, Atick JJ, Reid RC. Efficient coding of natural scenes in the lateral geniculate nucleus: experimental test of a computational theory. J Neurosci. 1996; 6:3351–3362. [PubMed: 8627371]

Daniels JD, Pettigrew JD, Norman JL. Development of single-neuron responses in kitten’s lateral geniculate nucleus. J Neurophysiol. 1978; 41:1373–1393. [PubMed: 731284]

Davenport CM, Detwiler PB, Dacey DM. Effects of pH buffering on horizontal and ganglion cell light responses in primate retina: evidence for the proton hypothesis of surround formation. J Neurosci. 2008; 28:456–464. [PubMed: 18184788]

Davies WIL, Zheng L, Hughes S, Tamai TK, Turton M, Halford S, Foster RG, Whitmore D, Hankins MW. Functional diversity of melanopsins and their global expression in the teleost retina. Cell Mol Life Sci. 2011; 68:4115–4132. [PubMed: 21833582]

Daw NW. Colour-coded ganglion cells in the goldfish retina: Extension of their receptive fields by means of new stimuli. J Physiol. 1968; 197:567–592. [PubMed: 5666170]

Deans MR, Paul DL. Mouse horizontal cells do not express connexin26 or connexin36. Cell Commun Adhes. 2001; 8:361–366. [PubMed: 12064619]

Deng P, Cuenca N, Doerr T, Pow DV, Miller R, Kolb H. Localization of neurotransmitters and calcium binding proteins to neurons of salamander and mudpuppy retinas. Vision Res. 2001; 41:1771–1783. [PubMed: 11369041]

Deniz S, Wersinger E, Schwab Y, Mura C, Erdelyi F, Szabó G, Rendon A, Sahel JA, Picaud S, Roux M. Mammalian retinal horizontal cells are unconventional GABAergic neurons. J Neurochem. 2011; 116:350–362. [PubMed: 21091475]

DeVries SH. Exocytosed protons feedback to suppress the Ca^{2+} current in mammalian cone photoreceptors. Neuron. 2001; 32:1107–1117. [PubMed: 11754841]

DeVries SH, Li W, Saszik S. Parallel processing in two transmitter microenvironments at the cone photoreceptor synapse. Neuron. 2006; 50:735–748. [PubMed: 16731512]

Dixon DB, Takahashi K, Copenhagen DR. L-glutamate suppresses HVA calcium current in catfish horizontal cells by raising intracellular proton concentration. Neuron. 1993; 11:267–277. [PubMed: 8102533]

Djamgoz MB, Downing JE, Kirsch M, Prince DJ, Wagner HJ. Plasticity of cone horizontal cell functioning in cyprinid fish retina: effects of background illumination of moderate intensity. J Neurocytol. 1988; 17:701–710. [PubMed: 3210048]

Djamgoz MB, Kolb H. Ultrastructural and functional connectivity of intracellularly stained neurones in the vertebrate retina: correlative analyses. Microsc Res Tech. 1993; 24:43–66. [PubMed: 8435500]

Djamgoz MB, Ruddock KH. Effects of picrotoxin and strychnine on fish retinal S-potentials: evidence for inhibitory control of depolarizing responses. Neurosci Lett. 1979; 12:329–334. [PubMed: 460729]

Dkhissi O, Julien JF, Wasowicz M, Dalil-Thiney N, Nguyen-Legros J, Versaux-Botteri C. Differential expression of GAD(65) and GAD(67) during the development of the rat retina. Brain Res. 2001; 919:242–249. [PubMed: 11701136]

Dmitriev AV, Mangel SC. A circadian clock regulates the pH of the fish retina. J Physiol. 2000; 522:77–82. [PubMed: 10618153]

Dmitriev AV, Mangel SC. Circadian clock regulation of pH in the rabbit retina. J Physiol. 2001; 21:2897–2902.

Dmitriev AV, Mangel SC. Retinal pH reflects retinal energy metabolism in the day and night. J Neurophysiol. 2004; 91:2404–2412. [PubMed: 14960560]

Dmitriev AV, Mangel SC. Electrical feedback in the cone pedicle: a computational analysis. J Neurophysiol. 2006; 95:1419–1427. [PubMed: 16319220]

Dong DW, Atick JJ. Temporal decorrelation: a theory of lagged and nonlagged responses in the lateral geniculate nucleus. Network: Comput Neural Systems. 1995; 6:159–178.

Donner K. Receptive fields of frog retinal ganglion cells: response formation and light-dark adaptation. J Physiol. 1981; 319:131–142. [PubMed: 6976428]

Donner K, Gronholm ML. Center and surround excitation in the receptive fields of frog retinal ganglion cells. Vision Res. 1984; 24:1807–1819. [PubMed: 6335936]

Dowling JE. Synaptic organization of the frog retina: an electron microscopic analysis comparing the retinas of frogs and primates. Proc R Soc London Ser B. 1968; 170:205–228. [PubMed: 4385244]

Dowling JE. Organization of vertebrate retinas. Invest Ophthalmol. 1970; 9:655–680. [PubMed: 4915972]

Dowling, JE. The Retina: An approachable part of the brain. Belknap Press; Cambridge, MA: 2012. Revised Edition

Dowling JE, Boycott BB. Organization of the primate retina: electron microscopy. Proc R Soc Lond B Biol Sci. 1966; 166:80–111. [PubMed: 4382694]

Dowling JE, Brown JE, Major D. Synapses of horizontal cells in rabbit and cat retinas. Science. 1966; 153:1639–1641. [PubMed: 5917075]

Dowling JE, Ripps H. S-Potentials in the skate retina. J Gen Physiol. 1971; 58:163–184. [PubMed: 5559621]

Dowling JE, Werblin FS. Organization of the retina of the mudpuppy, *Necturus maculosus* I Synaptic structure. J Neurophysiol. 1969; 32:315–338. [PubMed: 5787842]

Du JL, Yang XL. Subcellular localization and complements of $GABA_A$ and $GABA_C$ receptors on bullfrog retinal bipolar cells. J Neurophysiol. 2000; 84:666–676. [PubMed: 10938294]

Duebel J, Haverkamp S, Kuner T, Euler T. Two-photon imaging reveals somatodendritic chloride gradient in retinal ON-type bipolar cells expressing the biosensor clomeleon. Neuron. 2006; 49:81–94. [PubMed: 16387641]

Enroth-Cugell C, Lennie P. The control of retinal ganglion cell discharge by receptive field surrounds. J Physiol. 1975; 247:551–578. [PubMed: 1142301]

Enroth-Cugell C, Robson JG. The contrast sensitivity of retinal ganglion cells of the cat. J Physiol. 1966; 187:517–552. [PubMed: 16783910]

Enroth-Cugell C, Lennie P, Shapley RM. Surround contribution to light adaptation in cat retinal ganglion cells. J Physiol. 1975; 247:579–588. [PubMed: 1142302]

Enroth-Cugell C, Robson JG, Schweitzer-Tong DE, Watson AB. Spatiotemporal interactions in cat retinal ganglion cells showing linear spatial summation. J Physiol. 1983; 341:279–307. [PubMed: 6620181]

Ettaiche M, Deval E, Cougnon M, Lazdunski M, Voilley N. Silencing acid-sensing ion channel 1a alters cone-mediated retinal function. J Neurosci. 2006; 26:5800–5809. [PubMed: 16723538]

Fahey PK, Burkhardt DA. Effects of light adaptation on contrast processing in bipolar cells in the retina. Vis Neurosci. 2001; 18:581–597. [PubMed: 11829304]

Fahey PK, Burkhardt DA. Center-surround organization in bipolar cells: symmetry for opposing contrasts. Vis Neurosci. 2003; 20:1–10. [PubMed: 12699078]

Fahrenfort I, Klooster J, Sjoerdsma T, Kamermans M. The involvement of glutamate-gated channels in negative feedback from horizontal cells to cones. Prog Brain Res. 2005; 147:219–229. [PubMed: 15581709]

Fahrenfort I, Sjoerdsma T, Ripps H, Kamermans M. Cobalt ions inhibit negative feedback in the outer retina by blocking hemichannels on horizontal cells. Vis Neurosci. 2004; 21:501–511. [PubMed: 15579217]

Fahrenfort I, Steijaert M, Sjoerdsma T, Vickers E, Ripps H, van Asselt J, Endeman D, Klooster J, Numan R, ten Eikelder H, von Gersdorff H, Kamermans M. Hemichannel-mediated and pH-based feedback from horizontal cells to cones in the vertebrate retina. PLoS One. 2009; 4:e6090. [PubMed: 19564917]

Fain GL. Interactions of rod and cone signals in the mudpuppy retina. J Physiol. 1975; 252:735–769. [PubMed: 1206574]

Field GD, Sher A, Gauthier JL, Greschner M, Shlens J, Litke AM, Chichilnisky EJ. Spatial properties and functional organization of small bistratified ganglion cells in primate retina. J Neurosci. 2007; 27:13261–13272. [PubMed: 18045920]

Fisher SK, Boycott BB. Synaptic connections made by horizontal cells within the outer plexiform layer of the retina of the cat and the rabbit. Proc R Soc Lond B Biol Sci. 1974; 186:317–331. [PubMed: 4154444]

Fletcher EL, Kalloniatis M. Localisation of amino acid neurotransmitters during postnatal development of the rat retina. J Comp Neurol. 1997; 380:449–471. [PubMed: 9087525]

Flores-Herr N, Protti DA, Wassle H. Synaptic currents generating the inhibitory surround of ganglion cells in the mammalian retina. J Neurosci. 2001; 21:4852–4863. [PubMed: 11425912]

Frishman LJ, Linsenmeier RA. Effects of picrotoxin and strychnine on non-linear responses of Y-type cat retinal ganglion cells. J Physiol. 1982; 324:347–363. [PubMed: 7097604]

Frishman LJ, Freeman AW, Troy JB, Schweitzer-Tong D, Enroth-Cugell C. Spatiotemporal frequency responses of cat retinal ganglion cells. J Gen Physiol. 1987; 89:599–628. [PubMed: 3585279]

Fuortes MG, Schwartz EA, Simon EJ. Colour-dependence of cone responses in the turtle retina. J Physiol. 1973; 234:199–216. [PubMed: 4766220]

Fuortes MG, Simon EJ. Interactions leading to horizontal cell responses in the turtle retina. J Physiol. 1974; 240:177–198. [PubMed: 4852507]

Gamba G. Molecular physiology and pathophysiology of electroneutral cation-chloride cotransporters. Physiol Rev. 2005; 85:423–493. [PubMed: 15788703]

Gerschenfeld HM, Piccolino M. Sustained feedback effects of L-horizontal cells on turtle cones. Proc R Soc Lond B Biol Sci. 1980; 206:465–80. [PubMed: 6102393]

Gerschenfeld HM, Piccolino M, Neyton J. Feed-back modulation of cone synapses by L-horizontal cells of turtle retina. J Exp Biol. 1980; 89:177–192. [PubMed: 7205131]

González D, Gómez-Hernández JM, Barrio LC. Species specificity of mammalian connexin-26 to form open voltage-gated hemichannels. FASEB J. 2006; 20:2329–2338. [PubMed: 17077310]

Gottesman J, Burkhardt DA. Response properties of C-type horizontal cells in the retina of the bowfin. Vision Res. 1987; 27:179–189. [PubMed: 3576978]

Gray EG, Pease HL. On understanding the organisation of the retinal receptor synapses. Brain Res. 1971; 35:1–15. [PubMed: 5134225]

Greferath U, Grunert U, Fritschy JM, Stephenson A, Mohler H, Wassle H. $GABA_A$ receptor subunits have differential distributions in the rat retina: in situ hybridization and immunohistochemistry. J Comp Neurol. 1995; 353:553–571. [PubMed: 7759615]

Greferath U, Grunert U, Muller F, Wassle H. Localization of $GABA_A$ receptors in the rabbit retina. Cell Tissue Res. 1994; 276:295–307. [PubMed: 8020065]

Guo C, Stella SL Jr, Hirano AA, Brecha NC. Plasmalemmal and vesicular gamma-aminobutyric acid transporter expression in the developing mouse retina. J Comp Neurol. 2009; 512:6–26. [PubMed: 18975268]

Guo C, Hirano AA, Stella SL Jr, Bitzer M, Brecha NC. Guinea pig horizontal cells express GABA, the GABA-synthesizing enzyme GAD 65, and the GABA vesicular transporter. J Comp Neurol. 2010; 518:1647–1669. [PubMed: 20235161]

Haberecht MF, Schmidt HH, Mills SL, Massey SC, Nakane M, Redburn-Johnson DA. Localization of nitric oxide synthase, NADPH diaphorase and soluble guanylyl cyclase in adult rabbit retina. Vis Neurosci. 1998; 15:881–890. [PubMed: 9764531]

Hamasaki DI, Flynn JT. Physiological properties of retinal ganglion cells of 3-week old kittens. Vision Res. 1977; 17:275–284. [PubMed: 867848]

Hammond P. Receptive field mechanisms of sustained and transient retinal ganglion cells in the cat. Exp Brain Res. 1975; 23:113–128. [PubMed: 1183499]

Hanani M, Vallerga S. Rod and cone signals in the horizontal cells of the tiger salamander retina. J Physiol. 1980; 298:397–405. [PubMed: 7359420]

Hanitzsch R, Kuppers L. The influence of HEPES on light responses of rabbit horizontal cells. Vision Res. 2001; 41:2165–2172. [PubMed: 11448709]

Hare WA, Owen WG. Spatial organization of the bipolar cell's receptive field in the retina of the tiger salamander. J Physiol. 1990; 421:223–245. [PubMed: 2348392]

Hare WA, Owen WG. Effects of 2-amino-4-phosphonobutyric acid on cells in the distal layers of the tiger salamander's retina. J Physiol. 1992; 445:741–757. [PubMed: 1501153]

Hare WA, Owen WG. Receptive field of the retinal bipolar cell: a pharmacological study in the tiger salamander. J Neurophysiol. 1996; 76:2005–2019. [PubMed: 8890310]

Hare WA, Owen WG. Effects of bicarbonate versus HEPES buffering on measured properties of neurons in the salamander retina. Vis Neurosci. 1998; 15:263–271. [PubMed: 9605528]

Harsanyi K, Mangel SC. Modulation of cone to horizontal cell transmission by calcium and pH in the fish retina. Vis Neurosci. 1993; 10:81–91. [PubMed: 8381021]

Hartline HK, Ratliff F. Inhibitory interaction of receptor units in the eye of Limulus. J Gen Physiol. 1957; 40:357–376. [PubMed: 13398569]

Hartline HK, Wagner HG, Ratliff F. Inhibition in the eye of Limulus. J Gen Physiol. 1956; 39:651–673. [PubMed: 13319654]

Haugh-Scheidt L, Ripps H. pH regulation in horizontal cells of the skate retina. Exp Eye Res. 1998; 66:449–463. [PubMed: 9593638]

Haverkamp S, Grünert U, Wässle H. The cone pedicle, a complex synapse in the retina. Neuron. 2000; 27:85–95. [PubMed: 10939333]

Hering, E. Zur Lehre vom Lichtsinne. Carl Gerold's Sohn; Vienna: 1878.

Hille, B. Ion Channels of Excitable Membranes. 3. Sinauer Associates, Inc; Sunderland, MA: 2001.

Hirano AA, Brandstätter JH, Brecha NC. Cellular distribution and subcellular localization of molecular components of vesicular transmitter release in horizontal cells of rabbit retina. J Comp Neurol. 2005; 488:70–81. [PubMed: 15912504]

Hirano AA, Brandstätter JH, Vila A, Brecha NC. Robust syntaxin-4 immunoreactivity in mammalian horizontal cell processes. Vis Neurosci. 2007; 24:489–502. [PubMed: 17640443]

Hirano AA, Brandstätter JH, Morgans CW, Brecha NC. SNAP25 expression in mammalian retinal horizontal cells. J Comp Neurol. 2011; 519:972–988. [PubMed: 21280047]

Hirasawa H, Kaneko A. pH changes in the invaginating synaptic cleft mediate feedback from horizontal cells to cone photoreceptors by modulating Ca^{2+} channels. J Gen Physiol. 2003; 122:657–671. [PubMed: 14610018]

Hoang QV, Qian H, Ripps H. Functional analysis of hemichannels and gap-junctional channels formed by connexins 43 and 46. Mol Vis. 2010; 16:1343–1352. [PubMed: 20664797]

Hubel DH, Wiesel TN. Receptive fields of optic nerve fibers in the spider monkey. J Physiol. 1960; 154:572–580. [PubMed: 13716437]

Huberman AD, Feller MB, Chapman B. Mechanisms underlying development of visual maps and receptive fields. Ann Rev Neurosci. 2008; 31:479–509. [PubMed: 18558864]

Hughes TE, Grünert U, Karten HJ. $GABA_A$ receptors in the retina of the cat: an immunocytochemical study of wholemounts, sections, and dissociated cells. Vis Neurosci. 1991; 6:229–238. [PubMed: 1647196]

Hurlbert A, Wolf K. Color contrast: a contributory mechanism to color constancy. Prog Brain Res. 2004; 144:147–160. [PubMed: 14650846]

Hurvich LM, Jameson D. An opponent-process theory of color vision. Psychol Rev. 1957; 64:384–404. [PubMed: 13505974]

Ichinose T, Lukasiewicz PD. Inner and outer retinal pathways both contribute to surround inhibition of salamander ganglion cells. J Physiol. 2005; 565:517–535. [PubMed: 15760938]

Ikeda H, Sheardown MJ. Transmitters mediating inhibition of ganglion cells in the cat retina: iontophoretic studies *in vivo*. Neuroscience. 1983; 8:837–853. [PubMed: 6135176]

Ikeda H, Wright MJ. The outer disinhibitory surround of the retinal ganglion cell receptive field. J Physiol. 1972; 226:511–544. [PubMed: 4343631]

Jackman SL, Babai N, Chambers JJ, Thoreson WB, Kramer RH. A positive feedback synapse from retinal horizontal cells to cone photoreceptors. PLoS Biol. 2011; 9:e1001057. [PubMed: 21559323]

Jacoby J, Kreitzer MA, Alford S, Qian H, Tchernookova BK, Naylor ER, Malchow RP. Extracellular pH dynamics of retinal horizontal cells examined using electrochemical and fluorometric methods. J Neurophysiol. 2011 in press.

Janssen-Bienhold U, Schultz K, Gellhaus A, Schmid P, Ammermüller J, Weiler R. Identification and localization of connexin26 within the photoreceptor-horizontal cell synaptic complex. Vis Neurosci. 2001; 18:169–178. [PubMed: 11417791]

Jefferys JG. Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. Physiol Rev. 1995; 75:689–723. [PubMed: 7480159]

Jellali A, Stussi-Garaud C, Gasnier B, Rendon A, Sahel JA, Dreyfus H, Picaud S. Cellular localization of the vesicular inhibitory amino acid transporter in the mouse and human retina. J Comp Neurol. 2002; 449:76–87. [PubMed: 12115694]

Jenkins A, Munoz M, Tarttelin EE, Bellingham J, Foster RG, Hankins MW. TA opsin, melanopsin, and an inherent light response within retinal interneuron's. Curr Biol. 2003; 13:1269–1278. [PubMed: 12906786]

Jensen RJ. Involvement of glycinergic neurons in the diminished activity of ganglion cells in the dark-adapted rabbit retina. Vis Neurosci. 1991; 6:43–53. [PubMed: 1851036]

Johnson J, Tian N, Caywood MS, Reimer RJ, Edwards RH, Copenhagen DR. Vesicular neurotransmitter transporter expression in developing postnatal rodent retina: GABA and glycine precede glutamate. J Neurosci. 2003; 23:518–529. [PubMed: 12533612]

Johnson MA, Vardi N. Regional differences in GABA and GAD immunoreactivity in rabbit horizontal cells. Vis Neurosci. 1998; 15:743–753. [PubMed: 9682875]

Jonz MG, Barnes S. Proton modulation of ion channels in isolated horizontal cells of the goldfish retina. J Physiol. 2007; 581:529–541. [PubMed: 17331999]

Jouhou H, Yamamoto K, Homma A, Hara M, Kaneko A, Yamada M. Depolarization of isolated horizontal cells of fish acidifies their immediate surrounding by activating V-ATPase. J Physiol. 2007; 585:401–412. [PubMed: 17932147]

Kalamkarov G, Pogozheva I, Shevchenko T, Koskelainen A, Hemila S, Donner K. pH changes in frog rods upon manipulation of putative pH-regulating transport mechanisms. Vision Res. 1996; 36:3029–3036. [PubMed: 8917766]

Kalloniatis M, Fletcher EL. Immunocytochemical localization of the amino acid neurotransmitters in the chicken retina. J Comp Neurol. 1993; 336:174–193. [PubMed: 7902364]

Kalloniatis M, Marc RE, Murry RF. Amino acid signatures in the primate retina. J Neurosci. 1996; 16:6807–6829. [PubMed: 8824321]

Kamermans M, Fahrenfort I. Ephaptic interactions within a chemical synapse: hemichannel-mediated ephaptic inhibition in the retina. Curr Opin Neurobiol. 2004; 14:531–541. [PubMed: 15464885]

Kamermans M, Fahrenfort I, Schultz K, Janssen-Bienhold U, Sjoerdsma T, Weiler R. Hemichannel-mediated inhibition in the outer retina. Science. 2001; 292:1178–1180. [PubMed: 11349152]

Kamermans M, Kraaij D, Spekreijse H. The dynamic characteristics of the feedback signal from horizontal cells to cones in the goldfish retina. J Physiol. 2001; 534:489–500. [PubMed: 11454966]

Kamermans M, Spekreijse H. The feedback pathway from horizontal cells to cones. A mini review with a look ahead. Vision Res. 1999; 39:2449–2468. [PubMed: 10396615]

Kaneda M, Andrasfalvy B, Kaneko A. Modulation by Zn^{2+} of GABA responses in bipolar cells of the mouse retina. Vis Neurosci. 2000; 17:273–281. [PubMed: 10824681]

Kaneko A. Physiological and morphological identification of horizontal, bipolar and amacrine cells in goldfish retina. J Physiol. 1970; 207:623–633. [PubMed: 5499739]

Kaneko A. Receptive field organization of bipolar and amacrine cells in the goldfish retina. J Physiol. 1973; 235:133–153. [PubMed: 4778132]

Kaneko A, Tachibana M. Retinal bipolar cells with double colour-opponent receptive fields. Nature. 1981; 293:220–222. [PubMed: 7278979]

Kaneko A, Tachibana M. Effects of γ-aminobutyric acid on isolated cone photoreceptors of the turtle retina. J Physiol. 1986a; 373:442–461.

Kaneko A, Tachibana M. Blocking effects of cobalt and related ions on the gamma-aminobutyric acid-induced current in turtle retinal cones. J Physiol. 1986b; 373:463–479. [PubMed: 3746680]

Kaplan E, Benardete E. The dynamics of primate retinal ganglion cells. Prog Brain Res. 2001; 134:17–34. [PubMed: 11702542]

Kim HG, Miller RF. Physiological and morphological correlations of horizontal cells in the mudpuppy retina. J Neurophysiol. 1992; 67:829–840. [PubMed: 1588385]

Klaassen LJ, Sun Z, Steijaert MN, Bolte P, Fahrenfort I, Sjoerdsma T, Klooster J, Claassen Y, Shields CR, Ten Eikelder HM, Janssen-Bienhold U, Zoidl G, McMahon DG, Kamermans M. Synaptic transmission from horizontal cells to cones is impaired by loss of connexin hemichannels. PLoS Biol. 2011; 9:e1001107. [PubMed: 21811399]

Kleinschmidt J. Signal transmission at the photoreceptor synapse. Role of calcium ions and protons. Ann N Y Acad Sci. 1991; 635:468–470. [PubMed: 1660251]

Kleinschmidt J, Dowling JE. Intracellular recordings from gecko photoreceptors during light and dark adaptation. J Gen Physiol. 1975; 66:617–648. [PubMed: 1194887]

Klooster J, Nunes Cardozo B, Yazulla S, Kamermans M. Postsynaptic localization of gamma-aminobutyric acid transporters and receptors in the outer plexiform layer of the goldfish retina: An ultrastructural study. J Comp Neurol. 2004; 474:58–74. [PubMed: 15156579]

Koehler CL, Akimov NP, Renteria RC. Receptive field center size decreases and firing properties mature in ON and OFF retinal ganglion cells after eye opening in the mouse. J Neurophysiol. 2011; 106:895–904. [PubMed: 21613583]

Kolb H. Organization of the outer plexiform layer of the primate retina: Electron microscopy of Golgi-impregnated cells. Phil Trans R Soc Lond B. 1970; 258:261– 283. [PubMed: 22408829]

Kolb H. The connections between horizontal cells and photoreceptors in the retina of the cat: electron microscopy of Golgi preparations. J Comp Neurol. 1974; 155:1–14. [PubMed: 4836060]

Kolb H. The organization of the outer plexiform layer in the retina of the cat: Electron microscopic observations. J Neurocytol. 1977; 6:131–153. [PubMed: 856949]

Kolb H, Jones J. Synaptic organization of the outer plexiform layer of the turtle retina: an electron microscope study of serial sections. J Neurocytol. 1984; 13:567–591. [PubMed: 6481412]

Koulen P, Brandstätter JH, Enz R, Bormann J, Wässle H. Synaptic clustering of $GABA_C$ receptor rho-subunits in the rat retina. Eur J Neurosci. 1998; 10:115–127. [PubMed: 9753119]

Kraaij DA, Spekreijse H, Kamermans M. The nature of surround-induced depolarizing responses in goldfish cones. J Gen Physiol. 2000; 115:3–16. [PubMed: 10613914]

Kreitzer MA, Collis LP, Molina AJ, Smith PJ, Malchow RP. Modulation of extracellular proton fluxes from retinal horizontal cells of the catfish by depolarization and glutamate. J Gen Physiol. 2007; 130:169–182. [PubMed: 17664345]

Krizaj D, Mercer AJ, Thoreson WB, Barabas P. Intracellular pH modulates inner segment calcium homeostasis in vertebrate photoreceptors. Am J Physiol Cell Physiol. 2011; 300:C187–C197. [PubMed: 20881233]

Kuffler SW. Discharge patterns and functional organization of mammalian retina. J Neurophysiol. 1953; 16:37–68. [PubMed: 13035466]

Kwan YW, Kass RS. Interactions between H^+ and Ca^{2+} near cardiac L-type calcium channels: evidence for independent channel-associated binding sites. Biophys J. 1993; 65:1188–1195. [PubMed: 8241399]

Lam DM, Ayoub GS. Biochemical and biophysical studies of isolated horizontal cells from the teleost retina. Vision Res. 1983; 23:433–444. [PubMed: 6880040]

Lam DM, Lasater EM, Naka KI. Gamma-aminobutyric acid: a neurotransmitter candidate for cone horizontal cells of the catfish retina. Proc Natl Acad Sci USA. 1978; 75:6310–6313. [PubMed: 32538]

Lamb TD. Spatial properties of horizontal cell responses in the turtle retina. J Physiol. 1976; 263:239–255. [PubMed: 1018237]

Lankheet MJM, Van Wezel RJA, Prickaerts JHHJ, Van deGrind WA. The dynamics of light adaptation in cat horizontal responses. Vision Res. 1993; 33:1153–1171. [PubMed: 8333166]

Lasansky A. Synaptic organization of cone cells in the turtle retina. Phil Trans R Soc Lond B. 1971; 262:365– 381.

Lasansky A. Cell junctions at the outer synaptic layer of the retina. Invest Ophthalmol. 1972; 11:265–275. [PubMed: 4112852]

Lasansky A. Organization of the outer synaptic layer in the retina of the larval tiger salamander. Phil Trans R Soc Lond B. 1973; 265:471–489. [PubMed: 4147132]

Lasansky A. Contacts between receptors and electrophysiologically identified neurones in the retina of the larval tiger salamander. J Physiol. 1978; 285:531–542. [PubMed: 217992]

Lasansky A. Synaptic action mediating cone responses to annular illumination in the retina of the larval tiger salamander. J Physiol. 1981; 310:205–214. [PubMed: 7230033]

Lasansky A, Vallerga S. Horizontal cell responses in the retina of the larval tiger salamander. J Physiol. 1975; 251:145–165. [PubMed: 1185613]

Lasater EM. A white-noise analysis of responses and receptive fields of catfish cones. J Neurophysiol. 1982; 47:1057–1068. [PubMed: 7108571]

Lasater EM, Lam DM. The identification and some functions of GABAergic neurons in the distal catfish retina. Vision Res. 1984; 24:497–506. [PubMed: 6740969]

Lee BB, Martin PR, Grünert U. Retinal connectivity and primate vision. Prog Retin Eye Res. 2010; 29:622–639. [PubMed: 20826226]

Lee H, Brecha NC. Immunocytochemical evidence for SNARE protein-dependent transmitter release from guinea pig horizontal cells. Eur J Neurosci. 2010; 31:1388–1401. [PubMed: 20384779]

Leeper HF, Copenhagen DR. Mixed rod-cone responses in horizontal cells of snapping turtle retina. Vision Res. 1979; 19:407–412. [PubMed: 473609]

Levick WR. Receptive fields of cat retinal ganglion cells with special reference to alpha cells. Prog Retin Eye Res. 1996; 15:457–500.

Li CY, Zhou YX, Pei X, Qiu FT, Tang CQ, Xu XZ. Extensive disinhibitory region beyond the classical receptive field of cat retinal ganglion cells. Vision Res. 1992; 32:219–228. [PubMed: 1574837]

Li W, Keung JW, Massey SC. Direct synaptic connections between rods and OFF cone bipolar cells in the rabbit retina. J Comp Neurol. 2004; 474:1–12. [PubMed: 15156575]

Lin CT, Li HZ, Wu JY. Immunocytochemical localization of L-glutamate decarboxylase, gamma-aminobutyric acid transaminase, cysteine sulfinic acid decarboxylase, aspartate aminotransferase and somatostatin in rat retina. Brain Res. 1983; 270:273–283. [PubMed: 6136312]

Lin P, Slaughter M. Glycine receptor subunit composition alters the action of GABA antagonists. Visual Neurosci. 2007; 24:513–521.

Lin ZS, Yazulla S. Heterogeneity of GABAA receptor in goldfish retina. J Comp Neurol. 1994; 345:429–439. [PubMed: 7929911]

Linberg KA, Fisher SK. Ultrastructural evidence that horizontal cell axon terminals are presynaptic in the human retina. J Comp Neurol. 1988; 268:281–297. [PubMed: 3360989]

Linton JD, Holzhausen LC, Babai N, Song H, Miyagishima KJ, Stearns GW, Lindsay K, Wei J, Chertov AO, Peters TA, Caffe R, Pluk H, Seeliger MW, Tanimoto N, Fong K, Bolton L, Kuok DL, Sweet IR, Bartoletti TM, Radu RA, Travis GH, Zagotta WN, Townes-Anderson E, Parker E, Van der Zee CE, Sampath AP, Sokolov M, Thoreson WB, Hurley JB. Flow of energy in the outer retina in darkness and in light. Proc Natl Acad Sci USA. 2010; 107:8599–8604. [PubMed: 20445106]

Lipin MY, Smith RG, Taylor WR. Maximizing contrast resolution in the outer retina of mammals. Biol Cybern. 2010; 103:57–77. [PubMed: 20361204]

Liu J, Li GL, Yang XL. An ionotropic GABA receptor with novel pharmacology at bullfrog cone photoreceptor terminals. Neurosignals. 2006–2007; 15:13–25.

Liu J, Zhao JW, Du JL, Yang XL. Functional GABA(B) receptors are expressed at the cone photoreceptor terminals in bullfrog retina. Neuroscience. 2005; 132:103–13. [PubMed: 15780470]

Loeliger M, Rees S. Immunocytochemical development of the guinea pig retina. Exp Eye Res. 2005; 80:9–21. [PubMed: 15652521]

Lukasiewicz PD. Synaptic mechanisms that shape visual signaling at the inner retina. Prog Brain Res. 2005; 147:205–218. [PubMed: 15581708]

Maffei L, Fiorentini A, Cervetto L. Homeostasis in retinal receptive fields. J Neurophysiol. 1971; 34:579–587. [PubMed: 4329780]

Makani S, Chesler M. Rapid rise of extracellular pH evoked by neural activity is generated by the plasma membrane calcium ATPase. J Neurophysiol. 2010; 103:667–676. [PubMed: 19939954]

Maksimova EM. Effect of intracellular polarization of horizontal cells on the activity of ganglionic cells of fish retina. Biofizika. 1969; 14:537–544. [PubMed: 5397722]

Malchow RP, Yazulla S. Light adaptation of rod and cone luminosity horizontal cells of the retina of the goldfish. Brain Res. 1988; 443:222–239. [PubMed: 3359267]

Mangel SC. Analysis of the horizontal cell contribution to the receptive field surround of ganglion cells in the rabbit retina. J Physiol. 1991; 442:211–234. [PubMed: 1665857]

Marc RE, Murry RF, Fisher SK, Linberg KA, Lewis GP, Kalloniatis M. Amino acid signatures in the normal cat retina. Invest Ophthalmol Vis Sci. 1998; 39:1685–1693. [PubMed: 9699558]

Marchiafava PL. Horizontal cells influence membrane potential of bipolar cells in the retina of the turtle. Nature. 1978; 275:141–142. [PubMed: 692683]

Maricq AV, Korenbrot JI. Calcium and calcium-dependent chloride currents generate action potentials in solitary cone photoreceptors. Neuron. 1988; 1:503–515. [PubMed: 2483100]

Marr, D. Vision. W.H. Freeman; San Francisco: 1982.

Marshak D, Dowling JE. Synapses of cone horizontal cell axons in goldfish retina. J Comp Neurol. 1987; 256:430–443. [PubMed: 3571515]

Masland RH. Maturation of function in the developing rabbit retina. J Comp Neurol. 1977; 175:275–286. [PubMed: 903424]

Masland RH, Ames A 3rd. Responses to acetylcholine of ganglion cells in an isolated mammalian retina. J Neurophysiol. 1976; 39:1220–1235. [PubMed: 993829]

Massey SC, O'Brien JJ, Trexler EB, Li W, Keung JW, Mills SL, O'Brien J. Multiple neuronal connexins in the mammalian retina. Cell Commun Adhes. 2003; 10:425–430. [PubMed: 14681052]

Mataruga A, Kremmer E, Müller F. Type 3a and type 3b OFF cone bipolar cells provide for the alternative rod pathway in the mouse retina. J Comp Neurol. 2007; 502:1123–1137. [PubMed: 17447251]

McGuire BA, Stevens JK, Sterling P. Microcircuitry of bipolar cells in cat retina. J Neurosci. 1984; 4:2920–2938. [PubMed: 6502212]

McMahon MJ, Packer OS, Dacey DM. The classical receptive field surround of primate parasol ganglion cells is mediated primarily by a non-GABAergic pathway. J Neurosci. 2004; 24:3736–3745. [PubMed: 15084653]

Michael CR. Receptive fields of single optic nerve fibers in a mammal with an all-cone retina. I Contrast-sensitive units. J Neurophysiol. 1968; 31:249–256. [PubMed: 4879855]

Miesenböck G, De Angelis DA, Rothman JE. Visualizing secretion and synaptic transmission with pH-sensitive green fluorescent proteins. Nature. 1998; 394:192–195. [PubMed: 9671304]

Miller RF, Dacheux RF. Synaptic organization and ionic basis of On and Off channels in mudpuppy retina. I Intracellular analysis of chloride-sensitive electrogenic properties of receptors, horizontal cells, bipolar cells and amacrine cells. J Gen Physiol. 1976; 67:639–659. [PubMed: 932668]

Miller RF, Dacheux RF. Intracellular chloride in retinal neurons: measurement and meaning. Vision Res. 1983; 23:399–411. [PubMed: 6880038]

Missotten, L. The Ultrastructure of the Retina. Arscia Uitgaven N.V; Brussels: 1965.

Mitarai G, Goto T, Takagi S. Receptive field arrangement of color-opponent bipolar and amacrine cells in the carp retina. Sens Processes. 1978; 2:375–382. [PubMed: 755292]

Mitchell CK, Huang B, Redburn-Johnson DA. GABA(A) receptor immunoreactivity is transiently expressed in the developing outer retina. Vis Neurosci. 1999; 16:1083–1088. [PubMed: 10614588]

Molina AJ, Verzi MP, Birnbaum AD, Yamoah EN, Hammar K, Smith PJ, Malchow RP. Neurotransmitter modulation of extracellular H^+ fluxes from isolated retinal horizontal cells of the skate. J Physiol. 2004; 560:639–657. [PubMed: 15272044]

Morgans CW, El Far O, Berntson A, Wässle H, Taylor WR. Calcium extrusion from mammalian photoreceptor terminals. J Neurosci. 1998; 18:2467–2474. [PubMed: 9502807]

Morigiwa K, Vardi N. Differential expression of ionotropic glutamate receptor subunits in the outer retina. J Comp Neurol. 1999; 405:173–184. [PubMed: 10023808]

Mosinger JL, Yazulla S, Studholme KM. GABA-like immunoreactivity in the vertebrate retina: a species comparison. Exp Eye Res. 1986; 42:631–644. [PubMed: 3487464]

Mosinger J, Yazulla S. Double-label analysis of GAD- and GABA-like immunoreactivity in the rabbit retina. Vision Res. 1987; 27:23–30. [PubMed: 3303678]

Muller JF, Dacheux RF. Alpha ganglion cells of the rabbit retina lose antagonistic surround responses under dark adaptation. Vis Neurosci. 1997; 14:395–401. [PubMed: 9147490]

Mumm JS, Godinho L, Morgan JL, Oakleey DM, Schroeter EH, Wong RO. Laminar circuit formation in the vertebrate retina. Prog Brain Res. 2005; 147:155–169. [PubMed: 15581704]

Murakami M, Shimoda Y, Nakatani K, Miyachi E, Watanabe S. GABA-mediated negative feedback from horizontal cells to cones in carp retina. Jpn J Physiol. 1982; 32:911–926. [PubMed: 7169699]

Naka KI. Neuronal circuitry in the catfish retina. Invest Ophthal. 1976; 15:926–935.

Naka KI. The cells horizontal cells talk to. Vision Res. 1982; 22:653–660. [PubMed: 6287724]

Naka KI, Nye PW. Role of horizontal cells in organization of the catfish retina receptive field. J Neurophysiol. 1971; 34:785–801. [PubMed: 5097157]

Naka KI, Witkovsky P. Dogfish ganglion cell discharge resulting from extrinsic polarization of the horizontal cells. J Physiol. 1972; 223:449–460. [PubMed: 5039283]

Nelson R, Pflug R, Baer SM. Background-induced flicker enhancement in cat retinal horizontal cells. I Spatial properties. J Neurophysiol. 1990; 64:326–340. [PubMed: 2213121]

Neyton J, Piccolino M, Gerschenfeld HM. Involvement of small-field horizontal cells in feedback effects on green cones of turtle retina. Proc Natl Acad Sci U S A. 1981; 78:4616–4619. [PubMed: 6945602]

Normann RA, Pochobradsky J. Oscillations in rod and horizontal cell membrane potential: evidence for feed-back to rods in the vertebrate retina. J Physiol. 1976; 261:15–29. [PubMed: 825636]

Norton AL, Spekreijse H, Wolbarsht ML, Wagner HG. Receptive field organization of the S-potential. Science. 1968; 160:1021–1022. [PubMed: 5647849]

Nye PW, Naka KI. The dynamics of inhibitory interaction in a frog receptive field: a paradigm of paracontrast. Vision Res. 1971; 11:377–392. [PubMed: 5558923]

Oakley B, Wen R. Extracellular pH in the isolated retina of the toad in darkness and during illumination. J Physiol. 1989; 419:353–378. [PubMed: 2516127]

O'Bryan PM. Properties of the depolarizing synaptic potential evoked by peripheral illumination in cones of the turtle retina. J Physiol. 1973; 235:207–223. [PubMed: 4778138]

Ohtsuka T, Kouyama N. Synaptic contacts between red-sensitive cones and triphasic chromaticity horizontal cells in the turtle retina. Brain Res. 1985; 346:374–377. [PubMed: 4052787]

Ohtsuka T, Kouyama N. Electron microscopic study of synaptic contacts between photoreceptors and HRP-filled horizontal cells in the turtle retina. J Comp Neurol. 1986; 250:141–156. [PubMed: 3745508]

Okawa H, Sampath AP, Laughlin SB, Fain GL. ATP consumption by mammalian rod photoreceptors in darkness and in light. Curr Biol. 2008; 18:1917–1921. [PubMed: 19084410]

Osborne NN, Patel S, Beaton DW, Neuhoff V. GABA neurones in retinas of different species and their postnatal development in situ and in culture in the rabbit retina. Cell Tissue Res. 1986; 243:117–123. [PubMed: 3510739]

Packer OS, Verweij J, Li PH, Schnapf JL, Dacey DM. Blue-yellow opponency in primate S cone photoreceptors. J Neurosci. 2010; 30:568–572. [PubMed: 20071519]

Palmer MJ, Hull C, Vigh J, von Gersdorff H. Synaptic cleft acidification and modulation of short-term depression by exocytosed protons in retinal bipolar cells. J Neurosci. 2003; 23:11332–11341. [PubMed: 14672997]

Pan F, Massey SC. Rod and cone input to horizontal cells in the rabbit retina. J Comp Neurol. 2007; 500:815–831. [PubMed: 17177254]

Pattnaik B, Jellali A, Sahel J, Dreyfus H, Picaud S. $GABA_C$ receptors are localized with microtubule-associated protein 1B in mammalian cone photoreceptors. J Neurosci. 2000; 20:6789–6796. [PubMed: 10995822]

Payne JA, Rivera C, Voipio J, Kaila K. Cation-chloride co-transporters in neuronal communication, development and trauma. Trends Neurosci. 2003; 26:199–206. [PubMed: 12689771]

Peichl L, Wassle H. The structural correlate of the receptive field center of a ganglion cells in the cat retina. J Physiol. 1983; 341:309–324. [PubMed: 6620182]

Perlman I, Normann RA. The effects of GABA and related drugs on horizontal cells in the isolated turtle retina. Vis Neurosci. 1990; 5:469–477. [PubMed: 1963078]

Perlman I, Normann RA. Light adaptation and sensitivity controlling mechanisms in vertebrate photoreceptors. Prog Ret Eye Res. 1998; 17:523–563.

Pflug R, Nelson R, Ahnelt PK. Background-induced flicker enhancement in cat retinal horizontal cells. I Temporal and spectral properties. J Neurophysiol. 1990; 64:313–325. [PubMed: 2213120]

Picaud S, Pattnaik B, Hicks D, Forster V, Fontaine V, Sahel J, Dreyfus H. $GABA_A$ and $GABA_C$ receptors in adult porcine cones: evidence from a photoreceptor-glia co-culture model. J Physiol. 1998; 513:33–42. [PubMed: 9782157]

Piccolino M. The feedback synapse from horizontal cells to cone photoreceptors in the vertebrate retina. Prog Ret Eye Res. 1995; 14:141–196.

Piccolino M, Gerschenfeld HM. Lateral interactions in the outer plexiform layer of turtle retinas after atropine block of horizontal cells. Nature. 1977; 268:259–261. [PubMed: 196208]

Piccolino M, Gerschenfeld HM. Activation of a regenerative calcium conductance in turtle cones by peripheral stimulation. Proc R Soc Lond B Biol Sci. 1978; 201:309–315. [PubMed: 27806]

Piccolino M, Gerschenfeld HM. Characteristics and ionic processes involved in feedback spikes of turtle cones. Proc R Soc Lond B Biol Sci. 1980; 206:439–463. [PubMed: 6102392]

Piccolino M, Neyton J, Gerschenfeld HM. Peripheral antagonism in the small field L-horizontal cells (L2-HC) of turtle retina. Vision Res. 1981; 21:1579–1580. [PubMed: 7336587]

Piccolino M, Pignatelli A, Rakotobe LA. Calcium-independent release of neurotransmitter in the retina: a “copernican” viewpoint change. Prog Retin Eye Res. 1999; 18:1–38. [PubMed: 9920497]

Piccolino M, Wade NJ. Galileo’s eye: a new vision of the senses in the work of Galileo Galilei. Perception. 2008; 37:1312–1340. [PubMed: 18986060]

Pinto LH, Pak WL. Light-induced changes in photoreceptor membrane resistance and potential in Gecko retinas. II Preparations with active lateral interactions. J Gen Physiol. 1974; 64:49–69. [PubMed: 4837686]

Popel B, Eckhorn R. Dynamic aspects of cat retinal ganglion cell’s center and surround mechanisms: a white noise analysis. Vision Res. 1981; 21:1693–1696. [PubMed: 7336603]

Pöppel E. Long-rangecolour-generating interactions across the retina. Nature. 1986; 320:523–525. [PubMed: 3960134]

Pottek M, Hoppenstedt W, Janssen-Bienhold U, Schultz K, Perlman I, Weiler R. Contribution of connexin26 to electrical feedback inhibition in the turtle retina. J Comp Neurol. 2003; 466:468–477. [PubMed: 14566943]

Pourcho RG, Owczarzak MT. Distribution of GABA immunoreactivity in the cat retina: a light- and electron-microscopic study. Vis Neurosci. 1989; 2:425–435. [PubMed: 2487080]

Prochnow N, Hoffmann S, Vroman R, Klooster J, Bunse S, Kamermans M, Dermietzel R, Zoidl G. Pannexin1 in the outer retina of the zebrafish, *Danio rerio*. Neuroscience. 2009; 162:1039–1054. [PubMed: 19409451]

Puller C, Haverkamp S. Bipolar cell pathways for color vision in non-primate dichromats. Vis Neurosci. 2011; 28:51–60. [PubMed: 21070688]

Puller C, de Sevilla Müller LP, Janssen-Bienhold U, Haverkamp S. ZO-1 and the spatial organization of gap junctions and glutamate receptors in the outer plexiform layer of the mammalian retina. J Neurosci. 2009; 29:6266–6275. [PubMed: 19439604]

Qian HH, Li LH, Chappell RL, Ripps H. GABA receptors of bipolar cells from the skate retina: actions of zinc on GABA-mediated membrane currents. J Neurophysiol. 1997; 78:2402–2412. [PubMed: 9356392]

Ratliff F, Hartline HK. The responses of Limulus optic nerve fibers to patterns of illumination on the receptor mosaic. J Gen Physiol. 1959; 42:1241–1255. [PubMed: 13664924]

Raynauld JP, Laviolette JR, Wagner HJ. Goldfish retina: a correlate between cone activity and morphology of the horizontal cell in cone pedicules. Science. 1979; 204:1436–1438. [PubMed: 451577]

Reeves, A. Visual adaptation. In: Chalupa, LM.; Werner, JS., editors. The Visual Neurosciences. MIT Press; Cambridge, MA: 2004. p. 851-862.

Ribelayga C, Cao Y, Mangel SC. The circadian clock in the retina controls rod-cone coupling. Neuron. 2008; 59:790–801. [PubMed: 18786362]

Ribelayga C, Mangel SC. Absence of circadian clock regulation of horizontal cell gap junctional coupling reveals two dopamine systems in the goldfish retina. J Comp Neurol. 2003; 467:243–253. [PubMed: 14595771]

Ribelayga C, Mangel SC. Identification of a circadian clock-controlled neural pathway in the rabbit retina. PLoS One. 2010; 5:e11020. [PubMed: 20548772]

Rieke F, Schwartz EA. A cGMP-gated current can control exocytosis at cone synapses. Neuron. 1994; 13:863–873. [PubMed: 7946333]

Rinner O, Gegenfurtner KR. Cone contributions to colour constancy. Perception. 2002; 31:733–746. [PubMed: 12092799]

Ripps H, Qian H, Zakevicius J. Properties of connexin26 hemichannels expressed in *Xenopus* oocytes. Cell Mol Neurobiol. 2004; 24:647–665. [PubMed: 15485136]

Rodieck RW, Stone J. Analysis of receptive fields of cat retinal ganglion cells. J Neurophysiol. 1965; 28:833–849.

Ruddock KH, Svaetichin G. The effects of maintained light stimulation on S-potentials recorded from the retina of a teleost fish. J Physiol. 1975; 244:569–588. [PubMed: 1133771]

Rusoff AC, Dubin MW. Development of receptive-field properties of retinal ganglion cells in kittens. J Neurophysiol. 1977; 40:1188–1198. [PubMed: 903800]

Russell JM. Sodium-potassium-chloride cotransport. Physiol Rev. 2000; 80:211–276. [PubMed: 10617769]

Rüttiger L, Braun DI, Gegenfurtner KR, Petersen D, Schönle P, Sharpe LT. Selective color constancy deficits after circumscribed unilateral brain lesions. J Neurosci. 1999; 19:3094–3106. [PubMed: 10191325]

Saarikoski J, Ruusuvuori E, Koskelainen A, Donner K. Regulation of intracellular pH in salamander retinal rods. J Physiol. 1997; 498:61–72. [PubMed: 9023768]

Saito HA. Pharmacological and morphological differences between X- and Y-type ganglion cells in the cat's retina. Vision Res. 1983; 23:1299–1308. [PubMed: 6659377]

Saito T, Miller WH, Tomita T. C- and L-type horizontal cells in the turtle retina. Vision Res. 1974; 14:119–123. [PubMed: 4130386]

Sakai HM, Naka KI. Synaptic organization of the cone horizontal cells in the catfish retina. J Comp Neurol. 1986; 245:107–115. [PubMed: 3958241]

Sakai HM, Naka KI. Neuron network in catfish retina: 1968–1987. Prog Retin Res. 1988; 7:149–208.

Sakuranaga M, Naka KI. Signal transmission in the catfish retina. I Transmission in the outer retina. J Neurophysiol. 1985; 53:373–389. [PubMed: 2984347]

Satoh H, Kaneda M, Kaneko A. Intracellular chloride concentration is higher in rod bipolar cells than in cone bipolar cells of the mouse retina. Neurosci Lett. 2001; 310:161–164. [PubMed: 11585592]

Savchenko A, Barnes S, Kramer RH. Cyclic-nucleotide-gated channels mediate synaptic feedback by nitric oxide. Nature. 1997; 390:694–698. [PubMed: 9414163]

Schaeffer SF, Raviola E, Heuser JE. Membrane specializations in the outer plexiform layer of the turtle retina. J Comp Neurol. 1982; 204:253–267. [PubMed: 6276452]

Schnitzer J, Rusoff AC. Horizontal cells of the mouse retina contain glutamic acid decarboxylase-like immunoreactivity during early developmental stages. J Neurosci. 1984; 4:2948–2955. [PubMed: 6502214]

Schubert T, Huckfeldt RM, Parker E, Campbell JE, Wong RO. Assembly of the outer retina in the absence of GABA synthesis in horizontal cells. Neural Dev. 2010; 5:15. [PubMed: 20565821]

Schwartz EA. Responses of bipolar cells in the retina of the turtle. J Physiol. 1974; 236:211–224. [PubMed: 4818497]

Schwartz EA. Calcium-independent release of GABA from isolated horizontal cells of the toad retina. J Physiol. 1982; 323:211–227. [PubMed: 6808119]

Schwartz EA. Transport-mediated synapses in the retina. Physiol Rev. 2002; 82:875–891. [PubMed: 12270946]

Shelley J, Dedek K, Schubert T, Feigenspan A, Schultz K, Hombach S, Willecke K, Weiler R. Horizontal cell receptive fields are reduced in connexin57-deficient mice. Eur J Neurosci. 2006; 23:3176–3186. [PubMed: 16820008]

Sherry DM, Mitchell R, Standifer KM, du Plessis B. Distribution of plasma membrane-associated syntaxins 1 through 4 indicates distinct trafficking functions in the synaptic layers of the mouse retina. BMC Neurosci. 2006; 7:54. [PubMed: 16839421]

Shields CR, Klooster J, Claassen Y, Ul-Hussain M, Zoidl G, Dermietzel R, Kamermans M. Retinal horizontal cell-specific promoter activity and protein expression of zebrafish connexin 52.6 and connexin 55.5. J Comp Neurol. 2007; 501:765–779. [PubMed: 17299759]

Shields CR, Tran MN, Wong RO, Lukasiewicz PD. Distinct ionotropic GABA receptors mediate presynaptic and post-synaptic inhibition in retinal bipolar cells. J Neurosci. 2000; 20:2673–2682. [PubMed: 10729348]

Shiells RA, Falk G, Naghshineh S. Action of glutamate and aspartate analogues on rod, horizontal and bipolar cells. Nature. 1981; 294:592–594. [PubMed: 6273752]

Shimbo K, Toyoda JI, Kondo H, Kujiraoka T. Color-opponent responses of small and giant bipolar cells in the carp retina. Vis Neurosci. 2000; 17:609–621. [PubMed: 11016579]

Shou T, Wang W, Yu H. Orientation biased extended surround of the receptive field of cat retinal ganglion cells. Neuroscience. 2000; 98:207–212. [PubMed: 10854751]

Skrzypek J, Werblin F. Lateral interactions in absence of feedback to cones. J Neurophysiol. 1983; 49:1007–1016. [PubMed: 6854354]

Slaughter MM, Miller RF. 2-Amino-4-phosphonobutyric acid: A new pharmacological tool for retina research. Science. 1981; 211:182–185. [PubMed: 6255566]

Snellman J, Nawy S. cGMP-dependent kinase regulates response sensitivity of the mouse On bipolar cell. J Neurosci. 2004; 24:6621–6628. [PubMed: 15269274]

Snellman J, Mehta B, Babai N, Bartoletti TM, Akmentin W, Francis A, Matthews G, Thoreson W, Zenisek D. Acute destruction of the synaptic ribbon reveals a role for the ribbon in vesicle priming. Nat Neurosci. 2011; 14:1135–1141. [PubMed: 21785435]

Solomon SG, Lennie P. The machinery of colour vision. Nat Rev Neurosci. 2007; 8:276–286. [PubMed: 17375040]

Srinivasan MV, Laughlin SB, Dubs A. Predictive coding: a fresh view of inhibition in the retina. Proc R Soc Lond B Biol Sci. 1982; 216:427–459. [PubMed: 6129637]

Stell WK. Inputs to bipolar cell dendrites in goldfish retina. Vision Res. 1983; 23:1143–1150. [PubMed: 6649434]

Stell WK, Lightfoot DO. Color-specific interconnections of cones and horizontal cells in the retina of the goldfish. J Comp Neurol. 1975; 159:473–502. [PubMed: 1092733]

Stell WK, Lightfoot DO, Wheeler TG, Leeper HF. Goldfish retina: functional polarization of cone horizontal cell dendrites and synapses. Science. 1975; 190:989–990. [PubMed: 1188380]

Sterling, P.; Demb, JB. Retina. In: Shepherd, GM., editor. The Synaptic Organization of the Brain. 5. Oxford University Press; New York: 2004. p. 217-269.

Stone S, Schutte M. Physiological and morphological properties of OFF- and ON-center bipolar cells in the *Xenopus* retina: effects of glycine and GABA. Vis Neurosci. 1991; 7:363–376. [PubMed: 1751422]

Stone S, Witkovsky P. Center-surround organization of *Xenopus* horizontal cells and its modification by gamma-aminobutyric acid and strontium. Exp Biol. 1987; 47:1–12. [PubMed: 3666094]

Stone S, Witkovsky P, Schütte M. A chromatic horizontal cell in the Xenopus retina: intracellular staining and synaptic pharmacology. J Neurophysiol. 1990; 64:1683–1694. [PubMed: 1705962]

Szikra T, Barabas P, Bartoletti TM, Huang W, Akopian A, Thoreson WB, Krizaj D. Calcium homeostasis and cone signaling are regulated by interactions between calcium stores and plasma membrane ion channels. PLoS One. 2009; 4:e6723. [PubMed: 19696927]

Tatsukawa T, Hirasawa H, Kaneko A, Kaneda M. GABA-mediated component in the feedback response of turtle retinal cones. Vis Neurosci. 2005; 22:317–324. [PubMed: 16079007]

Teranishi T, Kato S, Negishi K. Lateral spread of S-potential components in the carp retina. Exp Eye Res. 1982; 34:389–399. [PubMed: 7067747]

Thibos LN, Werblin FS. The response properties of the steady antagonistic surround in the mudpuppy retina. J Physiol. 1978a; 278:79–99. [PubMed: 671342]

Thibos LN, Werblin FS. The properties of surround antagonism elicited by spinning windmill patterns in the mudpuppy retina. J Physiol. 1978b; 278:101–116. [PubMed: 671274]

Thoreson WB, Babai N, Bartoletti TM. Feedback from horizontal cells to rod photoreceptors in vertebrate retina. J Neurosci. 2008; 28:5691–5695. [PubMed: 18509030]

Thoreson WB, Bryson EJ. Chloride equilibrium potential in salamander cones. BMC Neurosci. 2004; 5:53. [PubMed: 15579212]

Thoreson WB, Burkhardt DA. Effects of synaptic blocking agents on the depolarizing responses of turtle cones evoked by surround illumination. Vis Neurosci. 1990; 5:571–583. [PubMed: 2085473]

Thoreson WB, Burkhardt DA. Ionic influences on the prolonged depolarization of turtle cones in situ. J Neurophysiol. 1991; 65:96–110. [PubMed: 1900325]

Tian N. Synaptic activity, visual experience and the maturation of retinal synaptic circuitry. J Physiol. 2008; 586:4347–4355. [PubMed: 18669531]

Tokutake Y, Freed MA. Retinal ganglion cells – spatial organization of the receptive field reduces temporal redundancy. Eur J Neurosci. 2008; 28:914–923. [PubMed: 18691326]

Tootle JS. Early postnatal development of visual function in ganglion cells of the cat retina. J Neurophysiol. 1993; 69:1645–1660. [PubMed: 8509831]

Toyoda, J-l; Fujimoto, M. Analyses of neural mechanisms mediating the effect of horizontal cells polarization. Vision Res. 1983; 23:1143– 1150. [PubMed: 6649434]

Toyoda J-L, Kujiraoka T. Analysis of bipolar cell responses elicited by polarization of horizontal cells. J Gen Physiol. 1982; 79:131–145. [PubMed: 6278053]

Toyoda JI, Saito T, Kondo H. Three types of horizontal cells in the stingray retina: their morphology and physiology. J Comp Neurol. 1978; 179:569–579. [PubMed: 641228]

Toyoda JI, Tonosaki K. Effect of polarisation of horizontal cells on the on-centre bipolar cell of carp retina. Nature. 1978; 276:399–400. [PubMed: 213734]

Tranchina D, Gordon J, Shapley R. Spatial and temporal properties of luminosity horizontal cells in the turtle retina. J Gen Physiol. 1983; 82:573–598. [PubMed: 6644270]

Trenholm S, Baldridge WH. The effect of aminosulfonate buffers on the light responses and intracellular pH of goldfish retinal horizontal cells. J Neurochem. 2010; 115:102–111. [PubMed: 20633206]

Trexler EB, Bukauskas FF, Bennett MV, Bargiello TA, Verselis VK. Rapid and direct effects of pH on connexins revealed by the connexin46 hemichannel preparation. J Gen Physiol. 1999; 113:721–742. [PubMed: 10228184]

Troy JB, Bohnsack DL, Diller LC. Spatial properties of the cat X-cell receptive field as a function of mean light level. Vis Neurosci. 1999; 16:1089–1104. [PubMed: 10614589]

Troy JB, Oh JK, Enroth-Cugell C. Effect of ambient illumination on the spatial properties of the center and surround of Y-cell receptive fields. Vis Neurosci. 1993; 10:753–764. [PubMed: 8338811]

Troy JB, Shou T. The receptive fields of cat retinal ganglion cells in physiological and pathological states: where we are after half a century of research. Prog Retin Eye Res. 2002; 21:263–302. [PubMed: 12052385]

Trümpler J, Dedek K, Schubert T, de Sevilla Müller LP, Seeliger M, Humphries P, Biel M, Weiler R. Rod and cone contributions to horizontal cell light responses in the mouse retina. J Neurosci. 2008; 28:6818–6825. [PubMed: 18596157]

Tsukamoto Y, Smith RG, Sterling P. “Collective coding” of correlated cone signals in the retinal ganglion cell. Proc Natl Acad Sci USA. 1990; 87:1860–1864. [PubMed: 2308947]

Twig G, Levy H, Perlman I. Color opponency in horizontal cells of the vertebrate retina. Prog Retin Eye Res. 2003; 22:31–68. [PubMed: 12597923]

VanLeeuwen M, Fahrenfort I, Sjoerdsma T, Numan R, Kamermans M. Lateral gain control in the outer retina leads to potentiation of center responses of retinal neurons. J Neurosci. 2009; 29:6358–6366. [PubMed: 19439613]

VanLeeuwen M, Joselovitch C, Fahrenfort I, Kamermans M. The contribution of the outer retina to color constancy: A general model for color constancy synthesized from primate and fish data. Vis Neurosci. 2007; 24:277–290. [PubMed: 17592668]

Vardi N, Kaufman DL, Sterling P. Horizontal cells in cat and monkey retina express different isoforms of glutamic acid decarboxylase. Vis Neurosci. 1994; 11:135–142. [PubMed: 8011576]

Vardi N, Masarachia P, Sterling P. Immunoreactivity to GABAA receptor in the outer plexiform layer of the cat retina. J Comp Neurol. 1992; 320:394–397. [PubMed: 1377202]

Vardi N, Sterling P. Subcellular localization of GABAA receptor on bipolar cells in macaque and human retina. Vision Res. 1994; 34:1235–1246. [PubMed: 8023433]

Vardi N, Zhang LL, Payne JA, Sterling P. Evidence that different cation chloride cotransporters in retinal neurons allow opposite responses to GABA. J Neurosci. 2000; 20:7657–7663. [PubMed: 11027226]

Varela C, Blanco R, De La Villa P. Depolarizing effect of GABA in rod bipolar cells of the mouse retina. Vision Res. 2005; 45:2659–2667. [PubMed: 15923018]

Ventura DF, de Souza JM, Devoe RD, Zana Y. UV responses in the retina of the turtle. Vis Neurosci. 1999; 16:191–204. [PubMed: 10367955]

Versaux-Botteri C, Pochet R, Nguyen-Legros J. Immunohistochemical localization of GABA-containing neurons during postnatal development of the rat retina. Invest Ophthalmol Vis Sci. 1989; 30:652–659. [PubMed: 2649448]

Verweij J, Kamermans M, Spekreijse H. Horizontal cells feed back to cones by shifting the cone calcium-current activation range. Vision Res. 1996; 36:3943–3953. [PubMed: 9068848]

Verweij J, Hornstein EP, Schnapf JL. Surround antagonism in macaque cone photoreceptors. J Neurosci. 2003; 23:10249–10257. [PubMed: 14614083]

Vessey JP, Lalonde MR, Mizan HA, Welch NC, Kelly ME, Barnes S. Carbenoxolone inhibition of voltage-gated Ca channels and synaptic transmission in the retina. J Neurophysiol. 2004; 92:1252–1256. [PubMed: 15028741]

Vessey JP, Stratis AK, Daniels BA, Da Silva N, Jonz MG, Lalonde MR, Baldridge WH, Barnes S. Proton-mediated feedback inhibition of presynaptic calcium channels at the cone photoreceptor synapse. J Neurosci. 2005; 25:4108–4117. [PubMed: 15843613]

Vigh J, Witkovsky P. Sub-millimolar cobalt selectively inhibits the receptive field surround of retinal neurons. Vis Neurosci. 1999; 16:159–168. [PubMed: 10022487]

Vu TQ, Payne JA, Copenhagen DR. Localization and developmental expression patterns of the neuronal K-Cl cotransporter (KCC2) in the rat retina. J Neurosci. 2000; 20:1414–1423. [PubMed: 10662832]

Wagner HG, MacNichol EF Jr, Wolbarsht ML. The response properties of single ganglion cells in the goldfish retina. J Gen Physiol. 1960; 43:45–62. [PubMed: 19873528]

Wagner HJ. Light-dependent plasticity of the morphology of horizontal cell terminals in cone pedicles of fish retinas. J Neurocytol. 1980; 9:573–590. [PubMed: 7441304]

Wagner HJ, Djamgoz MB. Spinules: a case for retinal synaptic plasticity. Trends Neurosci. 1993; 16:201–206. [PubMed: 7688159]

Wang H, Standifer KM, Sherry DM. GABA(A) receptor binding and localization in the tiger salamander retina. Vis Neurosci. 2000; 17:11–21. [PubMed: 10750823]

Wang P, Slaughter MM. Effects of GABA receptor antagonists on retinal glycine receptors and on homomeric glycine receptor alpha subunits. J Neurophysiol. 2005; 93:3120–3126. [PubMed: 15728760]

Wang Y, Mangel SC. A circadian clock regulates rod and cone input to fish retinal cone horizontal cells. Proc Natl Acad Sci USA. 1996; 93:4655–4660. [PubMed: 8643459]

Warrant EJ. Seeing better at night: life style, eye design and the optimum strategy of spatial and temporal summation. Vision Res. 1999; 39:1611–1630. [PubMed: 10343855]

Wässle H, Koulen P, Brandstätter JH, Fletcher EL, Becker CM. Glycine and GABA receptors in the mammalian retina. Vision Res. 1998; 38:1411–1430. [PubMed: 9667008]

Weckström M, Laughlin S. Extracellular potentials modify the transfer of information at photoreceptor output synapses in the blowfly compound eye. J Neurosci. 2010; 30:9557–9566. [PubMed: 20631184]

Weiler R, Wagner HJ. Light-dependent change of cone-horizontal cell interactions in carp retina. Brain Res. 1984; 298:1–9. [PubMed: 6326947]

Weinstein GW, Hobson RR, Baker FH. Extracellular recordings from human retinal ganglion cells. Science. 1971; 171:1021–1022. [PubMed: 5542805]

Werblin FS. Response of retinal cells to moving spots: intracellular recording in *Necturus maculosus*. J Neurophysiol. 1970; 33:342–350. [PubMed: 5439341]

Werblin FS. Adaptation in a vertebrate retina: intracellular recording in *Necturus*. J Neurophysiol. 1971; 34:228–241. [PubMed: 5545938]

Werblin FS. Lateral interactions at inner plexiform layer of the vertebrate retina: antagonistic responses to change. Science. 1972; 175:1008–1010. [PubMed: 5009392]

Werblin FS, Copenhagen DR. Control of retinal sensitivity. 3 Lateral interactions at the inner plexiform layer. J Gen Physiol. 1974; 63:88–110. [PubMed: 4359065]

Werblin FS, Dowling JE. Organization of the retina of the mudpuppy, *Necturus maculosus* II Intracellular recording. J Neurophysiol. 1969; 32:339–355. [PubMed: 4306897]

Wheeler TG, Naka KI. The modes of chromatic interactions in the retina. Vision Res. 1977; 17:1015–1018. [PubMed: 595409]

Wilson, M. Retinal synapses. In: Chalupa, LM.; Werner, JS., editors. The Visual Neurosciences. MIT Press; Cambridge, MA: 2004. p. 279-303.

Witkovsky P, Burkhardt DA, Nagy AR. Synaptic connections linking cones and horizontal cells in the retina of the pikeperch (*Stizostedion vitreum*). J Comp Neurol. 1979; 186:541–559. [PubMed: 15116688]

Wong KY, Dowling JE. Retinal bipolar cell input mechanisms in giant danio. III ON-OFF bipolar cells and their color-opponent mechanisms. J Neurophysiol. 2005; 94:265–272. [PubMed: 15758056]

Wright R, Raimondo JV, Akerman CJ. Spatial and temporal dynamics in the ionic driving force for $GABA_A$ receptors. Neural Plasticity. 2011; 2011:728395. [PubMed: 21766044]

Wu SM. Effects of gamma-aminobutyric acid on cones and bipolar cells of the tiger salamander retina. Brain Res. 1986; 365:70–77. [PubMed: 3947987]

Wu SM. Input-output relations of the feedback synapse between horizontal cells and cones in the tiger salamander retina. J Neurophysiol. 1991; 65:1197–1206. [PubMed: 1651374]

Wu SM. Feedback connections and operation of the outer plexiform layer of the retina. Curr Opin Neurobiol. 1992; 2:462–468. [PubMed: 1525544]

Wu SM. Synaptic organization of the vertebrate retina: general principles and species-specific variations: the Friedenwald lecture. Invest Ophthalmol Vis Sci. 2010; 51:1263–1274. [PubMed: 20185835]

Xin D, Bloomfield SA. Dark- and light-induced changes in coupling between horizontal cells in mammalian retina. J Comp Neurol. 1999; 405:75–87. [PubMed: 10022197]

Yamamoto F, Borgula GA, Steinberg RH. Effects of light and darkness on pH outside rod photoreceptors in the cat retina. Exp Eye Res. 1992; 54:685–697. [PubMed: 1623953]

Yamamoto K, Jouhou H, Iwasaki M, Kaneko A, Yamada M. Strongly pH-buffered ringer's solution expands the receptive field size of horizontal cells in the carp retina. Zoolog Sci. 2008; 25:419–427. [PubMed: 18459824]

Yamasaki EN, Barbosa VD, De Mello FG, Hokoc JN. GABAergic system in the developing mammalian retina: dual sources of GABA at early stages of postnatal development. Int J Dev Neurosci. 1999; 17:201–213. [PubMed: 10452364]

Yang CY, Lin ZS, Yazulla S. Localization of $GABA_A$ receptor subtypes in the tiger salamander retina. Vis Neurosci. 1992; 8:57–64. [PubMed: 1310871]

Yang XL. Characterization of receptors for glutamate and GABA in retinal neurons. Prog Neurobiol. 2004; 73:127–150. [PubMed: 15201037]

Yang XL, Fan TX, Shen W. Effects of prolonged darkness on light responsiveness and spectral sensitivity of cone horizontal cells in carp retina in vivo. J Neurosci. 1994; 14:326–334. [PubMed: 8283240]

Yang XL, Gao F, Wu SM. Modulation of horizontal cell function by $GABA_A$ and $GABA_C$ receptors in dark- and light-adapted tiger salamander retina. Vis Neurosci. 1999; 16:967–979. [PubMed: 10580732]

Yang XL, Wu SM. Synaptic inputs from rods and cones to horizontal cells in the tiger salamander retina. Sci China B. 1990; 33:946–954. [PubMed: 2242218]

Yang XL, Wu SM. Feedforward lateral inhibition in retinal bipolar cells: input-output relation of the horizontal cell-depolarizing bipolar cell synapse. Proc Natl Acad Sci USA. 1991; 88:3310–3313. [PubMed: 1849650]

Yazulla S. Cone input to bipolar cells in the turtle retina. Vision Res. 1976; 16:737–744. [PubMed: 960598]

Yazulla S. Endocannabinoids in the retina: from marijuana to neuroprotection. Prog Retin Eye Res. 2008; 27:501–526. [PubMed: 18725316]

Yazulla S, Kleinschmidt J. Carrier-mediated release of GABA from retinal horizontal cells. Brain Res. 1983; 263:63–75. [PubMed: 6132667]

Yazulla S, Studholme KM, Vitorica J, de Blas AL. Immunocytochemical localization of GABAA receptors in goldfish and chicken retinas. J Comp Neurol. 1989; 280:15–26. [PubMed: 2537342]

Zhang AJ, Jacoby R, Wu SM. Light- and dopamine-regulated receptive field plasticity in primate horizontal cells. J Comp Neurol. 2011; 519:2125–2134. [PubMed: 21452210]

Zhang AJ, Wu SM. Receptive fields of retinal bipolar cells are mediated by heterogeneous synaptic activity. J Neurosci. 2009; 29:787–797.

Zhang J, Wu SM. Physiological properties of rod photoreceptor electrical coupling in the tiger salamander retina. J Physiol. 2005; 564:849–862. [PubMed: 15746168]

Zhang J, Zhang AJ, Wu SM. Immunocytochemical analysis of GABA-positive and calretinin-positive horizontal cells in the tiger salamander retina. J Comp Neurol. 2006; 499:432–441. [PubMed: 16998928]

Zhang Z, Nguyen KT, Barrett EF, David G. Vesicular ATPase inserted into the plasma membrane of motor terminals by exocytosis alkalinizes cytosolic pH and facilitates endocytosis. Neuron. 2010; 68:1097–1108. [PubMed: 21172612]

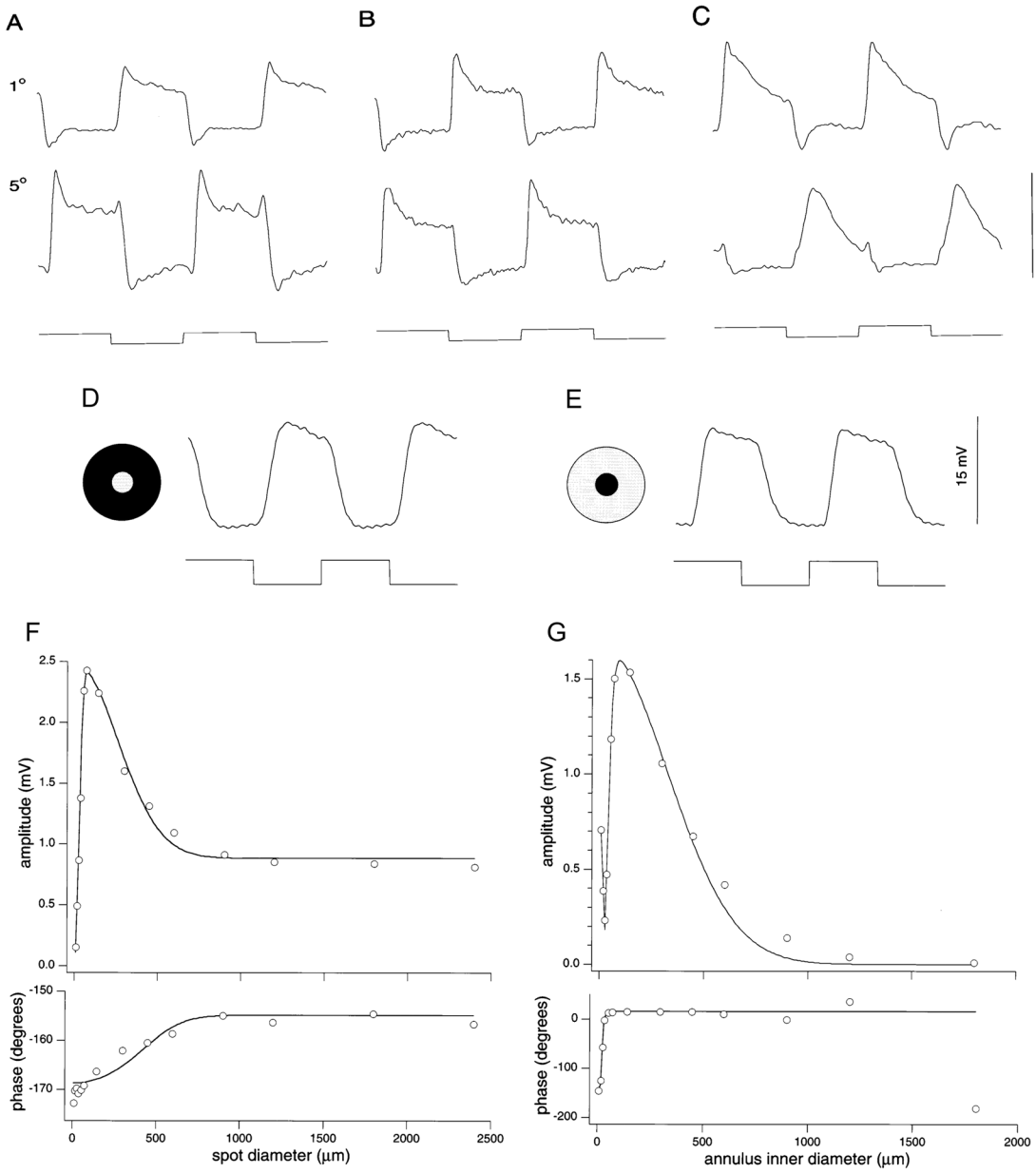

Fig. 1.

The receptive field surround of monkey cone-driven bipolar cells exhibits both surround activation and surround antagonism when the mean background illumination is maintained in the photopic range. (A–C)Responses of three diffuse monkey cone bipolar cells to 100% luminance contrast. (A, B)Two OFF-center bipolar cells hyperpolarized to a 1° diameter spot that stimulated only the receptive field center (upper traces) and depolarized to a 5° spot that stimulated both center and surround (lower traces). Temporal frequency was 2.44 Hz in A and 1.22 Hz in B. (C) ON-center bipolar cell depolarized to the 1° spot (upper trace) and hyperpolarized to the 5° spot (lower trace). Stimulus temporal frequency was 2.44 Hz. Scale bar = 6 mV for traces in A and 2 mV for traces in B and C. Stimulus waveform is shown below the traces. (D–G) Center-surround receptive field structure of an OFF-center, midget cone bipolar cell from monkey retina. (D) Cell hyperpolarized to a small 150 μm diameter

spot centered on the receptive field. (E) Cell depolarized to an annulus (inner diameter = 150 μm; outer diameter = 1200 μm). Stimulus waveform is shown below the traces in D and E. (F, G) Responses of the same cell to sinusoidally flickering spots (2.44 Hz) of increasing size (F) and sinusoidally flickering annuli (2.44) Hz) of increasing inner diameter (G). All stimuli were centered on the receptive field and presented on a steady photopic background of the same mean luminance as the stimuli (1000 td). Modulation contrast was 100%. Fourier analysis was used to determine the amplitude and phase of the cell's center (spot) and surround (annular) responses at the temporal frequency of the stimulus modulation. Upper plots in F and G show response amplitude, lower plots show response phase. Solid lines in F and G are the difference of Gaussians model fits to the data. The ratio of the surround to center weights for this cell was 0.7. The phase of the responses in degrees is relative to the phase of the sinusoidally flickering spots and annuli. Modified from Dacey et al. (2000).

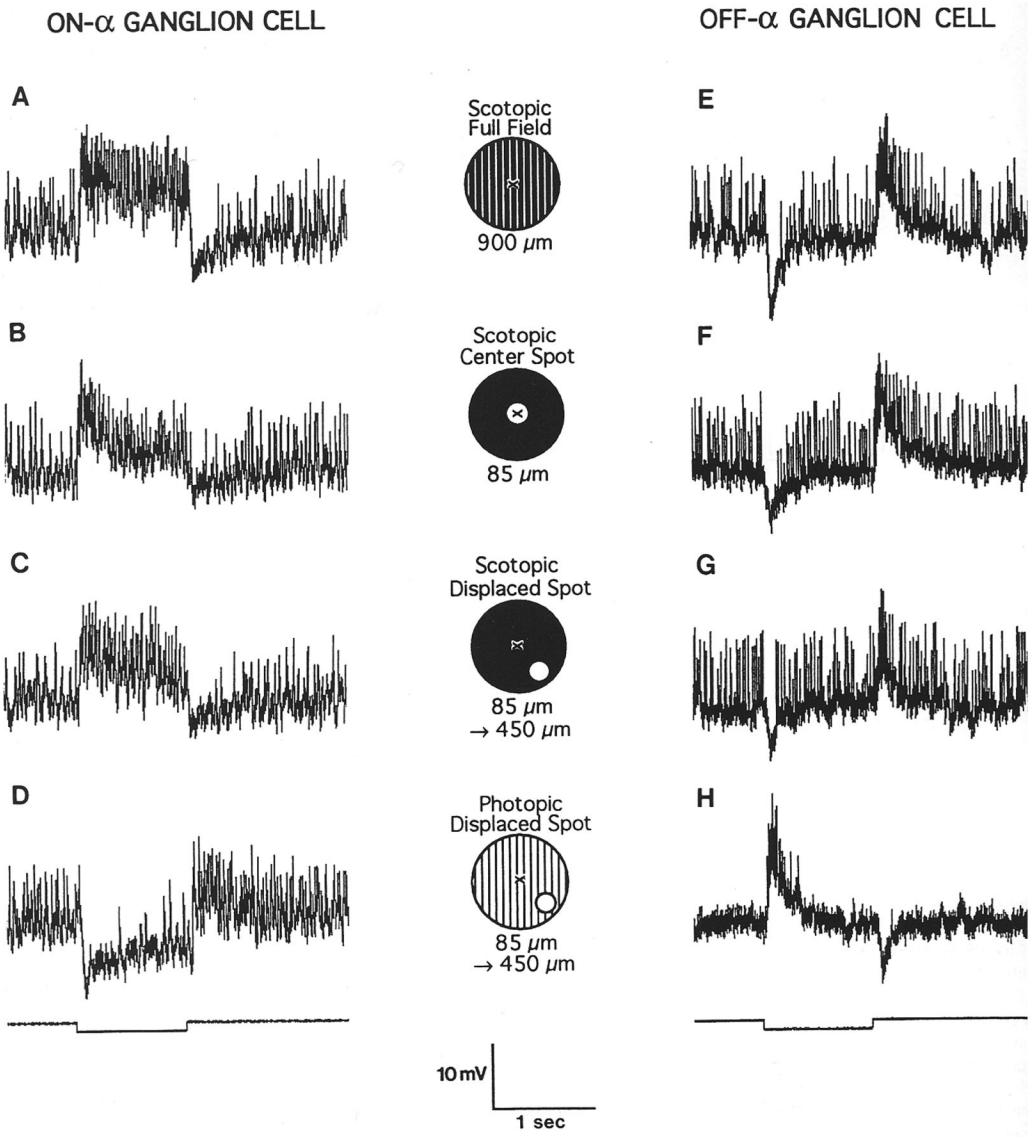

Fig. 2.

ON-center and OFF-center alpha (brisk transient) rabbit ganglion cells produce both center and surround light responses under photopic background conditions, but the surround is absent or minimal under scotopic conditions. Under dark-adapted, scotopic background illumination conditions, ON-center (A, B, and C on left side) and OFF-center (E, F, and G on right side) ganglion cells evoked center responses to full-field scotopic illumination (A and E), to a dim spot stimulus centered on the cell soma (B and F), and to a dim spot stimulus displaced to the edge of the receptive field, 450 μm from the soma (C and G). Under maintained light-adapted photopic background illumination, the ON-center (D) and OFF-center (H) ganglion cells generated opposite polarity surround responses to a small spot stimulus displaced to the edge of the receptive field, 450 μm from the soma. Spots (85 μm diameter) were 2.5 log units brighter than the background in all cases. Occurrence of light stimuli is indicated by the step traces below the voltage responses. Modified from Muller and Dacheux (1997).

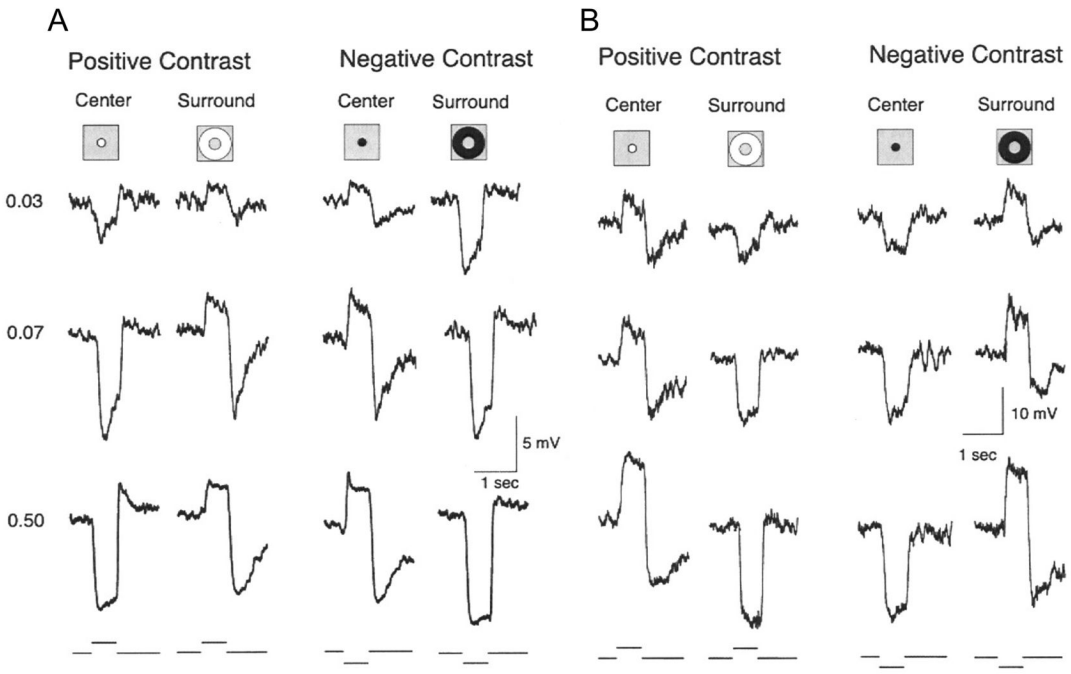

Fig. 3.

Responses of an OFF-center bipolar cell (A) and an ON-center bipolar cell (B) to contrast steps of positive and negative contrast presented in the center and surround of the receptive field. (A) The center stimulus was a spot of 272 μm in diameter. The surround stimulus was a concentric annulus of 393 μm inner diameter (i.d.) and 2030 μm outer diameter (o.d.) (B) The center stimulus was a spot of 515 μm in diameter. The surround stimulus was a concentric annulus of 757 μm i.d. and 2030 μm o.d. The contrasts of the steps were ±.03, ±.07, and ±.50 as shown on the left. The retina was adapted to a steady, 20 cd/m^{2}background field of 2030 μm in diameter. Modified from Fahey and Burkhardt (2003).

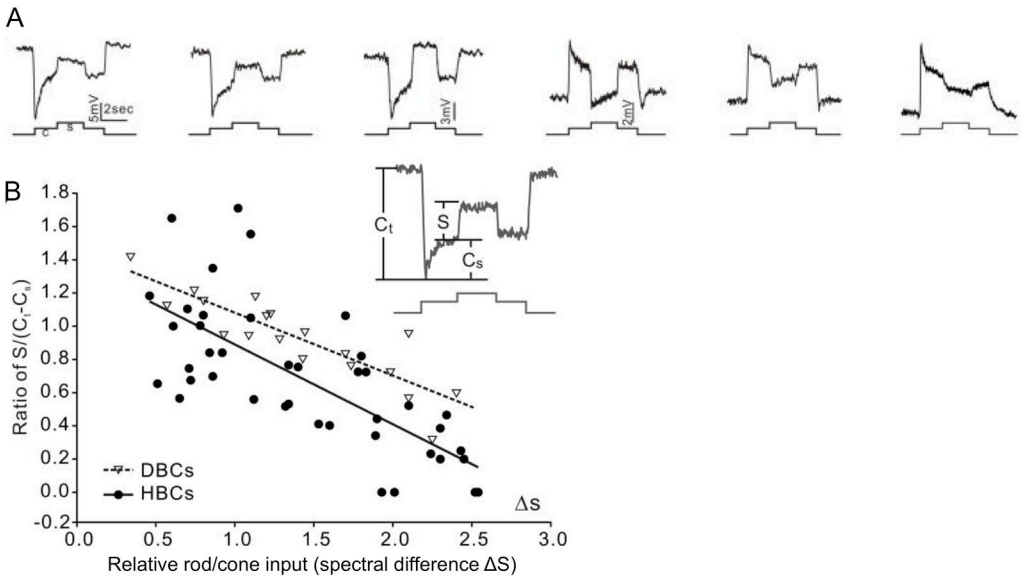

Fig. 4.

Light response characteristics of six bipolar cell types (A) and scatter plots of their receptive field properties (B). (A) Voltage responses of the six bipolar cell types elicited by a center light spot (300 μm diameter) and a surround light annulus (700 μm inner diameter, 2000 μm outer diameter). The surround light annulus was of the same intensity (700 nm, −2 log I_o, where I_o was the unattenuated intensity of 500 nm light = 2.05×10^7 photons/μm^2/s) for all 6 cells whereas the intensity of the center light spot was adjusted so that it allowed the annulus to produce the maximum response. (B) Scatter plots of relative surround/center response ratio [$S/(C_t - C_s)$] versus spectral difference ΔS of ON-center bipolar cells (open triangles and dashed line) and OFF-center bipolar cells (filled circles and solid line). Straight lines are linear regression lines of the data points. S, C_t, and C_s are the surround, transient center, and sustained rebound responses, respectively. The spectral difference ΔS of a cell was defined as $S_{700} - S_{500}$, in which S_{700} and S_{500} are the intensities of 700 and 500 nm light stimuli that elicit responses of the same amplitude. Because ΔS of rods is ~3.4 and that for cones is ~0.1 in the tiger salamander retina (Yang and Wu, 1990), bipolar cells with $\Delta S > 2.0$ were defined as rod-dominated, those with $\Delta S < 1.0$ were defined as cone-dominated, and those with $1.0 < \Delta S < 2.0$ were defined as mixed rod-cone bipolar cells. Modified from Zhang and Wu (2009).

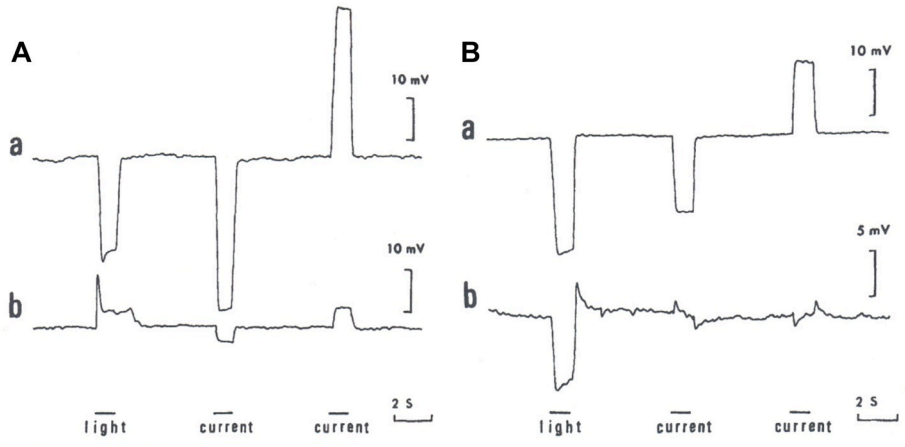

Fig. 5.

Examples of simultaneous recordings in the carp retina from a luminosity-type (L-type) H1 cone horizontal cell and a nearby ON-center bipolar cell (A) and a different L-type H1 cone horizontal cell and a nearby OFF-center bipolar cell (B). (A) Responses of the L-type horizontal cell (a) and the ON-center bipolar cell (b) to diffuse white light and to polarization of the horizontal cell by a current of 20 nA. (B) Responses of an L-type horizontal cell (a) and a nearby OFF-center bipolar cell (b) to diffuse white light and to polarization of the horizontal cell by a current of 20 nA. Similar effects of current injections into chromaticity-type (C-type) cone horizontal cells on nearby ON-center and OFF-center bipolar cells as shown here were also observed (Toyoda and Kujiraoka, 1982). Following light adaptation of the fish retina, L-type H1 cone horizontal cells hyperpolarize to all wavelengths (400–700 nm) of visible light, whereas one kind of C-type (H2) cone horizontal cell depolarizes to red (e.g., 650 nm) stimuli but hyperpolarizes to blue and green stimuli, and a second kind of C-type (H3) cone horizontal cell depolarizes to green (e.g., 500 nm) stimuli but hyperpolarizes to blue and red stimuli. L-type and C-type cone horizontal cells all hyperpolarize to full-field (diffuse) white light stimuli. Modified from Toyoda and Kujiraoka,1982 (©1982 Rockefeller University Press).

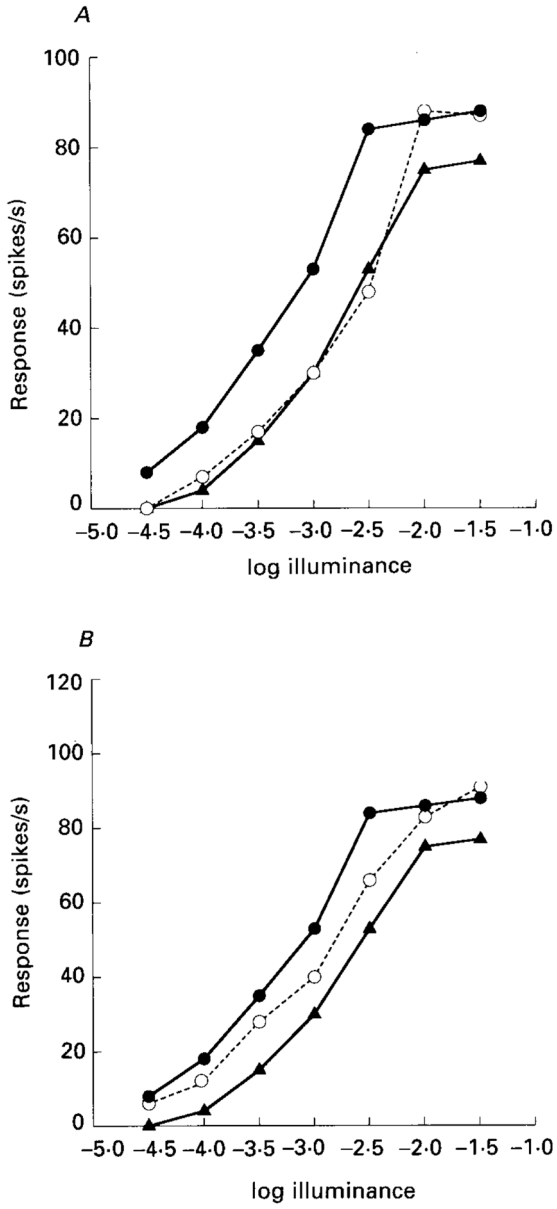

Fig. 6.

(A, B) Antagonism of the spot (receptive field center) responses of an ON-center brisk sustained rabbit ganglion cell by light stimulation of the receptive field surround with an annulus or by hyperpolarizing current injections into a nearby horizontal cell. The magnitude of the antagonistic effect on the spot response of the ganglion cell was greater with larger amplitude (10 nA), than with smaller amplitude (4 nA), current injections. Each data point represents the average response of the ganglion cell (spikes/s) to five flashes of the spot stimulus. (A) Spot alone (filled circles), spot and annulus (open circles), and spot and 10 nA hyperpolarizing current (filled triangles) data are shown. (B) Spot alone (filled circles), spot and 4 nA hyperpolarizing current (open circles), and spot and 10 nA hyperpolarizing current (filled triangles) data are shown. The spot (400 μm diameter) was presented alone, in conjunction with a constant intensity annulus (i.d. = 750 μm; o.d. = 3 mm), or in conjunction with the hyperpolarizing phase of a sinusoidally modulated current

(0.1 Hz) injected into the horizontal cell located 225 μm laterally from the ganglion cell. A full-field light background of 0.5 cd/m^2 (mesopic range) was present throughout the course of the experiment. Modified from Mangel (1991).

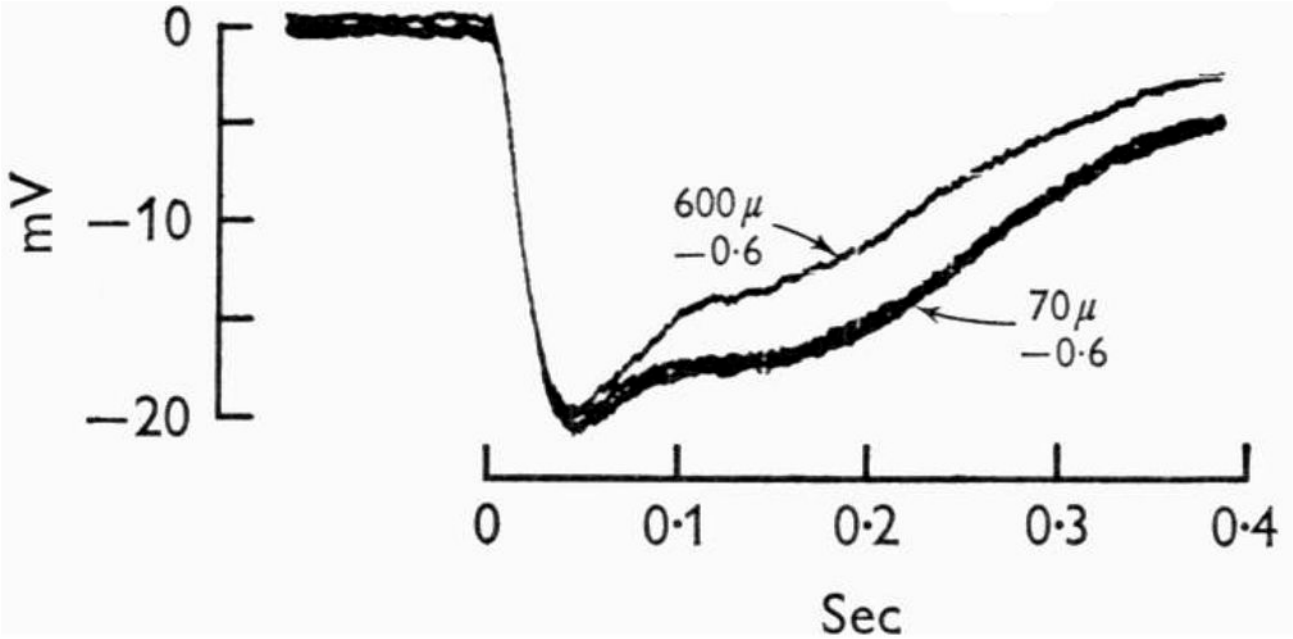

Fig. 7.
Responses of a turtle cone to small (70 μm) and large (600 μm) spots of equal intensity light. The small and large spots evoked the same peak hyperpolarization but the large spots also evoked a delayed depolarization (Baylor et al., 1971).

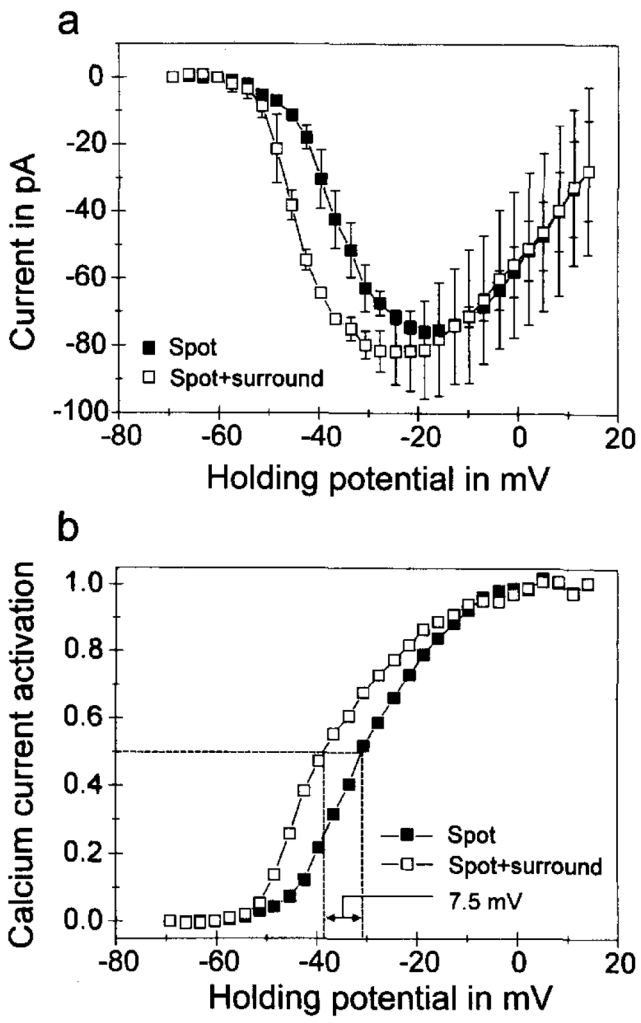

Fig. 8.

Effects of negative feedback from horizontal cells onto cone I_{Ca} in goldfish retina. Compared to I_{Ca} measured while steadily illuminating the cone with a small spot of light (filled squares), illumination of the receptive field surround (open squares) caused I_{Ca} to activate at more negative membrane potentials (A), shifting activation leftward along the voltage axis (B). Note the increase in peak amplitude of I_{Ca} that accompanies this leftward shift (Verweij et al., 1996).

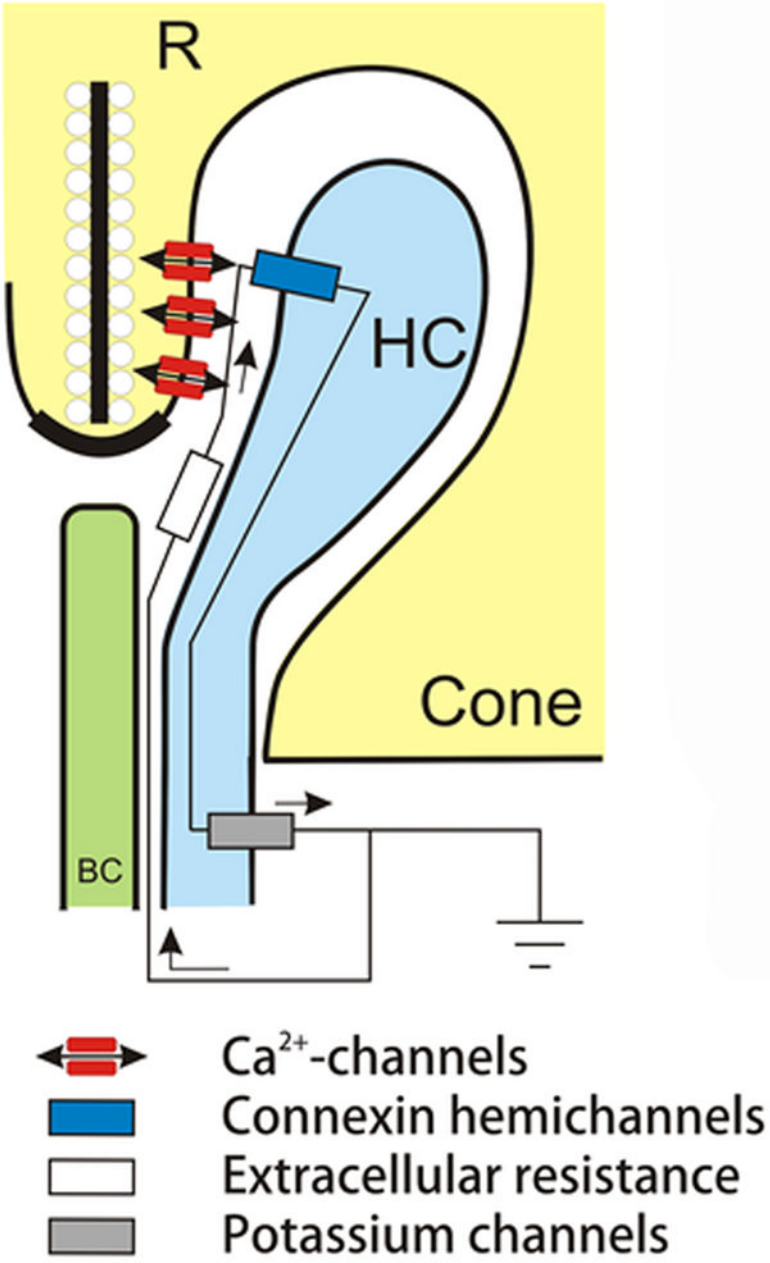

Fig. 9.

Schematic representation of the ephaptic feedback hypothesis. Horizontal (HC) and bipolar cell (BC) dendrites enter the invaginating cone synapse. The synaptic ribbon is represented as a vertical black bar (R) surrounded by white synaptic vesicles. The location of cone Ca^{2+} channels are shown in red, connexins in the HC membrane are shown in blue, and leak potassium channels are shown in gray (Fahrenfort et al., 2009).

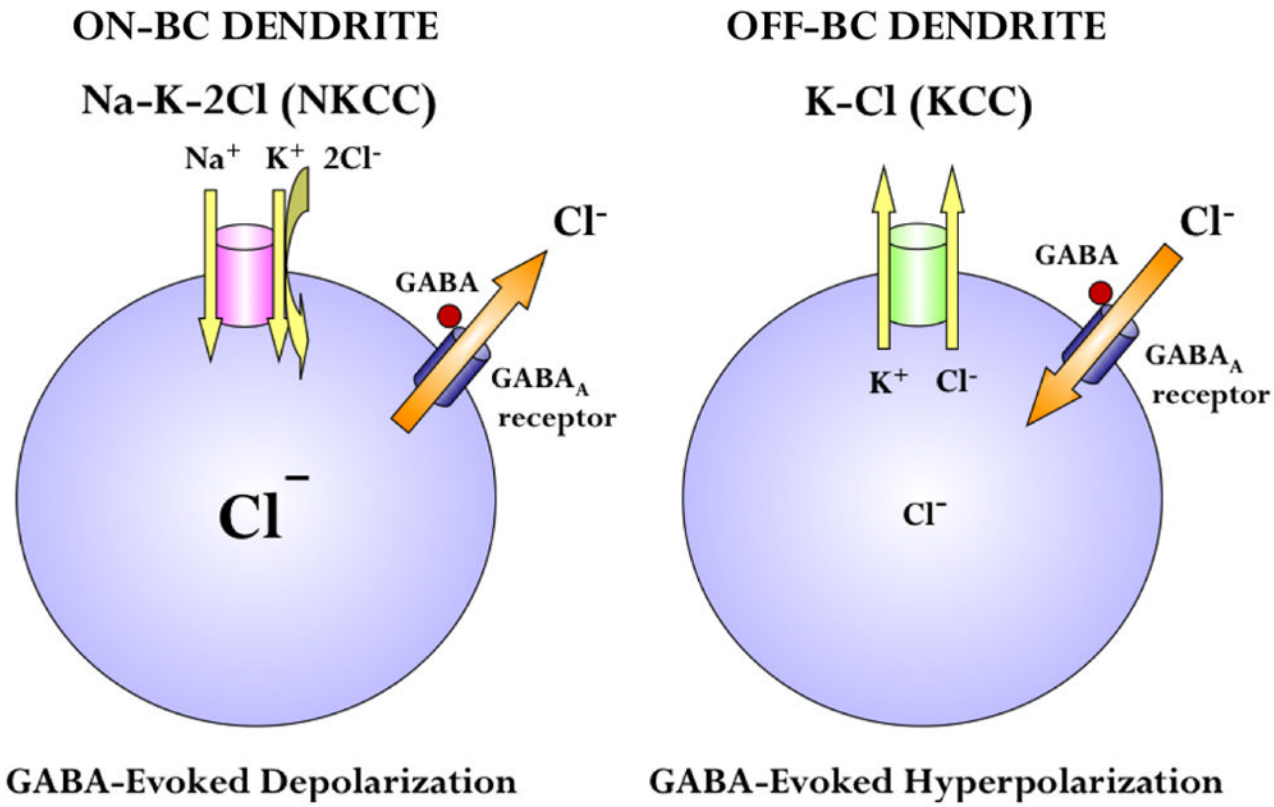

Fig. 10.

The chloride cotransporters, Na-K-2Cl (NKCC) and K-Cl (KCC), determine whether $GABA_A$ receptor activation, which opens chloride (Cl^-) channels, depolarizes or hyperpolarizes neurons, respectively. ON-center cone bipolar cell (BC) dendrites express NKCC and OFF-center cone bipolar cell dendrites express the KCC subtype, KCC2. See text for details.

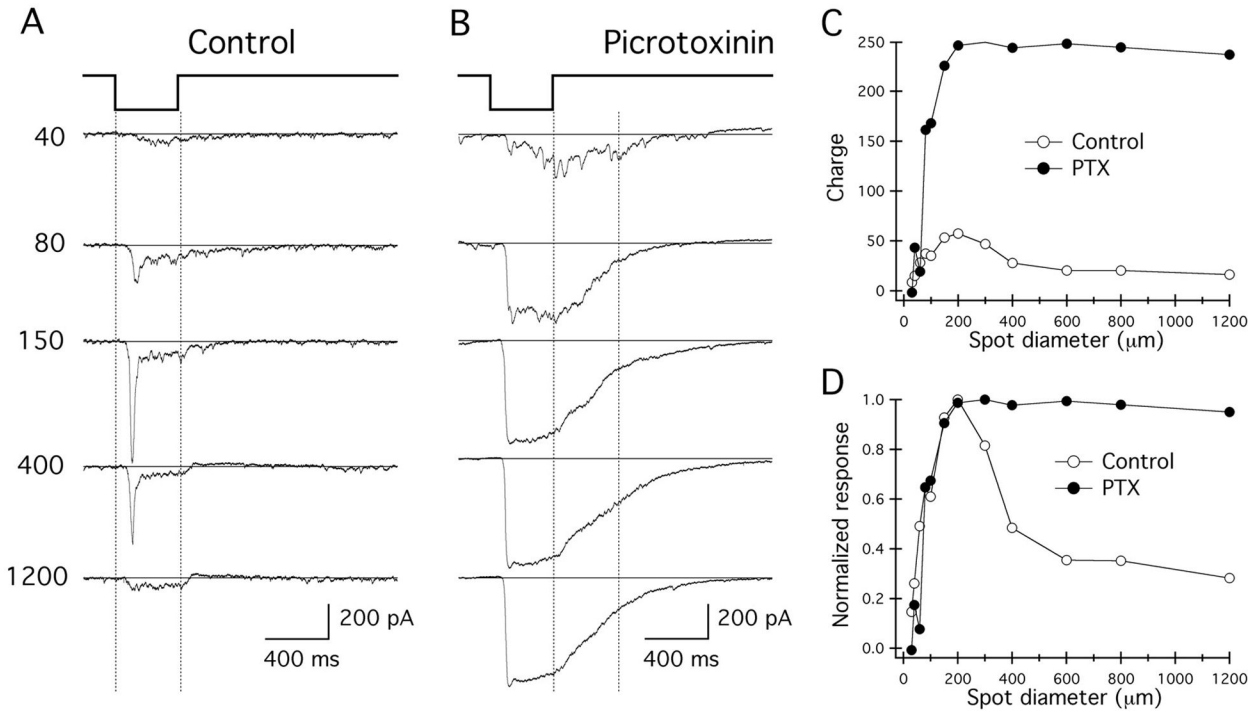

Fig. 11.

Light-induced currents of an OFF rabbit ganglion cell that was voltage clamped at the Cl^- reversal potential (V_H of −45 mV) to reveal the excitatory signal arriving from bipolar cells. (A) Spots of increasing diameters elicited transient inward currents that were strongly attenuated with large spots. (B) Application of picrotoxinin (100 μM) caused a substantial increase of the light-evoked currents and became more sustained, and large spots did not attenuate the currents. (C) Area–response curves showing the charge transfer (in picocoulombs) of the currents in A and B, respectively. (D) Normalized area–response curves of the records in A and B, respectively. In the control record, the large spot attenuation is apparent, and during application of picrotoxinin this attenuation appears to be primarily blocked. The intensity of the background illumination (= 0.7 cd/m^2) maintained the retina under mesopic light conditions. Modified from Flores-Herr et al. (2001).