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Inhibitory Interneurons in the Retina: Types, Circuitry, and Function*

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horizontal cell, amacrine cell, feedback inhibition, feedforward inhibition, visual processing

Abstract

Visual signals in the vertebrate retina are shaped by feedback and feedforward inhibition in two synaptic layers. In one, horizontal cells establish fundamental center-surround receptive-field properties via morphologically and physiologically complex synapses with photoreceptors and bipolar cells. In the other, a panoply of amacrine cells imbue ganglion cell responses with spatiotemporally complex information about the visual world. Here, I review current ideas about horizontal cell signaling, considering the evidence for and against the leading, competing theories. I also discuss recent work that has begun to make sense of the remarkable morphological and physiological diversity of amacrine cells. These latter efforts have been aided tremendously by increasingly complete connectivity maps of inner retinal circuitry and new genetic tools that enable study of individual, sparsely expressed amacrine cell types.

INTRODUCTION

In the vertebrate retina, photoreceptors transduce light energy into a neural signal that is relayed via bipolar cells to ganglion cells, whose axons form the optic nerve and the sole connection between the retina and the rest of the central nervous system (CNS). Visual signals along this radial, glutamatergic pathway are shaped by two lateral inhibitory networks (**Figure 1*a***). The first, in the outer plexiform layer (OPL), comprises horizontal cells that provide feedback and feedforward inhibition to photoreceptors and bipolar cells, respectively, thereby generating the initial center-surround receptive fields in the visual pathway. In the second inhibitory network, amacrine cells in the inner plexiform layer (IPL) shape visual signals in bipolar cell synaptic terminals and ganglion cell dendrites, computing and encoding many complex features of the visual world.

This deceptively simple circuit diagram is made substantially more complicated by morphologically and mechanistically complex synapses, particularly those in the OPL, and an imposing diversity of subtypes within each cell class, especially in the inner retina. Most mammalian retinas contain just 3–4 different photoreceptors and 1–2 different horizontal cells, but the synaptic mechanisms underlying horizontal cell–mediated feedback inhibition onto cone photoreceptors have proved quite difficult to determine conclusively. In the inner retina, ~15 different bipolar cells (Helmstaedter et al. 2013, Wassle et al. 2009) contact more than 30 different ganglion cells (Baden et al. 2016) in the precisely stratified IPL neuropil, and more than 45 different amacrine cells influence these excitatory connections via presynaptic (feedback) and postsynaptic (feedforward) inhibition (Helmstaedter et al. 2013, MacNeil & Masland 1998). Making sense of the synaptic mechanisms underlying horizontal cell feedback and the visual processing requiring such amacrine cell diversity are two major goals facing retinal neuroscience in the next decade; this review focuses on the current ideas and recent experiments directed toward achieving these goals.

Perhaps no area of neuroscience has benefitted more than retinal physiology from recent advances in mouse genetics together with emerging anatomical approaches to dense neural circuit reconstruction (connectomics). Transgenic mouse lines expressing fluorescent proteins under the control of specific promoters now make it possible to identify—and, in many cases, manipulate—individual cell subtypes reliably within the intact retina (Siegert et al. 2009, Wassle et al. 2009, Zhu et al. 2014). Moreover, the first substantial effort at a dense reconstruction of a mammalian CNS circuit targeted the IPL of the mouse retina (Helmstaedter et al. 2013). Although this initial connectome does not provide unequivocal information regarding synaptic connectivity, it has proved to be a powerful tool for generating hypotheses that can now be tested in transgenic mouse lines. The confluence of these remarkable technical advances presents an exciting, unprecedented opportunity to relate in biophysical detail the structure and function of this elegant neural network.

Here, following a brief overview of retinal circuitry, I consider horizontal cells and the primary theories for how they mediate feedback inhibition onto cones and feedforward inhibition to bipolar cells. This is followed by a longer discussion of amacrine cell diversity and functional roles in visual processing in the inner retina. Recent work on several specific amacrine cell subtypes is discussed, with particular focus on interesting new insights into visual processing. The goal in this latter part of the review is to provide a sufficient circuit and functional context to discuss some of the most interesting questions facing the field—not only regarding specific amacrine cell types and circuit computations but also larger themes concerning the entire cell class.

A VERY BRIEF OVERVIEW OF RETINAL CIRCUITRY

A basic knowledge of neuronal types and connectivity in the vertebrate retina is required to understand the discussion below. The following outline of retinal circuitry is intended only as a

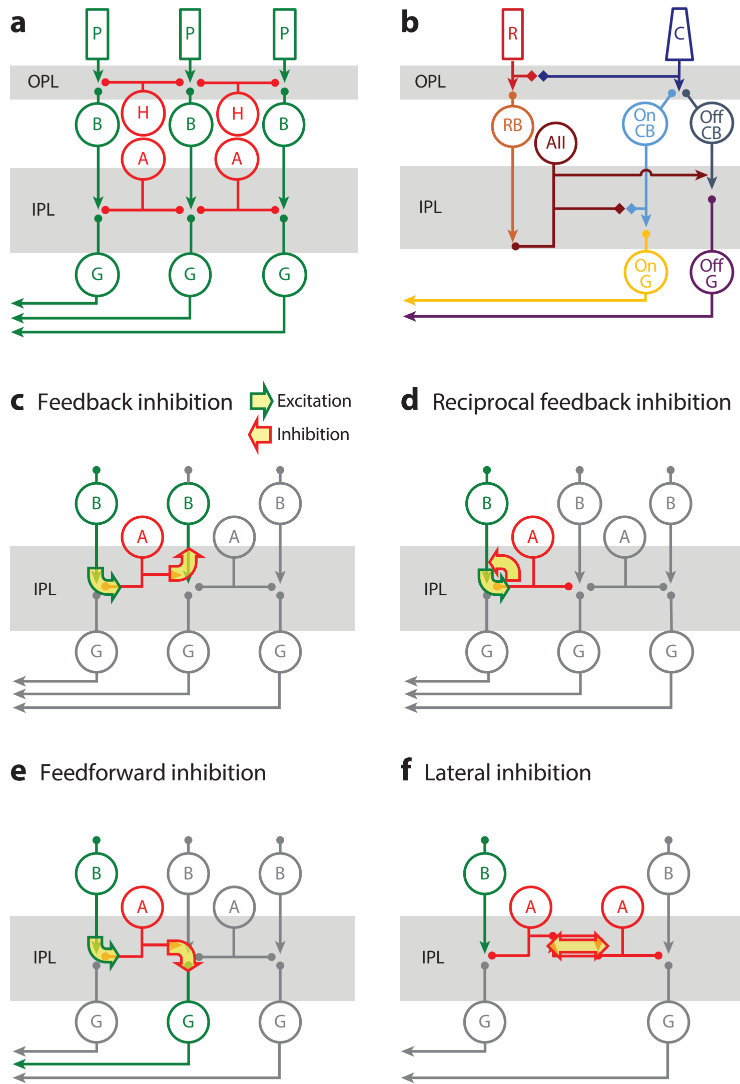

Figure 1

Schematics of vertebrate retinal circuitry. (*a*) General scheme of major cell types. (*b*) Interaction between the rod and cone pathway (horizontal cells removed for clarity). ◆◆ indicate gap junctions. Adapted from Vaney (1994). (*c*) Feedback inhibition from an amacrine cell to a bipolar cell. Analogous connections occur between horizontal cells and photoreceptors (not shown). (*d*) Reciprocal feedback inhibition from an amacrine cell to the same bipolar cell that provided it excitatory input. Horizontal cells also make reciprocal feedback to photoreceptors. (*e*) Feedforward inhibition from an amacrine cell to a ganglion cell. Horizontal cells may make feedforward inhibitory synapses to bipolar cells. (*f*) Lateral inhibitory connections are made among amacrine cells within and between subtypes. Abbreviations: A, amacrine cell; AII, AII (A2) amacrine cell; B, bipolar cell; G, ganglion cell; H, horizontal cell; IPL, inner plexiform layer; OPL, outer plexiform layer; P, photoreceptor.

cursory (and sparsely referenced) primer. For more detailed information and references to the relevant primary literature, the reader is commended to several excellent texts (Dowling 2012, Rodieck 1998, Sterling 1998), a recent review (Demb & Singer 2015), and an informative website (see Related Resources). Readers familiar with the retina can safely skip this section.

The retina lines the back of the eye, and light must pass through the layers of circuitry to reach the photoreceptors, which are closely associated with the retinal pigment epithelium (RPE). The RPE provides essential metabolic support, particularly to the photoreceptors, and forms a protective barrier between the retina and the circulatory and immune systems.

Photoreceptors

Most vertebrate retinas contain rod and cone photoreceptors, although the relative proportion of each varies widely across species. The retinas of nocturnal animals like mice—and hunters like humans, cats, and owls—contain a large majority of rods (∼95%), which are much more sensitive than cones and mediate night (scotopic) vision. At the other end of the spectrum, most birds and some diurnal mammals, like tree shrews and ground squirrels, possess cone-dominated retinas. In primates, cone photoreceptors are expressed most densely in or near the fovea, where the photoreceptor array and downstream circuitry are optimized for high-acuity daytime vision. Primates generally possess three types of cones that are distinguished by their preference for blue, red, and green light. Most other mammals have two different cones, whereas some nonmammalian species (reptiles, birds, and fish) have as many as five. Cone chromatic sensitivity also varies widely with species: Mice, the most popular mammalian experimental model, express ultraviolet-sensitive and green-sensitive cones, whereas some reptiles express infrared-sensitive cones. Spectral sensitivity is dictated by subtle differences in the light-absorbent opsin proteins expressed by photoreceptors. Because in most species all rods exhibit a similar preference for green light, scotopic vision typically does not encode color information. In vertebrate photoreceptors, an absorbed photon triggers an intracellular signaling cascade that hyperpolarizes the membrane and temporarily slows the ongoing release of glutamate-filled vesicles from photoreceptor presynaptic terminals. Photoreceptors do not fire action potentials: The light-evoked hyperpolarization is a graded response that varies with the number of photons absorbed. In addition to the chemical synapses made onto bipolar and horizontal cells, photoreceptors also make electrical (gap junction) connections with one another.

Bipolar Cells

The light-evoked neural signal from photoreceptors is received differently by numerous (∼15 in mammals) different postsynaptic bipolar cell subtypes. Some bipolar cells express ionotropic glutamate (typically AMPA or kainate) receptors and so are depolarized by the ongoing glutamate release from photoreceptors in the dark. When light increments decrease glutamate release from photoreceptors, these bipolar cells hyperpolarize and so are referred to as OFF bipolar cells. Their counterparts, ON bipolar cells, depolarize in response to light because they express a metabotropic glutamate receptor (mGluR6) that hyperpolarizes the postsynaptic membrane when activated in darkness. Rod bipolar cells, which receive their input from rod photoreceptors and constitute about half the bipolar cells in rod-dominated retinas, are ON bipolar cells. All other bipolar cell subtypes receive their input primarily from cones and are usually referred to as ON or OFF cone bipolar cells (**Figure 1*b***). Most bipolar cells do not fire action potentials but respond to light stimuli with small, graded changes in membrane potential.

Horizontal Cells

Horizontal cells, described in greater detail below, mediate lateral interactions in the OPL (**Figure 1*a***). They receive light-evoked synaptic input from photoreceptors via ionotropic glutamate receptors and so, like OFF bipolar cells, hyperpolarize in response to light increments. They are thought to mediate feedback inhibition to photoreceptors and feedforward inhibition to bipolar cells, although the underlying synaptic mechanisms remain controversial.

Ganglion Cells

Ganglion cells are the output neurons of the retina and send their axons through the optic nerve to the rest of the brain. Their receptive fields reflect dramatic convergence within the retinal circuitry: The human retina contains only one million ganglion cells but more than one hundred million photoreceptors. Ganglion cells receive excitatory synaptic input from bipolar cells via glutamatergic synapses in the IPL. OFF cone bipolar cells contact ganglion cell dendrites in the outer half of the IPL, and ON cone bipolar cells make their synapses in more inner layers of the IPL. For many years, ganglion cells were characterized primarily on the basis of fundamental response characteristics dictated by their bipolar cell inputs (i.e., whether they responded to light onset, offset, or, in the case of ON-OFF ganglion cells, both). Gradually, ganglion cells became distinguished on the basis of more complex features of their receptive fields that are shaped by interactions in the IPL with inhibitory amacrine cells. A recent report in mouse retina counts some 30 different ganglion cell types (Baden et al. 2016), each of which is thought to encode some particular feature of the visual world: Some ganglion cells respond to motion in a particular direction, others to local edges or expanding shadows.

Amacrine Cells

Amacrine cells are described in greater depth below. For now, it is sufficient to say that, like ganglion cells, they receive their excitatory inputs from bipolar cells; they also make feedback synapses onto bipolar cell terminals (**Figure 1*c***)—sometimes reciprocal feedback to the same bipolar cells that provide them input (**Figure 1*d***). Amacrine cells also make feedforward synapses onto ganglion cell dendrites (**Figure 1*e***) and lateral inhibitory synapses onto other amacrine cells (**Figure 1*f***). These various synaptic motifs, as well as the remarkable diversity of amacrine cell subtypes, are thought to underlie more complex, spatiotemporal processing that gives rise to some three dozen different versions of the visual world encoded by ganglion cells, although the specific functional roles of most amacrine cells remain completely mysterious. Nearly all amacrine cells release an inhibitory neurotransmitter, either GABA or glycine, and many (perhaps all) release a second neurotransmitter—either a monoamine, neuropeptide, soluble gas, lipid, other amino acid, or acetylcholine. True to their name, conferred by Ramón y Cajal (*a-makrós-inos*, meaning "without long fiber"), most amacrine cells possess no axon—instead, synaptic outputs arise from the same dendrites that receive synaptic inputs, enabling some amacrine cells to perform multiple visual computations in parallel.

Distinct Rod and Cone Pathways in the Mammalian Retina

As indicated above, rod photoreceptors in mammalian retinas connect preferentially to rod bipolar cells (**Figure 1*b***). Unlike their cone-driven counterparts, rod bipolar cells typically do not contact ganglion cells; instead, they make excitatory, glutamatergic synapses onto AII (A2) amacrine cells

in the deepest layer of the IPL. AII amacrine cells relay the ON signal from rod bipolar cells to the presynaptic terminals of ON cone bipolar cells via a (sign-conserving) electrical (gap junction) synapse and to OFF bipolar cell terminals via a (sign-inverting) inhibitory glycinergic synapse. In this way, the circuit is able to incorporate both scotopic and photopic visual signaling without requiring even more ganglion cell types.

HORIZONTAL CELLS MEDIATE SURROUND INHIBITION IN THE OUTER RETINA

Lateral inhibition, a common feature in the first stages of even primitive visual systems, including the eel (Adrian & Matthews 1928) and the horseshoe crab (Hartline et al. 1956), gives rise to center-surround receptive-field properties in all layers of the vertebrate retina (Baylor et al. 1971, Kuffler 1953, Werblin & Dowling 1969). Horizontal cells, laterally oriented interneurons located in the OPL (**Figure 1*a***), were implicated in surround inhibition early on (Baylor et al. 1971, Werblin & Dowling 1969). Although their morphological features vary substantially between species, the general role for horizontal cells in visual signaling is consistent across different retinas: They mediate lateral signaling that opposes the primary, radial feedforward signal to produce center-surround receptive fields, a fundamental response feature that increases spatial acuity and is present throughout the visual system. Mammalian retinas typically contain only 2–3 distinguishable horizontal cell subtypes (Boycott et al. 1978, Kolb 1974) (**Figure 2*a***), which appear to make similar synaptic contacts with photoreceptors and bipolar cells (Kolb 1974); studies of horizontal cell synaptic physiology in fish, amphibians, and mammals rarely distinguish between horizontal cell subtypes.

Horizontal cells provide lateral feedback inhibition to photoreceptor terminals and feedforward inhibition to bipolar cell dendrites within morphologically complex triad synapses (Dowling & Boycott 1966) (**Figure 2*b***). Typically, an invagination in the photoreceptor terminal envelops one to two bipolar cell processes and two horizontal cell processes. This stereotyped, restrictive diffusion environment plays a prominent role in shaping both feedforward glutamatergic signals from photoreceptors (DeVries et al. 2006) and, as detailed below, feedback signals from horizontal cells. The mechanisms underlying both feedback signaling from horizontal cells to photoreceptors and feedforward signaling to bipolar cells are unconventional and may vary somewhat across species and visual conditions; consequently, competing theories have generated considerable interest and controversy in the field for years. The primary issues and ideas are addressed only briefly here; particularly interested readers are referred to an excellent, more thorough review of this complicated literature by Thoreson & Mangel (2012).

Candidate Mechanisms Underlying Horizontal Cell Feedback

Photoreceptors hyperpolarize in response to increments in light intensity (Tomita 1965, Werblin & Dowling 1969). Light responses depend on both the intensity and the spatial extent of the stimulus, as responses to larger light spots are more transient (Baylor et al. 1971) (**Figure 2*c***). When the surround response was isolated by preapplying a small, bright, steady background spot over a cone photoreceptor, flashing a larger spot elicited a delayed depolarization whose time course mimicked the difference in the responses to the two spot sizes (Baylor et al. 1971, O'Bryan 1973). A similar depolarization was observed in a cone when a nearby horizontal cell was hyperpolarized, suggesting that horizontal cells contribute surround inhibition to photoreceptors, a phenomenon studied most commonly in cones but also observed in rods (Thoreson et al. 2008). Horizontal

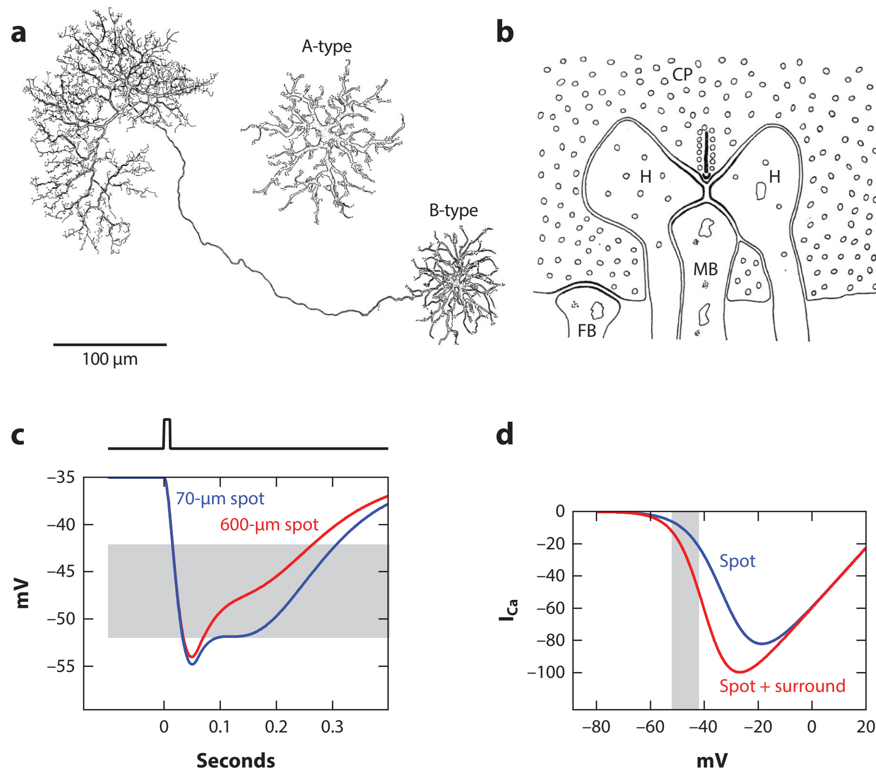

Figure 2

Horizontal cells in the vertebrate retina. (*a*) A- and B-type horizontal cells from cat retina [modified from Boycott et al. (1978) with permission from the Royal Society]. (*b*) Schematic of a triad synapse in rhesus macaque monkey retina [modified from Dowling & Boycott (1966) with permission from the Royal Society]. (*c*) Responses in a turtle cone to light flashes of different spatial extent. Response to a larger spot shows a late depolarization that is due to lateral feedback from horizontal cells. Flash (∼10-ms) time course indicated above. Gray region subtends the same membrane potential range as in panel *d*. Adapted from Baylor et al. (1971). (*d*) Ca_v channel current–voltage relationship in cones, with and without surround activation of horizontal cells. Feedback shifts the activation range of the Ca_v current and increases the maximal amplitude. The shift may reflect ephaptic interactions between horizontal cells and photoreceptors, whereas the conductance increase (and, possibly, also the shift) may be due to light-evoked changes in pH in the synaptic cleft. Adapted from Verweij et al. (1996). Abbreviations: CP, cone pedicle; FB, flat bipolar cell; H, horizontal cell; I_{Ca}, calcium channel–mediated current; MB, midget bipolar cell.

cell feedback consequently shapes the center-surround receptive fields of neurons throughout the retinal circuit, including ganglion cells (Davenport et al. 2008), but the mechanisms underlying the feedback signal have proved difficult to identify conclusively. Three theories, briefly described below, have received the most attention.

GABAergic signaling. Most feedback inhibition in the brain occurs via GABAergic synapses, making this an obvious candidate mechanism. Light stimulation hyperpolarizes surrounding horizontal cells and could, in theory, reduce sustained GABA release onto photoreceptor terminals, resulting in a net depolarization (Kaneko & Tachibana 1986). Accordingly, horizontal cells in

most species contain GABA and are able to release it when depolarized. Although synaptic vesicles often are not prominent in electron micrographs of horizontal cell dendrites (e.g., Dowling & Boycott 1966, Kolb 1974; but see Zampighi et al. 2011), the processes contain the protein machinery required to fill and release vesicles of GABA (Hirano et al. 2005), and photoreceptor terminals express GABA receptors (Yang 2004). Physiological observations argue against the GABA hypothesis, however. First, the chloride equilibrium potential is relatively less negative in cones, at least in salamander (Thoreson & Bryson 2004), so that any GABAergic input actually might be depolarizing rather than hyperpolarizing. Second, feedback causes changes in photoreceptors (described below) that are not readily explained by a GABAergic mechanism (but see Liu et al. 2013). Third, horizontal cell feedback is not blocked reliably by GABA receptor antagonists (Thoreson & Burkhardt 1990; Verweij et al. 1996, 2003), although it is eliminated by genetically deleting vesicular GABA transporters in horizontal cells (Hirano et al. 2016).

Ephaptic interactions between horizontal cells and photoreceptors. An interesting physiological effect of horizontal cell feedback that counters most GABA hypotheses is the observation that surround illumination or horizontal cell depolarization shifts the apparent voltage activation range of voltage-gated Ca^{2+} (Ca_v) channels in photoreceptors (Byzov & Cervetto 1977, Hirasawa & Kaneko 2003, Thoreson et al. 2008, Verweij et al. 1996) (**Figure 2*d***). Given that the range of a photoreceptor's membrane potential during a light response coincides with the steepest part of the L-type Ca_v-channel activation curve (**Figure 2*c*,*d***), even relatively small negative shifts in the activation curve could cause substantial increases in Ca_v current in the photoreceptor during a light response and generate the observed feedback depolarization. This apparent membrane potential shift has been attributed by some to an ephaptic mechanism (Byzov & Shura-Bura 1986): According to this theory, the morphologically complex triad synaptic cleft presents a sufficient electrical resistance so that ionic current flowing into the cleft and through channels (hemigap junctions) (Kamermans et al. 2001) in the horizontal cell membrane creates a drop in potential; in other words, the synaptic cleft becomes more negative than the rest of the extracellular space. This local negativity decreases the potential difference across the photoreceptor presynaptic membrane, a local apparent depolarization that activates more Ca_v channels and gives rise to a feedback depolarization that can be measured in the soma. This model explains much of the experimental data, although its physical plausibility has been challenged (Dmitriev & Mangel 2006), and a recent study indicates that the time course of horizontal cell feedback is slower than expected from an ephaptic mechanism (Warren et al. 2016).

Regulation of Ca_v channels by protons in the synaptic cleft. Ephaptic interactions may explain the shift in Ca_v activation but not the concomitant increase in maximal Ca_v conductance (Gerschenfeld et al. 1980, Hirasawa & Kaneko 2003, Verweij et al. 1996) (**Figure 2*d***). Photoreceptor Ca_v channels are negatively regulated by extracellular protons (Barnes & Bui 1991, DeVries 2001); a light-evoked decrease in cleft proton concentration could, therefore, give rise to the observed increase in Ca_v conductance and also a leftward shift in Ca_v voltage dependence (Barnes & Bui 1991, DeVries 2001). pH buffers block the influence of horizontal cells on cone Ca_v currents (Cadetti & Thoreson 2006, Hirasawa & Kaneko 2003), suggesting that horizontal cells contribute to alkalization of the cleft. One of several proposed mechanisms is that glutamate increases intracellular acidification of horizontal cells (Dixon et al. 1993, Trenholm & Baldridge 2010), perhaps leading to greater proton efflux in the dark. Light-evoked decreases in glutamate release from cone photoreceptors would then decrease proton efflux from horizontal cells, alkalizing the cleft and enhancing Ca_v currents. A recently suggested alternative actually combines roles for GABA and pH (Liu et al. 2013): GABA release is proposed to activate ionotropic

autoreceptors on horizontal cells, gating a bicarbonate conductance that would acidify the cleft in the dark. Definitive experimental support for these or any other mechanism remains elusive; the case for pH regulation is weakened further by potentially confounding effects of pH buffers and observations from several groups that light-evoked changes in pH are very small and slow (e.g., Borgula et al. 1989), although local changes within the synaptic cleft may be larger.

Horizontal Cell Feedforward Inhibition of Bipolar Cells

Feedforward inhibition from horizontal cells to bipolar cells has been studied far less than feedback, and its prevalence across species, particularly mammals, is uncertain. Feedforward inhibition has been examined independently of feedback inhibition in salamander ON bipolar cells by pharmacologically blocking photoreceptor inputs (Hare & Owen 1992, Yang & Wu 1991), thereby isolating surround inhibition from horizontal cells. Under these conditions, surround illumination elicits a hyperpolarizing response (Hare & Owen 1992). The prevailing interpretation is that this reflects GABAergic signaling between horizontal and bipolar cells, given that, as mentioned above, horizontal cells release GABA and bipolar cells express GABA receptors in their dendrites (Greferath et al. 1994, Vardi & Sterling 1994). This idea persists despite the fact that GABA receptor antagonists do not block surround inhibition in bipolar cells, at least in salamander (Hare & Owen 1996). Similar experiments have not been reported in mammalian retina, although in mouse rod bipolar cells, GABA receptor antagonists do block inhibitory signals that may derive from horizontal cells (Herrmann et al. 2011).

The uncertain GABA receptor pharmacology remains a significant caveat that requires further investigation, but several other findings support feedforward GABAergic signaling, or at least activation of a postsynaptic chloride conductance in bipolar cell dendrites. In particular, the circuit appears to have solved the particular problem of how horizontal cells, which hyperpolarize in response to light, could provide antagonistic surround signals to both ON and OFF bipolar cells: ON and OFF bipolar cells express different chloride transporters (Vardi et al. 2000, Vu et al. 2000) that appear to establish a chloride gradient along the length of the cell (Duebel et al. 2006) and make the chloride equilibrium potential more depolarized in ON bipolar cells than in OFF bipolar cells (Miller & Dacheux 1983). Accordingly, paired recordings between connected cell pairs in turtle retina demonstrated that horizontal cell hyperpolarization, as would occur in response to surround illumination, hyperpolarizes ON bipolar cells and depolarizes OFF bipolar cells (Marchiafava 1978), signals that would effectively oppose the center signal in each cell type.

AMACRINE CELLS SHAPE VISUAL SIGNALING IN THE INNER RETINA

Synaptic inhibition from amacrine cells shapes both spatial and temporal characteristics of receptive fields of bipolar cells and ganglion cells, enriching the diversity and information content of visual signals in the inner retina. Feedback inhibition from amacrine cells to bipolar cell terminals refines their center-surround receptive fields (Flores-Herr et al. 2001), sharpens the timing of bipolar cell responses (Dong & Hare 2003), and can regulate the gain of feedforward signals (Grimes et al. 2015). Feedforward inhibition—and, in some cases, excitation—from amacrine cells confers both spatial and temporal complexity to the receptive fields and light-evoked responses of ganglion cells (e.g., Lee et al. 2016, Tien et al. 2016, Werblin 1970, Werblin & Copenhagen 1974). Bistratified amacrine cells mediate so-called crossover inhibition between the ON and OFF layers of the IPL (Roska & Werblin 2001), thereby expanding the palette of available computations.

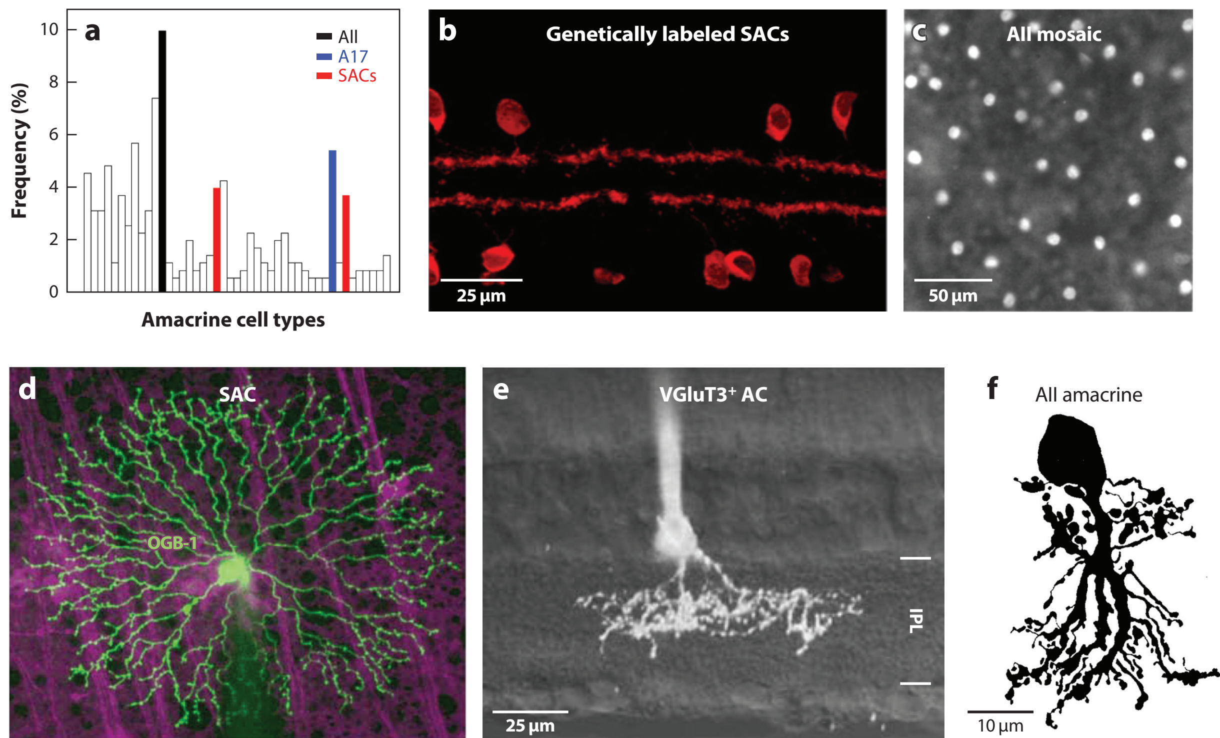

Figure 3

Amacrine cells. (*a*) Relative numbers of amacrine cells in the mouse retina [data from Helmstaedter et al. (2013)], with three popularly studied subtypes highlighted. (ON and OFF SACs are counted separately.) (*b*) SACs in mouse retina expressing a fluorescent protein under control of the ChAT promoter [adapted from Ivanova et al. (2010) with permission from Elsevier]. (*c*) Mosaic of AII amacrine cells in cat retina stained with diamidino-phenylindole [adapted from Vaney (1985) with permission from the Royal Society]. (*d*) SAC in rabbit retina filled with OGB-1 (*green*); nerve fibers below are stained with sulforhodamine [adapted from Hausselt et al. (2007) with permission]. (*e*) VGluT3^{+} amacrine cell, identified in a mouse retinal slice via expression of yellow fluorescent protein and filled with an intracellular dye [adapted from Grimes et al. (2011)]. (*f*) Golgi-impregnated AII amacrine cell from cat retina [adapted from Kolb & Famiglietti (1974), with permission from AAAS]. Abbreviations: AC, amacrine cell; ChAT, choline acetyltransferase; IPL, inner plexiform layer; OGB-1, Oregon Green BAPTA-1; SAC, starburst amacrine cell.

A Rich Diversity of Amacrine Cell Types

The estimated number of amacrine cells in the mammalian retina has roughly doubled several times over the last 125 years (Helmstaedter et al. 2013, MacNeil & Masland 1998, Polyak 1941, Ramón y Cajal 1892). Even the most recent count of 45 different amacrine cells (Helmstaedter et al. 2013) is likely a slight underestimate, because some very sparse, wide-field amacrine cells (Lin & Masland 2008) were probably missed in the dense reconstruction of a limited tissue volume. Any single amacrine cell type constitutes only a small fraction of the entire population (Helmstaedter et al. 2013, MacNeil & Masland 1998) (**Figure 3*a***), making reliable physiological study of most individual subtypes extremely difficult, at least until the recent development of cell type–specific genetic markers (Ivanova et al. 2010, Siegert et al. 2009, Zhu et al. 2014) (**Figure 3*b***).

Before genetic tools became available, the primary classification of amacrine cell subtypes typically was based on dendritic morphology (MacNeil & Masland 1998), particularly the lateral extent of the dendritic arbor and its stratification depth within the IPL. Amacrine cells in the

rabbit retina have been classified as narrow field (dendritic arbor diameter <125 μm), medium-field (125–400 μm) and wide field (>400 μm) (MacNeil & Masland 1998). Many narrow-field amacrine cells stratify in multiple layers of the IPL and are thought to mediate interactions between the ON and OFF channels (Roska & Werblin 2001). By contrast, the sparse dendrites of wide-field amacrine cells typically stratify narrowly within a single layer of the IPL (Helmstaedter et al. 2013, Lin & Masland 2008). Although differences between subtypes are sometimes rather subtle, morphology is extremely consistent within subtype (Helmstaedter et al. 2013, MacNeil & Masland 1998), and similarly shaped cells consistently form evenly spaced so-called mosaics across the retina (Helmstaedter et al. 2013, Vaney 1985, Wassle & Riemann 1978) (**Figure 3*c***) and exhibit similar neurotransmitter phenotypes (e.g., Sandell & Masland 1986) and circuit connectivity (Helmstaedter et al. 2013)—all typically reliable indications of a single cell type.

Why does the mammalian retina contain so many different amacrine cells? Perhaps the most likely answer is that a wide range of computations are required to generate the many versions of the visual world encoded by different ganglion cells (Masland 2012). This idea raises many interesting questions about inner retinal circuitry and amacrine cell function: Is each amacrine cell subtype dedicated to computing information for a single ganglion cell type? Alternatively, might individual amacrine cells perform specific visual computations that are accessed by any ganglion cell type that requires them? Does each cell type perform a single specific function, or can individual amacrine cells multitask? How do inhibitory connections between amacrine cells (Eggers & Lukasiewicz 2010) enrich visual information processing? And how do different amacrine cells transform synaptic input into synaptic output; in other words, how do the mechanisms and spatial extent of dendritic signal processing compare between amacrine cell types? So far, experimental answers to these questions (discussed below) vary substantially depending on the amacrine cell under study. Some amacrine cells appear dedicated to a single task in service of a single cell or circuit feature, whereas others are more versatile and contribute to different kinds of visual computations. Finally, some amacrine cells appear to shift their role depending upon visual conditions or developmental stage. Although the field continues to gain deeper insight into the complexity and fascination for the elegance of individual amacrine cell types, general themes across subtypes have been slow to emerge.

Amacrine Cell Output Connectivity

If each amacrine cell subtype were dedicated to a single ganglion cell type, one would expect their output synapses to be restricted accordingly. As mentioned at the outset, the test of this prediction has been aided tremendously by the recently completed dense reconstruction of a mouse IPL (Helmstaedter et al. 2013). This heroic tour de force, in which 840 neurons—bipolar cells, amacrine cells, and ganglion cells—were identified and reconstructed within a 114-μm × 80-μm area of the IPL, revealed the clearest vision to date of amacrine cell diversity. It also provided information about nearly 600,000 contacts between the neurons in the volume. The resulting connectivity matrix clearly suggests that many amacrine cells contact multiple ganglion cell types and/or multiple amacrine cell types. An important caveat of this study, however, is that the tissue preparation was optimized for reliable tracing of dendritic processes at the expense of clear synaptic morphology. Without clear presynaptic active zones or postsynaptic densities, synapses were inferred from the area of cell–cell contacts, and so the presynaptic and postsynaptic elements of each contact could not be distinguished. Moreover, although the authors showed in conventionally stained tissue that contact area is quite a reliable indicator of synaptic connectivity, it is not perfect; for example, one of the most consistent so-called connections in the reconstructed

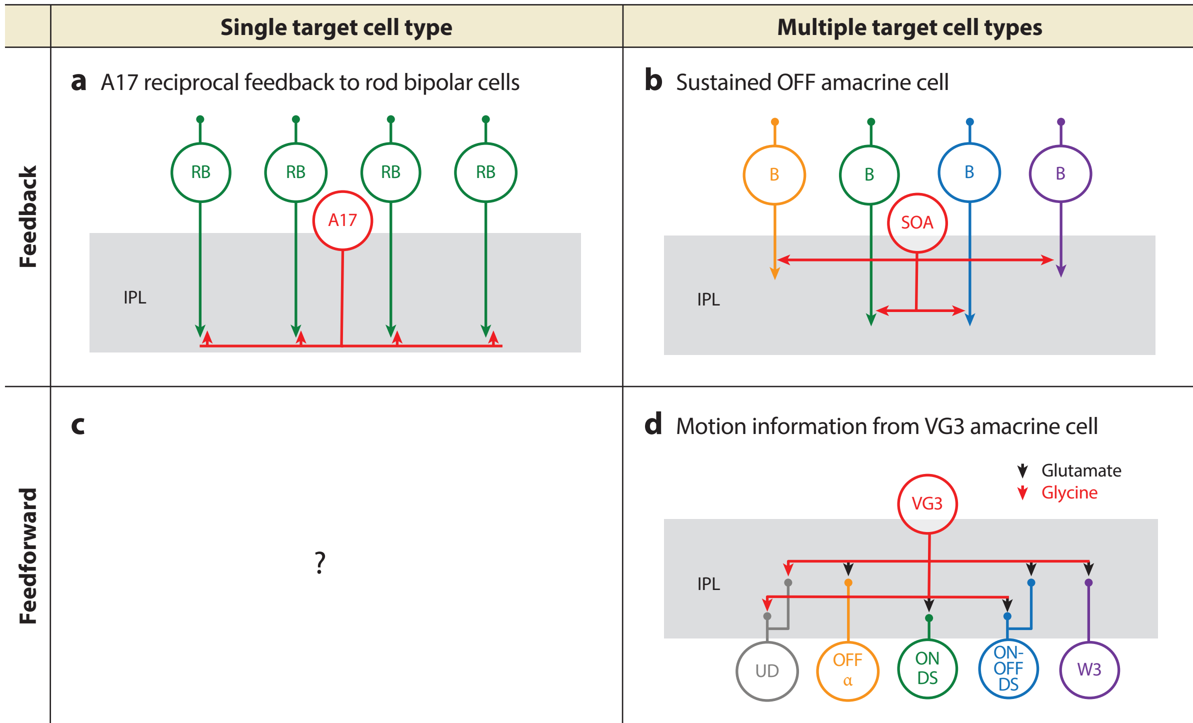

Figure 4

Examples of amacrine cell circuit motifs. (*a*) A17 amacrine cells provide feedback inhibition to a single cell type, RBs. (*b*) In the salamander retina, sustained OFF amacrine cells provide feedback to many different bipolar cells (de Vries et al. 2011). (*c*) A monogamous feedforward amacrine cell has not been identified. Although most feedforward inhibition from SACs appears to target directionally selective ganglion cells (Ding et al. 2016, Helmstaedter et al. 2013), SACs may also inhibit other ganglion cell types as well. Similarly, although cholinergic excitation from SACs in the mature retina also targets primarily directionally selective ganglion cells, many different cell types express ACh receptors (Strang et al. 2010), suggesting that the cholinergic signal may be directed more broadly. (*d*) VG3 amacrine cells send information about object motion to several different ganglion cell types. Much of their feedforward signaling is actually excitatory. VG3 schematic adapted from Lee et al. (2016). Abbreviations: B, bipolar cell; DS, directionally selective ganglion cell; IPL, inner plexiform layer; RB, rod bipolar cell; SAC, starburst amacrine cell; SOA, sustained OFF amacrine cell; UD, uniformity detector.

volume was between AII and A17 amacrine cells, which both receive synaptic input from rod bipolar cells, typically as postsynaptic neighbors within the same dyad synapses (i.e., a synapse comprising one presynaptic active zone and two postsynaptic elements), but do not make synapses with each other. Other data sets permit positive identification of presynaptic and postsynaptic elements (Anderson et al. 2011, Ding et al. 2016), but a complete circuit reconstructions have not yet been performed. Thus, although the current IPL connectome (Helmstaedter et al. 2013) provides an invaluable guide to amacrine cell morphology and diversity, specific details regarding synaptic connectivity may require further confirmation.

Some amacrine cells appear to contact a very limited variety of target cell types. The A17 amacrine cell may constitute the most extreme example, directing its output almost exclusively to rod bipolar cells at reciprocal synapses (Nelson & Kolb 1985) (**Figure 4*a***). Starburst amacrine cells (SACs) (**Figure 3*d***) are nearly as monogamous, contacting primarily directionally selective

ganglion cells (DSGCs) or other SACs (Briggman et al. 2011, Ding et al. 2016, Famiglietti 1991). Notwithstanding the AII/A17 caveat noted above, this specific connectivity was generally confirmed by connectomic results (Helmstaedter et al. 2013). Many amacrine cells, however, clearly contact multiple cell types. AII amacrine cells contact both ON and OFF cone bipolar cells, OFF ganglion cells, and one another (Famiglietti & Kolb 1975). Dopaminergic amacrine cells contact AII and other amacrine cells in the IPL (Contini & Raviola 2003, Kolb et al. 1991, Pourcho 1982) and horizontal cells in the OPL (Herrmann et al. 2011, Kolb et al. 1991). In the salamander retina, a single sustained OFF amacrine cell influences the visual responses of many ganglion cell types via broadly distributed GABAergic inhibitory feedback synapses onto bipolar cell terminals (de Vries et al. 2011) (**Figure 4*b***). Similar experiments have not been performed in mammalian retina, although recent studies show that VGluT3 and vasoactive intestinal peptide (VIP)–expressing amacrine cells contact several different ganglion cell types as part of distinct visual computations (Famiglietti & Kolb 1975; Kim et al. 2015; Lee et al. 2015, 2016; Park et al. 2015; Tien et al. 2015, 2016) (**Figures 3*e*** and **4*d***).

One aspect of amacrine cell connectivity that may prove more difficult to characterize physiologically is lateral inhibitory interactions within and between amacrine cell types (**Figure 1*f***). Evidence for lateral inhibition is most apparent in examining feedback inhibition from amacrine cells onto bipolar cell terminals (Eggers & Lukasiewicz 2006, 2010; Roska et al. 1998) and feedforward inhibition to ganglion cells (Roska et al. 1998, Zhang et al. 1997). In either case, blocking one inhibitory receptor subtype can actually enhance inhibitory signaling overall, apparently because of disinhibition of amacrine cells. For example, blocking $GABA_A$ receptors enhances $GABA_C$ receptor–mediated feedback inhibition of bipolar cell terminals (Eggers & Lukasiewicz 2006, 2010; Roska et al. 1998). Blocking glycine receptors enhances both feedforward and feedback GABAergic signaling (Roska et al. 1998, Zhang et al. 1997), indicating that inhibitory interactions can occur between different amacrine cell types. Inhibition within a single amacrine cell type also occurs: Reciprocal synaptic inhibition between GABAergic SACs sharpens directional tuning in SAC dendrites (Ding et al. 2016, Lee & Zhou 2006, Munch & Werblin 2006).

Multiple Neurotransmitters Equip Individual Amacrine Cells for Multiple Tasks

Henry Dale first hypothesized that individual neurons release only one type of neurotransmitter (Dale 1935), although it eventually became clear that many neurons release both a fast neurotransmitter (e.g., glutamate, GABA, glycine, ACh) and a modulatory transmitter, often a peptide (Hokfelt 1991), that acts more slowly and over a more diffuse spatial scale (referred to as volume transmission). Later, evidence that single neurons could release multiple fast neurotransmitters was first shown in cholinergic/GABAergic SACs (O'Malley & Masland 1989). As indicated above, nearly all amacrine cells release either GABA or glycine (but apparently never both), and many release at least one other neurotransmitter, a fascinating yet still poorly understood feature that may enable individual cells to play multiple roles in visual processing. It is particularly intriguing that at least two amacrine cells, described below, release both excitatory and inhibitory fast neurotransmitters.

Starburst amacrine cells release GABA and ACh. As noted above, SACs release both GABA and ACh (O'Malley & Masland 1989), two fast neurotransmitters that exert inhibitory and excitatory effects, respectively, in postsynaptic targets. SACs release GABA onto DSGCs and also neighboring SACs. GABA release occurs from synaptic varicosities at the tips of SAC dendrites

(Ding et al. 2016, Euler et al. 2002, Famiglietti 1991, Lee & Zhou 2006) and is directionally tuned (Euler et al. 2002, Fried et al. 2002, Hausselt et al. 2007, Kittila & Massey 1997, Lee & Zhou 2006); although SACs are strikingly symmetrical neurons overall (**Figure 3*d***), individual SAC dendrites respond more strongly to centrifugal motion (i.e., from the soma toward the dendritic tips) (Ding et al. 2016, Euler et al. 2002, Hausselt et al. 2007, Vlasits et al. 2016) owing to a combination of dendritic physiology (Hausselt et al. 2007) and reciprocal inhibitory interactions with other SACs (Ding et al. 2016, Lee & Zhou 2006). Sections of SAC dendrites therefore appear to operate independently of one another, such that dendrites within a single SAC may prefer the whole range of directions (Euler et al. 2002). SAC dendrites preferring one direction connect quite specifically to DSGCs preferring the opposite direction (Briggman et al. 2011), thereby establishing the asymmetric inhibitory network postulated to underlie directional selectivity (Barlow & Levick 1965). The role for ACh in SAC signaling is more enigmatic. Early in development, reciprocal cholinergic signaling between SACs underlies wavelike propagation of activity across the retina SACs (Feller et al. 1996, Meister et al. 1991, Wong et al. 2000, Zhou & Zhao 2000), previsual yet correlated activity that drives development of downstream visual circuitry (Xu et al. 2011). SACs lose their ACh sensitivity after the first postnatal week (Zheng et al. 2004) but continue to release ACh and activate nicotinic receptors on ganglion cells—particularly DSGCs—into adulthood (Lee et al. 2010). Direction selectivity (DS) persists in the absence of cholinergic signaling (Ariel & Daw 1982), and a specific role for ACh in DS remains unclear. Another mystery is that ACh receptor–mediated inputs to DSGCs are much less directionally tuned than GABAergic inputs (Fried et al. 2002, Kittila & Massey 1997, Yonehara et al. 2011), despite arising from the same SAC dendrites. One possible explanation is that cholinergic inputs are not targeted to DSGC dendrites with the same specificity as GABAergic synapses (Briggman et al. 2011). Another (perhaps less likely) possibility is that GABA and ACh are released from SAC dendrites via fundamentally different mechanisms, such that only GABA is released with any directional preference. Whatever the mechanism, it would appear that ACh input from SACs, like glutamatergic input from bipolar cells, provides directionally untuned excitatory drive to DSGCs that is then shaped by directionally tuned GABAergic inhibition. ACh released from SACs also may exert more widespread (and potentially inhibitory) effects via metabotroic ACh receptors, which are expressed in many different retinal cell types (Strang et al. 2010).

VG3 amacrine cells release glutamate and glycine. Despite the neurotransmitter pharmacopeia expressed by amacrine cells, the discovery of a glutamatergic amacrine cell nonetheless came as a surprise. An otherwise glycinergic amacrine cell was found to express a vesicular glutamate transporter, VGluT3 (Haverkamp & Wassle 2004), and to release both glutamate (Kim et al. 2015, Lee et al. 2014) and glycine (Lee et al. 2016, Tien et al. 2016) onto postsynaptic ganglion cells. $VGluT3^+$ amacrine cells (VG3-ACs) (Kim et al. 2015) exhibit complex dendritic arbors that cross back and forth between the ON and OFF layers of the IPL (Grimes et al. 2011) (**Figure 3*e***) and receive excitatory and inhibitory input at light onset and offset (Grimes et al. 2011, Kim et al. 2015, Lee et al. 2014). VG3-ACs respond specifically to motion of small objects within their receptive field but are inhibited by global motion (Kim et al. 2015). Accordingly, VG3-ACs provide glutamatergic input to ON and ON-OFF DSGCs (Lee et al. 2014), OFF α ganglion cells (Lee et al. 2016), and W3 ganglion cells (Kim et al. 2015, Lee et al. 2014), which respond to small object motion in any direction (Zhang et al. 2012). Glutamatergic targets of VG3-ACs share the property of being activated by visual contrast, suggesting that the VG3-AC, with its contrast/motion-sensitive receptive field, performs a specific visual computation for multiple ganglion cell types that express response features in common. Consistent with this idea,

VG3-ACs also provide inhibitory glycinergic input to so-called uniformity detectors, ganglion cells that are suppressed by contrast of either polarity (Lee et al. 2016, Levick 1967, Tien et al. 2016) (**Figure 4*d***). VG3-ACs therefore constitute a clear example of functional modularity within the inner retinal circuitry (Lee et al. 2016, Tien et al. 2016) that may efficiently expand the computational repertoire of ganglion cells.

Some amacrine cells release fast and slow neurotransmitters. Although the second, slower neurotransmitter in bilingual neurons is often a neuropeptide (Hokfelt 1991), interneurons in several brain regions release dopamine in addition to GABA (Kosaka et al. 1987), and dopamine neurons in the ventral tegmental area also release glutamate (Sulzer & Rayport 2000). In the retina, dopaminergic interplexiform cells—amacrine cells that send processes into both the OPL and IPL—also release GABA (Contini & Raviola 2003, Hirasawa et al. 2012). The vesicular transporters for both neurotransmitters are colocalized at presynaptic sites adjacent to AII amacrine cells at the outer border of the IPL (Contini & Raviola 2003), and amperometric recordings indicate coincident GABA and dopamine signals (Hirasawa et al. 2012), suggesting that both transmitters may be packaged into the same vesicles and released together. The postsynaptic targets and physiological impact of the two transmitters are, however, quite distinct: Although $GABA_A$ receptors on AII amacrine cells directly appose the release sites (Contini & Raviola 2003), dopamine receptors do not and are instead dispersed throughout the retina (Nguyen-Legros et al. 1999). Whereas GABA release may specifically and locally regulate AII amacrine cells, dopamine mediates broad control of gap junctional coupling between many cell types, including photoreceptors (Ribelayga et al. 2008), horizontal cells (Mangel & Dowling 1985), and AIIs (Hampson et al. 1992, Kothmann et al. 2009), and may regulate GABA release from horizontal cells (Herrmann et al. 2011).

One classic combination of a fast neurotransmitter and modulatory peptide released by individual amacrine cells is GABA and VIP (Casini & Brecha 1992), the latter of which is expressed in retinas of many species (Tornqvist et al. 1982). Analyses of mouse lines expressing fluorescent indicators driven by the VIP promoter suggest that three amacrine cell subtypes express VIP and that all VIP-positive amacrine cells express GABA as well (Akrouh & Kerschensteiner 2015, Park et al. 2015, Zhu et al. 2014), consistent with earlier work in rabbit (Casini & Brecha 1992). The different VIP-positive subtypes vary with respect to IPL stratification, dendritic arbor density and area, and light response characteristics, which are shaped by crossover inhibitory interactions between the ON and OFF layers (Akrouh & Kerschensteiner 2015, Park et al. 2015). Specific roles for VIP amacrine cells in retinal circuitry remain unsettled. Stimulation via channelrhodopsin, transgenically expressed in VIP-positive cells, evoked strong GABAergic responses in ON-OFF, W3, and OFF δ retinal ganglion cells (RGCs) (Park et al. 2015), but postsynaptic responses to VIP and effects on RGC light responses have not been examined yet. Although the localization of receptors for VIP in the retina has not been studied in detail, autoradiography experiments suggest that they are expressed broadly (Harmar et al. 2004), possibly indicating that the neuropeptide may exert widespread effects.

AII amacrine cells play different roles at different times of day. AII amacrine cells are known to release just one kind of neurotransmitter (glycine) (Pourcho & Goebel 1985), but they are included in this discussion of bilingual amacrine cells because they also communicate to postsynaptic ON cone bipolar cells (as well as other AII amacrine cells) via electrical (gap junction) synapses (Dacheux & Raviola 1986, Famiglietti & Kolb 1975, Kolb & Famiglietti 1974) (**Figure 1*b***) made by their thin, arboreal dendrites. Glycinergic outputs are made onto OFF cone bipolar cell terminals by the lobular dendrites arising closer to the soma (**Figure 3*f***), sometimes

at reciprocal synaptic connections (Strettoi et al. 1992), and also onto a subset of OFF ganglion cells (Kolb & Famiglietti 1974, Manookin et al. 2008, Murphy & Rieke 2008, van Wyk et al. 2009). These dual synaptic mechanisms enable AIIs to preserve the sign of scotopic signals in rod bipolar cells that are transferred to ON cone bipolar cells and, at the same time, invert the signals for the OFF bipolar cells and OFF ganglion cells. Interestingly, the electrical synapses with ON cone bipolar cells also operate during the day—in the opposite direction—so that AII amacrine cells can relay photopic ON inhibitory signals to ganglion cells (Manookin et al. 2008), thereby enabling them to respond selectively to approaching dark objects (Munch et al. 2009). Electrical synapses made with other AIIs also change with time of day: AIIs are essentially uncoupled in absolute darkness but become more strongly coupled within the scotopic range (Bloomfield & Volgyi 2004) because of phosphorylation of the connexin 36 (Cx36) protein by CamKII, which is activated by calcium influx through extrasynaptic NMDA receptors (Kothmann et al. 2012). As light levels increase to photopic conditions, AIIs decouple again, as Cx36 is dephosphorylated by a phosphatase activated by dopamine receptors (Kothmann et al. 2009).

AIIs are relatively small cells (**Figure 3*f***), but their extensive gap junction connections may complicate their otherwise electrotonically straightforward morphology (Vardi & Smith 1996). In addition, AIIs fire small (<10-mV) action potentials (Boos et al. 1993, Cembrowski et al. 2012) mediated by voltage-gated sodium (Na_v) channels remotely expressed in a single, thin, electrotonically remote process that slows and attenuates the spikes (Cembrowski et al. 2012), thereby enabling Na_v channels to exert subtle, local effects on AII light responses (Tian et al. 2010).

Amacrine Cells Exhibit a Range of Input–Output Transformations

As reviewed briefly above, amacrine cells exhibit a broad range of morphological features, neurotransmitter phenotypes, and functional roles within the retinal circuitry. They also exhibit remarkable diversity in how they transform synaptic input into synaptic output, although most amacrine cells forsake the typical morphological segregation of inputs and outputs to dendritic and axonal arbors, respectively. Instead, postsynaptic responses often trigger presynaptic transmitter release without employing action potentials or involving the soma. The A17 amacrine cell may exhibit the most local input–output coupling, as calcium entering through postsynaptic glutamate receptors triggers GABA release (Chávez et al. 2006) (**Figure 5*a***) within each of hundreds of small, independently operating varicosities located along mostly passive dendrites (Grimes et al. 2010). At the other end of the spectrum, some wide-field amacrine cells use active membrane conductances or NMDA receptor–mediated spikes to propagate visual signals hundreds of microns across the retina (Bloomfield & Volgyi 2007, Dacey 1989, Manookin et al. 2015) (**Figure 5*d***). Many other amacrine cells exhibit input–output transformations that fall within these two extremes. SACs in mouse retina transform proximal synaptic input into outputs that are made more distally along the same dendritic branches (Ding et al. 2016, Vlasits et al. 2016) (**Figure 5*b***), yet the biophysical features that give rise to centrifugal motion preference within SAC dendrites (Euler et al. 2002, Hausselt et al. 2007) remain incompletely understood. AII amacrine cells and other narrow-field subtypes mediating crossover inhibition (Roska & Werblin 2001) receive inputs and make outputs in opposing functional layers of the IPL (**Figure 5*c***) and may use active membrane conductances (e.g., Tian et al. 2010) or intracellular calcium signaling (e.g., Chávez & Diamond 2008) to boost input–output coupling. In many recently studied, morphologically complex amacrine cells, like the VG3- and VIP-positive amacrine cells discussed above, the mechanisms linking synaptic input to output remain to be elucidated.

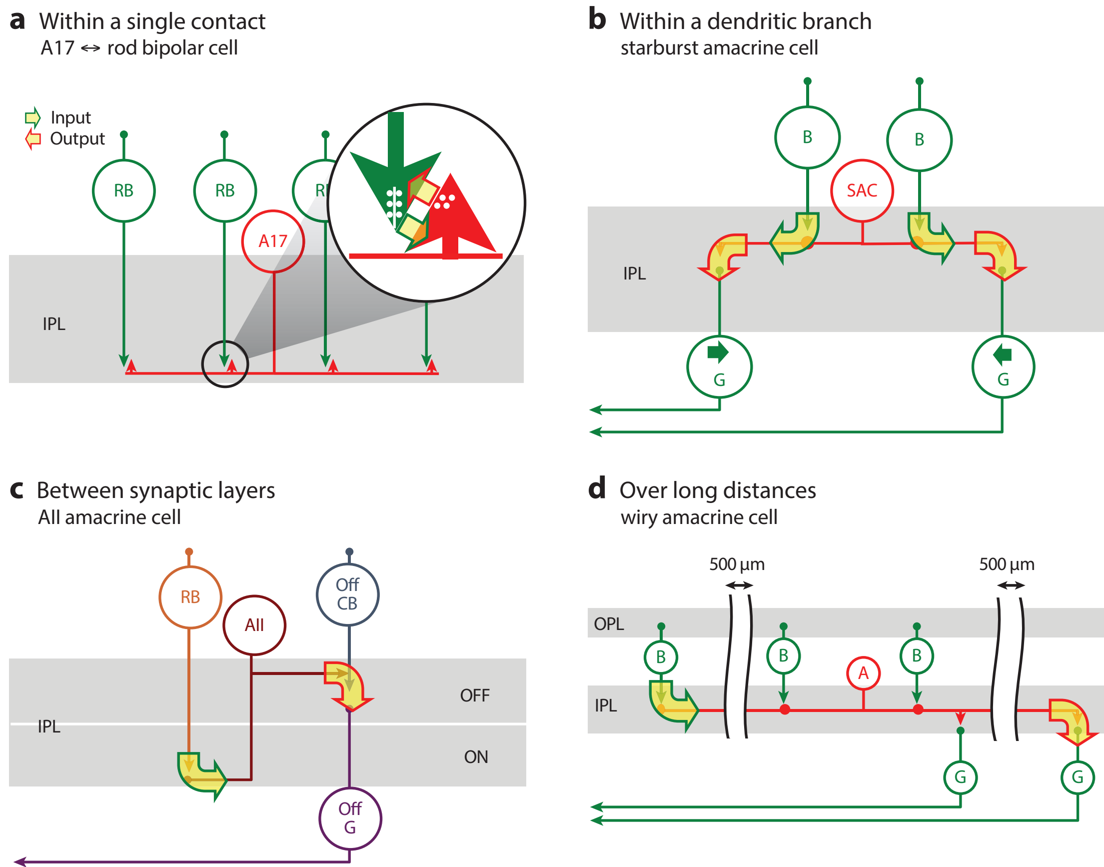

Figure 5

Coupling between synaptic inputs and outputs in amacrine cells. (*a*) A17 amacrine cells exhibit extremely local input–output coupling: Calcium entering through postsynaptic glutamate receptors can trigger GABA release (Chávez et al. 2006). (*b*) Inputs and outputs occur on the same SAC dendritic branches. Sections of the SAC dendritic arbor operate independently, enabling a single SAC to transmit feedforward inhibition that is tuned to different directions (Euler et al. 2002). (*c*) AII amacrine cells mediate a form of crossover inhibition in the rod pathway, transforming excitatory input from rod bipolar cells in the ON layer to inhibitory output to cone bipolar cells in the OFF layer. (*d*) Extremely wide-field "wiry" amacrine cells in the monkey retina employ dendritic, NMDA receptor–mediated spikes to propagate signals as far as a millimeter across the retina (Manookin et al. 2015). Abbreviations: A, amacrine cell; B, bipolar cell; G, ganglion cell; IPL, inner plexiform layer; Off CB, OFF cone bipolar cell; Off G, OFF ganglion cell; OPL, outer plexiform layer; RB, rod bipolar cell; SAC, starburst amacrine cell.

SUMMARY POINTS

1. Visual signaling in the vertebrate retina is shaped by two classes of interneurons: Horizontal cells establish center-surround receptive fields in the outer retina, and amacrine cells confer rich spatiotemporal complexity in the inner retina.
2. Horizontal cells provide feedback "inhibition" to photoreceptors—the quotation marks are used because feedback actually depolarizes photoreceptors, truncating their intrinsic light-evoked hyperpolarization. The mechanisms underlying feedback at these morphologically complex synapses remain controversial.

3. Horizontal cell feedback may employ GABAergic transmission, effaptic interactions, a change in pH within the synaptic cleft, or some combination of these mechanisms that causes a shift in the apparent voltage dependence of presynaptic calcium channels in the photoreceptor presynaptic membrane.
4. Amacrine cells constitute the most diverse cell class in the retina, with approximately 50 different subtypes in the mouse. Some amacrine cells appear dedicated to shaping signals in one or a few postsynaptic target cell types, whereas others distribute their outputs more broadly.
5. Many amacrine cells release more than one type of neurotransmitter, suggesting that individual cells play multiple processing roles. At least two amacrine cell types release both excitatory and inhibitory neurotransmitters.
6. Amacrine cells often receive synaptic inputs and make synaptic outputs within the same dendritic processes, so that information does not necessarily flow through the soma. This distributed form of visual processing may make more efficient use of cellular resources, but it complicates electrophysiological investigation of amacrine cell synaptic physiology.
7. Different amacrine subtypes employ different strategies to transform synaptic input to output. Some input–output coupling is very local, within a micron-sized varicosity, whereas in other cells, input and output are separated by as much as a millimeter.

FUTURE ISSUES

1. At some point, the field should reach consensus regarding the mechanisms underlying horizontal cell feedback.
2. Feedforward inhibitory signaling from amacrine cells to bipolar cells remains relatively lightly studied and deserves more attention. This is likely to be easier now that individual bipolar cell subtypes can be identified reliably in the mouse retina with genetic markers.
3. Despite tremendous progress in our understanding of starburst amacrine cell (SAC) circuitry and signaling, the precise biophysical mechanisms underlying intrinsic ("autonomous") direction selectivity within SAC dendrites remain to be completely clarified. SACs stand as a bellwether marking the field's progress toward understanding the range of dendritic signaling mechanisms in different amacrine cell types.
4. As more amacrine cell subtypes are studied in physiological detail, signaling and circuitry motifs and themes hopefully will emerge and help the field gain a clearer conceptual picture of the cell class as a whole.

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