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'Illuminating Synapses and Circuitry in the Retina

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In the central nervous system, space is at a premium. This is especially true in the retina, where synapses, cells and circuitry have evolved to maximize signal processing capacity within a thin, optically transparent tissue. For example, at some retinal synapses, single presynaptic active zones contact multiple postsynaptic targets; some individual neurons perform completely different tasks depending on visual conditions, while others execute hundreds of circuit computations in parallel; and the retinal network adapts, at various levels, to the ever-changing visual world. Each of these features reflects efficient use of limited cellular resources to optimally encode visual information.

Postsynaptic diversity encodes multiple visual channels

At many synapses in the retina (Figure 1A), and elsewhere in the brain, multiple postsynaptic receptor subtypes encode responses at a single synapse, expanding the complexity of signaling between pre- and postsynaptic cells. In addition, specialized synaptic arrangements in the retina often enable multiple postsynaptic neurons, each bearing distinct receptors, to receive synaptic input from the same presynaptic active zone, thereby dividing visual information into separate channels.

The absorption of photons in rods or cones induces membrane hyperpolarization that temporarily decreases ongoing vesicular glutamate release from photoreceptor synaptic terminals. Each cone synaptic ribbon delivers transmitter to several different postsynaptic bipolar cells, immediately dividing the visual signal into parallel channels that are driven by different general classes of postsynaptic glutamate receptor. ON bipolar cells are hyperpolarized by synaptic glutamate via a metabotropic glutamate receptor-mediated signaling cascade and therefore depolarize in response to light. OFF bipolar cells, driven by ionotropic glutamate receptors, hyperpolarize in response to light. OFF signals are further divided among multiple bipolar cell types at the same synapse that express distinct glutamate receptors [1–3] (Figure 1B). Recording from synaptically connected cones and OFF bipolar cells in retinal slices, DeVries [2] showed that different OFF cone bipolar cell types express different postsynaptic glutamate receptors: b2 cells express AMPA receptors (GluARs) and b3 and b7 cells express kainate receptors (GluKRs). Both GluARs and GluKRs bind and unbind glutamate rapidly, but GluKRs recover from desensitization much more slowly [4], a key determinant of the postsynaptic response in OFF bipolar cells. DeVries, et al. [3] went on to show that the receptor subtype expressed by each OFF bipolar cell matches its distance from the release site and the consequent time course of activation by neurotransmitter (Figure 1B). Confocal microscopy revealed that GluKR-expressing bipolar cells contact cones hundreds of nanometers from the presynaptic active zone, whereas GluAR-expressing processes contact cones much closer to the release site [3]

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(Figure 1B, bottom). In an elegant physiological experiment, the authors recorded from two postsynaptic bipolar cells receiving direct input from common active zones. During simultaneous responses to the same transmitter quanta, EPSCs in GluAR cells were faster than those in GluKR cells [3] (Figure 1B, top). Both GluARs and GluKRs are activated rapidly by high agonist concentrations, suggesting that GluKR-expressing bipolars respond more slowly to synaptic glutamate because their receptors are located farther from the release site and therefore encounter a lower concentration of neurotransmitter. This distant location may enable these cells to average individual components of the transmitter barrage from cones that, together with their GluKRs' slow recovery from desensitization, reduces synaptic noise, especially compared to their GluAR-expressing counterparts [3].

Cone bipolar cells make excitatory synaptic contacts onto retinal ganglion cells (RGCs), which typically receive these inputs via both GluARs and NMDA receptors (GluNRs). Spontaneous synaptic events exhibit a fast GluAR component, but in some RGCs they lack a slower GluNR component [5–8]. This is because GluNRs at some synapses are localized primarily in perisynaptic membranes and so are activated only when multiple vesicles are released or glutamate transporters are blocked [7,9]. Exclusively perisynaptic GluNR localization is more prevalent at ON synapses; at OFF synapses GluNRs in the postsynaptic density (PSD) can be activated by glutamate released from single vesicles [7,9]. GluNRs containing GluN2A subunits are typically found within RGC PSDs, while GluN2B-containing receptors are usually perisynaptic, even at OFF synapses [9] (Figure 1C). Although perisynaptic GluNRs would be more difficult to activate synaptically, Sagdullaev and colleagues [7] suggested that they may enable RGCs to respond over a broader stimulus range, because they would become saturated less easily than if they were in the synaptic cleft. Subsequent work by Manookin and colleagues [10] indicates that reality is likely much more complicated. For example, GluNR contribution to light-evoked signaling varies within general subtypes: in some OFF RGCs, GluNRs signal only in response to stronger stimuli while, in others, GluNRs signal over the entire response range. Further work is needed to clarify the specific roles for GluNRs in each RGC subtype.

The multifunctional AII amacrine cell

With more than two dozen different amacrine cells in the mammalian retina [11], one might expect each type to serve just one primary function. For example, AII (A2) amacrine cells are well known to play a key role in night (rod-mediated, or scotopic) vision by transmitting ON signals in the rod pathway to the cone pathway via electrical and chemical (inhibitory) synapses to ON and OFF cone bipolar cells, respectively (Figure 2A). This seems like enough for one cell to do, but several recent studies show that AII also operate during daytime (cone-mediated, or photopic) vision, being driven by ON cone bipolars through gap junctions (Figure 2B, C). The AII receives input during the day through the same electrical synapses that it uses to send output at night, an interesting example of synaptic multitasking that enables AII to participate in visual signaling across the retina's entire response range [12–14]. AII make gap junctions with about 80% of the ON cone bipolars [15], suggesting that AII likely influence a broad range of visual responses under both scotopic and photopic conditions [13,16].

Early anatomical studies indicated that, in addition to the canonical circuitry described above, AII also make glycinergic synaptic contacts directly onto RGCs in the outer (OFF) region of the IPL [17] (Figure 2B). Recent work from three different labs offer compelling, complementary insights into how the ON cone bipolar --> AII --> OFF RGC pathway contributes to visual signaling. Recording network noise in ON and OFF RGCs, Murphy and Rieke [18] showed that signals in AII influence excitatory inputs to ON RGCs and inhibitory inputs to OFF RGCs in parallel. This correlation of opposing signals in

neighboring ON and OFF RGCs enhances the differences between the two visual channels [18]. Demb's group demonstrated that AII inhibitory input to OFF RGCs is decreased in response to light decrement, thereby disinhibiting OFF RGCs, adding to the excitatory input from OFF bipolar cells and extending the dynamic range of OFF signals [12,19]. Finally, Münch and colleagues showed that AII input to a specific OFF RGC subtype underlies a modular circuit that may enable would-be prey to detect the looming shadows of approaching predators [20].

ON cone bipolar cells, acting through a glycinergic interneuron, have been shown to inhibit their OFF counterparts [12,21,22] (Figure 2C), further extending the dynamic range of signaling in the OFF pathway. AIIs are the logical choice to mediate this form of "crossover inhibition" [23], although direct evidence remains elusive. As shown recently by Liang and Freed [21], this synaptic inhibition rectifies signaling in OFF cone bipolars, probably by hyperpolarizing the steady-state presynaptic membrane potential closer to the activation threshold for the presynaptic Ca_v channels. In addition to enabling the OFF bipolar cell to transmit OFF signals over a larger response range, this rectification minimizes spurious ON signals in OFF RGCs. ON cone bipolar cells, by contrast, rest above the Ca_v threshold and can therefore encode OFF signals by hyperpolarizing and, consequently, reducing their steady-state release rate. This imbalance of ON and OFF signaling may reflect the image statistics of the natural world [21], which has more negative contrast than positive [24].

See globally, act locally

Microcircuits typically are thought to comprise interactions between a small number of neurons, but recent studies of dendritic physiology indicate that multiple signaling subunits can operate independently within individual cells [25]. This local processing often occurs in electrotonically remote dendritic segments, rendering them less accessible to somatic recording electrodes. Recent studies, often employing optical imaging, have begun to shed light on the mechanisms underlying microcircuit function.

Direction-selective (DS) RGCs compute the direction of image motion over their entire receptive field, which is typically 200–400 μm (Figure 3A), but they can also encode directional stimuli traversing less than a tenth that distance [26,27]. Thus, the circuit encoding direction must be repeated many times across the dendritic field of the cell. Directionally-tuned inhibition, a key component to the DS circuit [28–30], is provided by starburst amacrine cells (SBACs) [31], whose dendrites extend over 250–400 μm [32] – an area, again, much larger than the DS microcircuit, indicating that SBAC dendrites also locally compute and transmit DS signals. Having thin, electrotonically isolated dendrites, SBACs are well suited for compartmentalized signaling (Figure 3B). Although somatic EPSPs in SBACs are only weakly DS, calcium signals in dendritic segments are more robustly DS and tuned independently of their neighboring segments, suggesting that synaptic output, which occurs at the distal tips of the same dendrites, is also locally controlled [33–35].

Although DS RGCs receive directional input onto their dendrites, the resulting postsynaptic potentials, if passively summed at the soma, are only weakly directional and poorly correlated with spike output [36]. Thus, action potentials generated only at the axon hillock cannot produce directional spike output. Directional tuning of local, dendritic potentials ought to be sharper [37], and DS RGCs take advantage of this by initiating action potentials at multiple, functionally independent locations in their dendritic arbors. These dendritic spikes propagate to the soma and trigger action potentials in the axon [36]. By initiating spikes in their dendrites, DS RGCs preserve local, directional information contained in the

synaptic input and also enhance directional tuning over a wide range of stimulus conditions [37].

Another amacrine cell, the A17, appears to take local processing to the extreme: a recent report argues that each of the ~500 synaptic varicosities in an A17 dendritic arbor operates independently to provide reciprocal feedback inhibition to rod bipolar cell terminals [38] (Figure 3C). Input and output are locally coupled within each varicosity by GluARs, which admit Ca^{2+} that directly triggers GABA release [39]. Very thin dendrites electrotonically isolate varicosities, and BK channels suppress Ca_v channel activation over the lower end of the response range [38,40]. Consequently, synaptic Ca^{2+} signaling (and presumably GABA release) occurs independently in each varicosity [38]. Given the general role of amacrine cells in shaping computational subunits within RGC receptive fields, such local processing may be a common feature among other cells in this class.

Necessity is the mother of adaptation

To encode a visual world with a range in luminance ($\sim 10^{10}$) that far exceeds the dynamic range of individual RGCs ($\sim 10^2$), the retina must adapt, and it must do so on different timescales, from rapid changes between saccades (milliseconds) to slower, circadian transformations (hours) (Figure 4A). In several cases, short-term synaptic plasticity enables the retina to adapt to changing stimuli without duplicating circuitry [19,41–43].

One major reason that synapses adaptively control their own gain is to avoid signal saturation, a significant hazard in a convergent circuit like the retina. At scotopic light levels, gain control occurs primarily at the synapses between rod bipolar cells and AIIs [41]. Dunn and Rieke [42] used paired flashes of light to demonstrate that short-term depression accounts for this adaptation and occurs even in response to stimuli near the visual threshold. The time constant of recovery from depression (~ 85 ms) is fast enough to permit nearly full recovery during the inter-saccade interval (~ 200 ms); depression is synapse-specific and so can control gain with high spatial resolution, preserving responsivity in neighboring cells.

Synaptic depression may underlie adaptation at low light levels, but cell-intrinsic mechanisms appear to contribute in brighter conditions, as shown by Dunn et al. [44]. Under photopic conditions, adaptation first occurs at cone bipolar-RGC synapses (compare middle and lower panels in Figure 4B), but at higher intensities adaptation occurs primarily in the cones themselves (Figure 4B, top panel). The mechanisms underlying synaptic gain control in cone bipolar cells have not been identified, but fast depletion and slow replenishment of the readily releasable vesicle pool underlies depression at rod bipolar and cone photoreceptor ribbon synapses [45,46] and may account, at least in part, for synaptic adaptation in cone bipolar cells.

As rapidly changing visual signals are typically the most relevant, the retinal circuitry accentuates the onset of object motion by adapting to persistent (“background”) information in the visual scene. Olveczky and colleagues [47] measured a 2-fold attenuation of firing in object motion-sensitive (OMS) RGCs in response to a differential motion stimulus (Figure 4C). The authors cleverly manipulated the spatial frequency and periods of “object” and “background” gratings to show that adaptation exhibits high spatial resolution and occurs independently in neighboring regions, suggesting that depression of synaptic transmission between individual cone bipolar cells and OMS cells accounts for the attenuation. This adaptation also increased the spike correlation between two OMS cells that “see” the same object, thereby emphasizing the initial response (object motion detection) and potentially facilitating object “tracking” by multiple OMS cells via correlated firing.

Summary

The retina remains one of the best systems in the CNS for drawing direct, mechanistic connections between fundamental synaptic physiology and circuit function. Given the exciting progress described above and the remarkable range of powerful, new tools and methods becoming available, the future of synaptic research in the retina is clearly in the photopic range (i.e., bright).

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References

1. DeVries SH, Schwartz EA. Kainate receptors mediate synaptic transmission between cones and 'Off' bipolar cells in a mammalian retina. *Nature*. 1999; 397:157–160. [PubMed: 9923677]
2. DeVries SH. Bipolar cells use kainate and AMPA receptors to filter visual information into separate channels. *Neuron*. 2000; 28:847–856. [PubMed: 11163271]
- 3. DeVries SH, Li W, Saszik S. Parallel processing in two transmitter microenvironments at the cone photoreceptor synapse. *Neuron*. 2006; 50:735–748. The authors combine physiology, pharmacology, anatomy and modeling to show that multiple OFF bipolar cell types, driven by the same cone synapses, encode different types of information due to distinct postsynaptic glutamate receptors and physical location within the synapse. [PubMed: 16731512]
4. Wilding TJ, Huettner JE. Activation and desensitization of hippocampal kainate receptors. *J Neurosci*. 1997; 17:2713–2721. [PubMed: 9092592]
5. Chen S, Diamond JS. Synaptically released glutamate activates extrasynaptic NMDA receptors on cells in the ganglion cell layer of rat retina. *J Neurosci*. 2002; 22:2165–2173. [PubMed: 11896156]
6. Matsui K, Hosoi N, Tachibana M. Excitatory synaptic transmission in the inner retina: paired recordings of bipolar cells and neurons of the ganglion cell layer. *J Neurosci*. 1998; 18:4500–4510. [PubMed: 9614227]
- 7. Sagdullaev BT, McCall MA, Lukasiewicz PD. Presynaptic inhibition modulates spillover, creating distinct dynamic response ranges of sensory output. *Neuron*. 2006; 50:923–935. A range of physiological evidence argues that ON and OFF RGC synapses differ in terms of GluNR expression and presynaptic modulation by GABA_C receptor feedback, and that these distinctions affect the dynamic range of light-evoked signaling. [PubMed: 16772173]
8. Taylor WR, Chen E, Copenhagen DR. Characterization of spontaneous excitatory synaptic currents in salamander retinal ganglion cells. *J Physiol*. 1995; 486 (Pt 1):207–221. [PubMed: 7562636]
9. Zhang J, Diamond JS. Subunit- and pathway-specific localization of NMDA receptors and scaffolding proteins at ganglion cell synapses in rat retina. *J Neurosci*. 2009; 29:4274–4286. [PubMed: 19339621]
10. Manookin MB, Weick M, Stafford BK, Demb JB. NMDA receptor contributions to visual contrast coding. *Neuron*. 2010; 67:280–293. [PubMed: 20670835]
11. MacNeil MA, Masland RH. Extreme diversity among amacrine cells: implications for function. *Neuron*. 1998; 20:971–982. [PubMed: 9620701]
- 12. Manookin MB, Beaudoin DL, Ernst ZR, Fligel LJ, Demb JB. Disinhibition combines with excitation to extend the operating range of the OFF visual pathway in daylight. *J Neurosci*. 2008; 28:4136–4150. [PubMed: 18417693]
13. Pang JJ, Abd-El-Barr MM, Gao F, Bramblett DE, Paul DL, Wu SM. Relative contributions of rod and cone bipolar cell inputs to AII amacrine cell light responses in the mouse retina. *J Physiol*. 2007; 580:397–410. [PubMed: 17255172]
14. Xin D, Bloomfield SA. Comparison of the responses of AII amacrine cells in the dark- and light-adapted rabbit retina. *Vis Neurosci*. 1999; 16:653–665. [PubMed: 10431914]

15. Petrides A, Trexler EB. Differential output of the high-sensitivity rod photoreceptor: AII amacrine pathway. *J Comp Neurol*. 2008; 507:1653–1662. [PubMed: 18241050]
16. Field GD, Greschner M, Gauthier JL, Rangel C, Shlens J, Sher A, Marshak DW, Litke AM, Chichilnisky EJ. High-sensitivity rod photoreceptor input to the blue-yellow color opponent pathway in macaque retina. *Nat Neurosci*. 2009; 12:1159–1164. [PubMed: 19668201]
17. Famiglietti EV Jr, Kolb H. A bistratified amacrine cell and synaptic circuitry in the inner plexiform layer of the retina. *Brain Res*. 1975; 84:293–300. [PubMed: 1111833]
- 18. Murphy G, Rieke F. Signals and noise in an inhibitory interneuron diverge to control activity in nearby retinal ganglion cells. *Nat Neurosci*. 2008; 11:318–326. [PubMed: 18223648]
19. Beaudoin DL, Manookin MB, Demb JB. Distinct expressions of contrast gain control in parallel synaptic pathways converging on a retinal ganglion cell. *J Physiol*. 2008; 586:5487–5502. [PubMed: 18832424]
- 20. Munch TA, da Silveira RA, Siebert S, Viney TJ, Awatramani GB, Roska B. Approach sensitivity in the retina processed by a multifunctional neural circuit. *Nat Neurosci*. 2009; 12:1308–1316. The authors show that approach sensitivity in PV-5 ganglion cells requires a modular receptive field involving direct inhibitory input from glycinergic AII amacrine cells. The experiments highlight a specific daytime function for a neuron long thought to be involved exclusively in night vision. [PubMed: 19734895]
- 21. Liang Z, Freed MA. The ON pathway rectifies the OFF pathway of the mammalian retina. *J Neurosci*. 2010; 30:5533–5543. [PubMed: 20410107]
22. Molnar A, Werblin F. Inhibitory feedback shapes bipolar cell responses in the rabbit retina. *J Neurophysiol*. 2007; 98:3423–3435. [PubMed: 17928553]
23. Molnar A, Hsueh HA, Roska B, Werblin FS. Crossover inhibition in the retina: circuitry that compensates for nonlinear rectifying synaptic transmission. *J Comput Neurosci*. 2009; 27:569–590. [PubMed: 19636690]
24. Ratliff CP, Borghuis BG, Kao YH, Sterling P, Balasubramanian V. Retina is structured to process an excess of darkness in natural scenes. *Proc Natl Acad Sci U S A*. 107:17368–17373. [PubMed: 20855627]
25. Branco T, Häusser M. The single dendritic branch as a fundamental functional unit in the nervous system. *Curr Opin Neurobiol*. 20:494–502. [PubMed: 20800473]
26. Barlow HB, Levick WR. The mechanism of directionally selective units in rabbit's retina. *J Physiol*. 1965; 178:477–504. [PubMed: 5827909]
27. Grywacz NM, Amthor FR, Merwine DK. Directional hyperacuity in ganglion cells of the rabbit retina. *Vis Neurosci*. 1994; 11:1019–1025. [PubMed: 7947395]
28. Borg-Graham LJ. The computation of directional selectivity in the retina occurs presynaptic to the ganglion cell. *Nat Neurosci*. 2001; 4:176–183. [PubMed: 11175879]
29. Fried SI, Munch TA, Werblin FS. Mechanisms and circuitry underlying directional selectivity in the retina. *Nature*. 2002; 420:411–414. [PubMed: 12459782]
30. Taylor WR, Vaney DI. Diverse synaptic mechanisms generate direction selectivity in the rabbit retina. *J Neurosci*. 2002; 22:7712–7720. [PubMed: 12196594]
31. Yoshida K, Watanabe D, Ishikane H, Tachibana M, Pastan I, Nakanishi S. A key role of starburst amacrine cells in originating retinal directional selectivity and optokinetic eye movement. *Neuron*. 2001; 30:771–780. [PubMed: 11430810]
32. Tauchi M, Masland RH. The shape and arrangement of the cholinergic neurons in the rabbit retina. *Proc R Soc Lond B Biol Sci*. 1984; 223:101–119. [PubMed: 6151180]
33. Euler T, Detwiler PB, Denk W. Directionally selective calcium signals in dendrites of starburst amacrine cells. *Nature*. 2002; 418:845–852. [PubMed: 12192402]
- 34. Häusselt SE, Euler T, Detwiler PB, Denk W. A dendrite-autonomous mechanism for direction selectivity in retinal starburst amacrine cells. *PLoS Biol*. 2007; 5:e185. [PubMed: 17622194]
35. Lee S, Zhou ZJ. The synaptic mechanism of direction selectivity in distal processes of starburst amacrine cells. *Neuron*. 2006; 51:787–799. [PubMed: 16982423]
- 36. Oesch N, Euler T, Taylor WR. Direction-selective dendritic action potentials in rabbit retina. *Neuron*. 2005; 47:739–750. [PubMed: 16129402]

37. Schachter MJ, Oesch N, Smith RG, Taylor WR. Dendritic spikes amplify the synaptic signal to enhance detection of motion in a simulation of the direction-selective ganglion cell. *PLoS Comput Biol.* 2010;6.
- 38. Grimes WN, Zhang J, Graydon CW, Kachar B, Diamond JS. Retinal parallel processors: more than 100 independent microcircuits operate within a single interneuron. *Neuron.* 2010; 65:873–885. Using electrophysiology, calcium imaging, electron microscopy and modeling, this study provides a detailed description of multiple mechanisms at work to allow one interneuron to provide multiple, independent local feedback circuits in the retina. [PubMed: 20346762]
39. Chavez AE, Singer JH, Diamond JS. Fast neurotransmitter release triggered by Ca influx through AMPA-type glutamate receptors. *Nature.* 2006; 443:705–708. [PubMed: 17036006]
40. Grimes WN, Li W, Chavez AE, Diamond JS. BK channels modulate pre- and postsynaptic signaling at reciprocal synapses in retina. *Nat Neurosci.* 2009; 12:585–592. [PubMed: 19363492]
41. Dunn FA, Doan T, Sampath AP, Rieke F. Controlling the gain of rod-mediated signals in the Mammalian retina. *J Neurosci.* 2006; 26:3959–3970. [PubMed: 16611812]
- 42. Dunn FA, Rieke F. Single-photon absorptions evoke synaptic depression in the retina to extend the operational range of rod vision. *Neuron.* 2008; 57:894–904. [PubMed: 18367090]
43. Manookin MB, Demb JB. Presynaptic mechanism for slow contrast adaptation in mammalian retinal ganglion cells. *Neuron.* 2006; 50:453–464. [PubMed: 16675399]
- 44. Dunn FA, Lankheet MJ, Rieke F. Light adaptation in cone vision involves switching between receptor and post-receptor sites. *Nature.* 2007; 449:603–606. The authors identify the synapse from cone bipolar to retinal ganglion cells as a site of luminance adaptation under daylight conditions and show that adaptation at this synapse occurs at lower light levels than adaptation within cone photoreceptors. [PubMed: 17851533]
45. Jackman SL, Choi SY, Thoreson WB, Rabl K, Bartoletti TM, Kramer RH. Role of the synaptic ribbon in transmitting the cone light response. *Nat Neurosci.* 2009; 12:303–310. [PubMed: 19219039]
46. Singer JH, Diamond JS. Vesicle depletion and synaptic depression at a mammalian ribbon synapse. *J Neurophysiol.* 2006; 95:3191–3198. [PubMed: 16452253]
- 47. Olveczky BP, Baccus SA, Meister M. Retinal adaptation to object motion. *Neuron.* 2007; 56:689–700. Using traditional electrophysiology techniques, and clever patterns of light to stimulate the retina, this study shows that the response to relative object motion decreases over time, and tests several hypothesis about the origin of this adaptation. [PubMed: 18031685]
48. Vaney DI, Gynther IC, Young HM. Rod-signal interneurons in the rabbit retina: 2. AII amacrine cells. *J Comp Neurol.* 1991; 310:154–169. [PubMed: 1955580]
49. Reinagel P, Zador AM. Natural scene statistics at the centre of gaze. *Network.* 1999; 10:341–350. [PubMed: 10695763]
50. Rieke F, Rudd ME. The challenges natural images pose for visual adaptation. *Neuron.* 2009; 64:605–616. [PubMed: 20005818]
- 51. Baccus SA, Meister M. Fast and slow contrast adaptation in retinal circuitry. *Neuron.* 2002; 36:909–919. [PubMed: 12467594]

Figure 1.

Postsynaptic diversity at retinal synapses. (A) Schematic of mammalian retina, modified from [48]. R, rod; C, cone; RB, rod bipolar cell; On CB, ON cone bipolar cell; Off CB, OFF bipolar cell; A17, A17 amacrine cell; AII, AII amacrine cell; On G, ON RGC; Off G, OFF RGC; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. Several cell types, including horizontal cells, other amacrine cells, and Müller glial cells, have been omitted for clarity. (B) *top*, Simultaneous recordings from b2 (black) and b3 (red) OFF cone bipolar cells receiving input from the same presynaptic cone active zone. Simultaneous events indicated by arrows. From [3]. *bottom*, schematic of cone synapse, modified from [3]. OFF bipolar cell processed are labeled according to whether they express GluARs ('A') or GluKRs ('K'). HC, horizontal cell. (C) Synaptic schematic (*left*) and average spontaneous EPSCs (sEPSCs, *right*) recorded from ON (*top*) and OFF (*bottom*) RGCs (from [9]). In ON RGCs (*top*), responses in control (black) are mediated entirely by GluARs. A slower GluNR component emerges only when glutamate transporters are blocked with TBOA (green). The GluNR component is blocked by the GluNR2B-selective antagonist Ro-25,6981 (Ro, red). Subsequent application of the non-specific GluNR antagonist CPP had no further effect. In OFF RGCs (*bottom*), control sEPSCs (black) decay more slowly than in ON RGCs. TBOA slows the sEPSC decay even further (green), an effect that is reversed by Ro (red). CPP (blue) removes a slow component that is present in control, indicating that GluNRs are activated even when glutamate uptake is intact.

Figure 2.

AII amacrine cells participate in multiple signaling pathways. (A) In the classical pathway, AIIs receive excitatory ON input from rod bipolar cells (RB) and make sign-conserving electrical synapses to ON cone bipolar cells (On CB, green arrow) and sign-inverting inhibitory (glycinergic) synapses to OFF cone bipolars (Off CB, red arrow). (B) During photopic (daytime) vision, cone-driven ON cone bipolars signal through gap junctions to (green arrow) AII, which make direct glycinergic connections to OFF RGCs (off G, red arrow). See [12,18–20]. (C) AII driven by ON cone bipolars also inhibit OFF cone bipolars, allowing the ON pathway to rectify the OFF pathway [21].

Figure 3.

Computational subunits within the dendritic arbors of different retinal neurons. (A) Dendritic spikes enable DS RGCs to preserve subunit-specific information about stimulus direction [36]. (B) Local signaling in SBAC dendrites is a critical feature of directional selectivity [28–31]. (C) Reciprocal GABAergic feedback occurs in functionally independent synaptic varicosities on A17 amacrine cell dendrites [38]. A17 image taken by William Grimes and Sanjeev Kaushalya.

Figure 4.

Local adaptation to luminance and contrast. (A) Positions of visual fixation (circles) and saccade trajectories (lines) plotted for one human viewer illustrate some of the challenges for retinal processing. Within one visual field, retinal neurons must encode low contrast areas of high and low mean luminance (blue circles 1 and 2, respectively), as well as areas of high contrast (blue circle 3). Modified from [49]. (B) Normalized current responses to flashes of light on backgrounds of different luminance are plotted for cone photoreceptors, midget cone bipolar cells, and midget RGCs. Rod input was minimized with a background light that suppressed rods without affecting cones. When the background is increased from baseline (“dark,” black) to 1,000 R*/cone/s (red), gain control is evident in the midget RGCs but not in the cones or midget bipolars, indicating it occurs at the synapse from midget bipolar cell to midget RGC. Increasing the background to 10,000 R*/cone/s (blue) caused gain control to occur within the cones themselves, thus demonstrating two separate locations for luminance adaptation within this circuit. Modified from [50]; data originally reported in [44]. (C) RGC adaptation to differential motion. *top*, schematic of the visual stimulation used in [47]: a grating in a central circle was surrounded by a separately controlled background grating. The gratings could be moved together, simulating “global” motion, or separately (“differential” motion). *bottom*, a spike histogram shows that an OMS RGC accommodates to differential motion, thereby accentuating motion onset. Adapted from [47].