

Retinal Physiology: Non-Bipolar-Cell Excitatory Drive in the Inner Retina

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The long-held view that bipolar cells provide the exclusive excitatory drive to the mammalian inner retina has been challenged: new studies indicate that, instead, at least two cells that lack the dendrites characteristic for bipolar cells, and therefore resemble amacrine cells, excite inner retinal circuits using glutamate.

Back in the early 1960s, pioneers of vision science first began charting principles that govern early visual processing in vertebrates. They laid the foundations that still guide our understanding of retinal organisation (reviewed in [1]): three classes of excitatory neurons, namely the photoreceptors, bipolar cells and the retinal ganglion cells that provide the output neurons of the retina, constitute the ‘vertical’, excitatory pathway of the retina. Intermingled in two sequential synaptic layers, horizontal cells and amacrine cells provide lateral inhibition and thereby shape the signal transfer from photoreceptors to bipolar cells and from bipolar cells to retinal ganglion cells, respectively. Photoreceptors and bipolar cells excite their respective postsynaptic partner through glutamate release from specialised synaptic structures (ribbons), whereas inhibition is typically mediated by GABA or glycine released from classical synapses.

It has, however, long been known that this cannot be the full story: In addition to GABA or glycine, many amacrine cells use a secondary neurotransmitter, such as neuromodulatory agents like dopamine or neuropeptides but also classical excitatory transmitters [2]. For instance, starburst amacrine cells, famous for their role in generating retinal direction selectivity, in addition to GABA, release acetylcholine, the excitatory transmitter of the neuromuscular junction [3]. But even for the well-studied starburst amacrine cell circuit, the exact role of acetylcholine remains elusive (discussed in [4,5]) — except for the finding that it appears to generally modulate retinal ganglion cell activity in a paracrine fashion. Amacrine

cell-driven excitation was therefore considered a side-note, the exception from the rule — until recently.

Now, several studies [6–10], including one [11] in this issue of *Current Biology*, define not just one but two new and rather distinct circuits in which amacrine-like neurons contribute important excitatory drive, each with a clear function assigned. The first is the ‘glutamatergic amacrine cell’ (GAC), which differentially releases glutamate and glycine at traditional synapses, thereby directly feeding several types of retinal ganglion cells [6–10]. The second, described in the paper in this issue [11], is affectionately dubbed the ‘glutamatergic monopolar interneuron’ (GluMi), and is stranger still: like bipolar cells, this cell type features full-blown ribbons to release glutamate; unlike bipolar cells, however, the GluMi completely lacks a dendrite and thus, from a connectivity point of view, carries the features of an amacrine cell.

A New Way of Driving Retinal Ganglion Cell Circuits

In mice, a good baker’s dozen of bipolar cell types stratify in different levels of the retina’s inner plexiform layer (reviewed in [12]), where they provide glutamatergic excitation to the more than 30 retinal ganglion cell circuits that have been identified [13]. The organisation of the bipolar cell output synapse, the so-called ‘dyad’, is highly conserved: Here, a bipolar cell ribbon synapse serves two postsynaptic processes that originate from either a retinal ganglion cell/amacrine cell pair or from two amacrine cells. Traditionally, amacrine cells provide inhibitory feedback to bipolar cells and/

or feedforward inhibition to retinal ganglion cells. While the inhibition a bipolar cell receives does not necessarily come from the same amacrine cell type(s) — there are plenty of additional, non-dyad-associated amacrine cell inputs at the bipolar cell axon terminal — the overall signal flow of excitation and inhibition was considered to be understood: excitation comes from bipolar cells, while inhibition comes from amacrine cells. This now has changed with the discovery of the ‘new’ amacrine/bipolar cell hybrids.

So how do these neurons fit into the system? For the GluMi the answer seems simple: despite lacking a dendrite and thus any direct contact with photoreceptors, they replace the bipolar cell in the dyad [11]. GACs, on the other hand, occupy the slot traditionally reserved for amacrine cells [10]. Yet, both GluMIs and GACs have in common that they provide direct glutamatergic excitation to retinal ganglion cells. While this likely happens in tandem with one or more types of bipolar cells — at least in the case of the much-studied W3 retinal ganglion cell [14], the mouse version of the ‘local-edge detector’ — GACs even appear to provide the main excitatory drive [8].

Importantly, both GluMIs and GACs drive retinal ganglion cells in a ‘non-traditional’ excitatory way: Unlike most bipolar cells, the GluMi appears to be strongly depolarised at rest — perhaps a replacement of the ‘missing’ depolarising drive from the dendrite? The cell is therefore expected to constantly release glutamate and thus generate an excitatory ‘tone’. Upon patterned visual

stimulation, the GluMi itself receives transient inhibition, which is then relayed through a transient decrease in glutamate release to the retinal ganglion cell. Effectively, it thus relays an inhibitory amacrine cell signal, superimposed on a general excitatory tone. While tonic release also appears to be a common feature of bipolar cells [15,16], the GluMi takes this to extreme levels by eliminating the modulatory component bipolar cells receive from the photoreceptor. Why this is functionally advantageous at this site of the retinal network remains to be investigated.

The GAC, on the other hand, acts more like an ‘empowered’ amacrine cell. Like many amacrine cells, it provides glycinergic inhibition to some retinal ganglion cell types, among them the so-called ‘suppressed-by-contrast’ cells [13]. In addition, however, and apparently at functionally independent synaptic sites of the same cell, it provides non-ribbon-associated glutamatergic drive to at least four other retinal ganglion cell types [6–8]. As such, the GAC’s evolutionary origin looks more like an amacrine cell taking up functional bipolar cell features, as opposed to a bipolar cell taking up amacrine cell features, as is the case for GluMIs (Figure 1).

Evolution Will Find a Way?

What can we learn from this? In the past decade, retinal ‘dogmas’ have been falling at an alarming rate. For example, the finding that both rod photoreceptors and their retinal pathways can remain active in bright light blurred the lines between traditionally segregated cone and rod photoreceptor pathways at different brightness regimes [17]. Here, even the central amacrine cell of the rod ‘night-vision’ pathway, the ‘All’ cell, found itself a diametrically opposite ‘daytime job’ (discussed in [18]). Similarly, retinal neurons that were traditionally thought to signal through graded changes in membrane potential (photoreceptors, horizontal cells, bipolar cells) are principally capable of generating active, regenerative potentials, or ‘spikes’ (reviewed in [19]), thus greatly expanding the retina’s computational arsenal.

It therefore appears that we are gradually converging at a view of retinal organisation that only approximately fits

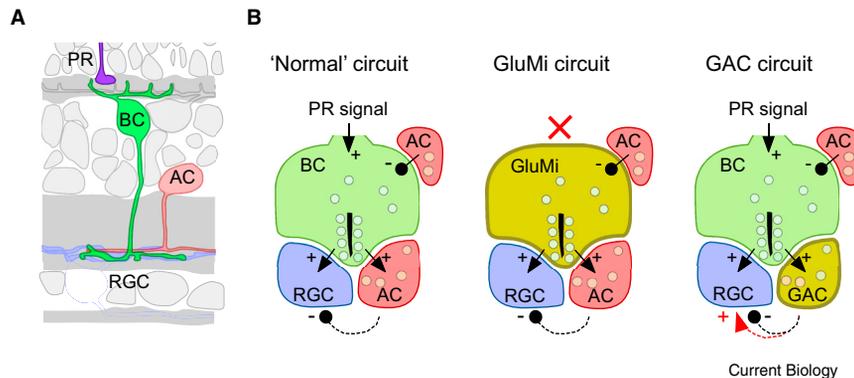


Figure 1. Integration of the new amacrine/bipolar cell hybrids into inner retinal circuits.

(A) Signal flow in the retina. Photoreceptors (PR) feed into bipolar cells (BC), which in turn drive retinal ganglion cells (RGCs). Amacrine cells (AC) provide local inhibitory context. (B) Classically, a bipolar cell carries the photoreceptor drive into the inner retina where it releases glutamate onto amacrine and retinal ganglion cells. Amacrine cells in turn inhibit bipolar and retinal ganglion cells. (left). Despite lacking direct photoreceptor drive, the GluMi replaces the bipolar cell (middle) while the GAC replaces an amacrine cell process yet releases either glutamate or glycine onto different postsynaptic sites (right). Dotted lines indicate connections that may or may not occur at the same synaptic site. Figure adapted from [12].

into neat categories but is distinctly rough around the edges. Perhaps every long-held rule will eventually find its counterexample, but rather than abandoning long-held wisdom altogether, new findings add colour and context to the retina’s rich tapestry. After all, evolution does not strive to conserve organisational principles but presumably works the other way round: Organisation emerges as a solution to the compromise between efficient (sensory) encoding of the world that is appropriate for any one animal, energy efficiency and space constraints. If now a ‘new’ function needs to be implemented as an animal explores a new visual niche, there is usually more than one way to do that, not all of which have to respect the organisational integrity of the existing circuitry. For example, a single A17 cell, one of the larger amacrine cells in the mouse retina, provides >100 rod bipolar cells with individually tailored local inhibitory feedback [20] — here a large cell apparently represents a working solution for a highly local synaptic interaction.

Perhaps this is where the amacrine/bipolar cell hybrids come in. If, for example, a particular computational function was required both as an excitatory and an inhibitory signal, there is more than one solution to this problem. One could flip a bipolar cell’s signal polarity using an amacrine cell. Or, as seems to be the case for the GAC, one could use an existing amacrine cell and

‘simply’ add glutamatergic signalling to its repertoire, thus perhaps saving that additional, costly neuron. As such, these amacrine/bipolar cell hybrids may reflect the need for (more) excitatory drive in the inner retina. Why this need is not satisfied by bipolar cells and how this additional source of glutamate may fit into the intricate balance of excitation and inhibition in the inner retina remain open questions. Certainly, whether or not more exception-from-the-rule elements are waiting to be discovered, these new findings should serve as a reminder that even the extensively-studied mouse retina continues to provide textbook-revisiting material.

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Ecology: The Upside-Down World of Coral Reef Predators

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Examination of a large aggregation of sharks demonstrates that trophic pyramids with greater amounts of high-level predators than prey can occur on coral reefs. This is possible because the high-level predators obtain food from sources outside their home location.

Most of us learn in school that trophic pyramids are just that: pyramids — i.e. systems with broad bases of primary producers supporting ever smaller amounts of animals as higher trophic levels are being reached. These pyramids occur because biological energy flow must conform to the physical laws of thermodynamics [1]. For example, in a kelp forest there is a high biomass of kelp, smaller amounts of urchins and other herbivores that eat the kelp and even fewer fish that eat the urchins. In 2008, Stuart Sandin and colleagues [2] literally turned the trophic pyramids of coral reefs on their heads. Working at Palmyra Atoll in the central Pacific Ocean they reported

an inverted trophic pyramid where the biomass of sharks and other large predators on this unfished coral reef was much greater than the biomass of animals at lower trophic levels. This observation created heated debate amongst coral reef scientists as to whether such inverted biomass pyramids could in fact exist, and if so, under what conditions [1,3,4]. Further surveys of relatively pristine coral reef communities have revealed other locations where inverted pyramids exist [5,6], and it turns out they also exist in other habitats, including planktonic communities [7] and some kelp forests [8]. Previous attempts to understand this phenomenon [3] have used ecological

models to show that inverted pyramids were theoretically possible in three situations — when prey populations have higher turnover rates compared to predator populations, where predators or prey move between systems and thus obtain or provide trophic subsidies, or where prey hide in refuges. More recently, theory and simulation were applied to show that subsidies were the main way in which extreme inverted biomass pyramids could be supported [1]. Critically, this work demonstrated that the turnover rate mechanism proposed by Sandin and colleagues [2] cannot cause inverted pyramids. While these theoretical considerations have been useful to further