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NLM Citation: Kolb H. Roles of Amacrine Cells. 2005 May 1 [Updated 2007 Apr 30]. In: Kolb H, Fernandez E, Nelson R, editors. Webvision: The Organization of the Retina and Visual System [Internet]. Salt Lake City (UT): University of Utah Health Sciences Center; 1995-.
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Roles of Amacrine Cells

Helga Kolb

Created: May 1, 2005; Updated: April 30, 2007.

General Characteristics

Amacrine cells of the vertebrate retina are interneurons that interact at the second synaptic level of the vertically direct pathways consisting of the photoreceptor-bipolar-ganglion cell chain. They are synaptically active in the inner plexiform layer (IPL) and serve to integrate, modulate, and interpose a temporal domain to the visual message presented to the ganglion cell. Amacrine cells are so named because they are nerve cells thought to lack an axon (1). Today, we know that certain large-field amacrine cells of the vertebrate retina can have long "axon-like" processes, which probably function as true axons in the sense that they are output fibers of the cell (see a later section on dopaminergic amacrine cells). However, these amacrine axons remain within the retina and do not leave the retina in the optic nerve, as do the ganglion cell axons (Fig. 1).

Since the time of Cajal, we have known that amacrine cells come in all shapes, sizes, and stratification patterns. Since those days, many more morphological subtypes have and continue to be described from additional Golgi studies, intracellular recordings, and immunocytochemical staining. Thus, we presently have a classification of amacrine cells consisting of about 40 different morphological subtypes (Fig. 2).

It is useful and most easily understandable to group the amacrine cell types into the general descriptors of narrow-field (30-150 µm), small-field (150-300 µm), medium-field (300-500 µm) and wide-field (>500 µm) based on a measurement of their dendritic field diameters (2). Then, the next most important criterion of classification involves knowing the stratification of the cells. It is generally agreed now that the IPL can be subdivided into five equi-thickness strata or sublayers (1) into which amacrine, bipolar, and ganglion cell processes can be assigned. All of these cell types are now classified primarily on the stratum or strata of the IPL in which their dendrites or axons are located. This is because, as mentioned in previous chapters, the IPL of vertebrate retinas can be divided into areas of neuropil, where specific cells are put into synaptic contacts and form circuits only with cells earmarked for a particular functional role.

Many varieties of amacrine cell are monostratified (restricted to a single stratum), whereas others are bi- or tri-stratified. When amacrine or ganglion cell processes pass through all the strata of the IPL from distal to proximal or *vice versa*, they are called diffuse cells. Superimposed upon Cajal's five strata subdivision of the IPL is a sublaminar division of the IPL. The first two strata, 1-2, are known as sublamina **a** of the IPL, whereas strata 3-5 are known as sublamina **b** by this scheme (3). It will be remembered from previous chapters that sublamina **a** contains bipolar axons and ganglion cell connections that lead to OFF-center ganglion cell physiology, whereas sublamina **b** contains bipolar to ganglion cell connections resulting in ON-center ganglion cell physiology (4).

Fig. 3 shows drawings of some small field amacrine cells of the monkey retina as seen in vertical sections. Small-field cells like these can be well visualized in section because their dendritic trees are contained within the depth of the section. However, large-field cells are not so well described in the section where their dendrites get cut off.

It was only when whole-mount preparations, from Golgi staining (5, 6) or immunocytochemical staining (7), were attempted that we could classify such cells. Then the full extent of their dendritic trees, which can be up to 1 mm in spread, could be visualized (see Fig. 4a) and a whole new understanding of amacrine cells became available.

A new technique of intracellular staining by a photochemical method has been developed In Richard Masland's group as an alternative to the unreliable Golgi technique (8). Amacrine cells of the rabbit retina are labeled with the nuclear stain DAPI and then selected, single-nuclei are irradiated by a narrow beam of light to drive DAPI to the oxidation of non-fluorescent dihydrorhodamine-123 to the fluorescent rhodamine-123. The complete cell body and the dendritic tree are thus revealed under viewing in the fluorescence or confocal microscopes. By this method, 30 or so different varieties of amacrine cell can be photographed and drawn in full detail in the rabbit retina. Twenty-two varieties of amacrine cell have been seen in Golgi preparations in cat and primate retinas, so either some have been missed that were seen in rabbit, or else they are not as well deveoped in these less complex mammalian retinas. In any event, the narrow-field and medium-field types revealed by MacNeil and Masland's work (8) are shown in Fig. 4b and Fig. 4c. Another five different, wide-field, monostratified types were also encountered in rabbit retina by this method (not illustrated). They correspond closely to the wide-field types seen in monkey, cat, and human (2, 9, 10).

Amacrine Cell Circuitry as Revealed by Electron Microscopy

Kidd (11) and later Dowling and Boycott (12) were the first to identify the three types of profiles that contribute to the IPL by electron microscopy. The electron micrograph (Fig. 5) shows the cytological criteria on which we now recognize bipolar, amacrine, and ganglion cell profiles in the neuropil. Thus bipolar cell axonal endings are recognized by being filled with synaptic vesicles and having a ribbon-shaped density (red spots) pointing to two postsynaptic profiles (amacrine and ganglion). Amacrine profiles are also filled with synaptic vesicles but make synapses characterized by membrane densities at which the vesicles are particularly clustered (yellow spots). Ganglion cell profiles are recognized as being only postsynaptic to either bipolar axons or amacrine processes, containing no vesicles but instead a content of neurotubules, ribosomes, and glycogen granules.

Amacrine cell synapses are frequently seen to be reciprocal to bipolar ribbon input, i.e., the amacrine returns a synapse in the vicinity of the ribbon input synapse (arrowheads). Most amacrine cells are inhibitory neurons in the vertebrate retina, containing the common inhibitory neurotransmitters GABA or glycine. GABAergic amacrine cells, in particular, typically make reciprocal synapses with bipolar cells. A17 is the most well studied of the GABAergic reciprocal amacrine cells in the retina, and we shall return to this cell later.

We have learned much concerning the synaptic relationships of certain narrow-field amacrine cells as well as bipolar and small ganglion cell types, such as midget ganglion cells of the primate retina, from reconstructions of serial-section electron micrographs. The circuitry of the AII amacrine cell in the cat retina was first appreciated by this means (13, 14). However, with the advent of intracellular dye injection of electron-dense materials (horseradish peroxidase, HRP, or the photo reduction of Lucifer yellow) after physiological recordings or the development of electron-dense immunostains for electron microscopy, neurocircuitry was made easier for us. We could look at amacrine cells and their synaptic inputs by study of fewer sections, and it was not as critical to photograph every single section in a series. The amacrine cell of interest would always be clearly marked black and easily found in the synaptic neuropil. It is from this technique that we have learned most about amacrine cells and their circuitry in the mammalian retina. The remainder of this chapter will describe the morphology, circuitry, and intracellular responses of the amacrine cells that are most completely understood at present.

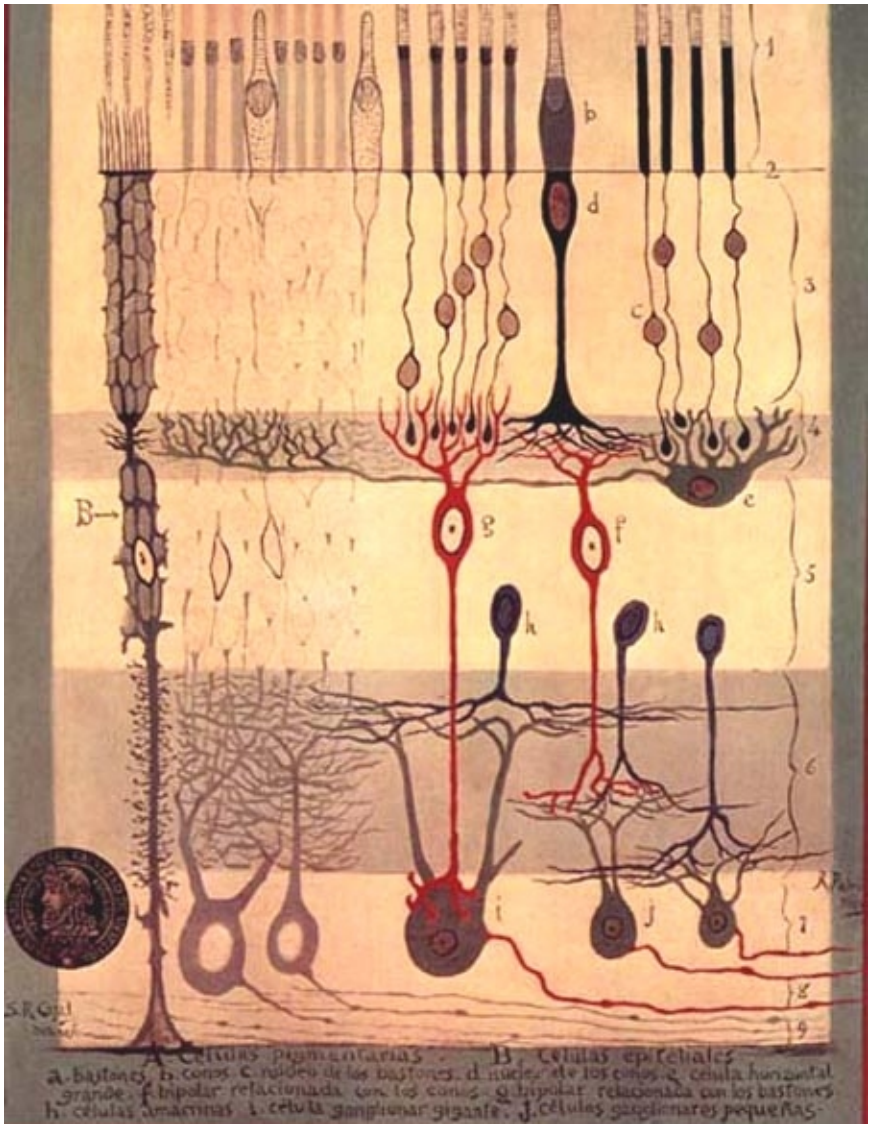


Figure 1. Drawing of the retina made by Cajal.

A2: Narrow-field, Cone Pathway Amacrine Cell

A2 is a narrow-field amacrine with a 20-60-µm-wide dendritic tree composed of multi-branched, beaded, and appendage-bearing dendrites, mostly confined to stratum 2 of the IPL (Fig. 6).

Intracellular recordings from A2 cells (formerly called A4) indicate that these cells give true slow potential, hyperpolarizing response to light (OFF-center) at all positions of the slit in their receptive fields, and they have no sign of an inhibitory surround (15).

A2 cells receive bipolar input from OFF-center types of cone bipolar cell of sublamina **a** and make reciprocal synapses to these bipolar axons. A2 amacrine cells then synapse upon OFF-center ganglion cell dendrites of sublamina **a**. The A2 cell makes an inhibitory synapse upon these ganglion cells, because it is thought to be a GABAergic cell type (16).

A possible role is in disinhibition of the ganglion cells' center responses. Alternatively, A2 cells, despite being small-field types, might have a role in the generation of antagonistic surrounds of ganglion cells (17). A2 cells receive a great many amacrine inputs to their dendritic trees, which could be from wider field cells than they are

Figure 2. Picture of Camillo Golgi.

are themselves, so giving them a much larger receptive field size than their actual dendritic tree size would indicate (Fig. 7).

AII: A Bistratified Rod Amacrine Cell

In Fig. 8 are shown four examples of the best-studied amacrine of all in the vertebrate retina: the AII "rod amacrine" of the mammalian retina. These cells have been recorded from by microelectrodes, and dyes have been iontophoresed into the cell after the intracellular recordings (18). The AII cell was first described from Golgi staining and electron microscopic examination (13, 19).

AII is a narrow-field amacrine (dendritic tree diameter typically 30-70 μm) with a bistratified morphology: the mitral-shaped cell body gives off a single, stout apical dendrite, and a cluster of lobular appendages (round blobs just below the cell body) (Fig. 9) arise from the main dendrite in sublamina **a** of the IPL. The finer "arboreal dendrites" (20) penetrate down into sublamina **b** to end close to the ganglion cell layer. In the human retina, such an AII amacrine cell is seen in a surface view of a wholemount.

In cat and rabbit retinas, from which AIIs have been recorded, the AII cell is a rod-dominated depolarizing (ON-center) cell (18, 21, 22). Thus, in the center of its receptive field the cell gives a transient depolarizing response with a pronounced sustained plateau (ON-center) and a long, drawn-out hyperpolarization after light off. By 140 μm to either side of the center, the response to a light flash is now an inverted response, indicating a hyperpolarizing surround (OFF-surround) (18) (Fig. 10).

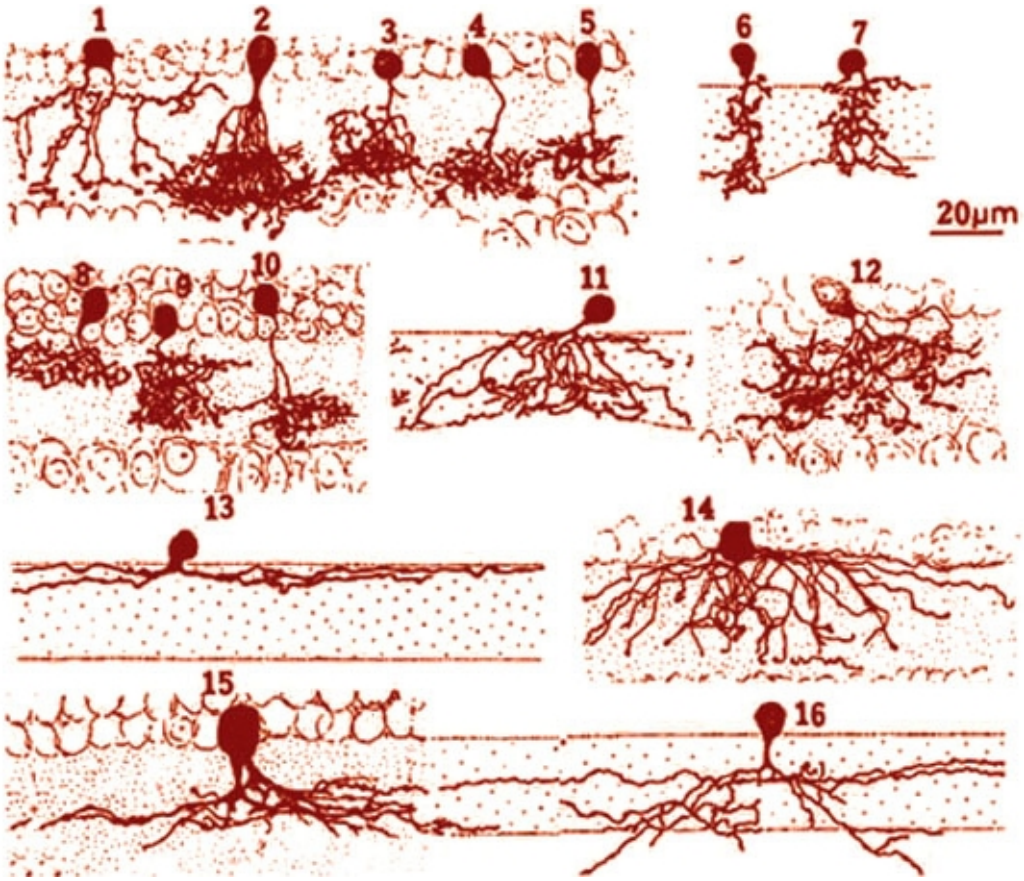


Figure 3. Stratification patterns of small and medium-field amacrine cells in primate retina. From Polyak (81).

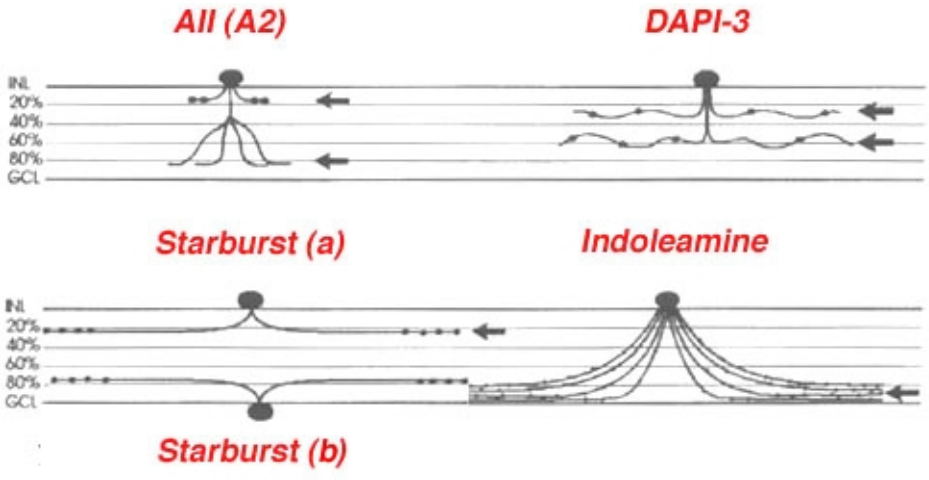


Figure 4a. Golgi-stained, wide-field amacrine cells as seen in whole-mount retina of the cat. Amacrines are classified by number and strata of the IPL in which they branch.

Electron microscopy has shown that the AII is primarily postsynaptic to rod bipolar axon terminals in lower sublamina **b** of the IPL (30% of its input) (23). Its major output is upon ganglion cells that have dendrites only in sublamina **a**, i.e., AII cell lobular appendages synapse upon OFF-center a and b ganglion cells (17) (Fig. 11).

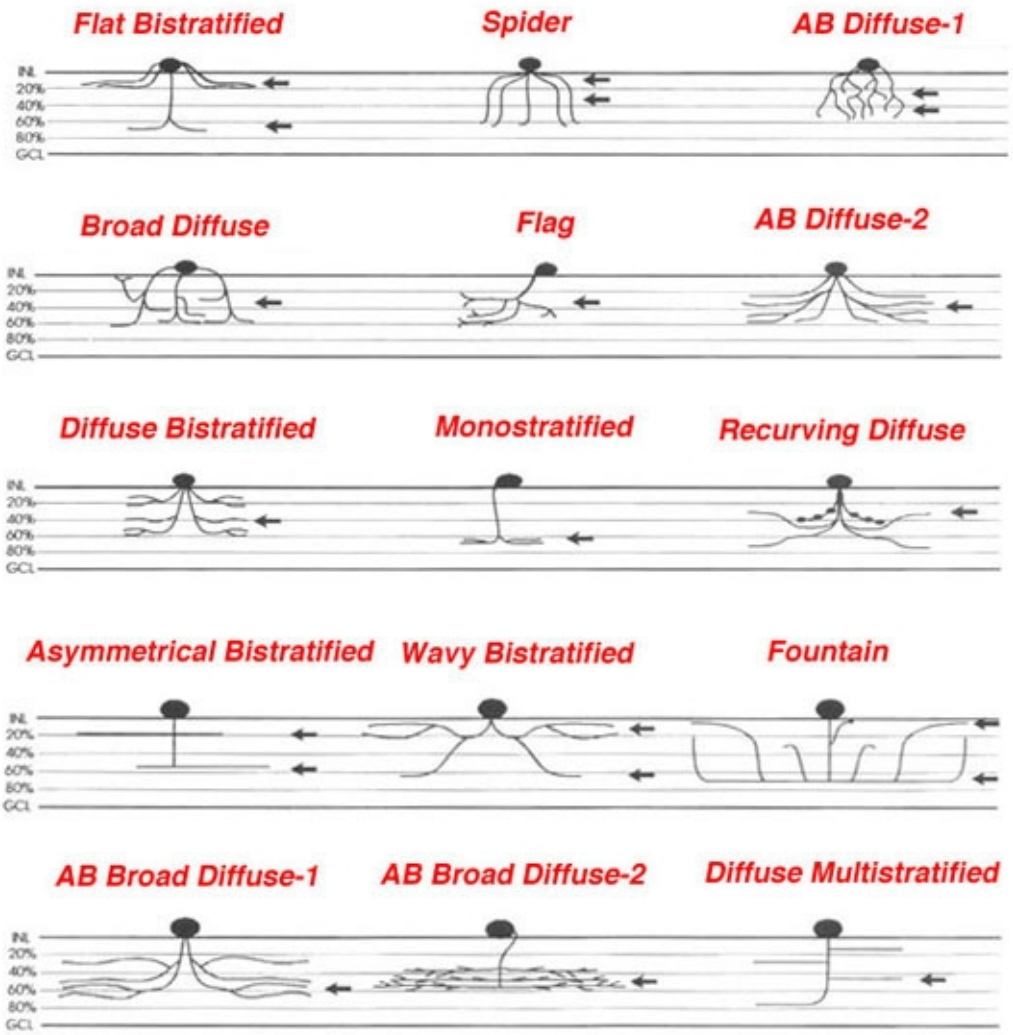


Figure 4b. Small-field and medium-field amacrine cells of the rabbit retina. AII cells, DAPI-3 cells, starburst type a cells, and indoleamine-containing cells are shown.

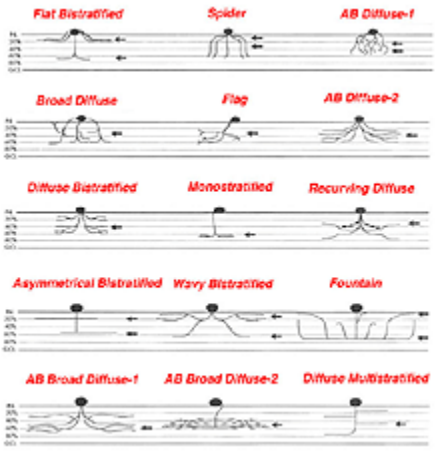


Figure 4c. Narrow- and medium-field cells of the rabbit retina.

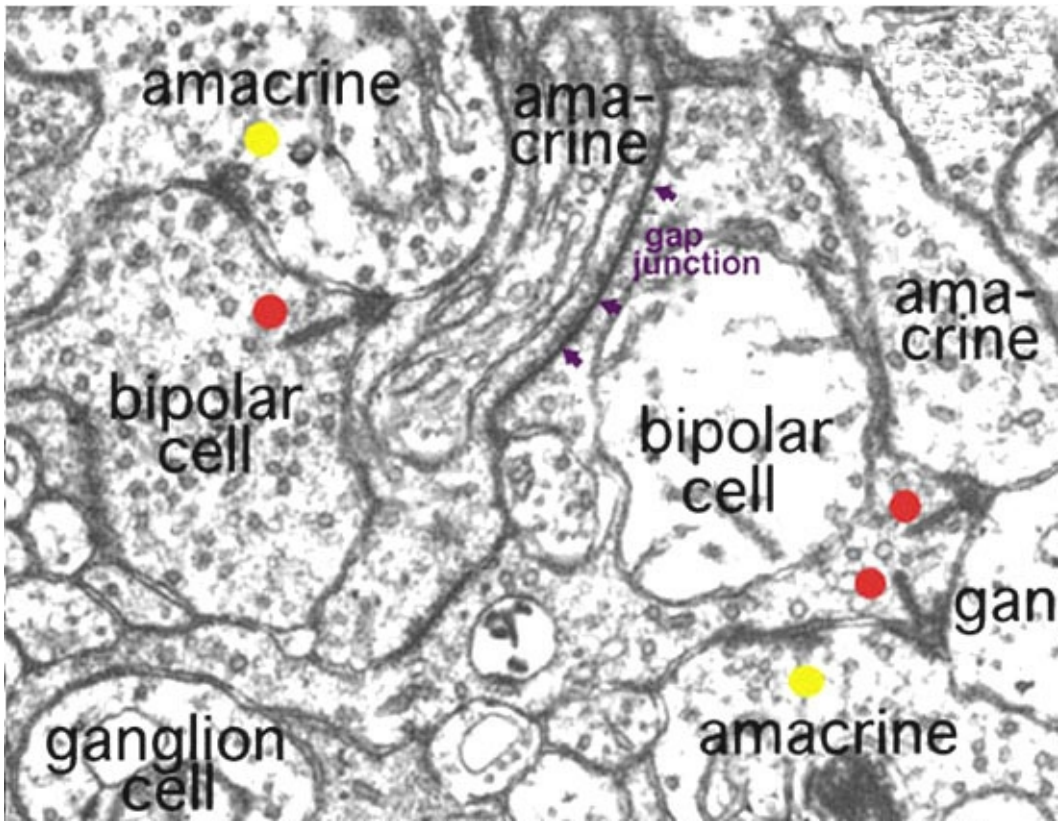


Figure 5. Electron micrograph of the various synapses in the IPL. Red dots indicate bipolar ribbon synapses; yellow dots are reciprocal amarcine synapses. Small arrows point to a gap junction between a bipolar cell and an All amacrine cell profile.

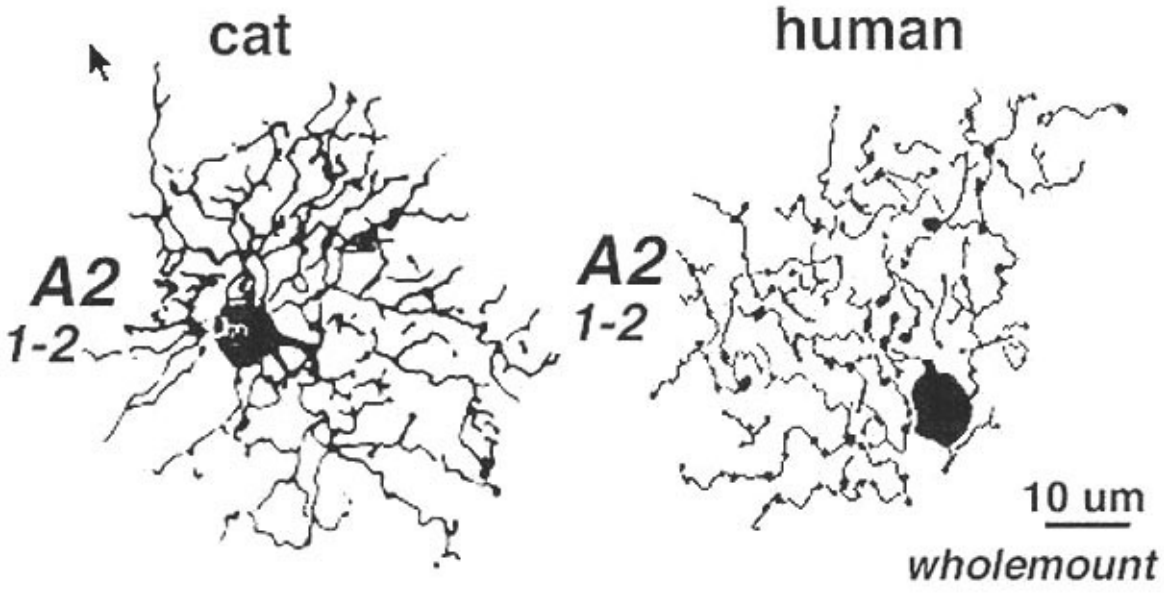


Figure 6. Golgi drawings of A2 amacrine cells.

The AII also passes rod-driven information through the ON-center cb5 cone bipolar to ON-center a and b ganglion cells by means of gap junctions (Fig. 12, black spots on AII primary dendrites to pink cb axon). A little

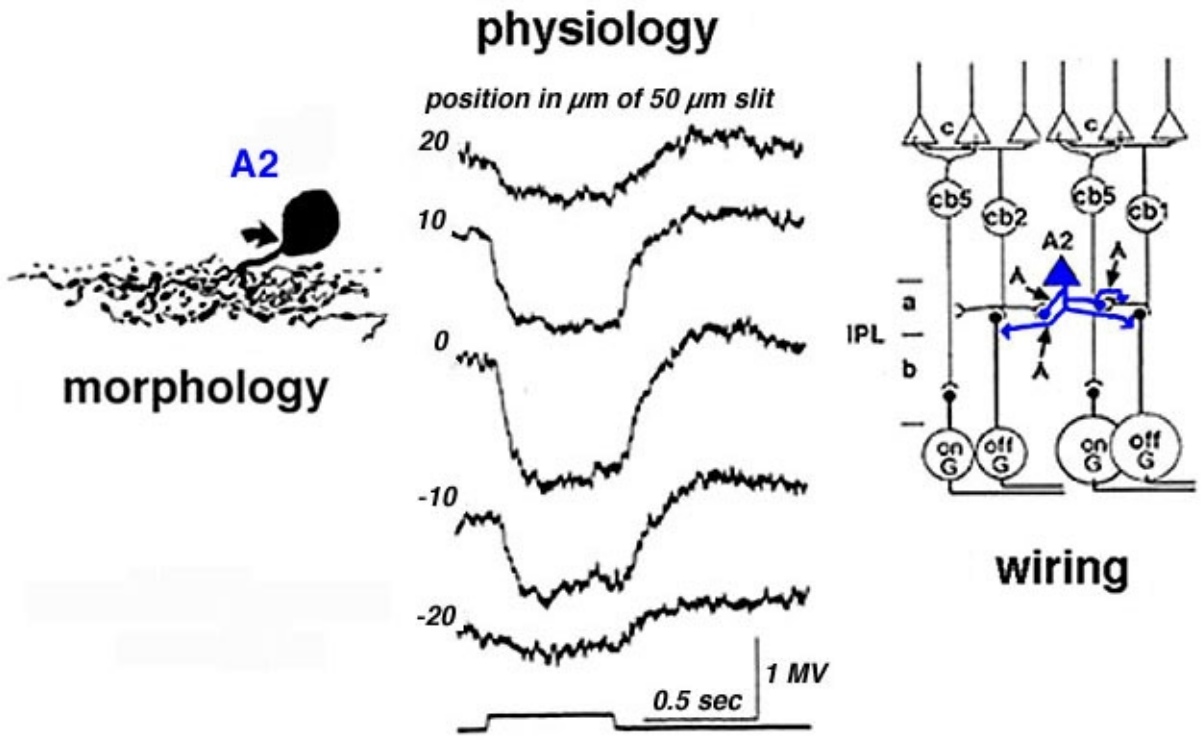


Figure 7. Summary diagram of A2 amacrine cells.

OFF-center cone bipolar input is provided to the AII lobular appendages by cb1 and cb2 OFF-center cone bipolar cells in sublamina **a** (19% of input) (Fig. 12, yellow cb profiles) (23).

Thus, AII cells do carry some cone pathway components to their ON-center responses, which could come from excitatory input from ON-center cb5 at the gap junctions or from the direct cb1 or cb2 synapses, which would have to be inhibitory, in this case. AII amacrine cells are also couple across the retina in a weak electrical syncytium by virtue of their gap junctions between their arboreal dendrites in sublamina **b** (Fig. 12, gj, lower right; see an animation of the wiring pattern) (13, 18, 24).

The dopaminergic amacrine cell provides a considerable number of synapses to the AII cell, either directly upon its cell body or upon its lobular appendages (Fig. 11, A, red arrowheads) (25, 26). Dopamine cells are thought to have a function in the inner retina to uncouple AII amacrine cells from both their contacts with the depolarizing cone bipolar and the AII amacrine coupled network (24, 27). As much as 51% of the input to AII amacrine cells is from various other amacrine cells though, and most of these inputs occur in the central part of the cells' dendritic tree in strata 3-4 (23). AII amacrine cells are glycine immunoreactive (28, 29) and contain the calcium-binding proteins parvalbumin, calbindin, and calretinin (Fig. 13) (30).

The AII amacrine cells are the major carriers of rod signals to the ganglion cells in the retina. As such, they play a role in speeding up the slow potential rod messages for presentation to ganglion cells (18, 31). Their distribution in the retina suggests that they tile the complete retina (32). AII amacrine cells peak in density at 1.5 mm from the foveal center in monkey and at the area centralis in cat (33). In addition, because of their high density across all parts of the retina and their synaptic involvement with millions of rod bipolar cells, they may contribute in a major way to the pattern ERG (34).

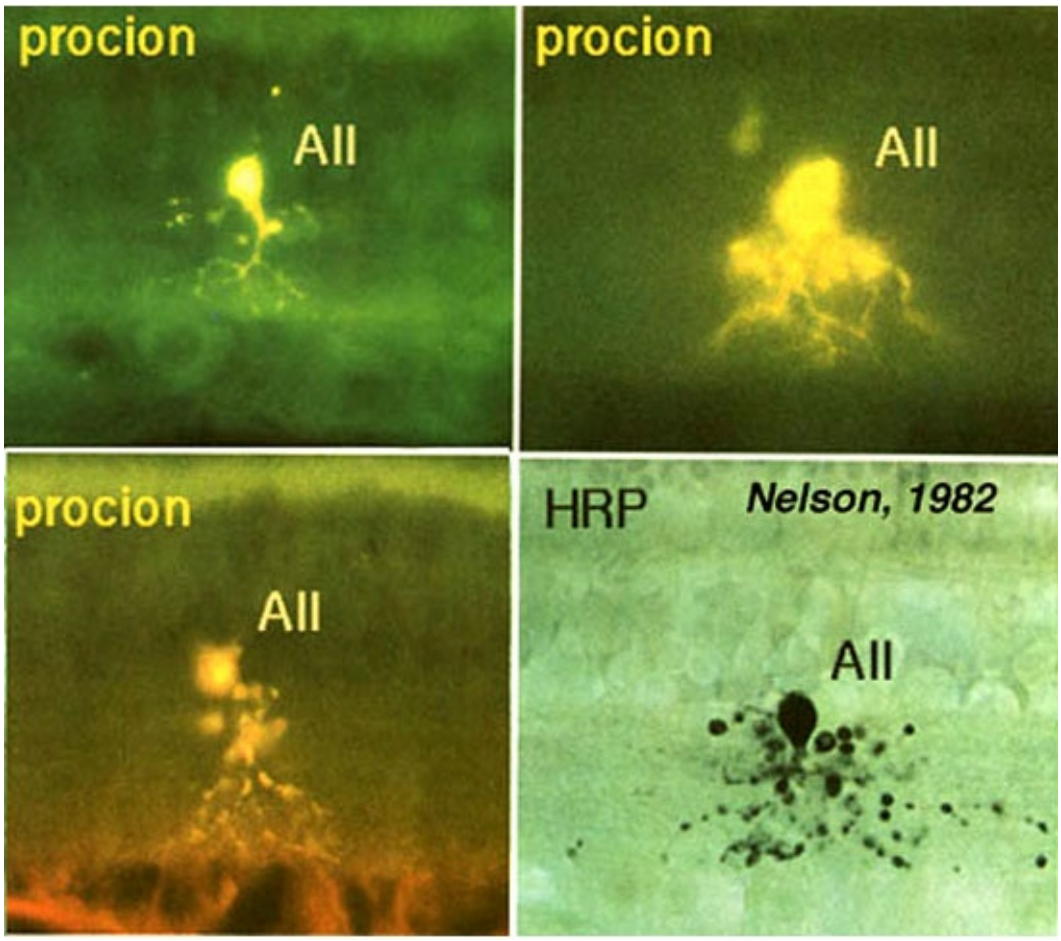


Figure 8. AII amacrine cells stained with different methods.

A8: A Bistratified Cone Amacrine Cell

A8 is a bistratified, narrow-field amacrine cell that is easy to confuse with AII in whole-mount, stained retina. It actually looks like an upside-down AII cell. A8 has short, wispy processes coming from the apical dendrite to ramify in sublamina **a** of the IPL, whereas heavy-beaded dendrites penetrate down to sublamina **b** to run in strata 4 and 5. This cell type may correspond to the DAPI-3 of the rabbit retina, described by Vaney (32) and Bloomfield (21) (Fig. 14).

The A8 cell has been intracellularly recorded and studied by electron microscopy after iontophoresis of horseradish peroxidase. In Fig. 15, we shown two of the most important synapses of this cell type.

The A8 amacrine cell is involved in the cone pathways of the cat retina, rather than the rod pathways that the AII is committed to. Thus, in sublamina **a**, excitatory cone-driven signals come from cone bipolar cells such as cb2, which we know are OFF-center in physiology (Fig. 16, yellow cb profile), and in sublamina **b** from cb6, another OFF-center bipolar cell (Fig. 16, cb, pink profile) (35). Altogether cone bipolar synapses account for 42% of the input to A8 cells. Lesser rod bipolar input (20%) also occurs to the lower dendrites in sublamina **b** of the IPL. Like AII amacrine cells, A8 cells also engage in gap junctions with a cone bipolar type of sublamina **b**, but the bipolar is a different type and, in addition to the gap junction, makes the common ribbon synapse to A8 dendrites (Fig. 16; see an animation of the wiring pattern). A8's major output is to beta ganglion cell dendrites in sublamina **a** of the IPL (above GC). We have not seen A8 synapses to alpha cells in the cat retina (36).

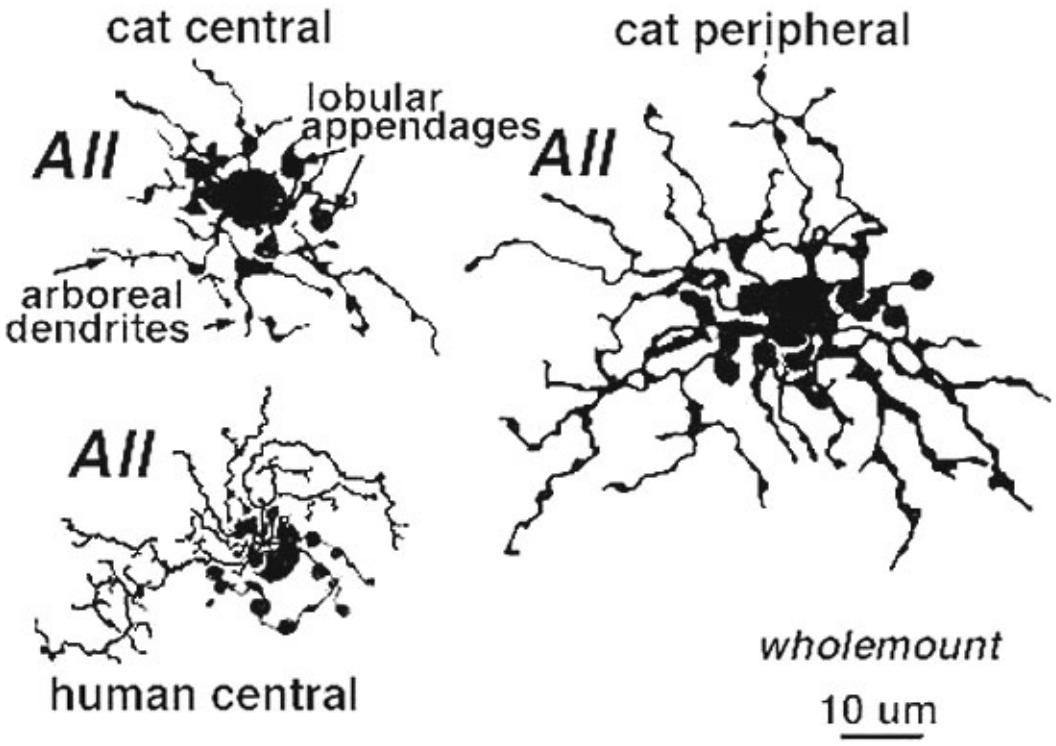


Figure 9. AII amacrine cells.

The intracellular response of A8 indicates a hyperpolarization to light at the receptive field center with a rather transient OFF-response to light. The transientness could reflect the amacrine synapses (38% of input) occurring over all parts of its dendritic tree (Fig. 16, red arrowheads) (0, response is at largest magnitude).

Both rod-driven and cone-driven signals contribute to the response. Its receptive field extent can be mapped with a slit of light. As the slit is stepped some distance to either side of the center of the receptive field, the response of the cell inverts and a depolarizing or ON-surround appears by 700 μm from the central position (Fig. 17, top and bottom trace) (36).

Some part of the amacrine input to A8, particularly that upon its cell body and proximal dendrites in stratum 1 of the IPL, may be from dopaminergic amacrine cells (A18) (25). So it is probable that this cell type is also under the control of the dopaminergic amacrine cells, similar to the AII amacrine cell (see above). Thus, the dopamine cell may control A8's spatial characteristics through gating its gap junctions in light and dark. A8 is intensely glycine immunoreactive (28, 29). We have suggested that A8 cells also function in the disinhibition of ganglion cell receptive field centers (36).

A13: A Small-field Diffuse Amacrine Cell of the Cone System

Cell A13 is a diffusely branched cell with a large cell body (12 μm diameter) and fine dendrites bearing distinct beads at regular intervals that run through mostly strata 3-5 of sublamina **b** of the IPL to end up along the top of ganglion cell bodies. The complete tree covers a 100-μm area (Fig. 18).

Electron microscopy shows that A13 cells, similar to A8 cells, get only a minor rod bipolar cell (12%) input, whereas three different types of cone bipolar cell have major synaptic input (28%). The cone bipolar inputs are from axons in sublamina **a**, stratum 3-4 of sublamina **b**, and stratum 5 of sublamina **b**. A13 cells appear to make reciprocal synapses upon cone bipolar cells and possibly also upon rod bipolar cells. Amacrine cells provide

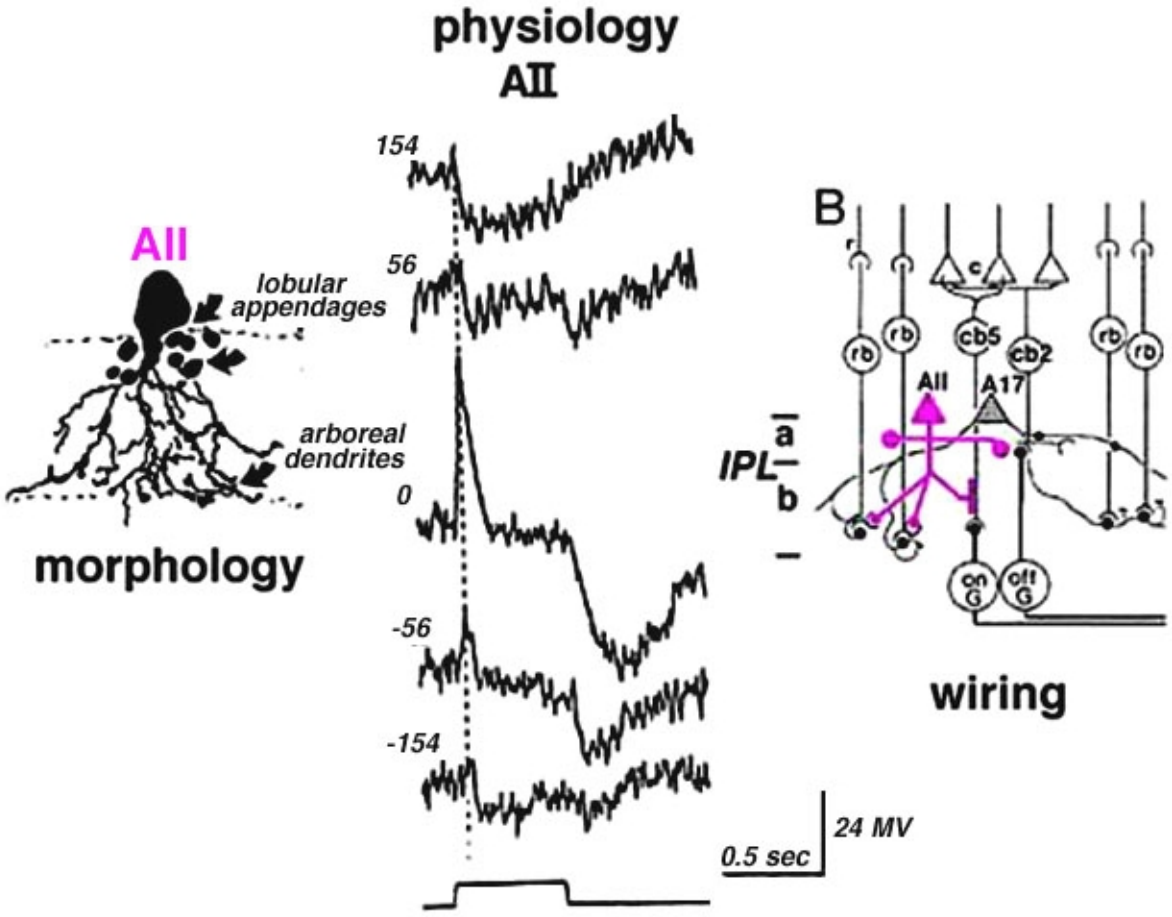


Figure 10. Schematic diagram of the morphology, physiology, and wiring pattern of the AII amacrine cell.

much more synaptic input than bipolar cells (60%). A13 makes synaptic output to OFF-center ganglion cells, of both alpha and beta types, in sublamina **a**. Gap junctions link A13 cells at their beaded dendrites (36) (Fig. 19; see an animation of the wiring pattern).

The intracellular response of A13 is a slow potential, hyperpolarizing response, looking much like a horizontal cell response in the cat retina. Mixtures of rod and cone signals contributed to the intracellular response of A13 cells. Its receptive field is large and does not appear to exhibit a surround. The spatial extent of the receptive field is very suggestive of a coupled electrical syncytium of cells at least seven cells wide (Fig. 20) (36).

A17: The Wide-field Reciprocal Rod Amacrine Cell

A17 is a wide-field *diffuse* amacrine. Its dendritic tree can span close to a millimeter of retinal surface. Its very fine dendrites bear pronounced beads at regular intervals along their lengths. The majority of the dendritic tree runs in sublamina **b** of the IPL, along the top of the ganglion cell layer in stratum 5 as a dense network of fine fibers. Over 1000 beads have been counted on such A17 amacrine cells in the cat retina (37), and as we shall see later, the beads are the synaptic points where reciprocal synapses with rod bipolar cells occur (38) (Fig. 21).

Electron microscopy shows that A17 cells are the predominant reciprocal amacrine cell at the rod bipolar cell axon terminals in sublamina **b** of the IPL. In addition, their fine dendrites in sublamina **a** receive some synapses from the dopaminergic amacrine cell A18 (Fig. 22). However, there has not yet been discovered any synaptic output of the A17 except the reciprocal synapses with the rod bipolar axon.

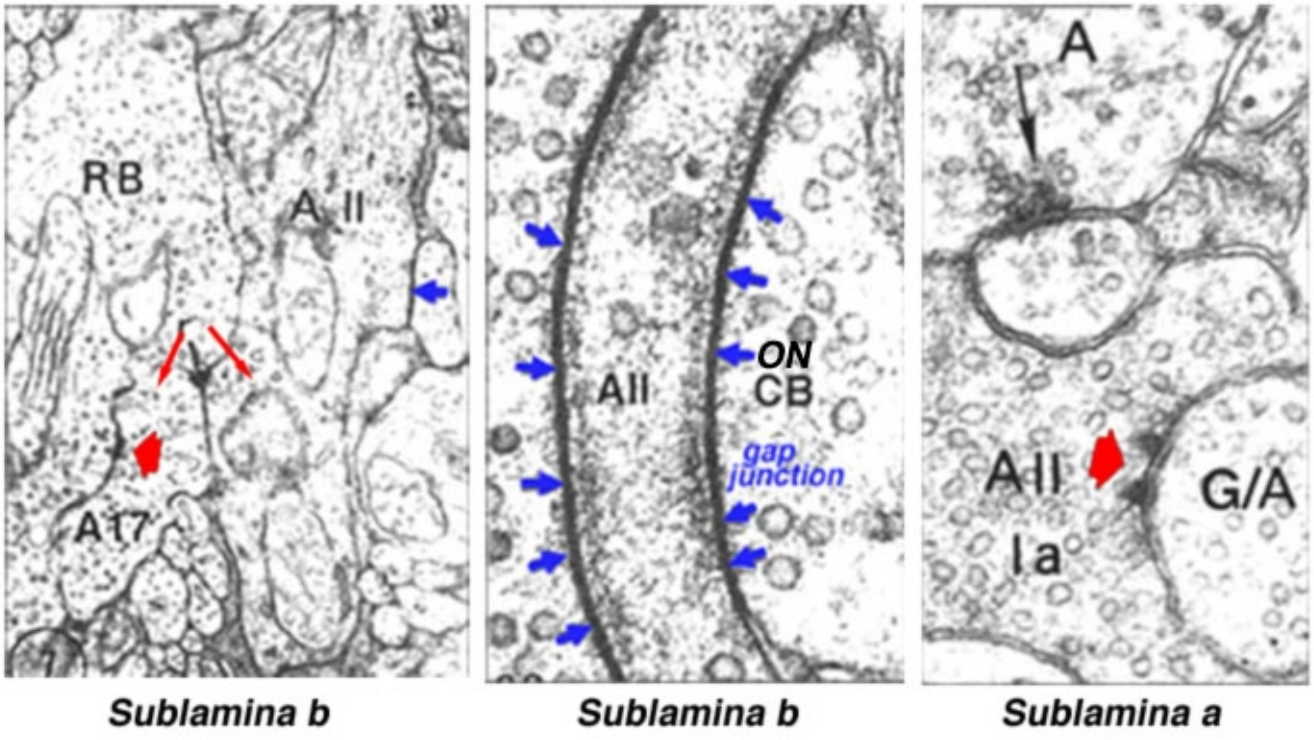


Figure 11. Electron micrographs of AII amacrine synapses.

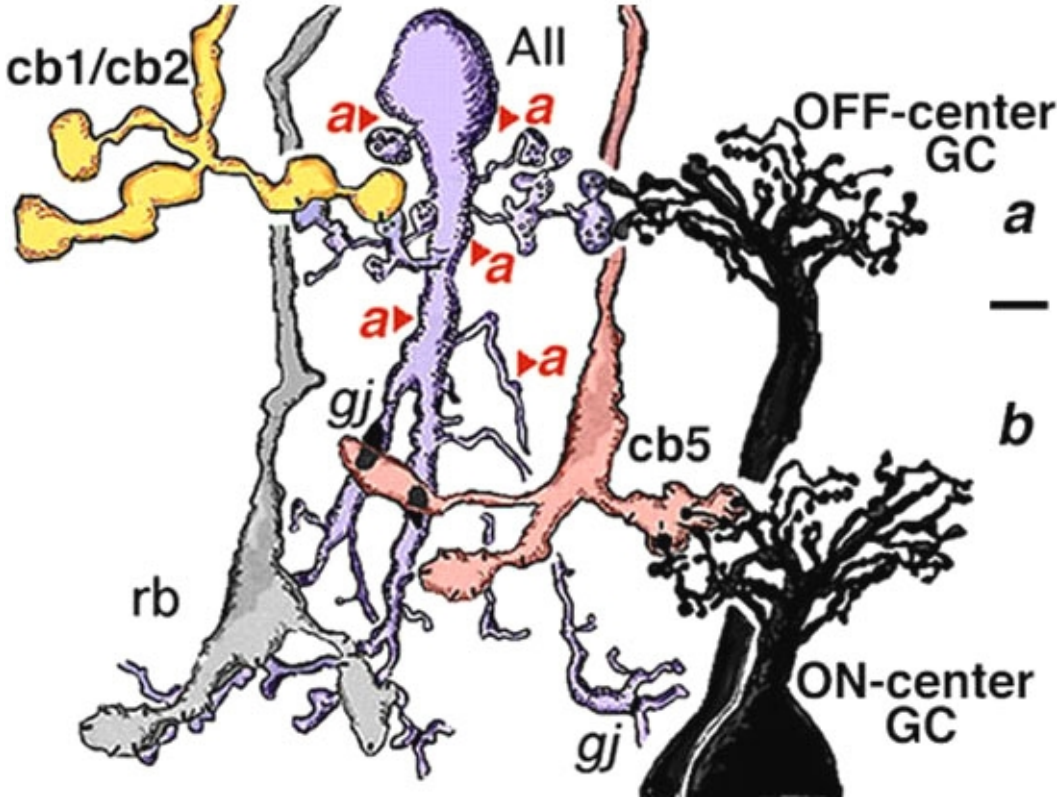
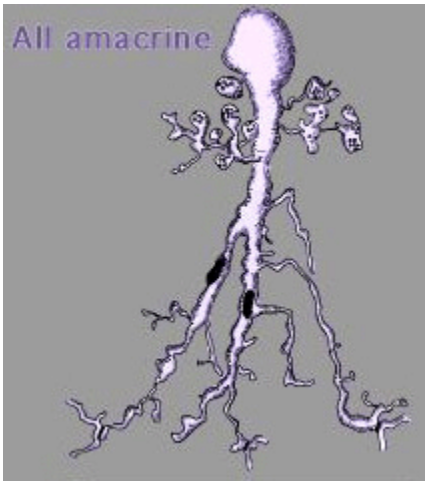


Figure 12. Schematic drawing of the wiring pattern of the AII amacrine cell.



Movie 1. Animation of the wiring pattern of the AII amacrine cells.
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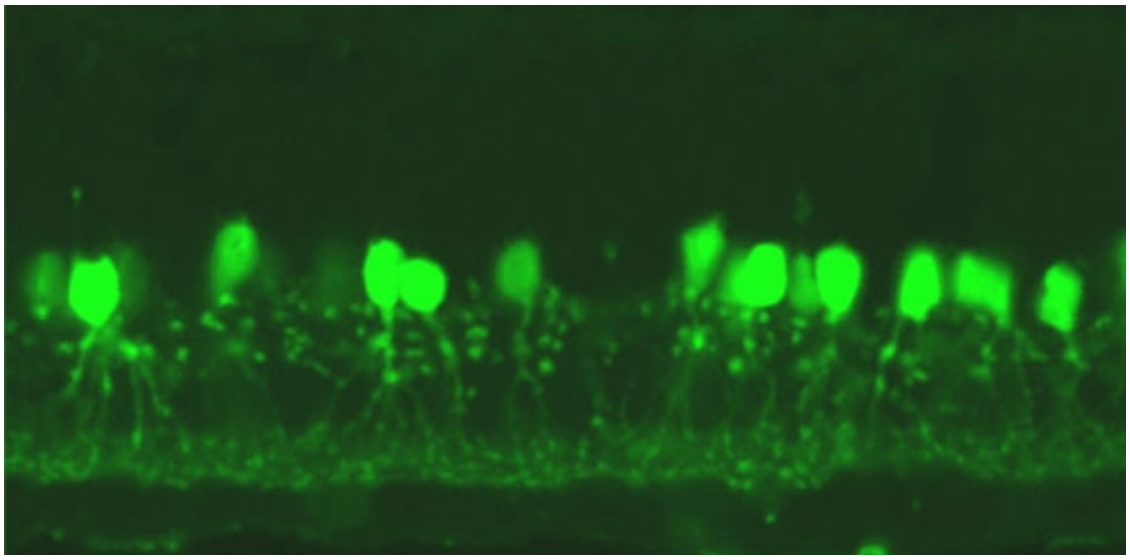


Figure 13. Parvalbumin staining of AII amacrine cells in hamster retina.

A17 cells are driven almost exclusively by rod-matched stimulating conditions. In the intensity series is shown using wavelengths of light matched for rods at rod- and cone-stimulating wave lengths. The responses at each light intensity superimpose, indicating that only a single receptor mechanism is present, that due to the rods. At all intensities, the response is a depolarization and, up until the highest intensities (Fig. 23, bottom trace), essentially a slow potential response. At the highest light intensity, the response becomes slightly transient, although there is a depolarizing plateau phase. The response now resembles that of its input neuron, the rod bipolar cell (22). A17 cells do not appear to have inhibitory surrounds, although they exhibit spatially dependent characteristics to their response amplitudes with far surround stimulation (37).

The A17 cell wiring diagram is shown in Fig. 23. Its huge coverage of the IPL neuropil by its up-to-a-millimeter dendritic spread allows it to collect scotopic rod signals from several thousand rod bipolar axons. Its high sensitivity to scotopic conditions (rod-driven light intensities) suggests hat this amacrine plays a role in converging rod signals from huge areas of retina and in amplifying them at very low light intensities. A17 is

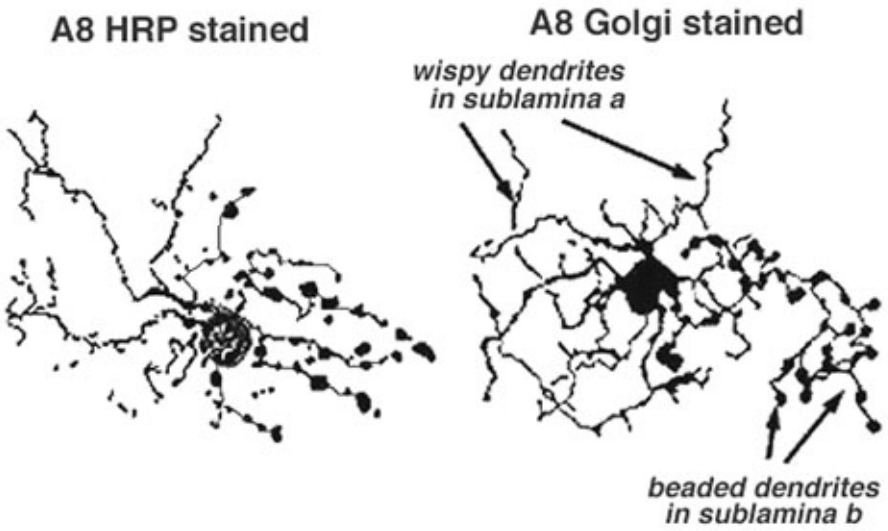


Figure 14. Golgi and HRP appearance of A8 amacrine cells.

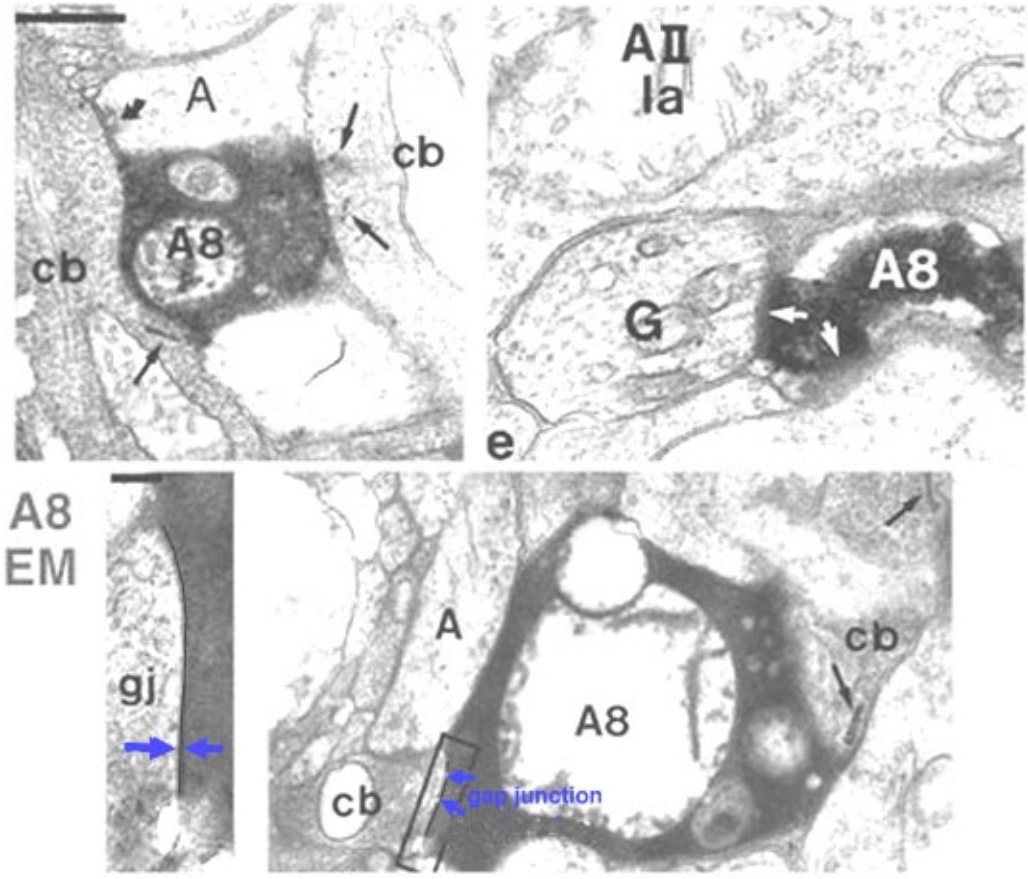


Figure 15. Electron micrograph of A8 synapses in the IPL.

known to accumulate serotonin in rabbit retina (39) but is thought to be a GABAergic neuron in terms of neurotransmission in all mammalian retinas (16).

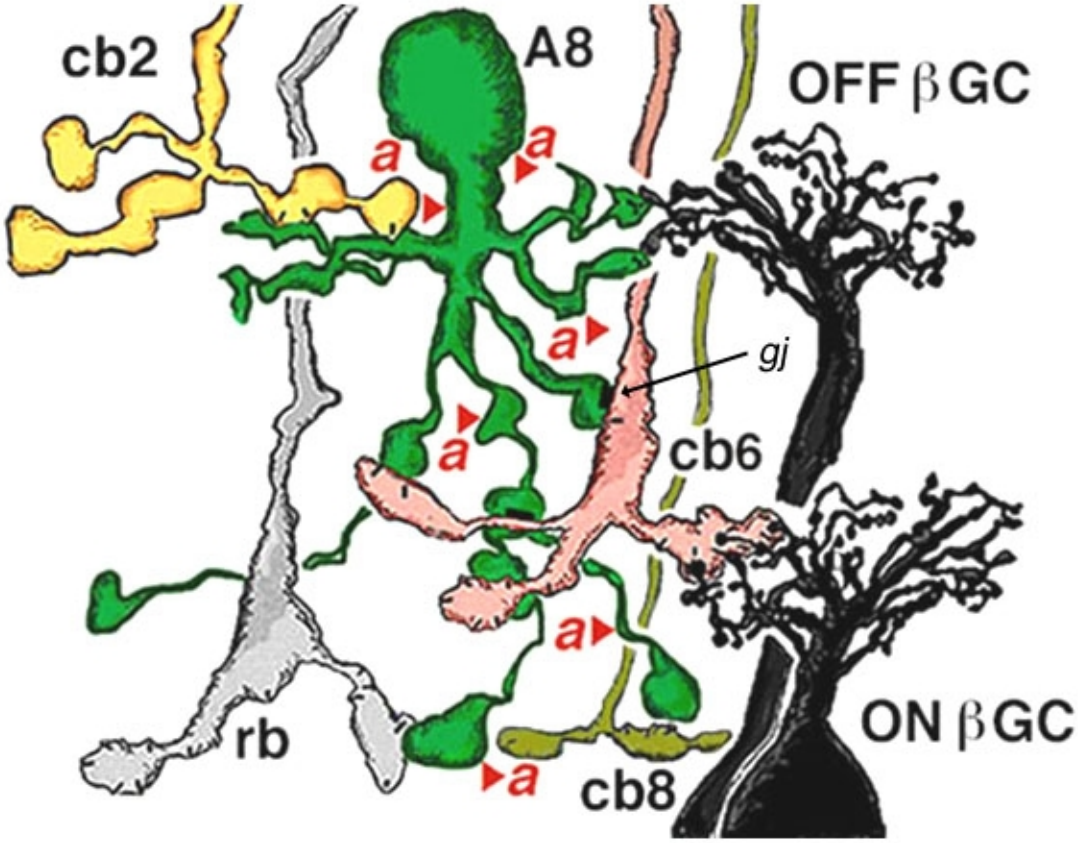


Figure 16. Summary diagram of the wiring pattern of the A8 amacrine cell.

Movie 2. Animation of the wiring pattern of the A8 amacrine cells.

Download video

A19 and A20: ON-OFF Wide-field Amacrine Cells

A19 and A20 are similar appearing, wide-field radiate amacrine cells with 300-500-µm-diameter fields. However, their fields are further expanded to several mm by the presence of fine axon-like processes coming either from the ends of tapering dendrites (A19, A20) or from primary dendrites or even from the cell body (Fig. 24).

They differ in stratification levels levels in the IPL, although A19 stratifies on the sublamina **a**/**b** border and A20 in stratum 2 of sublamina **a.** A19 has distinctly spiny dendrites, whereas A20 has long, smooth, spineless but beaded dendrites.

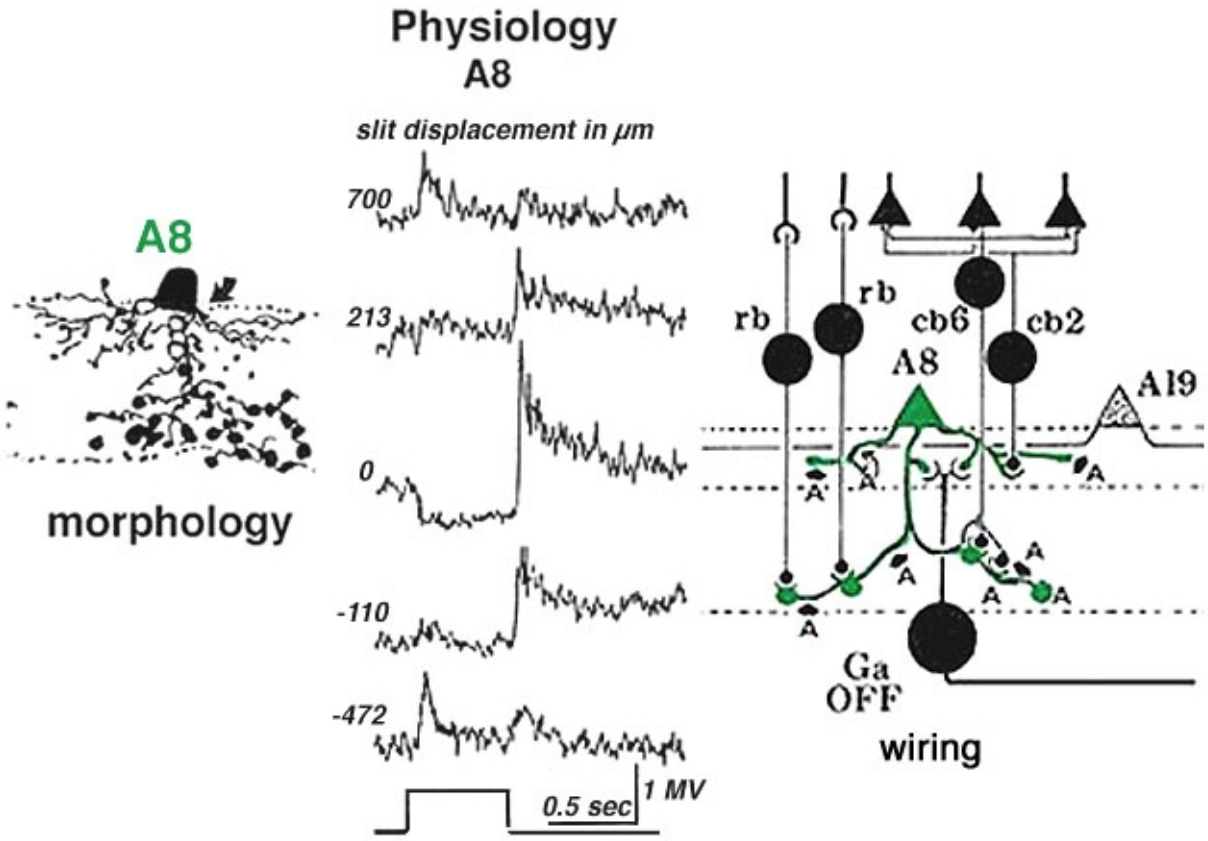


Figure 17. Summary diagram of the A8 amacrine cell.

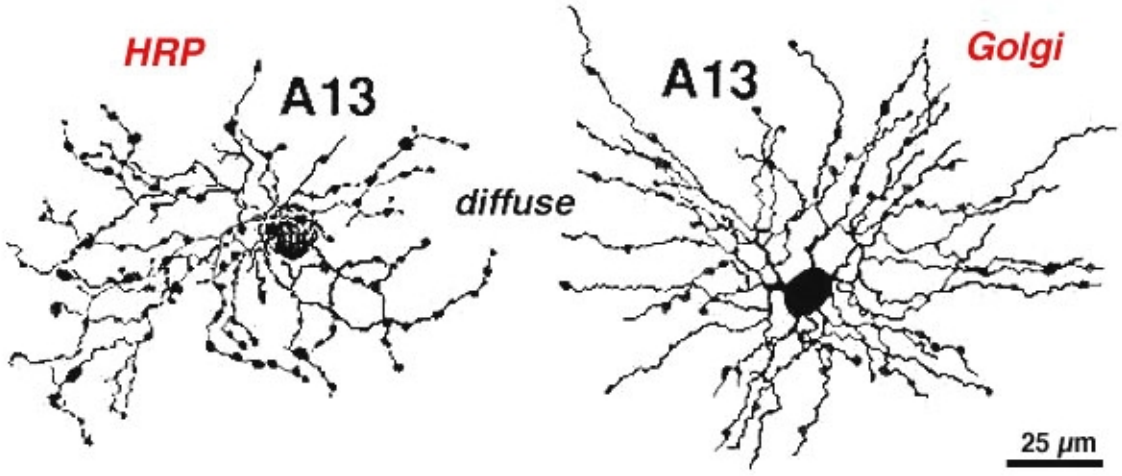


Figure 18. HRP and Golgi appearance of A13 amacrine cells.

A19 and A20 are both transient depolarizing ON-OFF cells, otherwise known as ON-OFF amacrine cells in response type. Such cells have been difficult to record long-term responses from in a mammalian retina (40), and the example illustrated in Fig. 25 of an A19 is one of the longest held, and thus a receptive field was mapped.

The receptive fields are large, i.e., >550 μm radius, rather larger than their immediate dendritic tree sizes, and undoubtedly due to their axon-like extensions (40). Neither A19 nor A20 exhibited antagonistic surrounds.

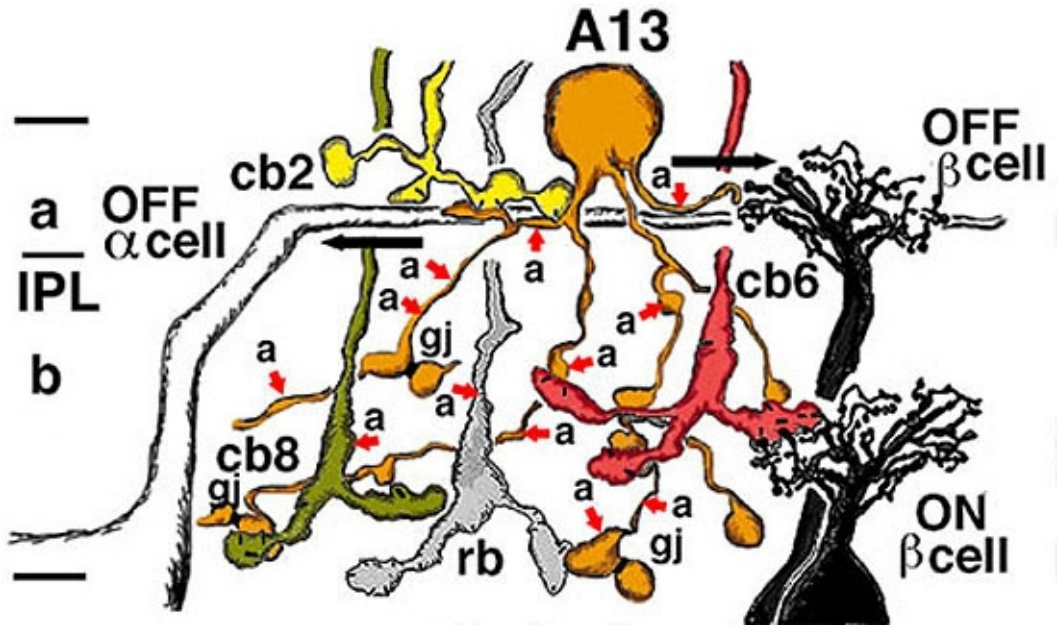
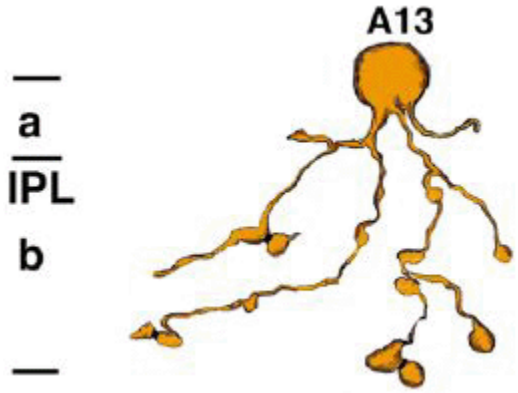


Figure 19. Wiring pattern of the A13 amacrine cell.



Movie 3. Animation of the wiring pattern of the A13 amacrine cell.
Download video

Electron microscopy for circuitry of A19 and 22 has been performed. A19 receives two types of cone bipolar input (24%): the first is from OFF-center cb2 cone bipolar cells of sublamina **a**, while the other is ON-center input from cb5 at the sublamina **a/b** border, where cb5 passes in to sublamina **b**. OFF- and ON-center bipolar input could account for this cell's ON-OFF physiology. The predominant input is from amacrine cells of sublamina **a**, though (76%). Some of the amacrine inputs could be from rod amacrine AII cells, others from A2 cells, while some looked like they could be from other A19 cells. A19's output is reciprocal synapses to both types of bipolar (40%), to unknown dark amacrines (40%) and possibly some fine-diameter ganglion cell dendrites (20%) (40) (Fig. 26).

Gap junctions may connect A19 dendrites one to another (Fig. 11, A19, gj). A19 is GABAergic (16).

A20 cells, running in upper stratum 2 of sublamina **a**, have slightly different synaptic relationships with other nerve cells in the neuropil from A19, which will be remembered, sits on the sublamina **a/b** border (Fig. 27). Thus, A20 receives some cone bipolar inputs in stratum 1/2 and 2 (7%), but they are dominated by amacrine cell

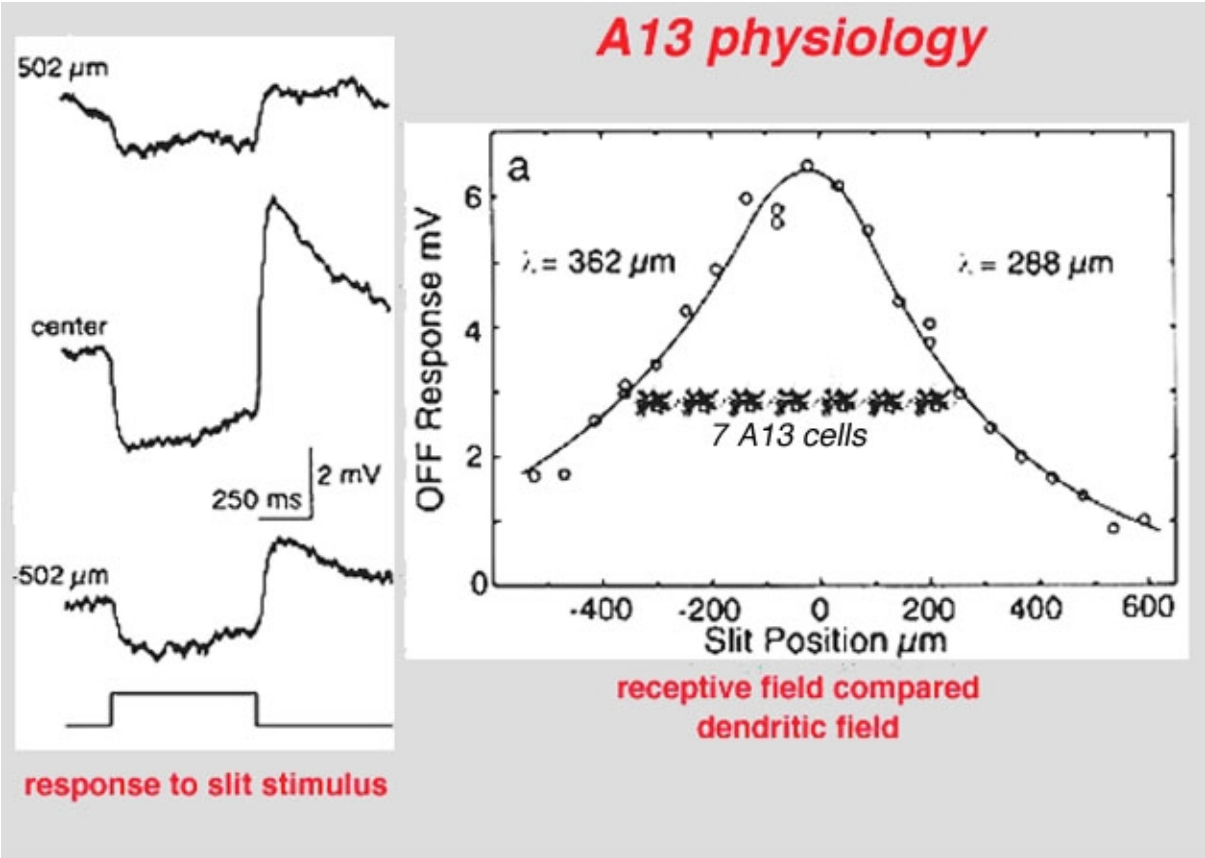


Figure 20. Physiology of the A13 amacrine cell.

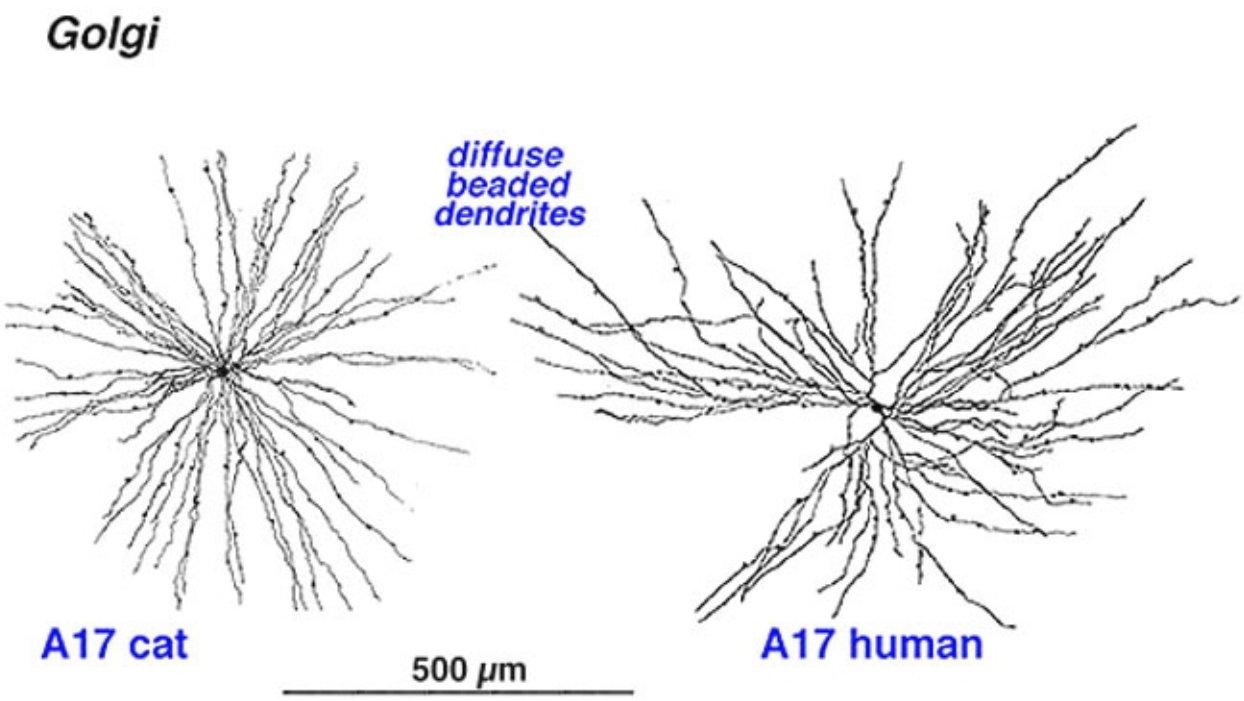


Figure 21. Golgi staining of A17 amacrine cells.

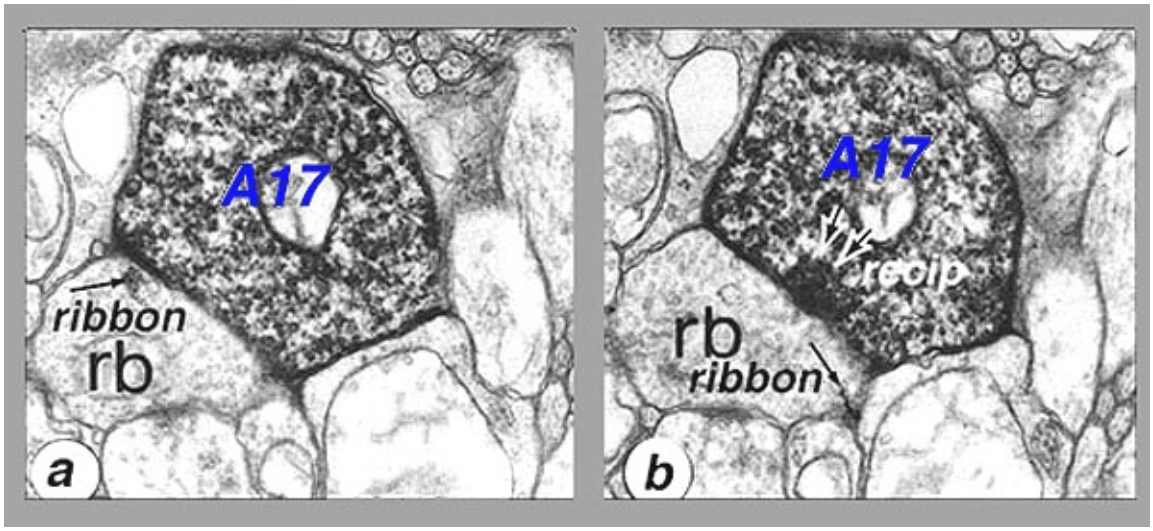


Figure 22. Electron micrograph of reciprocal synapse.

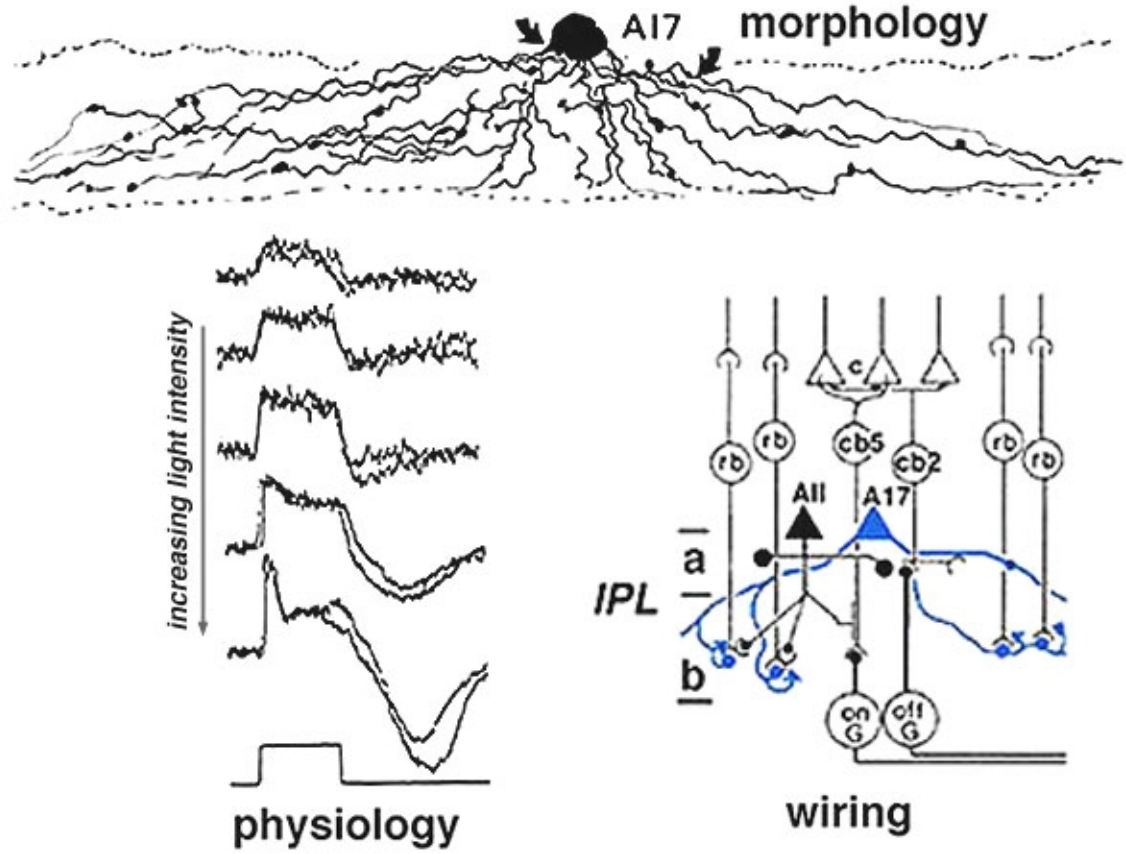


Figure 23. Summary diagram of the morphology, physiology, and wiring pattern of the A17 amacrine cell.

inputs (93%). Much of this input is recognizable as being from lobular appendages of rod AII cells. A20's output is about equally as reciprocal synapses to bipolar cells (5%) and synapses to amacrine cells (5%), but the cells have major output to alpha ganglion cells of sublamina **a** (90%). The latter ganglion cells would be OFF-center types, of course.

Both A19 and A20 cells are probably involved in the transfer of fast messages from one area of retina to another. They may be the basis of the proximal negative response recordable in the intraretinal ERG and in the shift effect in Y-type ganglion cells.

A22: A Putative Substance P-containing, ON-OFF Neuron of the Cone System

Immunocytochemical staining with antibodies against the neuropeptide substance P (SP) reveals a large-field amacrine cell in human retina (41). The SP-containing amacrine is possibly equivalent to the wide-field A22 cell of cat that has been intracellularly recorded as an ON-OFF cell (Fig. 27) (40).

SP-containing and A22 cells are wide-field amacrine cells (dendritic trees of 500-µm span), often having large cell bodies (14-16 µm) displaced to the ganglion cell layer, with their major dendritic stratification in strata 3 and 4 of sublamina **b** of the IPL. Both cells have long axon-like processes that pass up into sublamina **a** to run for up to 1 mm and also down into stratum to run over ganglion cell bodies. Their major dendrites are covered with spines (Fig. 28).

Electron microscopy shows that the spines are postsynaptic with reciprocal synapses to cone bipolar cells. They also receive synapses from unidentified amacrine cells and other SP-IR cell dendrites. They are presynaptic to ganglion cell dendrites and directly to ganglion cell bodies (possibly some of the latter are of SP-IR ganglion cells). Their axonal processes are presynaptic to amacrine and ganglion cells in stratum 5 and in stratum 1 of the IPL. Probably the latter ganglion cells are OFF-center (see above). They receive cone bipolar input from a cone bipolar type in stratum 1 of the IPL. Almost certainly A22 cells, SP-IR amacrine cells of cat and human, are GABAergic (42). This ON-OFF cell probably plays a similar role as the A19 and A20 cells above in being recordable in the proximal negative response (PNR) (43) and being involved in fast-moving aspects of visual coding (Fig. 29).

A18: The Dopaminergic Amacrine Cell

The dopaminergic amacrine cell types have been revealed by immunostaining with an antibody directed against tyrosine hydroxylase (TOH) (the rate-limiting enzyme for dopamine) and are wide-field cells that stratify almost exclusively in stratum 1 of the IPL (under the amacrine cell bodies). It has been identified with A18 cells or type 1CA (CA = catecholamine) of the Golgi studies (2, 10). Their dendrites form a densely packed network of processes leaving only few "rings" for other amacrine cell bodies and major dendrites to pass through. The rings are are beaded dendrites that appear to be synaptic points on amacrine cells, particularly the AII amacrine cell of the rod system (Fig. 30). Another feature of dopamine cells is only seen after dye injection (44) or immunostaining (45) (Fig. 31), and this that their dendrites emit long, axon-like processes running in different strata of the IPL, in the ganglion cell layer and sometimes into the outer plexiform layer (OPL).

A second type of dopaminergic cell has been described in the monkey and human retinas (28, 46). This type 2 CA cell is described as a "wispy" cell in Golgi studies (10) (Fig. 32).

There is still not a convincing electrophysiological study of the dopamine cell in the mammalian retina. However, in turtle and fish retinas, the equivalent to type 1 CA cells is an ON-center cell. In turtle, the cell gives as light ON transient, which continues as a sustained depolarization during the light ON. At light OFF, it has a very distinct, slow, sustained hyperpolarization that lasts for several seconds. The increasing spot sizes bring out the depolarizing ON-plateau, whereas with an annulus, a sustained OFF-surround is evident (see Fig. 33a) (47).

Synaptic relations of Type 1 CA cells have been studied by electron microscopy. This amacrine makes most of its synaptic arrangements in stratum 1 of the IPL as would be predicted from its branching pattern. Sparse cone bipolar input occurs to the cell's primary dendrites in stratum 1. The cone bipolar input is either from a diffuse

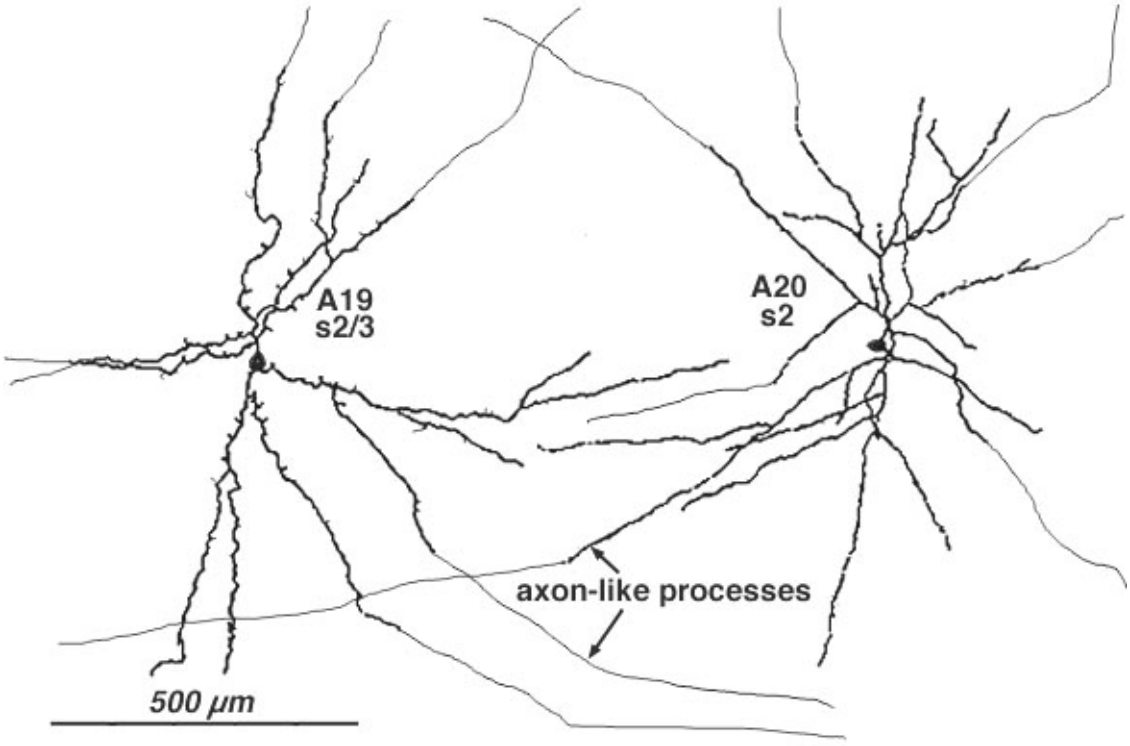


Figure 24. A19 and A20 amacrine cell subtypes.

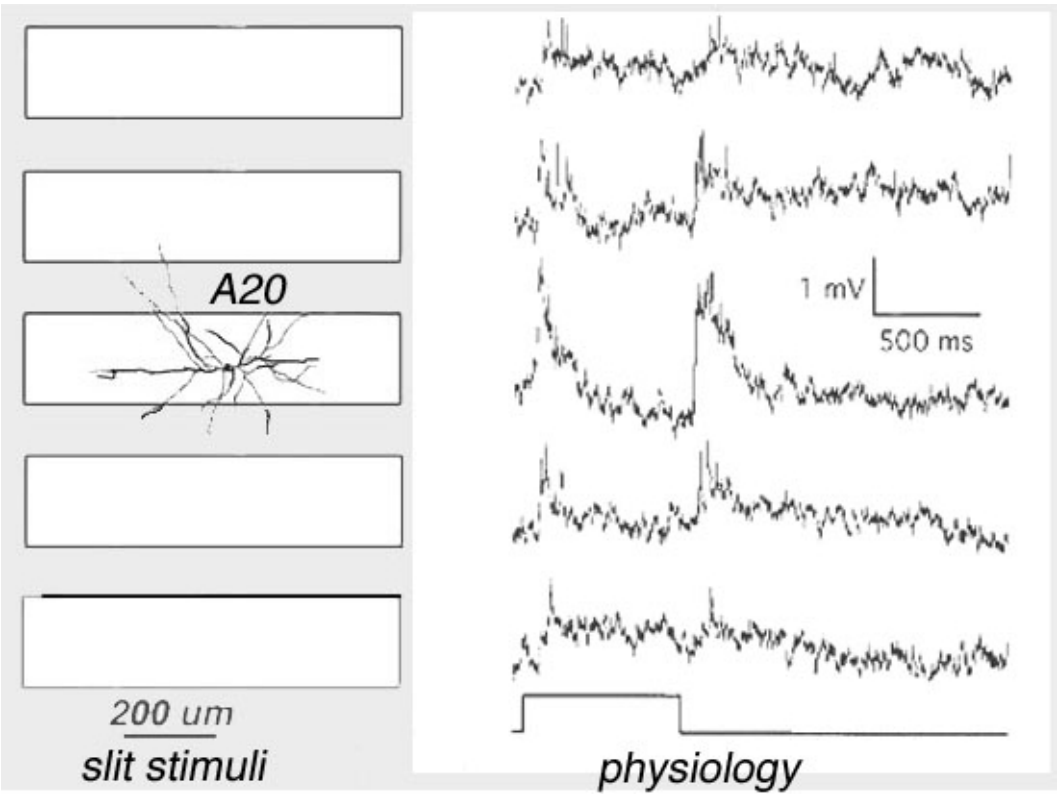


Figure 25. Physiological responses of the A20 amacrine cell.

cone bipolar that has axons in startum 1 or else from giant bistratified cone bipolar cells known to be present in cat and monkey retinas. Both bipolar types are probably hyperpolarizing (OFF-center) in response. Thus, the

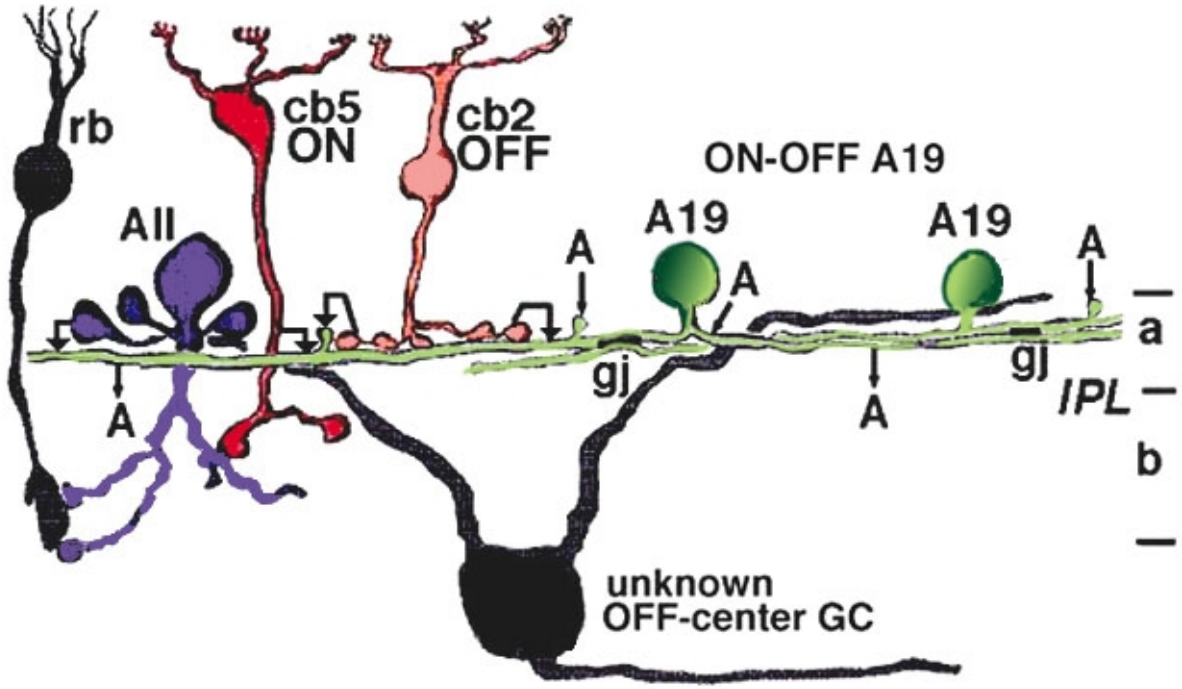


Figure 26. Wiring diagram of the ON-OFF A19 amacrine cell.

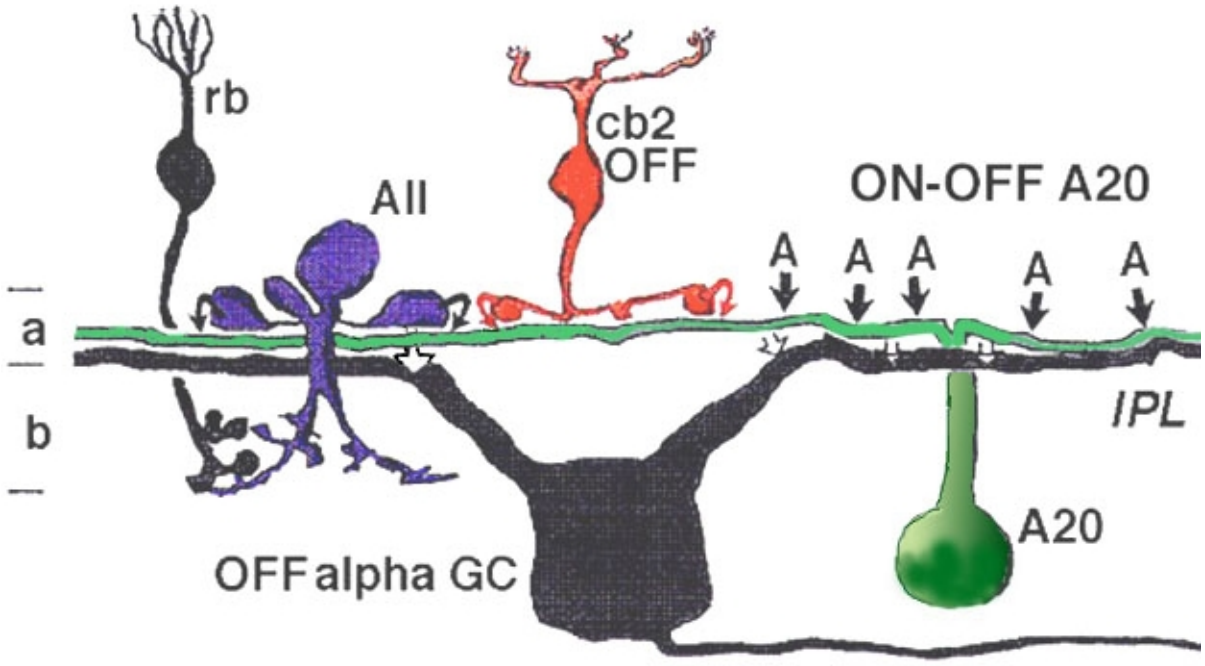


Figure 27. Wiring diagram of the ON-OFF A20 amacrine cell.

fact that the dopamine amacrine cell is a depolarizing ON-center cell makes the OFF-center bipolar input difficult to understand. Both the cell body and primary dendrites in stratum 1 of the IPL also receive GABAergic and glycinergic amacrine cell inputs. Therefore, it has been suggested (48) that the GABAergic amacrine input

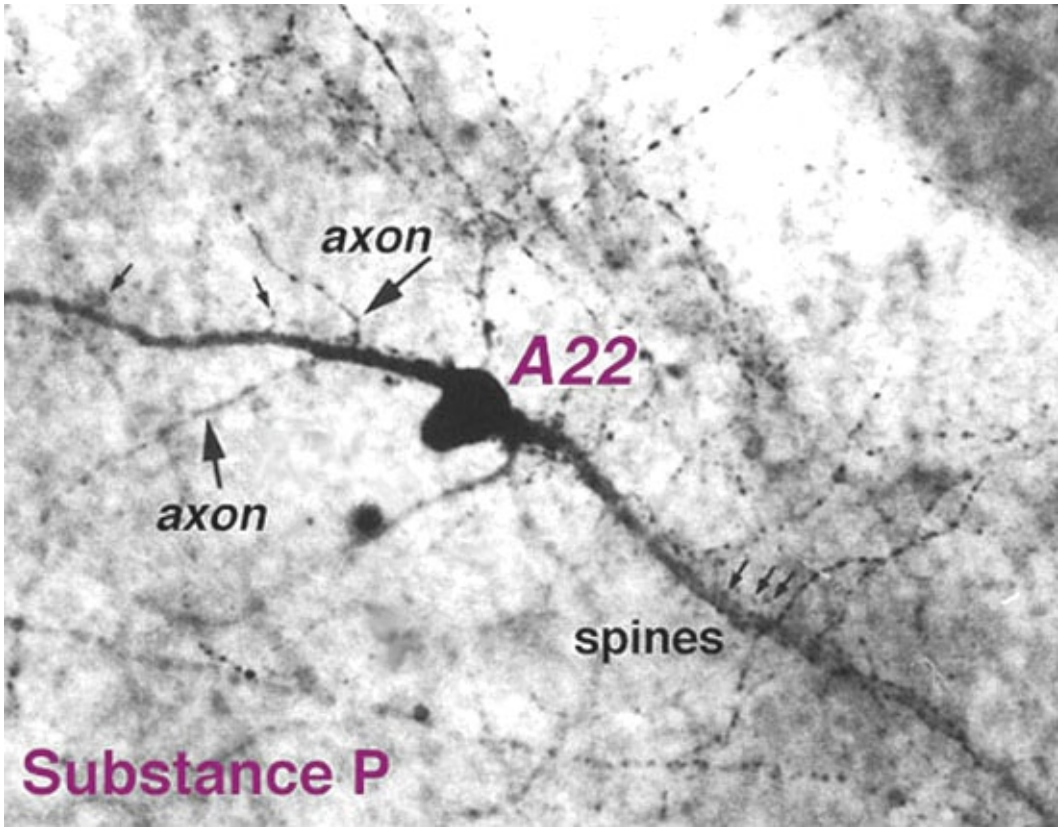


Figure 28. Substance P-containing amacrine cell in human retina.

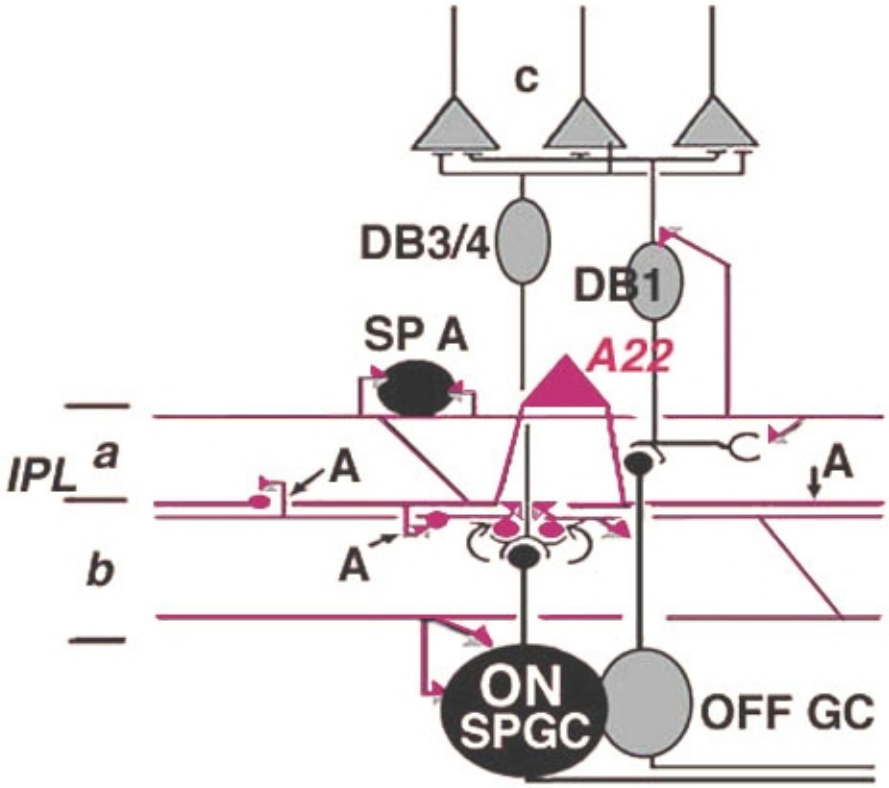


Figure 29. Diagram of the organization of the A22 amacrine cell.

comes from a GABAergic amacrine intermediary between the OFF-center bipolar and the dopamine cell, thereby giving the dopamine cell its ON-center response (Fig. 33b). The major output of the A18 cell is in the fine network of dendrites and axon terminals surrounding the cell bodies and apical dendrites of AII and A8 cells (25). The rings of dopamine processes surround many unfilled, stained cell bodies (Fig. 31). So we also think it probable that the dopamine cell in the mammal makes ring contacts upon both A17 and A13 cell bodies and main dendrites in stratum 1 of the IPL (Fig. 33b). Dopamine cell axons also contact AII dendrites in sublamina **b** of the IPL, and the few processes that run into the OPL make synapses upon the GABAergic interplexiform cell (25).

Dopamine cells in the fish retina are true interplexiform cells (IPC) and have profuse arborations in the inner nuclear layer and very extensive synapses upon the three types of horizontal cells. In the inner plexiform layer, the dopamine IPC makes some synaptic connections with the Mb (rod-dominated) bipolar axon terminals (49) (Fig. 34a).

Dopamine IPCs are thought to be influential upon the horizontal cells by decreasing their light responsiveness (50) and modulating their spatial extent by uncoupling their gap junctions (51). Horizontal cells in all retinas are joined by gap junctions in a strong syncytium (52) (reviewed by Negishi et al. (53)). Dopamine uncouples horizontal cells from the syncytium by interacting with D1 receptors, on the horizontal cell bodies and dendrites, linked to the second messenger cyclic AMP (see Dowling (54) and Witkovsky and Dearry (55) for reviews on dopamine effects in the retina). In the mammalian retina, a similar but lesser amount of uncoupling of horizontal cells due to dopamine has been reported (56, 57) (Fig. 34b).

The dopamine cell is, however, primarily an amacrine cell and not an interplexiform cell in the mammalian retina; thus, their effect on inner retina circuitry would be expected to be more pronounced than on the outer retina. We know that ganglion cells have their spiking properties variously altered by dopamine and by agonists and antagonists of dopamine and D1 receptors (58-61). These neuromodulatory effects are thought to occur via amacrine intermediaries, particularly the AII cell, or by diffusion of dopamine transmitter from a distance to ganglion cell bodies and dendrites, because there are no direct contacts of dopamine amacrine cells and ganglion cell dendrites. Both D1 and D2 receptors have been seen upon some ganglion cell bodies (62-64). The second effect of dopamine in the inner retina is thought to be upon amacrine cell coupling via gap junctions, somewhat analogous to the effect upon gap junction between horizontal cells in the outer plexiform layer. Dopamine uncouples AII amacrine cells in the mammalian retina, mediated through a D1 receptor (see above) (65, 66).

ACh Amacrines: Mirror Symmetric Starburst Cells

Golgi studies and intracellular Lucifer yellow staining has revealed amacrine cells that are known to use acetylcholine as a neurotransmitter (67). These cells have also been called "starburst" amacrine cells and are particularly striking in appearance in turtle, rabbit, and ground squirrel retinas (32, 68-71) (Fig. 35 and Fig. 36).

ACh amacrines occur as two mirror symmetric pairs of cells. One type, ACh-a type, has its cell body in the amacrine cell layer, and its dendrites stratify in stratum 2 of sublamina **a.** The other type, ACh-b type, has a cell body displaced to the ganglion cell layer, and its dendrites stratify in stratum 4 of sublamina **b.** ACh-b cells are medium-field in size but have a tremendous overlap of their dendritic trees such that as many as 70 cells overlap a single central cell in peripheral retina (33, 71). ACh-a type cells have slightly larger dendritic tree sizes (13% larger), and their overlap values can reach 90 or more (24). The ACh cells in the human retina are similar to those in rabbit but less dramatic in shape and branching pattern (see below). ACh starburst cells are particularly striking in the turtle retina, where the mirror symmetric amacrines are arranged in an essentially one-to-one relationship (Fig. 37a and Fig. 37b) (see a rotation of the mirror symmetric starburst cells).

Golgi ACh-containing starburst amacrine cells of the rabbit retina have been extensively studied by electron microscopy (72). Cone bipolar and amacrine cell inputs are distributed irregularly over the entire dendritic tree,

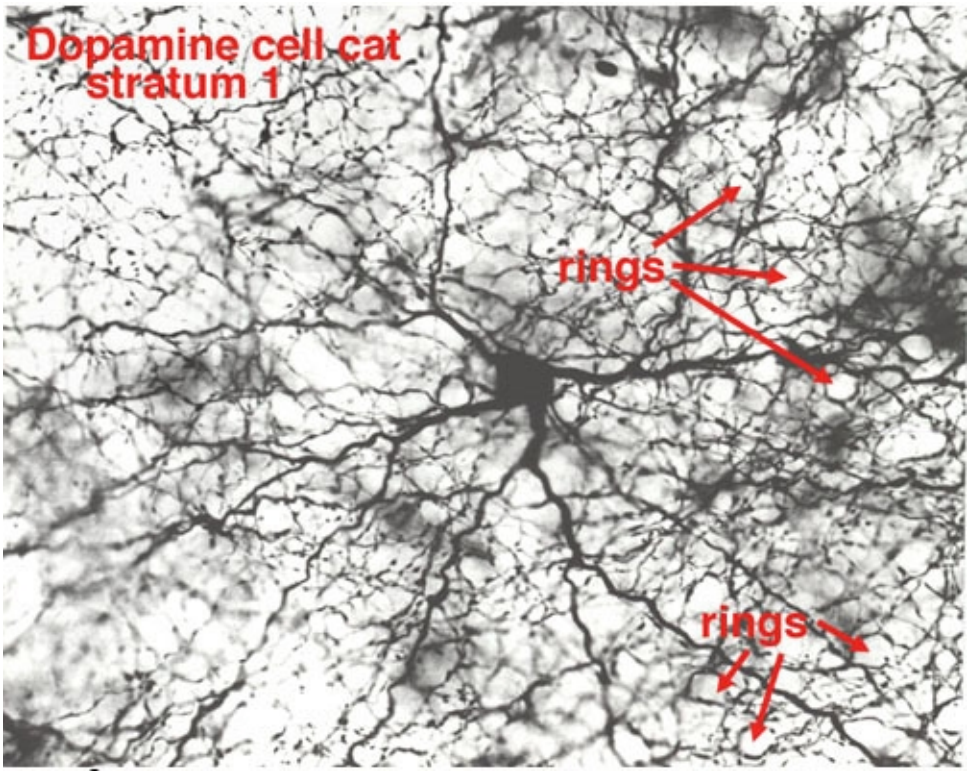


Figure 30. Immunostaining with antibodies to TOH. A18 amacrine cells stain and have overlapping dendrites that form into rings.

but the proximal dendrites to the cell body, containing small spines, are particularly choice for bipolar input. A small amount of AII amacrine input may occur to the proximal dendrites of the ACh-a type cell. The varicosities on the distal dendrites (see above) are the only sites of synaptic output to ganglion cells. The postsynaptic ganglion cells for both ACh-a and ACh-b type cells, are thought to be ON-OFF directional selective bistratified ganglion cells (32, 66, 71-75). Additionally, the monostratified ON-directionally selective ganglion cell may be postsynaptic to the ACh-b type cell (72) (Fig. 38).

Both mirror symmetric pairs of starburst cells of the rabbit retina have been intracellularly recorded from and dye marked by Bloomfield (21). The a-type of the pair is an OFF-center cell, giving a transient burst of small spikes at light off, whereas the ACh-b type is an ON-center cell (Fig. 38, top traces, above). Both types have antagonistic surrounds (Fig. 38, bottom trace).

ACh amacrine cells are thus thought to be involved in the generation of directional selectivity (DS) in certain retinal ganglion cells, particularly in rabbits and turtles with visual streak topography. They may not be as well developed in form and function in foveal-based retinas, such as cat and human (Fig. 39).

DAPI-3 Cells in the Rabbit Retina

In 1997, another bistratified, medium-field amacrine cell that is nucleus stained with DAPI was revealed by intracellular dye injection of Lucifer yellow. It was given the name DAPI-3 (76). Since then, the DAPI-3 cell has also been revealed by the fluoresecent rhodamine probe used by MacNeil and Masland (8) (see Fig. 4a, Roles of amacrine cells) and glycine immunoreactivity in the rabbit and ground squirrel retinas (77, 78). DAPI-3 cells are medium-field in size, i.e.. have a 100-µm field diameter and a profusion of overlapping dendrites, as seen in whole-mount views (Fig. 40b) that prove to be the two tiers of branches of a bistratified cell (Fig. 40d). One of the tiers of dendrites in sublamina **a** run just below the ACh-a type (starburst a type), and the other tier run in sublamina **b**, just above the ACh b type (starburst b type) cells (Fig. 40d).

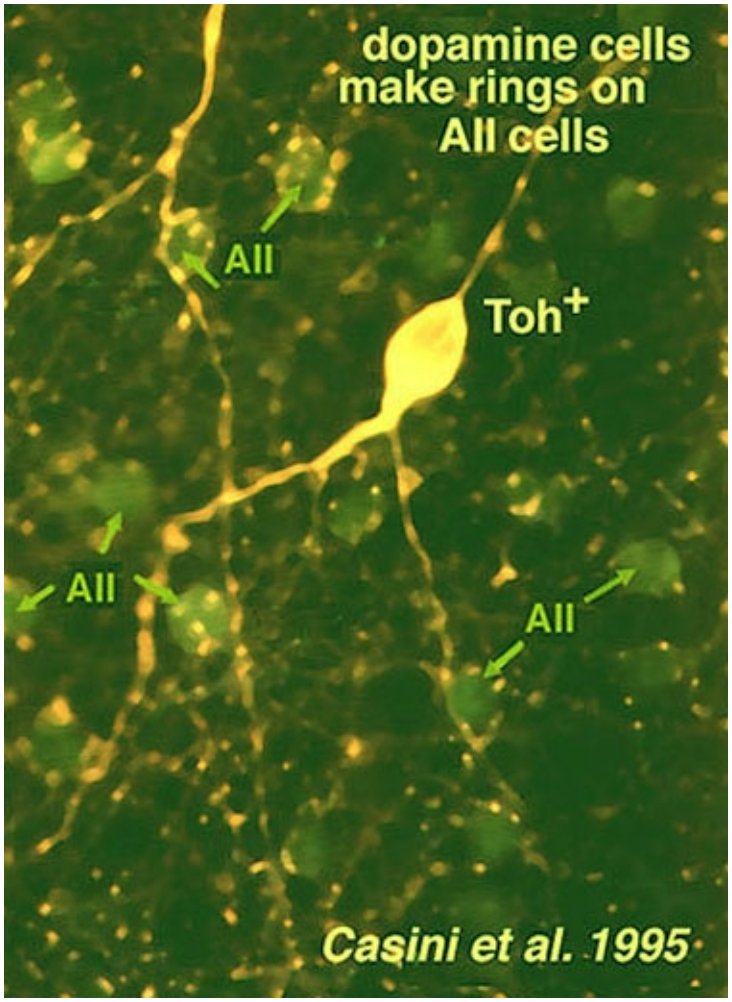


Figure 31. Dopaminergic and AII cells. From Casini et al. (82).

The DAPI-3 cell proves to be glycinergic and can be stained with the glycine transporter (Fig. 40c, green). It is also immunopositive for $GABA_A$ receptors (Fig. 40c, red). Thus, the cell appears to be orange in the figure (Fig. 40c, red and green combine to make orange-stained cells with a blue DAPI nucleus, arrows). The starburst ACh cells stains with CHAT in Fig. 40d, and the overlapping dendrites of the DAPI-3 cell stained for $GABA_A$ receptors are juxtaposed to the cholinergic cell's dendrites.

Zucker and Ehinger's (79) nice study on the DAPI-3 cells and immunostaining with the glycine and $GABA_A$ transporter/receptors allowed them to draw a summary diagram of the probable manner on which the DAPI-3 amacrine cells interact with the starburst ACh cells (Fig. 41). The DAPI-3 cell is acetylcholine receptive at nicotinic and muscarinic synapses and feeds back upon the starburst cell via a glycinergic synapse (glycine receptors have been identified on starburst cells). The DAPI-3 cell also contacts the cone bipolar cell that has input to the starburst cell. We know the starburst cell contains GABA in addition to acetylcholine, and the starburst cell can presumably feed forward to the DAPI-3 cell at a GABAergic synapse with $GABA_A$ receptors on the DAPI-3 cells. The starburst cell is known to synapse upon a directionally selective ganglion cell type in rabbit retina (Fig. 41). It is not clear yet whether the DAPI-3 cell exists in other mammals that do not have a pronounced visual streak as does the rabbit.

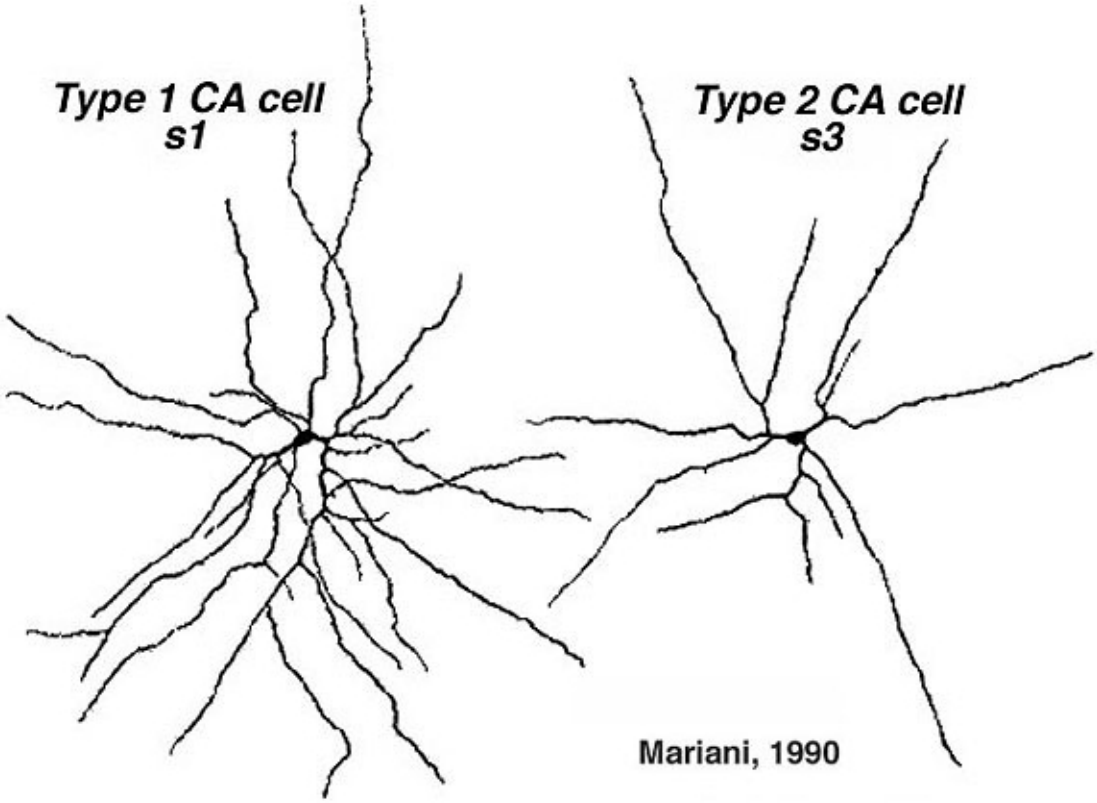


Figure 32. Types of dopaminergic cells.

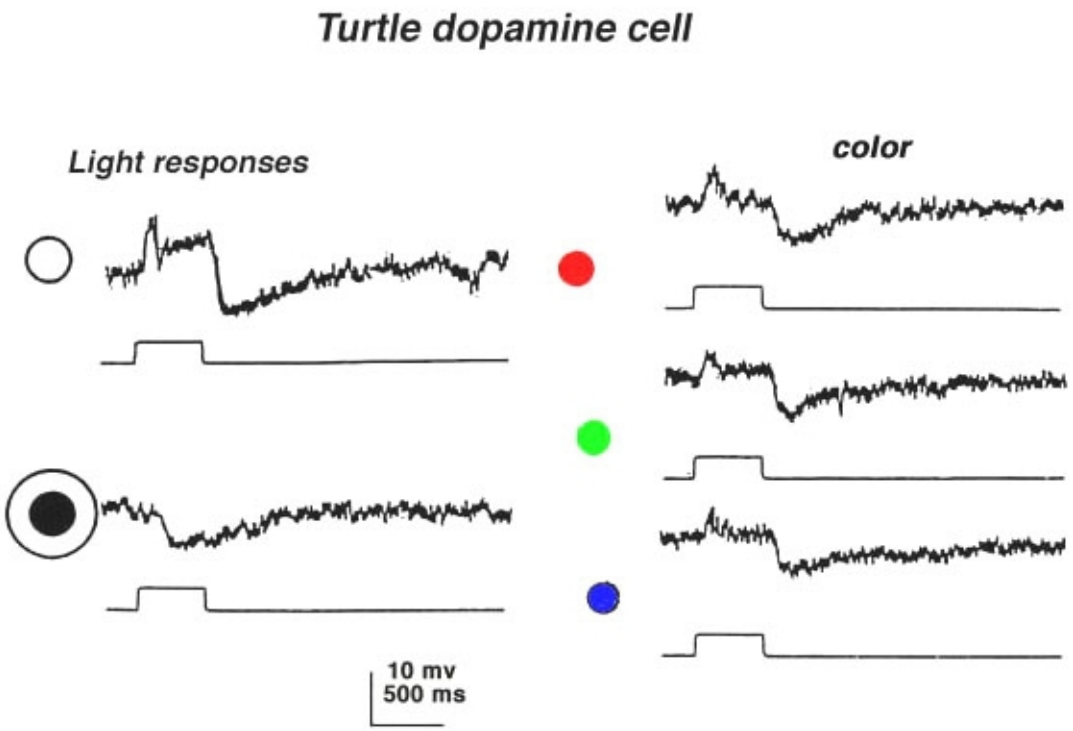


Figure 33a. Light responses of the dopaminergic amacrine cell in the turtle retina (47).

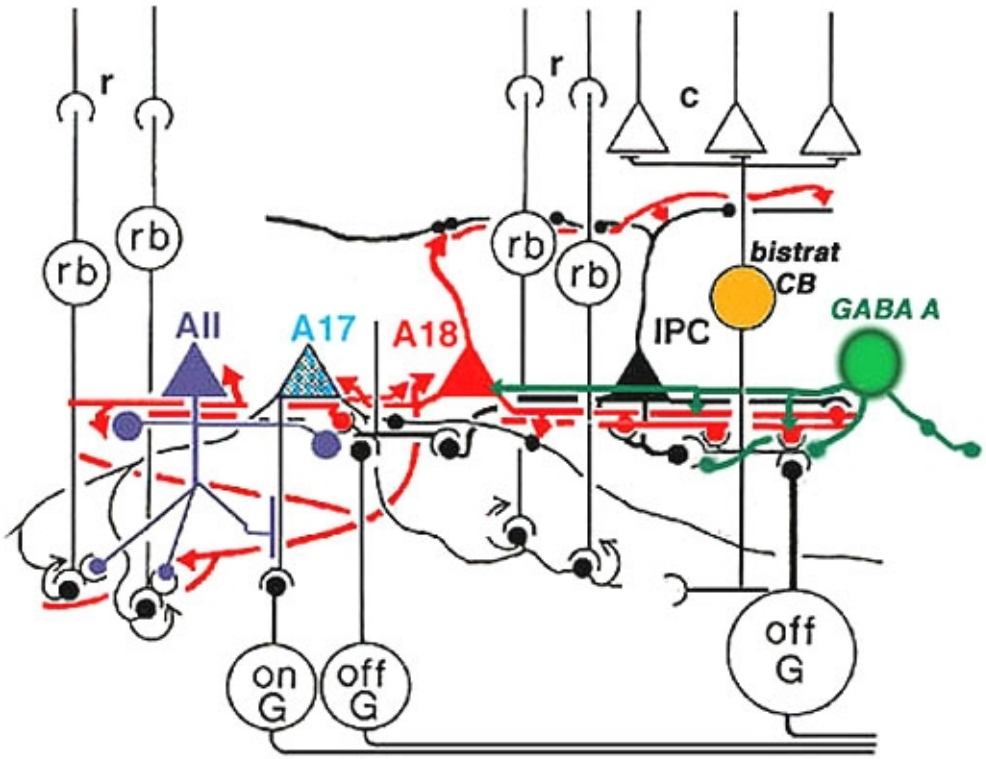


Figure 33b. Wiring diagram of the A18 amacrine cell.

Midget System Amacrine Cell

The calcium binding protein calretinin is found in three types of amacrine cell in the monkey and human retinas (80). The most numerous population are the AII amacrine cells, but a small- to medium-field diffuse amacrine cell and a large-field, stratified A19 type are also calretinin immunoreactive (IR). Of these non-AII cell types, the small diffuse (or tristratified cell type, difficult to know which) is of particular interest.

Its appearance is shown in Fig. 42 (A, arrow) in immunostained slice preparations. The cell has a large cell body, but unlike the AII cells (Fig. 42, AII), many fine dendrites are given off the cell body instead of the typical AII thick primary dendrite. The dendrites pass down to all levels of the IPL as thin, beaded, and branched processes (Fig. 42, fine arrows). This small-field diffuse calretinin-IR cell is found in high numbers in the foveal, rod-free area of the retina and in lesser numbers in the peripheral retina. Electron microscopic examination of foveal diffuse calretinin-IR cells has shown that they get synaptic input from ON- and OFF-midget bipolar terminals, reciprocate synapses to these bipolars, and have synaptic output to ON-center midget ganglion cells (Fig. 43, wiring diagram). In more central to peripheral retina where rods are present, the diffuse calretinin-IR amacrines are probably also in synaptic interplay with both diffuse bipolar cells and larger parasol ganglion cells (Fig. 43). Because these calretinin-IR amacrines are found in the fovea and have particular relationships with the midget bipolar and ganglion cell systems, we have suggested that they may have a role in the antagonistic surround generation for midget ganglion cells. Moreover, they could also contribute to color opponency in these ganglion cells (80).

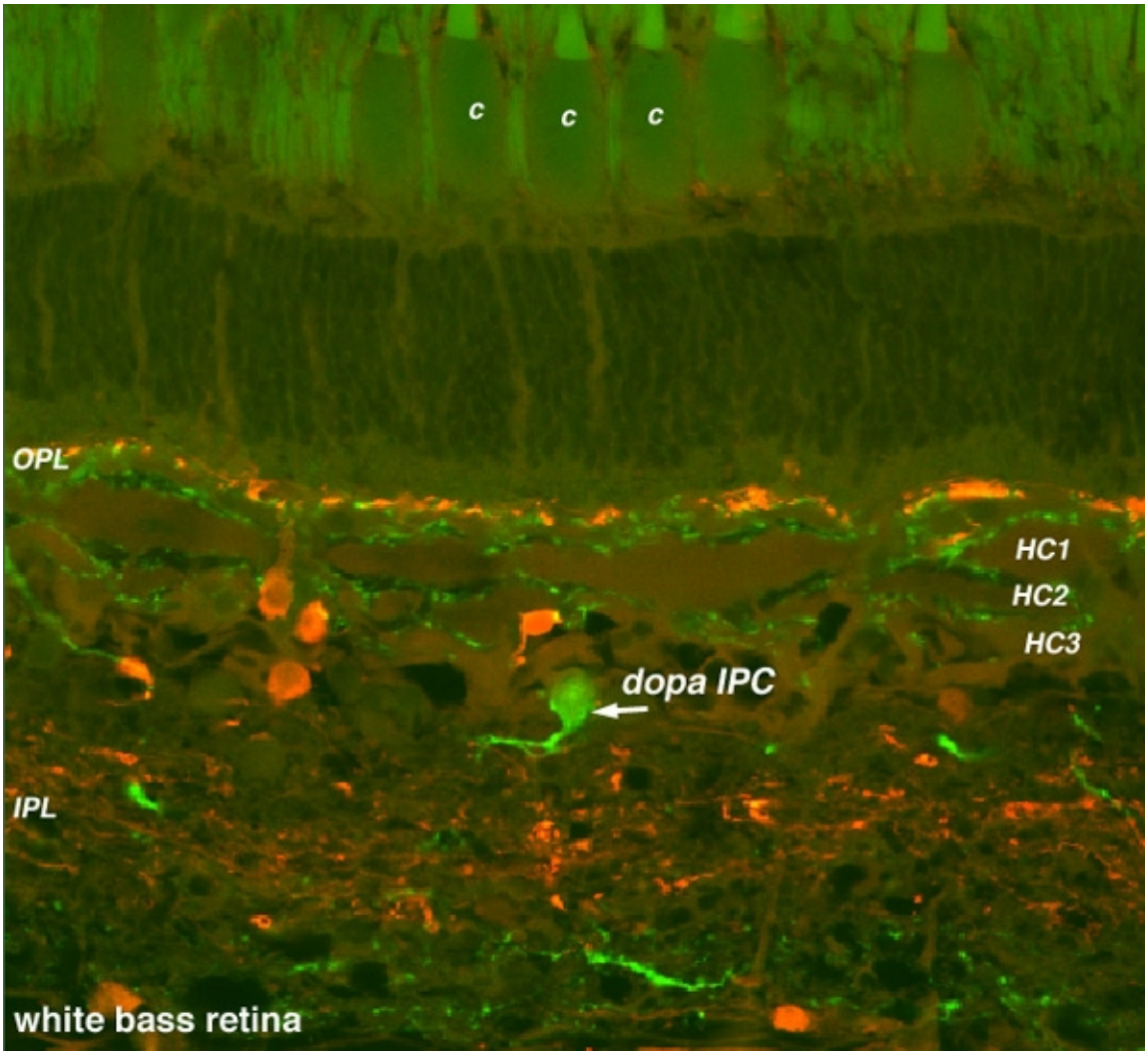


Figure 34a. The dopaminergic interplexiform cell of the fish retina.

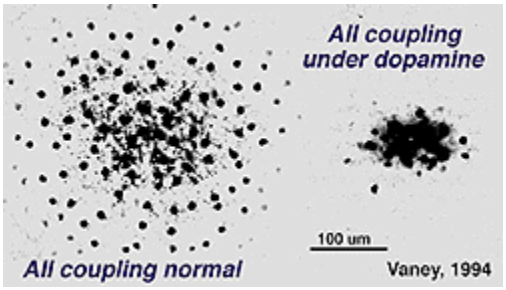


Figure 34b. Effects of dopamine on AII amacrine cell coupling.

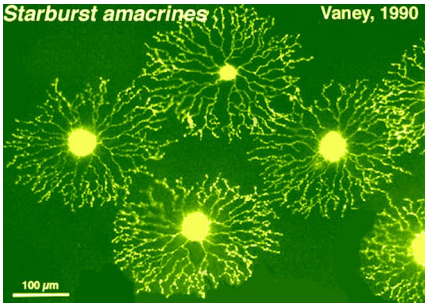


Figure 35. Starbust amacrine cells as stained with Lucifer yellow in whole-mount rabbit retina. From Vaney (32).

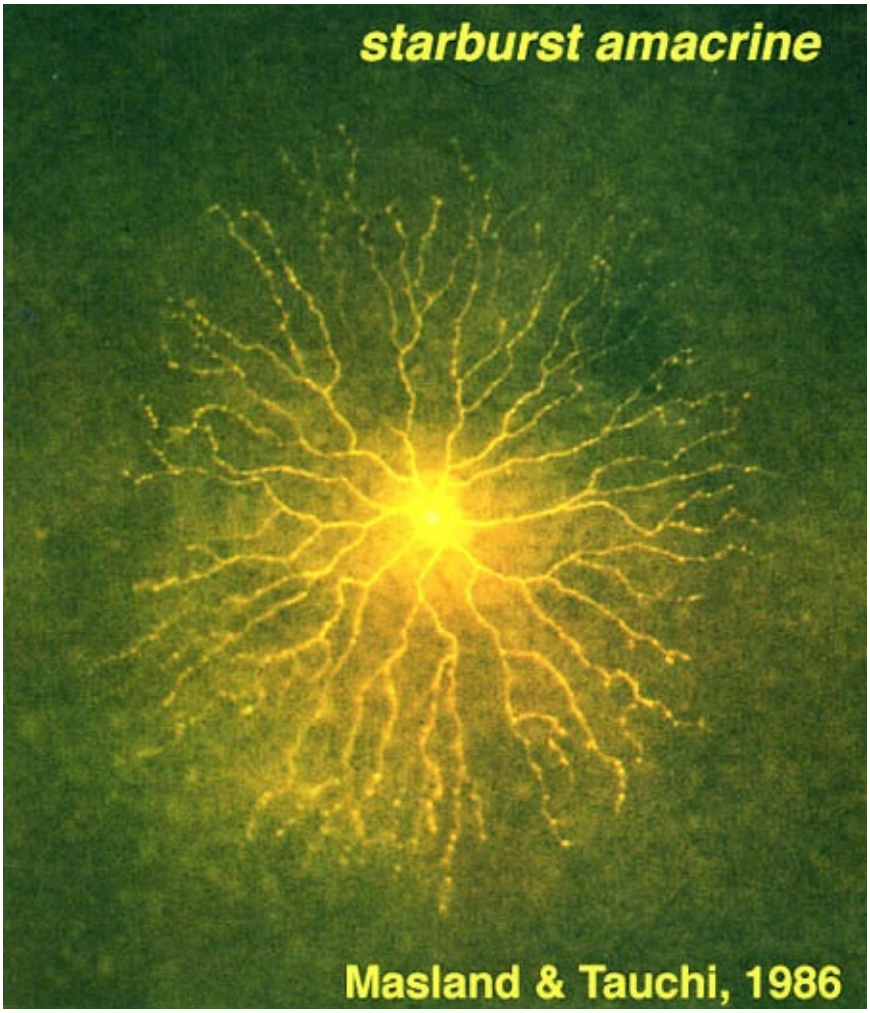


Figure 36. Lucifer yellow labeling of a starburst amacrine cell. From Masland and Tauchi (67).

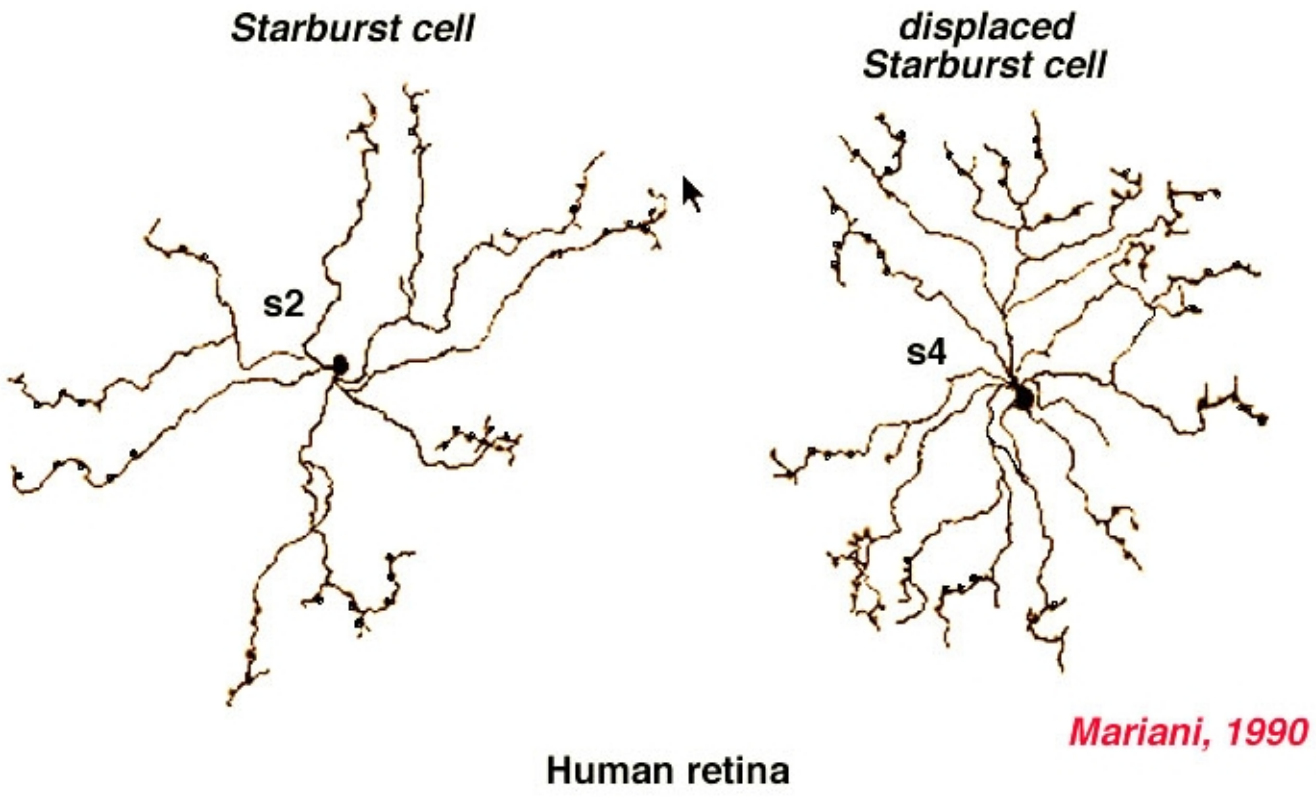


Figure 37a. Golgi staining of ACh-containing amacrine cells in human retina. From Mariani (10).

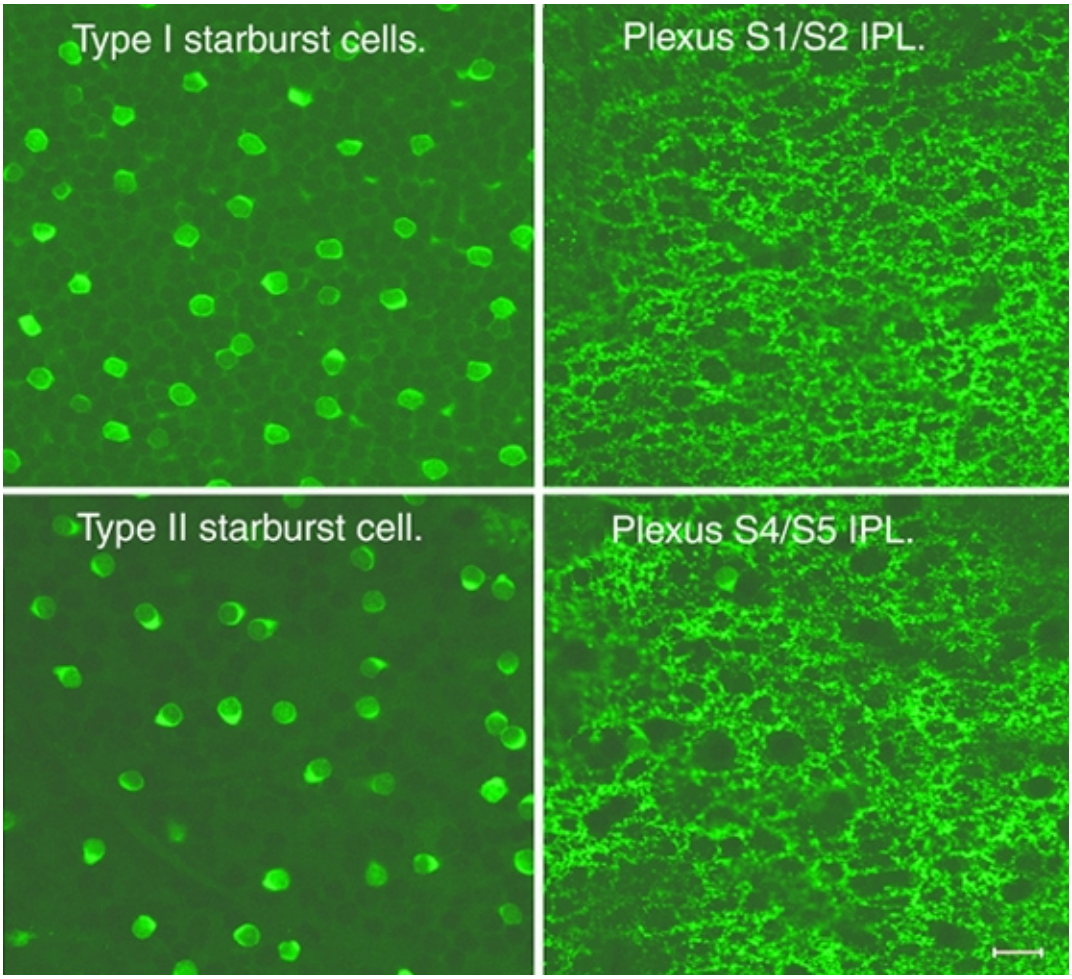
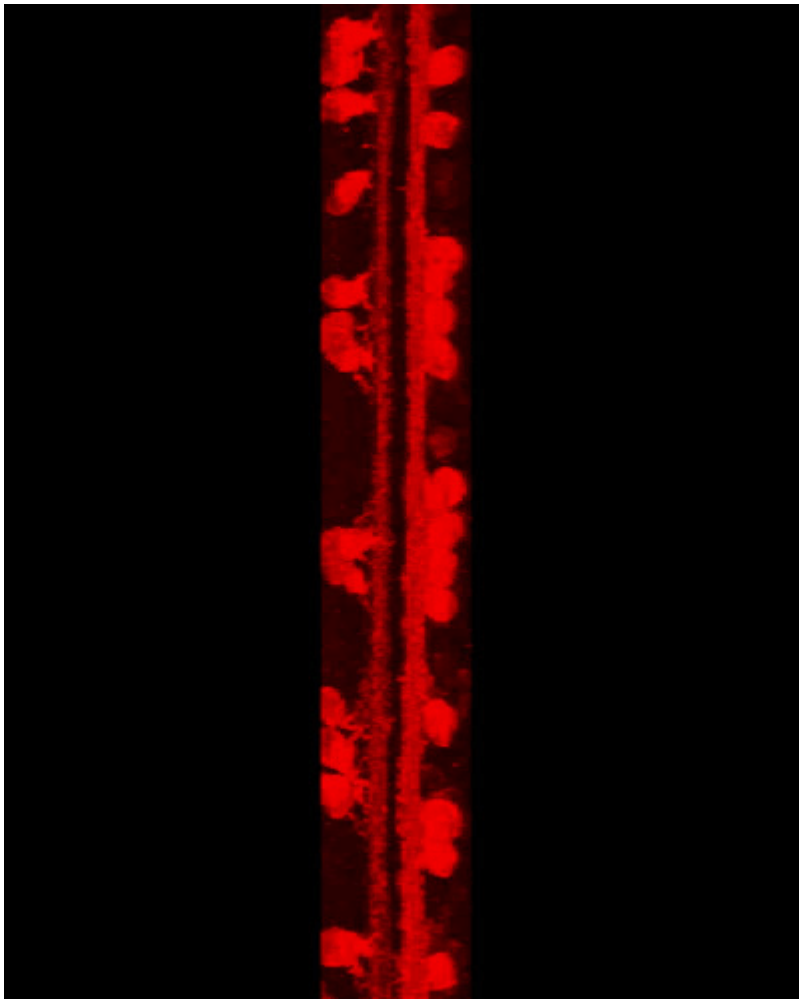


Figure 37b. Immunioabeling of a starburst amacrine cell with ChAT in turtle whole-mount retina.



Movie 4. A rotation of the mirror symmetric starburst cells of the turtle retina. Immunostaining to ChAT. Courtesy Nicolas Cuenca.
Download video

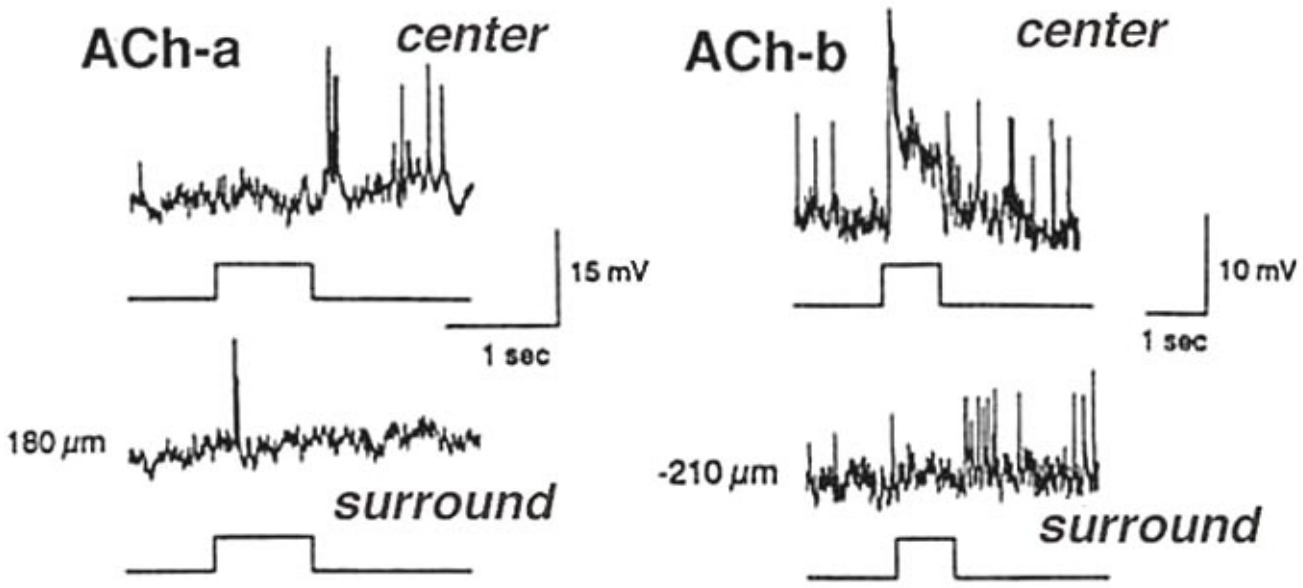


Figure 38. Intracellular recordings of ACh-containing amacrine cells. From Bloomfield (21).

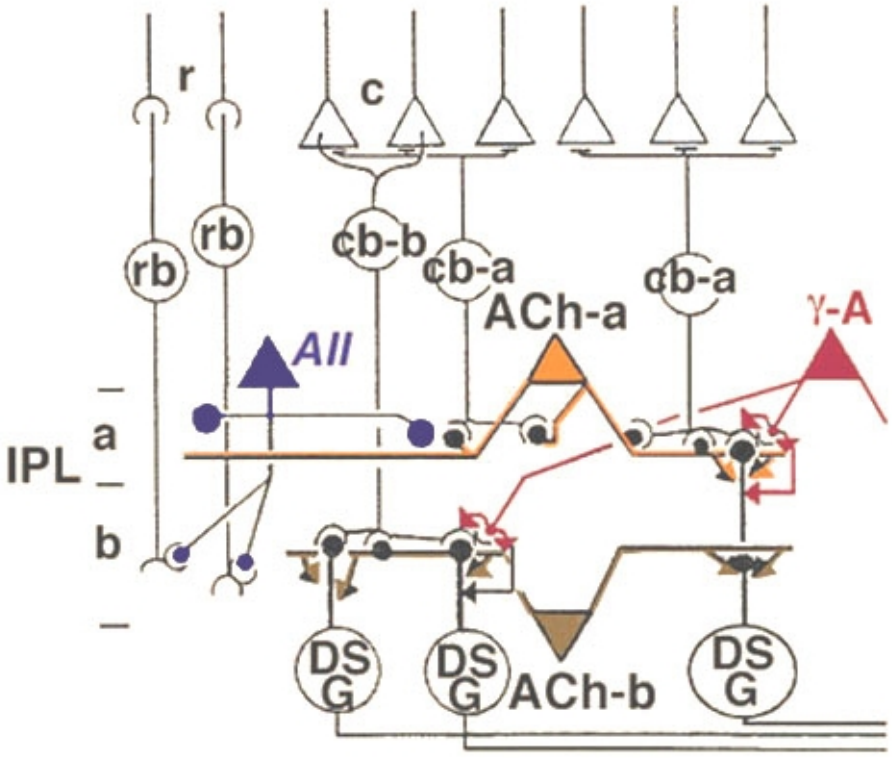


Figure 39. Wiring diagram of the two types of ACh-containing amacrine cells.

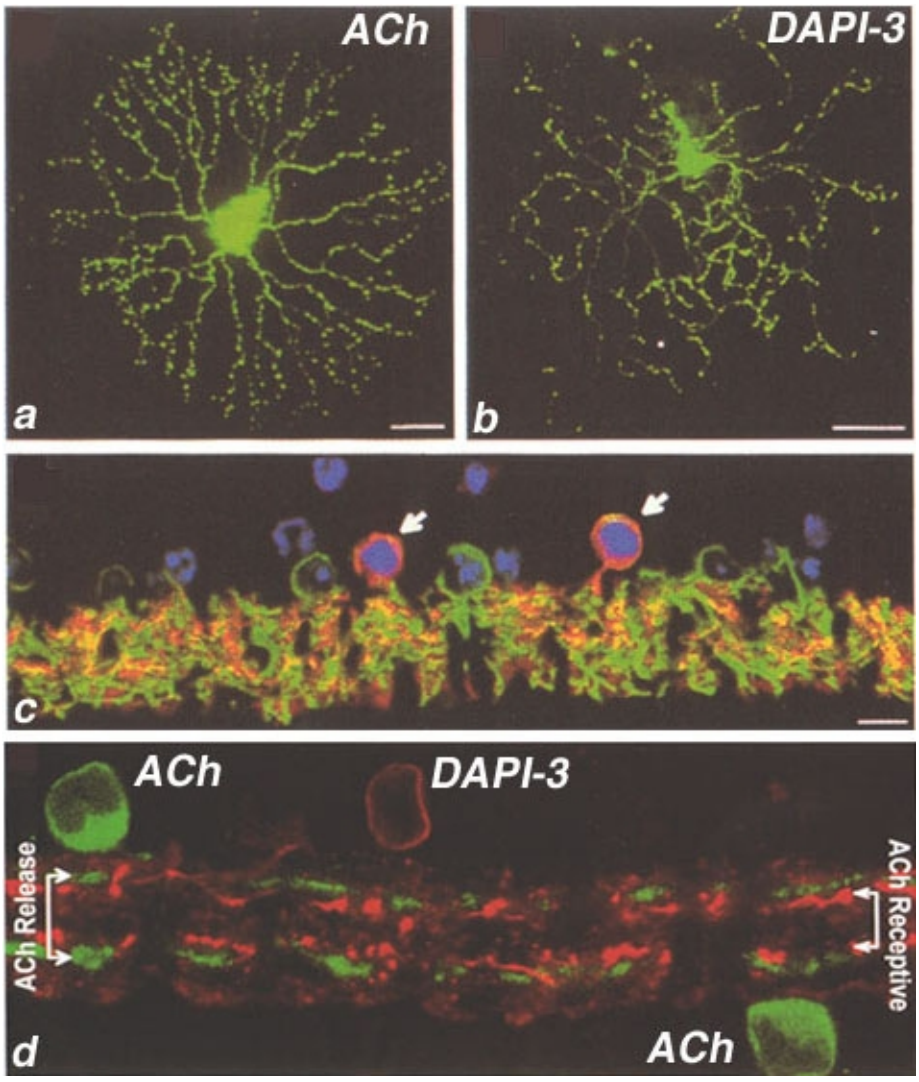


Figure 40. A comparison between DAPI-3 cells and cholinergic ACh cells. Adapted from Zucker and Ehinger (79).

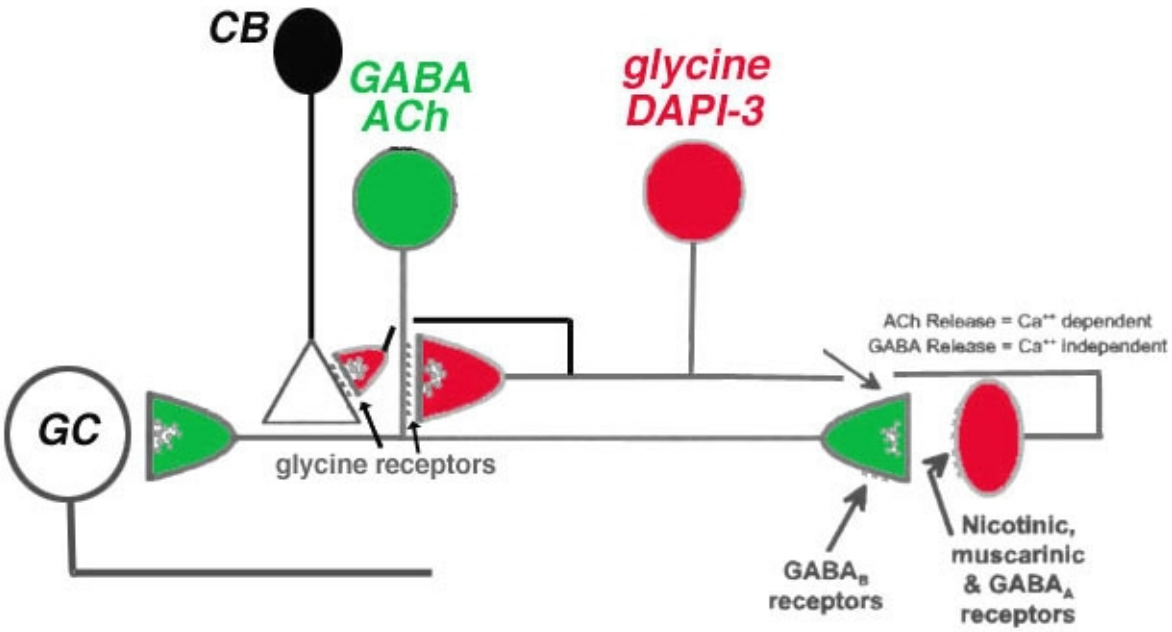


Figure 41. Wiring diagram of the DAPI-3 cell and its relationship to the ACh amacrine cell.

Figure 42. Cryostat sections of calretinin-IR monkey retina to show the different amacrine cell types that are immunoreactive. Three calretinin-IR cells are shown, of which only one has all the features of an AII amacrine cell (AII). The middle cell (A, curved arrow) has very fine, beaded dendrites running in S1, S3, and S5 (fine arrows). The third cell is difficult to identify (A).

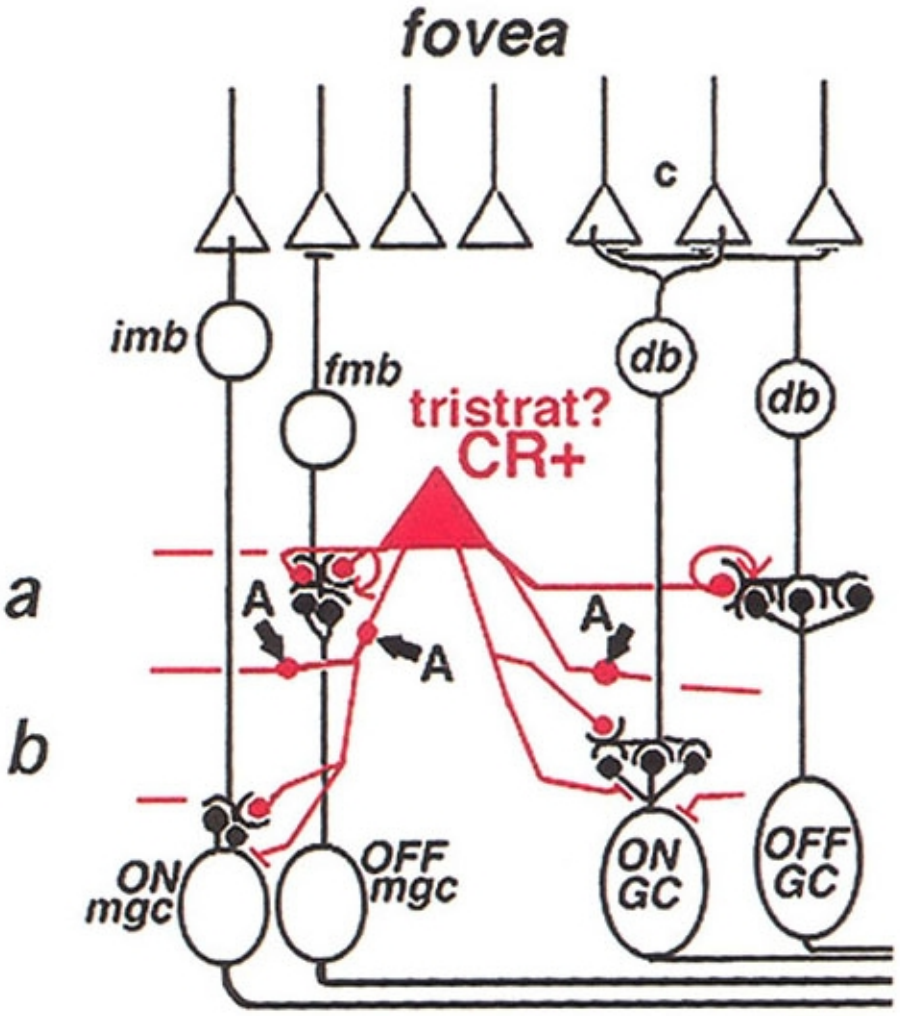


Figure 43. The calretinin-IR amacrine of the rod-free fovea (red cell) receives inputs from diffuse cone bipolar cells (db) and both invaginating and flat midget bipolar cells (imb and fmb) and many amacrine cells types (A arrows). It makes synapses upon ON-center midget (ON mgc) and other ON-center ganglion cells (ON GCs) in sublamina b of the IPL. OFF-center ganglion cells (OFF GC) in sublamina a could be indirectly affected by the tristratified calretinin-IR amacrines through their reciprocal synapses to dbs or fmb bipolar cells (return arrows).

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