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CHAPTER 2

Comparative anatomy of major retinal pathways in the eyes of nocturnal and diurnal mammals

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Introduction

One of John Dowling's greatest contributions to our understanding of the retina was the elucidation of the basic synaptic circuitry of the primate retina in a series of light and electron microscope studies (Dowling and Boycott, 1966; Boycott and Dowling, 1969; Kolb et al., 1969). Upon the heels of these studies followed the first intracellular recordings and marking of neurons in the mud-puppy retina that are now classics in the field (Dowling and Werblin, 1969; Werblin and Dowling, 1969). These seminal papers helped us focus back on the older questions of what are the fundamental neural types of the retina, how do they respond to light stimuli and how do they interact to form functional circuits. Cross species comparisons were then begun in the Dowling lab and we began asking questions about how different are the visual systems of various species, and how have such visual systems become adapted to the environment the animal lives in.

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From the time of Santiago Ramón y Cajal (1892, 1911) and later Stephen Polyak (1941) we had good descriptions of Golgi impregnated neurons in a variety of vertebrate retinas. Certainly Cajal (1892) recognized the basic similarity of retinal organization across species. All vertebrate retinas contain photoreceptors, horizontal cells, bipolar cells, ganglion cells and the cell class Cajal first named, amacrine cells. But the various species differed remarkably in the numbers and morphologies of cell types within these basic retinal cell classes. Cajal and Polyak's fascinating material has made comparative studies irresistible to many of us, and invites speculation on how such ocular diversity might have evolved.

Gordon Walls published a monumental work in 1942 addressing the evolution of the eye from the standpoint of species-specific retinal specializations with a particular emphasis on photoreceptors. Lettvin et al. (1959) had originally proposed that all the various cell types seen by Cajal in the frog's retina and their numerous stratified interactions in the inner plexiform layer (IPL) were important for coding complex receptive fields of ganglion cells and gave different ganglion cells specific feature detecting

capabilities. Dowling (1970) tried to simplify this concept by proposing the idea that species could be divided into those with complex retinas exemplified by the frog and those with simple retinas exemplified by the primate retina. The involvement of numerous amacrine cells in the IPL circuitry as opposed to a simple straight through bipolar and ganglion cell connectivity pattern was considered to be the basic difference between species that processed much of the visual message in the retina over those that were corticate in design. Later Hughes (1977) examined retinal anatomy from the viewpoint of behavioral patterns and environments and Jacobs (1981, 1993) has spent many years giving us an understanding of the spectral characteristics of retinas and ranges of color vision in different species.

So much comparative information has now accumulated from all these studies and in this chapter we would like to summarize our present understanding of the fundamental strategies that some mammals have adopted in their adaptive radiation to process visual information in their retinas. We will compare retinas of species with a nocturnal lifestyle with retinas of species with a diurnal lifestyle.

Retinal circuitry of mammalian retinas: trends, and design characteristics

Mammals have a limited number of photoreceptor cell types when compared with other vertebrates (see chapter by Kolb et al. this volume). Based upon their spectral sensitivity, teleost fish, in general, have at least four types of cone photoreceptors plus rods; reptiles and birds have rods plus one class of double cone and four classes of single cones; while most mammals have only two classes of cone. The exception to the latter occurs in primates where trichromatic color vision appears to have reemerged, arising from three spectrally distinct cone types [short wavelength sensitive (SWS), middle wavelength sensitive (MWS), and long wavelength sensitive (LWS) cones] in addition to the rods (for a brief review of this topic, see Bowmaker, 1998). The evolution of different photoreceptor types, and the pathways that give rise to color vision have been the subject of much speculation (see, for example, Walls, 1942; Hughes, 1977; Ahnelt and Kolb, 2000), but it is only our recent ability to identify and sequence the various opsin genes that has added much factual information to such speculation (Bowmaker, 1998). In general, the retinas of most mammalian species are dominated by rods, with the interesting exception of those in squirrels (Long and Fisher, 1983; Ahnelt, 1985; Kryger et al., 1998) and tree shrews (Kühne, 1983; Immel and Fisher, 1985; Müller and Peichl, 1989), and it seems generally accepted now that rods evolved relatively late by comparison to cones. This probably occurred due to the evolution of early mammals in a relatively nocturnal environment. Also, during mammalian evolution some of the complexity of color vision seen in fish, birds and reptiles (apparently tetrachromatic in some cases) was replaced by dichromacy in most species (even monochromacy in two species of nocturnal primates (Jacobs et al., 1996)). Trichromacy reemerging in the evolution of certain primate species, again correlated with the environment in which the species was evolving (Bowmaker, 1998).

If a relatively large variety of cone photoreceptor types existed early, and these were used to generate chromatic information about the environment, then the neural pathways within the retina for processing this information must have existed early as well. Thus, a variety of cone pathways must have already existed in the retina at the time at which rods evolved. If cones were specifically connected to second and third-order neurons according to their chromatic sensitivity, then one might expect that a new and separate pathway would have evolved to handle information arising from the highly sensitive rods. Such does not seem to be the case. Instead, it appears that the rod system "plugged into" the existing cone pathways, in a sense "piggy-backing" the information for scotopic vision onto existing photopic pathways in the retina.

In this chapter we compare some specific neural pathways from the retinas of primarily nocturnal species, rats and cats, to that of the "unusual" cone-dominated retina of the diurnal ground squirrel, and make some further comparisons to the primates with their pure cone fovea and rod-dominated periphery. Examples from other species are also used to illustrate specific concepts.

Photoreceptor mosaics

As mentioned previously, virtually all mammals have rod-dominated retinas, with rods outnumbering cones by as much as 1000 : 1. Examples are shown in Figs. 1a and 2 for cat and rat retina. The rods are tightly packed in an extremely thick outer nuclear layer (ONL) consisting of 18 or more ranks of perikarya (Fig. 1a, cat peripheral retina; 3b hamster). The few cones in species like the rat (Fig. 2, <1%; Szél and Röhlich, 1992) or mouse (3%; LaVail, 1976) are slender and rod-like in shape with cell bodies at the outer limiting membrane (Fig. 3b, hamster). In general, dichromatic mammals have two spectral classes of cone, one, being a middle wavelength sensitive cone (MWS) with a λ_{max} between about 500 and 565 nm and the other the short wavelength sensitive (SWS; often referred to as "blue" cones) cone with its λ_{max} ranging from the ultraviolet (rodents) to blue range of the spectrum (365–450 nm; Bowmaker, 1998). The availability of antibodies that recognize these opsins has made it possible to map the distribution of the different cone types in a variety of species. In most species the longer wavelength-sensitive cone is distributed across the whole retina, while the shorter wavelength-sensitive cone is concentrated preferentially in the inferior retina. In some rodents (rat, Szél and Röhlich, 1992;

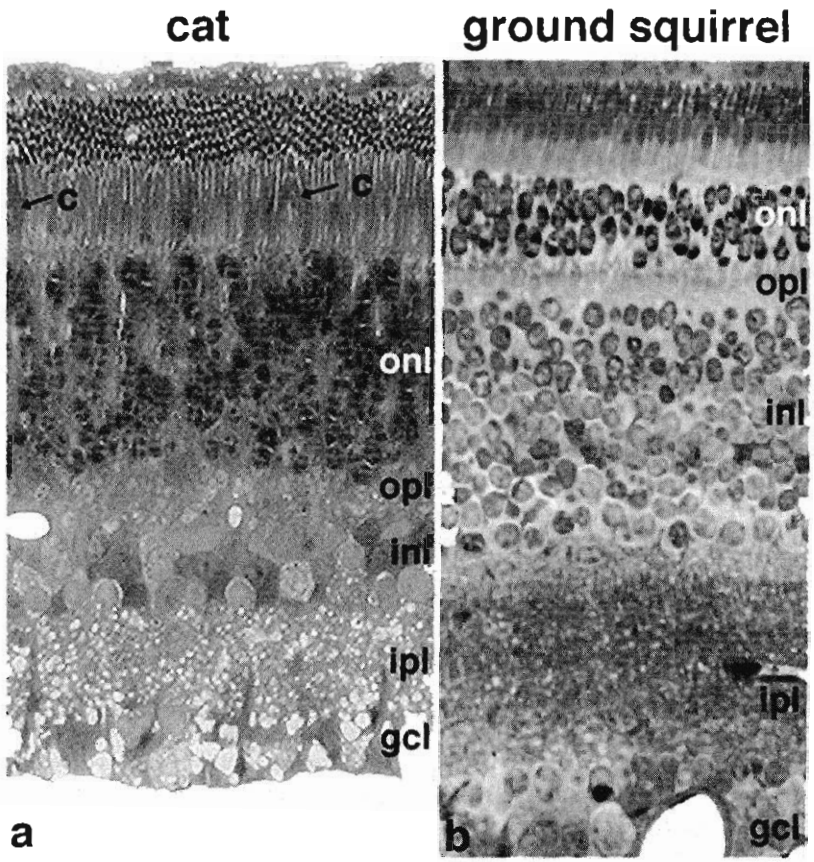


Fig. 1. (a) A light micrograph of a radial section through peripheral cat retina stained with toluidine blue. In this model of a nocturnal retina, only two cones (c, arrows) appear in a field of rods whose nuclei constitute a very thick outer nuclear layer (onl) (from Ahnelt and Kolb, 2000). (b) A similar preparation of ground squirrel retina demonstrates several features of the diurnal retina that differ from the nocturnal type. The short, stout cones of this retina comprise an ONL only 2 to 3 cells thick. In contrast with cat, the ground squirrel INL and IPL are very thick, accommodating many types of bipolar and amacrine cells whose many processes connecting with the dendrites of numerous types of ganglion cell contribute to the thick neuropil. opl = outer plexiform layer; inl = inner nuclear layer; ipl = inner plexiform layer; gcl = ganglion cell layer (from Long and Fisher, 1983).

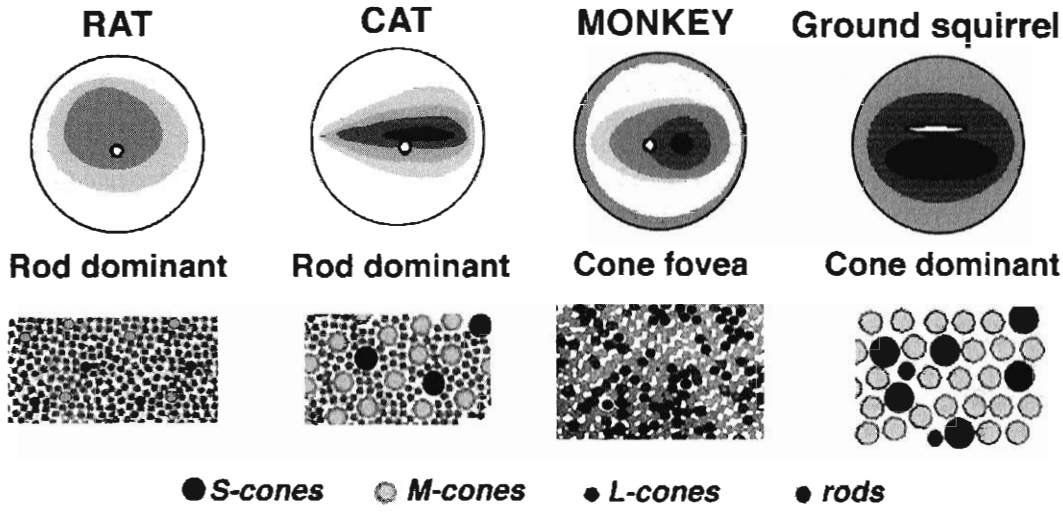


Fig. 2. Topographical depictions of rat, cat, monkey, and ground squirrel retina to show the density distribution of the cone photoreceptors (shading from dark (high density), to pale (low density)). The cone mosaics reflect the retinal specializations such as the *area centralis* (cat), fovea (monkey) or visual streak (ground squirrel) in the different retinas. The optic nerve is the white spot or slit. Below are examples of the photoreceptor mosaics in each species.

mouse, Calderone and Jacobs, 1995; hamster, Calderone and Jacobs, 1999) however, the two types of cone have non-overlapping populations. The cat retina (overall, about 3% cones) differs from that of the rodents by having an *area centralis* where cones reach a peak density (Fig. 2; Steinberg et al., 1973; Linberg et al., 2001), but the overall cone distribution is like that seen in the rodents and even in the *area centralis*, rods predominate over cones by as much as 10 : 1 (Steinberg et al., 1973).

Like most other mammals, ground squirrels are dichromatic, but with a retina dominated by cones (Figs. 1b, 3c). Indeed, for many decades it was thought that the ground squirrel, like the prairie dog (Fig. 3f) had a pure-cone retina, and thus it was regarded as a model system for foveal organization. Cones in these retinas are short and stocky compared to those of rat and cat, and the ONL is only 2–3 layers thick (compare Figs. 1a and 1b). As in the rod-dominated species discussed above, the cones in ground squirrel consist of SWS and MWS types (12% and 88% respectively; Long and Fisher, 1983; Ahnelt 1985; Kryger et al., 1998). The presence of rods was first demonstrated by ERG recordings and then by morphological analyses about 25 years ago (Green and Dowling, 1975; West and Dowling, 1975; Jacobs et al., 1976, 1980; Anderson and Fisher, 1976; Long and Fisher, 1983; Ahnelt, 1985). Rods and cones appear superficially alike in the ground squirrel retina (Fig. 3c), with the rod outer and inner segments being only slightly longer and thinner. Rods are now easily distinguished in the ground squirrel retina by immunolabeling with antibodies against rhodopsin (Fig. 3d; Kryger et al., 1998), and constitute 14% of the photoreceptor population across the retina. Their highest relative population (30%) is in the deep ventral periphery, while their lowest (5%) occurs in the visual streak. MWS cones contribute 80% to the total photoreceptor population and have their greatest density in the visual streak (Fig. 2); SWS cones constitute only 6% of the total number and have a rather uniform density across the whole retina (Kryger et al., 1998).

In primates trichromacy came about by the addition of a third cone type that evolved separately in the case of New and Old-World monkeys leading to separate MWS and long wavelength sensitive (LWS) cones in addition to the SWS cone (Bowmaker, 1998). Furthermore in catarrhine primates and man, the retina is characterized by a special emphasis on the development of a cone-dominated region, or macula, with its specialized cone-associated pathways (Figs. 2, 3a). In the center of the macula, or fovea, rods are excluded, while in

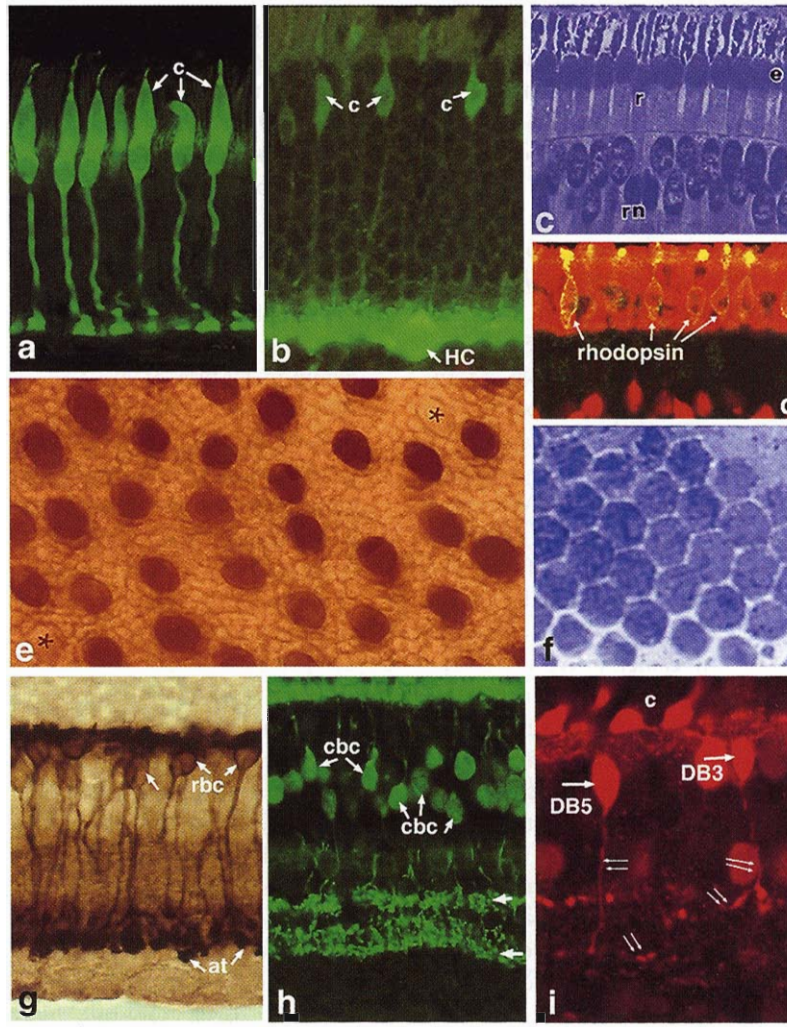


Fig. 3. (a) A confocal image of monkey cones (c, arrows) stained with a fluorescently tagged antibody against GCAP1. Entire cones, labeled from their outer segments to their pedicles, lie amidst unstained rods. (b) A less robust fluorescent image of the few cones (c, arrows) in hamster retina labeled with an antibody against calbindin D. Cone nuclei are restricted to the outermost row of cells in the outer nuclear layer which consists of many ranks of unstained rod nuclei. Horizontal cell nuclei (HC) are also positive for calbindin D. (c) A light micrograph of a radial section, stained with toluidine blue, through the outer retina of a ground squirrel. A single rod (r) lies among the many cones. The ellipsoid region (e) of the photoreceptors, filled with mitochondria, stain darkly. rn = rod nucleus (from Long and Fisher, 1983). (d) A confocal micrograph of a similar region of ground squirrel retina shows that all photoreceptors stain positively for antibodies against recoverin (red) while just the rods (arrows) also colocalize antibodies against rhodopsin (yellow). A type of bipolar cell also appears recoverin-positive. (e) A confocal image of a wholemount of human retina stained with antibodies against calbindin D. The immunoreactive inner segments of the M- and L-cones stand out against the unstained S-cones (*) and the smaller rods. (f) A tangential section of prairie dog retina stained with toluidine blue demonstrates the tight packing of cone inner segments typical of diurnal retinas. (g) A light micrograph of a radial section through rat retina stained with antibodies against protein kinase C known to stain mammalian rod bipolar cells. Rat rod bipolar cells (rbc, arrows) have their nuclei close to the outer edge of the inner nuclear layer while their axon terminals (at, arrows) stratify in the deepest stratum of the IPL adjacent to the ganglion cell layer. (h) In a fluorescent micrograph taken by confocal microscopy, antibodies against recoverin, here shown in green, stain two varieties of cone bipolar cell (cbc, arrows) in the ground squirrel retina, one more intensely than the other. The axon terminals of these cells stratify in two bands in the IPL (thick arrows), the lower thicker than the upper. (i) In another confocal preparation, antibodies against calbindin D label two types of bipolar cell in monkey retina, one (DB5) has axon terminals stratifying in the inner IPL (arrow pairs, left), and the other (DB3) in the outer IPL (arrow pairs, right). A type of amacrine cell also stains, as do the cone pedicles (c).

the perifoveal retina the number of rods gradually increases (Østerberg, 1935), eventually separating the closely packed cones into islands, creating two mosaics (Fig. 3e). In the central 1° of the foveal pit the LWS and MWS cones are packed into a hexagonal mosaic lacking SWS cones (Williams et al., 1981). The SWS cone population distribution has now been determined in a number of primate species (Curcio and Hendrickson, 1991; Wikler and Rakic, 1990) using antibody (Nathans et al., 1986) labeling. With increasing eccentricity the SWS-cone population rises in density to become 14% of the total cone population at the foveal slope (a ring 2 mm or 8° from the foveal center), then tapers to a steady 8% throughout the rest of the peripheral retina. The distribution of LWS and MWS cones has proved impossible to determine by antibody labeling since the molecular structure of the two differs by only a few amino acids. Nevertheless, using microspectrophotometry (Mollon and Bowmaker, 1992) and reflectance photometry (Roorda and Williams, 1999), small patches of these cones in the primate fovea have been mapped. Lacking any apparent regular mosaic, they appear to be packed into various sized arrays of the same type with the LWS cones the more numerous (at least in man; Figs. 2, 10c) (McMahon et al., 2000). Thus, it appears that the central few degrees of the trichromatic primate retina are dominated by red-sensitivity, while the peripheral retina, though still trichromatic psychophysically (G.H. Jacobs, personal communication) is dominated by green-sensitivity but with an additional blue-sensitive component derived from the presence of SWS cones. The latter pattern of dominance by the cones sensitive in the green portion of the spectrum—but with significant input from the SWS cones, is a pattern common to most dichromatic mammals (see Fig. 10b).

Neural pathways for nocturnal living

Specialized rod bipolar and amacrine cells

The predominance of rod photoreceptors and the evolution of specific pathways for processing rod information, must have given the early mammals a tremendous advantage of being able to function well at very low levels of ambient light. Rods, after all, are inherently more sensitive than cones with their ability to respond to the presence of a single photon (Hecht et al., 1942). The purpose of the rod pathway is to gather as much information about the presence of light as possible and this is done by the convergence of many rods onto rod bipolar cells (about 15–50 : 1 in the cat and rat retinas) and then the convergence of information through the bipolar cell pathways onto the ganglion cells (ranging from 100–1 to 5000–1 in central cat retina) (see Sterling et al., 1988). One common feature of most placental mammals is the presence of a separate rod bipolar cell type responding to the light ON signal. This cell is devoted solely to input from rod photoreceptors, which is in contrast to most non-mammalian vertebrates and non-placental mammals where the homologous cell is rod-dominant, but has cone input as well. Figure 3g shows the typical morphology and packing density of ON-rod bipolar cells in the rat retina as revealed by protein kinase C immunostaining (Greferath et al., 1990). Also, there does not appear to be an OFF-bipolar cell devoted solely to the rod pathway. In squirrels, the B4 "rod bipolar" has been shown to have some cone input (West, 1978), while the B3 bipolar cell, an apparent OFF-cone bipolar, also receives its input from rods as well as cones (Fig. 4a, large arrows) (Jacobs et al., 1976; West, 1978; Linberg et al., 1996).

In general, the mammalian rod bipolar cell is much more convergent than any of the cone bipolar subtypes. Each ON-rod bipolar makes dendritic contact with numerous rod spherules [cat: 16–25 (Boycott and Kolb, 1973; Freed et al., 1987; Greferath et al., 1990; Wässle et al., 1991); rabbit: 80–120 (Dacheux and Raviola, 1986; Young and Vaney, 1991); human: 30–45 (Kolb et al., 1992); monkey: 5(fovea)–60(periphery) (Boycott and Dowling, 1969; Boycott and Wässle, 1991; Grünert and Martin, 1991)] high in the outer plexiform layer (OPL) at invaginating, ribbon-related synapses (Fig. 4c). The rod bipolar cell carries the light-on signal to the lower portion of the inner plexiform layer (IPL), specifically to Cajal's strata 4 and 5 (Figs. 3g, 6a). Based upon the demonstration that ON and OFF signals were segregated into two sublaminae of the IPL, these lower-most layers (receiving ON input) were referred to as sublamina "**b**" while

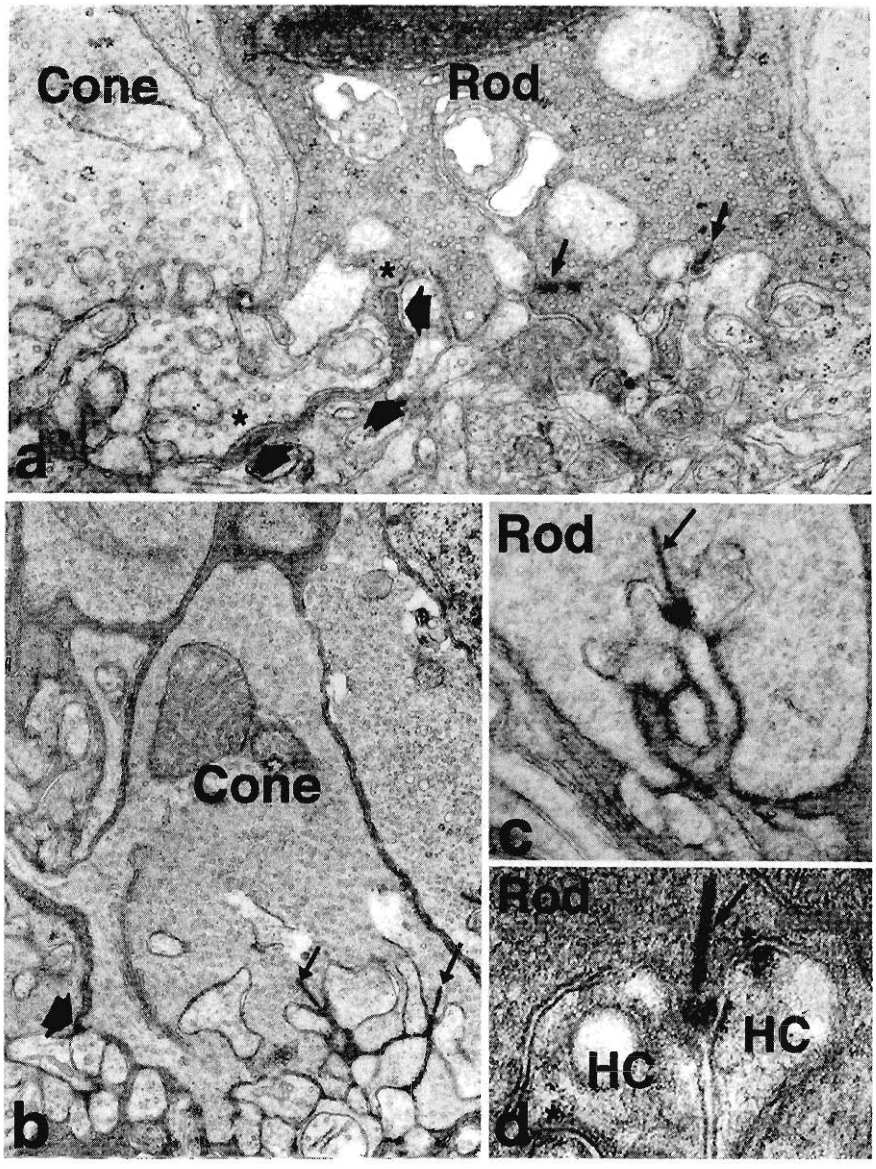


Fig. 4. (a) An electron micrograph of the photoreceptor terminals of the California ground squirrel. Unlike rod spherules in rod-dominant retinas, the cone-like rod terminals in squirrels have several synaptic invaginations with independent synaptic ribbons (small arrows). Note the electron-dense dendritic process (thick arrows) of a bipolar dendrite, that, rising across the OPL makes flat contacts (*) first with a cone pedicle then terminates on the rod terminal (*) (from Jacobs et al., 1976). (b) An electron micrograph of a cone pedicle from the retina of a cat. The multi-invaginated pedicle contains prominently large mitochondria and is presynaptic at ribbons (small arrows) to horizontal cells and ON-center bipolar cell invaginating dendrites. Numerous basal junctions are made by OFF-center bipolar cell dendrites. Note the contact (thick arrow) with a neighboring cone (from Kolb, 1977). (c) An electron micrograph of a rod spherule in the cat retina contains a single invagination at the rod's synaptic ribbon (arrow), where horizontal cell lateral elements and a central ON rod bipolar cell dendrite terminate. (d) An electron micrograph of a rod spherule invagination in peripheral human retina. Two horizontal cell dendrites (HC) form lateral elements in the triad opposing the ribbon synapse (arrow); each contains a small synapse (*) back onto the rod terminal membrane (from Linberg and Fisher, 1988).

the remaining two distal layers (receiving OFF input) were referred to as sublamina "**a**" by Nelson et al. (1978). Within sublamina **b** of the IPL, the rod signals are channeled into two separate amacrine cell pathways. While undoubtedly many varieties of amacrine cell are involved in the processing of rod signals, it appears that two major types, well-developed in the retinas of rod-dominated, nocturnal mammals, may bear the lion's share of the responsibility for this task. The major amacrine cell type associated with the rod pathway is a narrow-field, bistratified amacrine known as AII (Kolb and Famiglietti, 1974; Famiglietti and Kolb, 1975; Nelson, 1982; Dacheux and Raviola, 1986). In contrast, the A17 cell is an extremely wide-field amacrine with processes that ramify across the IPL, but run for hundreds of microns in stratum 5 (i.e. adjacent to the ganglion cell layer in sublamina **b**) where they create an overlapping plexus of beaded processes (Kolb and Nelson, 1984; Nelson and Kolb, 1985).

The AII amacrine

In species such as the cat (and probably in all rod-dominated retinas as well as the primate peripheral retina), the AII cells are numerous and have a closely packed arrangement tiling the retina (Vaney, 1985; Fig. 5d). They serve to collect rod signals at the rod bipolar axon terminals deep in sublamina **b** of the IPL. They then transmit these signals both in the inner and outer IPL to different types of cone bipolar cell. These cone bipolars synapse onto ganglion cell dendrites. Until the discovery of this pathway, it was assumed that rod bipolar cell axons must be presynaptic to ganglion cell dendrites or even cell bodies, because their large terminals end adjacent to the ganglion cell bodies. It was not until Kolb and Famiglietti (1974) were able to reconstruct the rod bipolar terminals in serial sections by electron microscopy, that this indirect pathway was revealed.

Figures 6a–c summarize the rod pathways of these rod-dominated mammalian species, showing the position of the AII amacrine cell as an intermediary between the rod and cone bipolars. Because the AII cell apparently allowed the rod photoreceptors to utilize already existing cone pathways for transmitting information to the ganglion cells, they are sometimes referred to as "piggy-back" neurons (Strettoi et al., 1992). The AII amacrine is an ON-center cell, and it passes signals from the ON-rod bipolar cell through gap junctions to the terminals of ON-cone (invaginating) bipolar cells in sublamina **b** of the IPL (Fig. 6). It is these cone-bipolars (orange bipolar cell, Fig. 6c) that ultimately pass information from the rod bipolar cell to an ON-center ganglion cells at chemical synapses (Fig. 6c; Kolb, 1979; Sterling et al., 1988). The AII cell (thought to be glycinergic) is also presynaptic to OFF-cone (flat) bipolars in sublamina **a** of the IPL (yellow bipolar, Fig. 6c). The OFF-cone bipolar in turn synapses onto an OFF-center ganglion cell. Just as frequently, the AII cell is directly presynaptic to the OFF-center ganglion cell (Fig. 6c; Kolb and Nelson, 1993). These chemical synapses appear on highly specialized branches off the main dendritic trunk of the AII cell called lobular appendages. The cells probably also integrate additional information from other amacrine cells at these specializations. For example, the lobular appendages are known to be postsynaptic to a dopaminergic amacrine cell (Fig. 10a) whose effect is thought to be the modulation of AII activity depending upon ambient illumination (Pourcho, 1982; Kolb et al., 1990; Voigt and Wässle, 1987; Jensen and Daw, 1986). The physiology of the AII amacrine cell is further complicated by the fact that they are linked to each other by gap junctions. Under scotopic conditions, the coupling of cells through these gap junctions makes the receptive field of any one AII amacrine huge, thus gathering input from large numbers of rods. Under photopic conditions, dopamine released from the dopaminergic amacrine cell apparently uncouples the gap junctions, shrinking the size of the receptive field. Thus, it appears that through their "piggy-back" connectivity onto the cone-system, the rod channel can drive the center responses of both ON- and OFF-center ganglion cells. This seems a parsimonious and clever evolutionary way for the huge numbers of rods in these species to use preexisting cone pathways for providing scotopic input to ganglion cells driven by cones under photopic conditions. Thus, rather than evolve a completely separate pathway, the rod system developed interneurons to take advantage of existing cone pathways which would be inactive in dim light.

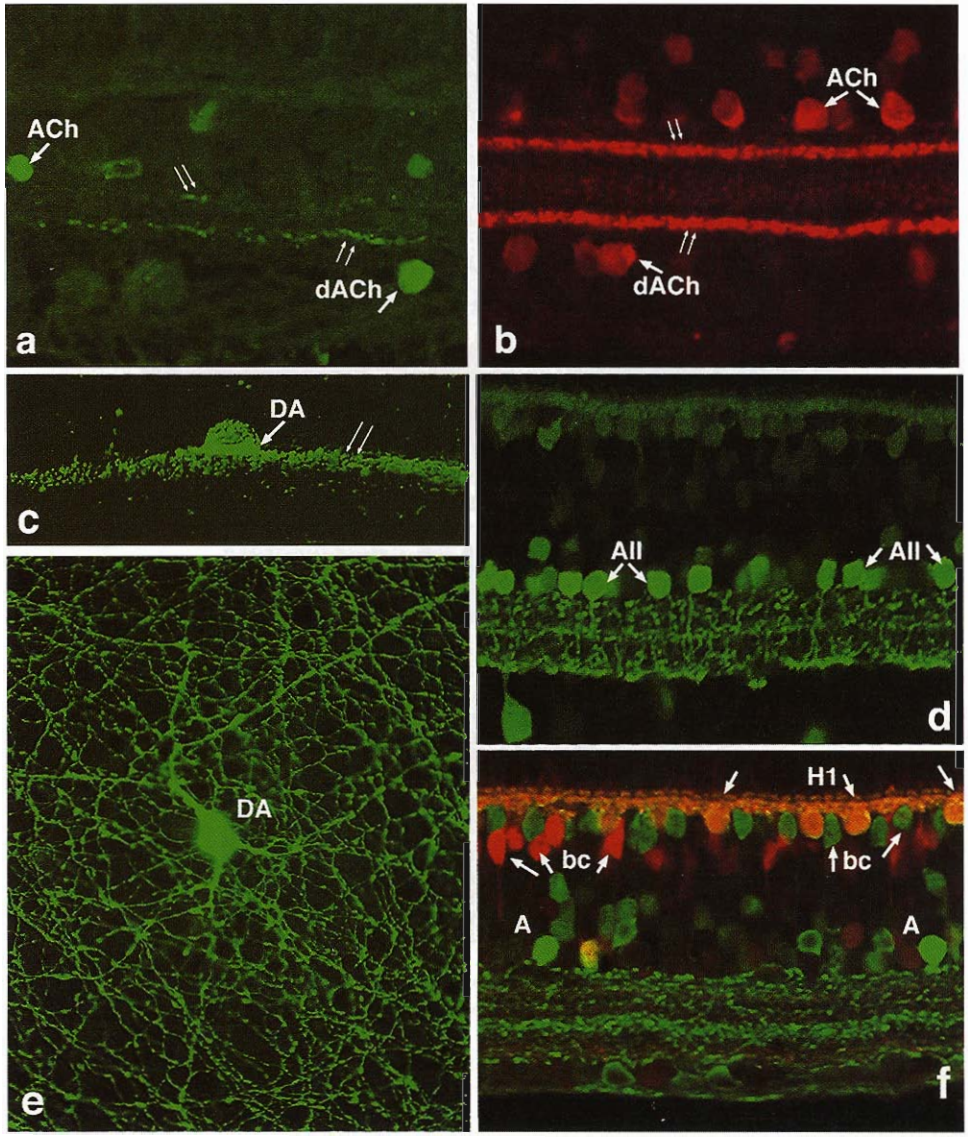


Fig. 5. (a) Confocal image of a radial section through a human retina that has been stained with antibodies against choline acetyltransferase (CHAT) a marker for the cholinergic starburst amacrine cells. Nuclei of one subtype (ACh) reside in the amacrine cell sublayer of the INL and has dendrites running in S2 of the IPL (upper pair of arrows); the other subtype (dACH) resides in the ganglion cell layer and has dendrites running in S4 (lower pair of arrows). (b) In a similar preparation of ground squirrel retina, many more nuclei of CHAT-positive starburst amacrines can be seen (ACh, dACh), contributing to two strongly labeled plexi of dendrites in the IPL (arrow pairs). A second population of amacrine cell nuclei are also faintly positive for CHAT. (c) A dopaminergic amacrine cell (DA, arrow) in the human retina stained with antibodies to tyrosine hydroxylase. The amacrine has a thin layer of dendrites running in S1 (arrow pair) under the amacrine cell bodies. (d) Rod AII amacrine cells are immunostained by antibodies to calretinin. These small-field, bistratified cells (AII, arrows) form a dense distribution tiling the retina with lobular appendages in the OFF layer and distal dendrites in the ON layer. (e) Wholemount view of a dopaminergic amacrine cell in the ground squirrel retina. The cell body (DA) is large and the overlapping dendrites of its and other cells' dendrites form a distinct plexus in stratum 1 of the IPL. (f) Immunostaining of horizontal cells (H1, arrows) in the ground squirrel retina showing that calretinin and calbindin D colocalize in these cells (orange). Many varieties of bipolar (bc, arrows) and amacrine cells (A) label with both calcium binding proteins but rarely colocalize the two.

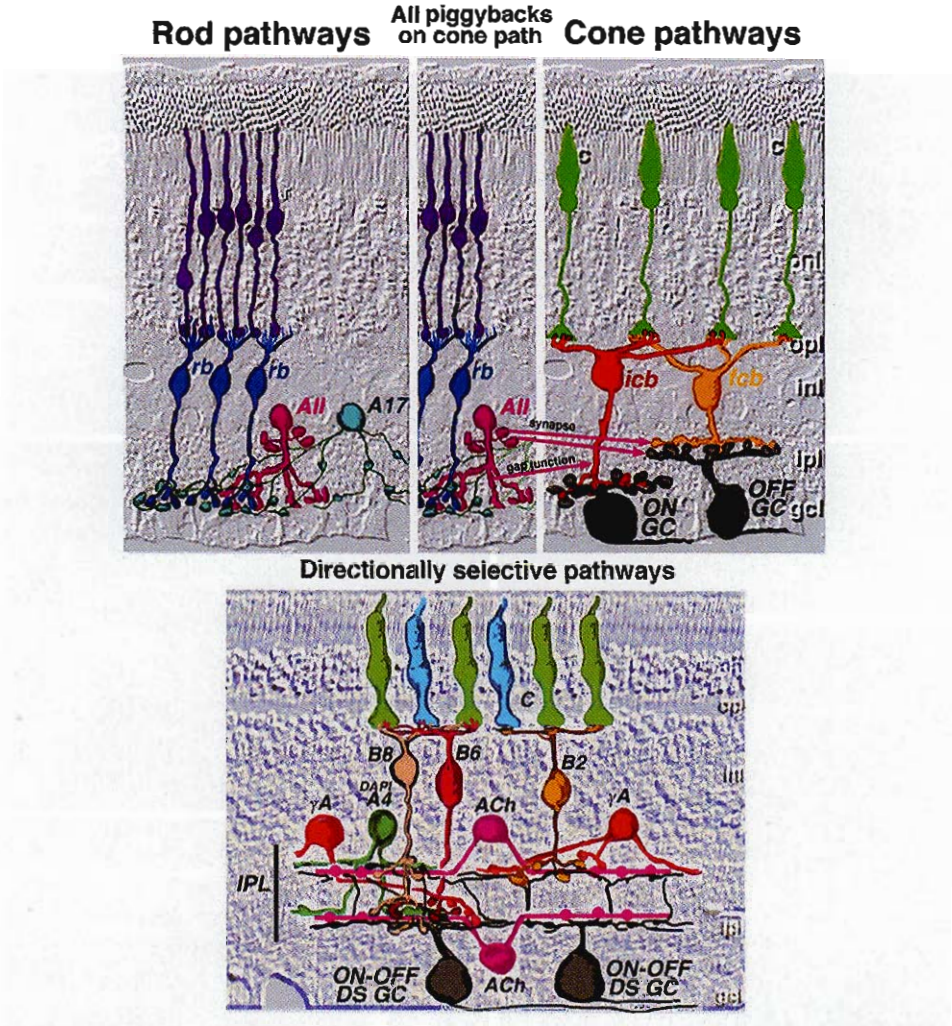


Fig. 6. The major retinal neurons contributing to the main retinal pathways are highlighted against a Nomarski image of unstained retina. (a) The rod pathway starts with hundreds of rods (r, purple) connecting to a single rod bipolar cell type (rb, blue) whose prominent axon terminals stratify in the deepest part of the IPL next to, but not onto, the ganglion cells. The narrow field, bistratified AII amacrine cell (AII, red) is post-synaptic at the rod terminal synapse, as are the beaded processes of the wide field A17 (turquoise) which also make reciprocal synapses back onto the rod bipolar terminal. (b) The AII amacrine carries or "piggy-backs" the rod signals to both ON- and OFF-cone pathways, making gap junctions between its lobular appendages and ON-cone bipolar cells (6c: icb, vermilion) in the inner IPL, and making conventional synaptic output onto the terminals of OFF-cone bipolar cells (6c: fcb, orange) and the dendrites of OFF-ganglion cells (6c: black, right) with its dendrites in the outer IPL. (c) The cone pathways are more numerous with multiple types of bipolar, amacrine, and ganglion cell involved. Unlike the rod pathway, however, cone bipolar cells directly synapse onto their targeted ganglion cells. Therefore this summary diagram is vastly simplified. First of all, the various subtypes of cone (c, green) make the two prominent types of contact with their cone bipolar cells, here represented by diffuse cone bipolar cells. Bipolar cell types whose dendrites make invaginating contacts with cone pedicles (icb, vermilion) have axon terminals in the deeper region of the IPL, called sublamina **b**, presynaptic to ON-ganglion cells (ON GC, black), while bipolar cell types whose dendrites make flat contacts with the cone terminals (fcb, orange), have axon terminals in the upper IPL (sublamina **a**) presynaptic to OFF-ganglion cells (OFF GC, black). (d) The directionally selective pathways involve neurons ramifying in the same strata of the IPL as do the dendrites of the physiologically defined ON–OFF directionally selective ganglion cells (ON–OFF DS GC, black), namely S2 and S4. The ground squirrel retina with its green and blue cones (c) is used as an example. Ramifying in S2 with the outer tier of ON–OFF DS GC processes are the processes of starburst amacrine (ACh, pink) resident in the INL, the terminals of the B2 cone bipolar cell (B2, orange) and certain other amacrines cells (A, red, right), as well as both upper tiers of dendrites of the small field, bistratified, DAPI amacrine cell (DAPI A4, dark green) and the bistratified bipolar cell (B8, salmon). Ramifying with the inner tier of ON–OFF DS GC processes are the major plexus of "displaced" starburst amacrine cells resident in the ganglion cell layer (ACh, pink), the terminals of the B6 bipolar cell (B6, crimson), the dendrites of certain amacrine cells (A, red, left), and both inner tiers of the bistratified A4 amacine (DAPI A4, dark green) and B8 bipolar cell (B8, salmon).

The A17 amacrine

The other well-studied rod pathway-specific interneuron is the wide-field A17, or so-called "rod reciprocal" amacrine (Fig. 6a; Kolb and Nelson, 1984; Nelson and Kolb, 1985). This cell is known to be GABAergic, but may also be serotonergic as well (Masland, 1988; Vaney, 1990). The A17 appears to be responsible for integrating and probably amplifying signals of the rod bipolar cells. They are known to interconnect rod bipolar axon terminals over an area of as much as 1 mm in diameter (Kolb et al., 1992). The A17 cells are purely driven by rods, are "ON" cells, and as might be expected from the size of their dendritic trees, have large receptive fields. While their input is from rod bipolar axon terminals, their output is back onto these same terminals in the form of a "reciprocal synapse" (Nelson and Kolb, 1985). The A17 cell is thought to function in a feedback manner with rod bipolar cells through GABAc ρ receptors (Fletcher and Wässle, 1999). Its function is thought to be that of pooling and integrating thousands of small amplitude rod bipolar events to increase the strength of the signal ultimately transmitted through the rod bipolar-AII-ganglion cell pathway.

Horizontal cells

Horizontal cells are the laterally spreading interneurons of the OPL, responsible for integrating information between photoreceptor and bipolar cells in this layer. The horizontal cells seem to play different physiological roles in lower vertebrates where they are probably responsible for providing both antagonistic surround and color opponency information (Werblin and Dowling, 1969; Werblin, 1991; Werblin et al., this volume). Although this is still considered an unresolved issue, the recent evidence of Dacey et al. (1996) seems to indicate that they do not play these roles in the retinas of mammals or primates.

If our two nocturnal species, cats and rats share a commonality of the rod pathway in the inner retina, the same cannot be said of the outer retina. Indeed, there are large variations in horizontal cell structure amongst these and other mammals that make for fascinating, if somewhat complex speculation about their function (Gallego, 1986; Peichl and González-Soriano, 1994; Peichl et al., 1998). The cat retina contains two types of horizontal cell (Fisher and Boycott, 1974; Kolb, 1974; Boycott et al., 1978), the so-called A-type (Fig. 7), an axonless cell which connects only to cone photoreceptors, and the axon-bearing B-type, structurally one of the most complex neurons described in any retina (Fig. 7), which has connections with both rods and cones. Indeed, defined by the fact that it receives both rod and cone input, the B-type cell is the most common horizontal cell type found in rod-dominated retinas. The A-type cell, however, has apparently been lost in the evolution of the heavily rod-dominated retinas of rats and mice (Peichl and González-Soriano, 1994).

The B-type horizontal cell is not only structurally but also physiologically unusual. The dendrites, arising from the cell body contact only cone photoreceptors, while the elaborate axon terminal branches contact only rod photoreceptors. Because these cells generate only graded potentials, the two ends of the cell are thought to function in isolation from each other due to the length and thinness of the connecting axon (Nelson et al., 1975). The large and elaborate axon terminal can interconnect literally thousands of rod spherules in the OPL. Their axon terminal tips penetrate rod spherules at the synaptic invagination and end as lateral elements slightly more distal than the invaginating rod bipolar dendrites (Fig. 4c). The question of whether horizontal cells influence either the rod itself by a feedback pathway or the rod bipolar by a feed-forward pathway is still open to debate. The only structural correlate of such horizontal cell-to-rod photoreceptor contact is from an ultrastructural study of human retina. Small clusters of synaptic vesicles and associated presynaptic densities were reported in the horizontal cell terminals within the rod invaginations (asterisk, Fig. 4d; Linberg and Fisher, 1988). These apparent synapses are located so that the horizontal cell axon terminal is presynaptic to rod bipolar cell dendrites in the outer OPL and then presynaptic to the rod itself within the synaptic invagination. The rod bipolar cell has been reported to have a weak surround component to its receptive field, but it is not certain if it originates in the OPL or IPL (Dacheux and Raviola, 1986). At the opposite end of the axon-bearing B-type cell, the dendritic tips clustered along

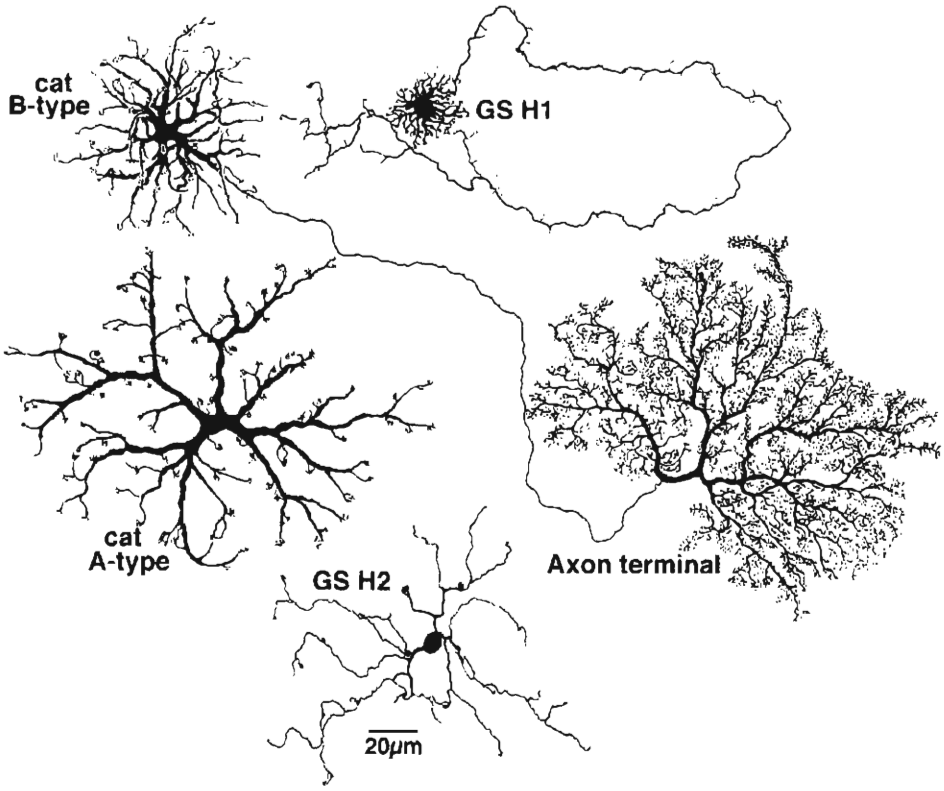


Fig. 7. Examples of Golgi-impregnated horizontal cells from cat and ground squirrel wholemounted retinas are shown at the same scale for purposes of comparison. The axon-bearing or B-type cell for both species has a dendritic end that is cone-connected, and an axon terminal portion contacting rods. The huge number of rods in the nocturnal cat retina can easily be appreciated by the vast number of rods contacted by a single axon terminal (cat B-type) compared with the sparsely branching ground squirrel horizontal cell terminal (GS H1). The axonless A-type horizontal cells are believed to be cone driven with significant S-cone input. The feline example (cat A-type) is sturdier and contacts many more cones than the sciurid example (GS H2). (Cat: from Fisher and Boycott, 1974; squirrel: from Linberg et al., 1996.)

the radiating dendritic branches (Fig. 7) innervate overlying cone pedicles. Specifically, they form the "lateral elements" at each of the many cone ribbon triads (Fig. 4b). In these cone terminal invaginations, Vardi et al. (1998) have reported the presence of $GABA_A$ receptors at the interface of lateral postsynaptic elements and the cone terminal (also see Kolb et al., this volume). Clearly, there is much to learn about the function of these highly complex interneurons.

The GABAergic interplexiform cell

The GABAergic interplexiform cell is found in rod-dominated mammalian retinas. This cell was first described in cat and squirrel monkey retinas (Gallego, 1971; Boycott et al., 1975; Kolb and Famiglietti, 1976; Kolb and West, 1977), and eventually proved to be distinctly different than the dopaminergic interplexiform cell of teleosts and primates (Dowling and Ehinger, 1975; Frederick et al., 1982). Whereas this latter type is presynaptic to cone horizontal cells in the OPL (Dowling and Ehinger, 1975; Frederick et al., 1982), the mammalian GABAergic variety is presynaptic to rod and cone bipolar cells instead (cat, Kolb and West, 1977; human, Linberg and Fisher, 1986). The dopaminergic interplexiform cell is probably concerned with photopic pathways and regulating adaptational changes between light and dark, while the GABAergic interplexiform cell seems devoted to rod-driven circuitry (Marshak, this volume).

Neurons of the cone pathways form the basic circuitry of diurnal retinas

As implied above, the cone pathways consist of a more "direct" relay of information from the photoreceptors to the ganglion cells, in the sense that there is no equivalent to an AII amacrine cell interposed between the cone bipolar cells and the ganglion cells (Fig. 6c). Compared to the rod pathway neurons, there is, in general, also less convergence first between the cones and cone bipolars and then between cone bipolars and ganglion cells.

Two functional classes of cone bipolar cell

Two parallel cone pathways have developed in all vertebrate retinas, one serving to provide information to the brain about brighter than background stimuli (the ON-center channel), and the other about darker than background stimuli (the OFF-center channel). Kuffler (1953) first described these two basic responses of ganglion cell in recordings made from the cat retina. The discovery that all photoreceptors hyperpolarize to the presence of light (Tomita, 1965) raised the question of how these two types of responses arise in the ganglion cells. Later, it was shown in Golgi impregnated tissue studied by electron microscopy, that midget cone bipolar cells in monkey retina consisted of two distinct subtypes, one making invaginating, and the other making flat contacts with cone pedicles (e.g. Fig. 4a, squirrel retina; Kolb et al., 1969). Furthermore, these subtypes of bipolar cell contact different ganglion cell types (Kolb, 1970). These data elucidated the structural basis for the two types of ganglion cell responses. Later it was shown that the invaginating cone bipolar axons branch and contact ganglion cell dendrites in Cajal's strata 3, 4 and 5 of the IPL (next to the ganglion cell layer), and that the flat cone bipolar axons contact ganglion cells whose dendrites branch in the more distal IPL layers (Cajal's strata 1, 2). Intracellular recordings from cat ganglion cell revealed that those branching in the lower portion of the IPL (contacting the invaginating bipolar cells) are of the "ON" variety, while those branching in the upper portion (contacting the flat bipolar cells) are of the "OFF" variety (Nelson et al., 1978; see Fig. 6c). This effectively divided the IPL into two functional layers corresponding to the "OFF" response (sublamina **a**, Nelson et al., 1978), and ON response (sublamina **b**). This principle has held through each vertebrate species examined (Kolb, 1979; Nelson and Kolb, 1983; Cohen and Sterling, 1990). The ON-(invaginating) bipolars are now known to use metabotropic postsynaptic receptors (Slaughter and Miller, 1981; Nomura et al., 1994; Vardi et al., 1998) and a second messenger system involving a G-protein and calcium (Nawy and Jahr, 1990; Nawy, 2000), while the OFF-(flat) bipolars use the AMP/kainate ionotropic variety of glutamate receptor (Slaughter and Miller, 1983; Vardi et al., 1998; Brandstätter et al., 1997; DeVries and Schwartz, 1999; Kolb et al., this volume). The contact between both types of bipolar and their respective ganglion cell is excitatory, and probably mediated by AMPA or NMDA glutamate receptors (Miller et al., this volume). Although all fall within the "invaginating" or "flat" categories, based upon the branching patterns of their dendrites and axon terminals, as many as 8–10 different subtypes of cone bipolar cell probably exist in all vertebrate retinas (Figs. 3h, i, 5f, 6, 10).

Horizontal cells and the cone pathways

In diurnal species, the A-type (axonless) horizontal cell, with its pure-cone input is usually very well-developed (Fig. 7). In addition, the dendritic end of the axon-bearing horizontal cell (B-type) is also purely cone-connected. A different nomenclature is used for primate and ground squirrel horizontal cells (see Peichl et al., 1998). Both have a horizontal cell that connects only to cones and is called H2. As in the case of the B-type horizontal cell in the cat retina, the sciurid and primate H1 cell connects to cones via its dendrites, and rods through its axon terminals, although their terminal branches are never as elaborate as the cat's. In the ground squirrel the H1 axon is sparse with terminals which match the relatively sparse population of rods (Fig. 7; Linberg et al., 1996). The H2 cell in primates (Ahnelt and Kolb, 1994; Dacey et al., 1996), and probably ground squirrel as well (Linberg et al., 1996) seems to have a particular affinity for the SWS cones. Interestingly, the H2 cell in primates appears to connect only to

cones, even along its short, curly, and sparsely branched "axon" (Kolb et al., 1980; Boycott et al., 1987; Wässle et al., 1989). On largely morphological grounds, a third type of horizontal cell (HIII) has recently been identified in human (Kolb et al., 1994) and *Cebus* retina (dos Reis et al., 2000). Whether these truly represent a physiologically separate subclass of horizontal cell remains controversial (Peichl et al., 1998) as does a proposed third type in rabbit retina (Famiglietti, 1990; Hack and Peichl, 1999).

There is physiological evidence for feedback from horizontal cells to photoreceptors. The hyperpolarization of cones by light results in a hyperpolarization of horizontal cells (i.e. sign conserving), which in turn results in a depolarization (i.e. sign inverting) of the cones. The exact nature of this feedback is not understood (for a discussion, see, Rodieck, 1998; p. 109), although there is evidence from non-mammalian species that both GABAergic and nitrogenergic mechanisms may be involved (Marc, 1992; Savchenko et al., 1997). Although searched for by many investigators, in many species, the structural correlates of this feedback synaptic action is lacking. Likewise, presumed synapses between horizontal cells and bipolar dendrites have been the subject of many studies, and yet remain elusive in most species (Dowling et al., 1966; Fisher and Boycott, 1974; Kolb, 1977). Electron microscopy has only shown definite synapses between A-type horizontal cells and bipolar cells in the rabbit retina (Fig. 8a), and only what has been termed a "rudimentary synapse" lacking vesicles in the cat retina (Fig. 8b). Prominent "desmosomal-like" junctions were identified early in primate OPL between horizontal cell and possible bipolar cell dendrites (Fig. 8c; Dowling and Boycott, 1966). Particle aggregations occur at these junctions (Raviola and Gilula, 1975) as do GluR4 and $GABA_A$ receptors (Haverkamp et al., 2000).

Are specialized neurons of the rod pathway present in cone-dominant retina?

As mentioned previously, there are a few mammalian retinas that are dominated by cones, prominently among them the ground squirrels with only 10–15% of their photoreceptors being rods (Figs. 1b, 2, 3c, d; West and Dowling, 1975; Long and Fisher, 1983). Even so, the ground squirrel photoreceptor mosaic is never free of rods (Long and Fisher, 1983; Ahnelt, 1985; Kryger et al., 1998).The rod terminals in these species are broad and "cone-like," having several invaginations with multiple synaptic ribbons, and receiving many flat as well as invaginating contacts from bipolar cells (Fig. 4a, rod; West and Dowling, 1975; Anderson and Fisher, 1976; Jacobs et al., 1976). While the ground squirrel has an identifiable scotopic system, there has to date been no exclusively rod-driven pathway identified in their retina. Indeed, in this species rods have their input into the cone system early on, because there are gap junctions between

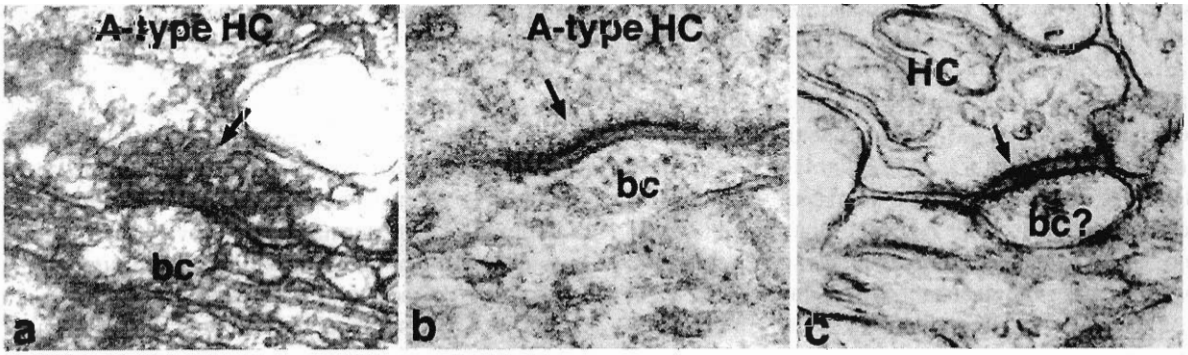


Fig. 8. Electron micrographs of various types of contacts made by horizontal cells in the OPL. (a). A conventional synapse with a presynaptic cluster of vesicles (arrow) is made by an A-type horizontal cell dendrite onto a bipolar cell dendrite (bc) in the rabbit OPL (from Fisher and Boycott, 1974). (b). A non-vesicular "synapse" (arrow) is made by an A-type horizontal cell process onto a bipolar cell dendrite (bc) in cat OPL (from Kolb 1974). A desmosome-like contact (arrow) joins horizontal (HC) and bipolar cell (bc?) dendrites in primate OPL (from Dowling and Boycott, 1966).

rods and cones (Jacobs et al., 1976), as well as an OFF- and two types of presumed ON- bipolar cells whose dendrites contact both rods and cones (West, 1978). The closest homologue to a rod bipolar cell in the ground squirrel retina is the so-called B4 bipolar because it has primarily rod input, and has its axon terminal deep the IPL, adjacent to the ganglion cells. This cell type can be immunostained with antibodies against protein kinase Cα (Greferath et al., 1990), a unique marker of rod bipolar cells in other mammals (e.g. Fig. 3g, rat retina). However, two other squirrel bipolar cell types, with exclusively cone input, also stain with this antibody (Cuenca et al., 2001). Furthermore, neither an AII nor A17 amacrine cell has been observed in Golgi impregnation or immunostaining studies of this retina (Linberg et al., 1996; Cuenca et al., 2001). The situation with horizontal cells in the ground squirrel retina is equally curious. The axon-bearing H1 (Linberg et al., 1996) with its sparse terminals spread along and sprouting from its short axon, would seem the obvious candidate for receiving rod input. However, West and Dowling (1975) found only cone input to both the dendrites and axon terminals in the Mexican ground squirrel, and Leeper and Charlton (1985) found no physiological evidence for rod input into a homologous cell type in the retina of the gray (tree) squirrel. The morphology of the axonless cell (H2, Linberg et al., 1996) suggests it to be equivalent to the axonless cells in other species, and thus purely cone driven (see Peichl et al., 1998). Thus, the rod input to horizontal cells in these retinas has not yet been identified. Overall, it seems likely that the rod photoreceptors "piggy-back" onto the cone bipolar system in the ground squirrel retina as in the rat and cat, but instead of utilizing a specialized amacrine cell (AII), the input occurs at the level of the photoreceptor terminal via rod–cone gap junctions and the specialized types of rod–cone bipolar cells. Indeed, DeVries and Baylor (1995) demonstrated in the 13-line ground squirrel that rod signals passed into cones by the gap junctions linking their terminals can be detected in OFF-center sluggish and ON–OFF direction-selective ganglion cells.

Interestingly, the GABAergic interplexiform cell which is associated with the rod pathway in both cat and primate has not yet been identified in the ground squirrel. However, the ground squirrel dopaminergic amacrine (a cell type which in some species is also clearly an interplexiform cell type) is clearly immunostained with tyrosine hydroxylase (Fig. 5e). Like the primate dopaminergic amacrine, this cell has a dendritic tree of overlapping fine dendrites in the upper IPL just beneath the amacrine cell bodies (Fig. 5c, human DA cell). Compared with the cat or primate dopamine cells, however, the rings in the dendritic plexus are not as clearly formed in the ground squirrel retina (compare Fig. 5e with Fig. 2g of cat, in Kolb et al., this volume). Moreover, ground squirrel dopamine cells are especially unusual with some very enlarged dendrites passing to the OPL where they branch and ultimately end in swellings apparently onto cone pedicles (Cuenca et al., 2001).

Neural pathways for complex feature detection such as movement and directional selectivity

The ground squirrel retina is renowned for the complex nature of its ganglion cell responses (Michael, 1968) such as responding to motion in general, and specifically to the directionality of a stimulus. Are there neural pathways in the ground squirrel retina that correlate with these complex ganglion cell properties? One type of amacrine cell, the "starburst," or "cholinergic" amacrine is thought to function in the generation of directionally selective responses in ganglion cells. The starburst amacrine cells occur as mirror-symmetric pairs across the IPL (Famiglietti, 1983; Tauchi and Masland, 1984; Masland and Tauchi, 1986); they are particularly elaborate in rabbit (Vaney, 1984; 1990) and ground squirrel retinas (Linberg et al., 1996). One type of starburst amacrine (a-type) has its cell body in the amacrine cell layer of the INL, with dendrites that stratify specifically to stratum 2 (OFF-sublamina **a**) of the IPL (Figs. 5a, b, 6d, 10). The other type, the "displaced" starburst amacrine (or b-type) has its cell body in the ganglion cell layer and dendrites that branch specifically in stratum 4 (ON-sublamina **b**) of the IPL (Figs. 5a, b, 6d, 10). The starburst cells have medium-sized receptive fields but also have tremendously overlapping dendritic trees. In the peripheral rabbit retina the dendrites from as many as 70 other cells overlap the dendritic field of

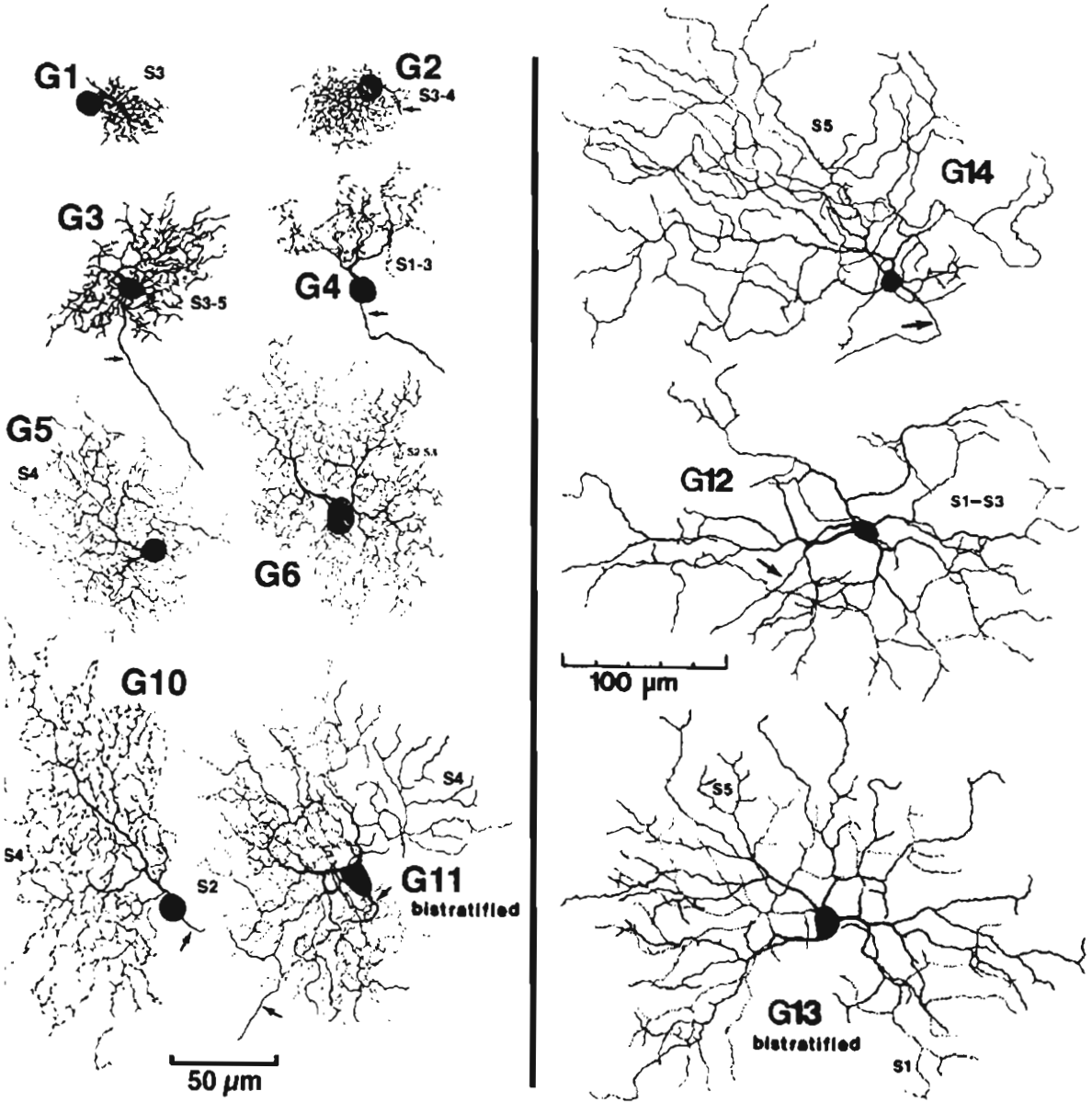


Fig. 9. Examples of several of the many types of ganglion cell in the ground squirrel retina typifies the numerous types of multi-branched and diffusely branching, bi- and tri-stratified ganglion cell seen in cone-dominated diurnal retinas (from Linberg et al., 1996).

a single labeled starburst cell (Tauchi and Masland, 1984; Vaney, 1984). Interestingly, the presence of elaborate starburst amacrines does not correlate with the proportion of cones, but rather the visual behavior of the species. These cells are especially well developed in diurnal species with visual streaks (Fig. 2), and with large populations of ganglion cells exhibiting complex responses such as ground squirrels, rabbits and turtles (Fig. 9; see Kolb et al., this volume). In nocturnal mammals, or those with foveate retinas, or ganglion cells exhibiting primarily "simple" (e.g. center-surround) properties, the starburst

amacrine cells tend to be less numerous, and more sparsely branched (Figs. 5a, 10).

The physiology of the starburst cells has been most thoroughly studied in rabbits. Both types have a center-surround organization with receptive field centers about the diameter of their dendritic fields. The a-type is an OFF-center cell giving a transient burst of small spikes when a light is turned off in the center of its field, while the b-type (displaced) cell gives an ON transient-sustained response (Bloomfield, 1992). The a-type cells receive input primarily from OFF-cone bipolars (Fig. 6d, cell B2), while ON-cone bipolars provide input to the b-type cell (Fig. 6d, cell B6). Bipolar input occurs primarily to spines on the proximal dendrites close to the cell body of both cell types. A distinctive feature of the starburst cells is the presence of beads on their distal dendrites (Fig. 10). At these sites both subtypes are presynaptic to a bistratified ON-OFF, directionally selective ganglion cell (e.g. G11 in ground squirrel, Fig. 9; Amthor et al., 1984; 1989; Famiglietti, 1987; 1991; Tauchi and Masland, 1984; Vaney, 1990; 1994; Vaney and Pow, 2000), while the b-type cell is presynaptic to an monostratified ON-directionally selective ganglion cell (such as G14 in ground squirrel, Fig. 9.; Famiglietti, 1991). Starburst cells themselves are not directionally selective, and, interestingly, removal of the displaced b-type in the ganglion cell layer does not change the response characteristics of the directionally selective cell to which they provide synaptic input (He and Masland, 1997).

Another amacrine cell type found exclusively in these retinas with visual streaks and complex ganglion cell receptive field properties is the "DAPI3" cell (Wright et al., 1997). This is a striking, small-field bistratified amacrine cell in ground squirrel (A4, Linberg et al., 1996), and rabbit. It is known to be glycinergic (Wright et al., 1997; Zucker and Ehinger, this volume). The DAPI3 cell's dendrites branch in strata 2 and 4, the same as those of the cholinergic amacrines and the ON–OFF directionally selective ganglion cells (Figs. 6d, 10c, DAPI/A4 cell in ground squirrel). A bistratified bipolar cell (B8, Linberg et al., 1996) has its axonal endings in these same two strata. Although the essential demonstration of contacts between these cells has not been done, it seems likely that the bistratified bipolar, the starburst cells, and the DAPI3 amacrine cell all participate in forming the receptive field properties of the bistratified ganglion cell.

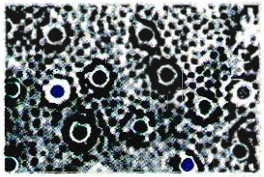
The foveal pathways of primates

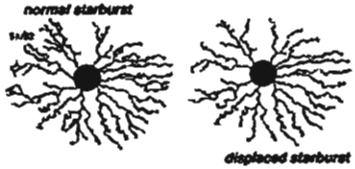
The fovea is a specialized area of retina that perhaps represents the ultimate in diurnal retinal design by excluding rods and rod pathway neurons completely. There are no rod photoreceptors, rod bipolar cells, nor AII amacrine cells within the central 5° of the primate retina (encompassing a diameter of about 0.8 to 1 mm around the point of visual fixation, i.e. the center of the fovea) (Kolb and Zhang, 1997; Kolb et al., 2000). The cone pathways within this region of the retina have the least convergence and represent the greatest resolving capabilities (i.e. highest visual acuity) of all visual systems except those of birds of prey. This is accomplished by the so-called "midget pathways." For comparison, the cone-dominated ground squirrel retina, never achieves a photoreceptor population purely composed of cones, the center of the visual streak having approximately 5% rods (Long and Fisher, 1983; Kryger et al., 1998).

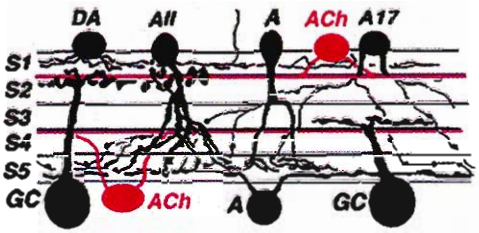
The midget pathways: high acuity and "red–green" color information

Within the fovea, small bipolar cells form a "private line" from a single cone to a single ganglion cell, and hence were given the name "midget" (Polyak, 1941). The midget ganglion cells are also known as "P cells" because they project to individual cells in the parvocellular layer of the lateral geniculate nucleus (Shapley and Perry, 1986). The midget pathway is also organized into ON- and OFF-center channels as described earlier for the "diffuse" cone pathways from peripheral retina. As such, every cone in the fovea will contact one ON- and one OFF-bipolar cell. Thus, the invaginating midget bipolar cells as part of the ON pathway connect to the dendrites of an ON-center midget ganglion cell in sublamina **b** of the IPL, while the flat midget bipolar cells as part of the OFF pathway connect to dendrites of an OFF-center midget ganglion cell in sublamina **a** (Fig. 10b, MGCa, MGCb). Because a single midget bipolar–ganglion cell circuit receives input

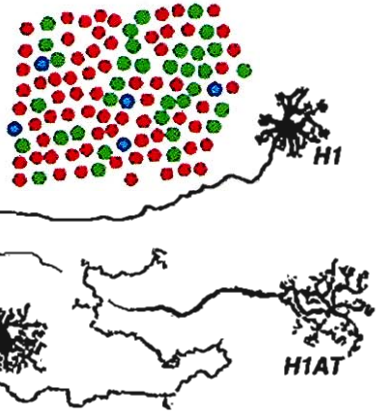
nocturnal retinas
rat, cat

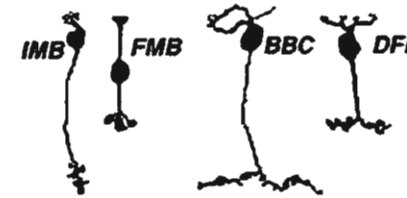


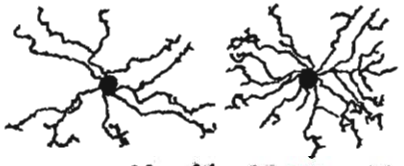


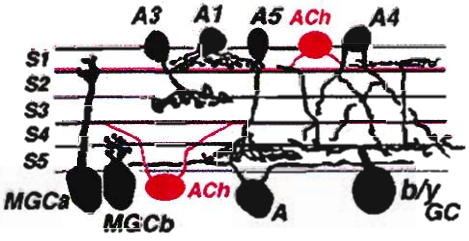


Trichromatic foveal retina
primate, man

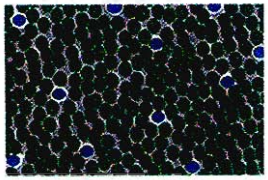


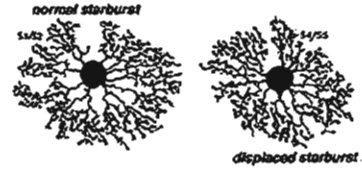






diurnal retinas
ground squirrel





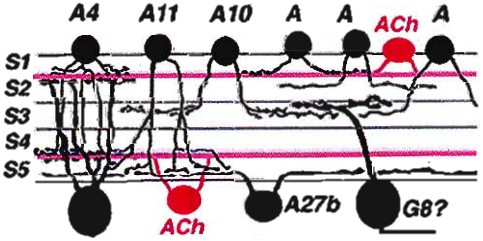


Fig. 10. Three columns summarize the three types of retina discussed in this chapter: diurnal, nocturnal, and primate foveal. The upper panel in each column depicts the photoreceptor mosaics typical for each retinal type. The middle portion of each column contains golgi-stained examples of major neurons in each type of retina, while the lowermost portion of each column recapitulates the neural circuitry central to each retinal type. (a) The nocturnal retina, exemplified here by cat and rat retinas, are populated largely by rods that separate the small population of green cones and even smaller number of blue cones from one another. The rod-connecting, axon-bearing B-type horizontal cell is well developed and its profusely branching axon terminal connects with thousands of rod terminals. The rat lacks the axonless A-type horizontal cell. The uniquely mammalian rod bipolar cell (RB) comprises almost 90% of all bipolar cell types, although several types of cone bipolar (B2, B3, B7) have been identified. The two varieties of starburst amacrine cell are similar to but less elaborate than seen in ground squirrel or rabbit. The two rod-associated amacrine cell types (AII, A17) figure prominently in the circuitry of this retinal type, being the main channel by which rod signals are shunted to the cone pathways and thence to higher visual centers. Nocturnal retinas have fewer varieties of complex ganglion cells; instead the alpha and beta types predominate. (b) The trichromatic foveal retina seen in some primates and humans is essentially rod-free and contains red, green, and some blue cones. At least two types of axon-bearing horizontal cell (B-type, H1, H2) are present, but no axonless type (A-type) has been found. Two types of midget bipolar cells predominate at the fovea (IMB, FMB) although other cone bipolar cell types have been described including several diffuse types (DFB) and a blue cone bipolar cell (BBC). Rod bipolar cells are lacking in the rod-free foveal center. The two types of starburst amacrine cell are sparsely branched, very unadorned and generally not very well developed. The rod associated amacrines AII and A17 do not participate in the foveal circuitry where smaller cone-connecting amacrine cells are seen (A1, A3, A4, A5). The ganglion cell population in the fovea is dominated by the ON- and OFF-midget ganglion cells (MGCa, MGCb) with a small but prominent population of the bistratified blue-ON yellow-OFF ganglion cells (b/y GC). (c) The diurnal retina is exemplified by the ground squirrel retina whose retinal mosaic consists of mostly green cones, a smaller population of blue cones and some rods (not shown). Diurnal retinas have well-developed cone-contacting horizontal cells, including the axonless A types (H2) and axon-bearing horizontal cells (H1) with sparsely branching axon terminals. A number of cone bipolar cells are seen (B1, B2, B3, B5, B6), most having small dendritic fields and non-convergent axon terminals monostratified to various specific strata of the IPL. The two starburst amacrine cell varieties are very elaborate, well developed and numerous. Many amacrine and ganglion cell types are typical of diurnal retinas and their many processes and types of synaptic interactions are reflected in the very thick IPL seen in these retinas.

from a single cone, it is *de facto* also connected in a spectrally specific manner so that each midget bipolar may receive its input from a SWS-, MWS-, or LWS-cone (Fig. 10b). Whether or not midget ganglion cells receive their input from the midget bipolars in a way that makes them spatially and spectrally opponent (Gouras, 1968) is still controversial. For example, a midget ganglion cell that had a center response to long-wavelength stimuli ("red") would have a surround that responded to mid-wavelength stimuli (green). Although not well studied, the more accepted scheme for the organization of such wavelength comparisons by the midget ganglion cells seems to be one in which the cell does not respond to wavelength in a center-surround manner, but would respond antagonistically across its whole field to the presence of "red" or "green" light (see Rodieck, 1998, Ch. 14 for a discussion). Regardless of the exact organization of their receptive fields, it is clear that the midget system carries relatively pure opponent information from the LWS and MWS cones into the brain.

A special pathway for "blue–yellow" color information

The pathway for SWS (blue sensitive) cones is very different from that of the LWS and MWS cones. The SWS cones are absent from the very central 1° of the foveal pit (Williams et al., 1981) but they reach a maximum density on the foveal slope. The synaptic pedicles of these cones have a "simpler morphology" than those of the other two cone types, and lack telodendria (Ahnelt et al., 1987; Kolb et al., 1997). The SWS system has a lower spatial and temporal resolution than those of the other two (Stockman et al., 1991; Humanski and Wilson, 1992). The SWS-cone is contacted by its own subtype of bipolar (Mariani, 1984; Kouyama and Marshak, 1992), which is presumed to be an ON-type since its contacts with the cone are mostly invaginating and ribbon related. The axon of the S-cone bipolar cell ends in the lowermost IPL (ON layer; Fig. 10b, BBC). Its dendrites mostly project to a single SWS cone but occasionally it reaches out to contact another cone of the same type (Mariani, 1984; Kouyama and Marshak, 1992). The S-cone bipolar carries ON signals to the lower dendrites of the blue-ON–yellow-OFF bistratified ganglion cell (Dacey and Lee, 1994). It is thought that the yellow-OFF response arises from an OFF-diffuse bipolar that contacts primarily the LWS- and MWS-cones with some input from the SWS cones. This bipolar cell would synapse onto the upper dendrites of the bistratified ganglion cell, in the OFF layer of the IPL (Fig. 10b; Dacey and Lee, 1994). As in the case of the other two-wavelength-sensitive systems, it is still unknown if the bistratified ganglion cell represents the sole input into the blue–yellow opponent system. Early electrophysiological investigations of monkey retinal ganglion cells indicated that this information was carried primarily by a SWS cone ON center ganglion cell type with a much larger receptive field than is typical of those in the LWS or MWS systems. This ganglion cell also did not appear to have a spatially antagonistic receptive field structure, but the "blue" and "yellow" opponent responses co-existed within the field. Interestingly, there is no conclusive recording from a "blue-OFF–yellow-ON" type of ganglion cell. The apparent specialized nature of the blue-yellow color system is emphasized by the fact that its ganglion cells are thought to project to a special layer of the lateral geniculate nucleus called the koniocellular (or K) layer (Irvin et al., 1993; Calkins et al., 1998; Calkins and Sterling, 1999).

Other foveal neurons

In the retina of fish and other lower vertebrates it seems fairly clear that horizontal cells are involved in constructing the center/surround organization and that these are specifically connected to the different spectrally sensitive classes of cone (Naka, 1976). There is physiological evidence that horizontal cells in mammalian retina do not function in a similar manner (Dacey et al., 1996). In and near the primate fovea, both horizontal cell types are numerous and closely packed. Interestingly, the rod-connecting axons of human H1 cells project away from the center of the rod-free fovea towards the region where rods first appear, thus avoiding the pure-cone foveal center. Foveal H2 (pure cone-input) cells are small, "bushy," and densely concentrated, reflecting the

large density of cones (Fig. 10b). The many varieties of small field amacrine cells are crowded at the fovea (Fig. 10b: A1, A3, A4, A5). Dopamine amacrine cells and starburst amacrine cells are scantily branched, concentrically organized around the fovea, and altogether poorly developed (Fig. 10b). The AII and A17 amacrine cells, with their clearly defined role in the rod pathway are excluded altogether and thus the midget ganglion cells of the fovea carry no signals originating from rods. Other types of ganglion cell, like the large-field phasic M cells (Shapley and Perry, 1986) are present at the fovea but are very small and scantily branched, whereas in comparison, the midget ganglion cells are stacked 8 cell bodies deep and have a great overlap in their dendritic fields. The greatly thickened inner plexiform layer in the fovea reflects the density of the various types of amacrine and ganglion cells in this region.

Summary and future directions

Figure 10 summarizes the characteristic neuronal types in the model retinal systems discussed here: the rod-dominated retinas of largely nocturnal species such as cat; the highly specialized, pure-cone region of the primate fovea; and the cone-dominated retina of the highly diurnal ground squirrel.

The retina of the cat as well as those of other rod-dominated species is characterized by a huge number of rod photoreceptors and convergent neurons for pooling rod signals. The latter are exemplified by horizontal cells with elaborate axon terminals that receive only rod input, a single type of ON rod bipolar cell forming 90% of the bipolar cell population, and the most well developed AII and A17 amacrine cells of any species studied to date. Amacrine cells associated with directional sensitivity (cholinergic starburst cells) are present, but meager, and ganglion cells tend to be of the "simple" center-surround type with large dendritic trees (Fig. 10a).

Understanding retinal circuitry in terms of visual behavior continues to be one of the greatest challenges facing vision scientists. Probably nowhere is this challenge more important than understanding pathways in the human fovea because of our reliance on high acuity vision and color information, and the number of people afflicted with diseases that effect macular vision. The center of the fovea has evolved a system of single, "private" pathways enabling every cone to send their signals to midget ganglion cells that carry information into the brain about acuity and red-green color opponency. Here cone bipolar cells are closely packed and horizontal cells have very small fields with both types interconnecting only a minimum number of cones. Outside the very center, but within the fovea, the SWS-cones are at their highest density as are the unique "blue" cone bipolar cells. Amacrine cells are small-field, and the ganglion cells are almost entirely of the midget types, with the exception being the so-called "blue-yellow" bistratified cell. Cholinergic systems and wide-field amacrine cells are poorly developed (Fig. 10b).

The cone-dominated retinas of diurnal squirrels (and rod-dominated species such as rabbits with a visual streak) tend to have retinas that do much processing of visual information before sending it on to the brain. Cone-devoted bipolar cell types are numerous, as are small-field multistratified amacrine and ganglion cells. Although dominated by cones, these retinas, like those of other non-primate mammals, are dichromatic and the retina seems to be specialized for contrasting opponent color information, detecting movement, and directionality. They have a highly developed cholinergic/starburst and DAPI amacrine cell systems. Rod pathway neurons are ill-developed, or, in some cases, absent (Fig. 10c).

There are many questions remaining about retinal circuitry, and much yet to be learned from studying the retinas of different species. Many questions remain about the functional role of the myriad types of amacrine cell that seem to exist in virtually every species. Is there a specialized OFF-rod bipolar pathway, or a "blue-OFF" pathway homologous to the "blue-ON" pathway? A glance at Fig. 9 shows many morphologically complex ganglion cells about which we know nothing in terms of circuitry or functionality. Whether or not there is a ganglion cell pathway for "red-green" color vision similar to that for the "blue-yellow" system as an alternative to the color-opponent midget system in primates is a hotly debated topic (Rodieck, 1998; Dacey, 2000). While we have learned a tremendous amount about retinal circuitry since the pioneering studies

of Dowling et al. (Dowling and Boycott, 1966; Dowling et al., 1966; Boycott and Dowling, 1969; Werblin and Dowling, 1969) there is still much work to be done utilizing comparative morphological and physiological techniques.

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