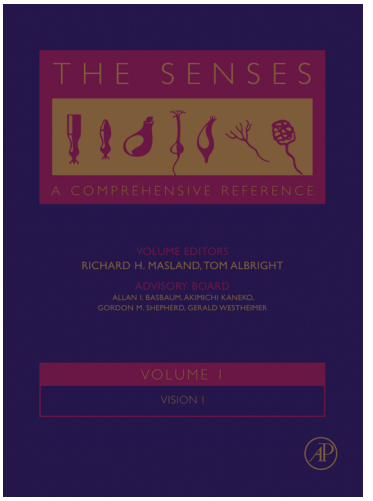

H Wässle, Decomposing a Cone's Output (Parallel Processing). In: Allan I. Basbaum, Akimichi Kaneko, Gordon M. Shepherd and Gerald Westheimer, editors The Senses: A Comprehensive Reference, Vol 1, Vision I, Richard Masland and Thomas D. Albright. San Diego: Academic Press; 2008. p. 313-340.

1.12 Decomposing a Cone's Output (Parallel Processing)

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1.12.1 Introduction

It is well established that visual signals in the brain are processed in parallel, with contours, color, movement, stereopsis, and even more specific features such as facial expressions being processed in different brain areas (Casagrande, V. A. and Xu, X., 2004). The visual pathway from the eye to the brain is also organized into parallel streams, and fiber groups of the optic tract project to different subcortical areas such as the suprachiasmatic nucleus, the ventral and lateral geniculate complex, the pretectum, the superior colliculus, and the accessory optic nuclei. These brain areas have different roles in visual function and accordingly receive inputs from retinal ganglion cells (RGCs) which perfectly subserve such specific roles. For example, the suprachiasmatic nucleus, which regulates circadian rhythms, or the pretectum, which adjusts the pupil size, receive inputs from the recently discovered melanopsin-containing ganglion cells. They have intrinsic light responses in their dendrites and transmit a sustained light signal (Berson, D. M., 2003). Parallel routes can also be distinguished in the visual pathway that is commonly attributed to conscious vision, namely the projection from the eye through the lateral geniculate nucleus (LGN) to the visual cortex. Here, in primates, the parvocellular and magnocellular pathways are well established, and a third parallel tract is relayed in the intralaminar regions, the K-layers, of the geniculate (Hendry, S. H. and Reid, C., 2000).

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Considerable processing and filtering of visual information occurs at the earliest stage of the mammalian visual system – the retina. In any mammalian retina there may well exist as many as 15 different ganglion cell types which cover the retina homogeneously with their dendritic fields. They represent 15 specific filters which encode in parallel different aspects of the image projected onto the retina. Ganglion cells receive specific inputs from bipolar and amacrine cells in the inner plexiform layer (IPL). The IPL is precisely stratified and the different ganglion cell types have their dendrites at specific levels within the IPL (Isayama, T. *et al.*, 2000; Sun, W. *et al.*, 2002; Dacey, D. M. *et al.*, 2003; Kong, J. H. *et al.*, 2005; Kim, T. J. and Jeon, C. J., 2006). The axons of bipolar cells, which transfer the light signals from the photoreceptors to the ganglion cells also terminate at distinct levels within the IPL (Ghosh, K. K. *et al.*, 2004). This suggests that the neurally encoded retinal image is different at different levels of the IPL, depending upon stratification of the various bipolar, amacrine, and ganglion cells (Roska, B. and Werblin, F., 2001). Bipolar cells provide the major excitatory drive for ganglion cells and their physiological signature, for instance OFF- or ON-light responses, is transferred onto ganglion cells. The physiological signature of bipolar cells in turn is defined by the glutamate receptors (GluRs) they express at their synaptic contacts with the cones. Parallel processing within the retina, therefore, begins already at the first synapse of the retina and here the molecular composition of GluRs represents the origin of the different channels (Wässle, H., 2004).

1.12.2 The Photoreceptor Synapse

1.12.2.1 The Presynaptic Complex

Cones respond to a light stimulus with a graded hyperpolarization and release their transmitter glutamate at a specialized synaptic terminal named cone pedicle. Transmitter release is high in darkness and is reduced by illumination of the cone. The cone pedicle is a giant synapse with multiple release sites and numerous postsynaptic partners (Figure 1). In the primate retina the cone pedicle increases from a diameter of approximately 4–5 µm close to the fovea to 8 µm diameter in peripheral retina. It contains between 20 and 50 presynaptic ribbons (Figures 1(c) and 1(e)), each of which is flanked by synaptic vesicles (Haverkamp, S. *et al.*, 2000; 2001). The synaptic terminal of rod photoreceptors, the rod spherule is smaller than the cone pedicle (~3 µm diameter) and contains one or two synaptic ribbons and release sites. The photoreceptor synaptic ribbon is a curved plate, ~30 nm thick, it extends ~200 nm into the cytoplasm and varies in length from 200 to 1000 nm. In rod spherules it is bent like a horseshoe (Figure 1(e)) and commonly cracks into two parts (Migdale, K. *et al.*, 2003). The ribbons are involved with the synaptic machinery of transmitter release and appear to represent a specialization of synapses, which have a sustained release of glutamate such as photoreceptors, bipolar cells, and auditory and vestibular hair cells (von Gersdorff, H., 2001; Heidelberger, R. *et al.*, 2005; Sterling, P. and Matthews, G., 2005). Proteins at the ribbon are just beginning to be identified and represent a specialization of the cytomatrix comparable and complementary to proteins present at the active zones of conventional synapses (tom Dieck, S. *et al.*, 2005; Deguchi-Tawarada, M. *et al.*, 2006). The proteins segregate into two compartments at the ribbon: a ribbon associated compartment including Piccolo, RIBEYE, CtBP1, RIM1, and the motor protein KIF3A, and an active zone compartment including RIM2, Munc 13-1, CAST1, and a calcium (Ca^{2+})-channel α1 subunit (Figure 1(b)). A direct interaction between the ribbon specific protein RIBEYE and bassoon seems to link the two compartments and is responsible for the integrity of the photoreceptor ribbon complex. In bassoon knockout mice the ribbons are no longer linked to the active zone and transmitter release is not possible (Dick, O. *et al.*, 2003). Fish deficient in RIBEYE lack an optokinetic response and have shorter synaptic ribbons in photoreceptors (Wan, L. *et al.*, 2005). The ribbons tether numerous synaptic vesicles (Usukura, J. and Yamada, E., 1987) and it has been suggested that they represent a conveyor belt transporting continuously synaptic vesicles toward the active zone (Gray, E. G. and Pease, H. L., 1971; Muresan, V. *et al.*, 1999). However, this is an oversimplification, because disruption of the actin cytoskeleton did not influence transmitter release (Heidelberger, R. *et al.*, 2002; Holt, M. *et al.*, 2004; Heidelberger, R. *et al.*, 2005). Ribbons, however, might serve as a platform along which vesicles can be primed for sustained release. Vesicles docked at the active zone probably represent the fast releasable pool. It has been estimated that a ribbon of a cone in the primate fovea has ~40 docking sites close to the active zone and 150 vesicles are packed along the ribbon (Sterling, P. and Matthews, G., 2005). The vesicles of all cones and of rods are loaded with glutamate through the vesicular glutamate transporter vGluT1 (Haverkamp, S.

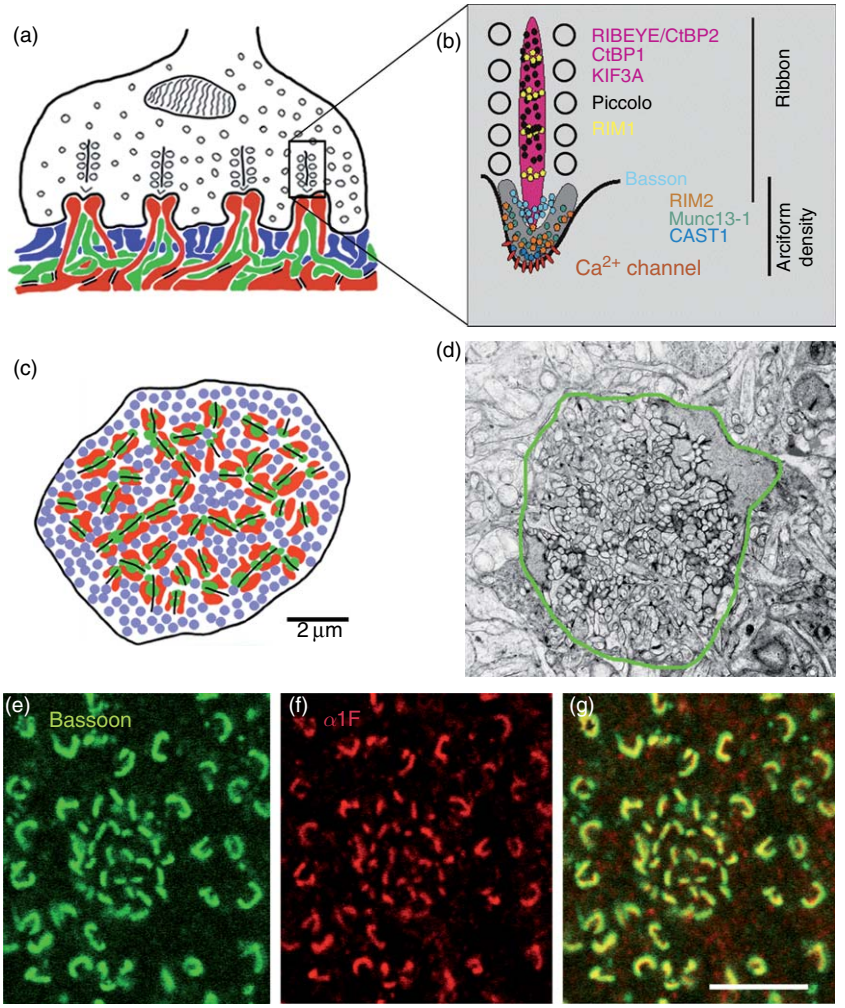


Figure 1 Structure of the cone pedicle, the synaptic terminal of cones. (a) Schematic vertical view of a cone pedicle. Four presynaptic ribbons are apposed to the invaginating dendrites of horizontal cells (red) and ON-cone bipolar cells (green). OFF-cone bipolar cell dendrites form contacts at the cone pedicle base (blue). (b) The presynaptic compartment is made up of the ribbon, the vesicles, and the arciform density. Adapted from tom Dieck, S., Altrock, W. D., Kessels, M. M., Qualmann, B., Regus, H., Brauner, D., Fejtova, A., Bracko, O., Gundelfinger, E. D., and Brandstätter, J. H. 2005. Molecular dissection of the photoreceptor ribbon synapse: physical interaction of Bassoon and RIBEYE is essential for the assembly of the ribbon complex. J. Cell Biol. 168, 825–836. The following proteins are associated with the ribbon: RIBEYE (Schmitz, F. *et al.*, 2000); CtBP1,2; KIF3A (Muresan, V. *et al.*, 1999); Piccolo; RIM1. The following proteins are associated with the arciform density: Bassoon; RIM2; Munc 13-1; CAST. The Ca^{2+} channels are inserted into the presynaptic membrane (Morgans, C. W. *et al.*, 2005). (c) Schematic horizontal view of a macaque monkey (primate) cone pedicle base. Ribbons (black lines), horizontal cell processes (red), and ON-cone bipolar cell dendrites (green) form a total of 40 triads. Numerous contacts of OFF-cone bipolar cells (blue) are found throughout the pedicle base. (d) Electron micrograph of a horizontal section taken underneath a primate cone pedicle (green outline). More than 500 individual processes contact this cone pedicle. (e–g) Fluorescence micrographs of a primate cone pedicle (center) surrounded by rod spherules, double labeled for bassoon (e) and the Ca^{2+} channel subunit α1F (f). Bassoon immunolabeling decorates the ribbons of the cone pedicle and the rod spherules (horseshoe-shaped). The superposition of (e) and (f) in (g) shows that the Ca^{2+} channels are in close vicinity of the synaptic ribbons. Scale bar = 5 µm.

et al., 2003; Johnson, J. *et al.*, 2003; Sherry, D. M. *et al.*, 2003). A subpopulation of approximately 10% of cones expresses vGluT2 in addition to vGluT1 (Fyk-Kolodziej, B. *et al.*, 2004; Wässle, H. *et al.*, 2006).

Exocytosis of the vesicles is finally triggered by voltage-gated Ca^{2+} channels clustered at the active zone. Immunostaining for the α1D and α1F subunits of L-type Ca^{2+} channels and Ca^{2+} entry have

been observed along the base of the ribbon (Figures 1(e)–1(g); Morgans, C. W., 2001; Wässle, H. *et al.*, 2003; Zenisek, D. *et al.*, 2003; 2004; tom Dieck, S. *et al.*, 2005). Mutations in the Ca^{2+} channel α1F result in impairment of the photoreceptor synaptic transmission and cause congenitory stationary nightblindness (Morgans, C. W. *et al.*, 2005). Ca^{2+} extrusion from the photoreceptor synaptic complex is mediated through the plasma membrane calcium ATPase (PMCA) localized along the sides of cone pedicles and rod spherules (Morgans, C. W. *et al.*, 1998; Duncan, J. L. *et al.*, 2006).

The potassium (K^+-) and Ca^{2+}-channels of cone pedicles and rod spherules can be modulated by several mechanisms which in turn also regulate the transmitter release. The metabotropic glutamate receptor 8 (mGluR8) at the photoreceptor synaptic terminals, acts as autoreceptor and upon glutamate binding the influx of Ca^{2+} is reduced (Koulen, P. *et al.*, 1999; 2005). Modulation of the voltage dependent Ca^{2+}-channels at the active zone is also a mechanism of horizontal cell feed back and will be discussed later. Cannabinoid receptors at cone pedicles regulate voltage-dependent K^+ currents (Struik, M. L. *et al.*, 2006). Finally, calcium extrusion modulates the amplitude and timing of transmission in cone pedicles and rod spherules (Duncan, J. L. *et al.*, 2006).

L- and M-cone pedicles are coupled to their immediate neighbors and to rod spherules through electrical synapses (gap junctions; Raviola, E. and Gilula, N. B., 1973) where connexin 36 is expressed. S-cone pedicles are only sparsely coupled (Tsukamoto, Y. *et al.*, 2001; Feigenspan, A. *et al.*, 2004; Hornstein, E. P. *et al.*, 2004; Li, W. and DeVries, H., 2004, O'Brien, J. J. *et al.*, 2004). This coupling allows the network to average out the uncorrelated noise in individual cones, and thereby to improve the response to a light stimulus (Lamb, T. D. and Simon, E. J., 1976). It also provides a route for the signal transfer from rod spherules to cone pedicles (see Mammalian Rod Pathways and Circuit Functions of Gap Junctions in the Mammalian Retina).

1.12.2.2 The Postsynaptic Partners

At the synaptic terminals of rods and cones, the light-evoked signals are transferred onto bipolar and horizontal cells (Figure 1(a)). Horizontal cells, of which there are between one and three types in mammalian retinas, provide lateral interactions in the outer plexiform layer (OPL). In the primate retina they are named H1 and H2 horizontal cells. Their dendritic tips are inserted into invaginations of the cone pedicle base which are formed at the ribbons. Two horizontal cell endings push up towards the ribbon and along the ribbon the two horizontal cells form a zone of contact between each other (Raviola, E. and Gilula, N. B., 1975).

Two kinds of bipolar cell contacts have been identified at cone pedicles: flat or basal contacts and invaginating contacts (Dowling, J. E. and Boycott, B. B., 1966). The dendritic tips of invaginating bipolar cells are inserted in between the two lateral horizontal cell dendrites, and this postsynaptic unit has been named a triad (Missotten, L., 1965). The dendritic tips of flat bipolar cells make numerous contacts at the cone pedicle base (Figures 1(a) and 1(c)).

Cone pedicles of the peripheral primate retina contain ~40 synaptic ribbons and invaginations, where they accommodate ~80 horizontal cell dendritic terminals (Figure 1(c)). L (red)- and M (green)-cones are connected to three or four H1 horizontal cells and make multiple contacts with every one of them. S (blue)-cones have only sparse, if any connections with H1 horizontal cells. L- and M-cones are also connected to three or four H2 horizontal cells, however, the number of contacts is smaller than with H1 cells. In contrast, S-cones have multiple contacts with H2 cells (Ahnelt, P. and Kolb, H., 1994). Cone pedicles of the peripheral primate retina accommodate ~80 dendritic tips of invaginating bipolar cells (Chun, M. H. *et al.*, 1996) and they are engaged in 200–300 flat contacts. Taken together, 400–500 synaptic contacts are found at individual cone pedicles (Figure 1(d)). Their details will be discussed later.

1.12.2.3 Feedback from Horizontal Cells

Horizontal cell dendrites are inserted as lateral elements into the invaginating contacts of cone pedicles (Figure 1(a)), and horizontal cell axon terminals form the lateral elements within rod spherules. Traditionally, it is assumed that horizontal cells release the inhibitory transmitter gamma-aminobutyric acid (GABA) and provide feedback inhibition at the photoreceptor synaptic terminal. As horizontal cells summate light signals from several cones, such feedback would cause lateral inhibition, through which a cone's light response is reduced by the illumination of neighboring cones. This mechanism is thought to enhance the response to the edges of visual stimuli and to reduce the response to areas of uniform brightness. However, the GABA-feedback model has recently been challenged because of the

lack of classical synapses from horizontal cells onto cones, the lack of GABA receptors on mammalian cones and the lack of GABA uptake into horizontal cells from the medium. Two alternative hypotheses of horizontal cell function have been proposed. One assumes that horizontal cell processes, which are inserted into cone pedicles and rod spherules, express connexins (hemigap junctions). Current that flows through the channels formed by the connexins changes the extracellular potential in the invaginations and thus shifts the activation curves of the cone pedicle Ca^{2+} channels. By this mechanism of electrical feedback, horizontal cells could modulate the glutamate release from cones and rods (Kamermans, M. *et al.*, 2001). The second hypothesis also postulates modulation of the Ca^{2+} channels that regulate the release of glutamate from cones; however, the mechanism responsible is a change in pH within the invagination, caused by voltage-dependent ion transport through the horizontal cell membrane (Hirasawa, H. and Kaneko, A., 2003). There is also evidence that light-dependent release of GABA from horizontal cells provides feed-forward inhibition of bipolar cell dendrites (Haverkamp, S. *et al.*, 2000; Duebel, J. *et al.*, 2006). Irrespective of their precise mode of action, horizontal cells sum light responses across a broad region, and subtract it from the local signal. Because horizontal cells are coupled through gap junctions (see Circuit Functions of Gap Junctions in the Mammalian Retina), their receptive fields can be much wider than their dendritic fields (Hombach, S. *et al.*, 2004).

1.12.3 Morphological Types of Bipolar Cells

Bipolar cells of the mammalian retina can be subdivided according to their morphology into many different types (Figure 2). Cajal S. R. Y. (1893) recognized rod bipolar (RB) cells as a separate type (Figure 2: RB). Their dendrites make invaginating contacts with rod spherules and their axons terminate in the innermost part of the IPL (see Mammalian Rod Pathways). Several types of cone bipolar cells have been recognized in different mammalian species. In the rabbit retina 13 types have been described from Golgi staining and single cell filling (Famiglietti, E. V., 1981; McGillem, G. S. and Dacheux, R. F., 2001; MacNeil, M. A. *et al.*, 2004). In the cat retina 8–10 different types of cone bipolar cells have been recognized (Famiglietti, E. V., 1981; Kolb, H. *et al.*, 1981; Cohen, E. D. and Sterling, P., 1990a; 1990b). In the ground squirrel seven different types have been described (West, R. W., 1976).

The diagram in Figure 2 compares the bipolar cells of the mouse and rat retinas with those of the peripheral macaque monkey retina. The nine putative cone bipolar cell types (labeled 1–9) and the RB cells of the mouse and rat retina are arranged according to the stratification level of their axon terminals in the IPL. The cells were drawn from vertical sections following intracellular injections (Euler, T. and Wässle, H., 1995; Hartveit, E., 1996; Ghosh, K. K. *et al.*, 2004; Pignatelli, V. and Strettoi, E., 2004). Immunocytochemical markers have been found for five bipolar cell types of the mouse retina (Haverkamp, S. *et al.*, 2003; illustrated in Figure 3). The type 7 and type 9 bipolar cells of the mouse retina have also been labeled in transgenic mouse lines by the expression of green fluorescent protein (GFP; Huang, L. *et al.*, 2003; Haverkamp, S. *et al.*, 2005). The cone contacts of the nine bipolar cell types of mouse and rat have not yet been analyzed in detail, however, they contact between five and 10 neighboring cone pedicles with one exception: type 9 has a wide dendritic tree that appears to be cone selective and it will be shown later that it contacts S-cones.

Rat and mouse retinas are considered to be rod dominated because only 1% of their photoreceptors are cones (Szél, A. *et al.*, 1993). However, the perspective changes if one examines the absolute number of cones. The cone density is between 8000 and 10 000 cones mm^{-2}, comparable to midperipheral cat, rabbit, and monkey retina. Consequently the types and retinal distributions of cone bipolar cells are closely similar between mammalian species. The bipolar cells of the monkey retina, shown schematically in Figure 2, where determined initially from Golgi stained whole mounts (Boycott, B. B. and Wässle, H., 1991). There is a striking similarity between mouse, rat, and monkey bipolar cells with respect to the shapes and stratification levels of their axons, however, there is also a clear difference; midget bipolar cells (flat midget bipolar, FMB; invaginating midget bipolar, IMB) are only found in the monkey retina. FMB and IMB cells have dendritic trees which contact a single cone (Polyak, S. L., 1941; Figure 2 and Figure 4(a)). Following the nomenclature of Polyak S. L. (1941), bipolar cells contacting several neighboring cone pedicles were named diffuse bipolar cells (DB1–DB6; Boycott, B. B. and Wässle, H. 1991; Figures 2 and 4(c)).

In summary these studies suggest that there are about 10 types of cone bipolar cells in the mammalian

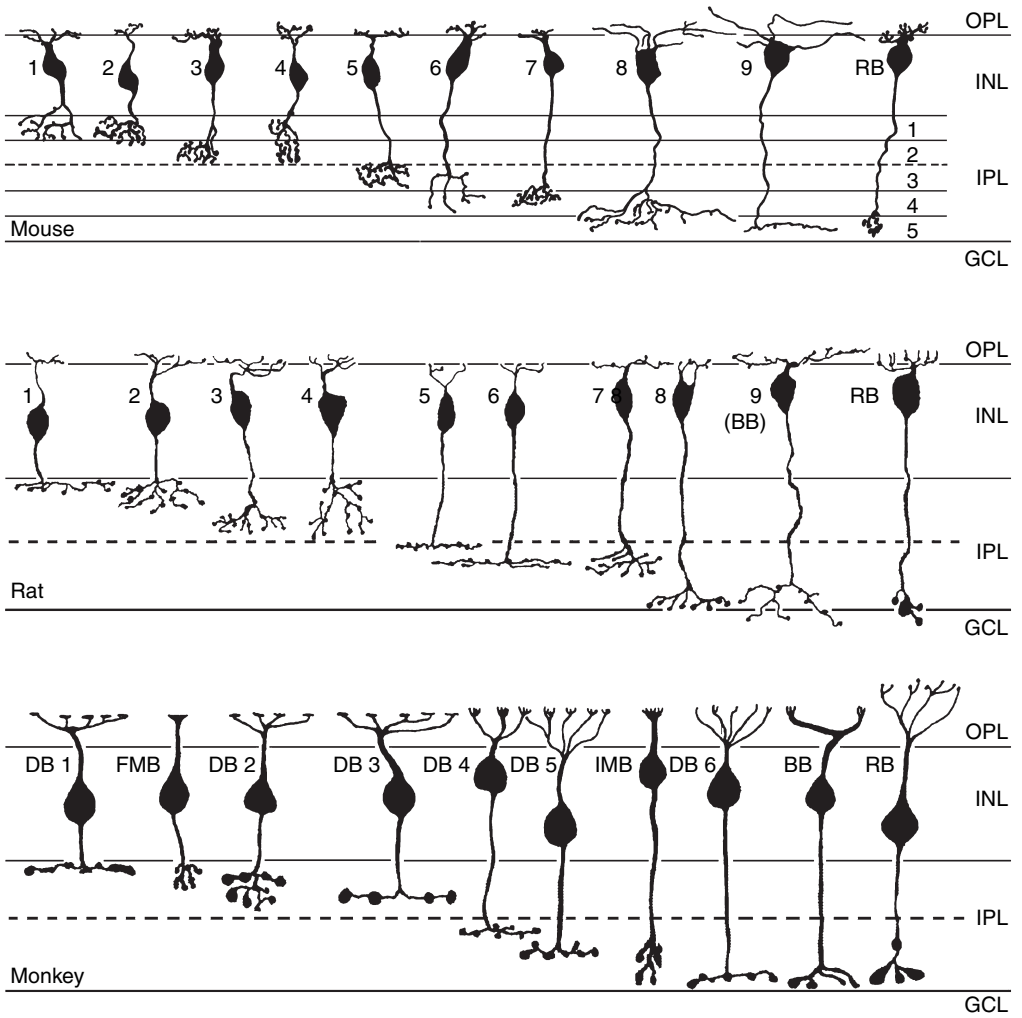


Figure 2 Schematic diagrams of bipolar cells of mouse, rat, and primate retina (Ghosh, K. K. *et al.*, 2004). The retinal layers are indicated (OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; it can be subdivided into five sublaminas of equal width; GCL, ganglion cell layer). The bipolar cell types were named according to the level of stratification of their axon terminals in the IPL. The dashed horizontal lines dividing the IPL represent the border between the OFF- (upper) and the ON- (lower) sublayers. Bipolar cells with axons terminating above this line represent OFF bipolar cells, those with axons terminating below this line represent ON bipolar cells (DB, diffuse bipolar cells; FMB, flat midget bipolar cells; IMB, invaginating midget bipolar cells; BB, blue-cone bipolar cells; RB, rod bipolar cells).

retina and their major defining features are the shape and stratification of their axons in the IPL and in some instances their cone contacts in the OPL (Hopkins, J. M. and Boycott, B. B., 1996; 1997). The major functional subdivision of bipolar cells is into ON- and OFF-bipolar cells. ON-bipolar cells are depolarized by a light stimulus, OFF-bipolar cells are hyperpolarized by a light stimulus (Werblin, R. S. and Dowling, J. E., 1969; Kaneko, A., 1970). Their axons terminate at different levels (strata) within the IPL: OFF in the outer half, ON in the inner half (Euler, T. *et al.*, 1996; Hartveit, E., 1996; Euler, T. and Masland, R. H., 2000; Berntson, A. and Taylor, W. R., 2000). Superimposed on this ON/OFF dichotomy are four types of OFF and five types of ON-cone bipolar cells. We are just beginning to understand their functional roles (Freed, M. A., 2000).

1.12.3.1 Midget Bipolar Cells of the Primate Retina

Before discussing the function of midget bipolar cells, the distribution of cells across the retina (topography) has to be considered (Wässle, H. and Boycott, B. B.,

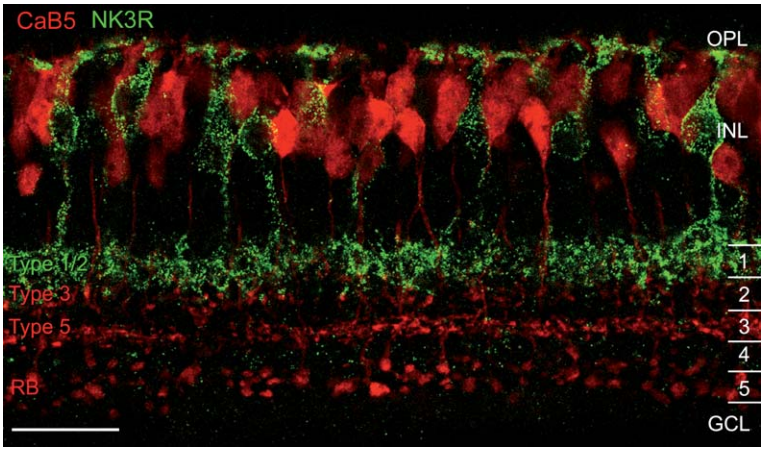


Figure 3 Immunocytochemical staining of mouse bipolar cells. Fluorescence micrograph of a vertical section through mouse retina double immunostained for the calcium-binding protein 5 (CaB5, red) and the neurokinin receptor 3 (NK3R, green). Three bipolar cell types (type 3, type 5 and RB express CaB5. Their axons terminate in the inner plexiform layer inner plexiform layer in sublamina 2, sublamina 3, and sublamina 5, respectively. Type 1/2 bipolar cells express NK3R and their axons are restricted to sublamina 1. GCL, ganglion cell layer; INL, inner nuclear layer; OPL, outer plexiform layer; RB, rod bipolar. Scale bar = 20 μm.

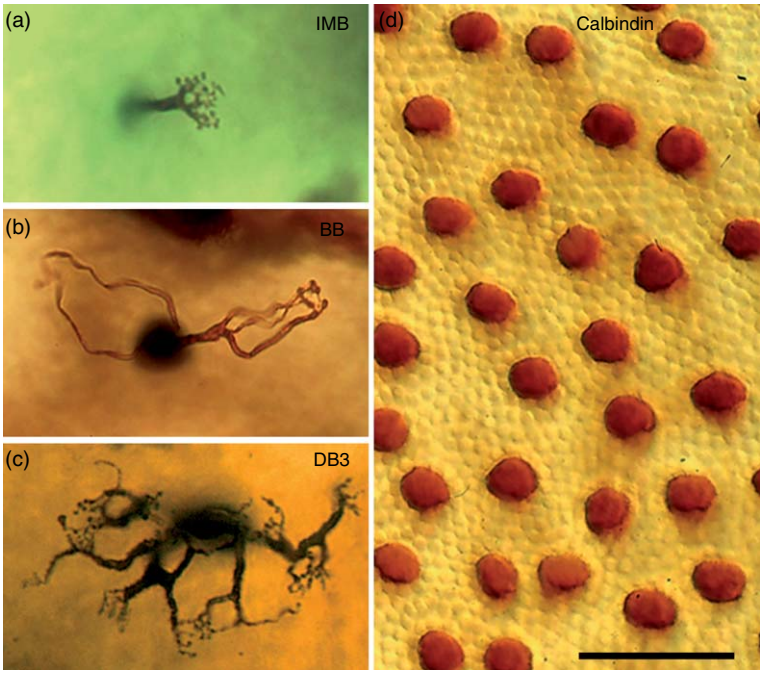


Figure 4 Bipolar cells and their cone contacts in the primate retina. Horizontal view of Golgi stained bipolar cells, with the plane of focus at their dendritic tips in the outer plexiform layer. (a) Dendritic tips of a invaginating midget bipolar cell (IMB). The micrograph in (d) shows the cone pattern (immunolabeled for the calcium-binding protein calbindin) at a comparable eccentricity, and the dendritic tips of the IMB cell in (a) are restricted in size to a single cone. (b) Dendritic branches of a blue-cone bipolar (RB) cell, which contact two widely spaced cones. Comparison with the cone pattern in (d) shows that this BB cell is cone-selective. (c) Dendritic branches of a diffuse bipolar cell (DB3) that would contact altogether nine neighboring cone pedicles. Scale bar = 20 μm.

1991). In the peripheral retina, there is a low density of cones, bipolar cells, and ganglion cells, whereas toward the center of the retina (the central area of cats, the visual streak of rabbits, or the fovea of primates) the density of these cells increases steeply. This results in greatly improved spatial resolution (visual acuity) at the fovea or central area. Concomitant with the increase in density, the cells' dendritic fields become smaller. During evolution, the spatial resolution of the primate eye and retina has been optimized. To achieve this, a high cone density and a low cone-to-RGC ratio have converged in the acuity pathway. The anatomic limits for this optimization are reached when each cone is connected through a midget bipolar cell to a midget ganglion cell, establishing a private line to the brain (Figures 4(a) and 4(d)). It has been suggested that only after this one-to-one connection in the central retina had evolved, 35 million years ago, did a subsequent mutation in the L-cone pigment create L- and M-cones of varying proportions at random spatial locations (Mollon, J. D. and Jordan, G., 1988; Mollon, J. D., 1989; Wässle, H. and Boycott, B. B., 1991; Boycott, B. B. and Wässle, H., 1999; Nathans, J., 1999). The midget system of the central retina was able to transmit this chromatic information to the brain where it could be used, for example to detect red fruit among green leaves. Recently it became possible to study the L-/M- and S-cone mosaics of the living human retina by the application of adaptive optics (Hofer, H. *et al.*, 2005). This revealed the irregular arrangement of L- and M-cones. Moreover it showed that the relative proportions of L- and M-cones greatly varied between human individuals (Roorda, A. and Williams, D. R., 1999). The midget system is able to transfer this irregular mosaic to the brain which apparently can compensate such variability, and color vision in human individuals is not affected by the different ratios of M- and L-cones (Neitz, J. *et al.*, 2002).

This midget theory of the evolution of trichromacy in primates has its basis in the general pattern of mammalian wiring. It is not necessary to postulate, in addition, specific mutations to change the cone selectivity of bipolar cells, the cone selectivity of GluRs, or the selectivity of ganglion cells (Calkins, D. J. and Sterling, P., 1999). It also explains why mammals other than primates have not evolved trichromacy: their cone bipolar cells sum the signals of several cones, and their RGCs sum the signals of many bipolar cells. A mutation that created M- and L-cones would be lost in this convergent network, which pools signals from many cones (Wässle, H., 1999). A recent transgenic mouse expressing human L- and M-opsins was not able to perform trichromatic color discrimination (Jacobs, G. H. *et al.*, 2004). However, in a further transgenic mouse where large patches of the cone mosaic expressed either L- or M-opsins trichromatic color discrimination was possible (Smallwood, P. M. *et al.*, 2003; Jacobs, G. H. *et al.*, 2007). The idea that trichromacy piggy-backs on the high acuity system of primates also postulates that the midget bipolar cells perform a double duty in visual signaling, acuity and trichromacy, an idea that has been promoted for some years (Ingling, C. R., Jr. and Martinez-Uriegas, E., 1983a; 1983b).

1.12.3.2 Blue-Cone Bipolar Cells

Placental mammals other than primates have only two types of cone: L-cones in which the visual pigment has an absorption maximum of greater than 500 nm and S-cones with an absorption maximum at less than 500 nm. They are, therefore, dichromats. In an evolutionary comparison of color pigments it has been estimated that the separation of the L- and S-cone pigments occurred more than 500 million years ago and thus represents the phylogenetically ancient, primordial color system (Mollon, J. D., 1989). The morphological substrate for the dichromatic color vision common to most placental mammals is the S-cone pathway (Calkins, D. J., 2001). Mariani A. P. (1983; 1984) described bipolar cells selective for S-cones in the macaque monkey retina. They have long, smoothly curved dendrites and contact between one and three cone pedicles (Figures 4(b) and 4(d)). Their axons terminate in rather large varicosities in the innermost part of the IPL, close to the ganglion cell layer (BB-cells in Figure 2). S-cone bipolar cells have been quantified by selective labeling with antibodies against cholecystokinin (CCK; Kouyama, N. and Marshak, D. W., 1992; Wässle, H. *et al.*, 1994). Their selective innervation of S-cones has been shown in old world and new world primates (Ghosh, K. K. *et al.*, 1997; Calkins, D. J. *et al.*, 1998), and it has been shown that they provide input to the inner tier of the dendritic tree of the small bistratified ganglion cells (Calkins, D. J. *et al.*, 1998). Small bistratified ganglion cells give blue-ON, yellow-OFF responses (Dacey, D. M. and Lee, B. B., 1994). In the retina of the ground squirrel light responses of a S-cone selective bipolar cell have been recorded and this bipolar cell was an ON-bipolar cell (Li, W. and DeVries, H., 2006).

Immunostaining with antisera specific for S-opsin has shown that S-cones constitute approximately 10% of the cones in most mammalian retinas (Szél, A. *et al.*,

1988; 1993). However, in some species S-cones have a very uneven topographical distribution across the retina and many cones express both L- and S-opsin (Glösmann, M. and Ahnelt, P. K., 1998; Applebury, M. L. *et al.*, 2000; Lukáts, A. *et al.*, 2005). So far only circumstantial evidence for the existence of S-cone selective bipolar cells in mammals other than primates has been presented (rabbit: Famiglietti, E. V., 1981; Jeon, C. J. and Masland, R. H., 1995; cat: Cohen, E. D. and Sterling, P., 1990a; 1990b; ground squirrel; West, R. W., 1976; rat: Euler, T. and Wässle, H., 1995; mouse: Ghosh, K. K. *et al.*, 2004; Pignatelli, V. and Strettoi, E., 2004). However, recently a transgenic mouse line could be studied, where Clomeleon, a genetically encoded fluorescence indicator, was expressed under the *thy1* promotor (Haverkamp, S. *et al.*, 2005). Clomeleon labeled ganglion cells, amacrine cells, and bipolar cells. Among the bipolar cells the S-cone-selective (blue cone) type could be identified, and the cone-selective contacts and the retinal distribution could be studied. The morphological details of the blue-cone bipolar cell match type 9 cells of rat and mice (Figure 2) and they are closely similar to the blue-cone bipolar cell of the primate retina (Figure 4(b)). It is interesting that in the ventral mouse retina, where most cones express both L- and S-opsin, blue-cone bipolar cells contact only those cones, which express S-opsin only, and they are the genuine blue cones of the mouse retina (Haverkamp, S. *et al.*, 2005).

1.12.3.3 Diffuse Bipolar Cells

Most bipolar cell types of the mammalian retina contact between five and seven neighboring cones (Figures 4(c) and 4(d)). Diffuse bipolar cells of the primate retina contact L- and M-cones in their dendritic field nonselectively (Boycott, B. B. and Wässle, H., 1991). They are, therefore, involved with the transfer of a luminosity signal, which is based on the combined sensitivity of L- and M-cones (Lee, B. B. *et al.*, 1990). Whether all diffuse bipolar cell types also contact S-cones is still a matter of discussion and it has been proposed that one type of diffuse bipolar cell avoids S-cones (Calkins, D. J. *et al.*, 1996). This type would be a good candidate to transfer a yellow (L-plus M-cone) signal into the IPL, where it could contact the outer tier of the dendritic tree of the small bistratified ganglion cells (Dacey, D. M. and Lee, B. B., 1994). Recordings from diffuse bipolar cells of the retina of the ground squirrel show that there are two groups of diffuse bipolar cells: one receives mixed input from S- and M-cones, while the other one receives an almost pure M-cone signal (Li, W. and DeVries, H., 2006).

1.12.3.4 Cone Contacts of Bipolar Cells

The cone pedicle has two kinds of synaptic specializations, which are occupied by bipolar cells: invaginating and flat contacts (Figure 1(a)). Reconstructions of Golgi-impregnated midget bipolar cells of the primate retina by serial electron microscopy (EM; Figure 5) showed a clear dichotomy: IMB cells made exclusively invaginating contacts, whereas FMB cells made only flat contacts (Kolb, H., 1970). Individual IMB cells make up to 25 contacts with a cone pedicle (Figure 5(a)), an FMB cell makes approximately 2.0–3.5 times that number of basal synapses (Hopkins, J. M. and Boycott, B. B., 1996; 1997). Most of the contacts of FMB cells are in the vicinity of the ribbons (Figure 5(b), triad associated, TA). Reconstructions of cone contacts of Golgi-impregnated diffuse bipolar cells by EM revealed that DB1, DB2, and DB3, which have their axon terminals in the outer IPL and are putative OFF bipolar cells, make exclusively basal junctions with the cone pedicle (Figure 5(c)). They always have TA and nontriad associated (NTA) contacts, the proportions varying according to the cell type, as does the average number of contacts per cone, which is between 10 and 20. Bipolar cells DB4, DB5, and DB6 have their axon terminals in the inner part of the IPL and are putative ON bipolar cells. They have an average of between four and eight invaginating synapses per cone pedicle. In addition they also form basal junctions, in a predominantly TA position (Hopkins, J. M. and Boycott, B. B., 1996; 1997). Thus, while the dichotomy invaginating = ON, flat = OFF holds for midget bipolar cells, it does not conform so clearly for diffuse bipolar cells. As discussed later, the type of synapse made by a bipolar cell at a cone pedicle, flat versus invaginating, is not the decisive feature; it is rather the GluR expressed there.

Recent results from the rodent and the rabbit retina have shown that some OFF-cone bipolar cells make also basal contacts with rod spherules and thus receive a direct input from rods (Hack, I. *et al.*, 1999; Tsukamoto, Y. *et al.*, 2001; Li, W. *et al.*, 2004; Protti, D. A. *et al.*, 2005). This represents a third route for the rod signal in addition to the RB cell circuit and the gap junctions between rods and cones (Volgyi, B. *et al.*, 2004).

The number of contacts per cone pedicle of a given diffuse bipolar cell varies across its dendritic field (Figure 5(c)). More contacts are made with cones in the center, and only few contacts are made

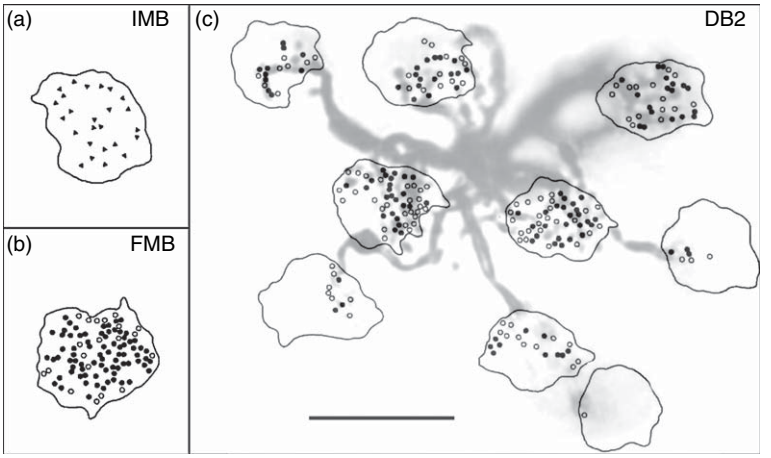


Figure 5 Cone contacts of bipolar cells of the primate retina. The cells were Golgi-stained and afterwards serially sectioned for electron microscopic analysis (Hopkins, J. M. and Boycott, B. B., 1996). (a) The 25 contacts of an invaginating midget bipolar cell are all invaginating. (b) The 97 contacts of a flat midget bipolar cell are all flat (●, triad associated; ○, nontriad associated). (c) reconstruction of the cone contacts of a diffuse bipolar cell DB2. The dendritic tree, as revealed by the Golgi staining, is inserted. This DB2 cell connects to nine cone pedicles, exclusively with flat contacts. Scale bar = 20 μm. Adapted from Boycott, B. B. and Wässle, H. 1999. Parallel processing in the mammalian retina: the Proctor Lecture. Invest. Ophthalmol. Vis. Sci. 40, 1313–1327.

with more peripheral cones, which predicts a Gaussian sensitivity profile. The dendrites of neighboring bipolar cells of a given type show different extents of overlap and their coverage factor is between one and four. This means that a cone pedicle may contact one to four bipolar cells of any given type. This is illustrated in Figure 6 for type 7 bipolar cells of a transgenic mouse line which expresses GFP under the control of the gustducin promotor (Huang, L. *et al.*, 2003). They were immunostained for GFP (Figure 6(a)) and their dendritic network (Figures 6(b) and 6(d)), cell bodies, and axon terminals (Figures 6(c) and 6(e)) are shown. The positions of cone pedicles are marked by the expression of GluR5 (Haverkamp, S. *et al.*, 2005). Analysis of individual bipolar cells in this network shows that bipolar cells contact approximately eight cone pedicles (convergence) and cone pedicles are innervated by approximately one bipolar cell (divergence). The cone density in this area is 13 000 mm^{-2}, the density of this bipolar cell type is 2000 mm^{-2}. Type 7 bipolar cells represent approximately 10% of the total cone bipolar cell population of the mouse retina. Some of the axon terminals are delineated by red circles in Figure 6(e) and it is obvious that they are precisely space filling, without any overlap. They are all within the same focal plane and therefore confined to a narrow stratum within the IPL (Figure 6(a)). This example shows the dendritic and axonal architecture of a defined bipolar cell type, and thus represents one of the parallel routes from the outer to the IPL.

1.12.4 Expression of Glutamate Receptors at Cone Pedicles

1.12.4.1 Glutamate Receptor Subunits

Molecular cloning has revealed a multiplicity of GluRs and receptor subunits. Ionotropic receptors are integral membrane proteins that form an ion channel. This channel, usually a nonselective cation channel, is made up of four subunits and opens upon glutamate binding. Three major groups of ionotropic GluRs can be distinguished: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors. They comprise the following subunits: AMPA (GluR1, GluR2, GluR3, GluR4); kainate (GluR5, GluR6, GluR7, KA-1, KA-2); NMDA (NR1, NR2A, NR2B, NR2C, NR2D and NR3A); further subunits are the orphan receptors δ1 and δ2. In addition multiple splice variants of the different subunits, have been identified, for example, the 10 splice variants of NR1 (Hollmann, M. and Heinemann, S., 1994; Dingledine, R. *et al.*, 1999; Kew, J. N. C. and Kemp, J. A., 2005). mGluRs belong to the family of receptors that have seven membrane-spanning domains and, when they

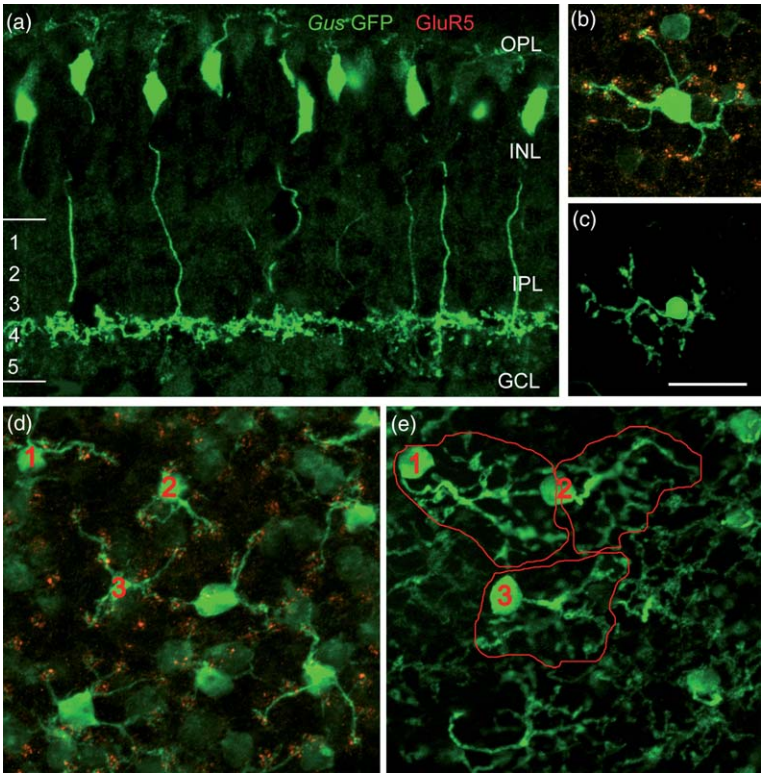


Figure 6 Array of type 7 bipolar cells of the mouse retina. The cells express green fluorescent protein (GFP) under the control of the α-gustducin promotor (Huang, L. *et al.*, 2003). (a) Fluorescence micrograph of a vertical section showing strong expression of GFP in type 7 bipolar cells their axon terminals in sublamina 3/4 of the inner plexiform layer (IPL). Faint expression can also be detected in some rod bipolar cell axon terminals in sublamina 5. (b, c) Horizontal view of the dendritic field and the axon terminal of an isolated type 7 bipolar cell. The dendrites in (b) contact all 12 cone pedicles within the dendritic field. They are labeled by the expression of the kainate receptor GluR5 (clusters of red dots). The axon terminal in (b) covers an area of $\sim$500 μm^2. (d, e) Horizontal view a patch of retina, where apparently all type 7 cells are labeled. Their dendritic trees in (d) contact an average number of 8.1 $\pm$ 1.3 ($n = 20$) cone pedicles (convergence). Dendritic fields of neighboring type 7 cells in this field show practically no overlap and, therefore, most cone pedicles are in contact with only one type 7 bipolar cell (divergence). The axon terminals of the type 7 bipolar cells in the IPL are space filling without much overlap (coverage of 1). This is indicated by the red outlines for three selected cells. GCL, ganglion cell layer; INL, inner nuclear layer; OPL, outer plexiform layer. Scale bar = 20 μm for (a), 17 μm for (b) and (c), 16 μm for (d) and (e).

bind glutamate, G protein, and second messenger systems are activated. So far eight different mGluRs have been identified (mGluR1–mGluR8). It is clear that a simple retinal scheme: glutamate released from photoreceptors acts on horizontal and bipolar cells and then, in turn glutamate released from bipolar cells activates amacrine and ganglion cells, can have any degree of complexity depending on the GluRs that are expressed.

1.12.4.2 ON-Bipolar Cell Glutamate Receptors

In a series of seminal experiments, Nakanishi and co-workers have cloned mGluR6, localized it with specific antibodies, and studied the function by gene directed (knockout) mutagenesis (Nomura, A. *et al.*, 1994; Masu, M. *et al.*, 1995). These experiments have shown that mGluR6 is expressed at the dendritic terminals of RB cells inserted into the rod spherules. In the mGluR6 knockout mouse, all ON-light responses were blocked (Masu, M. *et al.*, 1995; Renteria, R. C. *et al.*, 2003). Vardi N. *et al.* (1998) have shown that mGluR6 also is expressed in ON-cone bipolar cells at their invaginating, and occasionally flat, contacts with cone pedicles. Previous pharmacological studies had shown that light responses of all ON-bipolar cells are blocked by 2-aminophosphonobutyric acid (LAP-4; Slaughter, M. M. and Miller, R. F., 1981), a glutamate agonist at mGluR (group III) receptors (Pin, J. P. and Duvoisin, R., 1995). The signal cascade activated through

mGluR6 in ON-bipolar cells involves the G protein G alpha (o) (Dhingra, A. *et al.*, 2002; 2004), however, the membrane channel modulated by the cascade has not yet been identified (Nawy, S., 1999; Snellman, J. and Nawy, S., 2004). Recently a transgenic mouse was created, where the mGluR6 promotor drives the expression of GFP and all ON-bipolar cells were found to be labeled (Morgan, J. L. *et al.*, 2006). Taken together this shows that mGluR6 is the predominant GluR expressed in all ON-bipolar cells. However, it has to be emphasized that additional GluRs have been localized to them and their functions still need to be elucidated (Koulen, P. *et al.*, 1997; Vardi, N. *et al.*, 1998; Lo, W. *et al.*, 1998; Calkins, D. J., 2005). It is possible that they fulfill some modulatory roles in different ON bipolar cell types.

1.12.4.3 OFF-Bipolar Cell Glutamate Receptors

Immunocytochemical localization of GluR subunits to flat contacts of bipolar cells at the cone pedicle base has revealed a plethora of different GluRs. The AMPA receptor subunit GluR1 has exclusively been observed in flat contacts and has not been found in horizontal cell processes (Brandstätter, J. H., 2002). In retinas double labeled for the ribbon marker bassoon and for GluR1, GluR1 hot spots are located in close vicinity of the ribbons, suggesting a TA position (Figures 7(d)–7(f); Haverkamp, S. *et al.*, 2001). In the macaque monkey retina it was possible to compare the GluR1 expression of M/L- and S-cones. The same number of GluR1 hot spots was observed, however, they were more salient in S-cone pedicles (Haverkamp, S. *et al.*, 2001). Whether this represents a higher density of GluR1 expression at S-cones, or whether the hot spots are more closely packed at the smaller S-cone pedicles cannot be answered at present. Puller C. *et al.* (2007) could show that FMB cells of the primate retina express GluR1 at their contacts with cone pedicles. FMB cells have been shown to contact M/L- as well as S-cones in the macaque monkey retina (Klug, K. *et al.*, 2003). GluR1-labeled flat contacts have also been observed in the rodent

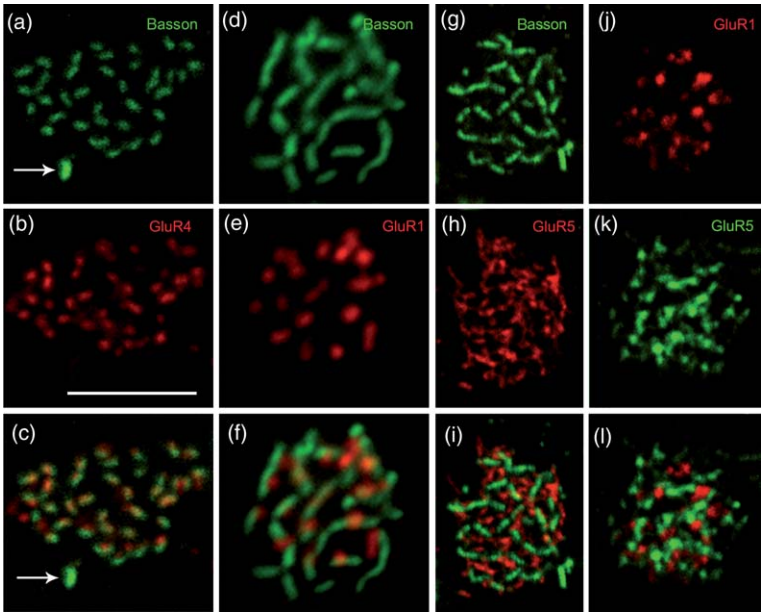


Figure 7 Horizontal confocal sections of cone pedicles of the primate retina that were double labeled for bassoon and glutamate receptor subunits (GluRs). (a) The ribbons of one cone pedicle and one rod spherule (arrow) are immunoreactive for bassoon (green). (b) GluR4 immunoreactive hot spots of the same section as in (a) (red). (c) Superposition of (a) and (b) shows that most of the GluR4 immunoreactive hot spots are in register with the ribbons. (d) Cone pedicle from the more central retina immunolabeled for bassoon. (e) GluR1 immunoreactive hot spots of the same section as in (d). (f) Superposition of (d) and (e) shows that GluR1 immunoreactive hot spots are associated, but not in perfect register, with the ribbons. (g) Cone pedicle immunolabeled for bassoon. (h) Same pedicle, immunolabeled for GluR5. (i) Superposition of (g) and (h) shows that GluR5 immunoreactive hot spots are found in between the ribbons. (j) and (k) Section through a cone pedicle that was double labeled for GluR1 ((j), red) and GluR5 ((k), green). (l) Superposition of (j) and (k) shows that GluR1 and GluR5 immunoreactive puncta are expressed at different synaptic contacts. Scale bar = 5 μm.

and cat retina (Qin, P. and Pourcho, R. G., 1999; Hack, I. *et al.*, 2001), however, the corresponding type of bipolar cell has not yet been identified.

The kainate receptor subunit GluR5 has also been observed in flat contacts and has not been found in horizontal cell processes. In retinas double labeled for the ribbon marker bassoon and for GluR5, the GluR5 hot spots are always displaced from the ribbons, suggesting a NTA position (Figures 7(g)–7(h)). When cone pedicles were double labeled for the AMPA receptor subunit GluR1 and the kainate receptor subunit GluR5 (Figures 7(j)–7(l)), the labeled hot spots did not coincide (Haverkamp, S. *et al.*, 2001). This suggests that they are expressed by two different types of OFF-cone bipolar cells. In retinas of primates, rodents, and ground squirrels there was a significant reduction of GluR5 hot spots at S-cone pedicles in comparison to M/L- and L-cone pedicles (Haverkamp, S. *et al.*, 2001; Li, W. and DeVries, H., 2004; Haverkamp, S. *et al.*, 2005). The OFF-cone bipolar cell expressing GluR5 makes, therefore, only sparse connections with S-cones. The kainate receptor subunit KA-2 has also been observed at bipolar cell flat contacts and not in horizontal cell processes (Brandstätter, J. H. *et al.*, 1997).

The GluR subunits GluR2, GluR2/3, GluR4, and GluR6/7 have also been localized to flat contacts of bipolar cells at the cone pedicle base, however, these subunits also decorated the processes of horizontal cells (Morigiwa, K. and Vardi, N., 1999). NMDA receptor subunits have not been observed at the flat contacts (Fletcher, E. L. *et al.*, 2000).

In conclusion: OFF-cone bipolar cells express at their flat contacts with cone pedicles the AMPA receptor subunits GluR1, GluR2, GluR2/3, and GluR4, they also express the kainate receptor subunits GluR5, GluR6/7, and KA-2. Therefore, different OFF-cone bipolar cell types can be connected to cone pedicles through AMPA receptors, or through kainate receptors. Further diversity is to be expected because AMPA and kainate receptors are composed of four subunits each, and different subunits can be combined to form the tetrameric receptor complex.

1.12.4.4 Horizontal Cell Glutamate Receptors

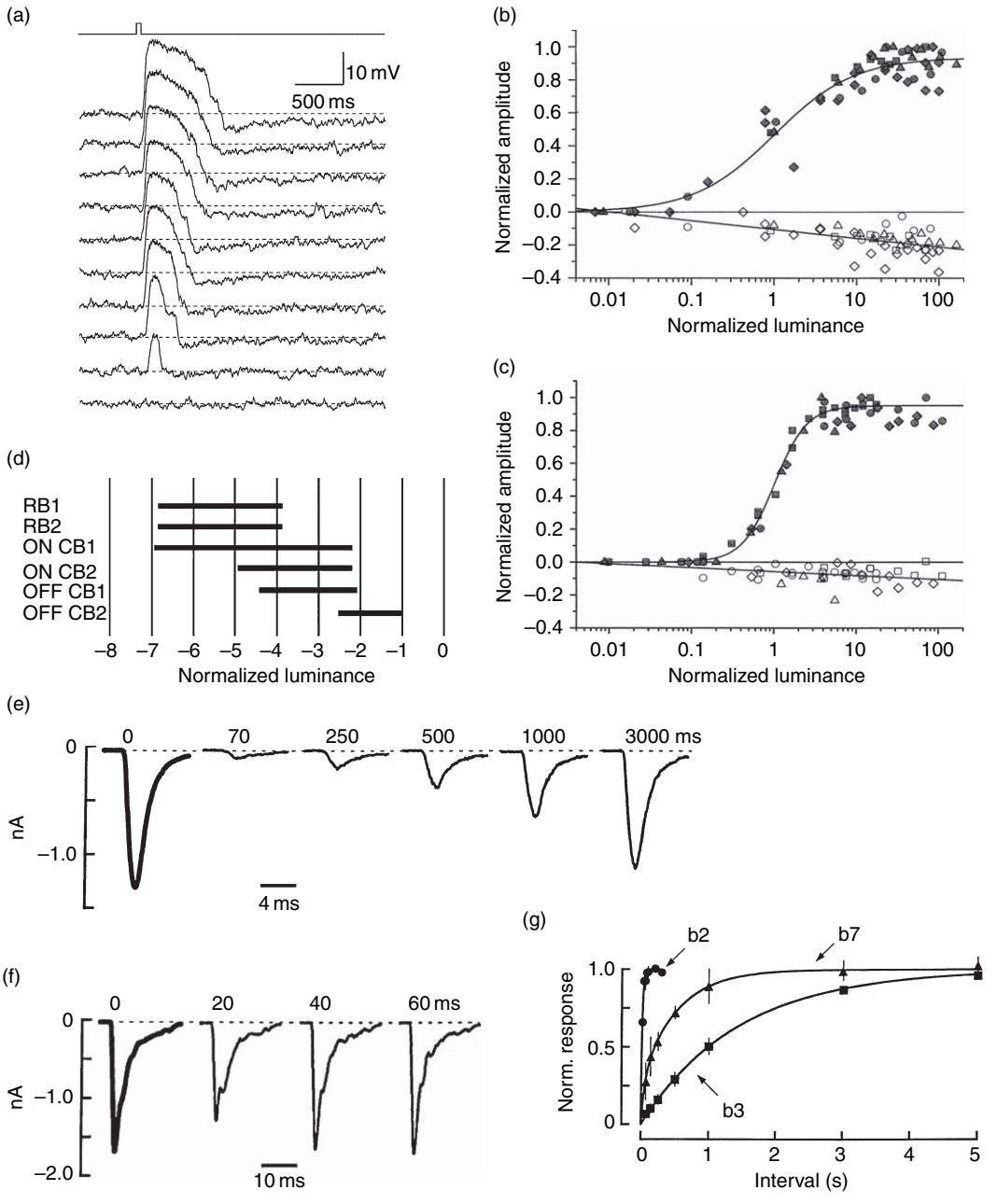
Horizontal cell dendrites of the primate retina express GluR hot spots at two postsynaptic locations: at the invaginating processes opposed to the presynaptic ribbons and at desmosomelike junctions between horizontal cell dendrites underneath the cone pedicle (Haverkamp, S. *et al.*, 2000). GluR2/3 and GluR4 clusters are found at the invaginating processes and at the desmosomelike junctions of all cone pedicles and these AMPA receptor subunits appear to constitute the dominant GluR expressed by horizontal cells (Figures 7(a)–7(c)). However, at M/L-cones pedicles horizontal cell dendrites also express the kainate receptor subunit GluR6/7. Since expression of GluR6/7 by horizontal cells was not observed at S-cone pedicles, the preferred target of H2 horizontal cells, it appears that only H1 horizontal cells express the GluR6/7 subunit (Haverkamp, S. *et al.*, 2001). The two horizontal types of the primate retina, therefore, not only have different shapes and cone contacts, but they express also different GluRs: H1 cells receive signals from cones through AMPA (GluR2/3, GluR4) and kainate (GluR6/7) receptors, H2 cells only through AMPA (GluR2/3, GluR4) receptors. Examination of GluR currents in horizontal cells from cultures human retina using whole-cell recordings showed that horizontal cells possess both AMPA and kainate receptors (Shen, W. *et al.*, 2004). Unfortunately the cells were not classified into H1 and H2 horizontal cells.

1.12.5 Light-Evoked Responses of Bipolar Cells

1.12.5.1 Temporal Transfer Characteristics

In the retinas of cold-blooded animals, especially the dogfish and the tiger salamander, the responses of bipolar cells to light have been studied extensively, contributing important results on the polarity (ON/OFF) and the time course (sustained/transient) of their responses, the currents involved, and the receptive field organization (Werblin, F. S., 1973; Kaneko, A. and Shimazaki, H., 1976; Saito, T. *et al.*, 1981; Saito, T. and Kujiraoka, T., 1982; Saito, T. *et al.*, 1985; Lasansky, A., 1992, Wu, S. M. *et al.*, 2000). Early recordings from intact mammalian retinas confirmed the ON/OFF dichotomy of cone bipolar cells (Nelson, R. *et al.*, 1981; Nelson, R. and Kolb, H., 1983) and showed that RB cells are ON-bipolar cells (Dacheux, R. F. and Raviola, E., 1986). Later, in patch clamp recordings from dissociated bipolar cells it was shown that RB cells express the metabotropic L-AP4 sensitive GluR, while cone bipolar cells express both ionotropic and metabotropic GluRs (Yamashita, M. and Wässle, H., 1991; de la Villa, P.

et al., 1995). Recordings from bipolar cells in rat retinal slices, together with a morphological identification of the cells and the application of glutamate agonists demonstrated that types 1, 2, 3, and 4 are OFF bipolar cells, while types 5, 6, 7, 8, 9, and RB cells are ON bipolar cells (Euler, T. *et al.*, 1996; Hartveit, E., 1996; 1997). In the retina of the ground squirrel dual recordings from synaptically connected cone pedicles and different bipolar cell types were performed (DeVries, S. H. and Schwartz, E. A., 1999; DeVries, S. H., 2000). The signal transfer between cones and OFF-cone bipolar cells was based on two different types of ionotropic GluRs: bipolar cell types b3 and b7 expressed kainate receptors, type b2 AMPA receptors. The three cell types showed substantial differences in their temporal properties as measured by their recovery from desensitization (Figures 8(e)–8(g)). Type b2 cells showed fast, b7



cells medium, and b3 cells show recovery. The rapidly recovering b2 cell AMPA receptors are well suited to signal transient components in the cone light response, whereas the slowly recovering b3 cell kainate receptors attenuate the transient components and consequently emphasize the steady (sustained) components. Further studies of the cone pedicle architecture of the retina of the ground squirrel showed that the b2 cells made TA contacts (DeVries, S. H. *et al.*, 2006) and consequently respond fast and transiently. The b3 and b7 cells made basal contacts further away from the triads (NTA) and glutamate released at the ribbons had a long way of diffusion, which resulted in smoothed and sustained responses of b3 and b7 cells. This shows that the cone to OFF bipolar synapse is an important locus in temporal processing. So far it has not yet been shown for the mammalian retina that the cone to ON bipolar synapse is also involved in temporal processing. However, Awatramani G. B. and Slaughter M. M. (2000) have shown that the cone to ON-bipolar synapse of the tiger salamander retina transduces either a sustained or a transient response.

In the rodent retina a specific expression of voltage-dependent sodium (Na^+) and K^+ channels was observed in retinal bipolar cells (Klumpp, D. J. *et al.*, 1995a; 1995b; Pan, Z. H. and Hu, H. J., 2000; Ma, Y. P. *et al.*, 2005). The presence of Na^+ channels in a subgroup of ON-cone bipolar cells accelerated their response kinetics and amplitudes. The results show that the expression of different GluRs at the cone pedicle base and the intrinsic, voltage-dependent Na^+- and K^+-channel shape the temporal transfer characteristic of the different bipolar cell types. Further temporal specificity is contributed by the expression of different voltage-dependent Ca^{2+}-channels at the bipolar cell output synapses (Protti, D. A. and Llano, I., 1998; Pan, Z. H., 2000; Protti, D. A. *et al.*, 2000). The transmitter release at the bipolar cells axon terminal is also controlled by the expression of hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels. Different classes of bipolar cells have a different inventory of HCN channels, which are densely clustered at their axon terminals (Müller, F. *et al.*, 2003; Ivanova, E. and Müller, F., 2006).

1.12.5.2 Spatial Transfer Characteristics

Midget bipolar cells of the primate retina contact, up to an eccentricity of ~10 mm, as a rule, one cone pedicle, diffuse bipolar cells between five and 10 cone pedicles. Dacey D. M. *et al.* (2000) measured the receptive field profiles of midget and diffuse bipolar cells at ~10 mm eccentricity and observed for both cell types an antagonistic center/surround organization: ON center/OFF surround and OFF center/ON surround. The mean center diameter of midget bipolar cells was 42 µm, which would encompass ~5–10 cones. The mean center diameter of diffuse bipolar cells was 92 µm, which would suggest input from 20 to 30 cones. The basis for the apparently large receptive field center sizes is electrical coupling of neighboring cone pedicles (Raviola, E. and

Figure 8 Electrophysiological recordings from bipolar cells of the mouse (a–d) and of the retina of the ground squirrel (e–g). (a) Whole cell recordings of the light-evoked depolarizations of a rod bipolar (RB) cell in a slice preparation of the mouse retina (light stimulus 50 ms, Vrest = 43 m V, intensity stepwise increased from 0 cd m^{-2} at the bottom to 43.5 cd m^{-2} at the top trace). The light-evoked potential is a depolarization followed by a hyperpolarization. (b) Sensitivity curves of four intact RB cells sowing the normalized amplitude (V/V_{max}) of the light-evoked voltage responses as a function of the normalized (I/I_{50}) stimulus intensity (logarithmic axis). Each symbol represents one cell (filled symbols depolarization, open symbols hyperpolarization). (c) Sensitivity curves of four axotomized RB cells. Comparison with (b) shows that they are steeper. Adapted from Euler, T. and Masland, R. H. 2000. Light-evoked responses of bipolar cells in a mammalian retina. J. Neurophysiol. 83, 1817–1829. (d) Dynamic range of the light responses of two RB, two ON-cone bipolar, and two OFF diffuse bipolar cells of the mouse retina. The abscissa shows the normalized stimulus intensity (logarithmic units). The horizontal bars indicate for the light intensity range from threshold (5%) to saturation (95% of the maximum response) of the light-evoked excitatory currents. Adapted from Wu, S. M., Gao, F., and Pang, J. J. 2004. Synaptic circuitry mediating light-evoked signals in dark-adapted mouse retina. Vision Res. 44, 3277–3288. (e–g) Whole-cell currents elicited in three types of OFF-bipolar cells (b2, b3, b7) of the retina of the ground squirrel by the application of brief pulses (15 ms) of glutamate (2 mM) separated by variable intervals. (e) The average first response (thick line) and subsequent responses (thin lines) are shown for a b3 cell. The interpulse interval is given above each trace. (f) Recordings of glutamate responses of a b2 cell. The recovery from desensitization of this b2 cell is much faster than that of the b3 cell shown in (e). (g) Normalized peak response is plotted against interpulse interval (b2, $n = 5$; b3, $n = 9$; b7, $n = 5$). Type b2 bipolar cells show the fastest recovery ($\tau = 18$ ms), followed by b7 and b3 cells. Type b2 cells signal through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, b7 and b3 cells through two different kainate receptors. Adapted from DeVries, S. H. 2000. Bipolar cells use kainate and AMPA receptors to filter visual information into separate channels. Neuron 28, 847–856.

Gilula, N. B., 1973; Tsukamoto, Y. *et al.*, 1992; Hornstein, E. P. *et al.*, 2004; 2005). It is also possible, that neighboring bipolar cells are electrically coupled (Feigenspan, A. *et al.*, 2004; Han, Y. and Massey, S. C., 2005).

The mean diameter of the antagonistic surround of midget and diffuse bipolar cells was 467 µm and 743 µm, respectively. For midget bipolar cells, the surrounds are about the same as the receptive field diameters of macaque H1 horizontal cells (Dacey, D. M., 2000). The diffuse bipolar cell surrounds are consistently larger, suggesting in addition to the horizontal cell input an input at their axon terminal system from a wide field amacrine cell type.

1.12.6 Intensity-Response Function

RB cells have the lowest response threshold for light stimuli amongst mammalian bipolar cells (Figures 8(a)–8(d)). The mean threshold (defined as 5% of the maximum response) of mouse RB cells is 0.1 Rh^* rod^{-1} s^{-1} and their dynamic range is ~3.3 log units (Wu, S. M. *et al.*, 2004). This is more than 1 log unit wider than the rod photocurrent (Field, G. D. and Rieke, F., 2002). The light-evoked response of RB cells increases monotomically (Figure 8(a)) and follows a Hill function (Figure 8(b)) with a Hill coefficient of 1.07 ± 0.19 (Euler, T. and Masland, R. H., 2000) and 1.15 ± 0.11 (Berntson, A. and Taylor, W. R., 2000). Euler T. and Masland R. H. (2000) measured also the intensity–response function of RB cells which had lost their axons (axotomized). The dynamic range of the axotomized RB cells was reduced by more than 1 log unit and the Hill curve was much steeper (Hill coefficient 2.39 ± 0.84; Figure 8(c)). A comparable reduction of the dynamic range of RB cells was also observed when the cells were superfused with GABA antagonists. Both results show, that GABAergic inhibition at RB axon terminals can modulate the intensity-response function of RB cells. This conclusion is also supported by recent measurements of bipolar cells in $GABA_C$ receptor knockout mice (McCall, M. A. *et al.*, 2002).

The thresholds for light stimuli of ON-cone bipolar cells of the mouse retina are generally higher than those for RB cells (Wu, S. M. *et al.*, 2004). Different types of ON-cone bipolar cells exhibit different thresholds and dynamic ranges, and thus cover only a small range of light intensities (~2 log units). The full range of intensities transferred to the inner retina is therefore encoded by different bipolar cells types (Figure 8(d)).

1.12.7 Synaptic Contacts of Bipolar Cells in the Inner Plexiform Layer

The axons of bipolar cells terminate in the IPL in lobular swellings (Figure 9). Some bipolar cell types, such as DB3 and DB6 of the primate retina and type 7

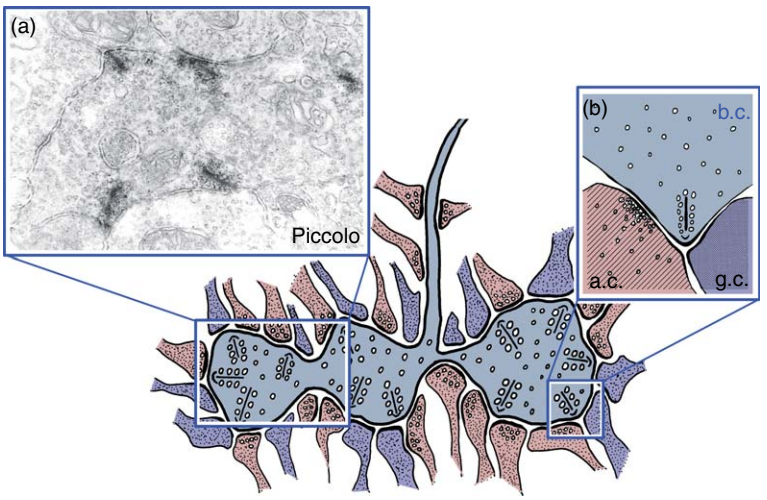


Figure 9 Synaptic output of bipolar cells in the inner plexiform layer. Schematic diagram of the axon terminal of a cone bipolar cell. It contains many presynaptic ribbons that are flanked by synaptic vesicles. (a) Electron micrograph of the axon terminal of a rod bipolar cell. Kindly provided by O. Dick. The five ribbons are marked by their expression of the ribbon associated protein piccolo. (b) Magnified view of a cone bipolar cell ribbon synapse (dyade). The presynaptic bipolar cell (b.c.) releases glutamate and the two postsynaptic partners (a.c., amacrine cell; g.c., ganglion cell) express two different sets of glutamate receptors. The amacrine cell in turn makes a synapse back onto the bipolar cell terminal (reciprocal synapse).

of the mouse retina keep their axon terminals within a narrow stratum (Figure 6; Chan, T. L. *et al.*, 2001; Jusuf, P. R. *et al.*, 2004; Lin, B. *et al.*, 2005). Hence their output will be restricted to the amacrine and ganglion cell dendrites they meet within that stratum. Other bipolar cells such as type 4 and type 6 of the mouse retina occupy with their axon terminals the complete OFF- or ON-sublamina, respectively (Ghosh, K. K. *et al.*, 2004). They are possible engaged in contacts with a wider variety of postsynaptic neurons. Midget bipolar cells of the primate retina represent a special case, because their axon terminals precisely match in width and depth the dendritic tops of midget ganglion cells, and they together form a densely interconnected glomerulus that can only be resolved by EM (Kolb, H. and Dekorver, L., 1991; Calkins, D. J. *et al.*, 1994; Jusuf, P. R. *et al.*, 2006). The axon terminals of neighboring bipolar cells of a given type usually tile the retina without much overlap in horizontal direction (RB cells: Young, H. M. and Vaney, D. I., 1991; midget cells: Wässle, H. *et al.*, 1994; calbindin bipolar cells of the rabbit: Massey S. C. and Mills S. L., 1996). Because of this basically onefold coverage the density of a given bipolar cell type is inversely proportional to the area occupied by the axon terminals (Figure 6(e)).

Bipolar cell axon terminals provide synaptic output through multiple ribbon synapses. The number of ribbon synapses made by midget bipolar cells of the macaque monkey retina ranged from nine to 48 (mean $\pm$ standard deviation 26.5 ± 9.3; Jusuf, P. R. *et al.*, 2006). An earlier report that this number differed between midget bipolar cells contacting M- or L-cones (Calkins, D. J. *et al.*, 1994) was not confirmed by Jusuf P. R. *et al.* (2006). The number of ribbon synapses made by RB cells of the rabbit retina was up to 30 compared to only 15 in the rat retina (Strettoi, E. *et al.*, 1990; Chun, M. H. *et al.*, 1993), which reflects the smaller size of RB axon terminals in rats (Figure 9(a)). The fine structure of the bipolar cell output synapses in the IPL was first described from EM by Missotten L. (1965). He identified the presynaptic ribbon surrounded by vesicles and the two postsynaptic elements. Dowling J. E. and Boycott B. B. (1966) named this synaptic arrangement a dyad. They recognized that one of the postsynaptic partners at cone bipolar cell dyads was usually a ganglion cell dendrite, while the other one was an amacrine cell process (Figure 9(b)). The amacrine cell process often made within about 0.5–1.0 µm of the dyad a conventional synapse back onto the bipolar cell axon terminal. This arrangement appears to be a reciprocal synapse and because most amacrine cells are inhibitory it is the structural correlate of negative feedback at the dyad. Bipolar cell axons receive in addition to reciprocal synapses also input from amacrine cells not related to the dyads (Sterling, P. and Lampson, L. A., 1986). In the case of RB cell dyads both postsynaptic partners are amacrine cells (AI and AII; Famiglietti, E. V. and Kolb, H., 1975; Kolb, H. and Famiglietti, E. V., 1976) and AI cells provide the reciprocal synapses (see Mammalian Rod Pathways).

The molecular composition of the presynaptic ribbon of bipolar cell dyads is similar to that of photoreceptor ribbons. RIBEYE, CtBP2, Kif3a, and Piccolo have all been localized to the bipolar cell ribbons (Muresan, V. *et al.*, 1999; Schmitz, F. *et al.*, 2000; tom Dieck, S. *et al.*, 2005; Deguchi-Tawarada, M. *et al.*, 2006; Jusuf, P. R. *et al.*, 2006) and this suggests that the mechanisms of glutamate release is also comparable to the photoreceptors synapses. Mb1-bipolar cells of the goldfish retina have a large, round axon terminal, and vesicle fusion, exocytosis, and endocytosis have been studied on this model system in great detail (von Gersdorff, H., 2001; Berglund, K. *et al.*, 2002; Heidelberger, R. *et al.*, 2002; Zenisek, D. *et al.*, 2000; Lagnado, L., 2003; Zenisek, D. *et al.*, 2003; Singer, J. H. *et al.*, 2004; Zenisek, D. *et al.*, 2004). The voltage signals that control neurotransmitter release from bipolar cells are graded with the intensity of the light stimulus and maintained according to the duration of the stimulus. These sustained signals stimulate a continuous cycle of vesicle exocytosis and endocytosis. The ribbon holds vesicles for exocytosis. The most direct evidence for this idea comes from the work of Zenisek D. *et al.* (2000) who used total internal reflection fluorescence microscopy (TIRF) to image individual vesicles in the synaptic terminal of Mb1-bipolar cells.

Glutamate release from bipolar cell terminals *a priori* depends upon the graded electrical response of the cell elicited by the light stimulus. However, it is also regulated by diverse feedback mechanisms acting at the dyad. (1) GABA or glycine released by the amacrine cells can feedback onto the bipolar cell terminal (Euler, T. and Masland, R. H., 2000; Shields, C. R. *et al.*, 2000; Matsui, K., *et al.*, 2001; Freed, M. A. *et al.*, 2003). (2) Bipolar cell terminals express mGluRs as autoreceptors that regulate voltage-dependent Ca^{2+}-channels (Awatramani, G. B. and Slaughter, M. M., 2001; Brandstätter, J. H. *et al.*, 1998; Palmer, M. J. *et al.*, 2003). (3) Bipolar cell axon

terminals express cannabinoid receptors, which regulate voltage-dependent K^+-channels (Fan, S. F. and Yazulla, S., 2005). (4) Synaptic vesicles release protons that inhibit Ca^{2+}-channels and thus inhibit locally the release (Hosoi, N. *et al.*, 2005).

1.12.8 Glutamate Receptors in the Inner Plexiform Layer

Bipolar cells release glutamate at their ribbon synapses (Tachibana, M., 1999) and the GluRs are clustered in the postsynaptic membranes adjacent to the ribbons. As a rule, only one member of the dyad expresses a given GluR subunit, which implies that the two postsynaptic partners express different GluRs (Hartveit, E. *et al.*, 1994; Qin, P. and Pourcho, R. G., 1996; Brandstätter, J. H. *et al.*, 1997; Qin, P. and Pourcho, R. G., 1999; Fletcher, E. L. *et al.*, 2000; Grünert, U. *et al.*, 2002). The postsynaptic clusters of GluRs appear as brightly immunofluorescent puncta when studied by light microscopy and their density and laminar distribution across the IPL differs for the different subunits (Figure 10).

1.12.8.1 α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor Subunits

The GluR1-immunoreactive puncta in the IPL have a stratified distribution and several bands of high and low expression can be recognized (Figure 10(a)). Some amacrine and ganglion cells are labeled extrasynaptically and GluR1 is probably expressed by a subset of these cell classes. GluR2/3-immunoreactive puncta occur at high density across the IPL with an increased density along the strata occupied by the dendrites of cholinergic amacrine cells (Figure 10(b)). The GluR4 subunit shows an even distribution of puncta across the OFF- and ON-sublamina of the IPL (Figure 10(c)). The GluR2/3 and the GluR4 subunits have been observed at the vast majority of bipolar cell ribbons in rabbit and primate retinas (Ghosh, K. K. *et al.*, 2001; Jusuf, P. R. *et al.*, 2006) which implies that at least one member of the dyad usually expresses an AMPA receptor. In the case of RB cells it has been shown that AII cells express the GluR2/3 and GluR4 subunits (Ghosh, K. K. *et al.*, 2001; Li, W. *et al.*, 2002). Physiological recordings from synaptically connected pairs of RB and AII cells have also shown

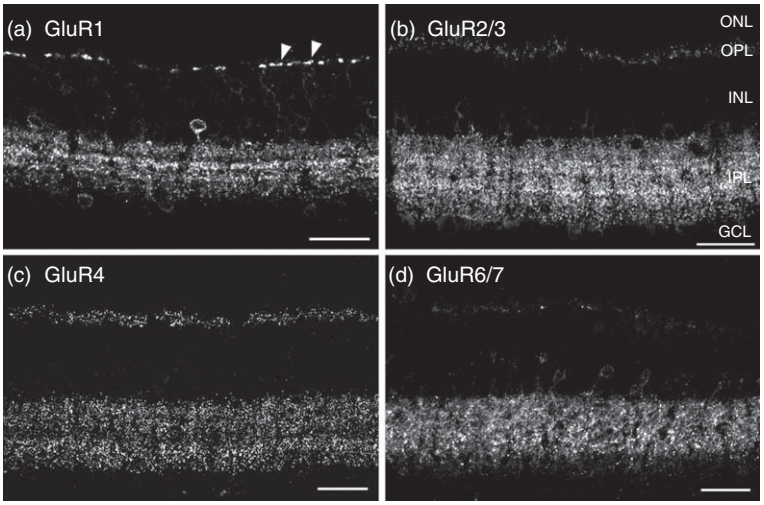


Figure 10 Expression of glutamate receptors (GluRs) in the inner plexiform layer (IPL) of the mouse retina. Confocal fluorescence micrographs of vertical sections that were immunolabeled for GluR subunits. (a) The GluR1 subunit is found extrasynaptically in bipolar, amacrine, and ganglion cells. The dashed line (arrowheads) in the outer plexiform layer (OPL) represents labeling of bipolar cell dendritic tips underneath cone pedicles. A punctate distribution representing synaptic clustering is found in the IPL. (b) The GluR 2/3 subunit shows punctate fluorescence in both the OPL and the IPL. (c) The GluR4 subunit is also found in synaptic hot spots both in the OPL and the IPL. The band of puncta in the OPL is rather wide in (b) and (c), suggesting that processes associated with rod spherules such as horizontal cell axon terminals are also labeled. (d) The kainate receptor subunit GluR 6/7 shows sparse label in the OPL, although many immunofluorescent puncta are present throughout the IPL. Scale bars = 25 μm. Adapted from Haverkamp, S. and Wässle, H. 2000. Immunocytochemical analysis of the mouse retina. J. Comp. Neurol. 424, 1–23.

that AMPA receptors mediate the signal transfer from RB to AII cells (Veruki, M. L. *et al.*, 2003; Singer, J. H. and Diamond, J. S., 2003).

1.12.8.2 Kainate Receptor Subunits

Immunoreactive puncta representing synaptic clusters of kainate receptor subunits KA2 and GluR6/7 have been found throughout the IPL (Figure 10(d); Qin, P. and Pourcho, R. G., 1996; Brandstätter, J. H. *et al.*, 1997; Qin, P. and Pourcho, R. G., 1999). Peng Y. W. *et al.* (1995) observed labeling of some amacrine and ganglion cells for GluR6/7, suggesting they both can express kainate receptors. Whole-cell recordings have shown that some amacrine cells express exclusively kainate receptors others express only AMPA receptors and many amacrine cells have a mixed population of GluRs (Dumitrescu, O. N. *et al.*, 2006). Kainate receptors were found to play only a minor role in generating the light-evoked synaptic currents of brisk sustained (X) type ganglion cells of the cat retina (Cohen, E. D., 2000). Synaptic clusters of the orphan receptor subunits $\delta 1/2$ have also been observed throughout the IPL (Brandstätter, J. H. *et al.*, 1997) postsynaptic to OFF-cone, ON-cone, and RB cells. However, in only one instance the postsynaptic partner was identified; the AI cell at RB cell terminals (Ghosh, K. K. *et al.*, 2001; Li, W. *et al.*, 2002). Unfortunately it is not yet known, which other GluR subunits, together with the $\delta 1/2$ subunits, constitute the GluR receptor channel of AI cells, however, kainate receptor subunits are the most probable candidates.

1.12.8.3 *N*-Methyl-D-Aspartate Receptor Subunits

Synaptic clusters of NMDA receptor NR1 subunits, which are a necessary constituent of all NMDA receptors, have been observed in the IPL, extending from the border of the amacrine cell layer to the innermost part of the IPL. There is a marked reduction of NMDA receptor clusters in the inner part of the IPL, where RB cells terminate (Fletcher, E. L. *et al.*, 2000; Kalloniatis, M. *et al.*, 2004), and signaling through NMDA receptors appears to have only a minor role in the signal transfer from RB cells to AI/AII cells (Boos, R. *et al.*, 1993; Singer, J. H. and Diamond, J. S., 2003; Veruki, M. L. *et al.*, 2003). The two subunits NR2A and NR2B have also a punctate distribution in the IPL; however, the density of puncta differs for the two subunits. Approximately four bands of higher density can be discerned for the NR2A subunit, in contrast to a prominent band in the center of the IPL in the case of the NR2B subunit. Only ~30% of the NR2A and NR2B clusters were found to coincide. These results suggest that there are at least three different types of postsynaptic NMDA receptor clusters in the IPL: those containing NR1/NR2A, NR1/NR2B, and only a small number composed of NR1/NR2A/NR2B.

NMDA receptors play an important role in the transfer of light signals from cone bipolar cells onto ganglion cells. This was first demonstrated in the retina of cold blooded animals (Mittman, S. *et al.*, 1990; Diamond, J. S. and Copenhagen, D. R., 1993; 1995; Matsui, K. *et al.*, 1998; Higgs, M. H. and Lukasiewicz, P. D., 1999). However, although light evoked, NMDA receptor mediated, postsynaptic currents were measured in these studies, spontaneous miniature postsynaptic currents (sEPSCs) lacked a NMDA receptor-mediated component. Light-evoked excitatory synaptic currents of brisk sustained (X) ganglion cells of the cat retina showed also a significant contribution from NMDAR (Cohen, E. D., 2000). In rat RGCs electrically evoked EPSCs recorded from ganglion cells were also mediated by both AMPA and NMDA receptors (Chen, S. and Diamond, J. S., 2002); however, sEPSCs were mediated solely by AMPA receptors. This problem was recently solved by the application of postembedding immunelectron microscopy: AMPA and NMDA receptors are both aggregated on ganglion cell dendrites postsynaptic to the bipolar cell ribbon. However, AMPA receptors are immediately adjacent to the ribbon and the glutamate release site, while NMDA receptors are found perisynaptically at some distance from the ribbon (Zhang, J. and Diamond, J. S., 2005). They are only activated during multivesicular, light-activated glutamate release and do not detect the small amount of glutamate released by the fusion of a single vesicle (Singer, J. H. *et al.*, 2004).

1.12.8.4 Metabotropic Glutamate Receptors

Of the eight different mGluR subtypes known presently, all but mGluR3 have been shown to be expressed and distinctly localized in the rodent retina (Tagawa, Y. *et al.*, 1999). They are clustered at the bipolar cell output synapses and EM has shown that they can occupy a pre- and/or postsynaptic position (Brandstätter, J. H. *et al.*, 1996; Koulen, P. *et al.*, 1996). Usually only one member of the dyad expresses a

given mGluR. The distribution of mGluR clusters across the IPL is different. The subtype mGluR2 for instance is enriched in two narrow bands of the IPL which coincide with the bands of the dendrites of cholinergic amacrine cells (Koulen, P. *et al.*, 1996). Postsynaptic clusters expressing the subtype mGluR7are enriched in four broad horizontal bands and show a reduced density along the cholinergic bands (Brandstätter, J. H. *et al.*, 1998). The different mGluR subtypes are unlikely to be involved with the direct signal transfer from bipolar cells onto the postsynaptic amacrine and ganglion cells. They are supposed to be modulators and it has been shown that $GABA_C$ receptors of RB cells are regulated down by mGluR1/5 agonists (Euler, T. and Wässle, H., 1998).

1.12.8.5 Co-Stratification of Pre- and Postsynaptic Partners in the Inner Plexiform Layer

Bipolar axons terminate at distinct levels within the IPL, and different types of amacrine and ganglion cells also keep their processes at specific levels within the IPL, which leads to the prediction that they also are engaged in mututal synaptic contacts (Figures 11(a)–11(d); Masland, R. H., 2001; Roska, B. and Werblin, F., 2001; Jusuf, P. R. *et al.*, 2004; Wässle, H., 2004; Lin, B. *et al.*, 2005; Coombs, J. *et al.*, 2006; Kim, T. J. and Jeon, C. J., 2006). However, this simple rule has only been verified in a few instances. Midget bipolar cells of the primate retina – both ON- and OFF-midget – contact midget ganglion cells and their axon terminal together with the ganglion cell dendrites form a kind of glomerulus (Kolb, H. and Dekorver, L., 1991; Calkins, D. J. *et al.*, 1994; Jusuf, P. R. *et al.*, 2006). Midget ganglion cells of the primate retina show sustained light responses and this predicts that midget bipolar cells also have sustained light responses.

Parasol ganglion cells of the primate retina also occur as OFF- and ON-pairs and their dendrites stratify in sublamina 2 and sublamina 4, respectively (Watanabe, M. and Rodieck, R. W., 1989; Dacey, D. M. and Packer, O. S., 2003; Dacey, D. M., 2004). OFF-parasol cells receive their major, excitatory input from DB3 bipolar cells (Calkins, D. J., 1999; Jacoby, R. A. *et al.*, 2000), ON-parasol cells from DB4/DB5 bipolar cells (Marshak, D. W. *et al.*, 2002). The DB3

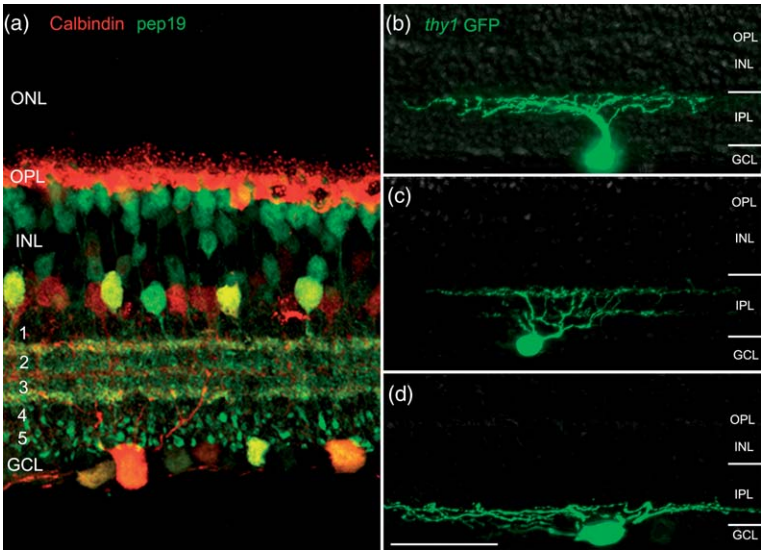


Figure 11 Stratification and functional subdivision of the inner plexiform layer (IPL). (a) Vertical section through a mouse retina that was double immunostained for calbindin (red) and for Pep 19 (green). Calbindin is expressed in horizontal, some amacrine, and some ganglion cells. Pep 19 labels rod bipolar (RB) cells, a subpopulation of cone bipolar, amacrine (among them the cholinergic amacrine cells) and ganglion cells. Their processes subdivide the IPL into distinct strata; among them are the OFF-(sublamina 1/2) and the ON-(sublamina 3/4) cholinergic strata. The axon terminals of RB cells terminate in stratum 4/5. Adapted from Haverkamp, S. and Wässle, H. 2000. Immunocytochemical analysis of the mouse retina. J. Comp. Neurol. 424, 1–23. (b) Vertical section through a transgenic mouse retina where ganglion cells express green fluorescent protein under the control of the thy1 promotor (Feng, G. *et al.*, 2000). This putative OFF (C2 type) ganglion cell stratifies in the outer IPL. (c) This bistratified (putative direction selective (DS)) cell stratifies at the same level as the cholinergic amacrine cells. This putative ON (A-type) ganglion cell stratifies in the inner IPL. Scale bar = 50 μm.

bipolar cell of the primate and the b2 cell of the ground squirrel are probably homologous types (DeVries, S. H., 2000). Since b2 cells receive their light signals through AMPA receptors, they have a high temporal transfer rate. This would be in accordance with the high flicker fusion frequency of parasol cells (Lee, B. B. *et al.*, 1988). Lin B. and colleagues (2005) studied the costratification of type 7 bipolar cell axon terminals and ganglion cell dendrites of the mouse retina. One monostratified ganglion cell and one bistratified cell tightly cofasciculate with the axon terminals of type 7 bipolar cells.

The small bistratified ganglion cells of the primate retina are the blue ON/yellow OFF ganglion cells (Dacey, D. M. and Lee, B. B., 1994). They have their inner dendritic tier in stratum 5 and their outer dendritic tier in stratum 1 of the IPL. The inner tier coincides with the axon terminal of blue-cone bipolar cells (BB in Figure 2), which provide the S-ON input. The outer tier collects synapses from DB2/DB3 bipolar cells and they provide the M- and L-OFF input (Calkins, D. J. *et al.*, 1998; Calkins, D. J., 2001). A further bistratified ganglion cell of the mammalian retina is the ON/OFF direction-selective (DS) ganglion cell (Amthor, F. R. *et al.*, 1989; Figure 11(c)). The inner and outer tier of its dendritic tree coincides with the level of stratification of ON- and OFF-cholinergic amacrine (Famiglietti, E. V., 1992) cells. Mouse cone bipolar cell axon terminals have been studied with respect to their costratification with the cholinergic strata (Ghosh, K. K. *et al.*, 2004; Pignatelli, V. and Strettoi, E., 2004), however, none of the nine types precisely coincided with the dendrites of cholinergic amacrine cells. In the rabbit retina it was shown that DS ganglion cells receive direct input from bipolar cells, however, the majority of their synaptic input is from amacrine cells (Dacheux *et al.*, 2003).Brown S. and Masland R. (1999) identified an ON-cone bipolar cell of the rabbit retina by its immunoreactivity for the carbohydrate epitope CD15 and demonstrated that CD15-positive bipolar cells axon terminals stratify within and slightly more distally of the ON-cholinergic band. In addition, they follow the pattern of the ON-cholinergic dendrites, and are, therefore, good candidates for providing synaptic input to the DS circuitry.

1.12.9 Conclusions

At least 10 different types of bipolar cells transfer the visual signals from the outer to the inner retina. RB cells are exclusively connected to rod spherules and they are involved with the transfer of scotopic signals. The major distinguishing anatomical feature of the different types of cone bipolar cells is the level of stratification of their axons in the IPL, where they preferentially contact those ganglion and amacrine cells which have their dendrites at the same level within the IPL. Some of the bipolar cells select certain types of cones, such as the midget bipolar cells of the primate retina or the blue-cone bipolar cells of most mammals and they transfer a chromatic signal into the IPL. However, most bipolar cells contact all cones, usually five to 10, within their dendritic field and they differ in their intrinsic properties. The major subdivision is into ON- and OFF-bipolar cells, and this is based on two different types of GluRs expressed at their dendrites: ionotropic GluRs in OFF-bipolars and mGluR6 in ON-bipolars. OFF-bipolar cells can be further subdivided according to the specific expression of AMPA or kainate receptors. The physiological consequences of this molecular diversity are different temporal resolution and possibly different threshold sensitivity. The axon terminals of bipolar cells in the IPL release glutamate at their output synapses. The release depends upon the intrinsic membrane properties of bipolar cells (HCN, K^+-, Na^+-, and Ca^{2+}-channels). It can also be modulated by the mGluR autoreceptors and possibly by other receptors, such as dopamine or cannabinoid receptors. Feedback from amacrine cells has been shown to regulate the bipolar cell intensity/response function. The postsynaptic partners of bipolar cells, amacrine, and ganglion cells also express different sets of GluRs, including NMDA receptors and mGluRs. How this molecular diversity is translated into the transfer of the light signal through the retina remains a challenging question.

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