

The Structure of Vertebrate Retinas

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Abstract: The vertebrate retina is formed from six distinct neuronal classes: (1) photoreceptors; (2) bipolar cells; (3) ganglion cells; (4) horizontal cells; (5) amacrine cells and (6) interplexiform cells. Most vertebrates possess a single type of rod photoreceptor and most non-mammals have morphologically pleomorphic cone photoreceptors displaying different pigments and/or connectivities. Cartilaginous fishes and mammals possess monomorphic cones of similar forms regardless of pigment content. Bipolar cells range from ≈ 10 types in mammals to over 15 in cyprinid fishes. Many non-mammals exhibit up to 4 types of cone-selective horizontal cells, plus a separate rod horizontal cell in fishes, while mammalian horizontal cells are usually of two types with the axon terminal of one contacting rods. Amacrine cells are diverse, with over 70 forms documented in cyprinid fish retinas and over 20 in mammals. Similar diversity characterizes ganglion cells, especially in cone-dominated non-mammals. The distributions of interplexiform cells are poorly known, but many vertebrates appear to have one or more types containing GABA, glycine, or dopamine. Photoreceptors, bipolar cells and most ganglion cells contain molecular signatures characteristic of glutamatergic neurons, while all amacrine cells contain primary GABAergic or glycinergic signatures, regardless of whether a secondary transmitter is present (acetylcholine, serotonin, peptides).

Key words: photoreceptors, retinal neurons, neuronal patterning, neuronal stratification

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This chapter is designed as a brief key to the structural elements of vertebrate retinas, taking its form in part from traditional field guides, in part from Walls' *The Vertebrate Eye and Its Adaptive Radiation* [1], and in part from two decades of Taniguchi symposia. The citations are restricted to representative classic and exemplary recent sources that link to other important references. Other chapters in this book will elaborate upon the forms and actions of specific cell types. The chapter is built on six figures with detailed captions serving as the text.

Figure 1: The plan of the retina

The retinas of vertebrates (except for those with intracephalic lateral eyes, e.g. myxinoids) are composed of three operational layers: (1) a rod and cone photoreceptor "input" layer interdigitating with apical processes of the retinal pigment epithelium (RPE: a polygonal epithelium monolayer that seals the retina from the choroidal circulation); (2) an intermediate neuronal layer connecting the input and output layers; and (3) a ganglion cell (GC) "output" layer forming the innermost neuronal layer, sealed from the vitreous by the foot pieces of Müller cells (MCs: the radial glia of the retina). These layers include six distinct *histological* layers: the *photoreceptor layer*, the *outer plexiform layer* (OPL), the *inner nuclear layer* (INL), the *inner plexiform layer* (IPL), the *ganglion cell layer* (GCL) and the *optic fiber layer* (OFL). Layers more distant from the brain in the synaptic chain are "distal" and those closer are "proximal." The photoreceptor layer is split by the external limiting membrane (ELM: a high-resistance layer of tight junctions among MC distal processes and photoreceptors) into: (1) a proximal *outer nuclear layer* (ONL)

formed of photoreceptor inner limbs and a honeycomb of MC processes; and (2) a distal layer of photoreceptor outer limbs, MC microvilli extending past the ELM, and apical RPE processes. The neural retina is composed of interconnected neurons: bipolar cells (BCs), horizontal cells (HCs), amacrine cells (ACs), interplexiform cells (IPCs, not shown), ganglion cells (GCs) and rare biphaxiform cells (not shown). Efferent fibers in many vertebrates enter the retina through the optic nerve and largely target ACs [2,3]. The OPL is the site of synaptic connectivity between photoreceptors and their targets: HCs, BCs and, sometimes, other photoreceptors. In most vertebrates the OPL is roughly laminated, cone synaptic pedicles forming a central layer and rod spherules positioned 1-5 μm distally. Proximal to the pedicles is a zone of mixed MC, BC, HC and IPC processes where some synaptic contacts take place. BC and HC preterminal dendrites arise there, coursing distally to contact photoreceptors. Rod and cone terminals are often partially insulated by MC processes. In avian retinas, the OPL is often bi- or tristratified, as there is insufficient room for all cone pedicles in one layer [4]. The INL in many vertebrates is divisible into overlapping distal \rightarrow proximal HC, BC, MC and AC layers [5,6]. The HC layer of most vertebrates shows further stratification [7,8], as does the AC layer of vertebrates with large cone densities [6]. The IPL is heavily laminated, reflecting the distal \rightarrow proximal layering of synaptic zones associated with construction of specific GC receptive field types [9]. The GCL in most vertebrates is a single layer of mixed neuronal types, predominantly containing GCs but also “displaced” ACs [10]. In animals with retinal areas of high cone density, the GCL can be packed six somas deep. The OFL includes GC axons, occasional astrocytes and is proximally delimited by the end feet of MCs. It is also a possible signal integration region: the “superficial” plexiform layer [11].

Glial cells (see Chapter by Puro): MCs are radial glia, comprising 30-50% of the retinal volume [5]. MC somas are located in the ACL or displaced towards the middle of the INL in thicker retinas. Proximal MC stalks enter the IPL and may divide into radial daughter stalks with lateral stratified extensions. MC end feet form the internal limiting membrane (ILM), in combination with astrocytes in some retinas: a permeability barrier of varied efficacy. Distal MC fibers wrap interstitial leaflets around BCs, branching heavily in the ONL in a honeycomb basket, and form the ELM. Microvillar extensions protrude past the ELM along the inner segments of photoreceptors. The ELM restricts molecular diffusion. Distinctive MC macromolecular signatures include glutamine synthetase, vimentin and glial fibrillary acidic protein (especially in traumatized MCs). Micromolecular signatures include high intracellular taurine/glutamine levels and low glutamate/glycine/GABA levels [5,12]. Some MC functions include glutamate transport [13] and carbon chain recycling [14] (all species); GABA transport [15] (mammals, snakes, chondrichthyans, cyclostomes); K^+ buffering and siphoning [16]. Astrocytes are abundant near the optic nerve head in many species, and are sparsely distributed among the endfeet of MCs across the retinas of several species [17]. They participate in forming the ILM in many vertebrates.

Retinal pigment epithelium (see Chapter by Tamai): The RPE is a monolayer of polarized epithelial cells coupled by gap junctions, forming the distal blood-retinal barrier. The basal surface apposes Bruch’s membrane and the basolateral surface is sealed from the apical RPE processes by tight junctions. RPE functions include [18]: transport of all-trans retinol from the basal and apical extracellular spaces; storage, isomerization, and oxidation of retinol; partitioning retinal to the subretinal space; recognition and phagocytosis of photoreceptor outer segments; transport of oxygen and metabolites into the retina; dehydration and ionic regulation of the subretinal space. RPE cells in pigmented animals contain prolate ellipsoidal melanosomes (melanin granules $\approx 1 \mu\text{m}$ long), whose function seems to be absorption of image-degrading stray photons. In many non-mammalians, especially fishes and anuran amphibians, RPE apical processes extend nearly to the ELM, ensheathing light-adapted cones [19]. In these species, melanosomes show vectorial movements, concentrating into RPE somas in dark-adaptation and dispersing into apical processes in light adaptation. Many marine fishes possess additional pigmented organelles associated with optical isolation of outer segments. Teleost RPE apical processes in dorsal retina contain immobile reflective plates (often guanine crystals) that further optically isolate cones. Melanosome concentration in the dark-adapted retina exposes the plates for “second-chance” capture of reflected photons by rods.

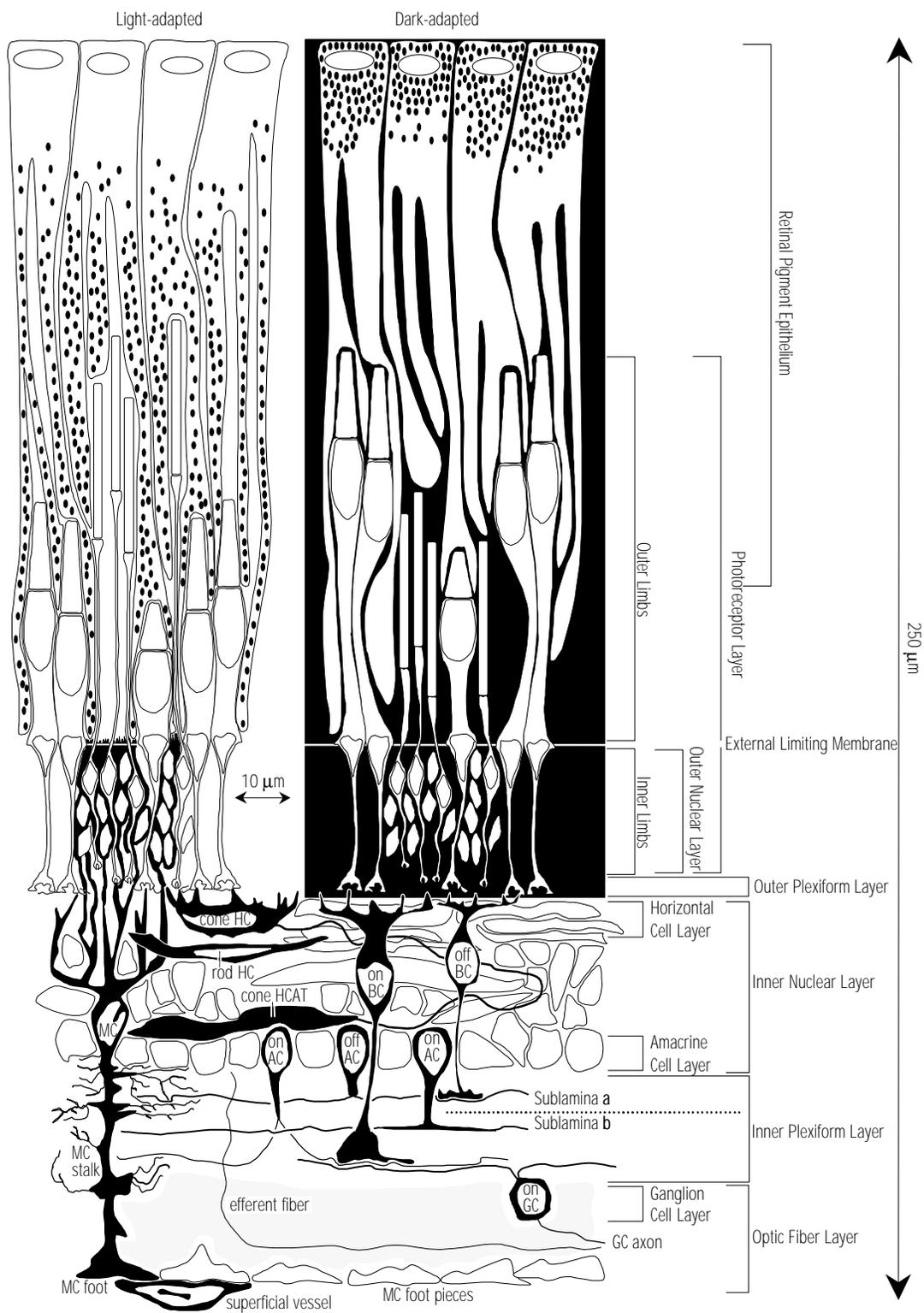


Figure 2: Basic photoreceptor forms. Far left: a *light-adapted* goldfish long single cone. Far right: a *dark-adapted* goldfish rod. Center top: a horizontal section through the basal outer segment of the cone. Center bottom: synaptic terminals of a cone and rod.

Most retinas are “duplex”, containing rods and cones. Pure rod retinas are rare (e.g. ratfishes). Cones and rods are specialized neuroepithelial cells with multiple compartments. The *outer segment* (OS) contains hundreds to thousands of free disks or contiguous membrane formed of flattened plasma membrane folds in which various opsins (the protein auxochrome of the visual pigment) are inserted (see Chapters by Shichida, Yau and Kawamura). The OS connects to the inner segment (IS) via a cytoplasmic neck through which a 9+0 cilium extends. The *ellipsoid*, the most distal part of the IS, contains a dense packet of mitochondria. The *myoid* contains diffuse structures including the endoplasmic reticulum and golgi apparatus. In teleosts and anurans the myoid is motile, contracting cones and extending rods in the photopic state and the reverse in the scotopic state, regulated in part by diffusible signals from the neural retina [20]. The ELM is the physical border between the outer and inner *limbs* of photoreceptors and defines the optical entrance aperture of the outer limb. In most vertebrates cone nuclei are positioned at the distal border of the ONL and often protrude past the ELM. In rod-rich species, rod nuclei form an irregular, stacked proximal sublayer. Rods and cones have an axon fiber, $\approx 0.5\text{-}2\ \mu\text{m}$ in diameter in many species, terminating as a synaptic ending at the distal margin of the OPL.

A cone outer segment (COS) often literally resembles a truncated cone. The plasma membrane forms tightly stacked free lamellae on most of the COS circumference but fuses with the plasma membrane on the ciliar side [19]. In most bony fishes an accessory outer segment (AOS) of unknown function and large volume connects to the COS by a thin isthmus extending up the ciliar side of the OS. The base of the OS in many non-mammalian cones and rods is ringed by a palisade of actin-stiffened cytoplasmic fingers that may extend over half the length of a COS in some species. Each COS is surrounded by apical RPE processes, although mammals and avians show a large space around each COS composed of a complex extracellular matrix. The myoid of teleost cones is an active motor complex, extended (microtubule mediated) in dark-adapted and contracted (actin-mediated) in light-adapted retinas [21]. Non-mammalian cone myoids are often striped by longitudinal fins that interdigitate with MV microvilli [19,22,23]. Proximal to the ELM the cones become smooth, with sparse cytoplasm around the nuclear bulge, narrowing proximally to an axon fiber that expands into a synaptic pedicle.

The cone pedicle (see Chapter by Copenhagen) is a cupola-shaped chamber filled with synaptic vesicles and a few cisterns, vacuoles and coated vesicles (endocytic compartments). Teleost cones possess ≈ 12 presynaptic specializations (up to 40 in primates) each shaped as a linear *synaptic ridge* beneath which the arciform density forms a groove into which one edge of the synaptic ribbon (a pentalaminar plate) is inserted. The ribbon “striping” is the cross-sectioned plate whose two cytoplasmic surfaces to serve as vesicle tethering sites, feeding two rows of docking and fusion sites along each slope of the ridge for vesicular glutamate release [24]. Most pedicles are contacted by large horizontal cell (HC) processes lateral to the ribbon, with dendrites of certain ON-center bipolar cells (BCs) usually occupying the center lacunae at various distances from the release site [25]. In many non-mammalians telodendrial processes of other cones may occupy a central postsynaptic position near the ribbon, presumably for synaptic cone-cone signaling [26]. OFF-center BCs are usually positioned away from the ribbon at specialized adhesion points with cones [27]. These sites may contain postsynaptic receptors but apparently do not indicate cone release sites. Diffusion from the synaptic ridge appears to suffice. Cones and BCs also possess potent glutamate transporters whose detailed spatial localization is unknown [28].

Rod outer segments (ROSs) differ from those of cones. After a few lamella are formed at the base of the ROS, the rims of facing extracellular membrane surfaces fuse and then separate from the plasma membrane, creating free disks within a plasma membrane case [29]. Rod disks often possess deep incisures where the plasma membrane sharply indents the disk [30]. In non-mammalians, calyceal processes are essential in shaping the growing ROS, but the lamellar zone and the processes are short. Most ROSs have no identifiable AOS. As in cones, the ellipsoidal mitochondrial pack is positioned at the distal limit of the IS. Fish rod myoids are motile and contract in dark-adapted and extend in light-adapted states; both processes involve actin binding [21]. Rod synaptic terminals are often smaller than those of cones and in most fishes and mammals, containing a single ribbon. Fish rod spherules enclose lateral rod HC ribbon contacts, with mixed rod-cone ON-center BC dendrites crowding into a central position and mixed rod-cone OFF-center BCs positioned away from the ribbon [31].

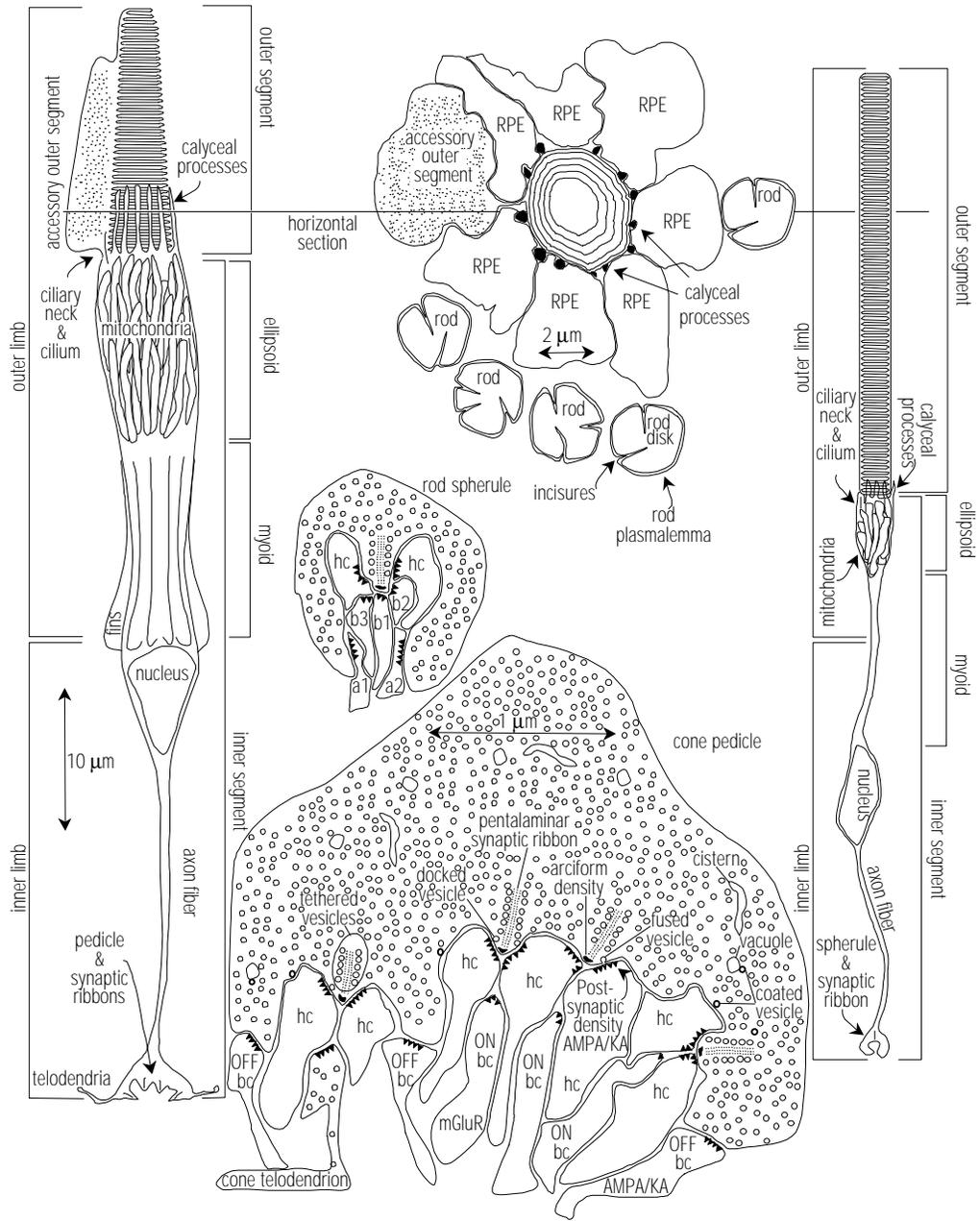


Figure 3: Diverse forms of vertebrate photoreceptor cohorts.

Different vertebrate systems have been exploited for structural, physiological, biochemical, developmental, genetic and psychophysical analyses of retinal function. Most non-mammalians have pleomorphic cones. The photoreceptor types of six popular models are presented here. The goldfish, *Carassius auratus* displays one form of teleost photoreceptor cohort containing double cones (DCs) of unequal members patterned with single cones (SCs), and rods filling remaining space [32,33]. Retinaldehyde (retinal) or dehydroretinal chromophores predominate in marine and fresh-water species/phases, respectively, though mixtures are common. The long goldfish DC (LD) contains a dehydroretinal-based pigment absorbing maximally at 625 nm: P625. The short (SD) cone contains P535. A variable number of long SCs contain P625 (LSR) or P535 (LSG) and short SCs (SS) contain P435. In young animals, miniature SS (MSS) cones with oblique axon fibers contain P360 [31]. Both rod and cone outer limbs can move tens of microns in response to adaptive signals. Other fishes have simpler cone sets and often display long-wave pigments in both members of either unequal or equal DCs. In most fishes rods outnumber cones 5-10:1.

The fresh water turtle *Psuedemys scripta elegans* typifies known chelonian retinas [35]. Unequal DCs are formed by a long principal (PC) and short accessory (AC) cone, both containing P620, with a yellow-orange carotenoid oil/wax droplet (o) in the PC. The AC lacks a droplet (as in all tetrapods) and has a distinctive paraboloid (p). The paraboloid is a glycogen storage body placed between the mitochondrial pack (m) and a supranuclear sac (s). Two SC types contain P620 and either red (r) or pale green (pg) droplets. P540 SCs contain a yellow orange (y) droplet and P460 SCs contain a clear droplet. P460 SCs have oblique axons. Rods (P520) lack oil droplets but have larger outer segments than cones, multiple synaptic ribbons and are sparser than in teleosts. Marine turtles have similar cell types but both droplets and pigments (retinal-based) are blue-shifted [50].

Avian retinas, represented here by the rock dove (*Columba livia*), have slender versions of the cones of reptiles [37]. PCs and ACs contain retinal-based P562 with a yellow-orange droplet in PCs and none in ACs (though yellowish granules often appear). P562 SCs have red droplets, P506 SCs have yellow droplets, P450 SCs have visibly clear droplets and P400 cones have UV-transparent droplets (t). Rods contain P506.

Amphibian retinas are diverse in photoreceptor form and switch from juvenile dehydroretinal to retinal-dominated adult pigments. Anurans such as *Rana pipiens*, possess two kinds of rods, named according to their appearance in a fresh, unbleached receptor mosaic. "Red" rods in adults contain P502 and smaller "green" rods contain P432. Not all frog cones have been classified but PCs contain P580 with a clear oil droplet and ACs contain P502 and no oil droplet. SCs with clear oil droplet contain P580, but blue and UV-sensitive cones are present in anurans. Certain urodeles, here represented by juvenile phase tiger salamanders (*Ambystoma tigrinum*), are polyploid organisms with huge cells: red (P520) and green rods (P432), PCs (P618), ACs (P520), and SCs (P618, P432, P380) [38-41].

Mammalians have cones of only two or three spectral types. Rods contain P500, red cones (long-wave sensitive, LWS) cones P556, green cones (mid-wave sensitive, MWS) P534, and blue cones (short-wave sensitive) P431 [42]. While superficially monomorphic, subtle shape differences exist between blue and non-blue cones, the former being slightly longer and more tapering [43]. Depending on whether the plane of section is distal (D) or proximal (P) relative to the ellipsoid of the blue cones, they may appear larger or smaller than surrounding cones in horizontal sections.

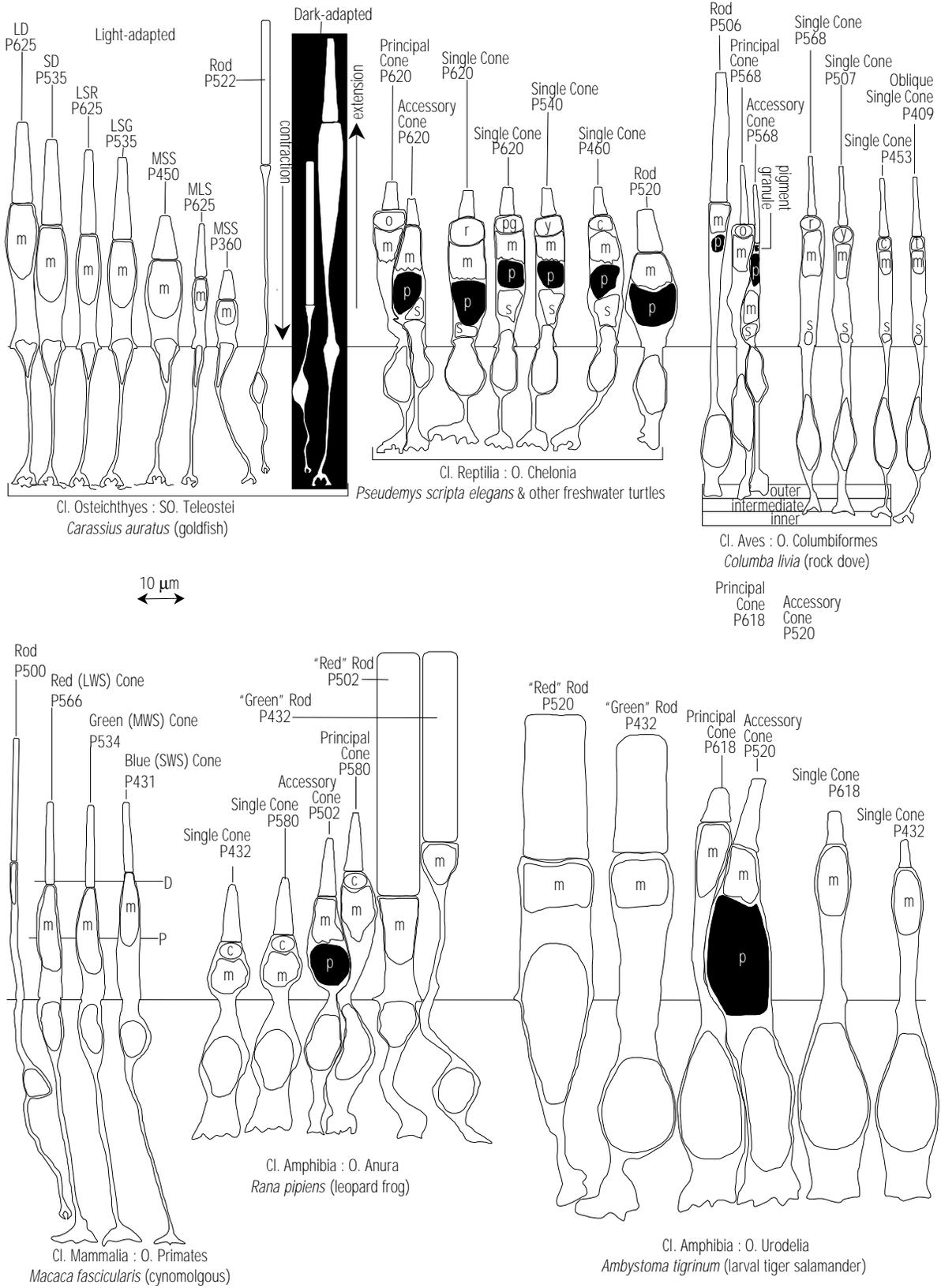


Figure 4: Vertebrate neuronal patterns:

The visual image is cast on the screen of the retina and the planar distribution of photoreceptors and neurons impacts the quality of the neural representation. Most vertebrates have no easily discernable patterning for cones containing middle or long-wave pigments but almost all have patterned short-wave or blue cones. In some cases, the cones are not locally patterned but are distributed differentially. In mice, green and blue cones are largely segregated to the dorsal and ventral parts of the retina, respectively [44]. In the primate retina there is a distinct differential depletion of blue cones in the fovea [45,46]. Bony fishes display the most orderly patterns, with true mosaics of DCs and SCs. In many fishes (e.g. perch and goldfish), the rhomboid is a common motif [32,46,47]. DCs form the sides of rhombs and SCs are positioned in the centers. When UV cones are present, they occupy some of the rhomb corners. Perch DCs are equal cones, while goldfish DCs are unequal, with LD and SD members usually taking alternating positions. Amphibian photoreceptor mosaics have not been thoroughly described, but green rods are randomly interspersed among the more numerous red rods. Mosaics are difficult to discern in reptiles or avians, but patterning is subtly present. The PCs and one type of SC in pigeon retinas fluoresce under 365 nm illumination and can be seen to form two distinct orderly arrays [48]. In primates, only blue cones have a non-random pattern [45,49]. Patterns are less obvious but still pervasive among the complex matrix of higher-order retinal neurons. When unique types of cells are isolated from contaminating cohorts, most retinal neurons are highly patterned, and random placements are rarities [50]. Even in retinas with many neuronal types it is possible to observe fine-scale, ordered neuronal placements: in the marine fish, the dragonet, three different kinds of BC terminals form distinct arrays [51]. On a scale two orders of magnitude greater, outer alpha GCs of a cichlid fish are independently patterned, with many different GC types interspersed [52].

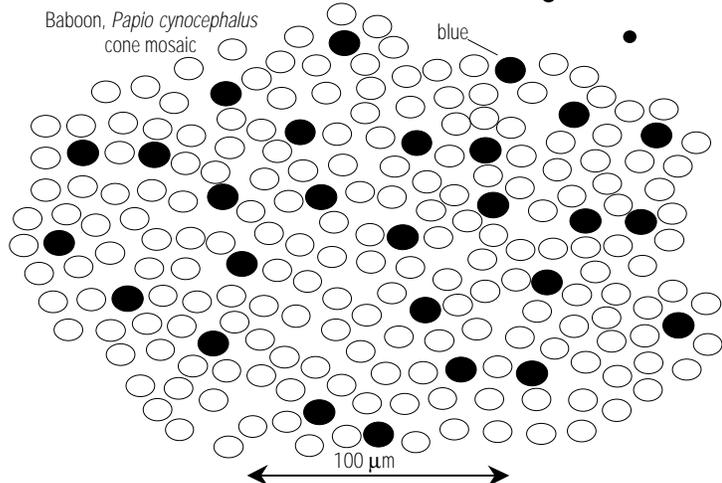
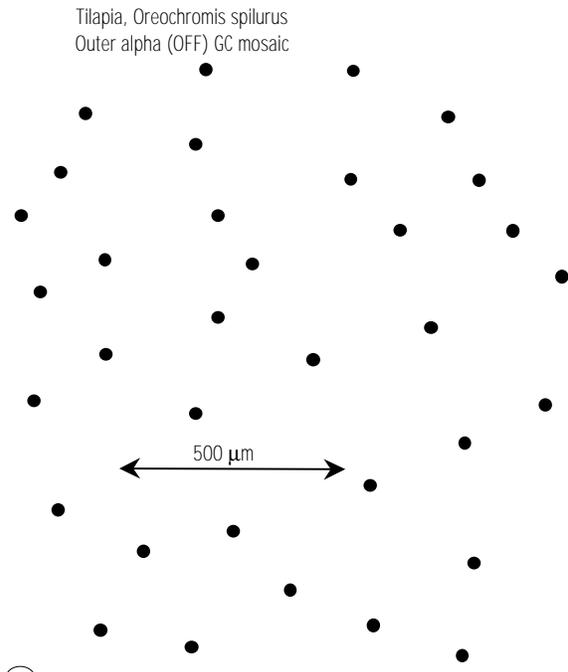
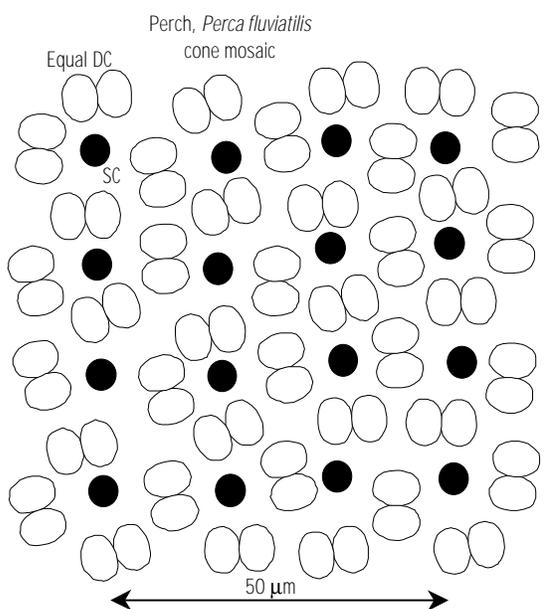
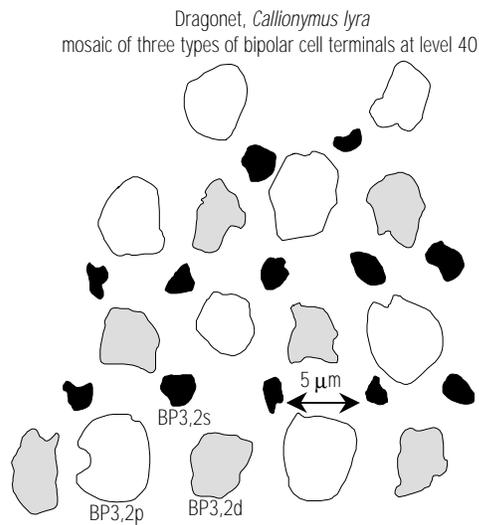
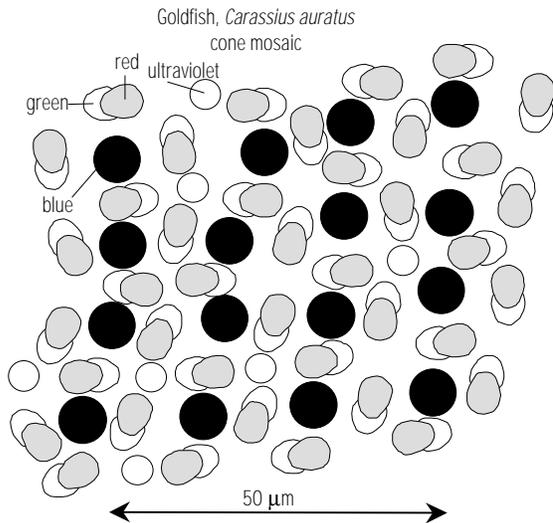


Figure 5. Signal flow in the retina (see Chapters by Kaneko, Wässle, Kaneko, Tachibana and Dacey). Vertical channels are glutamatergic and lateral channels are predominantly GABAergic/glycinergic.

The detailed forms of BCs, HCs, ACs and GCs have been described in many other sources and will be treated here only schematically [53-56]. The photoreceptor and BC neurotransmitter is glutamate [57]. In non-mammals, rod signals are collected by special subsets of BCs but, even so, one of those is clearly a homologue of the mammalian rod BC. ON-center cells bear type III metabotropic glutamate receptors (mGluR6) [58]. OFF-center BCs are driven through ionotropic AMPA/KA receptors. Multiple mixed rod-cone BCs are known in goldfish, differing in form, rod weightings and cone selectivities [59]. Pure cone BCs are diverse in fishes and the connectivities of most remain unknown, though pure green, pure blue and mixed cone BCs have been established [60,61]. The mammalian retinal BC cohort is simpler: one rod BC, \approx 7-9 types of diffuse cone BCs contacting all cone types [9]. Primates and ground squirrel retinas possess, in addition, both ON- and OFF-center midget BCs that contact but a single cone in central retina and a only few cones in the periphery. The restriction to a single cone means that foveal/central midget cells are potentially color-biased. Primates also have a blue cone BC [62].

BC axon terminal positions reveal the rich laminar organization of the IPL. OFF-center BCs terminate in the distal third to half of the IPL (sublamina **a**) and ON-center BCs in the proximal two-thirds to half (sublamina **b**) [63, 64]. AC and GC dendritic arbors laminate according their BC sources: OFF-center ACs/GCs in sublamina **a**, ON-center ACs/GCs in sublamina **b** and ON-OFF cells in both. GC populations in vertebrates are diverse and several known morphologies correlate with stimulus-response patterns [9](see Chapters by Rodeick and Sterling).

Lateral processing in the retina shapes attributes of vertical channels. HCs (see Chapters by Miyachi, Kaneko and Toyoda) are feedback and possibly feedforward inhibitory interneurons, many varieties of which display GABAergic markers [15]. The GABAergic nature of HC transmission remains controversial. Most HCs lack *bona fide* presynaptic specializations, although clear HC \rightarrow IPC vesicular contacts are known [65,66]. GABAergic HC feedback transmission is thought to be mediated by reverse transport (see Chapter by Schwartz). In fishes, GABAergic markers have been associated only with non-color coded cone HCs; all other HC types lack GABAergic markers [56]. All HCs seem to bear pharmacologically similar sets of AMPA/KA receptors. Pure rod HCs do not exist in tetrapods and rod contacts are made by axon terminal fields arising from cells whose somas contact cones [55]. While variations exist, most mammalian HCs resemble rabbit HCs. Type A HCs are strongly coupled, lack axons, have large processes and contact cones [55, 67]. Type B HC somas contact cones and have an extensive axonal arbor contacting rods [67]. The mechanism of mammalian HC feedback remains mysterious. It could be GABAergic, but most mammalian HCs cells apparently lack markers characteristic of CNS GABA neurons. Subcellular localizations of GABAergic markers have now been found in central rabbit HCs [68].

ACs (see Chapter by Masland) are the key lateral interneurons of the retina and are extremely diverse [53,54,56]. They directly shape BC responses by feedback/feedforward inhibition and GC responses by feedforward. Mammalian ACs contain GABA, glycine or both [5]. All non-mammalian ACs or IPCs contain GABA/glycine/both, except the dopaminergic interplexiform cell of teleost fishes [69]. ACs are highly stratified, reflecting BC organization. Every BC type receives extensive GABAergic AC input and anatomical evidence indicates that each BC likely has a unique cohort of AC inputs, though some ACs may service many BCs [15].

IPCs (see Chapter by Hashimoto) may exist in more forms than have been clearly delineated but the two best studied forms are the dopaminergic (DA) and glycinergic (gly) IPCs of teleost retinas [69]. DA IPCs primarily receive GABAergic input in the IPL and target cells in the OPL, typified by HCs. Gly IPCs are more complex and receive input from HCs, bypassing the BC filter altogether, and targeting cells in the inner retina.

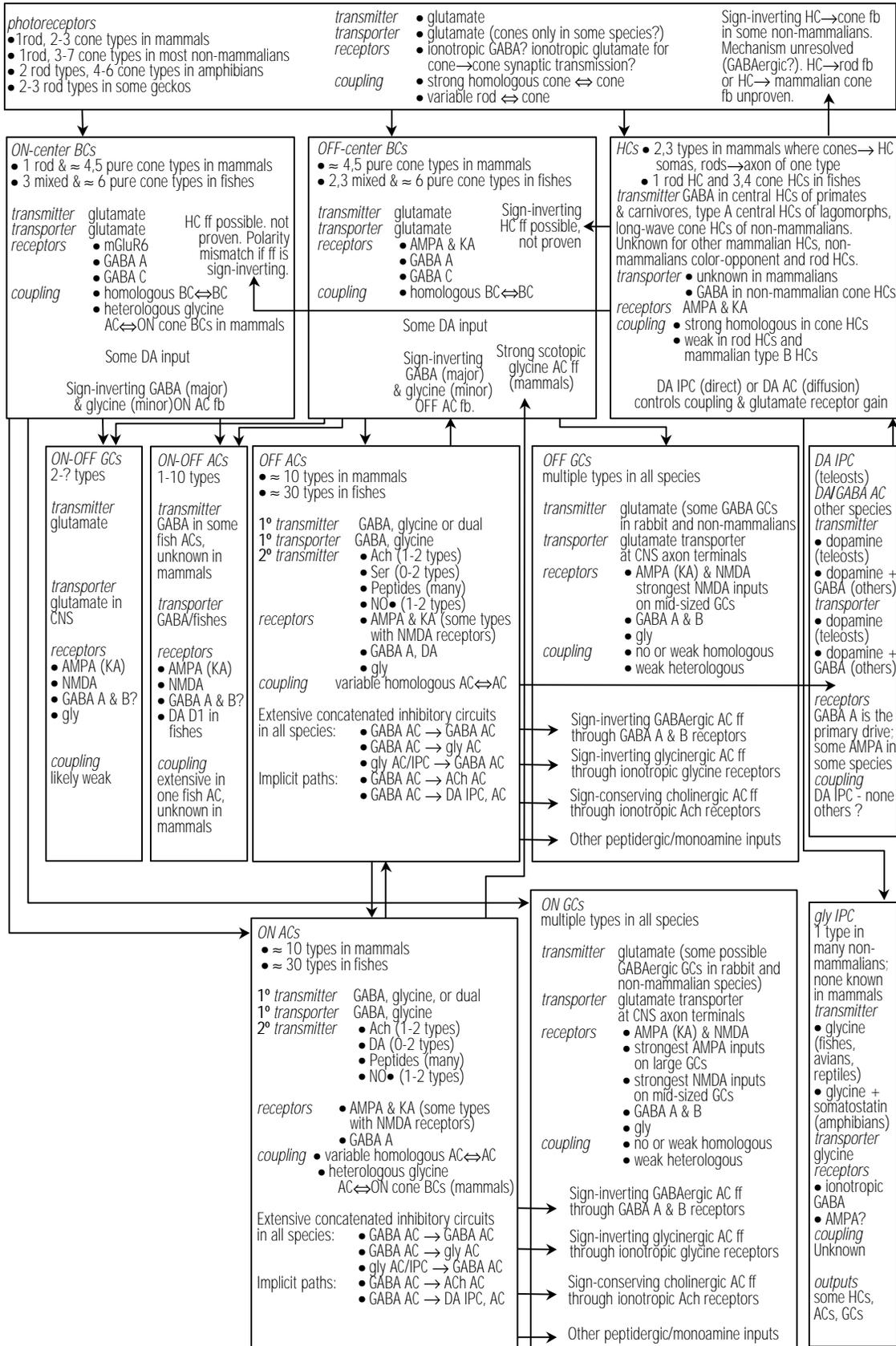


Figure 6: Functional lamination of the IPL

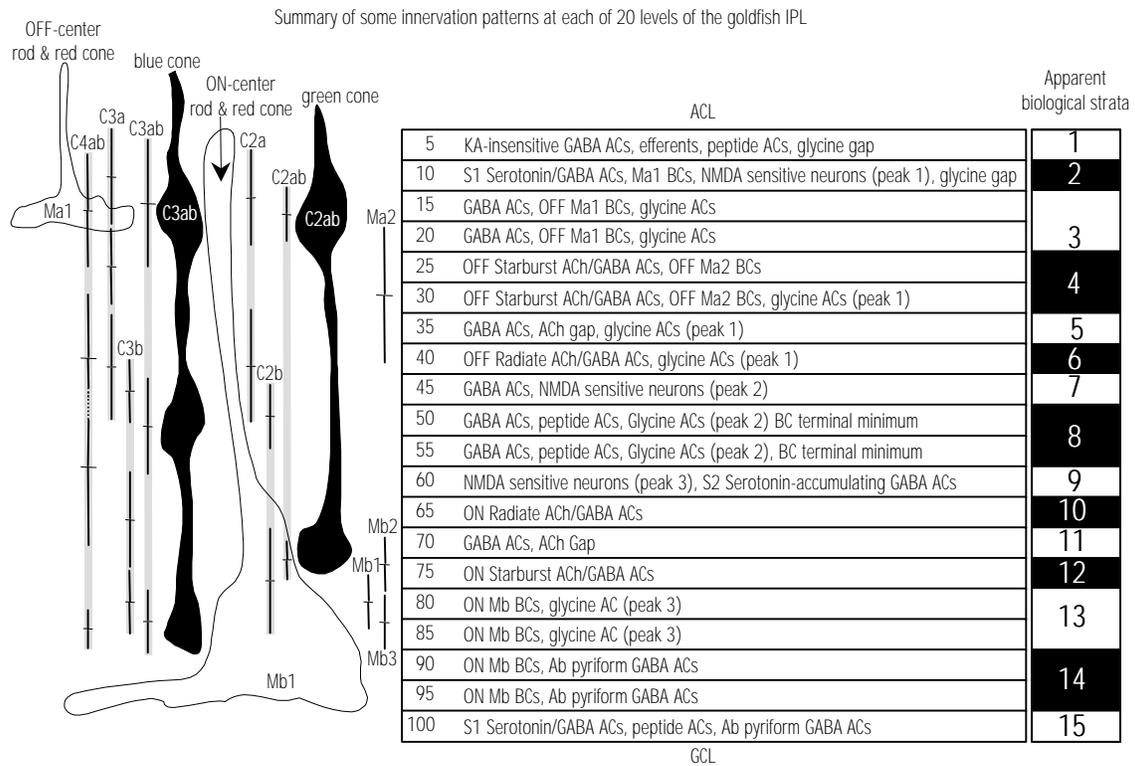
One of the most striking features of the retina is the lamination of the IPL, which is far richer than suggested by mere divisions into ON and OFF, or rod-ON /cone-ON / cone -OFF (see Chapter by Wässle). It has been traditional to divide the IPL into five arbitrary, equal sublayers, but biological lamination is clearly more complex. For example, the levels of the IPL at which various types of goldfish BCs terminate are known in detail, even if all the connections are not, and demonstrate that specific ganglion cells must send dendrites to different levels to acquire signals from those cells. OFF-center Ma BCs differentially stratify over levels 10-30 while ON-center Mb BCs stratify in levels 75-95. Pure cone BCs are very diverse and include cells with double (C2a, C2b) and triple (C3a, C3b) stratifications within sublayers a and b as well as across the entire IPL (C2ab – likely green cone BCs; C3ab – likely blue cone BCs; and C4ab – of unknown connectivity). Markers for molecules such as calbindin indicate that functional sublamination can be ever more precise and that individual neuronal strata can be less than 2 μm in width [70]. In many retinas, simple structural observations imply the existence of a minimum of 15 sublayers, some of which are very thick and likely to be subdivided further [50]. The GABAergic AC stratification pattern of the pigeon retina reveals a minimum of 15 sublayers [71]. Even the thin goldfish IPL (25-30 μm) is highly stratified. By accounting for the laminar positions of BCs, kainate (KA) and NMDA sensitivity, cholinergic processes (ACh), and various known types of ACs, a minimum of 15 functional sublayers emerges there also. If any GC differs from another type only slightly in its level of arborization in the IPL, the differential composition of that layer will confer upon unique stimulus selectivities on that GC. Indeed, the key characteristic of most of the 20-30 amacrine cell types of the rabbit retina is the stratification pattern of each cell's dendrites [71].

In summary, the diverse photoreceptor/neuronal types are arrayed in patterns, many of which have yet to be discovered, and their synaptic connections are partially revealed by the fine laminar organization of the inner plexiform layer. Differential distributions of neurotransmitters and receptor subtypes confer upon each cell distinct input/output characteristics. The molecular, structural and biophysical attributes of retinal processing will be discussed in the following chapters.

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