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Human retinal circuitry and physiology

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Abstract

Every second, in an average daytime light environment, hundreds of millions of photons enter the human eye and arrive at the photoreceptor layer of the retina. All our information about the visible world is contained in this rain of photons. The retina is a complex tissue, literally an extension of the brain, which transforms the rain of photons into bioelectric signals containing all the information available to the brain to interpret and respond to the external visual world. A considerable amount of processing takes place within the retinal tissue itself. Understanding what kind of processing takes place at each retinal stage is crucial for understanding normal vision, vision in the presence of diseases affecting the retina, and, ultimately, for the development of therapies to treat such diseases. This manuscript reviews the relation between structure and function of the different retinal pathways and addresses their possible roles for visual perception. **Keywords:** retina, physiology, parallel pathways, vision, perception.

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Introduction: Basic Anatomy

Neural, Glial and Epithelial Structures

The retina is responsible for sensing environmental light and transforming it into electrical impulses that can be read and further processed centrally. It is, in fact, an extension of the central nervous system, but with the advantage of being better understood than other central areas. The retinal tissue contains both neuronal and non-neuronal elements, which work together to enable vision and to maintain retinal homeostasis.

The retinal structure is highly conserved among vertebrate species. The human retina, as any other vertebrate retina, is neatly organized in layers (Figure 1), with nuclear strata that contain the neuronal cell bodies and interplexiform strata or neuropil, where the processes of these cells make contacts. As shown in Figure 1a, there are three nuclear layers (the *outer nuclear layer* or *ONL*, *inner nuclear layer* or *INL*, and *ganglion cell layer* or *GCL*) and two plexiform laminas (*outer plexiform layer* or *OPL* and *inner plexiform layer* or *IPL*).

The ONL contains the cell bodies of the light sensitive cells, or photoreceptors, whose outer segments (the photosensitive portions of the cells) are wrapped in a protective layer of pigmented epithelial cells ("p" in Figure 1b). Although the *retinal pigment epithelium* (RPE) is technically speaking not a part of the neural retina, it is fundamental for proper retinal function. Among other things, the RPE is involved in retinal homeostasis, being responsible for photoreceptor renewal, for the breakdown of toxic by-production of photoreceptor activity and for photopigment regeneration (Lamb & Pugh Jr., 2004), as well as in protecting the retina from light damage by the absorption of excessive photons (Tsacopoulos, Poitry-Yamate, MacLeish, & Poitry, 1998).

The somas of three main classes of retinal second-order neurons are localized in the INL: *horizontal cells* (HCs), *bipolar cells* (BCs), and *amacrine cells* (ACs). HCs and BCs contact the photoreceptors in arrangements called *triads* in the OPL (Sjostrand, 1958); ACs, BCs and *ganglion cells* (GCs) make contacts called *dyads* at different levels (also called *sublaminas*) of the IPL (Figure 1b and Figure 2). There are different subtypes of HCs, BCs, ACs and GCs, which form retinal subsystems, or processing channels, that are more or less specialized for particular tasks. The basic layout of these processing channels will be addressed in the section "Parallel Vertical Pathways".

The retina is vertically permeated by glial elements called *Müller cells*, whose processes wrap around neuronal cell bodies, axonal and dendritic processes (Figure 3). The functions of these non-neuronal elements, as in the case of the retinal pigment epithelium, are many (Distler & Dreher, 1996; Kalloniatis & Tomisich, 1999; Newman & Reichenbach, 1996; Tsacopoulos et al., 1998). For example, Müller cells maintain glucose and neurotransmitter homeostasis by removing glucose and the main retinal neurotransmitters, glutamate and GABA,

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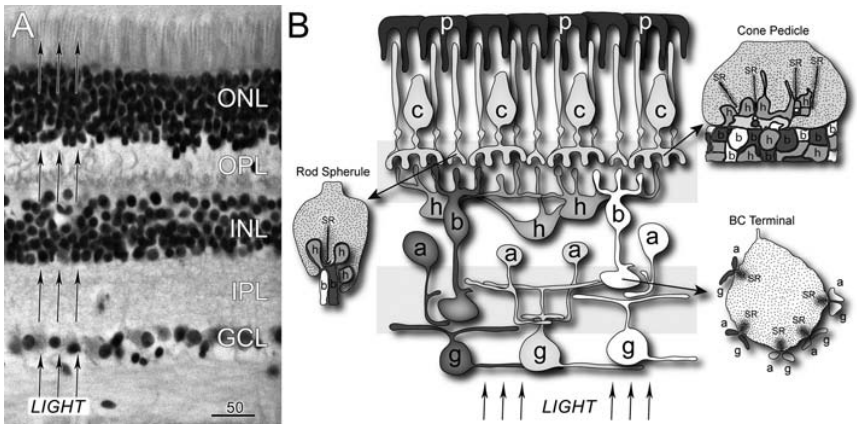

Figure 1. The retina. (A) Light micrograph of a histological section through the human retina at about 2 mm from the foveal center. ONL = outer nuclear layer; OPL = outer plexiform layer; INL = inner nuclear layer; IPL = inner plexiform layer; GCL = ganglion cell layer. Scale bar, 50 µm. Picture courtesy of Dr. Jan Klooster, The Netherlands Institute for Neuroscience. (B) Schematic drawing of the retina. The grey rectangles represent the OPL (top) and IPL (bottom). Not all retinal cell types are depicted here. P = pigment epithelium; c = cone; h = horizontal cell; b = bipolar cell; a = amacrine cell; g = ganglion cell. At the left and right sides of the drawing, the photoreceptor and bipolar cell synaptic complexes are depicted in detail. Left: triad at the rod spherule. Top right: triad at the cone pedicle. Bottom right: bipolar cell dyads in the IPL.

from the extracellular space. Müller cells then transform glucose into lactose, and GABA and glutamate into glutamine, which are then returned to the extracellular space and reutilized by neurons. Moreover, these glial cells buffer extracellular K^+ ions in order to guarantee the correct ionic gradients across cellular membranes (Newman & Reichenbach, 1996).

Müller cells further provide support for the neuronal structures and, most surprisingly, may act as living optical fibers within the eye: they can guide photons reaching the retinal surface to the photoreceptor outer segments in the outer retina (Franze et al., 2007). This way, image degradation by the inhomogeneous optical properties of the retinal neuronal elements, which scatter light as it travels from the inner to the outer retina (Hammer, Roggan, Schweitzer, & Muller, 1995), is reduced.

Two other types of glial elements, *astrocytes* and *microglia*, are present in vascularized retinas such as ours (Figure 4). These two cell types differ in origin, location and function. Astrocytes are of ectodermal origin, like Müller cells, and localize primarily in the so-called *retinal fiber layer*, which contains mostly GC axons. They wrap around these processes and the axon bundles that ultimately form the optic nerve. Astrocytes vary in morphology, depending on their precise retinal location and relation to blood vessels and neuronal processes (Trivino, Ramirez, Ramirez, Salazar, & Garcia-Sanchez, 1992).

Microglial cells, on the other hand, originate from the mesoderm and can be found in every layer of the retina. While astrocytes are probably responsible for synaptogenesis, nutrition, ionic homeostasis and the modulation of GC activity (Newman, 2003), the retinal microglia are involved in both the immune response against invading agents and the phagocytosis of endogenous debris (Langmann, 2007; Schuetz & Thanos, 2004).

Design Constraints and Cell Distribution

The visual system most likely evolved so as to code visual information optimally within the constraints imposed by biological tissue (such as noise in information transmission, energy/metabolic requirements, limitations in response speed of neurons, etc.). This means transmitting a maximum amount of information using a minimum amount of energy. As an example, the high metabolic cost of keeping a large number of optic nerve fibers (Laughlin, 2001; Lennie, 2003), combined with the mechanical constraints imposed by the need for rapid, relatively large eye movements (Barlow, 1952; Martinez-Conde, Macknik, & Hubel, 2004), led to the evolution of a thin optic nerve. To accommodate the need to both conserve energy and to keep the optic nerve thin, one of the solutions that evolved is a strong *convergence* of many photoreceptors onto second-order neurons (Figure 5a-b).

A beneficial effect of this strategy might be improved sensitivity, because convergence increases the probability of a photon activating a GC. On the other hand, convergence can diminish spatial resolution (e.g. visual acuity), since high spatial resolution requires a large number of nerve fibers with small, non-overlapping receptive fields. This kind of trade-off between specificity and sensitivity is present in many different aspects of perception, such as brightness and color, movement and form. In order to accommodate the conflicting needs of these different perceptual demands, the visual system developed a second strategy: *divergence* (Figure 5c).

In addition to converging onto second-order neurons, photoreceptor signals also diverge, that is, photoreceptors communicate with different neuronal types, each "specialized" in transmitting certain kinds of data (Sterling, 2003; Zhang & Sejnowski, 1999). This specialization implies that, in order to transmit as much information as possible,

many different neuronal types are needed. This is true for all retinal neurons, including the photoreceptors, which, as we shall see later, can also be divided into different subtypes.

A third strategy that ensures effective transmission of information to the brain is *regionalization*. In most animals, retinal neurons are not homogeneously distributed. Rather, the retina is roughly divided into central and peripheral areas, in which different neuronal types concentrate. The retinal periphery, for instance, is richer in rods and rod-driven neurons than the central retina (Figure 6b). This implies that visual sensitivity and motion perception are best in the peripheral visual field (Barlow & Mollon, 1982; Carrasco, McElree, Denisova, & Giordano, 2003), whereas color vision and visual acuity are best in the central visual field (De Valois & Abramov, 1966; Merigan & Katz, 1990).

This is especially true in foveate species such as the human. The *fovea* is a retinal specialization dedicated to high spatial resolution (Figure 6a). There, photoreceptors connect to second-order neurons on a one-to-one basis, in order to preserve the spatial detail of the information sent to the brain (Kolb, 1970). In the fovea and in its surrounding region, the so-called *parafovea*, convergence is the smallest and divergence is the largest. As we move from the fovea to the retinal periphery, the amount of convergence changes (Figure 6c). For instance, in the marmoset retina the foveal cone : BC ratio is around 0.1 and the BC : GC ratio is 0.3, but in the midperiphery these ratios change to 0.5 and 6.4, respectively. In the retinal periphery, these numbers raise to 4.6 for the cone : BC ratio and 13.6 for the BC : GC ratio (Chan, Martin, Clunas, & Grunert, 2001).

Another example of regionalization can be found in the very anatomy of retinal cells. Since convergence increases with eccentricity, so do the dendritic fields of BCs and GCs (Wässle & Boycott, 1991). Photoreceptors also change shape: since the general photoreceptor density decreases towards the periphery, their cross-sectional areas increase (Packer, Hendrickson, & Curcio, 1989). This actually increases the photon-collecting efficiency of peripheral rods and cones, which could compensate for a decreased light gathering efficiency of the eye towards the retinal periphery (Sterling & Demb, 2004).

Information Flow: Vertical and Lateral Pathways

Visual information is not simply conveyed from the retina to the brain. In order to make optimal use of its neuronal elements and transmission capacity, the retina transforms photoreceptor signals at each and every synapse. Therefore, many calculations take place in both plexiform layers before this information leaves the eye.

The laminated organization of the retina generates two streams of visual information (Figure 7): a main or *vertical pathway*, from the photoreceptors to BCs and from BCs to GCs, and a secondary *lateral pathway*, comprising local feedback circuits from HCs back to photoreceptors (Byzov, Golubtzov, & Trifonov, 1977; Kamermans et al., 2001; Stell, Lightfoot, Wheeler, & Leeper, 1975), and from ACs back to BCs (Kaneko & Tachibana, 1987; Tachibana & Kaneko, 1987; Yazulla, Studholme, & Wu, 1987). While the vertical flow is directly involved in sending signals to the brain, the lateral circuits adjust the gain of the pre-synaptic and post-synaptic cells (also defined as the post-synaptic voltage change resulting from a given pre-synaptic voltage change) at each stage, thereby optimizing signal transmission within the vertical pathway.

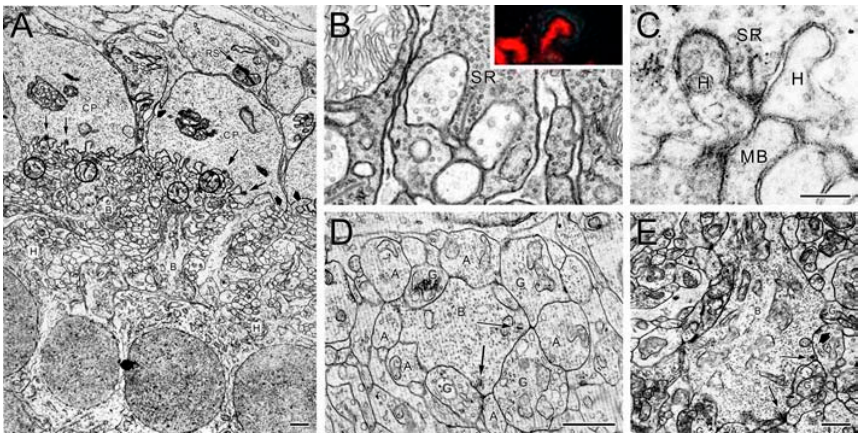

Figure 2. Synaptic organization of the plexiform layers. (A) Low-power electron micrograph of the human outer plexiform layer. Arrows indicate synaptic ribbons. Thick arrows indicate interreceptoral gap junctions. Circles indicate desmossomal junctions between adjacent horizontal cell dendrites. CP = cone pedicles; RS = rod spherules; B = bipolar cell; H = horizontal cell. Scale bar, 1μm. Reproduced with permission from Dowling and Boycott (1966). (B) Rod triad. Inset shows a confocal picture of a synaptic ribbon labeled with a fluorescent marker. SR = synaptic ribbon. From tom Dieck and Brandstätter (2006), with kind permission from Springer Science and Business Media. (C) Cone triad of the monkey retina. SR = synaptic ribbon; H = horizontal cell; MB = midget bipolar dendrite. Scale bar, 0.25 μm. Picture courtesy of Dr. Jan Klooster, The Netherlands Institute for Neuroscience. (D) Human and (E) Primate dyads. Arrows point to synaptic ribbons. B = bipolar cell terminal; A = amacrine cell; G = ganglion cell. Scale bars, 1 μm. Adapted with permission from Dowling and Boycott (1966).

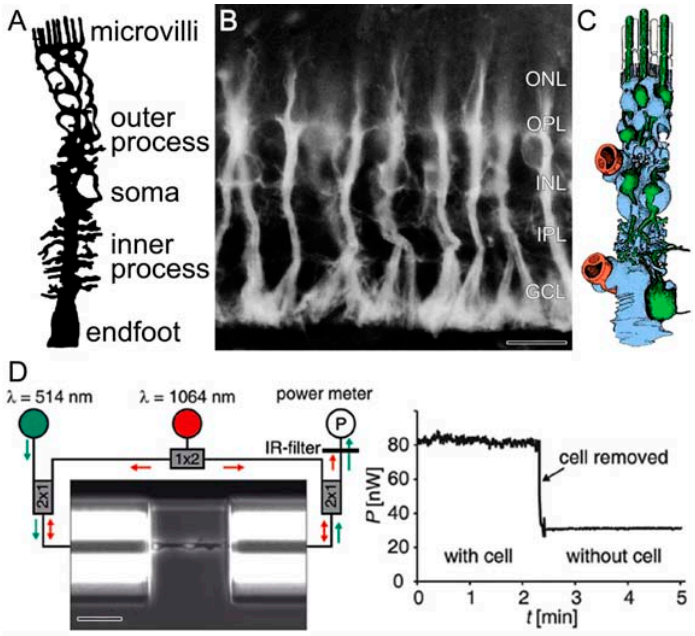

Figure 3. Müller cells. (A) Drawing of a rabbit Müller cell stained by the method of Golgi. Reprinted from Bringmann, Pannicke, Grosche, Francke, Wiedemann, Skatchkov, Osborne and Reichenbach (2006), copyright 2006, with permission from Elsevier. (B) Immunostaining of the rabbit retina for vimentin, a filament protein abundant in Müller cells. These glial elements are evenly spaced throughout the tissue and span the whole retinal thickness. Thin processes extend from the stout soma at both the OPL and IPL. Scale bar, 20 μm. From Robinson and Dreher (1990), copyright 1990 John Wiley & Sons, Inc. Reprinted with permission of John Wiley & Sons, Inc. (C) Schematic drawing of Müller cells and their relation to other neuronal and non-neuronal structures. Photoreceptors, BCs and GCs are shown in green, blood vessels in red. Reprinted from Bringmann et al. (2006), copyright 2006, with permission from Elsevier. (D) Light guidance properties. Left: a Müller cell is aligned with two optic fibers by counter-propagating infra-red beams. The left fiber emits visible light at 514 nm ("green"), whereas the right fiber collects the light transmitted through the Müller cell and guides it into a power meter. Right: power meter reading during the experiment. When the cell is removed from the optical path, the amount of light that reaches the power meter decreases, indicating that Müller cells behave much like optical fibers themselves. Scale bar, 50 μm. From Franze et al. (2007), copyright 2007 National Academy of Sciences, U.S.A.

Photoreceptors, HCs and BCs respond to light with sustained, graded membrane potential changes. This may be so because these neurons have short processes and do not need to transmit information over long distances: passive spread of potential along the cell membrane is enough for information to be transmitted from one end of the cell to the other. A second possible reason could be that such graded potentials are capable of discriminating a wider range of signals than all-or-none action potentials (Barlow, 1981). The first action potentials observed in the retina are those generated by ACs followed by GCs (Figure 7).

Vertical Transmission

Vertical transmission of visual information flows transversally across the retinal layers to the brain through three main cell types: photoreceptors, BCs and GCs. In the next paragraphs we will examine the main characteristics of these cell types and their respective roles in information coding.

Rods and cones

There are two main types of photosensitive transducers in the retina, rods and cones. They are named on morphological grounds: their outer segments differ in shape and in the way photosensitive pigments are packed within these segments (Figure 8a). The kinds of photopigments, as well as the regulation of a number of intracellular reactions, are also distinct in rods and cones. Altogether, these differences have a number of consequences for visual function, the most important being sensitivity and the range over which they are able to adjust sensitivity to ambient light levels. Rods are more sensitive to light than cones and enable us to see at dim light levels, even down to single-photon levels, whereas cones are most active when photons are plenty (for reviews, see Ebrey & Koutalos, 2001; and Pugh Jr. & Lamb, 2000). Rods have a limited ability to adapt to ambient light levels (Malchow & Yazulla, 1986, 1988; Pugh Jr. & Lamb, 2000), while cones can shift their operating range endlessly to avoid saturation (Burkhardt, 1994; Kox & Solessio, 2006; Pugh Jr. & Lamb, 2000).

In addition to light sensitivity, rods and cones also differ in their sensitivity to lights of distinct wavelengths (Figure 8d). Human rods have their maximal sensitivity around 495 nm (Dartnall, Bowmaker, & Mollon, 1983; Wald & Brown, 1958), whereas cones are divided into three distinct types according to the wavelength of peak absorption or λmax: short wavelength-sensitive cones (S-cones, $\lambda max \approx 420$ nm), middle wavelength-sensitive

cones (M-cones, $\lambda max \approx 530$ nm), and long wavelength-sensitive cones (L-cones, $\lambda max \approx 560$ nm) (Dartnall et al., 1983). The existence of photoreceptors with different peak absorptions is the first step in our ability to see colors. The next step lies in post-receptoral processing by second- and third-order neurons. Table 1 summarizes the main differences between rods and cones.

The dynamic range of a photoreceptor can be determined by measuring its light responses as a function of photon capture rates (for continuous illumination) or flash intensities. Whatever the measurement applied, although there is a big difference in the absolute threshold of the different kinds of photoreceptors, the dynamic ranges of both rods and cones are about 2 log units when no adaptive processes are taken into account (Baylor & Fuortes, 1970; Grabowski, Pinto, & Pak,

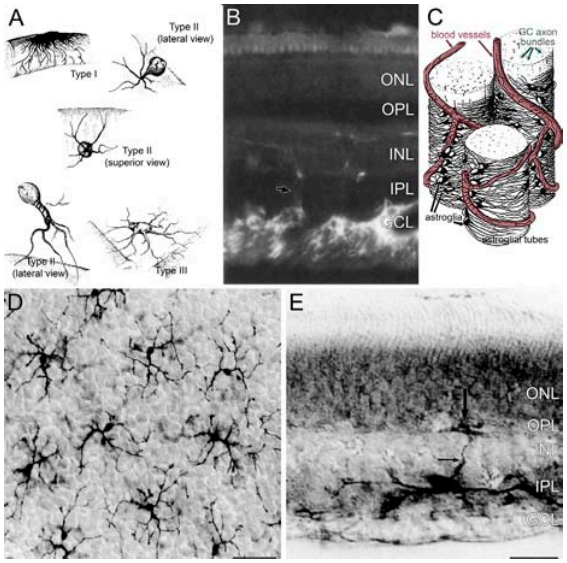

Figure 4. Other glial elements of the retina. (A) Three-dimensional drawing of rabbit perivascular astrocytes. Astrocyte morphology varies with retinal location and with the type of structure (axons or vessels) with which they relate. Reprinted from Trivino, Ramirez, Ramirez, Salazar and Garcia-Sanchez (1992), copyright 1992, with permission from Elsevier. (B) Vertical section through the human retina showing the localization of GFAP-positive astrocytes in the fiber layer. Some astrocytic processes advance into the IPL (arrow) and INL. Reprinted from Ramirez, Trivino, Ramirez, Salazar and Garcia-Sanchez (1994), copyright 1994, with permission from Elsevier. (C) Relationship between astrocytes, GC axon bundles and retinal blood vessels. Reprinted from Trivino, Ramirez, Salazar, Ramirez, Garcia-Sanchez (1996), copyright 1996, with permission from Elsevier. (D) Microglia from the rabbit retina, vertical section. An NDP-ase positive microglial cell located at the IPL extends a process through the INL (arrow) to the OPL (large arrow). Scale bar, 20 µm. From Schnitzer (1989), copyright 1989 John Wiley & Sons, Inc. Reprinted with permission of John Wiley & Sons, Inc. (E) Microglia of the rabbit retina, whole mount with focus plane at the IPL. Scale bar, 50 µm. From Schnitzer (1989), copyright 1989 John Wiley & Sons, Inc. Reprinted with permission of John Wiley & Sons, Inc.

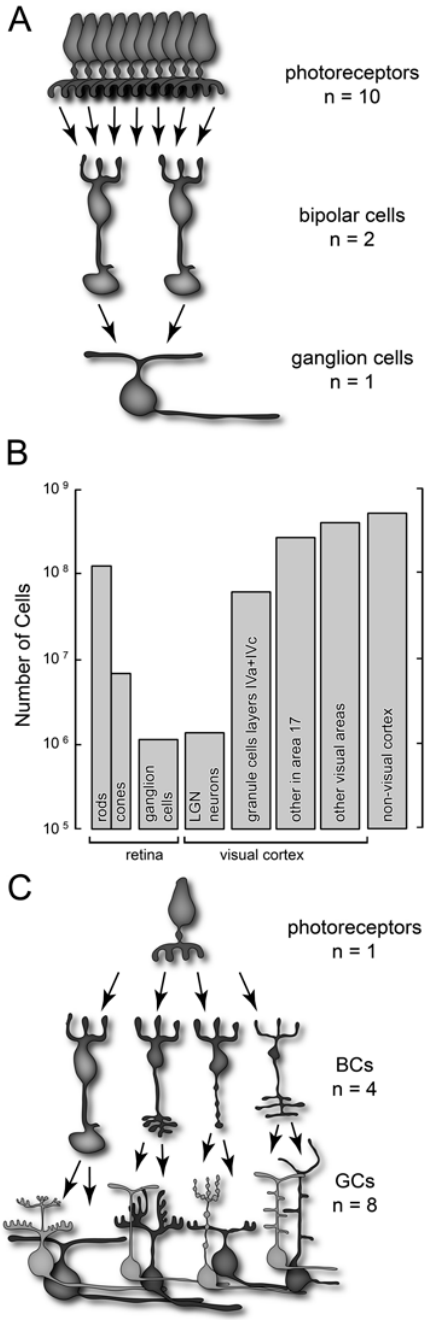

Figure 5. Convergence and divergence. (A) Example of convergence from photoreceptors onto second- and third-order neurons. In this case, 100 photoreceptors converge onto 2 BCs of the same physiological type, and these, in turn, converge onto 1 GC. (B) Estimated numbers of neurons at various levels in the visual pathway of the macaque monkey. The last column on the right shows the estimated number of cells in the non-visual areas of the cortex. The total number of neurons decreases by about 9 orders of magnitude from the photoreceptor layer to the GC layer, implying that due to this high degree of convergence, considerable information compression must take place within the retina. Replotted with permission from Barlow (1981). (C) Example of retinal divergence. A single photoreceptor sends its signal to 4 different physiological types of BCs, which, in turn, communicate with 8 different physiological types of GCs.

1972; Schneeweis & Schnapf, 1995). Furthermore, their spectral sensitivity overlap in great part (Figure 8d).

A photoreceptor light response is basically a change in membrane potential (Figure 8b). In the dark, photoreceptors are relatively depolarized in relation to other CNS neurons (around -45 mV), because cGMP-gated cation channels in their outer segments are held open in the absence of a stimulus (Baylor, 1987). Since these channels are non-specific (i.e. their reversal potential is around 0 mV), there is a standing inward current flowing, which keeps the photoreceptors at a relatively depolarized state. Light stimulation leads to the closure of these cation channels, decreasing this *dark current* and hyperpolarizing the cells (Figure 9).

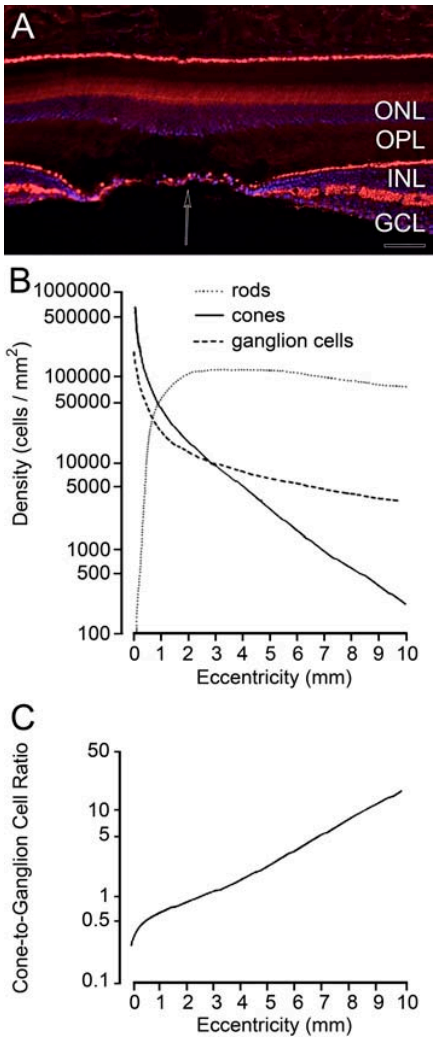

Figure 6. Regional distribution of neurons in the retina. (A) Vertical section through the human fovea. Picture courtesy of Dr. Jan Klooster, The Netherlands Institute for Neuroscience. (B) Density of rods, cones and GCs throughout the primate retina. Densities in the rhesus monkey retina were measured along the temporal horizontal meridian; zero eccentricity represents the fovea. Reproduced with permission from Boycott and Wässle (1991). (C) Cone-to-GC ratio throughout the monkey retina. Divergence is maximal in the fovea, where there are almost 3 GCs per cone. As eccentricity increases, divergence decreases and convergence increases. At the retinal periphery, there are more than 10 cones per GC. Reproduced with permission from Boycott and Wässle (1991).

But how does exactly a photoreceptor "see the light"? This is achieved by a process called *phototransduction*, which is comprised of a cascade of intracellular biochemical reactions triggered by light (Figure 9). These reactions, in turn, lead ultimately to the closure of the cGMP-gated channels in the outer segments and consequently to a voltage-dependent modulation (Schmitz & Witkovsky, 1997) of neurotransmitter (glutamate) release rate at the synaptic terminal of the photoreceptors. It is this modulation of glutamate concentration in the OPL that is sensed by glutamate receptors on BC and HC dendrites (Cervetto & MacNichol, 1972; Kaneko & Shimazaki, 1976; Murakami, Ohtsu, & Ohtsuka, 1972).

The phototransduction cascade is roughly similar in rods and cones. It starts with a G-protein-coupled receptor called *rhodopsin* in rods and *cone opsin* in cones. This protein is inserted into membranous disks in the outer segment of the photoreceptors and contains a light sensitive chromophore called *11-cis-retinal.* In the dark, this photoactive molecule is inactive, and so is its downstream cascade. *Guanylate cyclase* continuously produces cGMP from GTP, and *phosphodiesterase* continuously breaks some of this cGMP down. Together, the basal activity of these two enzymes keeps the concentration of cGMP in darkness high. Two to three cGMP molecules open an ionic channel in the outer segment membrane, the *cGMP-gated cation channel*, allowing Na^+ and Ca^{2+} ions to flow across the membrane and depolarize the cell. Na^+, Ca^{2+} and K^+ concentrations are restored by the activity of a $4Na^+$-Ca^{2+}/K^+ exchanger in the outer segment membrane, and by a $2K^+$-$3Na^+$ pump in the inner segment.

Upon absorption of a photon, the photopigment changes conformation, which "activates" the opsin, converting it into an extremely active enzyme that activates many molecules of *transducin* (Leskov et al., 2000), the G-protein coupled to this receptor. This is, thus, a stage of amplification. Each activated transducin activates one subunit of phosphodiesterase, enhancing its hydrolyzing activity and leading to a decrease in cGMP concentration. This is another amplification stage of phototransduction. The resulting fall in cGMP levels is the step directly leading to the closure of cGMP-gated channels and membrane hyperpolarization. When the light stimulus returns to baseline levels (or darkness), cGMP concentrations also return to basal levels, the cGMP-gated cation channels reopen, and the photoreceptor depolarizes back to its resting membrane potential (Baylor, 1987; Burns & Lamb, 2003; Luo, Xue, & Yau, 2008; Pugh Jr. & Lamb, 2000).

In order for photoreceptors to be able to respond in a timely fashion to changes in light stimuli, all the molecules activated in the G-protein cascade (rhodopsin, transducin, phosphodiesterase) need to inactivate.

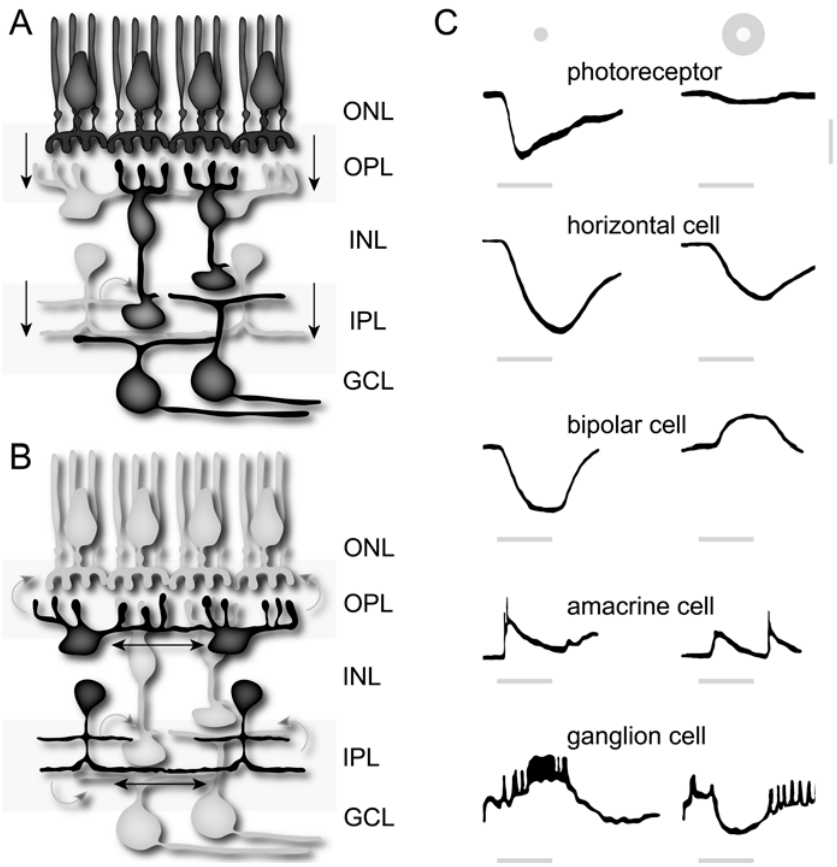

Figure 7. Information flow in the retina. (A) Vertical pathway. Signals flow via glutamatergic synapses from photoreceptors to BCs and from these to GCs (black arrows), which form ultimately the output of the retina to the brain. (B) Lateral pathway. In the outer retina, HCs are coupled via gap junctions and integrate visual signals laterally over large areas by sharing their membrane potential (black arrow). They then feed back to photoreceptors at the OPL (grey arrows). In the inner retina, ACs also perform lateral integration via either electrical or conventional synapses (black arrow). They can then feed back to BCs or synapse directly onto GCs at the IPL (grey arrows). (C) Graded potentials and action potentials. Intracellular recordings from the retina of the mudpuppy, *Necturus maculosus*. Responses of photoreceptors, HCs, BCs, ACs and BCs to equal energy light spots of 100 μm diameter (left) or annuli of 500 μm inner diameter (right). Photoreceptors, HCs and BCs respond to light with sustained potential changes, whereas ACs and GCs generate spikes. Horizontal bars depict stimulus timing (500-1000ms). Vertical bar = 5 mV. Redrawn with permission from Werblin and Dowling (1969).

Photoreceptors have evolved specialized proteins that participate in a series of inactivation steps and powerful negative feedback reactions that are often modulated by Ca^{2+}. Together, these processes also allow photoreceptors to light-adapt, that is, to shift their operating range according to the main light levels.

These reactions, described briefly below, were reviewed in great detail elsewhere (Burns & Lamb, 2003; Luo et al., 2008; Pugh Jr. & Lamb, 2000). Briefly, rhodopsin is first phosphorylated by an enzyme called *rhodopsin kinase*; the phosphorylated rhodopsin then tightly binds to a protein called *arrestin*. This decreases the catalytic activity of the molecule, stopping the activation of transducin molecules and phosphodiesterase. Eventually, the *all-trans* chromophore is separated from the opsin and replaced by a new pigment molecule in the *11-cis* configuration. Previously activated transducin molecules also inactivate, due to the intrinsic ATPase activity of the alpha subunit. This process is, however, quite slow, but is considerably sped up by the activity of the so-called *regulators of G-protein signaling* (or *RGS*) *proteins*. Because RGS proteins can only speed up the inactivation of transducin when it is bound to phosphodiesterase, their activity also decreases the rate of cGMP hydrolysis by this enzyme and leads to a fast shut down of the light response.

The phototransduction cascade leads to dramatic changes in the local Ca^{2+} concentrations, because the cGMP-gated channels in the outer segments are permeable to Ca^{2+}. It follows that many steps in the phototransduction process can be modulated by this ion. First, Ca^{2+}- binding proteins called *guanylate-cyclase activating proteins* or *GCAPs* normally facilitate the activity of guanylate cyclase, but Ca^{2+} inhibits this facilitation. When the cGMP-gated channels close due to a light stimulus and Ca^{2+} levels decrease, the production of cGMP increases because the inhibition of GCAPs stops. Second, the light-

Table 1. Main differences between rods and cones. Modified from Ebrey & Koutalos (2001); (1): Migdale et al. (2003); (2): Chun, Grunert, Martin and Wässle (1996); (3): Burns and Lamb (2003) and Pugh Jr. and Lamb (2000); (4): Dartnall, Bowmaker and Mollon (1983).

	Rods	**Cones**
General morphology	cylindrical outer segments	conical outer segments
Photopigment	rhodopsin	cone opsin
Number of ribbons	1-2[(1)]	20-40[(2)]
Light level	scotopic	photopic
Absolute sensitivity	high	low
Saturation	yes	no
Response speed	slow	fast
Ability to light adapt	limited[(3)]	large[(3)]
Rate of dark adaptation	slow	fast
Spectral sensitivity peak	around 500 nm[(4)]	depends on opsin[(4)]

induced decrease in Ca^{2+} speeds up rhodopsin inactivation, because rhodopsin kinase is normally inhibited by another Ca^{2+}-binding protein called *recoverin*. Finally, Ca^{2+} also changes the sensitivity of the membrane cation channels to cGMP, which is normally regulated via another Ca^{2+}-binding protein called *calmodulin*. Because all of these Ca^{2+}-mediated processes can actually lead to the reopening of the cGMP-gated channels during prolonged stimulation, they not only speed up recovery from brief light stimuli, but also underlie the ability of photoreceptors to light adapt to prolonged stimulation, shifting their operating range according to the mean ambient light levels.

The light-induced hyperpolarization of the photoreceptor modulates voltage-gated Ca^{2+} channels at the synaptic terminal, reducing the rate of exocytosis of synaptic vesicles loaded with glutamate (Choi et al., 2005; Heidelberger, Thoreson, & Witkovsky, 2005). Photoreceptors are quite unique neurons, because they continuously release glutamate at rest, whereas most CNS neurons are silent at rest and release bursts of neurotransmitter only when stimulated.

In order to cope with the high release rates of photoreceptors, organelles called *synaptic ribbons* are anchored in the synaptic terminals close to release sites (Figure 2). Ribbon zones dock 5-10 times more vesicles than conventional synapses, suggesting that synaptic ribbons facilitate release (Prescott & Zenisek, 2005; Rao-Mirotznik, Harkins, Buchsbaum, & Sterling, 1995; Sterling & Matthews, 2005). The precise mechanism through which synaptic ribbons may influence neurotransmitter release is, however, still a mystery.

Bipolar cells

Although photoreceptors only hyperpolarize to light stimulation, at the BC level this signal is split into two main streams of information: one BC type *hyperpolarizes* when a light stimulus falls within the center of its receptive field and another one *depolarizes* under the same stimulus conditions (Figures 7 and 10). The former are called hyperpolarizing or OFF BCs, and the latter are called depolarizing or ON BCs (Joselevitch & Kamermans, 2007; Kaneko & Hashimoto, 1969; Werblin & Dowling, 1969).

There seems to be some correlation between the polarity of the BC light responses to white light and the position of its dendrites in the triads (Figure 2a), as well as the stratification level of its axon terminal at the IPL (Figure 10). The axons of OFF BCs terminate in the most distal stratum or *sublamina a*, whereas those of ON BCs terminate more proximally, in *sublamina b* (Famiglietti, Kaneko, & Tachibana, 1977; Famiglietti & Kolb, 1976; Nelson & Kolb, 2003).

In the human retina, at least 11 different types of morphologically distinct BCs have been described (Boycott & Wässle, 1991; Kolb, Linberg, & Fisher, 1992; Mariani, 1983, 1984). These morphological types are arranged in two major classes: an ON BC connected exclusively to rods, and ON and OFF BCs that receive inputs exclusively from cones. Cone-driven BC axon terminals stratify roughly at one of the two main sublaminas, whereas some present, in addition, characteristic patterns of multilaminar spread of terminals in the IPL (Mariani, 1983). BCs with terminations in both sublaminas of the IPL were also identified in a number of other species (Connaughton & Nelson, 2000; Scholes, 1975; Scholes & Morris, 1973; Wu, Gao, & Maple, 2000), but their response properties have not been thoroughly investigated.

Patterns of convergence and divergence to and from BCs vary according to BC type and according to retinal

eccentricity. Even though the connectivity of many primate BCs is still being determined (see, for example, Telkes, Lee, Jusuf, & Grunert, 2008), at least for some cells there are numbers available. Flat midget BCs (labeled "FMB" in Figure 10a), for instance, are OFF-type neurons that contact only one cone and only one ganglion cell each in the fovea (Kolb, 1970). The same is true for their ON counterpart, the invaginating midget BCs (labeled "IMB" in Figure 10a). In the periphery, around three cones converge onto one FMB and one IMB, and between 8 and 13 FMBs converge onto one midget ganglion cell (Chan et al., 2001; Jusuf, Martin, & Grunert, 2006).

Since ON and OFF BCs are activated by the same glutamate release in the OPL, one might wonder how they can respond to light differently. This is achieved by expressing distinct sorts of glutamate receptors at the tips of their dendrites (Figure 11). OFF BCs use *ionotropic (iGluRs) receptors* (both AMPA and kainate, DeVries & Schwartz, 1999; DeVries, 2000), whereas ON BCs express *metabotropic receptors* (mGluR6) at their synaptic contacts with photoreceptors (Nakajima et al., 1993; Vardi, Duvoisin, Wu, & Sterling, 2000; Vardi & Morigiwa, 1997).

Ionotropic receptors, or iGluRs, are at the same time glutamate-binding proteins and non-specific cation channels (Eccles & McGeer, 1979). In the dark, when the agonist is present and activates these receptors, the membrane pores are kept open and an inward current flows through the OFF BC membrane, keeping OFF BCs depolarized (Kaneko & Saito, 1983; Saito & Kaneko, 1983). When photoreceptors are stimulated by light and decrease their neurotransmitter release, glutamate unbinds from the BC receptors, causing a conformational change in the cation channels, closing them. The consequent cessation of ionic flow through the cell membrane hyperpolarizes OFF BCs with a

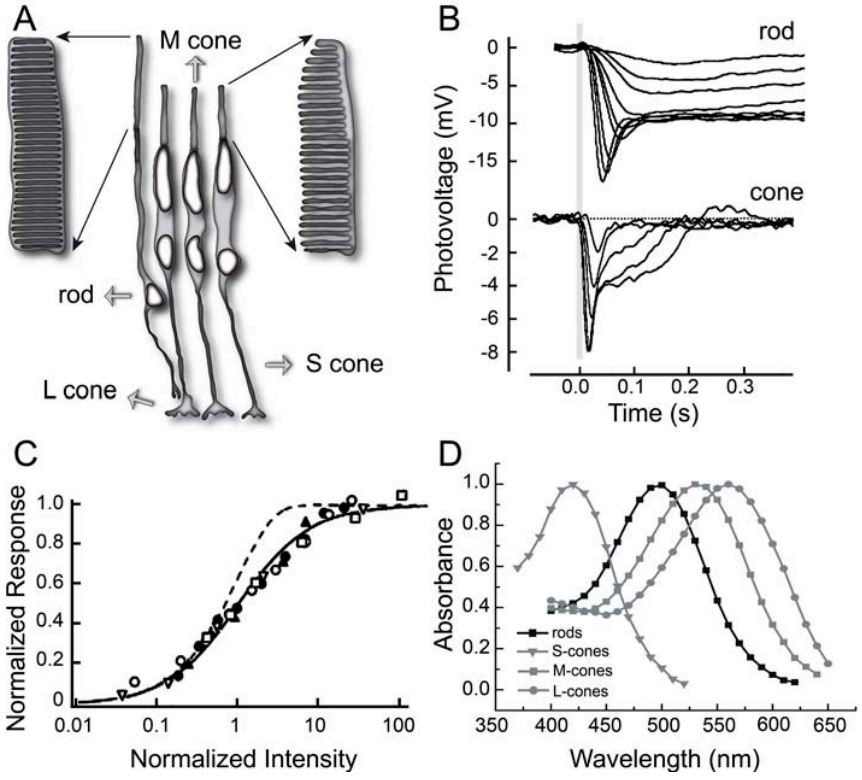

Figure 8. Photoreceptors. (A) Morphology of rods and cones from the monkey (*Macaca fascicularis*) retina. Redrawn from Marc (1999 copyright 1999, with permission from Elsevier. One of the most obvious differences between rods and cones lies in the morphology of the outer segments, enlarged to the side of each drawing. Rods have rod-like outer segments, while the shape of the cone outer segment tends to b conical. Furthermore, the membranous disks containing the visual pigment are stacked within the rod outer segment, while in cones these disk are contiguous to the outer segment membrane. (B) Photovoltage. Light responses of a rod (top) and of an L-cone (bottom) of the macaqu monkey retina to 500 nm stimulation at increasing intensities, measured with the perforated patch technique. Rod responses are much slow than cone responses: not only do they start later in relation to stimulus onset, but they also last longer. Timing of the light flash is indicated b the vertical grey bar. Adapted from Schneeweis and Schnapf (1995). Reprinted with permission from AAAS. (C) Photoreceptor dynamic rang Normalized response amplitudes of 5 macaque rods to light stimuli of increasing intensity. The intensity-response relation of a photorecepto can be fitted with a sigmoidal curve (solid line) that spans around 2 log units before reaching saturation if one does not take light adaptation in account. Adapted from Schneeweis and Schnapf (1995). Reprinted with permission from AAAS. (D) The mean absorbance spectra of the fou human photoreceptors: S-cones (λmax = 419.0 ± 3.6 nm, n = 5), rods (λmax = 496.3 ± 2.3 nm, n = 39), M-cones (λmax = 530.8 ± 3.5 nm, n 45) and L-cones (λmax = 558.4 ± 5.2 nm, n = 58). Replotted with permission after Dartnall et al. (1983).

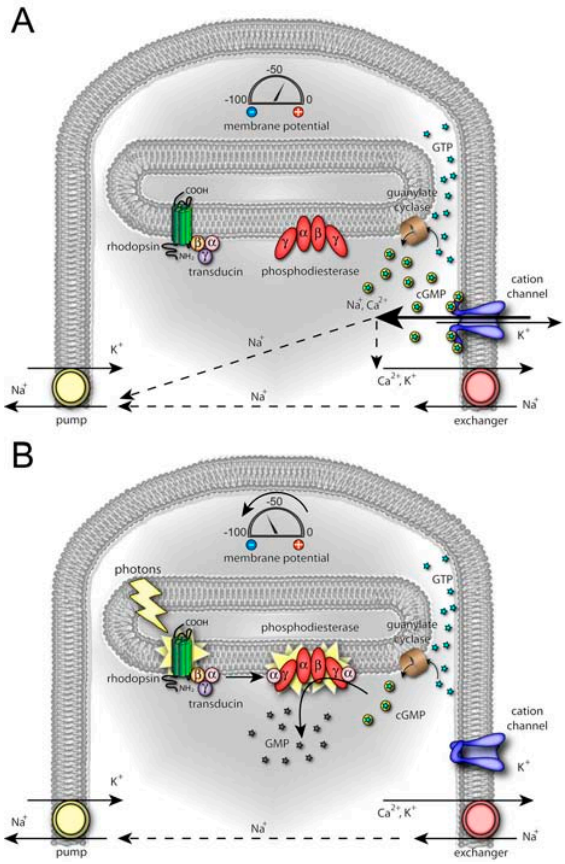

Figure 9. Phototransduction in rods. (A) The dark current. In the dark, the photoactive molecule rhodopsin is inactive, and so are its coupled G-protein, transducin, and the effector protein, phosphodiesterase. Guanylate cyclase keeps the cGMP concentration high by continuously converting GTP into cGMP. Two to three cGMP molecules open an ionic channel in the outer segment membrane, the cGMP-gated cation channel, allowing Na^+ and Ca^{2+} ions to flow across the membrane and depolarize the cell. Na^+, Ca^{2+} and K^+ concentrations are restored by the activity of a $4Na^+$-Ca^{2+}/K^+ exchanger in the outer segment membrane, and by a $2K^+$-$3Na^+$ pump in the inner segment. Adapted from Pugh Jr. and Lamb (2000) and Burns and Lamb (2000; 2003). (B) The transduction cascade. The absorption of photons activates rhodopsin molecules, each of which, in turn, activates up to hundreds of transducin molecules before they are inactivated (Leskov et al., 2000; Pugh Jr. & Lamb, 2000). One alpha subunit of transducin can bind to each of the two gamma subunits of phoshodiesterase, thereby increasing enormously its catalytic activity. As a consequence, cGMP molecules are hydrolyzed by PDE to GMP, free cGMP concentration decreases, and the cGMP-gated cation channel closes. This whole process leads ultimately to a membrane hyperpolarization. Adapted from Burns and Lamb (2003) and Pugh Jr. and Lamb (2000).

time course that closely follows the voltage changes experienced by the photoreceptors.

Metabotropic receptors or mGluRs, on the other hand, do not form pores in the ON BC membrane. They are, instead, G-protein-coupled receptors that work similarly to other G-protein receptors in the body, such as rhodopsin (Eccles & McGeer, 1979). In the dark, they activate a G-protein (Go_α in this case) that starts a cascade of events leading ultimately to the closure of a non-specific cation channel somewhere else in the cell (Euler & Masland, 2000; Nawy & Copenhagen, 1987; Saito, Kondo, & Toyoda, 1979). The localization of this cation channel, as well as the specific cascade leading to its modulation, are to date unknown. Nonetheless, the closure of these mGluR-driven channels in darkness keeps ON BCs hyperpolarized at rest. When glutamate levels in the synaptic cleft decrease with light, the synaptic activation decreases and cation channels open, allowing ions to flow into the cell and depolarizing the ON BC.

Ganglion cells

Consistent with the divergence of photoreceptor signals into parallel streams of information transmission at the BC level, GCs also come in many flavors. If there are four types of photoreceptors and 11 different types of BCs in the human retina, at least 17 types of GCs were described in primates (Dacey, 2004; Dacey & Packer, 2003; Field & Chichilnisky, 2007), indicating that photoreceptor signals diverge further at the IPL. Even though GCs express only ionotropic receptors, these neurons also follow the ON/OFF dichotomy initiated at the OPL, by contacting preferentially ON or OFF BCs in distinct IPL strata (Figure 12a).

Similar to what happens with BCs, some GCs also have multilaminar contact patterns in the IPL (Figure 12a). This means that, in addition to ON and OFF GCs, there are also cells that fire at both light onset and offset (ON/OFF GCs), as well as neurons that selectively fire ON or OFF-type responses, depending on the wavelength of the stimulus. Such GCs are common both to cold-blooded vertebrates such as fish (Daw, 1967, 1968) and turtle (Rocha, Saito, Silveira, de Souza, & Ventura, 2008), and to warm-blooded vertebrates, such as the cat (Daw, 1972; Ringo & Wolbarsht, 1986) and monkey (Dacey, 1999; Gouras & Zrenner, 1981). Examples can be found in Figure 18b and c.

Two main types of primate GCs were most extensively studied physiologically: parasol and midget GCs (Figure 12a, left), which come in both ON and OFF varieties (for reviews, see Dacey, 2000, 2004; Kaplan, Lee, & Shapley, 1990; Shapley & Perry, 1986). They comprise together more than half of the total GC population and project to the magnocellular and parvocellular layers of the LGN, respectively, being therefore also called M- and P-cells (Dacey, 2004). Because M-cells are broadband, they were assumed to underlie the perception of brightness. P-cells, on the other hand, due to their spectrally opponent responses, were long thought to be the neuronal substrate for color vision (Lennie, Pokorny, & Smith, 1993).

The function of parasol and midget GCs, however, is still unclear. There are many mismatches between some perceptual phenomena attributed to either cell type and

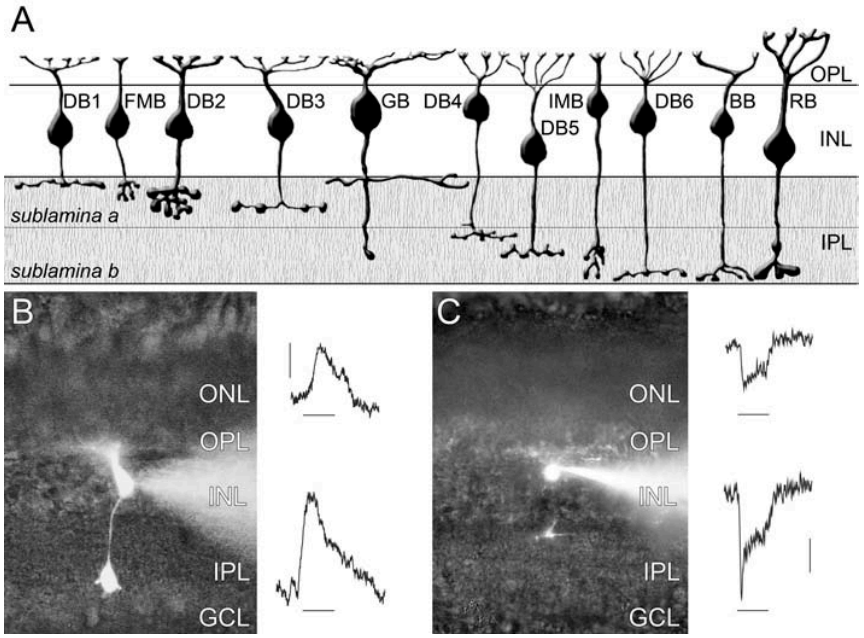

Figure 10. Bipolar cells. (A) Types of primate BCs and their stratification pattern in the OPL. Redrawn from Mariani (1989) and Boycott and Wässle (1999). Copyright 1989, with permission from Elsevier. Copyright 1999 by Investigative Ophthalmology & Visual Science. Reproduced with permission of Investigative Ophthalmology & Visual Science in the format Journal via Copyright Clearance Center. DB = diffuse bipolar; FMB = flat midget bipolar; GB = giant bistratified bipolar; IMB = invaginating midget bipolar; BB = blue bipolar; RB = rod bipolar. (B) ON BC properties. Left: Fluorescence micrograph of a recorded ON BC of the goldfish filled with Lucifer Yellow and still attached to the recording electrode. The axon terminal stratifies at the innermost part of the IPL. Right: Light responses of the same cell to a 250 μm slit and to a broad field at 550 nm and similar intensities (-0.44 and -0.68 log, respectively). Horizontal bars indicate stimulus timing (500 ms), vertical bar = 2 mV. From Joselevitch (2005). (C) OFF BC properties. Left: Fluorescence micrograph of a recorded OFF BC of the goldfish filled with Lucifer Yellow and still attached to the recording electrode. The axon terminal stratifies at the outermost part of the IPL. Right: Light responses of the same cell to a 250 μm slit and to a broad field at 550 nm and similar intensities (-0.11 log and -0.01 log, respectively). Horizontal bars indicate stimulus timing (500 ms), vertical bar = 4 mV. From Joselevitch (2005).

the physiology of their two "neuronal correlates". For instance: many percepts, such as acuity as determined by some methods, have a "magnocellular-like" spectral sensitivity but are not consistent with parasol ganglion cell distribution and physiology at all. Color vision, which supposedly is mediated by the parvocellular system, has poor spatial resolution; yet midget cells have smaller dendritic fields and contact less cones than parasol ganglion cells (Lennie et al., 1993).

Finally, the magno/parvocellular "dichotomy" was shown to be at least a "trichotomy" about a decade ago, with the characterization of the koniocellular pathway (for a review, see Hendry & Reid, 2000) and with recordings of retinal cells with neither parvo- nor magnocellular physiology (Calkins, Tsukamoto, & Sterling, 1998; Dacey & Lee, 1994). In cats, the division of ganglion cells into more than three physiological types has a history of at least three decades (reviewed in Shapley & Perry, 1986). Given the fact that there are 17 morphological types of GCs, it seems reasonable to assume that the magno/parvocellular division is only part of a much more complex story.

GCs are the first retinal neurons in the vertical pathway to respond to light with all-or-none action potentials (Figure 7c and 12b). This kind of signaling is needed because their axons extend for long distances along the optic nerve before reaching their targets in the brain. While action potentials permit long-distance transmission along such processes, they also limit considerably the amount of information that can be transmitted in a given amount of time, due to the number of spikes that a cell can produce per unit time (Barlow, 1981; Koch et al., 2004).

The limited bandwidth of GCs might be one of the reasons – if not the main reason – for the existence of parallel vertical pathways from the retina to the brain. Because one single GC type cannot encode optimally all aspects of a visual scene, different GC types "specialize" in certain tasks. For instance, high visual acuity needs GCs with small dendritic fields that collect from only a few photoreceptors or even a single photoreceptor in the fovea (Kolb, 1970; Wässle & Boycott, 1991). The signal-to-noise ratio of these GCs, however, is poorer than that of a neuron that responds to light in a sustained manner (Dhingra & Smith, 2004).

To improve contrast sensitivity and probably also spatial resolution, the visual system also needs GCs with wider dendritic fields that collect from many BCs, because summing inputs averages out uncorrelated

noise (Sterling, 2003). The benefits of multiple sampling and dendritic field overlap for contrast perception and visual acuity are discussed in detail in Borghuis, Ratliff, Smith, Sterling and Balasubramanian (2008), Eurich and Schwegler (1997), Hughes (1981) and Joselevitch and Kamermans (2008).

Energy consumption is also an important matter when it comes to retinal design and GC response properties. Even though photoreceptors are the most metabolically active cells in the body, generating spikes is also costly (Laughlin, 2001; Lennie, 2003). For certain types of information that do not need quick transmission (i.e. local edge detection), cells that do not fire at high rates are a more cost-efficient solution (Ames & Li, 1992; Koch et al., 2004). Together, these reasons justify the plethora of GC types found in the retina.

Lateral Interactions

Lateral interactions happen at both synaptic layers of the retina. HCs in the outer retina and ACs in the inner retina average the input they receive from photoreceptors and BCs, respectively, and send feedback signals, based on this average, to the photoreceptors and BCs that adjust their

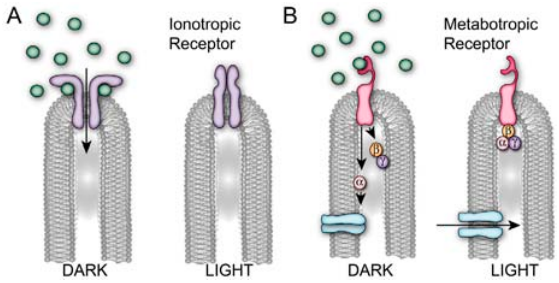

Figure 11. Glutamate receptors of bipolar cells. (A) Ionotropic receptors. Left: iGluRs are an assembly of multiple subunits (purple) that form a membrane pore in the BC dendrite (grey). This pore allows ions to flow to the interior of the cell in darkness, when glutamate (green) is bound. Right: In the light, the fall in glutamate concentration leads to the closure of these channels, hyperpolarizing the cells. (B) Metabotropic receptors. Left: mGluRs are composed by a single subunit with a glutamate-binding domain (pink). In darkness, glutamate (green) activates these receptors which, in turn, activate many G-protein molecules. The alpha subunit decouples from the beta-gamma complex and, by a mechanism still unknown, keeps an ionic channel (blue) somewhere else in the cell closed. Right: in the light, the absence of glutamate terminates G-protein activity, leading to channel opening.

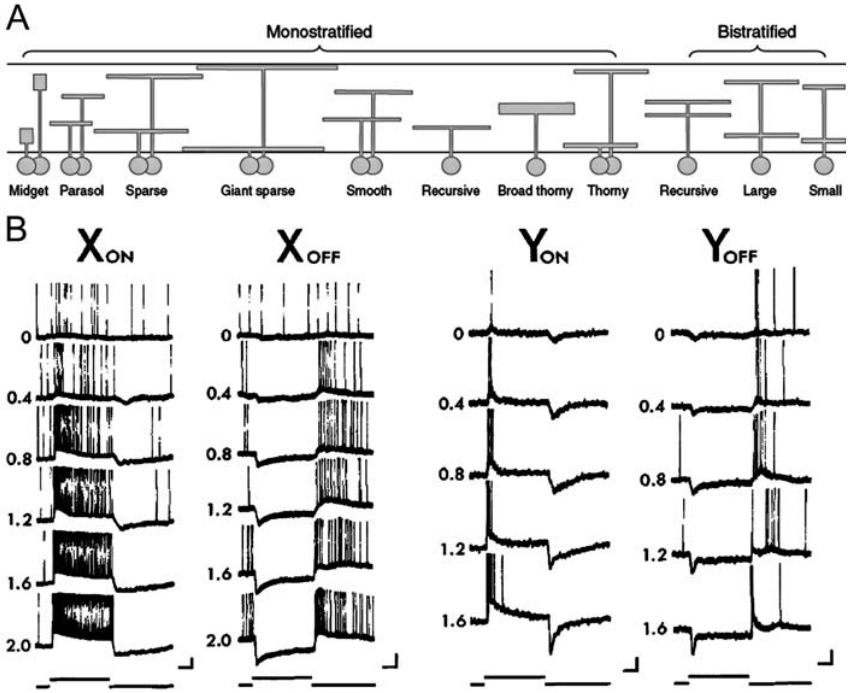

Figure 12. Ganglion cells. (A) Morphological types of primate GCs. Top: schematic drawing of the 17 different types of primate GCs described so far and their characteristic stratification pattern in the IPL. Reproduced from Figure 20.4.a, page 291 of Dacey (2004), copyright 2004, Massachusetts Institute of Technology, by permission of The MIT Press. (B) Response patterns recorded from cat GCs to light stimuli of increasing intensity. There are multiple classifications for GC responses (i.e. X/Y/W in the cat, brisk sustained/brisk transient/sluggish in the guinea pig, etc.), depending on response properties and the species studied. Overall, GC responses can be ON, OFF, or ON/OFF. The first type spikes at the onset of the light stimulus, the second spikes at the termination of a light stimulus, and the third spikes at both light on- and offset. There is some correlation between the type of response (ON, OFF or ON/OFF) and the stratification pattern of GC dendrites in the IPL. Stimulus intensity depicted to the left of each trace in log units. Bottom row shows stimulus timing. Horizontal bars = 200 ms; vertical bars = 5 mV. From Saito (1983), copyright 1983 John Wiley & Sons, Inc. Reprinted with permission of John Wiley & Sons, Inc.

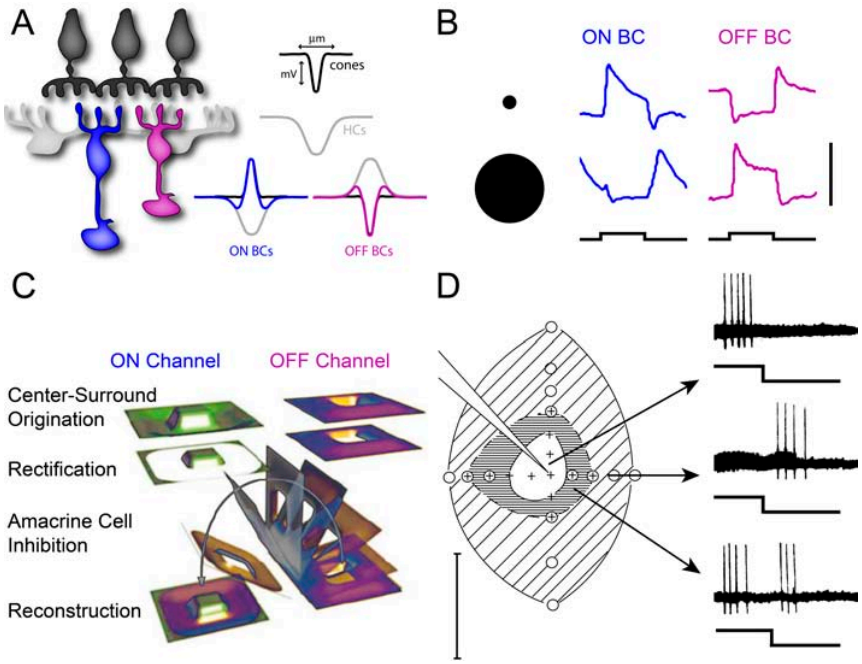

Figure 13. Center-surround organization. (A) Receptive field structure of outer retinal neurons. Upward deflection means depolarization, downward deflection means hyperpolarization. Cones only hyperpolarize to light falling onto their "receptive field", which is the retinal area where a stimulus can potentially activate them. The receptive field of individual cones has a Gaussian shape and is not extensive (black line), because cones are not strongly coupled. The receptive field of HCs also has a Gaussian shape, but is much broader as a consequence of the strong electrical coupling between these cells (grey). The combination of these two Gaussians at the BC level results in the so-called center-surround organization of BCs, which has roughly the shape of the subtraction between two Gaussians (colored lines): the photoreceptor feedforward input (black Gaussian) minus the HC feedback input (grey Gaussian). (B) BC response properties change with stimulus size. Responses of an ON (blue traces) and OFF BC (pink traces) of the primate retina to light stimulation with a spot comprising only 1 degree of visual angle (upper row) and 5 degrees of visual angle (bottom row). Response polarity reverses when both center and surround are activated. Square pulses depict stimulus timing. Scale bar = 2 mV. Reprinted from Dacey, Packer, Diller, Brainard, Peterson and Lee (2000), copyright 2000, with permission from Elsevier. (C) Model for the generation of the receptive field structure of inner retinal neurons. Top: receptive field structure of ON and OFF BCs. Upward deflection means depolarization, downward deflection means hyperpolarization. Middle: rectification occurs at the BC-GC synapse, that is, only BC depolarization elicits synaptic transmission. ON GCs surrounds and OFF GCs centers are then formed by active AC inhibition at the IPL. Adapted with permission from Roska et al. (2006). (D) GC response properties change with position. Left: receptive field organization of a cat ON GC. When stimulated with a small spot of light at different positions in relation to the recording electrode, GC responses vary from excitatory or ON (crosses, innermost area) to inhibitory or OFF (circles, outermost area), with an intermediate area in which cells respond to light with both ON and OFF discharges (circles with crosses, intermediate area). Scale bar = 1 mm. Right: Response examples of a cat ON GC recorded extracellularly to stimulation at three different areas within its receptive field. Square traces depict stimulus timing. Redrawn with permission from Kuffler (1953).

output. This adjustment is advantageous for many reasons.

In general, feedback circuits improve the reliability and stability of the neuronal output (Wu, 1992). They remove part of the noise from this signal by integrating over large areas and at the same time shift the dynamic ranges of both pre- and post-synaptic neurons such that the gain (or input-output relationship) of these synapses remains relatively high at different ambient light levels. This gain correction removes redundancy from the cone output and, in turn, assures adequate contrast sensitivity of the visual signal.

Contrast sensitivity is further improved by an important consequence of the lateral interactions via retinal feedback circuits, namely the classic center-surround organization characteristic of BCs and GCs (Kaneko, 1973; Kuffler, 1953; Werblin & Dowling, 1969), shown in Figures 7c and 13. This concentric center-surround organization finely tunes the output of ganglion cells, improving their spatial resolution.

Because HCs and ACs integrate over such large areas, the receptive field of the feedback signals is broader than that of the forward signal. As a result, the receptive fields of BCs and GCs are concentrically arranged into antagonistic zones: illumination of the surround decreases or fully antagonizes the response to illumination at the center of the receptive field (Kaneko, 1973; Kuffler, 1953; Werblin & Dowling, 1969).While the center is a result of direct photoreceptor input, the surround is partly generated by the feedback interactions between HCs and photoreceptors in the outer retina (Fuortes & Simon, 1974), and between ACs and BCs in the inner retina (Miller, 1979).

The main benefit of center-surround interactions in the retina might be the removal of redundant information, so that retinal neurons can make optimal use of their transmission capacity (Sterling & Demb, 2004). Redundancy can be, for

instance, correlations between photoreceptor signals when responding to the same mean intensity of a scene. This kind of correction is termed *predictive coding* (Srinivasan, Laughlin, & Dubs, 1982), because laterally integrating neurons average this mean intensity level, or redundant information, over a certain area and make a "prediction" for the intensity of the center, which is subsequently subtracted from the main signal via feedback. This way, only the relevant information (i.e. the changes around this mean) is passed on to the subsequent neural stages, reducing the need for generation of expensive (and redundant) spikes.

The visual system profits from feedback signals also in the temporal domain. Feedback modulates the duration of the neuronal output, thereby speeding up signal transmission along the vertical pathway. Since every chemical synapse is coupled to a delay, signal transmission from the outer retina to the brain would be considerably slowed down if such compensatory mechanisms did not exist.

But how do these lateral pathways actually work? While the vertical pathway relies on glutamate as its major neurotransmitter, HCs and ACs signal in alternative ways. The mechanism of outer retinal feedback is still under debate. Although HCs produce and release GABA in the outer retina (Marc, Stell, Bok, & Lam, 1978; Wu, 1992; Yazulla, 1986), the time constant of the GABAergic effect is not consistent with the quick feedback effects, but rather with some modulatory role in the feedback pathway (Fahrenfort, Sjoerdsma, & Kamermans, 2003). Accordingly, pH in the synaptic cleft also seems to modulate the strength of HC feedback to photoreceptors (Hirasawa & Kaneko, 2003; Vessey et al., 2005).

It was recently suggested that HCs control the photoreceptor output by an electrical or *ephaptical feedback mechanism* (Kamermans et al., 2001). Semi-gap junctional channels are expressed at the tips of the dendrites of these cells, and during a light response, they allow current to flow into HCs, changing thereby the local voltage of the extrasynaptic space. Because photoreceptor glutamate release is voltage-dependent (Schmitz & Witkovsky, 1997), this voltage change efficiently modulates the photoreceptor output and the gain of the photoreceptor-BC synapse.

In the inner retina, lateral integration relies mostly on conventional (chemical) synapses. Many neurotransmitters are involved in AC signaling. The two

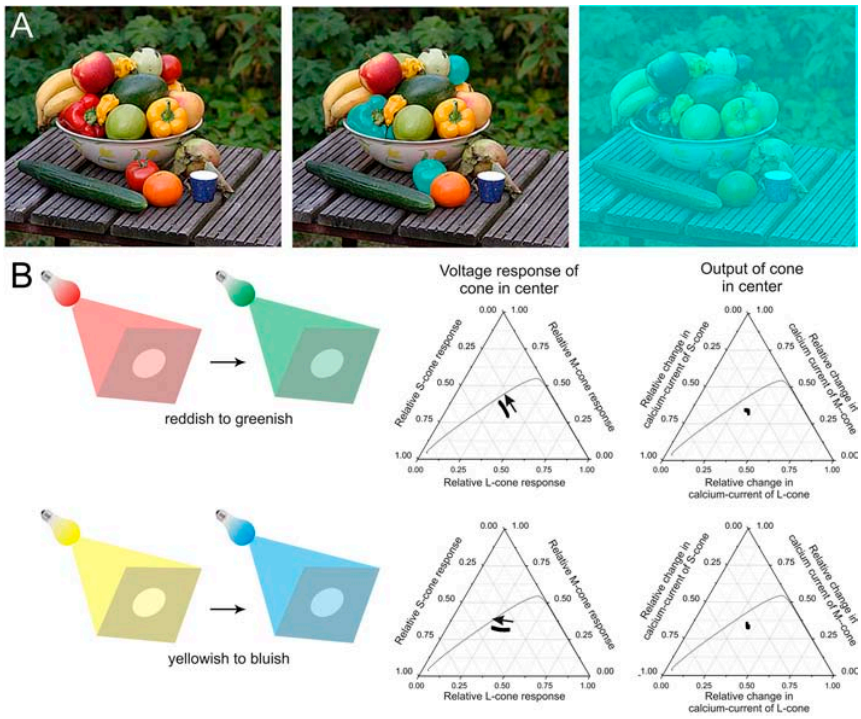

Figure 14. The role of horizontal cells in color constancy. (A) Demonstration of color constancy. Left: Under natural light, the red pepper and the tomatoes in the scene look red. Middle: The sensation of redness disappears when one applies a blue/green filter selectively on top of the pepper and tomatoes. Right: The sensation of redness reappears when the whole scene is displayed under blue/green light. Reprinted with permission from VanLeeuwen et al. (2007). (B) HC activity induce color constancy. Top: Modeled behavior of primate cones to the presentation of a white spot on a grey background when the illumination changes from reddish (left) to greenish (right). The color triangles represent the ratios of cone activity in the color space (left) and the cone outputs as measured by the HC-induced shift in cone Ca^{2+} current (right). The ratios of cone activity change as the illumination does (arrow). The cone output, however, remains constant as illumination changes, indicating that HC feedback efficiently corrects for the spectral composition of the illuminant. Bottom: Similar results for illumination ranging from yellowish to bluish. Reprinted with permission from VanLeeuwen et al. (2007).

major substances released by ACs in the IPL, however, seem to be GABA and glycine (Eggers & Lukasiewicz, 2006; Wässle & Boycott, 1991). In the next two sections, we will see how feedback from HCs and ACs can, in addition to correcting the photoreceptor and BC outputs, subserve perceptual phenomena such as color constancy and motion detection.

Horizontal cells

There are at least three types of HCs in the human retina, called HI, HII and HIII (Ahnelt & Kolb, 1994a; Kolb, 1970; Kolb et al., 1994). They differ slightly in morphology and in their photoreceptor contacts: HI contacts both rods and cones, whereas HII contacts exclusively cones. HIII has so far been shown to contact exclusively M- and L-cones (Ahnelt & Kolb, 1994a).

A very interesting role for HCs in the visual system has emerged from experiments in the fish retina (Kamermans, Kraaij, & Spekreijse, 1998; Kraaij, Kamermans, & Spekreijse, 1998). HCs contact all different spectral types of cones with more or less selectivity in different species (Ahnelt & Kolb, 1994a, 1994b; Dacey, Lee, Stafford, Pokorny, & Smith, 1996; Stell et al., 1975), and are electrically coupled (Dowling & Ripps, 1971; Marchiafava & Pasino, 1973; Naka, 1972). By sampling and sharing the responses of a large population of cones, they "get a feeling" about the spectral composition of the ambient illumination, and feed this information back into the photoreceptors.

Even though the HC-cone feedback pathway is called "negative", it can actually increase the gain (here defined as the modulation of cone glutamate release yielded by a certain cone voltage change) of the photoreceptor synapse, depending on the relative polarization of the different types of photoreceptors (Kamermans, Van Leeuwen, Numan, Sjoerdsma, & Fahrenfort, 2006; Kraaij, Spekreijse, & Kamermans, 2000; Skrzypek & Werblin, 1983). This is because the strength of the feedback signal varies with the amount of light falling onto individual photoreceptors. Unstimulated or weakly stimulated cones receive a stronger feedback signal than cones directly stimulated by light (Kraaij et al., 2000; Skrzypek & Werblin, 1983).

The consequence of this arrangement is that, if the environmental light is reddish (as during sunrise or sunset), the cones least sensitive to red light (S- and M- cones), and thereby least stimulated directly, will receive the strongest feedback. Their output will have higher gain than that of L-cones, and the output of the photoreceptor layer as a whole will be more blue-green (Kamermans et al., 1998; Kraaij et al., 1998). This effectively counterbalances the redness in the environment, just like the white balance system of a camera compensates for color casts in a scene (Kraaij et al., 1998; VanLeeuwen, Joselevitch, Fahrenfort, & Kamermans, 2007; Wu, 1992).

Such a "white balance" dynamically tunes the spectral sensitivity of the photoreceptors to the characteristics of the illuminant (Kamermans et al., 1998; VanLeeuwen et al., 2007). This basically represents the neuronal substrate for *color constancy* (Figure 14), which is the ability of the visual system to perceive colors in a somewhat constant manner, independently of the spectral composition of the environmental light (Jameson & Hurvich, 1989). Even though there are species-specific differences as regards retinal wiring and HC receptive field sizes, the

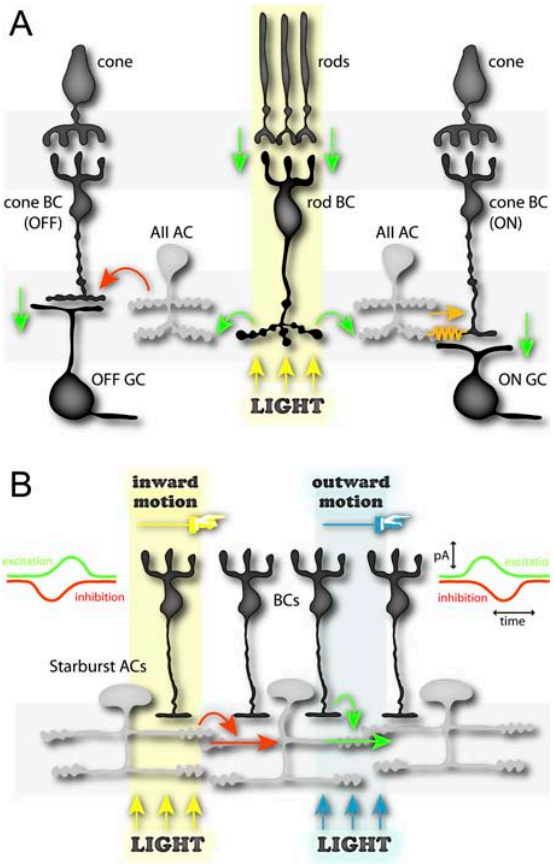

Figure 15. Some AC circuits. (A) AII ACs and the transmission of rod-driven signals. After a light stimulus (yellow) activates rods, rod signals flow to rod BCs and, from these, to AII ACs via conventional excitatory (glutamatergic) synapses (green arrows). AII ACs pass the signal further to ON cone BCs via electrical synapses (orange resistor and orange arrow) and to OFF cone BCs via inhibitory (glycinergic) synapses (red arrows). Finally, cone BCs transmit rod-driven signals to GCs via excitatory (glutamatergic) synapses (green arrows). (B) Starburst ACs and direction selectivity. Starburst ACs are intrinsically sensitive to the direction of motion due to the organization of their receptive fields. Their surrounds are generated by inhibition by neighboring ACs of the same type, such that there is an offset between excitatory and inhibitory inputs to these cells according to the direction of motion. Let us examine what happens with the AC in the center of the figure during two types of motion. Stimuli moving from the periphery towards the center of the receptive field (yellow bar) will first activate inhibition via other starburst amacrine cells (left red trace and arrows). Conversely, stimuli moving from the center to the periphery (blue bar) will first activate direct excitation (right green trace and arrows) via BCs.

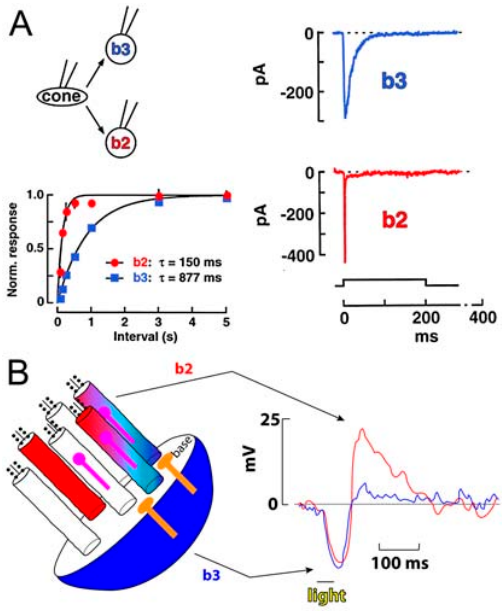

Figure 16. Temporal filtering at the cone-BC synapse. (A) Receptor makeup influence BC response dynamics. In this experiment, a cone and two different types of OFF BCs of the ground squirrel retina were voltage-clamped simultaneously (upper left scheme). The responses of these two OFF BC types differ markedly in kinetics: for prolonged voltage steps to the cone membrane, b2 responses are much more transient (right panel). The peak post-synaptic current in the BCs was measured during depolarizing pulses applied to the cone at different interstimulus intervals (bottom left graph). The two cells recover from desensitization with different time constants: b3 cells recover much slower. The differences in desensitization and recovery arise from the iGluRs expressed in these BCs: b2 cells have AMPA receptors, while b3 cells have kainate iGluRs. Reprinted from DeVries (2000), copyright 2000, with permission from Elsevier. (B) BC dendrites experience different microenvironments in the synaptic terminal. The cylinders represent invaginations within the cone pedicle. In these invaginations, glutamate concentration can be high (red) after vesicle fusion, but decreases as glutamate diffuses out of the pedicle (red to blue gradient). At the pedicle base, glutamate concentration is much lower (blue). The dendrites of b2 BCs (pink) are within the invaginations and experience, therefore, a completely distinct microenvironment as regards glutamatergic concentration than those of b3 BCs (orange), which only reach until the base of the cone pedicle. This difference presumably helps shape the light responses of these two BC types (right). Reprinted from DeVries et al. (2006), copyright 2006, with permission from Elsevier.

potential to induce color constancy is a general property of the system, whether in fish or mammalian species (VanLeeuwen et al., 2007).

Amacrine cells

ACs comprise the most diverse neuronal type in the retina. To date, more than 24 types have been described in man (Kolb et al., 1992). These cells are involved in multiple subcircuits in the inner retina, some of which include intricate loops of AC-AC connections (Marc & Liu, 2000; Roska, Nemeth, & Werblin, 1998). Much about these subcircuits and their function is still unknown. In this section, we will concentrate on some AC circuits whose functions are better understood.

Perhaps the best characterized AC circuit is the one involving *AII ACs and rod-driven signals* (Bloomfield & Dacheux, 2001). Technically speaking, this is not a feedback system. AII ACs are the most abundant AC cell type in the retina and serve as interneurons in the rod pathway (Figure 15a). They pool from around 25 rod-driven BCs via sign-conserving synapses and convey the rod-driven signal to the inner retina through gap junctions with cone-driven ON BCs (Mills, O´Brien, Li, O´Brien, & Massey, 2001) and through sign-inverting (glycinergic) synapses onto cone-driven OFF BCs (Bloomfield & Dacheux, 2001; McGuire, Stevens, & Sterling, 1984).

Starburst ACs are the second most abundant type of AC in the retina (Masland, 2005). They have been shown to play key roles in both developing and adult retinas. In the first case, starburst ACs communicate with each other through both cholinergic and GABAergic synapses (O'Malley, Sandell, & Masland, 1992), which in early post-natal days are excitatory, guaranteeing the generation and propagation of retinal activity waves (Zheng, Lee, & Zhou, 2004). These waves, in turn, are fundamental for the formation and stabilization of retinal synapses at the GC level and beyond (Katz & Shatz, 1996; Sernagor, Eglen, & Wong, 2001).

In the adult retina, starburst ACs seem to mediate *direction selectivity*. Some GCs respond strongly to stimuli moving in a preferred direction (i.e. left to right), but are completely silent when the very same stimulus is presented moving in the opposite direction (Barlow, Hille, & Levick, 1964; Barlow & Levick, 1965). Starburst ACs were shown to mediate this phenomenon by inhibiting GCs in a highly ordered manner (Fried, Munch, & Werblin, 2002). The processes of these cells are connected asymmetrically with direction-selective GCs, delivering strong inhibition only in the null direction (Figure 15b).

Other ACs have been suggested to participate in related phenomena such as the perception of object motion as opposed to background motion (Baccus, Olveczky, Manu, & Meister, 2008; Olveczky, Baccus, & Meister, 2003) and response suppression to quick eye movements (Roska & Werblin, 2003). Finally, one important aspect of most AC circuits is that they can *speed up* the visual signal as it travels from BCs to GCs (Bieda & Copenhagen, 2000; Nelson, 1982). This step is very important in the transformation of the sluggish, sustained potential changes found in the outer retina into the crisp spiking behavior of GCs, in addition to compensating for the synaptic delays mentioned earlier.

Information Processing: Parallel Vertical Pathways

As discussed previously, the divergence of photoreceptor signals onto different types of second-order neurons is needed in order to transmit information

efficiently to higher visual areas. This divergence generates a series of parallel vertical streams of information flow in the retina, each more or less specialized in transmitting certain aspects of the visual world to the brain.

Rod and Cone Pathways

Rod signals flow to the inner retina through three main pathways that differ in sensitivity (one of which is shown in Figure 15a). Each of these pathways selectively amplifies part of the dynamic range of the rods, allowing rod-mediated signals to be effectively transmitted throughout the span of rod sensitivity (Bloomfield & Dacheux, 2001; Volgyi, Deans, Paul, & Bloomfield, 2004).

At very low scotopic levels, photons are few and rod light responses are very small (Baylor, Lamb, & Yau, 1979). Under these circumstances, high amplification of rod responses is needed. The main route through which rod signals flow from the outer to the inner retina at starlight is through rod BCs, AII ACs and cone-driven ON and OFF BCs, as explained in the previous section (Bloomfield & Dacheux, 2001; Sharpe & Stockman, 2000; Taylor & Smith, 2004).

This pathway allows high sensitivity because all rod BCs use an mGluR to communicate with photoreceptors (Nakajima et al., 1993; Shiells, Falk, & Naghshineh, 1981; Slaughter & Miller, 1981). Since one single mGluR can activate multiple G protein molecules, this pathway amplifies the small rod responses to single-photon events (Falk, 1988; Shiells, 1994).

When light levels start to increase, so do rod light responses. Since rods and cones are electrically coupled (thick arrows in Figure 2a), when changes in the rod membrane potential are sizeable, part of this voltage will escape through the rod-cone gap junctions and modulate the cone glutamate release (DeVries & Baylor, 1995; Hornstein, Verweij, Li, & Schnapf, 2005; Schneeweis & Schnapf, 1995). Furthermore, rods also contact OFF "cone" BCs directly (Hack, Peichl, & Brandstatter, 1999; Tsukamoto, Morigiwa, Ueda, & Sterling, 2001; West, 1978). This way, even though the rod-rod BC synapse saturates at mesopic levels (Dacheux & Raviola, 1986), rod signals still can make it to the inner retina.

Cone signals, on the other hand, diverge to approximately 10 different BC types (Sterling, 2003; Wässle, 2004), whose functions and connectivity are not completely understood yet (Figure 10). This division of labor is necessary because in daylight the visual system is bombarded with a very large number of photons per unit area and time. Under these circumstances, the information contained in the cone responses exceeds the coding capacity of second-order neurons (Sterling, 2003). Each of these cone-driven information-processing channels carries presumably different parts of the message conveyed by the photoreceptors, in an attempt to optimally use the dynamic range and bandwidth of BCs, ACs and GCs.

In this manner, transmission channels with different *spatial filtering* properties come to exist at the BC level: *midget BCs* pool from few cones, *diffuse BCs* pool from

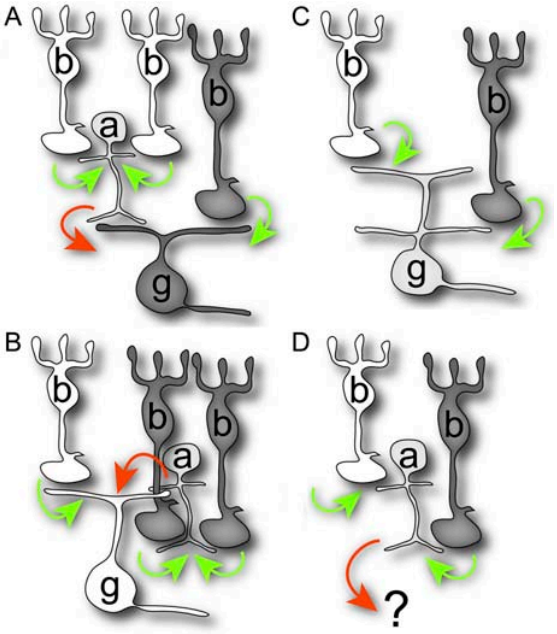

Figure 17. Some possible modes of cross-talk between ON (grey) and OFF (white) channels in the IPL. Excitatory synapses are symbolized by the green arrows, inhibitory synapses by the red arrows. (A) Indirect convergence via ACs (I). Circuits involved in the generation of center responses of an ON GC. This neuron receives direct excitatory input from an ON BC and inhibitory input from an AC which, in turn, is driven by OFF BCs. (B) Indirect convergence via ACs (II). Circuits involved in the generation of center responses of an OFF GC. This neuron receives direct excitatory input from an OFF BC and inhibitory input from an AC which, in turn, is driven by ON BCs. (C) Direct convergence onto a GC. Circuits involved in the generation of center responses from an ON-OFF GC. This neuron stratifies in both sublamina of the IPL, where it receives direct excitatory inputs from ON and OFF BCs. (D) Direct convergence onto an ON-OFF AC. This neuron stratifies in both sublamina of the IPL, where it receives direct excitatory inputs from ON and OFF BCs.

many. *Spectral filtering* for color vision also starts at the cone-BC synapse: while the primate retina possesses only three types of cones with highly overlapping spectral sensitivities (Figure 8d), the decorrelation of photoreceptor signals starts by comparing signals from BCs that pool from all spectral types of cones, such as diffuse BCs, and by BCs that selectively contact only one cone type, like the mammalian *blue cone BC* (Mariani, 1984) and the foveal midget BCs (Kolb, 1970, 2003; Wässle, 2004; Wässle & Boycott, 1991).

Finally, multiple cone-driven transmission channels enable the *temporal filtering* of visual information, that is, the selective transmission of fast components of the visual stimulus through neurons that respond transiently and the slow fluctuations through cells that respond in a more sustained manner to light. This is accomplished by a number of different strategies. One of them is to have different glutamate receptor configurations at the

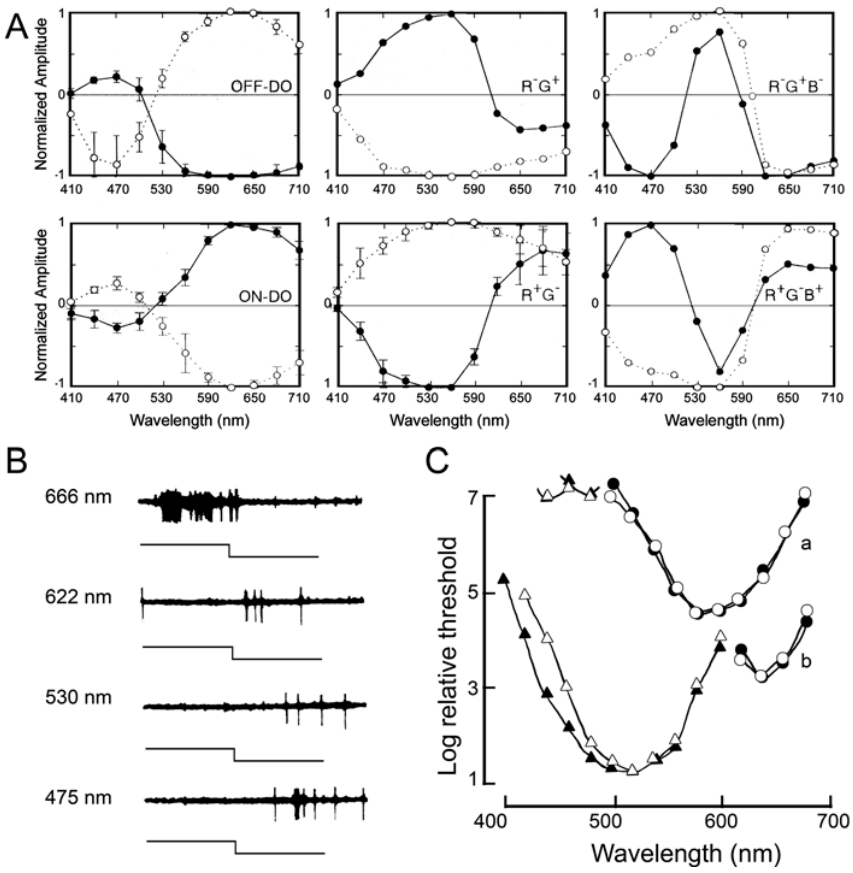

Figure 18. Broadband and opponent coding. (A) Spectrally opponent mixed-input BCs of the carp retina. Spectral curves of 6 types of opponent BCs to stimulation with a small spot (dark symbols) or with an annulus (open symbols) of different wavelengths under diffuse background illumination. In these cells, center and surround responses do not have the same spectral sensitivity, and in some cases the surround is also spectrally opponent. Upper row: cells with hyperpolarizing (OFF) center responses to long wavelength stimuli. Bottom row: cells with depolarizing (ON) center responses to long wavelength stimulation. OFF-DO: double-opponent (OFF type); R-G+: hyperpolarizing to red light, depolarizing to green light; R-G+B-: hyperpolarizing to red and blue lights, depolarizing to green light; ON-DO: double-opponent (ON type); R+G-: depolarizing to red light, hyperpolarizing to green light; R+G-B+: depolarizing to red and blue lights, hyperpolarizing to green light. Reproduced with permission from Shimbo, Toyoda, Kondo and Kujiraoka (2000). (B) Light responses of spectrally opponent primate GCs. Responses of a tonic GC of the rhesus monkey to stimulation with a 20 field covering both the receptive field center and surround. This neuron gives "ON" responses to long wavelength stimulation and "OFF" responses to wavelengths shorter than 666 nm. From Gouras and Zrenner (1981), copyright 1981, with permission from Elsevier. (C) Response thresholds of two GCs of the rhesus monkey (black and white symbols) to stimulation with a 0.2º spot covering mostly the receptive field center and a small part of the surround (a) and to stimulation with an annulus of 0.5 i.d and 1 o.d. covering mostly the receptive field surround and small part of the center (b). Circles and triangles represent responses of opposite polarity in the same cell. Adapted from De Monasterio (1979), copyright 1979, with permission from Elsevier.

BC dendrites (Figure 16a). An iGluR, for example, is formed by the co-assembly of different subunits that confer distinct characteristics to the cation pore, such as ionic permeability and desensitization dynamics (DeVries, 2000; DeVries & Schwartz, 1999). The mGluR of ON BCs may also differ in its desensitization dynamics, although little is known about its intracellular cascade (Snellman, Kaur, Shen, & Nawy, 2008).

Another strategy that allows for temporal filtering is the position of the BC dendrites in the cone synaptic complex (Figure 16b). Cells whose dendrites extend deeper into the synaptic terminal tend to be more transient than those whose dendrites end farther from the synaptic release sites (DeVries, Li, & Saszik, 2006), because the glutamate concentration and its modulation at these two different sites vary. Together, these cone-driven processing channels "chop" the visual image into bits that can be efficiently transmitted along the optic nerve.

ON and OFF Channels

One may ask at this point: why are there ON and OFF cells in the first place? A number of theories have been proposed. A possible reason is related to the discussion in the previous sections about the limited bandwidth of BCs and GCs. Since the HC-feedback system effectively subtracts background levels from the photoreceptor signal, this signal varies around a mean of

zero. ON and OFF BCs would each amplify half of the photoreceptor dynamic range, effectively doubling the dynamic range of the retinal output (Barlow, 1981).

This idea has problems, however, as discussed in detail elsewhere (Joselevitch & Kamermans, 2008; Vaney & Hughes, 1990). For instance, the responses of different ON and OFF cell types known so far are not mirror images of each other (Chichilnisky & Kalmar, 2002; Wheeler, 1979; Wu, Gao, & Pang, 2004), which implies that their combined output is not equivalent to doubling their bandwidth (Joselevitch & Kamermans, 2008). This points to the possibility that ON and OFF neurons carry different information to the brain (Chichilnisky & Kalmar, 2002; Wheeler, 1979), complementing each other nonetheless.

These information-processing channels have also been shown to cross-talk at several levels within the retina (reviewed in Joselevitch & Kamermans, 2008). Much like what lateral integration does, the combination of ON and OFF responses in the inner retina reduces redundancy and leads to an improvement of signal-to-noise ratio, by actively contributing to the receptive field surrounds of GCs (Figure 13c and 17; Levine & Shefner, 1977; Roska, Molnar, & Werblin, 2006).

Lastly, a role for ON and OFF channels in increasing the spatial resolution of the eye was suggested by some authors (Hughes, 1981; Joselevitch & Kamermans, 2008), based on the fact that ON and OFF GC dendrites overlap to a great extent (Vaney & Hughes, 1990; Wässle, Peichl, & Boycott, 1983). The interpolation of overlapping receptive fields could be a useful source of spatial information in non-foveate species and in the retinal periphery of foveate animals (Borghuis et al., 2008; Eurich & Schwegler, 1997; Eurich, Schwegler, & Woesler, 1997).

To date, however, none of the theories regarding the functional (evolutionary) significance of ON and OFF channels mentioned above have been either firmly established or convincingly rejected. Perhaps ON and OFF cell systems contribute to part or all of these useful information-processing features – extension of bandwidth/dynamic range, improved SNR, and increased spatial resolution.

Broadband and Opponent Neurons

Retinal neurons and the pathways they form can be further classified according to the polarity of their responses to the wavelength composition of light within the visible spectrum. The ability to discriminate between lights with different wavelength compositions, even when these are matched in intensity (or stimulus strength), is a fundamental feature essential for our ability to see colors. It has been assumed that neurons that respond differentially to certain wavelengths would underlie color vision, and because their responses have opposite polarities according to stimulus wavelength, they are called *opponent neurons* (Figure 18). Conversely, cells that give only one type of response (either ON or OFF) throughout the visible spectrum are denominated *broadband neurons*.

Opponent cells were first described by Gunnar Svaetichin in the fish retina (MacNichol & Svaetichin, 1958; Svaetichin & MacNichol, 1958). He recorded from HCs without knowing so, and since some HC types of teleosts are spectrally opponent, the scientific community embraced the idea that such opponent neurons were the neural substrate for color vision (see, for instance, Naka & Rushton, 1966). Shortly thereafter, BCs and GCs in the fish (Figure 18a) and then in the primate retina (Figure 18b and c) were also shown to display spectral opponency, turning the association between opponent coding and color vision the more tempting (Daw, 1972, 1973, 1984; de Monasterio, Gouras & Tolhurst, 1975a, 1975b; Gouras, 1972).

But are such opponent neurons really related to color vision? There seems to be no definitive answer to this question yet. As discussed in detail elsewhere (Joselevitch & Kamermans, 2007, 2008), there are many inconsistencies between the physiology of individual retinal spectrally opponent neurons and what would be expected from these cells, were they solely responsible for color perception. It seems more plausible that the activity of both broadband and opponent channels is necessary to process wavelength information in a reliable manner (Joselevitch & Kamermans, 2008).

An important function of broadband and opponent coding is the optimization of the amount of information to be transmitted to the brain. Much like what happens in the case of ON and OFF channels, opponent coding seems to be a way to reduce redundancy in the vertical pathway (Buchsbaum & Gottschalk, 1983; Lee, Wachtler & Sejnowski, 2002; Ruderman, Cronin, & Chiao, 1998). The absorption spectra of the cones overlap to a great extent (Figure 8d), which means that also in the spectral domain their light responses are highly correlated. If this correlation were not at least partially removed from the downstream retinal code, ganglion cells would need to produce more costly spikes to transmit visual information (Laughlin, 2001; Laughlin & Sejnowski, 2003).

How is this decorrelation achieved? To summarize, when cone signals are compared by second-order neurons, two strategies are possible: either the inputs are "added" or they are "subtracted" (note that I use these terms with quotation marks – the combination of inputs is not a linear process, due to the non-linear nature of some of its underlying mechanisms: a) the Ca^{2+} current of the pre-synaptic neurons, b) the relation between this Ca^{2+} current and glutamate release, c) the cooperation between glutamate and its receptors, d) the interactions between glutamate receptor-mediated currents in the post-synaptic neurons, and e) the interactions between glutamate-induced and non-glutamatergic currents in the post-synaptic neurons).

"Addition" implies that everything is taken into account – also what is redundant. "Subtraction" means that only the difference between the different photoreceptor

inputs is taken into account. Each of these strategies has drawbacks when used alone: by "adding" inputs, second-order neurons cannot differentiate between them; by "subtracting" inputs, only differences are registered, and therefore much information is lost. When these two strategies are combined, however, all the information is still there, both about what is redundant and about what is different between the photoreceptor types.

This is pretty much what happens in the fish outer retina and maybe in the mammal as well (see Dacey, 2000; Packer, Verweij, Schnapf, & Dacey, 2007): while broadband neurons "sum" the inputs from all cones in their receptive field center, opponent neurons do not. They "subtract" the signals coming from the different spectral types of cones, letting only the differences go through. This "subtraction" can be obtained through different strategies. It can either result from direct excitatory inputs to the receptive field center of a cell, as in the case of teleost opponent BCs in the outer retina (Wong & Dowling, 2005), or it can emerge from center–surround interactions. Some examples are the spectral opponency found in teleost horizontal cells (Kamermans & Spekreijse, 1995), primate opponent BCs (Dacey & Lee, 2001) and primate GCs (for reviews, see Kaplan et al., 1990; Wässle, 2004).

The greatest advantage of this kind of coding strategy is that, instead of using exclusive broadband lines for each spectral type of cones (which would be very redundant), the visual system can spare energy by using only one broadband channel and multiple opponent ones. Opponent channels spare energy because they lead to the production of less spikes at the GC level (remember that GC spiking rates cannot go negative).

This way, one can find evidence for the participation of spectrally opponent neurons in much more than only color perception. In primates, lesion studies suggested that these cells, in addition to color, are related to many percepts such as achromatic contrast, texture, fine pattern and fine stereopsis, as well as motion and flicker at high temporal frequencies (Schiller & Logothetis, 1990; Schiller, Logothetis & Charles, 1990). Spectrally opponent coding was also shown to contribute to the perception of brightness in humans (Stockman & Plummer, 2005; Stockman, Plummer, & Montag, 2005), contrary to the long-held assumption that this aspect of the visual world would be conveyed exclusively by broadband neurons (Livingstone & Hubel, 1988).

Parallel is Just a Word

Even though much has already been discovered about retinal circuits and the processing of visual information in the past hundred years of vision research, it seems more and more that we are only scratching the surface. Much is still to be determined about retinal neurons, their connectivity and coding strategies. One picture that emerges, though, is that the vertical transmission pathways in the retina are everything but truly parallel (Merigan & Maunsell, 1993).

As discussed in the previous sections, convergence and divergence live side by side at all retinal stages, in order to improve the signal-to-noise ratio of the visual signal and make optimal use of the neuronal bandwidth. This way, rod and cone channels converge onto the same BCs at mesopic levels. Similarly, ON and OFF broadband neurons combine their inputs at the OPL and IPL to actively generate the center-surround organization of BCs and GCs, respectively. Finally, the existence of opponent neurons is the result of the convergence of broadband inputs of different signs onto single cells.

Together, these neurons and their coding strategies enable the visual system to perform well in the most different environments by "dividing the load" of information processing. Some retinal circuits specialize in transmitting with high gain, some with low gain. Some specialize in high temporal frequencies, some in low temporal frequencies. Some are concerned with fine spatial resolution, while others transmit a coarser picture of the visual world to the brain.

Knowledge about these retinal circuitries and their roles in visual processing is crucial for any therapy intent on restoring visual function in a diseased eye. In view of how much we still *do not know* about these matters, it seems that visual research has still many years of exciting discoveries ahead.

Acknowledgments

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