and this confines their possible synaptic partners to cells with processes that occupy those same levels. Second, different types of bipolar cells have different numbers and distributions of synapses, without a gradation of intermediate forms between the types. The conclusion reflects more than neuroanatomical anecdote; a formal cluster analysis showed that cone bipolars segregate into discrete groups based on synapse number and distribution[16,19]. Third, individual bipolar cell types have characteristic sets of neurotransmitter receptors and calcium-binding proteins[20–22]. These molecular distinctions reflect different modes of intracellular signaling and different types of excitatory and inhibitory inputs from other retinal neurons, either at their inputs from cones or from amacrine cells that synapse on their axon terminals. At the cone synapses, different glutamate receptors are present. At their axon terminals, different bipolar cells can receive inhibitory glycinergic or GABAergic input via one of two different kinds of GABA receptors. The different receptors and their channels have differing affinities and rates of activation and inactivation, which give the cells different postsynaptic responsiveness[22–25].

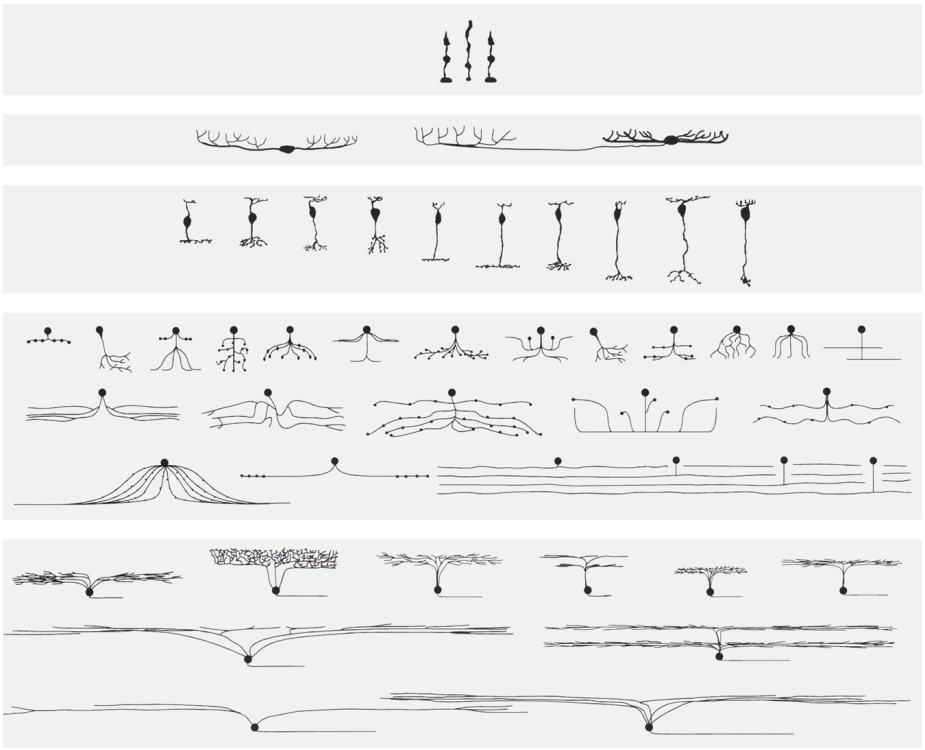

Fig. 1. The major cell types of a typical mammalian retina. From the top row to the bottom, photoreceptors, horizontal cells, bipolar cells, amacrine cells and ganglion cells. Amacrine cells, the most diverse class, have been studied most systematically in the rabbit[3,4], and the illustration is based primarily on work in the rabbit. Most of the cells are also seen in a variety of mammalian species. The bipolar cells are from work in the rat[39]; similar ones have been observed in the rabbit, cat[16] and monkey[17]. For steric reasons, only a subset of the wide-field amacrine cells is shown.

How are these differences manifested physiologically? First, the output of the cone photoreceptors is separated into ON and OFF signals (**Fig. 2b**). All cone synapses release glutamate, but bipolar cell types respond to glutamate differently. Some bipolar cells have ionotropic glutamate receptors: glutamate opens a cation channel, and the cell depolarizes. Other bipolar cells have a sign-inverting synapse mediated by metabotropic glutamate receptors, mainly mGluR6; these bipolar cells hyperpolarize in response to glutamate[26,27]. As it happens, photoreceptor cells work 'backward' (they hyperpolarize when excited by light, causing their synapses to release less glutamate), but the ensuing series of sign-reversals is not important for present purposes. When the retina is stimulated by light, one type of bipolar cell hyperpolarizes, and the other type depolarizes. OFF and ON bipolar cells occur in approximately equal numbers. The distinction, created at the first retinal synapse, is propagated throughout the visual system.

The classes of ON and OFF bipolars are each further subdivided; there are three to five distinct types of ON and three to five types of OFF bipolars (**Figs. 2c** and **3**). The purpose of the subdivision is, at least in part, to provide separate channels for high-frequency (transient) and low-frequency (sustained) information. Thus, there are separate ON-transient, ON-sustained, OFF-transient and OFF-sustained bipolar cells[28–30]. An elegant series of experiments shows that the distinction is caused by different glutamate receptors on the respective OFF bipolar cells; they recover from desensitization quickly in the transient cells and more slowly in the sustained cells[31].

An often-cited reason for splitting the output of the cones into separate temporal channels is to expand the overall bandwidth of the system. However, this would imply that the frequency bandwidth present at the output of a cone is too broad for transmission through the cone-to-bipolar synapse, which is uncertain given the many modes of synaptic transmission available. An alternative is that fractionating the temporal domain facilitates the creation of temporally distinct types of ganglion cells (**Fig. 4**).

An important point here is that there are no dedicated cones—cones that provide input, say, only to ON bipolars or only to OFF bipolars (as shown for simplicity in **Fig. 2**). Instead, the output of each cone is tapped by several bipolar cell types to provide many parallel channels, each communicating a different version of the cone's output to the inner retina (**Figs. 3**, **4** and **6**).

The foundations of color vision

The bipolar cells discussed so far are not chromatically selective, and this would prevent the retina from discriminating among wavelengths. A single type of cone, no matter how narrow its spectral tuning, cannot create color vision. A cone's synaptic output is a single signal, which can vary only in magnitude. For that reason, a cone's signal to the brain is inevitably ambiguous; there are many combinations of wavelength and intensity that will evoke the same output from the cone. To specify the wavelength of a stimulus, the outputs of at least two cones must be compared.