Visual System I, the Eye

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Lecture notes

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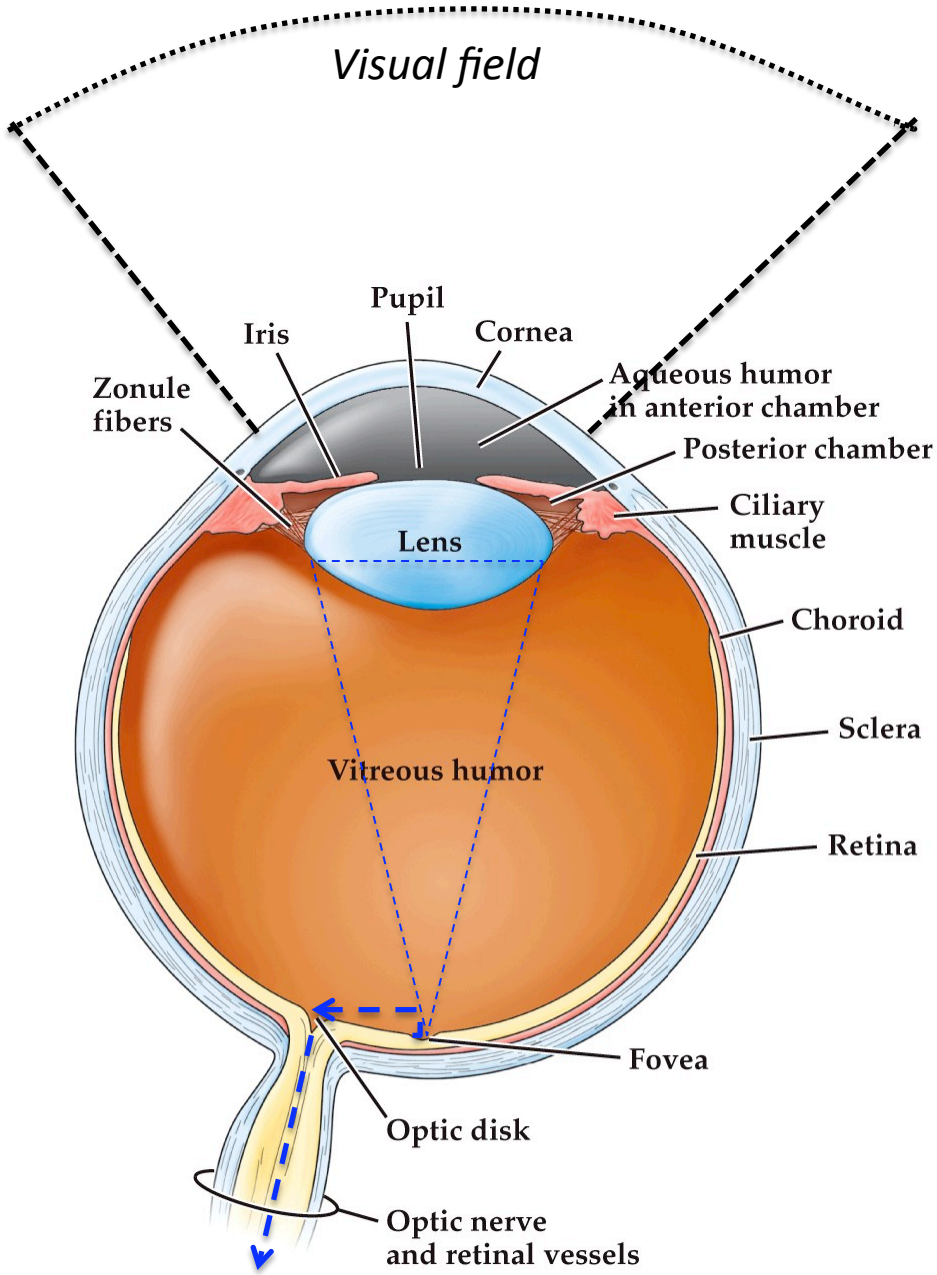
Text: Neuroscience, Chapter 11 by Dale Purves et al.
(Fifth edition-Publisher Sinauer)

Learning Objectives

- Understand the anatomy of the human eye
- How images are formed on the retina
- Understand the process of phototransduction
- Functional distribution of rods and cones
- Circuitry for detection of light contrast
- Retinal circuits responsible for light adaptation
- Concept of center-surround in ganglion cells



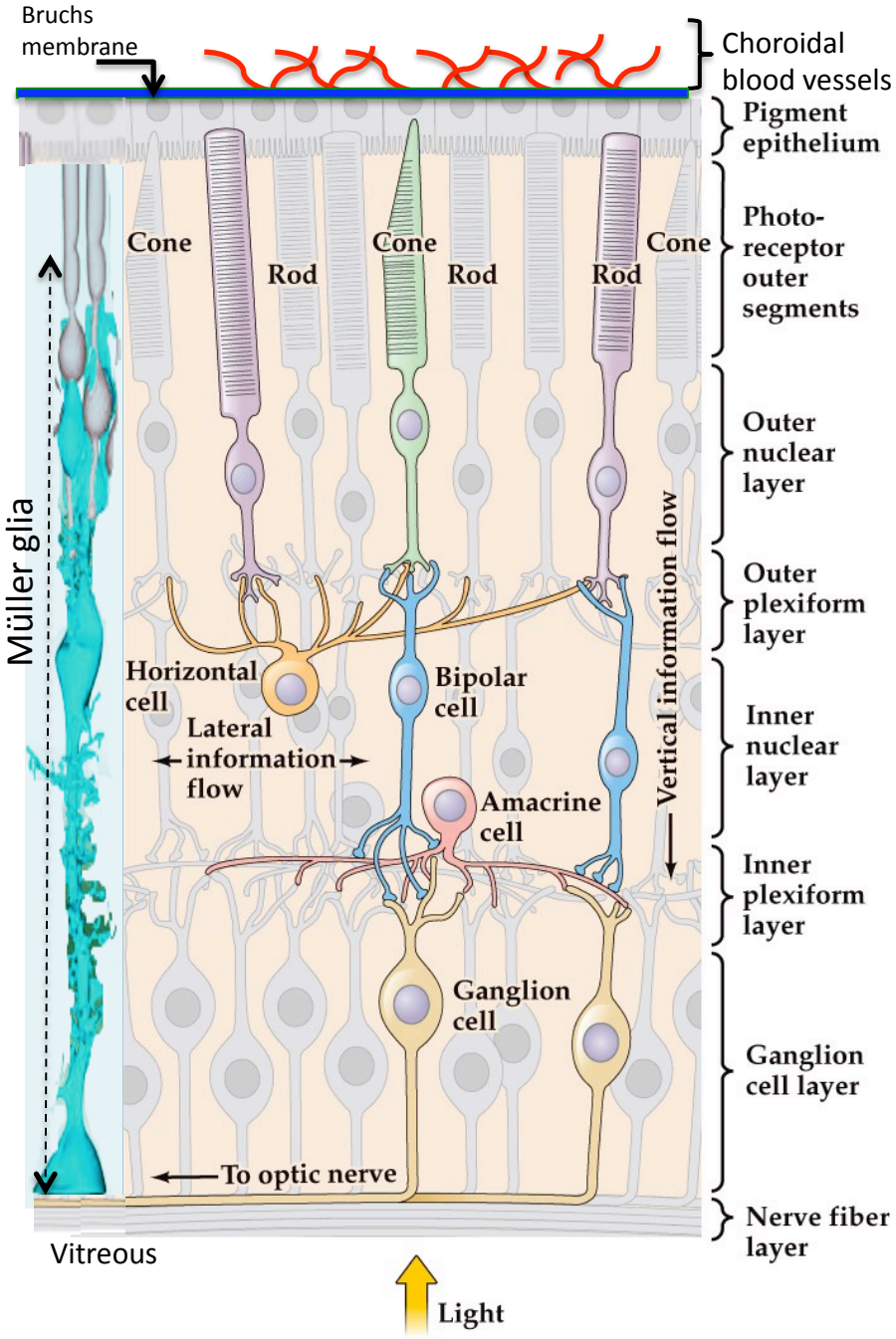
***NEUROSCIENCE 5e*, Figure 11.1**

The cornea provides ~60 percent of light refraction, which the lens sharpens by changing its shape. Contraction by ciliary muscles reduces tension on zonule fibers and allows the lens to become rounder for close-up focusing; this is known as **Accomodation**.

The central 10° of the retina is involved in tasks requiring high visual acuity (e.g. reading, texting). About 40° of the retina is engaged in most other visual tasks (e.g. machine operation). However, the most peripheral part of temporal retina is key for certain professionals (race car drivers and fighter pilots).

Image reception and visual transduction by photoreceptors converts light to chemical gradients, which post-synaptic retinal interneurons also use chemical gradients for early image processing. Final conversion of chemical signaling into action potentials occurs only in retinal ganglion cells that project to the brain.

The rod and cone photoreceptors (GPCRs) use the special ligand 11-cis retinal for light capture. This activation triggers a cascade of intracellular biochemical events called **phototransduction**.

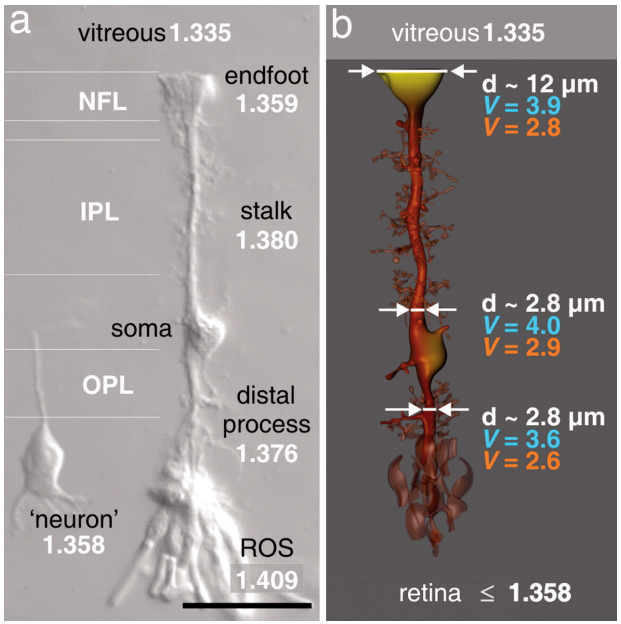


***NEUROSCIENCE 5e*, Figure 11.5 (Part 2)**

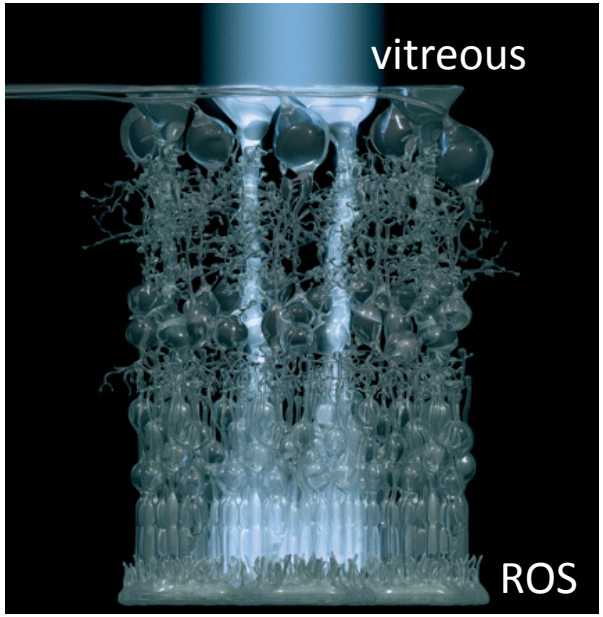
Why does light not get back-scattered by the inner retinal cells? The answer may lie in the ordered array of radial glia (Müller cells). Müller cells on average neighbor every photoreceptor cell and their processes run parallel to the light path from ganglion cell layer to the photoreceptor layer acting like a fiber optic system for focusing light on photoreceptors.

Müller cells also become activated during stress in the retina. They are chiefly responsible for detoxification of excess neurotransmitters (Glu, GABA, Gly, D-Ser). With tissue injury, activated Müller cells engage into a process known as reactive gliosis. Müller cells proliferate and also dedifferentiate into neural precursor cells to repopulate the destroyed photoreceptors and interneurons. Chronic reactive gliosis can be detrimental because it leads to the formation of scar tissue. This scar tissue pulls on delicate sensory neurons causing retinal folds and as well this tissue blocks the passage of light. Reactive gliosis is one of the common underlying features of many leading blinding eye diseases, including age-related macular degeneration, diabetic retinopathy and glaucoma.

Muller cells may act as fiber optic cables to focus light on photoreceptors

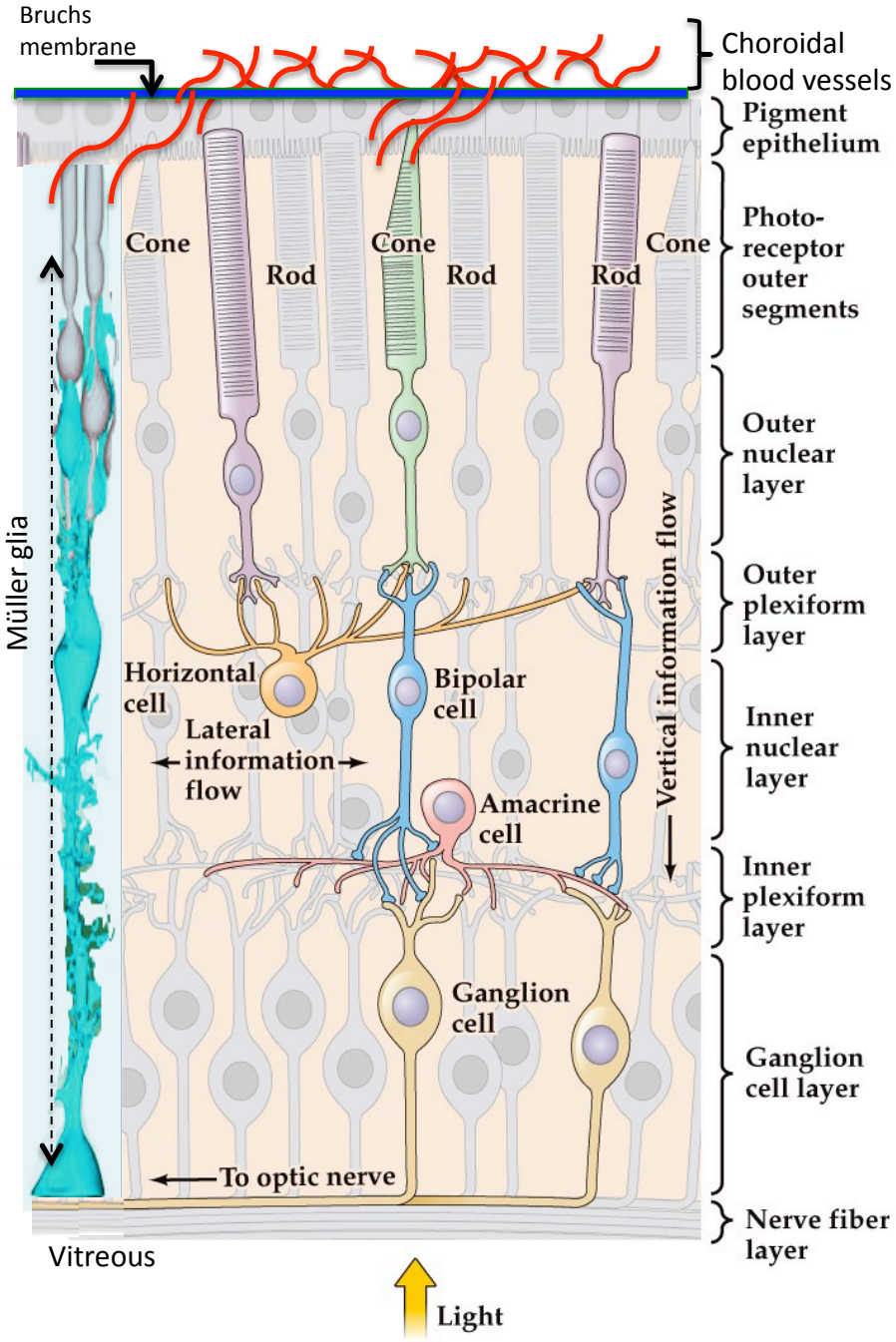


(a) Müller glial cell with rod outer segment (ROS) and a nearby bipolar cell (refractive indices are numbered). (**b**) The refractive index (ability to transmit light) is measure as the waveguide characteristic frequency (*V).* This value remains fairly constant at 700 nm (orange) for the endfoot, the inner process the outer process of the Müller cells and also at 500 nm (blue).



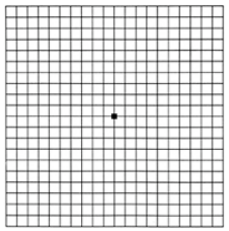
Cover image of PNAS: Müller glial cells act as living optical fibers, transporting light through the inverted retina of vertebrates. Image courtesy of Jens Grosche.

Franze K et al. PNAS 2007;104:8287-8292

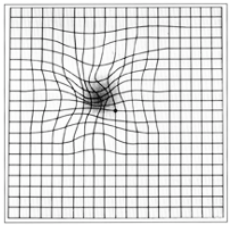


***NEUROSCIENCE 5e*, Figure 11.5 (Part 2)**

Age-related macular degeneration (AMD) affects central vision because cone cells at the fovea die (6 million Americans have it). This condition slowly develops into a more aggressive vascular proliferative condition in about 10% of cases. This involves the growth of choroidal blood vessels into the sensory retina through disruption of Bruchs membrane. Early AMD can be diagnosed with a visual task (Amsler grid test) and followed by intraocular fundus examination. Retinal pigment epithelium (RPE) dysfunction in the central foveal region leads to drusen deposits, which accumulate and promote cone photoreceptor cell loss.

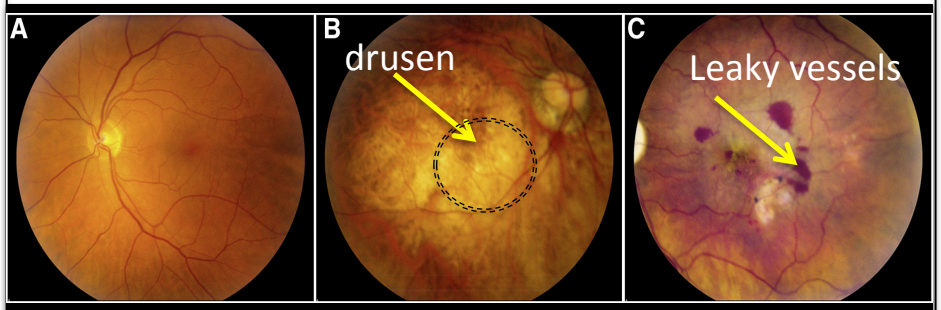


Normal

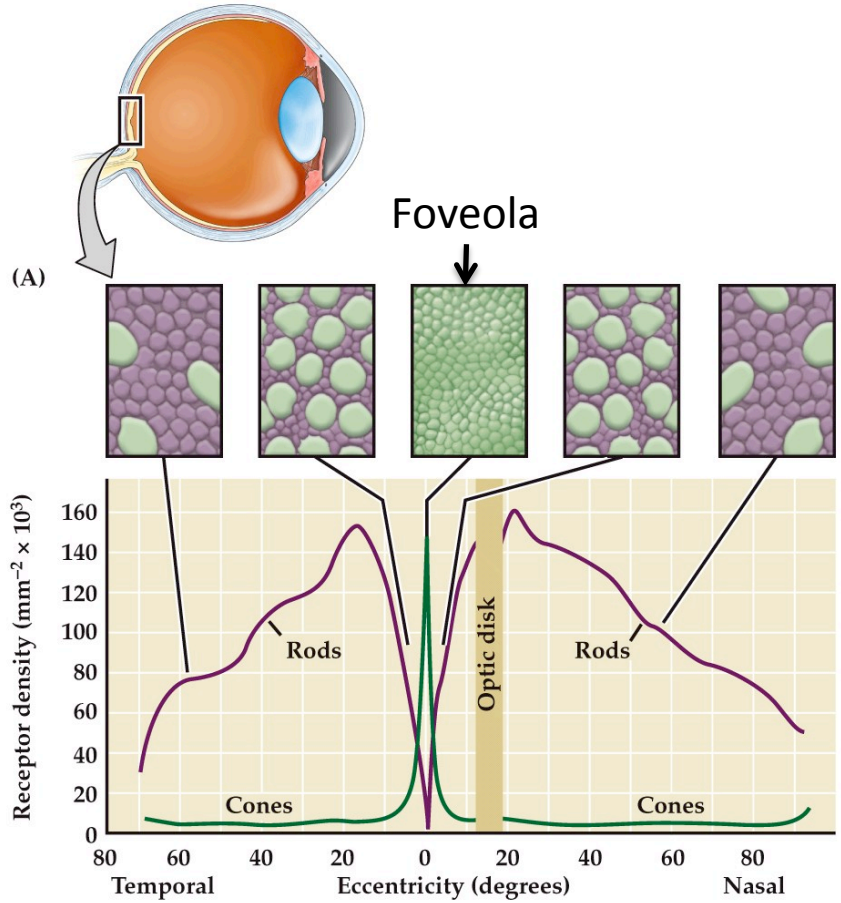


AMD

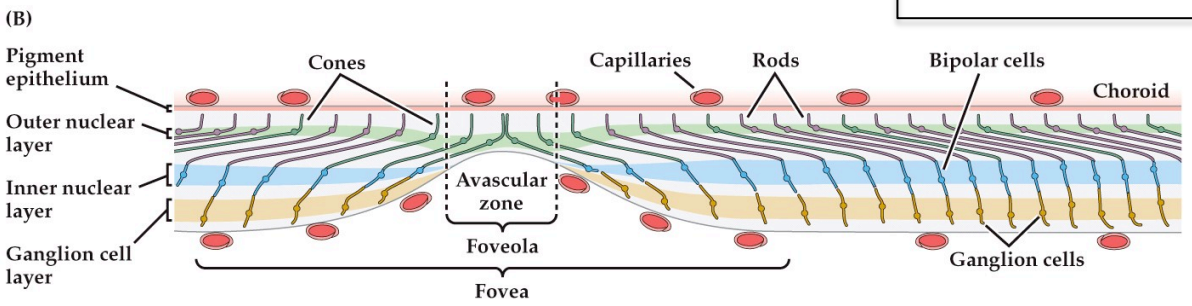
Amsler grid



Mechanisms of Age-Related Macular Degeneration. *Neuron* July 12, 2012



***NEUROSCIENCE 5e*, Figure 11.13 (Part 1)**



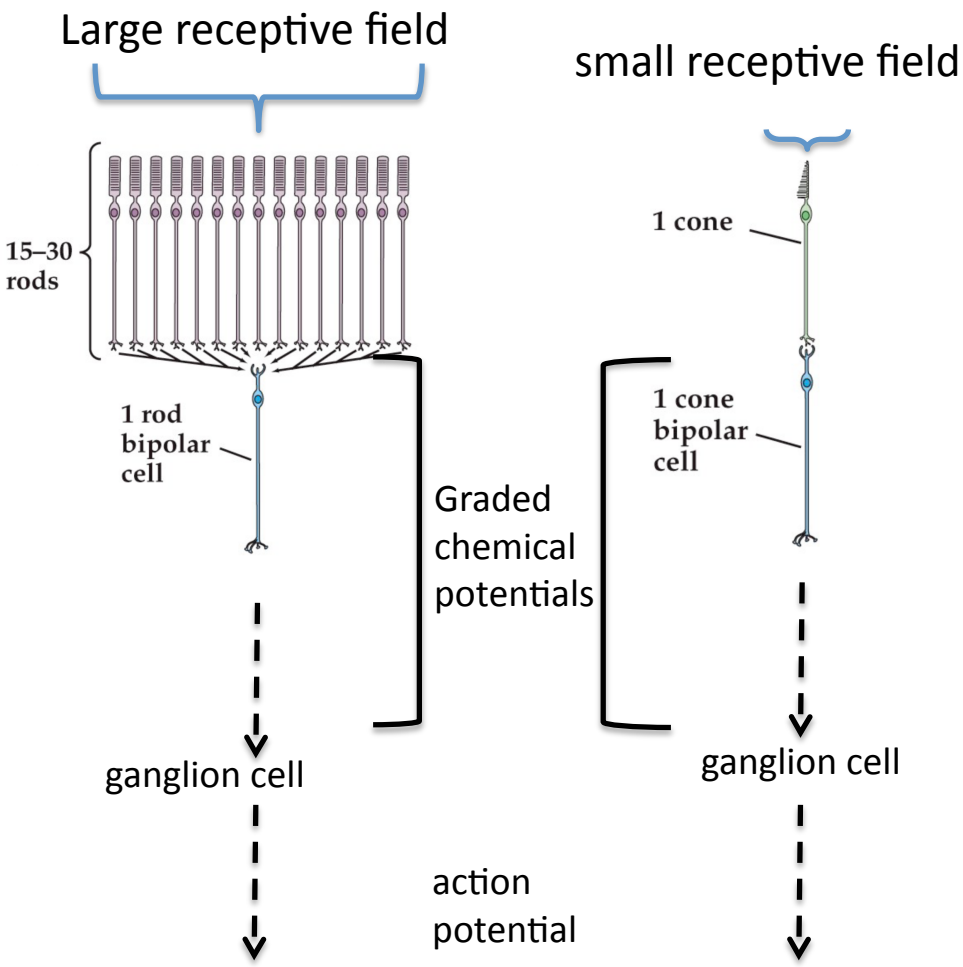
***NEUROSCIENCE 5e*, Figure 11.13 (Part 2)**

Real estate in the retina is premium. Key to how this tissue is functionally organized has to account for spatial vision, contrast sensitivity and visual acuity.

Rods are more abundant at periphery (temporal and nasal), maximally at 20^o from the fovea.

In the fovea (1.2 mm in diameter), cone density increases 200-fold and at its center, the foveola (300 micrometer), only cone cells exist where their tight packing is accomplished by having narrow outer segments. <u>This region is also free from any retinal blood vessels</u>.

Foveal metabolic functions are governed by the pigment epithelium, which is fed by an abundance of choriodal capillaries. Choroidal blood flow is also highest in fovea, being the tissue with the highest blood flow in the body!



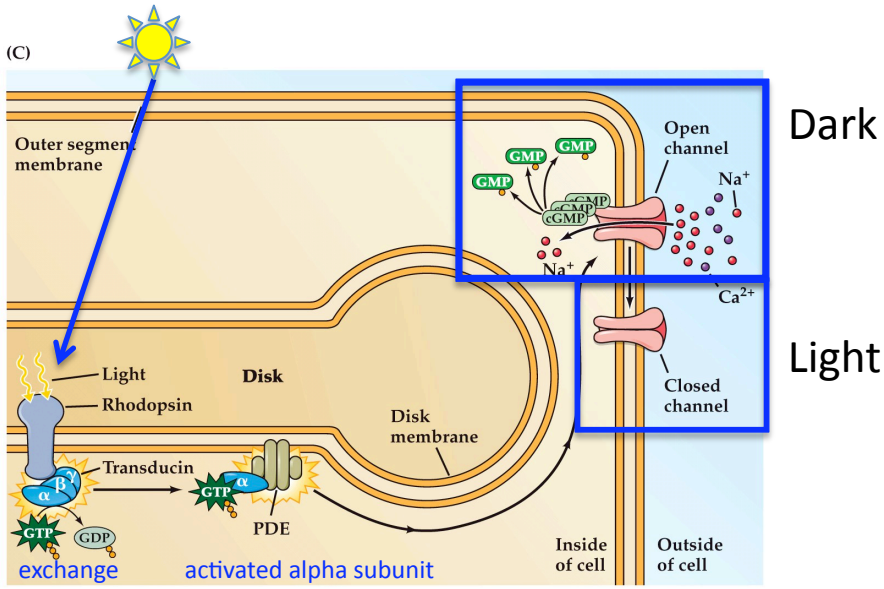
Rods and cones differ by their shape, light sensitivity, photopigment, anatomical distribution and synaptic connection with interneurons.

Rods have poor resolution due to large receptive field, but they are sensitive to very low levels of light (starlight- Scotopic vision).

Cones are most active at ambient lighting and sunlight (Photopic vision), and have low sensitivity. They have very high resolution due to small receptive fields.

Rods outnumber cones (90 million rods vs 4.5 million cones). Rods gain sensitivity by having 15-30 rods/bipolar cell; rod-bipolar cells in turn form synapses with amacrine cells through gap junctions. This additional interneuron forming a synapse with ganglion cell distinguishes the rod from cone circuits.

Single cone cells synapse with single bipolar cells that directly synapse with ganglion cells at the fovea. Cones do not saturate at high light intensity and can also recover 4X faster than rods to bright light, which allows us to read going from ambient light into bright light.



NEUROSCIENCE 5e, Figure 11.9 (Part 3)
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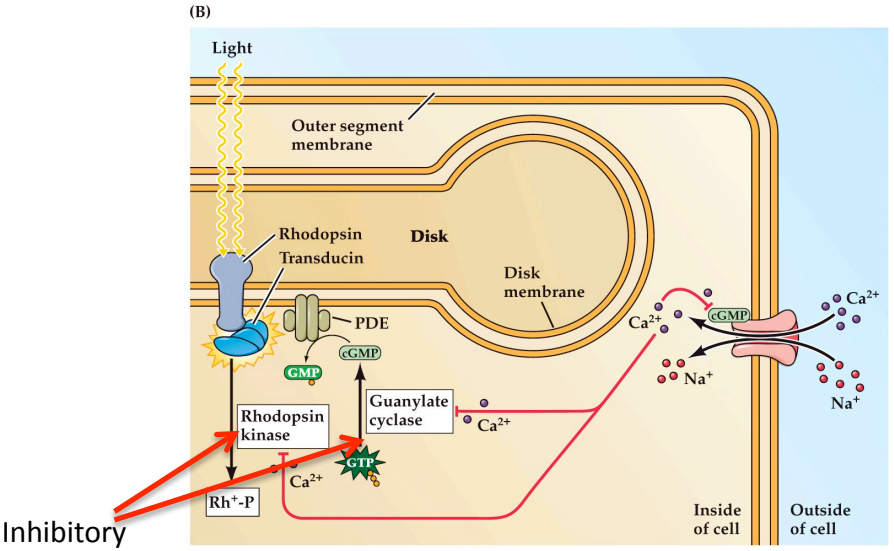

Inhibitory mechanisms

NEUROSCIENCE 5e, Figure 11.10 (Part 2)
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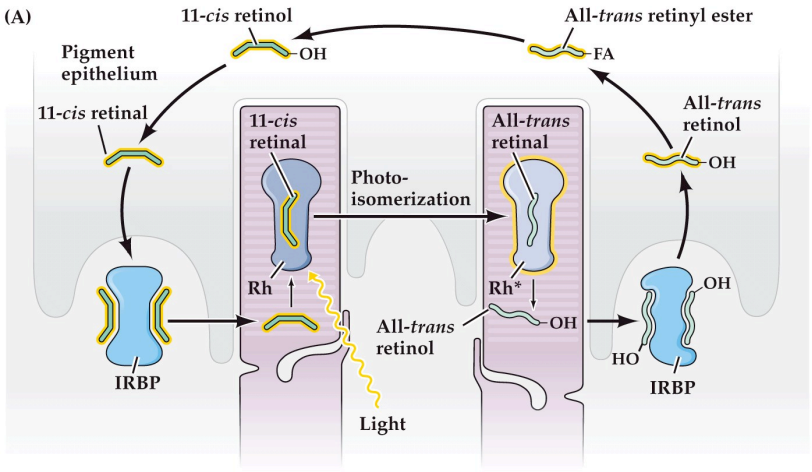
Phototransduction: In dark, Na+ and Ca++ enter through cGMP-gated channels, whereas K+ flows out keeping the cell essentially depolarized. cGMP maintains channels open in the dark for a continuous current (**dark current**). Light decreases the dark current in a graded manner by activating rhodopsin causing activation of transducin (G-protein) and downstream activation of phosphodiesterase that causes hydrolysis of cGMP. This decreased cGMP leads to closure of channels, resulting in decreased influx of Ca++. The receptor cell hyperpolarizes.

The cycle is turned off when transducin is inactivated by hydrolysis of bound GTP to GDP by a GTP-ase activating complex (GAP). The inactivation of the active subunit of transducin is the rate-limiting step for turning off the cascade.

Photoreceptor cell adaptation: Ca++ levels regulate photoreceptor cell adaptation to changing levels of illumination. Photoreceptors are most sensitive to light at low levels of illumination where Ca++ in outer segments are high. As illumination increases, sensitivity decreases, preventing saturation. High Ca++ leads to inhibition of guanylate cyclase activity and rhodopsin kinase, and reduced affinity of cGMP-gated channels for cGMP. With increase in light intensity the channels in the outer segments close, reducing Ca++ concentrations and downregulating several Ca++-mediated inhibitory effects. The removal of this “inhibitory brake” consequentially increases the activity of rhodopsin kinase allowing more arrestin to bind rhodopsin, increases cGMP levels and promotes cGMP binding to cGMP-gated channels. The regulatory effects of Ca++ on the phototransduction cascade is one part of a mechanism that adapts retinal sensitivity to the background levels of illumination.

The Retinoid Cycle is critical for the health of the retina



NEUROSCIENCE 5e, Figure 11.10 (Part 1)
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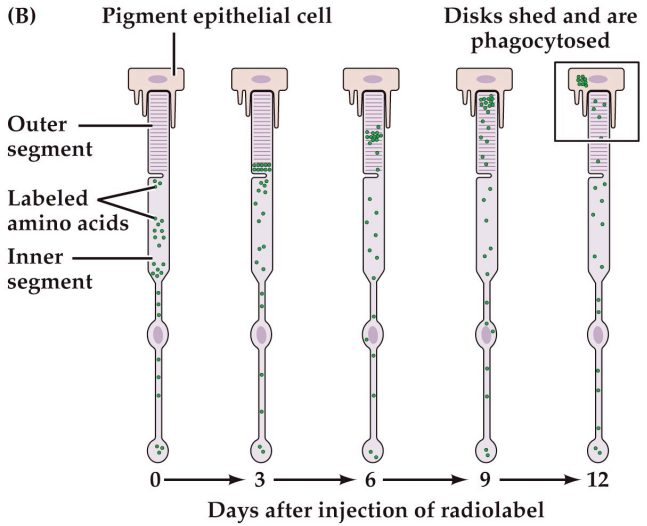

NEUROSCIENCE 5e, Figure 11.6 (Part 2)
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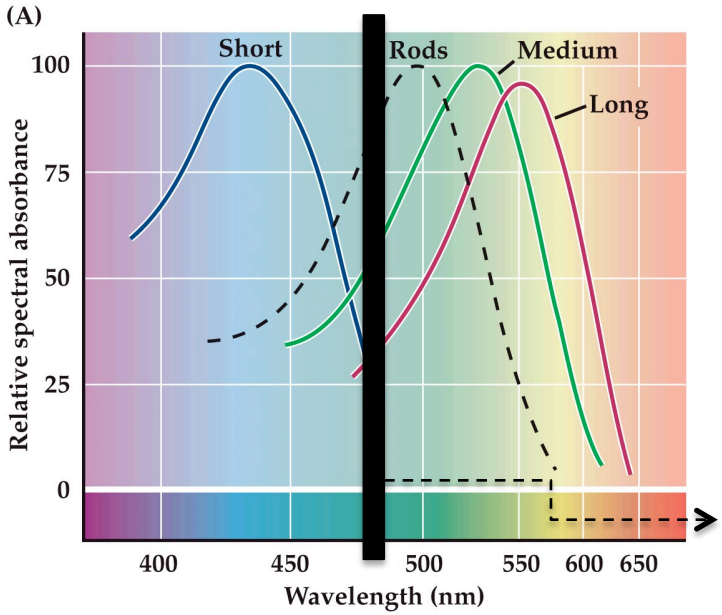
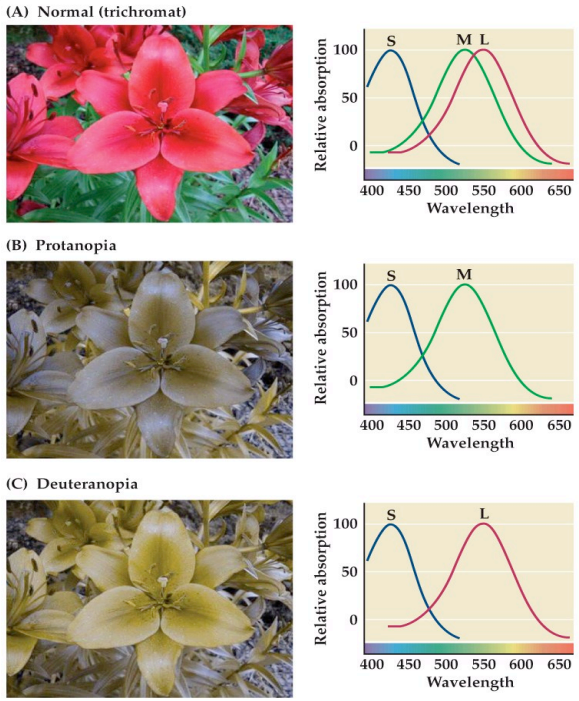
To ensure the rod cell's supply of 11-cis retinol and maintain the high metabolic rate of the retina, the retinal pigment epithelium (RPE) plays two key functions. One function is to maintain a constant supply of 11-*cis* retinal by recycling all-trans retinal that comes off from rhodopsin in the RPE where it is transported by the interphotoreceptor retinoid binding protein (IRBP) for biochemical reconversion. This cycle needs to be maintained so that rods are never depleted of 11-*cis* retinal. When humans are deprived of dietary vitamin A, the rod photoreceptor cells become selectively dysfunctional causing night blindness. Daylight vision is unaffected in these individuals. The second function of the RPE is for phagocytosis of disks from outer segment membranes. This finely tuned "garbage collection" function helps keep photoreceptor cells healthy so they can regenerate this membrane every 12 days.

Cone cells, on the other hand, depend on the Müller cells to supply 11-*cis* retinal for their regeneration. This has to happen much more rapidly in cones because of the need for faster adaptation to light. The biochemical pathway that regenerates 11-*cis* retinal in Müller cells is somewhat different from that in the RPE. *All*-trans retinol is isomerized to 11-*cis* retinol in Müller cells, which is transported to cones where it gets oxidized to 11-*cis* retinal. The retinoid cycle in Müller cells has only recently been established and implications of this pathway in human diseases where cone cells are involved are an active area of investigation.



Color perceived at the wavelenth band (black bar) is contributed by all 3 receptors

***NEUROSCIENCE 5e*, Figure 11.14 (Part 1)**



***NEUROSCIENCE 5e*, Figure 11.15**

Color Vision: Three types of cone cells that differ in their photoreceptor proteins confer differential sensitivity to short, medium and long wavelengths of light. Wavelengths that fall in between that optimal for the blue (short), green (medium) or red (long) cones will appear as a combination of colors. However, only 5-10% of cones are blue cones; red and green cones that are roughly of equal number also differ in numbers among individuals. Humans are trichromats and some individuals who lack red/green cones are dichromats. Others are anamolous trichromats due to genetic variation in copy number or due to genetic recombination between photopigment genes.

Color is also a matter of perception. What we interpret as a particular color is determined by its context. This influence arises from the object's surroundings and the illumination intensity.

Think about why blue light is not used as a navigation light on ships and aircrafts. Also, if an individual is red/green color blind how well do they visualize histological tissue sections.

Perception of Light Intensity

- The receptive field of the ganglion cell is the visual space in which changes in light intensity affects its action potential firing rate. A dynamic range of 10-billion-fold levels of contrast spanning the scotopic to photopic limits need to be accounted for in human visual contrast sensitivity.

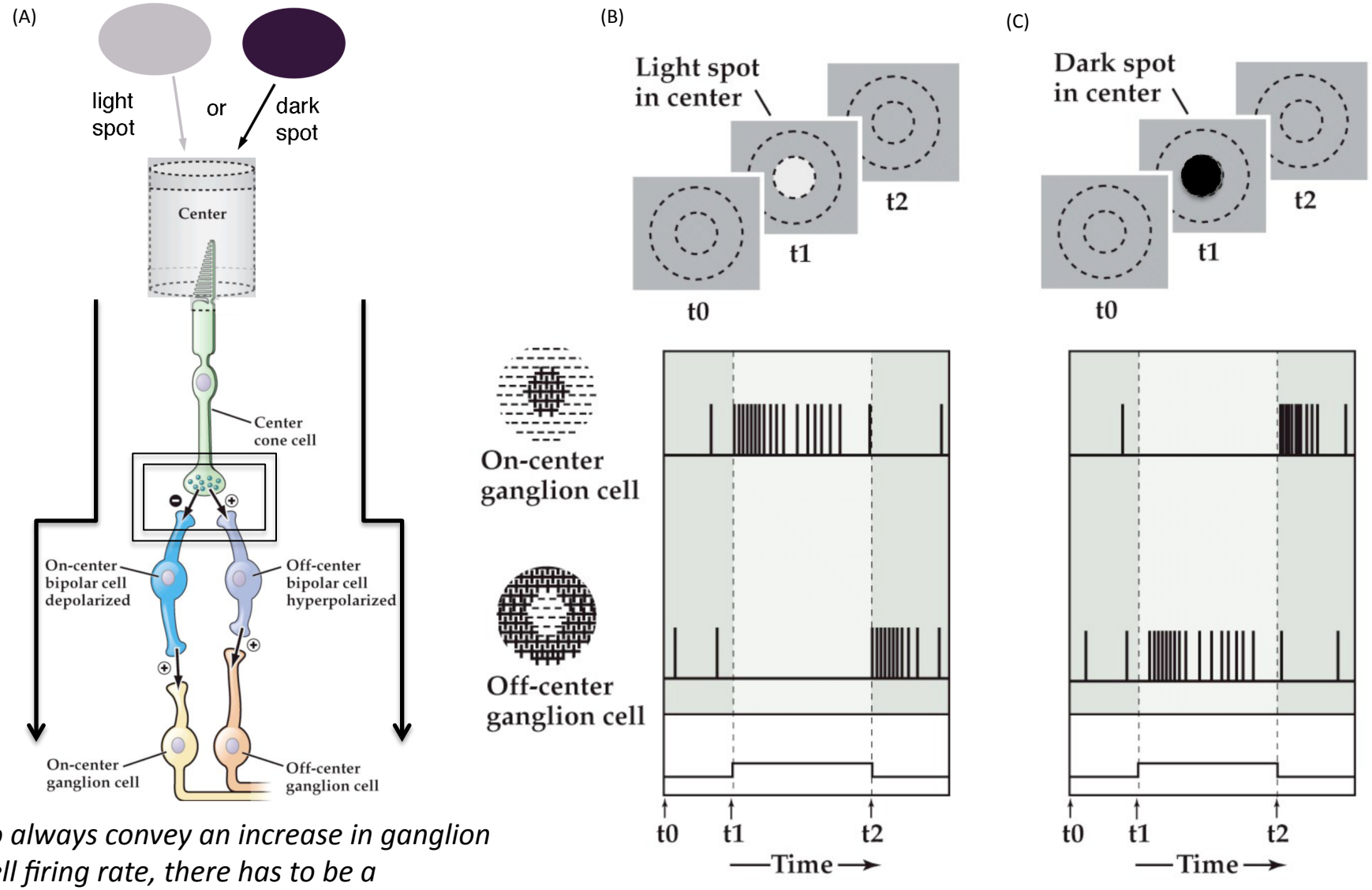
- Two types of ganglion cells transmit "luminance pathways" to the brain through separate inputs transmitting both the increases in light intensity and the decreases in light intensity, respectively.
  - On-center ganglion cells increase firing rate when light hits the center of the receptive field.
  - Off-center ganglion cells decrease firing rate when light hits the center of the receptive field.

- Having two classes of cells, with overlapping receptive fields and wide distribution, every part of visual space is analyzed (by supposedly equal numbers of on- and off-center ganglion cells). In reality, our visual space has lighter background (negative contrast). So, we have evolved to have more numbers of off-center ganglion cells than on-center ganglion cells.

- Ganglion cells rapidly adapt to intensity changes, and so their resting firing rate is low. When light intensity decreases an on-center ganglion cell (causing a decrease in firing rate), this is a weak signal transmitted to the brain. To offsets this weaker mechanism, the increase in firing rate from the off-center ganglion cell fulfils the need for positive communication with the brain.

- An increase in action potential firing rate from two independent ganglion cell sources, thus, reinforces the visual perception of both increase and decrease of light intensity.

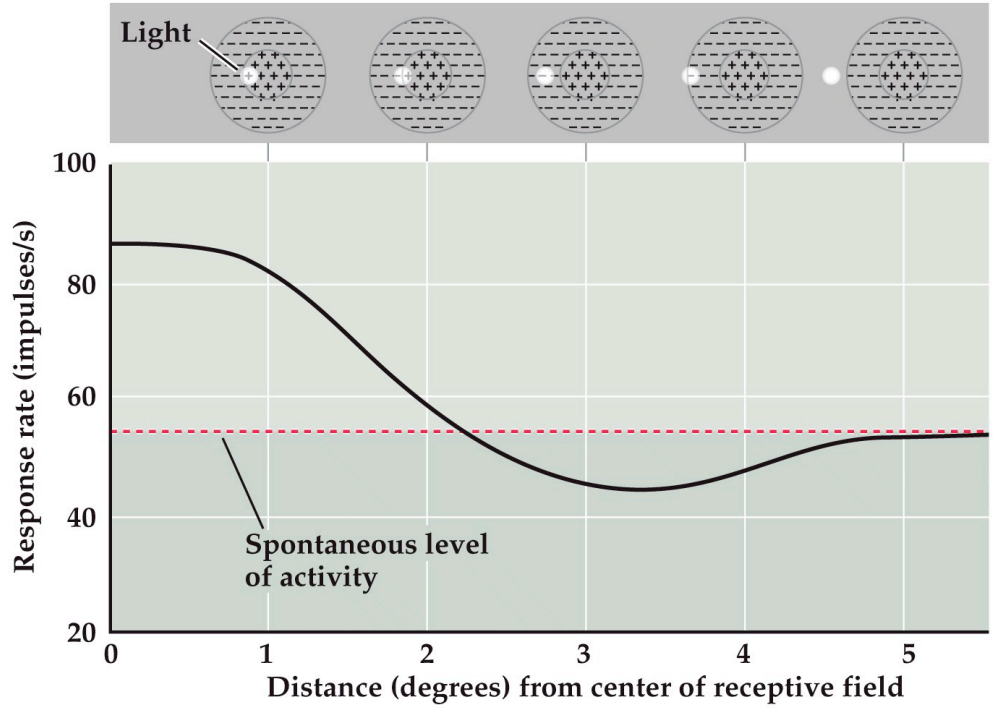
On-center and off-center ganglion cells relay increases and decreases in light intensity, respectively



To always convey an increase in ganglion cell firing rate, there has to be a switch at the level of the bipolar cell.

***NEUROSCIENCE 5e*, Figure 11.17**

Ganglion cells detect light contrast, not absolute level of light intensity

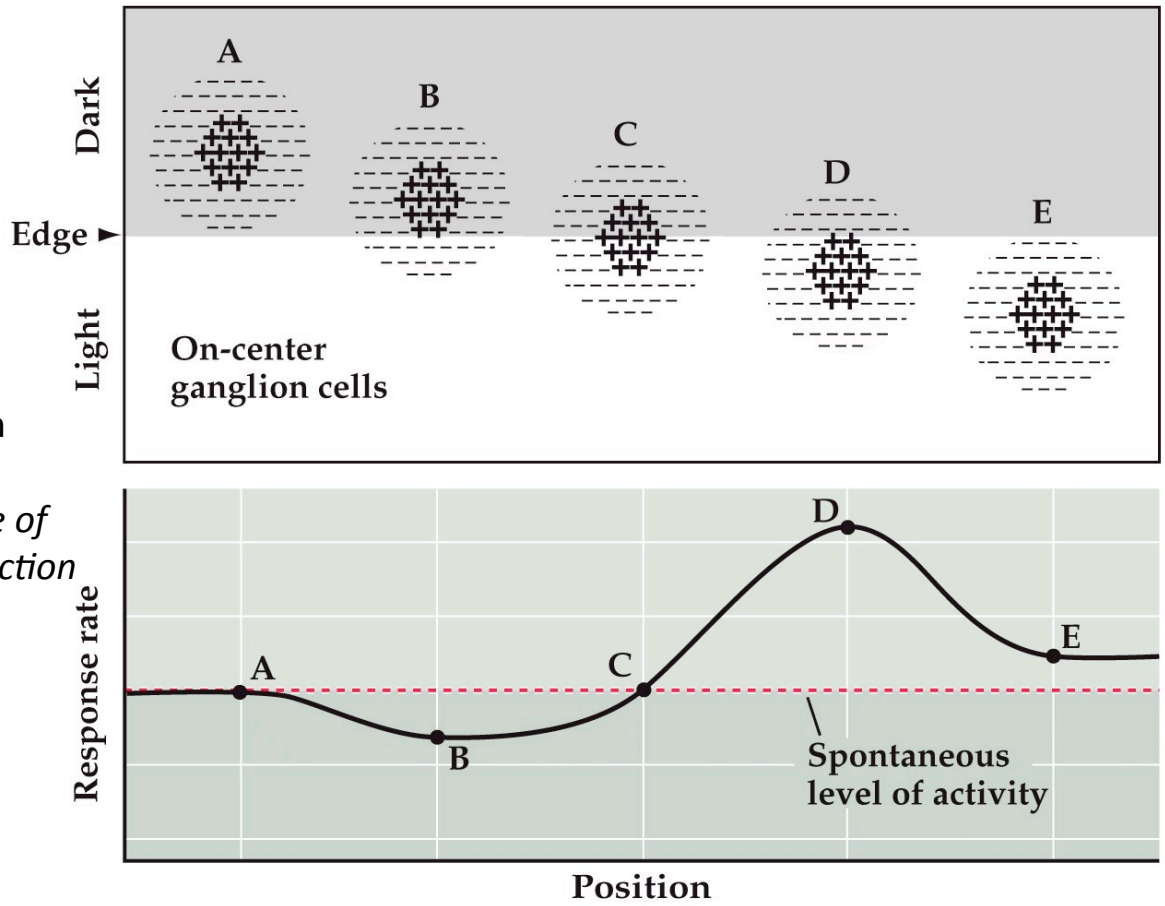


NEUROSCIENCE 5e, Figure 11.19 (Part 1)

Light intensity changes affect only the receptive field (center and surround).
Notice when light spot is outside the receptive field there is no change in firing rate from spontaneous basal rate.

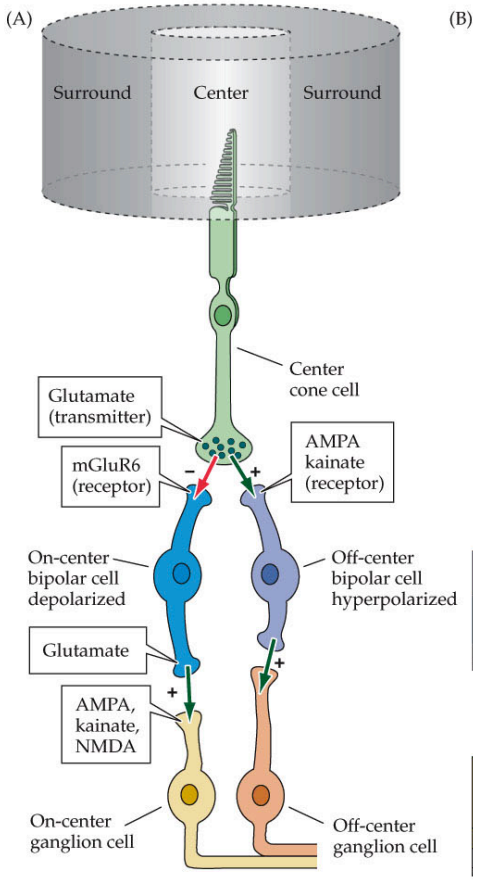
The ganglion cell responds to edges (difference between two levels of grey or color shades)

Ganglion cells respond most dramatically when there is maximum contrast of the center and surround regions. *You will be using this feature of your visual system during brain dissection and Nlabs.*



***NEUROSCIENCE 5e*, Figure 11.19 (Part 2)**

On-center and off-center ganglion cells receive inputs from two different types of bipolar cells



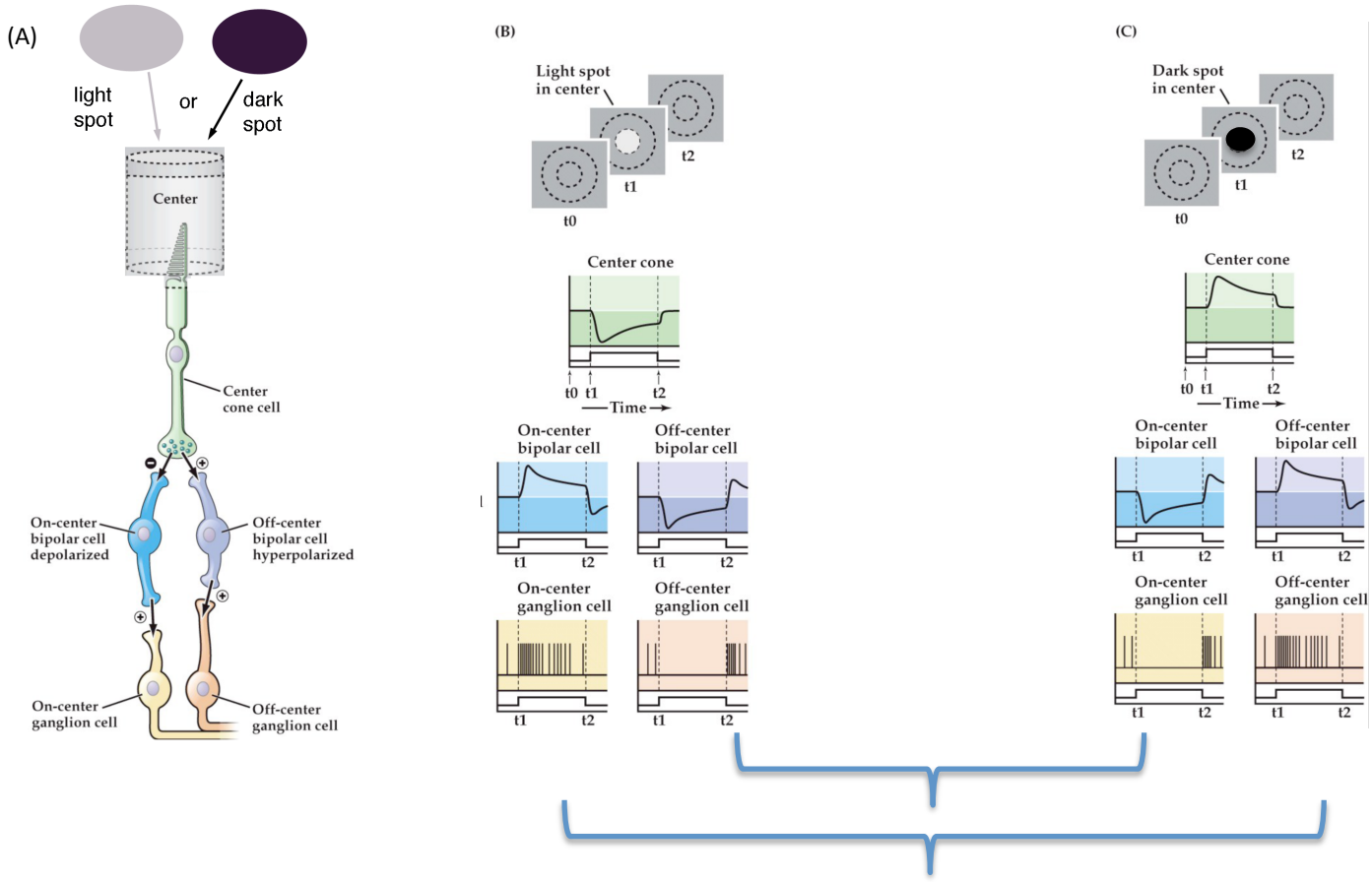
Two types of bipolar cells (on-center and off-center) with different types of Glu receptors respond in opposite ways to Glu.

On-center bipolar cells, forming synapses with on-center ganglion cells, have G-protein coupled metabotropic glutamate receptor (mGluR6) receptors that bind Glu and activate a cascade to close cGMP-gated Na+ channels. This hyperpolarizes the bipolar cell. So, when light intensity is increased, the release of Glu is decreased. This decreased Glu received at on-center bipolar cells promotes cGMP-gated Na+ channels to open and on-center bipolar cells become depolarized.

Off-center bipolar cells express AMPA and kainate receptors. So, when light intensity is increased, the decreased levels of Glu received at off-center bipolar cells causes them to become hyperpolarized.

The opposite effect is witnessed when light intensity is reduced; on-center bipolar cells become hyperpolarized and off-center bipolar cells depolarized.

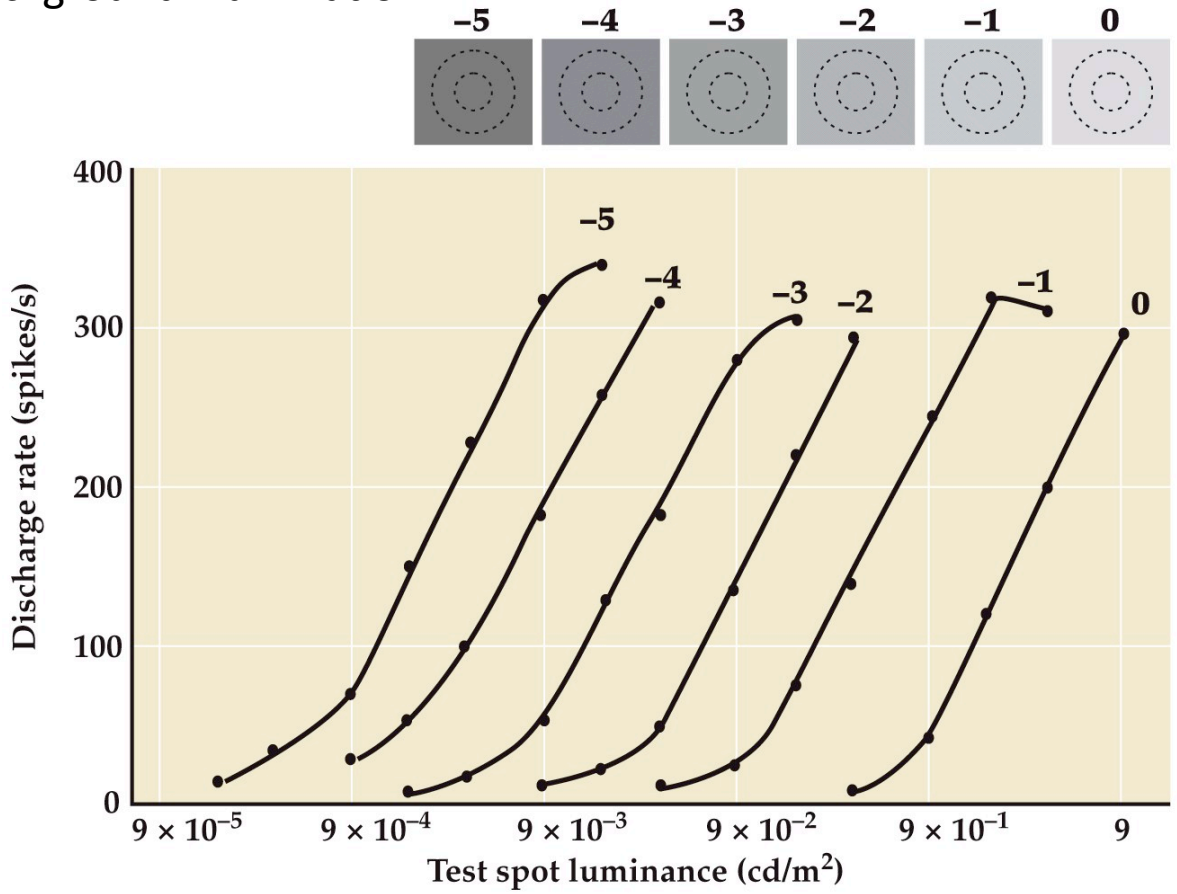
Bipolar and ganglion cell responses to changes in light intensity



Notice the similarity of on-center ganglion discharge response to a light spot in its center when compared to off-center ganglion cell discharge response when a dark spot falls in the center.

Center-Surround mechanisms also mediate ganglion cells to light adaptation

Effect of changing spot intensity holding background illumination constant from low (-5) to very high (0). The on-center ganglion cell response rate is responsive to the stimulus intensity over a range of ~2 log units, with being linear over a range of 1 log unit. Notice the greater dynamic range at very low background illumination.



NEUROSCIENCE 5e, Figure 11.20

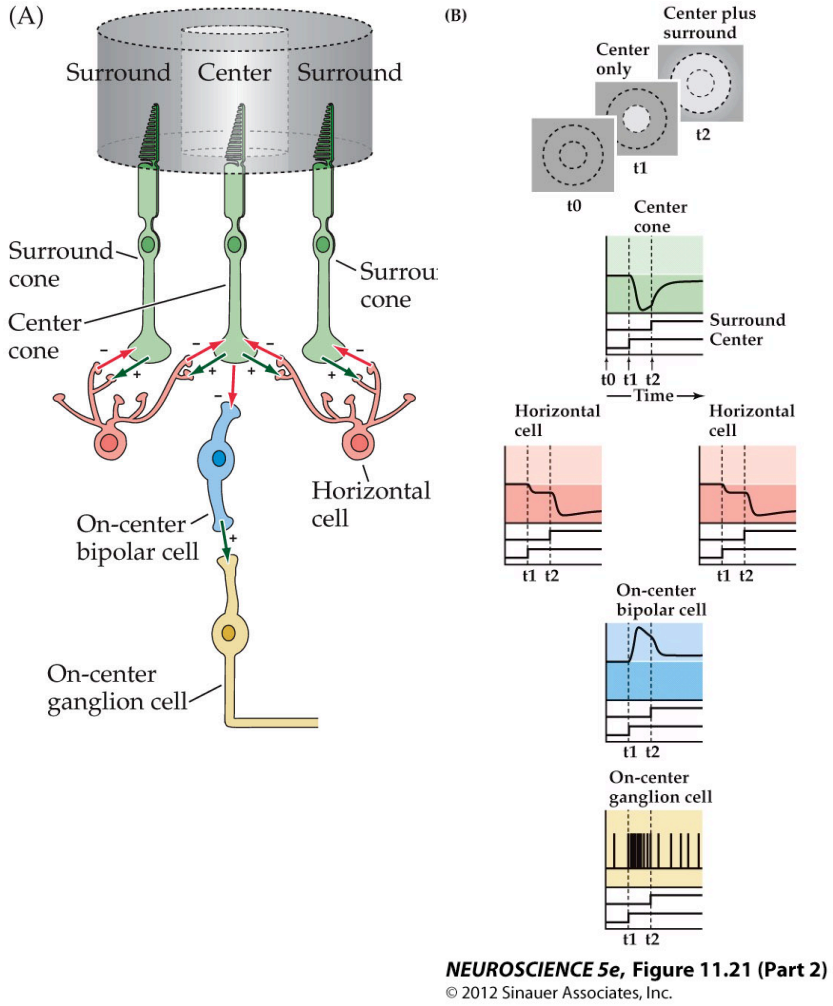
Circuitry of the receptive field surround

Horizontal cells span over large distances forming synaptic connections with other horizontal cells and use gap-junctions to communicate with cones.

Horizontal cells release GABA onto photoreceptor terminals to modulate neurotransmitter release by photoreceptor cells on bipolar cells

Glu from photoreceptors depolarizes horizontal cells, while GABA release from horizontal cells has hyperpolarizing affect on photoreceptor. The net effect is an antagonistic mechanism that the surround confers on the on-center ganglion cell.

Surround mechanism of Horizontal cells: further modulation of visual processing in retina



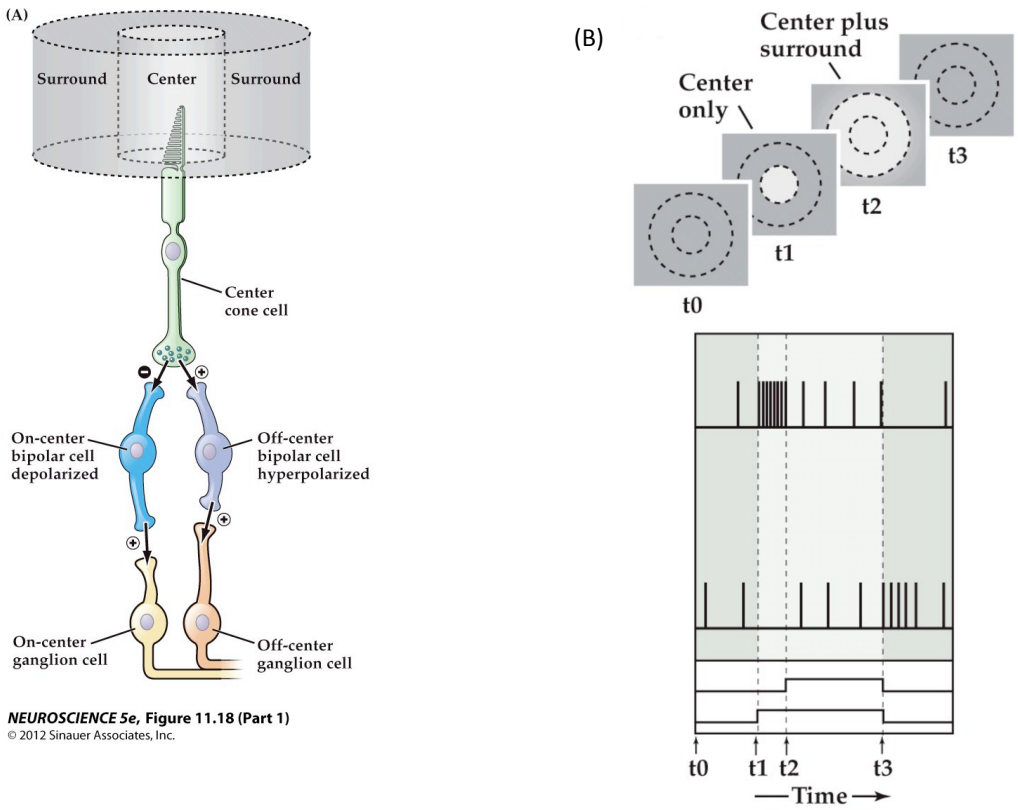
***NEUROSCIENCE 5e*, Figure 11.21 (Part 2)**

Spot of light in the center of on-center ganglion produces minimal response from horizontal cell so the influence of surround is low.

Larger spot of light that spills over to additional cones will activate the surround as a larger network of horizontal cells that become hyperpolarized from decrease in Glu.

Horizontal cells release GABA that is inhibitory. Horizontal cells that synapse with the on-center photoreceptor will induce their depolarization, essentially reducing the light-induced hyperpolarization response of the photoreceptor. As a consequence there will be a net reduction of the on-center ganglion cell firing rate.

An similar effect will be observed with an off-ganglion cell when a large dark spot covers the entire receptive field of the off-center ganglion cell.



***NEUROSCIENCE 5e*, Figure 11.18 (Part 1)**

The ganglion cell receptive field is affected by light (and dark) spots at both the center and surround. The center of a ganglion cell receptive field is surrounded by a concentric region, that when stimulated (see t2 in Fig B), antagonizes the response to stimulation of the center (t1 in Fig B). The firing rate of this on-center ganglion cell is reduced when the surround and center are simultaneously illuminated.