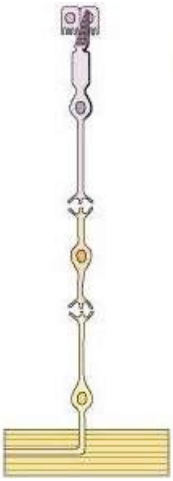
- Photoreceptors have arms that envelop the HC and BC processes
- The photoreceptors grab onto two processes of the horizontal cells, and one BC

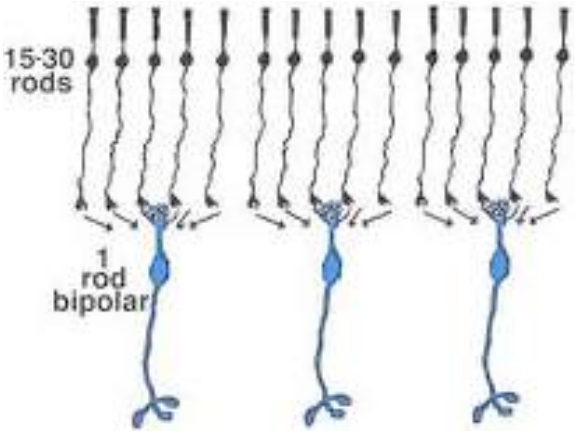
- **inner plexiform layer**
  - communication between BC and Ganglion Cell
  - at the same time there is modulation – Bipolar Cells talk to ganglion cells, but
  - BP also talk to AC
  - amacrine cells talk to other amacrine cells
  - amacrine cells also talk directly to GC

CONE PATHWAY



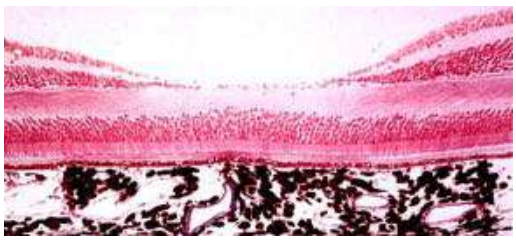
- in the fovea, cones communicate with 1 bipolar **cell type**, which communicates with 1 GC cell **type** which goes to the brain (1:1:1)
- however, the photoreceptor talks to another bipolar cell type that gives exactly the same information, but the mirror image
- but the brain still gets information from one cone, which comes out parallel to the brain
- the information that the brain sees is the information that comes out from one photoreceptor
- thus technically 1 cone to 2 BC to 2 GC, but the information is 1:1:1
- low convergence system - this means that there is high acuity but you need a lot of light to be able to see from the single photoreceptor

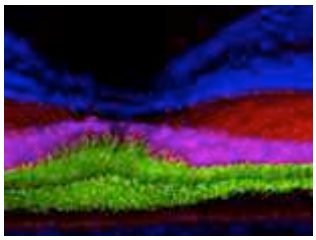
ROD PATHWAY



- lots of rods combine their output and synapse onto 1 BC
- the 1 BC then communicates to brain
- this is high convergence/ funnel system
  - Many rods feed to a few BCs.
- VA would be very bad because you need something bigger than the 30 photoreceptors combined to be able to resolve the image
- This is different to the cones – if you have two tiny things right next to each other, then the brain will be able to resolve
- However, for the rods – they would be registered as the same thing
- You don't see very well at night, however you can see a very small amount of light – because the tiniest light picked up by one of the rods is summed across 15-30 rods, and thus you are more likely to see it
- low acuity, high absolute light sensitivity

2 OPTIMIZING VISION: RETINAL STRUCTURE

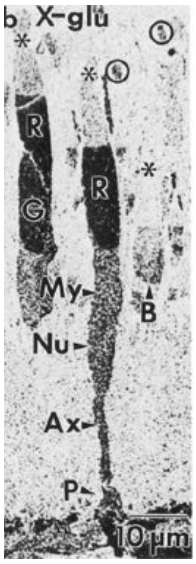


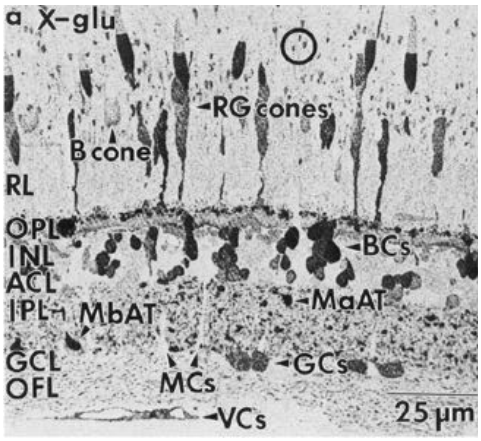


- there is an area in the fovea of the macula that is specialised
- at the bottom is the choroid (outside of the eye)
- the bottom of the slide is the sclera
- layer above the choroid is the neural retina
- the blank pit is the fovea
- there is a pushing of the retinal layers to the side, exposing just the single layer of the photoreceptors
- the macula (fovea) has a specialized area (the foveal pit) where all we have exposed to light is just the photoreceptors themselves

PHOTORECEPTROS RELEASE GLUTAMATE

- Photoreceptors accumulate glutamate
- glutamate is an amino acid
- normally an excitatory neurotransmitter in the brain, and is key in the retina
- photoreceptors release glutamate as neurotransmitter
- photoreceptors also Express enzymes important for glutamate formation.
- There is Evidence for release of glutamate, evidence for glutamate receptors on post-synaptic neurons (i.e. BCs)
- Also Evidence for degradation of glutamate
- Prior to 1990s, there was controversy over whether the neurotransmitter was something other than glutamate





{Marc et al 1990 J Neurosci 10:4006}

- The right diagram is a paper from an experiment in 1990s definitively showing that glutamate is contained in photoreceptors
- Goldfish have very complicated retinas – more photoreceptors than us and more types was well
- there is glutamate in second order neurons and ganglion cells as well
- when light hits, then less glutamate is released

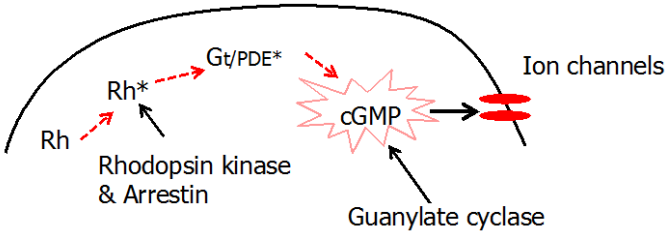
HOW IS THE SIGNAL STOPPED?

- How do we get a photoreceptor back to baseline so that it's ready to respond to the next light?
- For the largest flashes, then it takes a longer time to get back to baseline
- For a photoreceptor to be able to respond to a second flash of light several components must be restored:
    - 1) membrane potential returned to baseline.
    - 2) opening of cGMP channels again
    - 3) Restoration of rhodopsin to baseline state (need to get rhodopsin and vit A back to the baseline state)

LIMITING THE SIGNAL

Part 1: cGMP control

- cGMP controls the opening of ion channels
- cGMP is continuously produced by an enzyme called guancylate cyclase (dependent on calcium)
- thus when light hits, and cGMP is broken down, the guanylate cyclase is constantly making it
- after the light stops, then the GC continues to make the cGMP → once it's made again then the cGMP can open the ion channels again

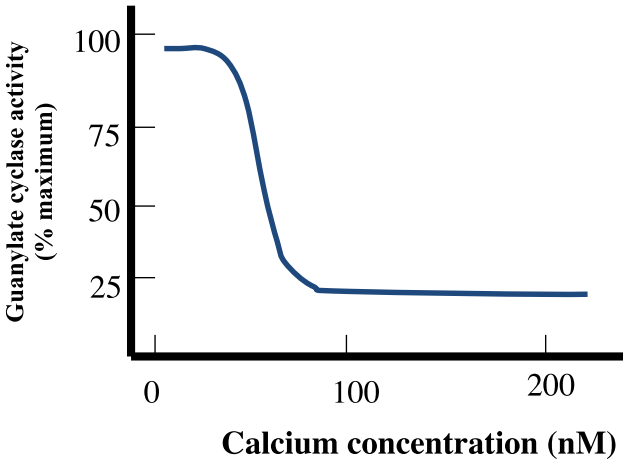


Part 2: restoration of rhodopsin

- how do you restore rhodopsin back to the baseline? There are other enzymes in the photoreceptor outer segment called rhodopsin kinase
- rhodopsin kinase phosphorylates the activated rhodopsin –
- this allows binding of arrestin onto rhodopsin
- Bound arrestin prevents activated rhodopsin binding to transducing
- This allows the rhodopsin to return to baseline state

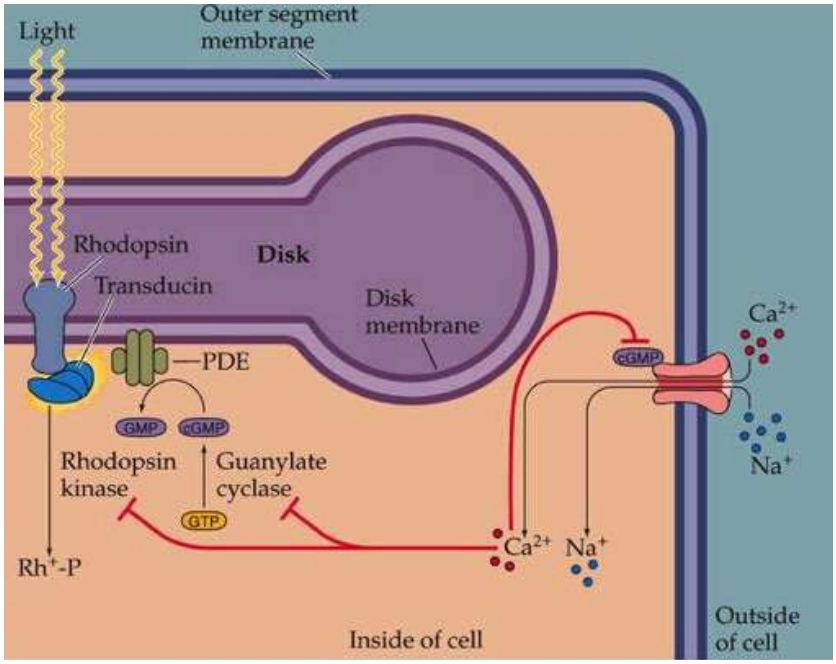
CONTROL OF CGMP: INFLUENCE OF CALCIUM

- sodium flows into the outer segment via the cGMP gated sodium channels
- calcium also passes into the photoreceptor outer segment via the same channels
- in addition to this, Ca2+ can enter via cGMP gated channels (VDCC)
- thus calcium levels change, and the way it changes affects the enzyme levels
- guanylate cyclase makes cGMP at high concentrations, and at low cGMP concentration, then no cGMP is made
- at a high calcium concentration (i.e. when the sodium channels are open and when the photoreceptor is depolarized in the dark), the guanylate cyclase enzyme is not doing much (low activity)
    - at high calcium concentration – not making cGMP
- when you shut the Na+ channel (when the photoreceptor is hit with light and hyperpolarised) – if hyperpolarized then the voltage gated calcium channels are also blocked – thus the two sources of calcium are blocked
    - thus calcium concentration inside the cell decreases
    - guanylate cyclase activity goes up
    - thus cGMP is made
    - thus calcium concentration can restore the cGMP and thus photoreceptor back to baseline condition



RESTORATION OF THE SIGNAL

- calcium will stop flowing into the cell when the cGMP gated Na+ channel and the voltage gated calcium channel is closed
- decreased calcium activates the guanylate cyclase – increased GC makes cGMP
- decreased ca2+ also activates other enzymes that are critical for restoring rhodopsin
- it increases activity of rhodopsin kinase, which allows more arrestin to bind
- decreased calcium increases affinity of cGMP for channels



HOW IS 11-CIS RETINAL RESTORED TO OPSIN?

- When light hits, the cis retinal turns to trans retinal – thus the trans retinal has to be converted back
- This happens via the Retinoid cycle, which occurs in the RPE
- When light hits, the cis retinal changes to trans retinal
- To get it back to cis, the vitamin A gets taken out of the photoreceptor and transported into the RPE
- Changes all- trans retinal to all-trans retinol (alcohol) by IRBP (interphotoreceptor retinoid binding protein)
- Then isomerissed to the 11-cis retinol, then changed to the aldehyde form (11-cis retinal)
- isomerization in the Retinal Pigment Epithelium (e.g., RPE65)