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Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

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Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

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BEVEZETÉS A FUNKCIONÁLIS NEUROBIOLÓGIÁBA

INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

By Imre Kalló

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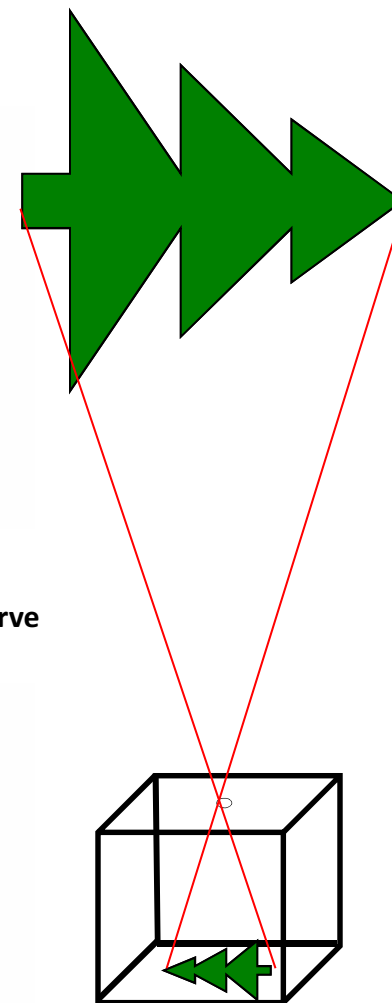
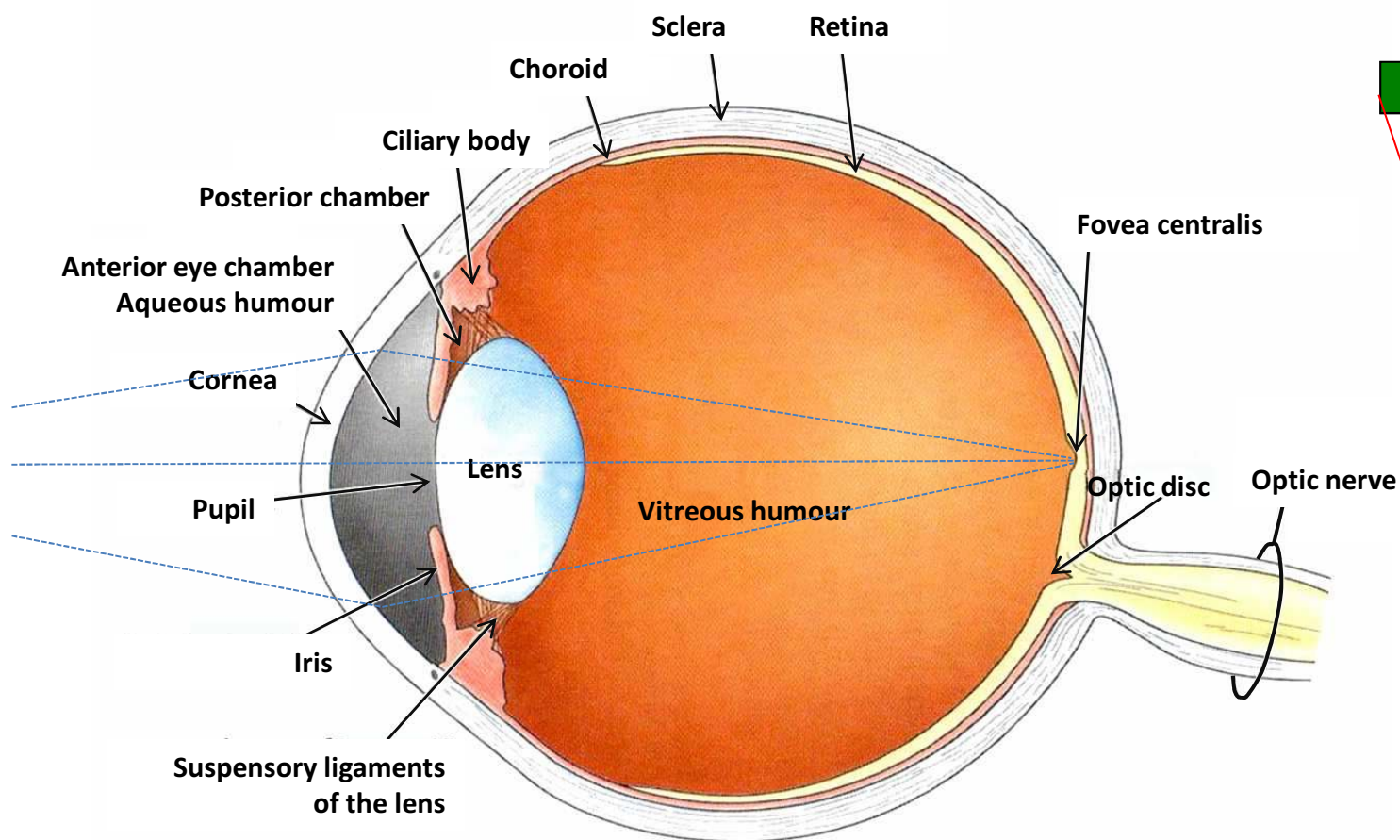
Retina

Imre Kalló & Róbert Gábor

Pázmány Péter Catholic University, Faculty of Information Technology

- I. Photoreception; receptor cells nourished by pigment epithelium
- II. Connectivity and function of horizontal, bipolar and amacrine cells.
- III. Ganglion cells and the visual pathway.

Anatomy of the visual organ.



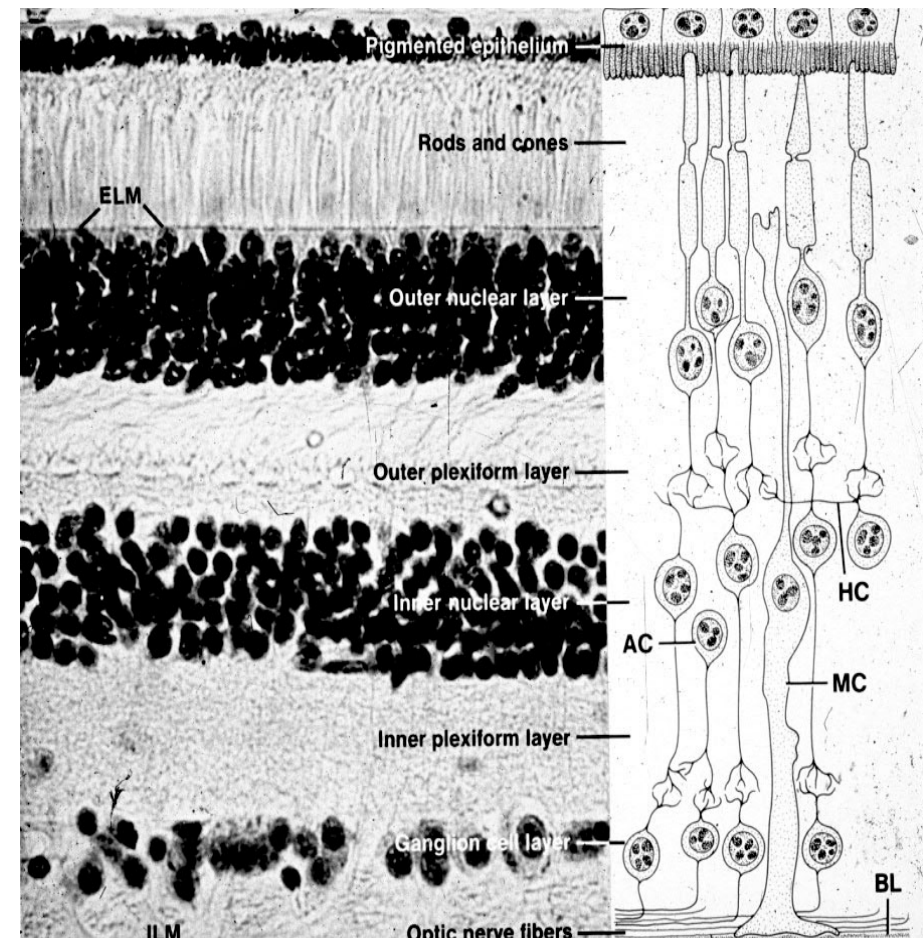


Anatomy of the visual organ.

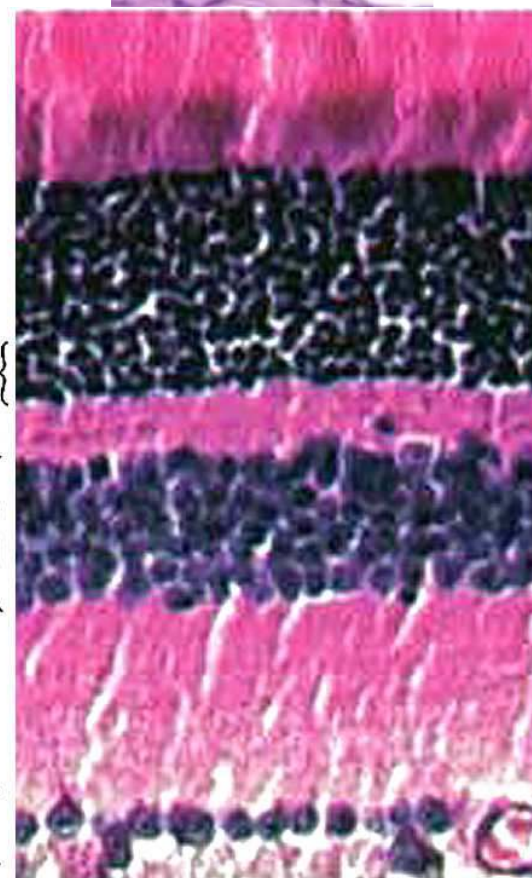
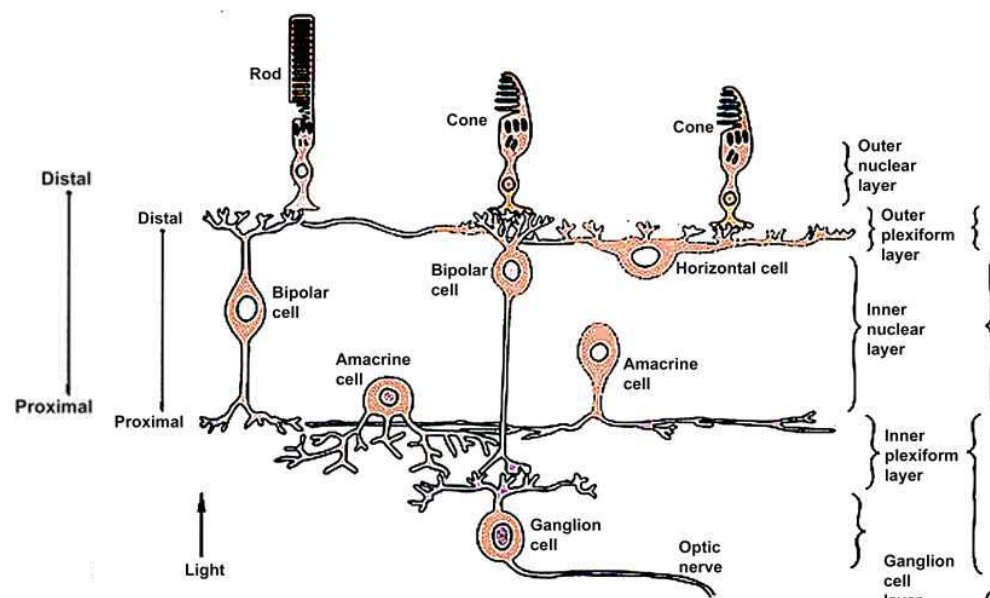
The human visual organ is a paired, light-proof „box” (eyeballs) with an adjustable diameter pinhole (pupil) on the front side. Light is passing through transparent media in front (i.e. tear, cornea, aqueous humor) and behind (i.e. the lens, vitreous humor) the pupil to reach the inner layer of the eyeball (retina), where the energy of light is converted to chemico-electric impulses. Light from objects located between 25 cm to far distances is focused onto the retina by the adjustment of lens convexity. The inverted image of the objects projected to the retina, however can be processed at high resolution only at the central fovea, where light reaches the cone receptor cells directly.

Histology of the retina

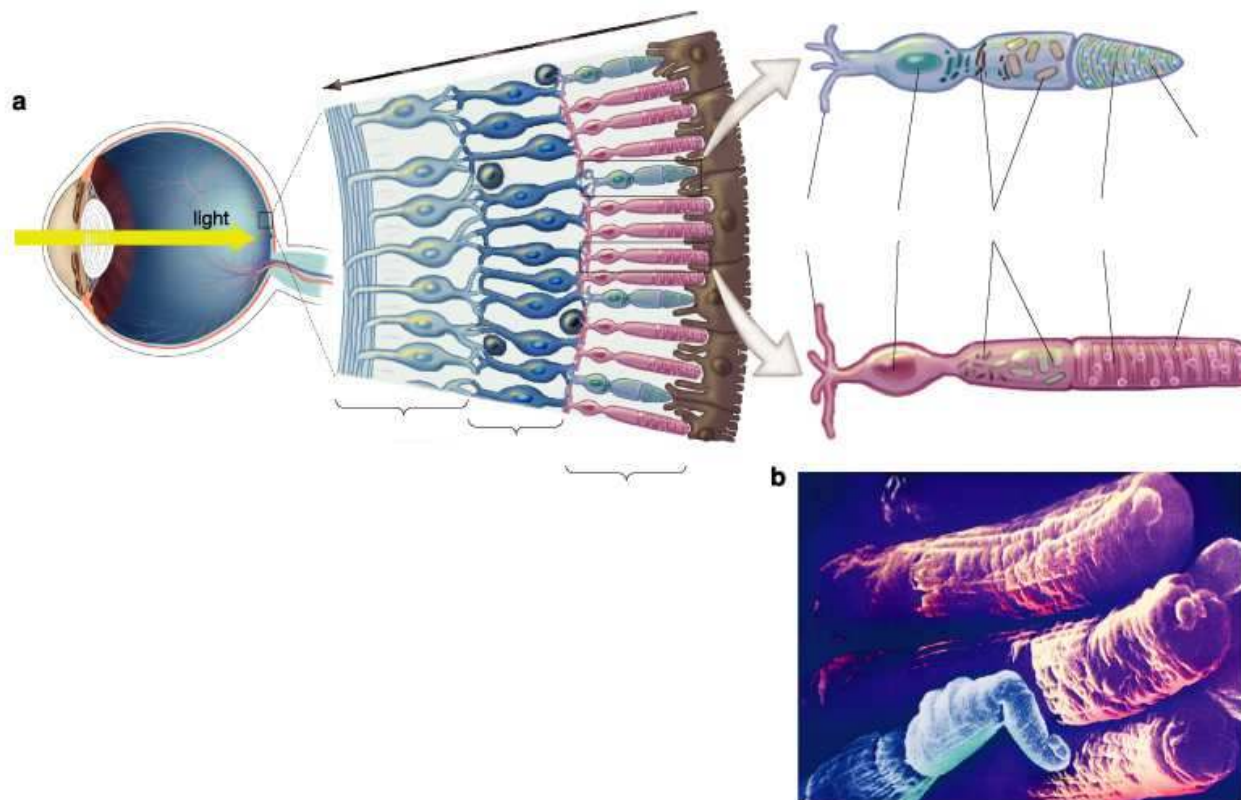
- **10 histologically distinguishable layers**
- **4 layers of cell bodies (nuclei)**
 - 1 layer of pigment cells
 - 1 layer of receptor cells
 - 2 layers of neurons
- **2 layers of synapses**
- **Vertical “through pathway”**
- **Horizontal influence on the information processing**



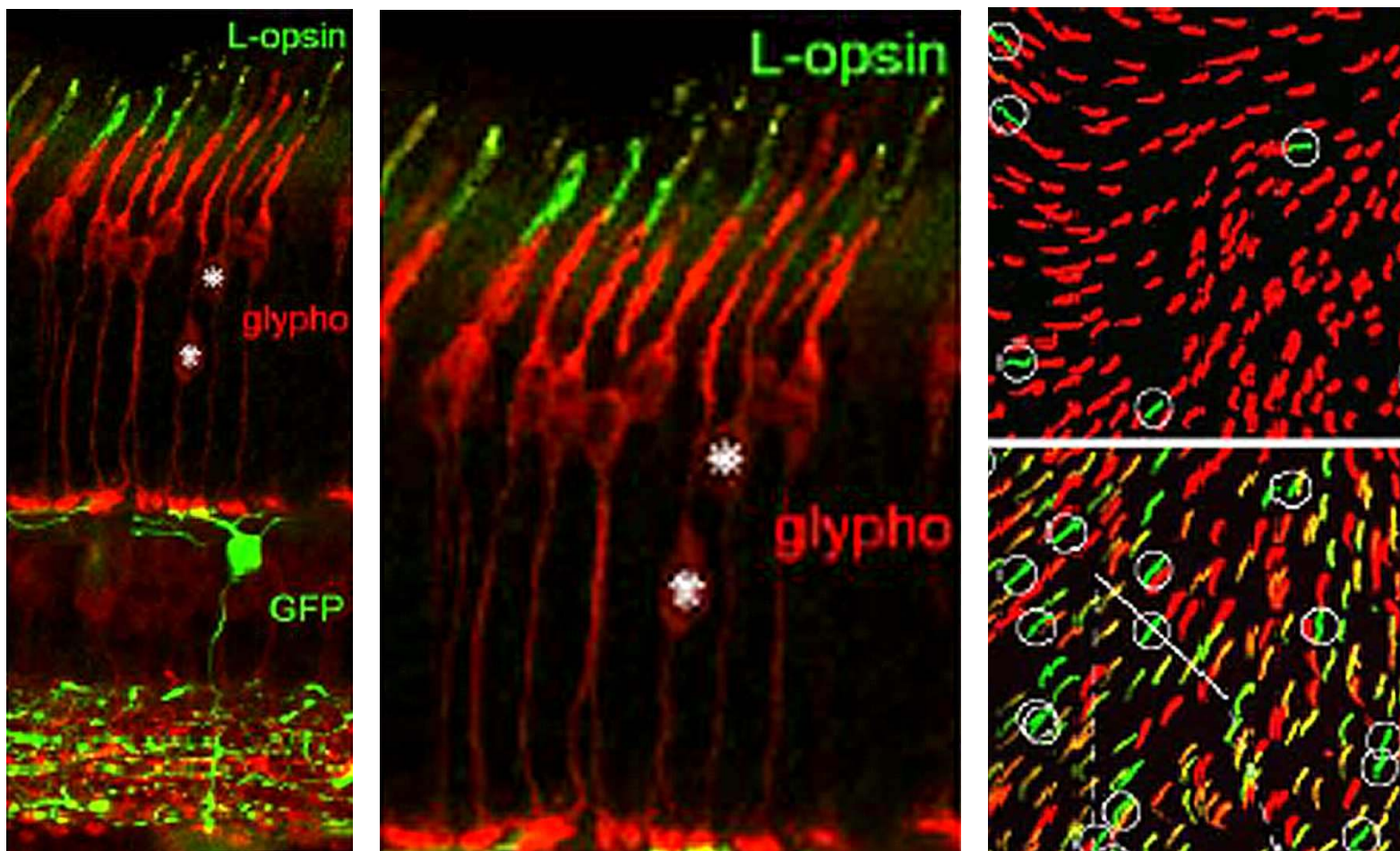
Connectivity of basic cell types of the retina



Path of the light in the eye



Photoreceptors



Photoreceptor cells: anatomy

- **Duplex retina**

- **Rods**

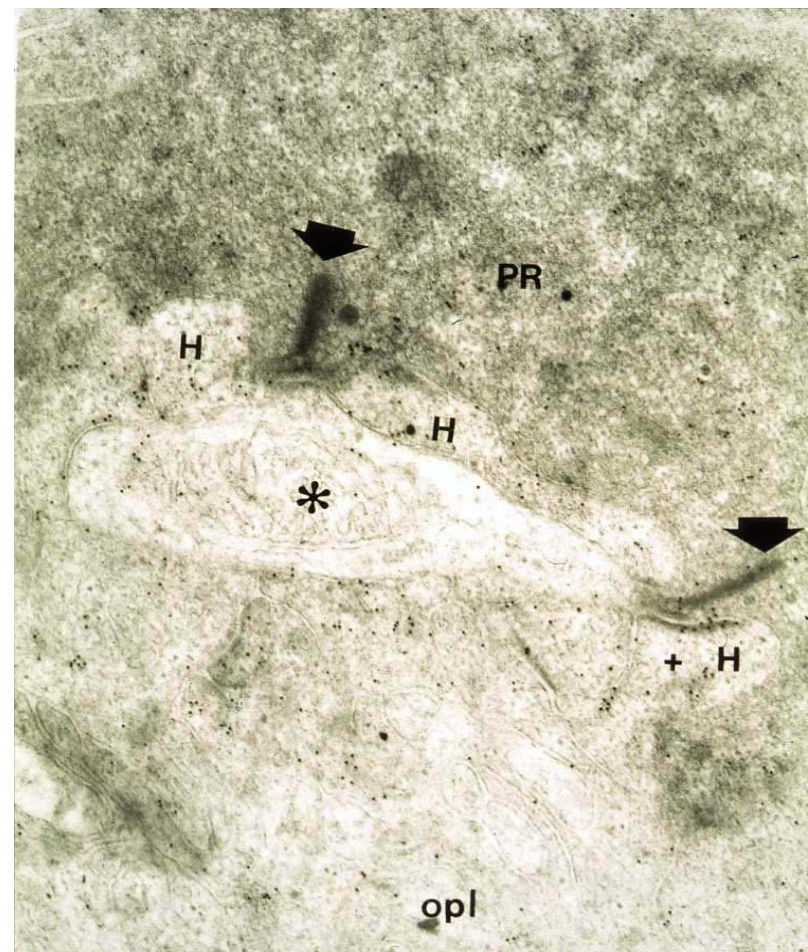
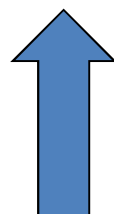
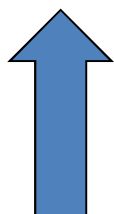
- one (or maybe two) types*
 - similar morphology*
 - long outer segment*
 - closed endomembrane system*

- **Cones**

- three, four types – wave-length*
 - sensitivity varies from*
 - group to group*
 - open endomembrane system*

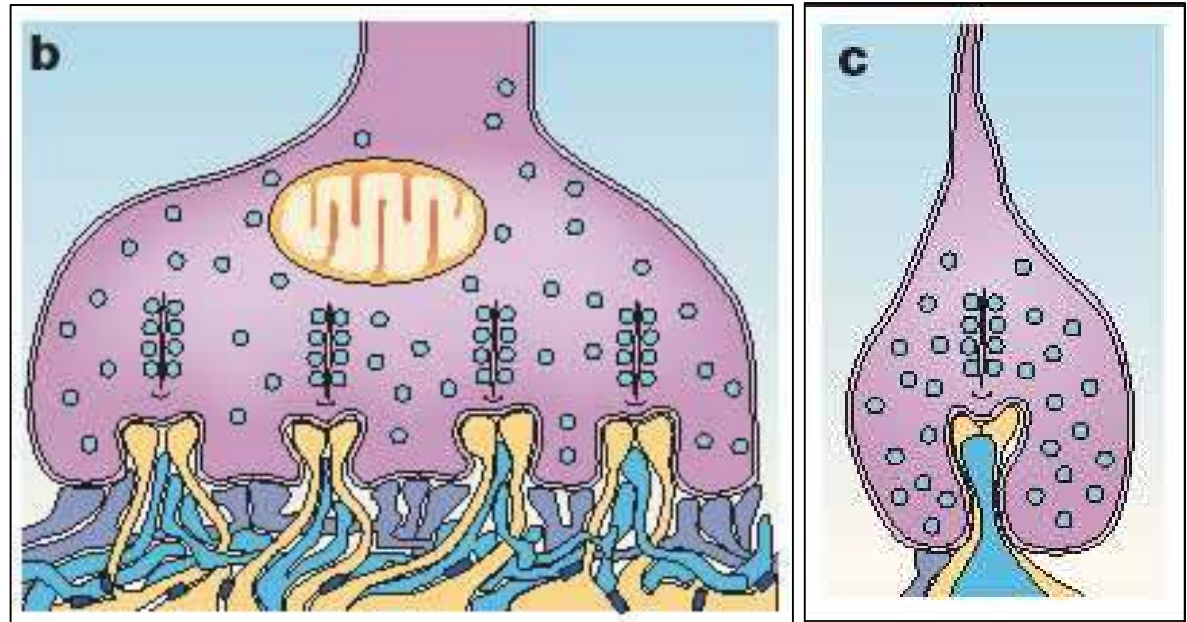


Synapses established by the photoreceptor cells I.

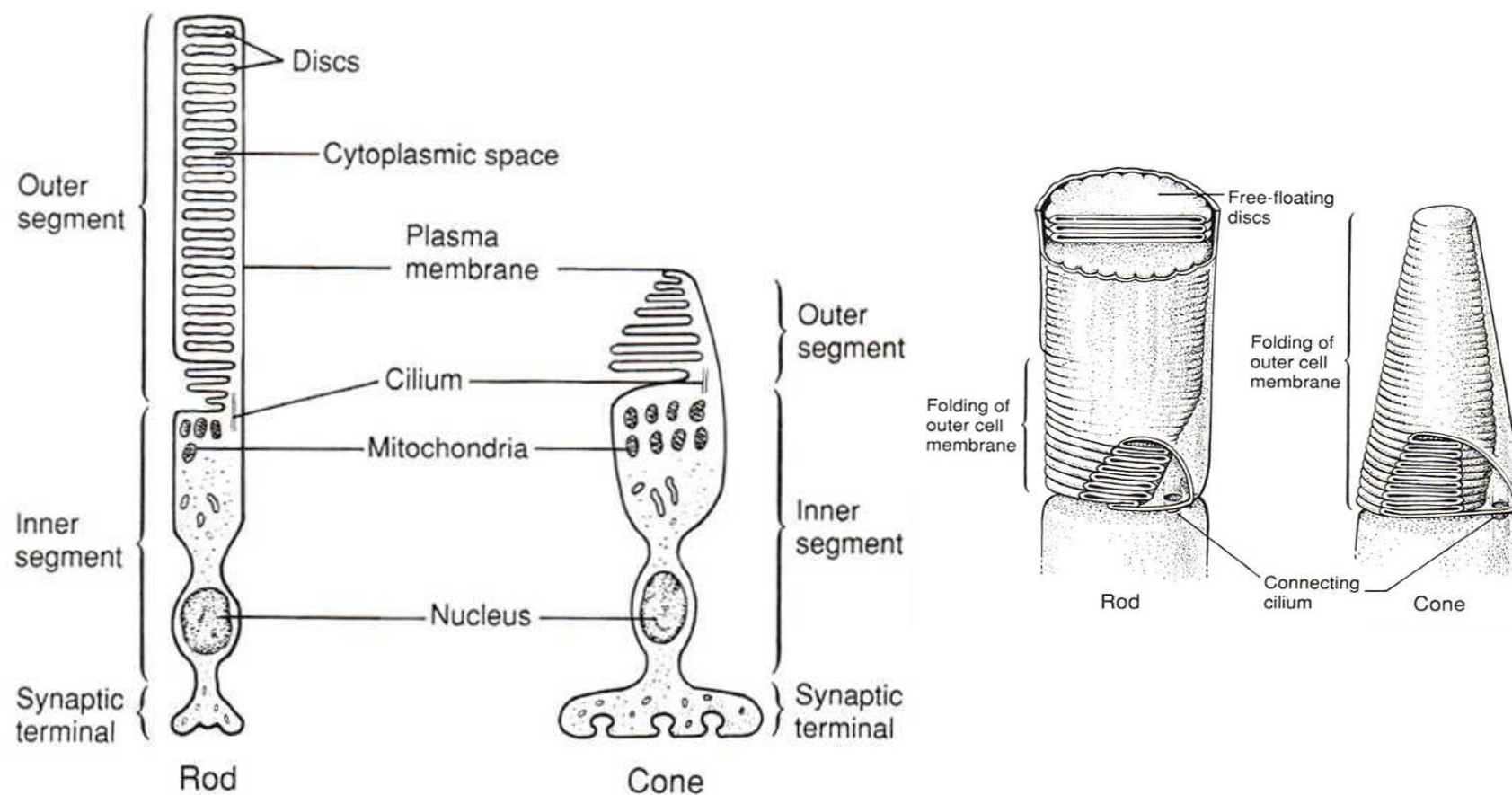


Synapses established by the photoreceptor cells II.

- *Inner segment*
- *Photoreceptor cell terminal*
- *„Ribbon” synapse*
 - Two pools of synaptic vesicles*
 - Presynaptic markers (eg. bassoon, rib eye)*
- *Postsynaptic triad*
- ***Dendrite of the bipolar cells in the middle, processes of horizontal cells laterally***
- ***„Invaginating” and „flat” connections***



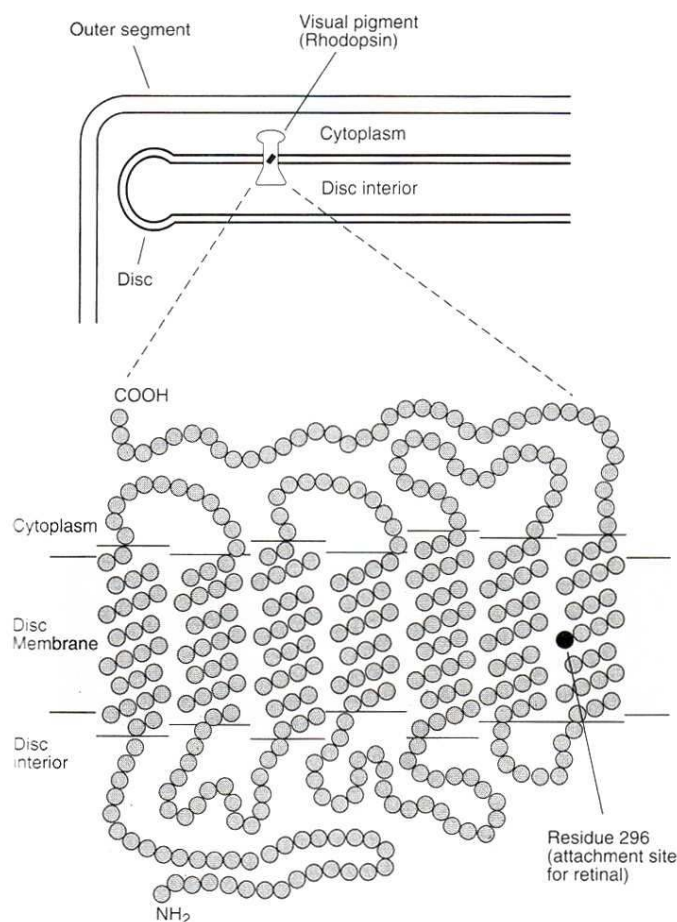
Photoreceptor cells



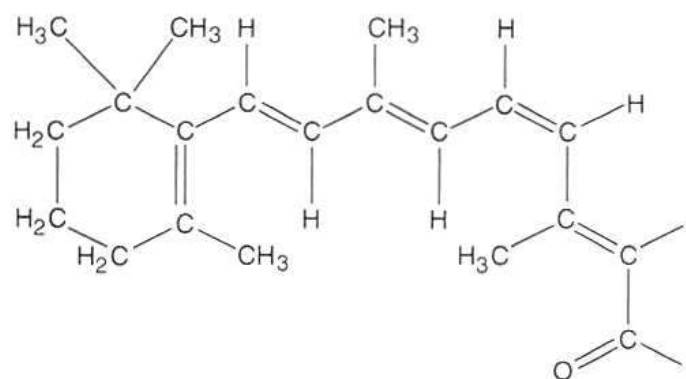
Types of photoreceptor cells

Class of cells	Types of cells	Subtypes	Notes
Photoreceptor Cells	Rods	Uniform	There are green and red light-sensitive rods in amphibians
	Cones	Cones sensitive for short wave-length light	There are UV-sensitive cones in certain species
		Cones sensitive for long wave-length light	Two (green and red) subgroups of cones in primates

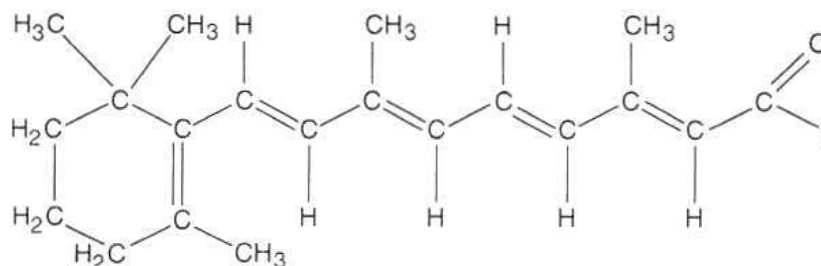
Outer segment events: photochemical reaction



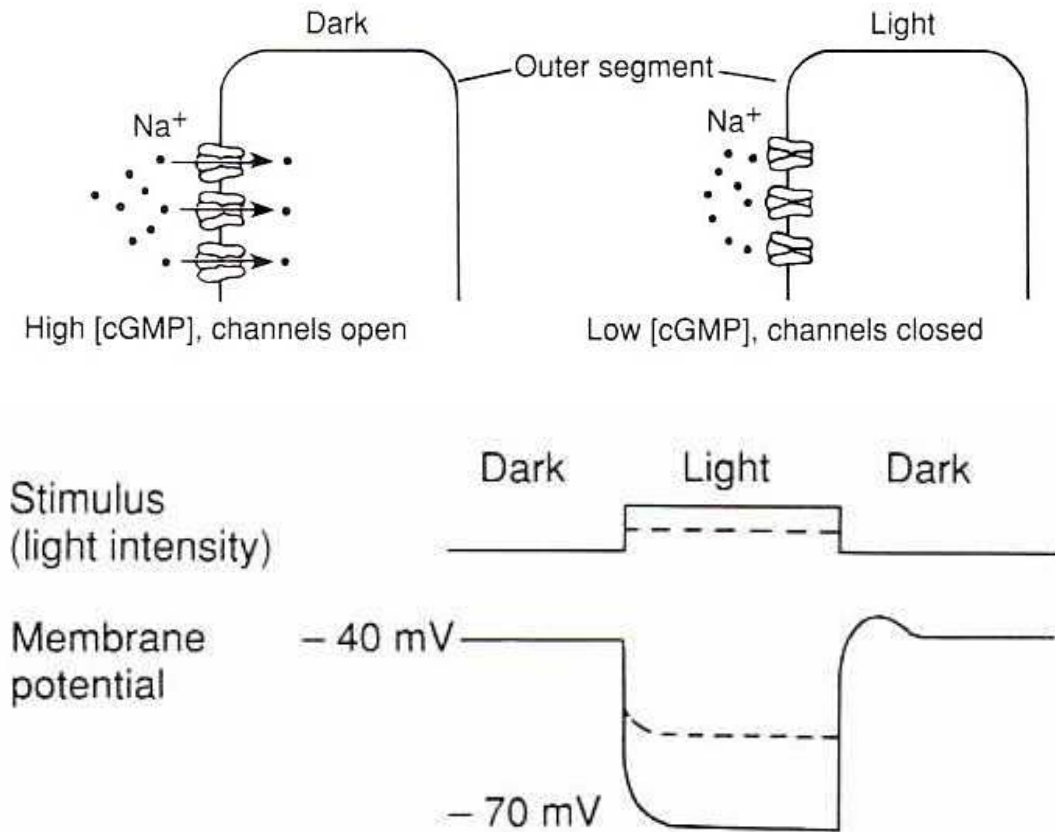
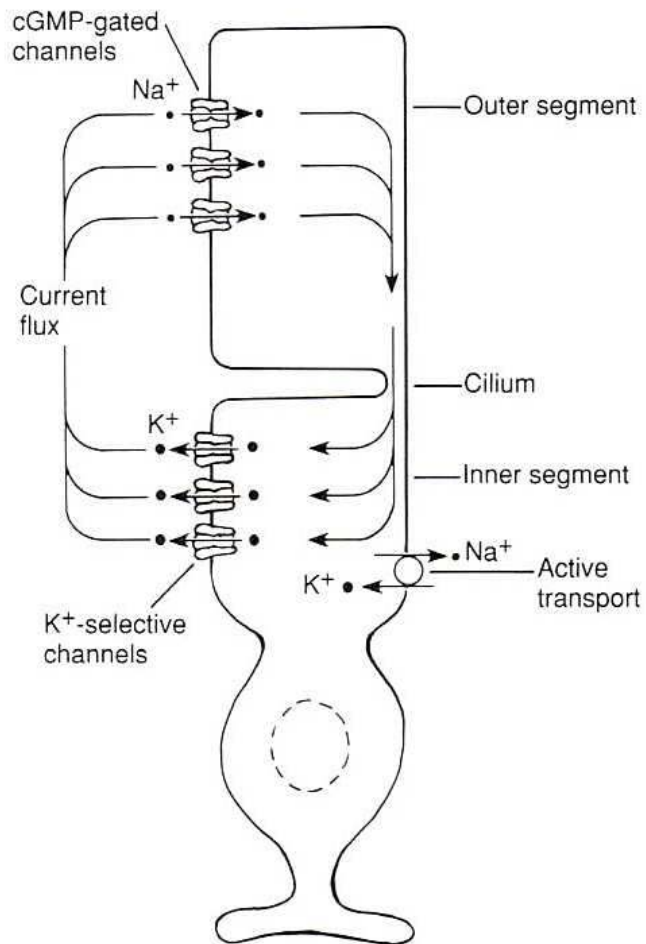
11-*cis* retinal
(M_r = 268)



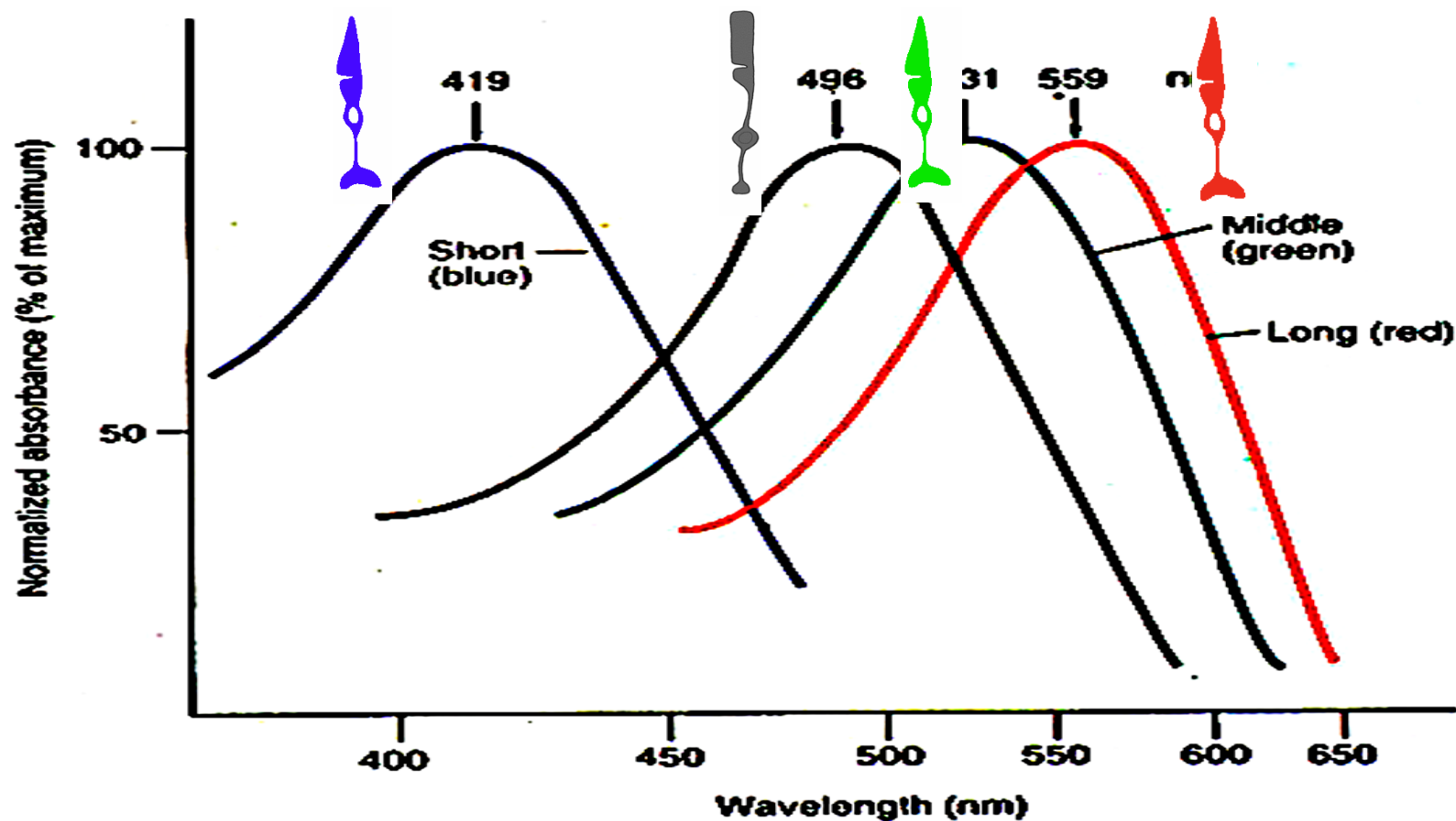
All-*trans* retinal



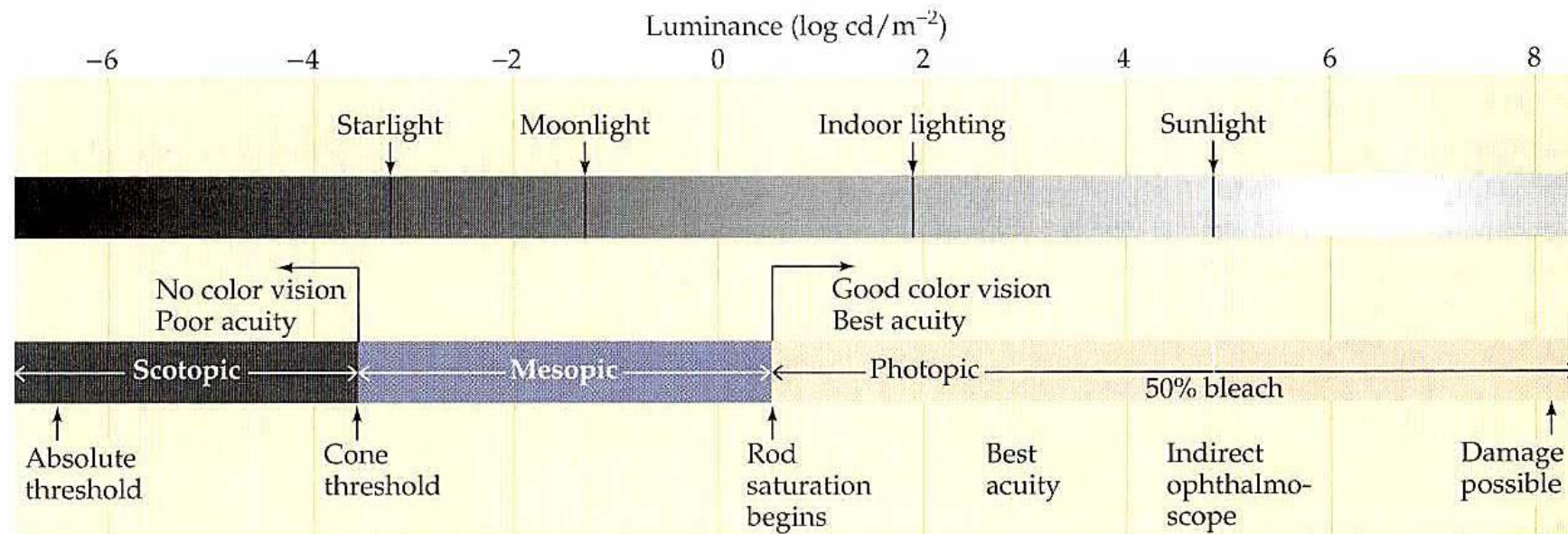
Outer segment events: sodium channels close - hyperpolarization



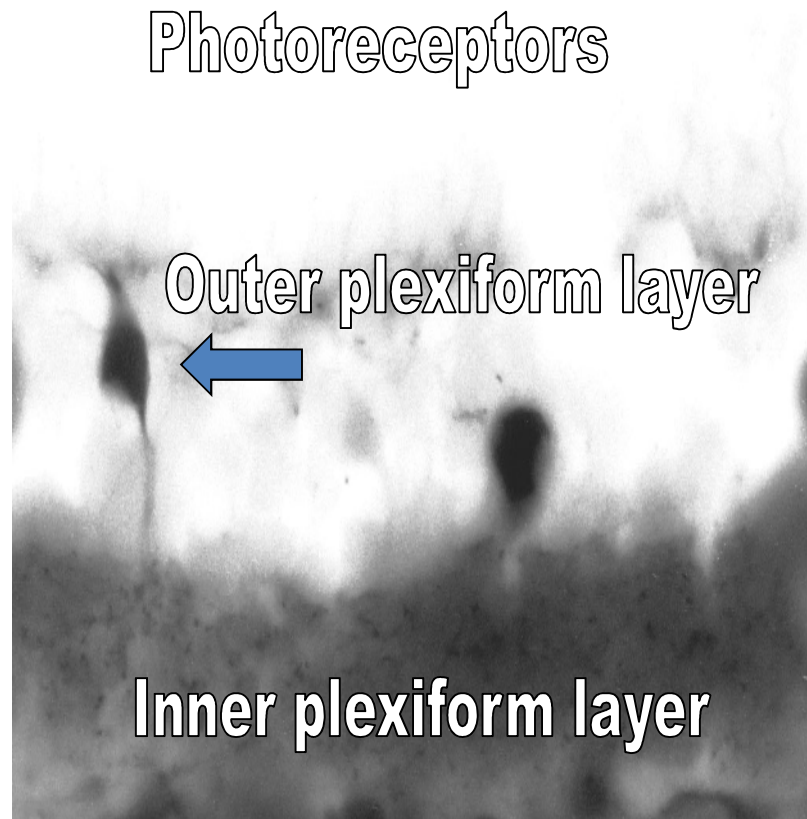
Absorbance maximum of photoreceptor cells



Light sensitivity of photoreceptors



Microanatomy of bipolar cells



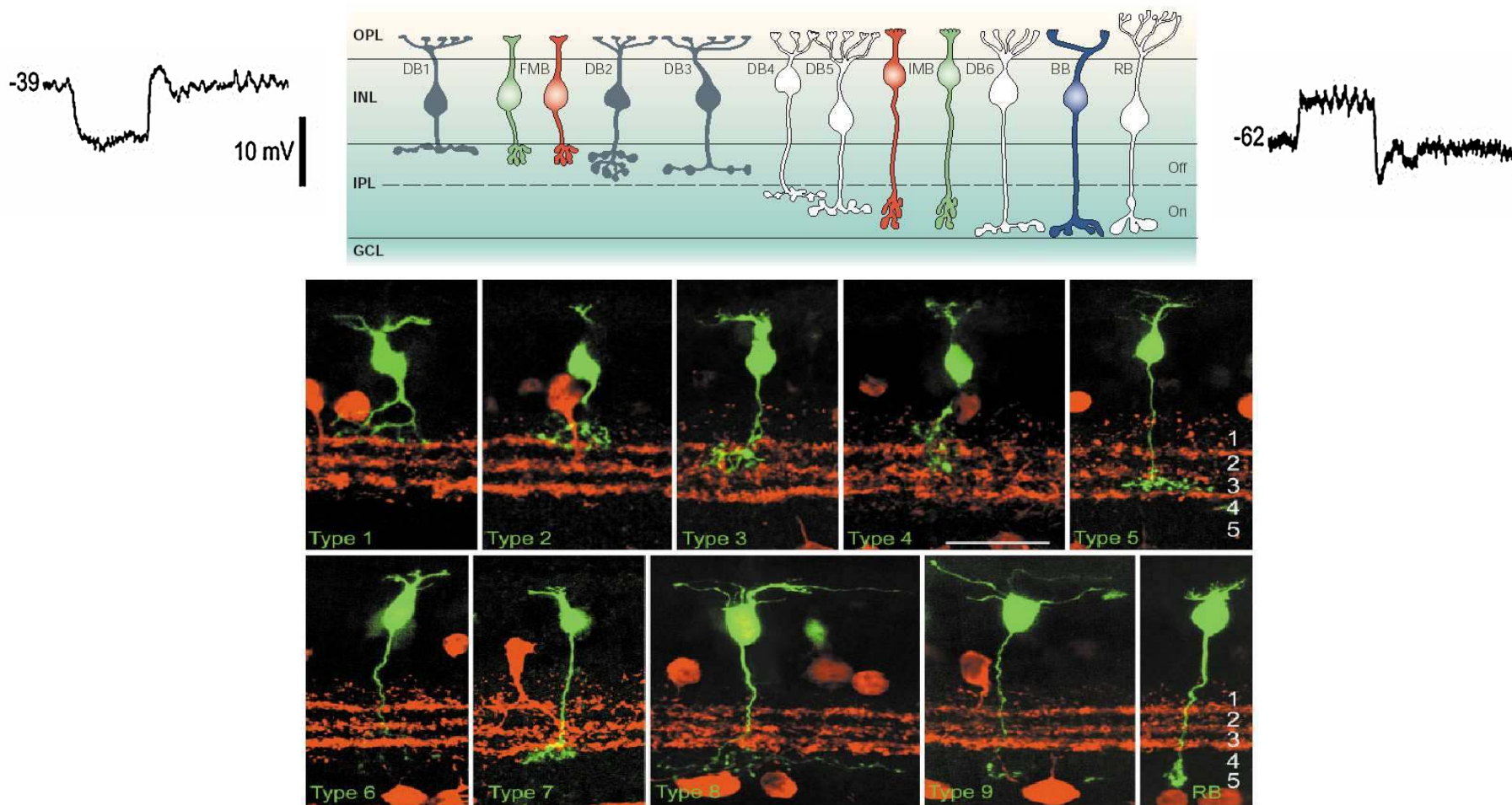
- ***Orientation of bipolar cells:***
dendritic tree is towards the photoreceptor cells, axon is in the inner plexiform layer (IPL)
- ***It connects the external and internal parts of the retina***
- ***It is crucial for processing the visual information***
- ***10 different types of bipolar cells are known in vertebrates***

Types of bipolar neurons

Class of cells	Types of cells	Subtypes	Notes
Bipolar Cells	Rod-bipolar cells	Uniform	Bipolar neurons of amphibians receive afferents from both cones and rods. In a few species there are blue bipolars.
	ON-type cone-bipolar cells	Many algroups	
	OFF-type cone-bipolar cells	Many algroups	

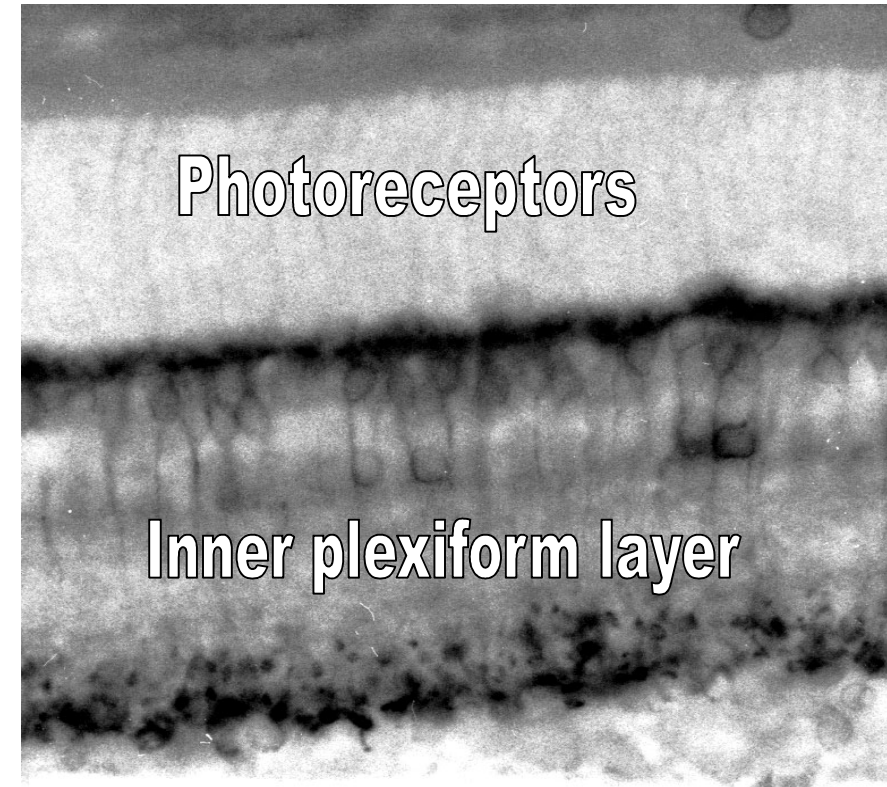
- ***Rod-bipolar cells: there are only in mammals***
- ***Significance: visual reception at low light intensity circumstances***
- ***Cone-bipolar cells: their sensitivity varies according to the wave-length***
 - ***Depolarizing cells (ON-type)***
 - ***Hyperpolarizing cells (OFF-type)***
- ***Cells with special receptive field***

Bipolar neurons



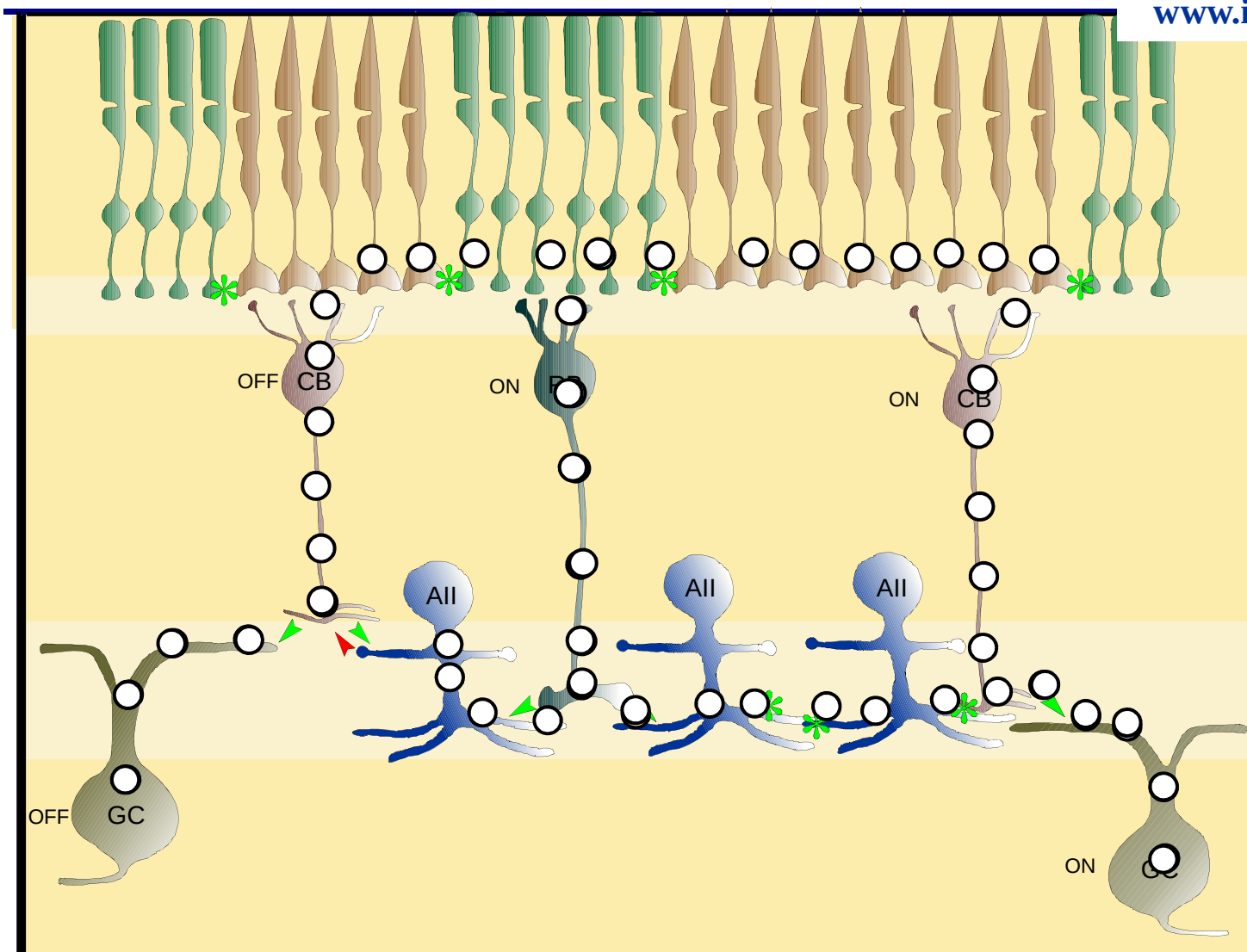
Neurochemistry of bipolar neurons

- **Rod-bipolars:**
PKC
- **Cone-bipolars:**
OFF: recoverin
ON: mGLUR6
- **Neurotransmitters used:**
Glutamic acid
- **Axon terminals:**
L-type VGC_{Ca}



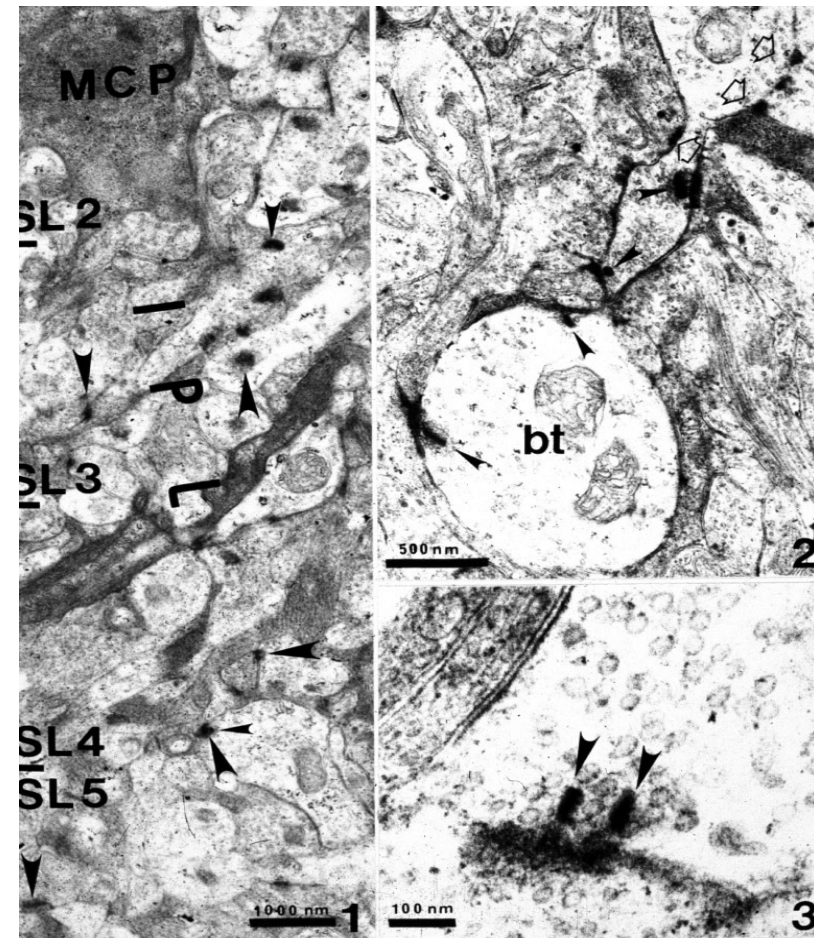
Introduction to functional neurobiology: Retina

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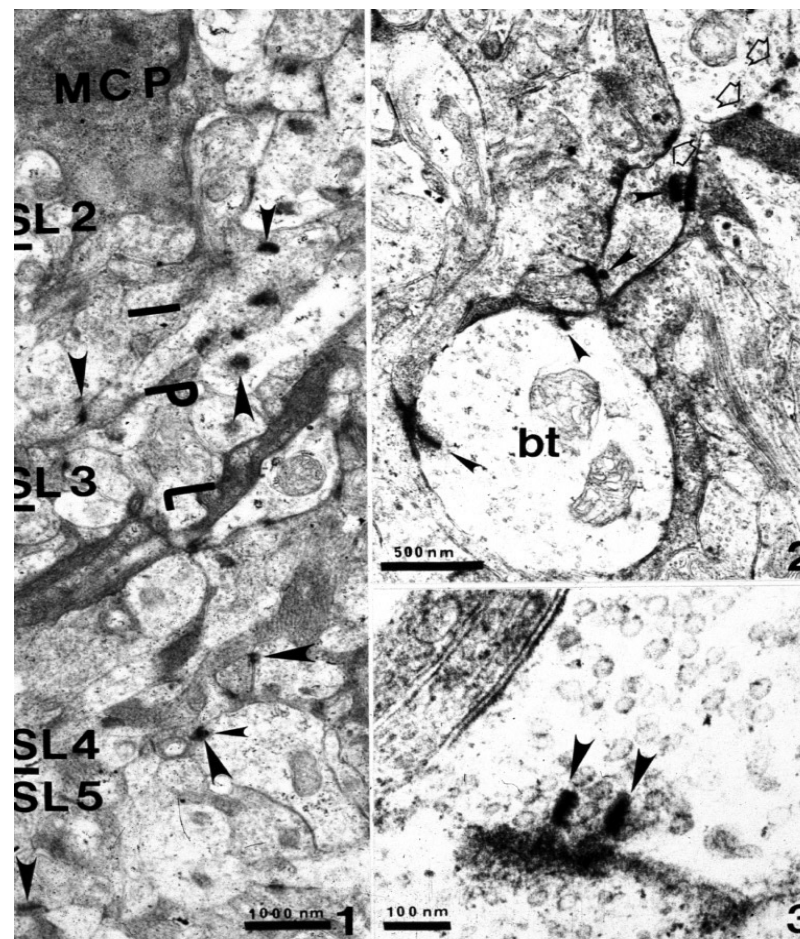
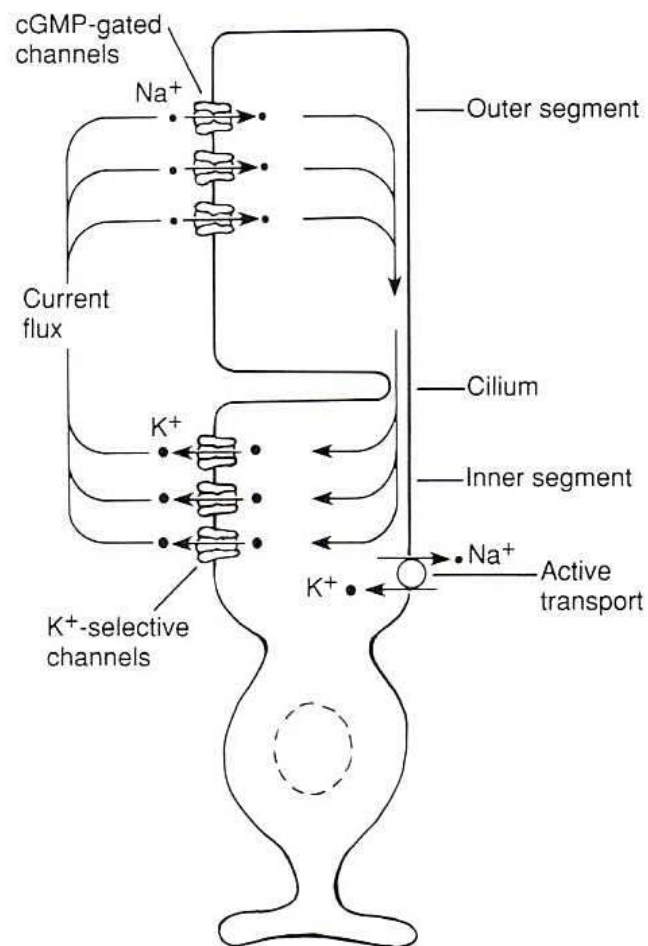


Synaptic connections of bipolar cells in the inner plexiform layer I.

- ***Axons, ribbon synapses***
- ***One terminal contains several ribbons, and establishes several outputs***
- ***Every 8-10th synapse of the inner plexiform layer is established by bipolar cells***
- ***Postsynaptic diad***

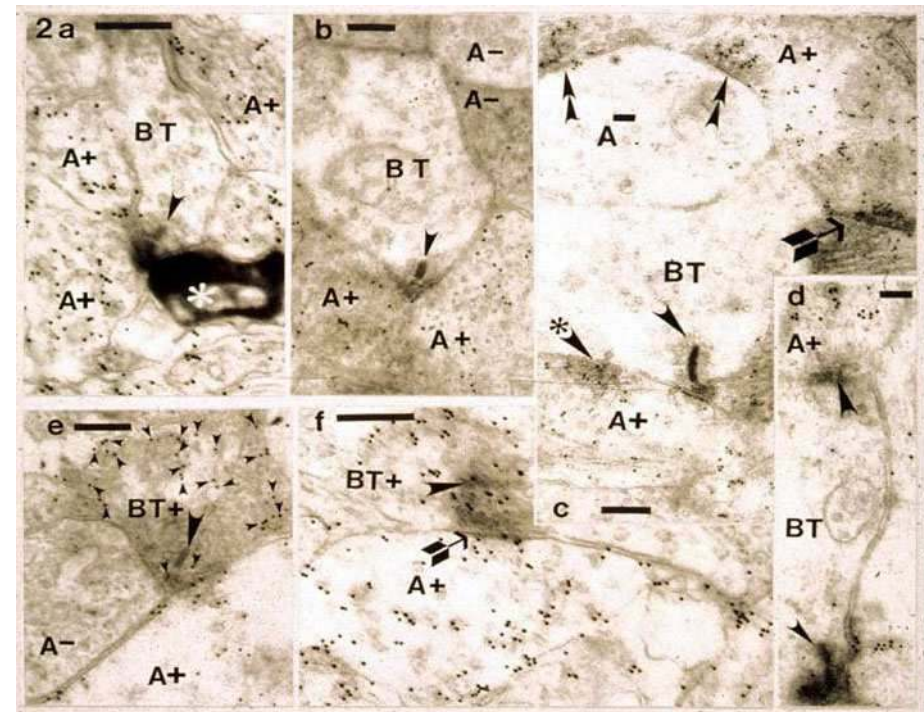


Synaptic connections of bipolar cells in the inner plexiform layer I.

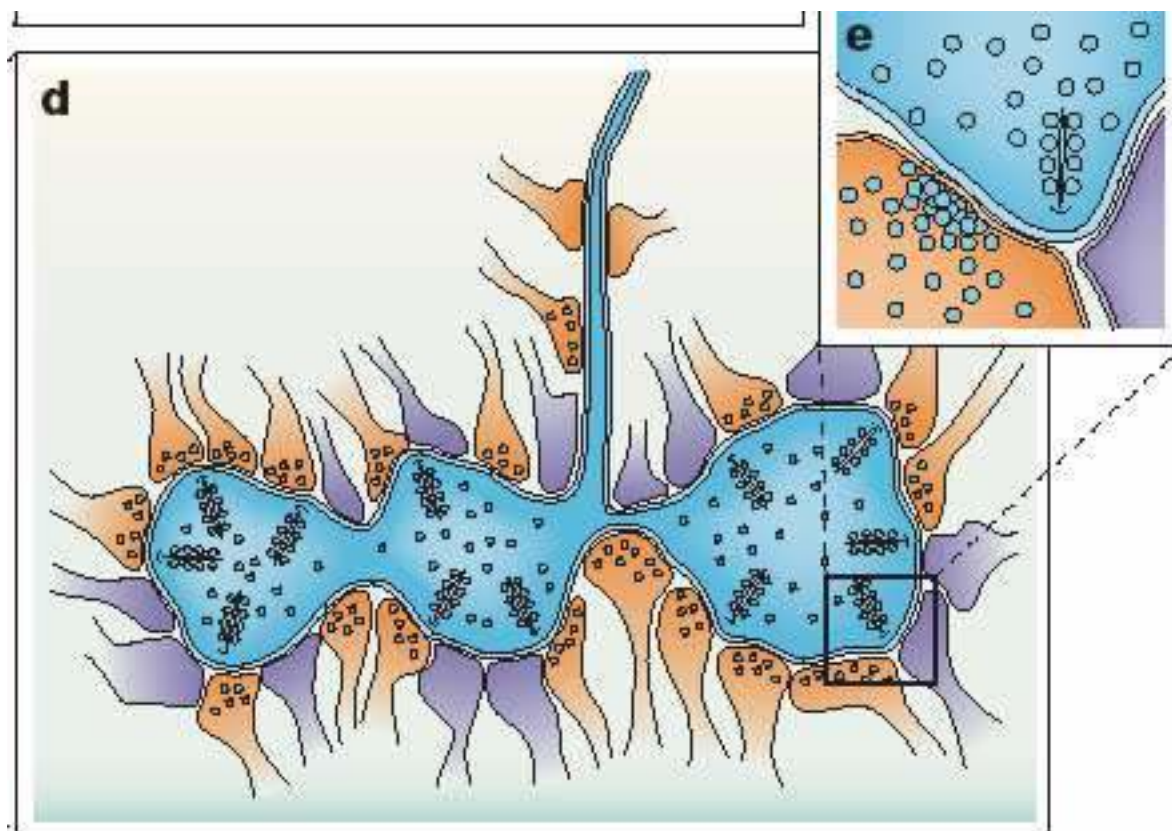


Synaptic connections of bipolar cells in the inner plexiform layer II.

- ***Bipolar axons terminals also receive afferents (from amacrine cells)***
- ***Most of the output is glutamatergic, in contrast the inputs are GABAergic***
- ***Axon terminals of the bipolar neurons contains both GABA_A and GABA_B receptors***

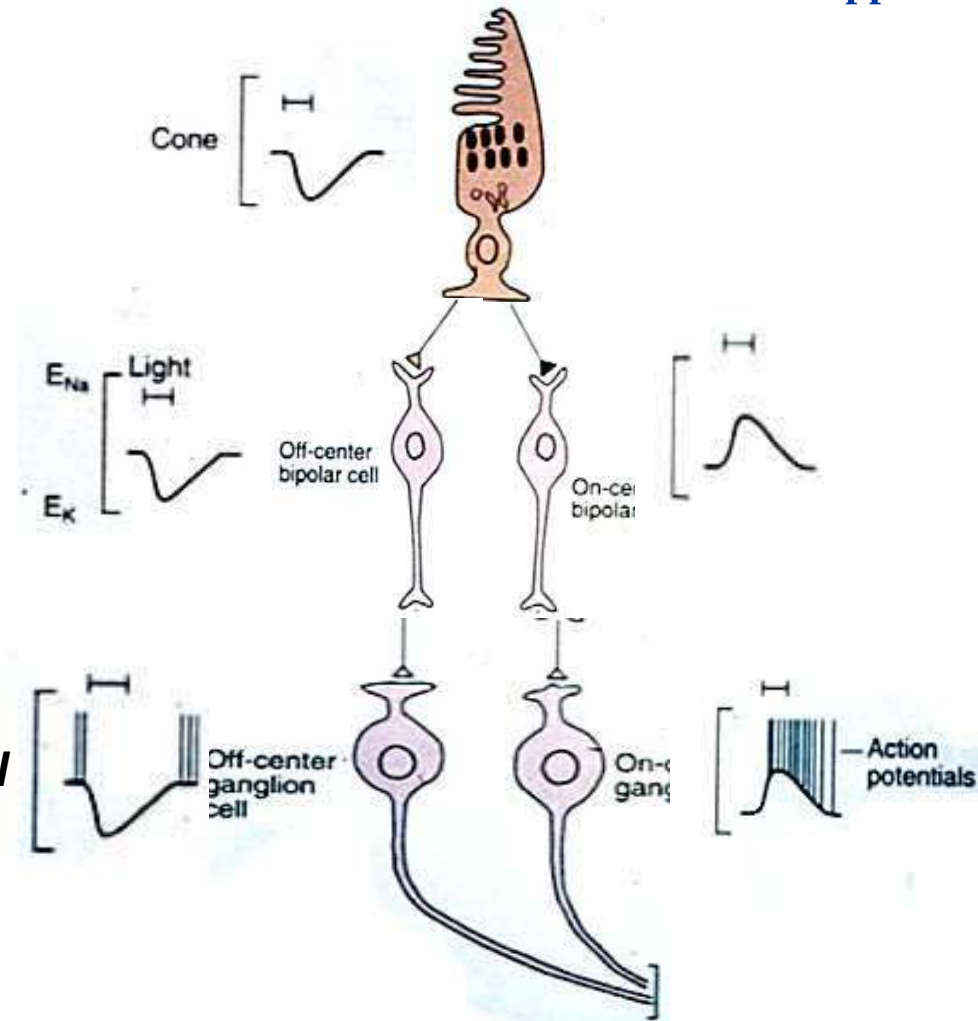


Synaptic connections of bipolar cells in the inner plexiform layer III.



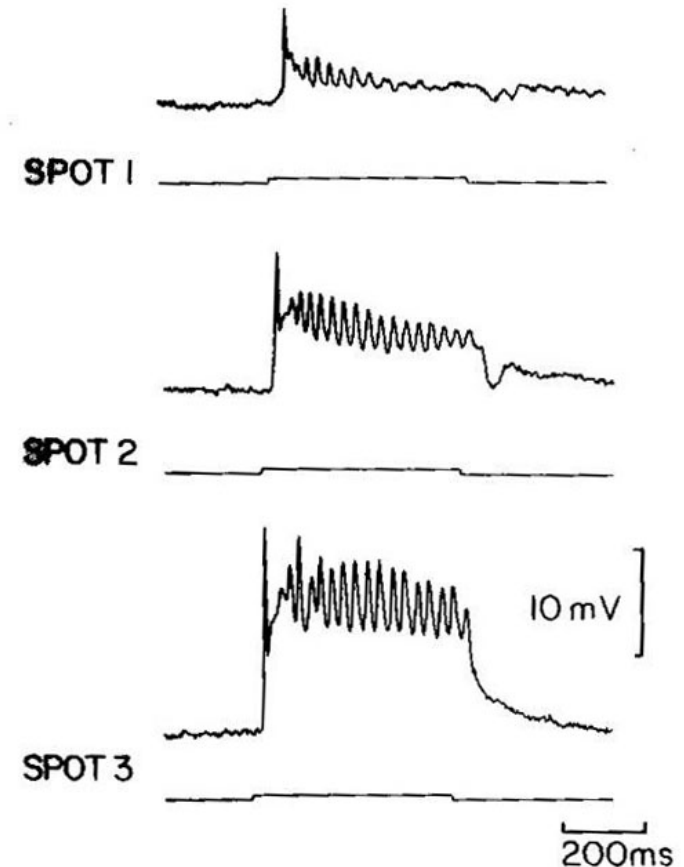
Physiology of bipolar cells

- **Hyperpolarising cells:**
AMPA and KA receptors, sign-conserving "OFF" cells
- **Depolarising cells:**
mGLUR6 receptors, sign-inverting "ON" cells
- **ON-OFF cells:** *only in non-mammal vertebrates*



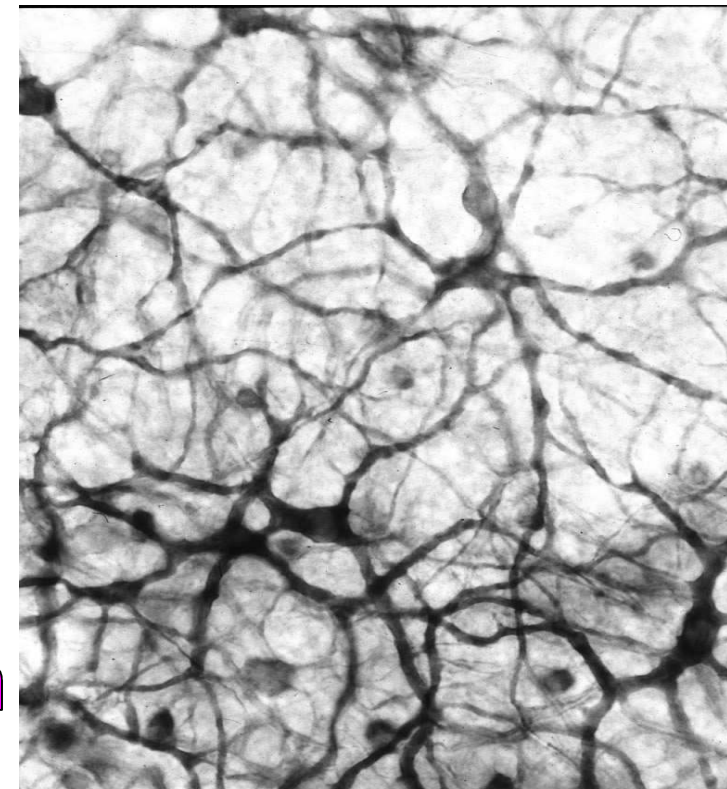
Bipolar neurons are sensitive to the size of the enlightened area

- ***Transient response turns into sustained response***
- ***Inhibition originating from the surrounding area decreases (see center/surround organisation)***
- ***Saturation***



Microanatomy of the horizontal cells

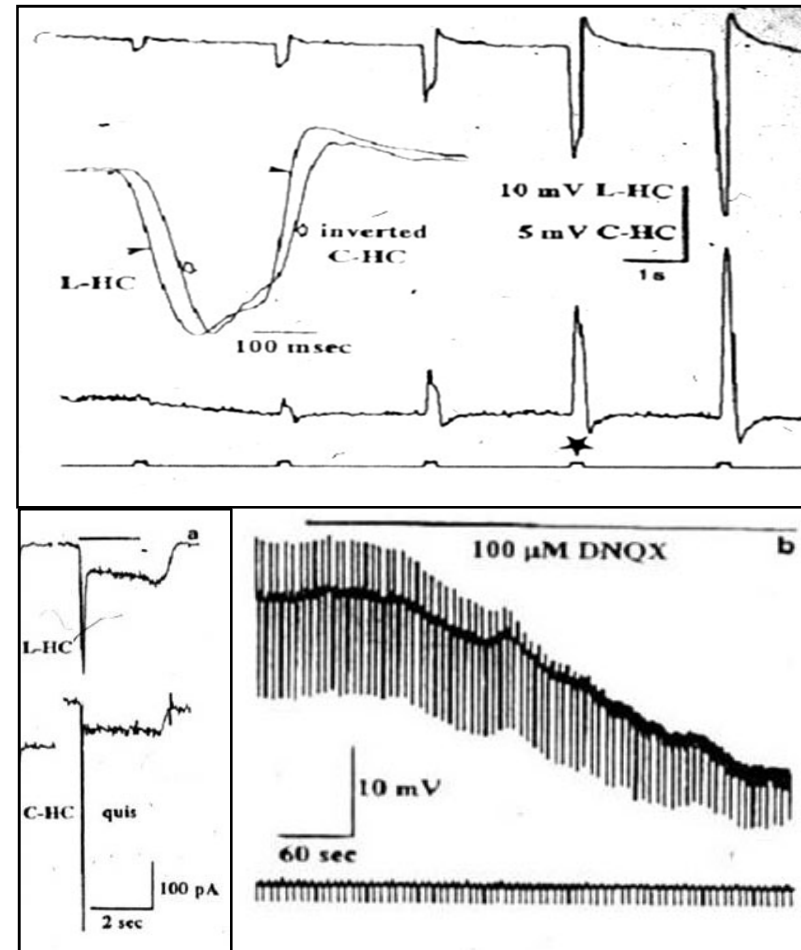
Class of cells	Types of cells	Subtypes	Notes
Horizontal Cells	Cells with axon	Uniform group	Many species have also chromatic horizontal cells
	Cells without axon	Uniform group	



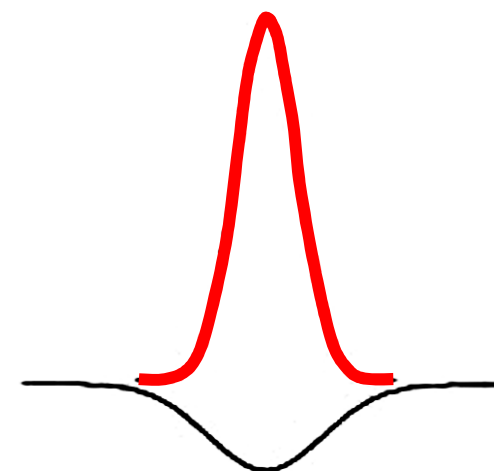
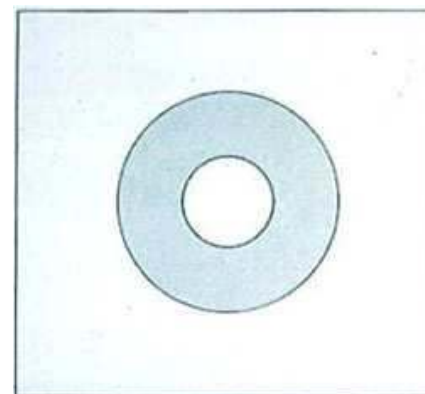
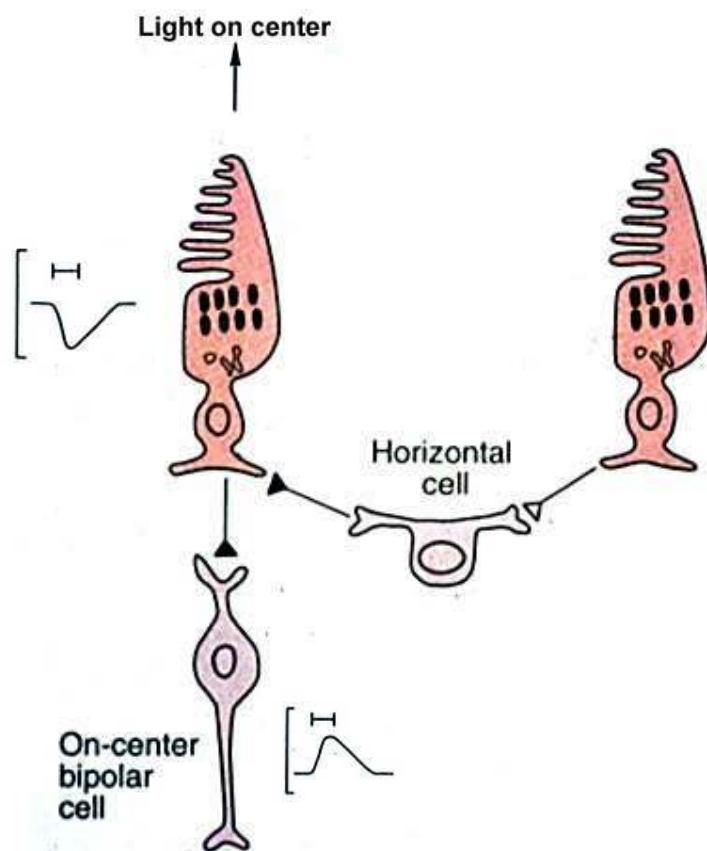
horizontal cells, wm

Physiology and neurochemistry of the horizontal cells

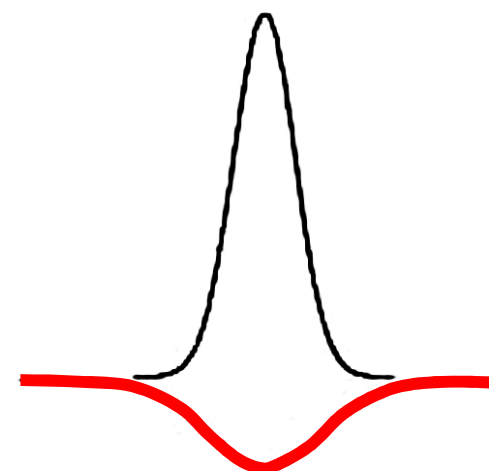
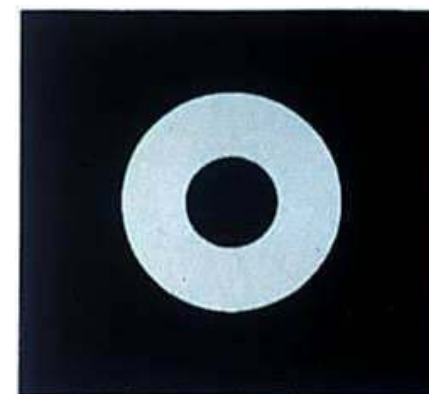
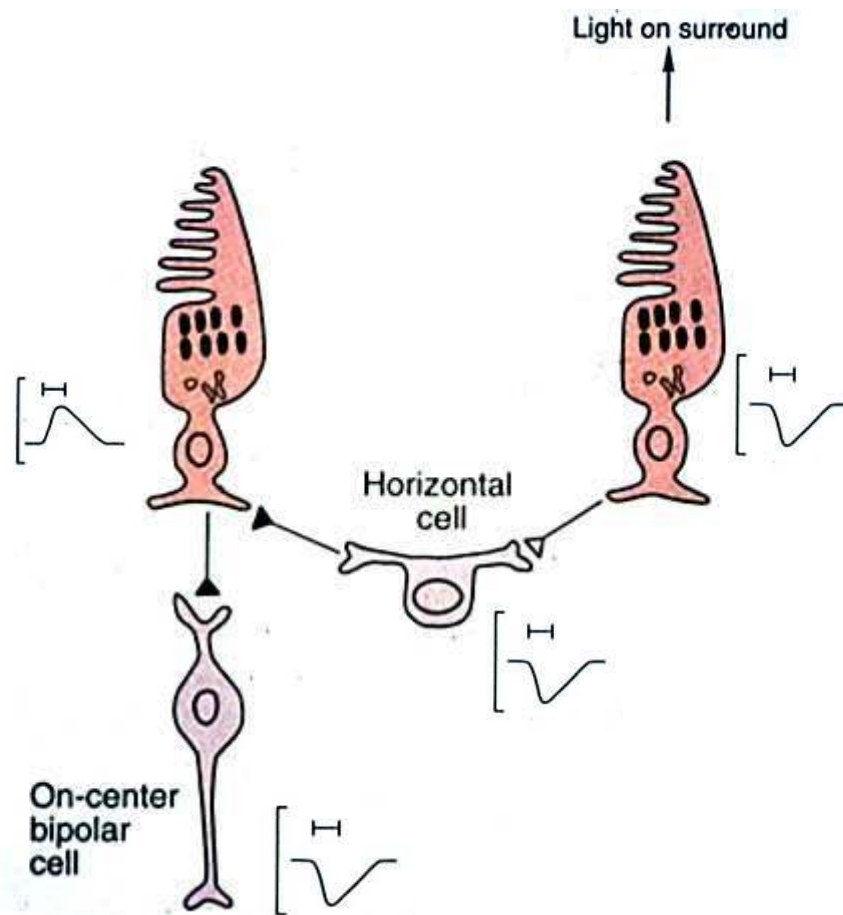
- **Hyperpolarizing and depolarizing cells**
- **Both cell types contain ionotropic glutamate receptors**
- **Neurotransmitter of the horizontal cells is GABA**
- **Histological marker of the horizontal cells is either PA or CaBP**
- **Lateral inhibition, centre-surround organization**



Light on center



Light on surround

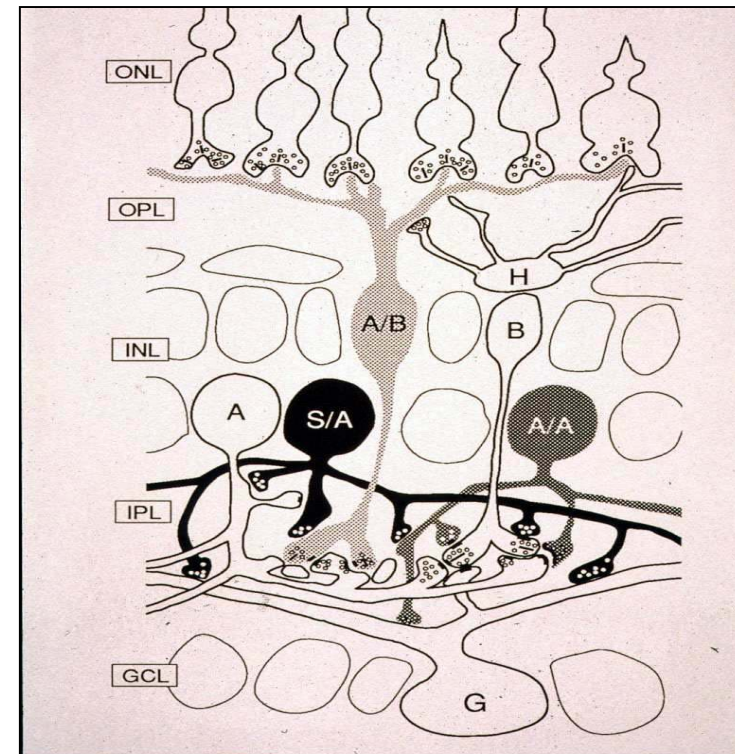


Cells of the inner part of the retina I.

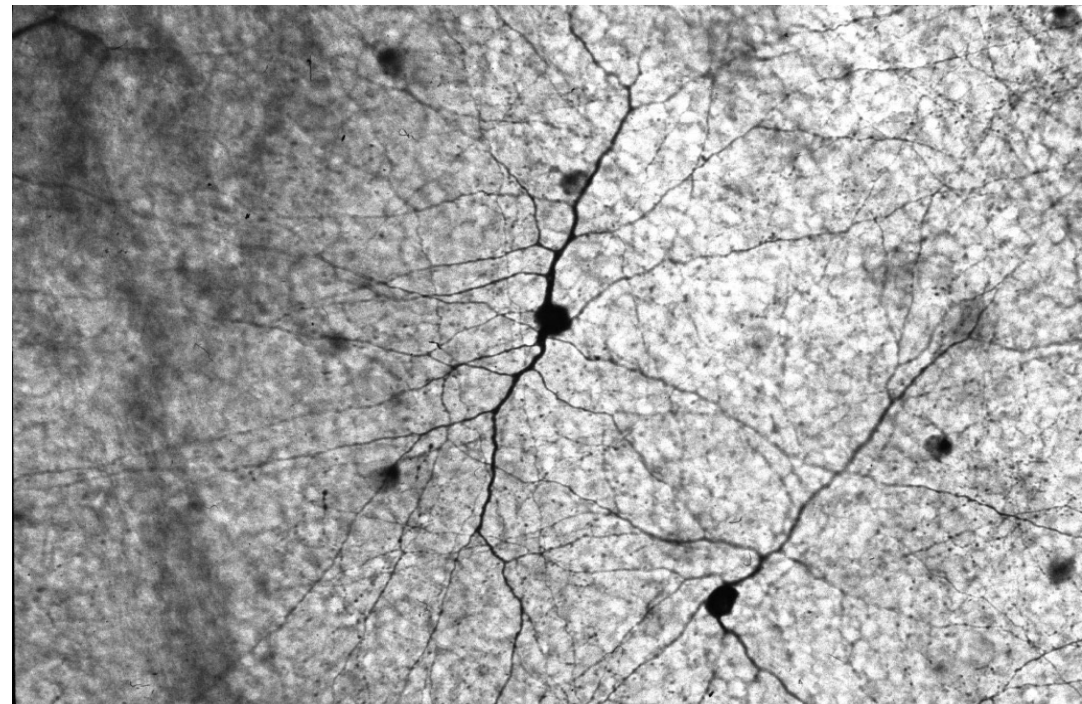
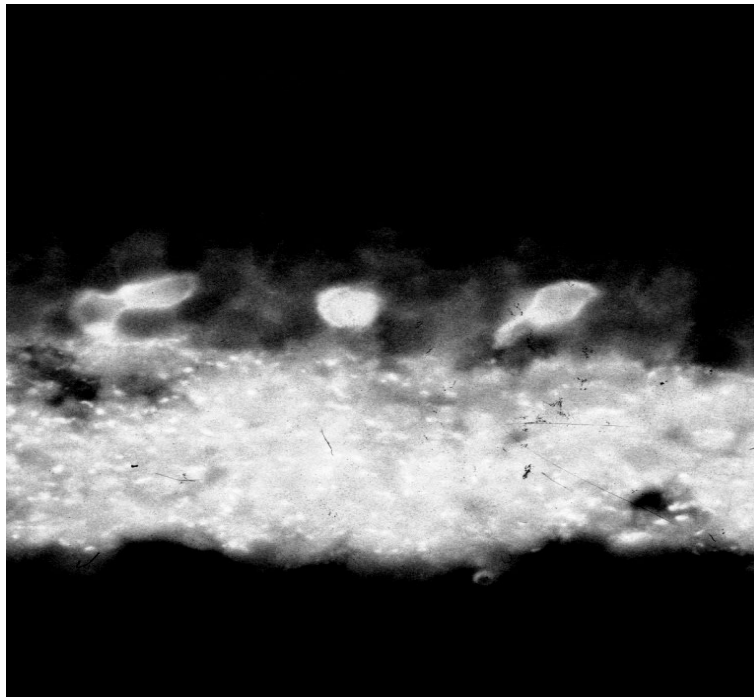
Class of cells	Types of cells	Subtypes	Notes
Amacrine Cells	Cells with wide dendritic field- cells with narrow dendritic field	Several subgroups from morphological, physiological and neurochemical point of view	The second column lists classification categories
	Cells with axon - cells without axon		
	Cells generating action potential – cells generating only local potential change		
	Cells located in normal position – Cells displaced		

Cells of the inner part of the retina II.

- **Bipolar cells**
- **Amacrine cells**
- **Ganglion cells**
- **Glial cells:**
Müller-cells (K-sipho model)
- **$A > A$, $B > A$, $A > B$, $B > G$ and $A > G$ synapses**
- **High complexity**



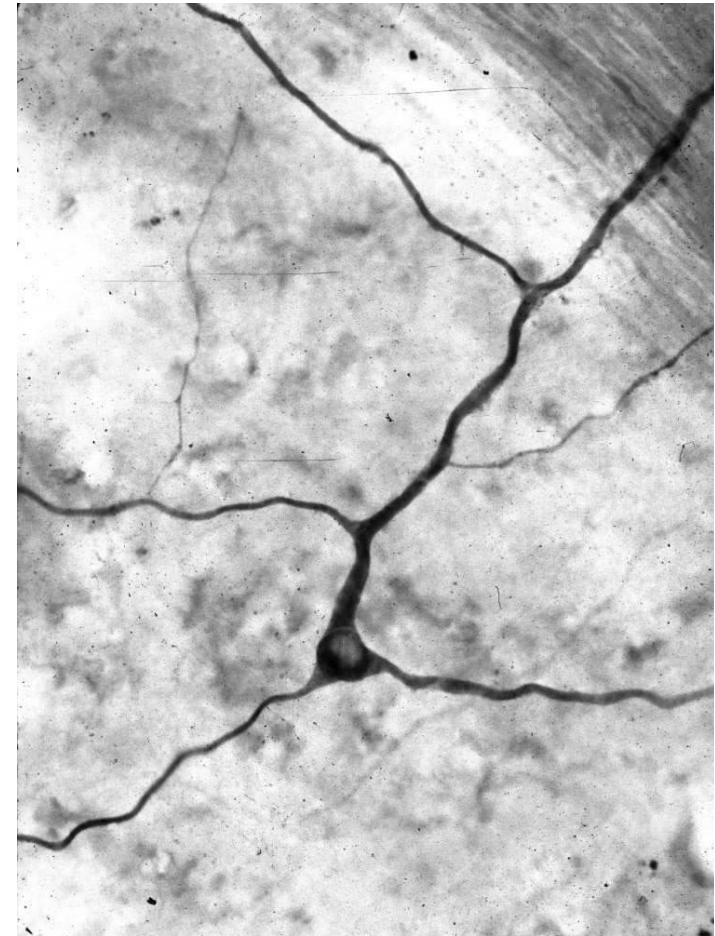
Microanatomy of amacrine cells I.



- ***Cells with narrow and wide dendritic tree***
- ***About 20-30 different cell types***
- ***Mosaic organization within the retina***

Microanatomy of amacrine cells II.

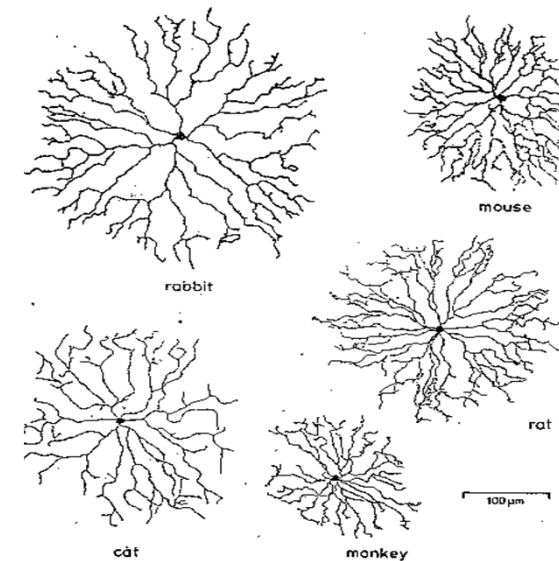
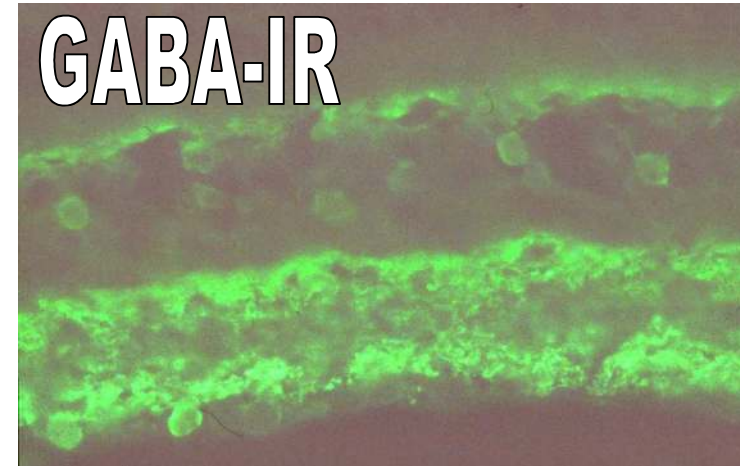
- *There are cells without axons, as well as ones with multiple axons (poliaxonal cells)*
- *Diffuse network of processes*
- *Many different neurotransmitters, frequent co-localisations*
- *Sublayers in the inner plexiform layer (uni-, bi-, tri- and multistratified cells)*



Neurochemistry of amacrine cells I.

- **Most of the cells use GABA or glycine, show narrow dendritic tree, and establish multiple synapses – 90% of all amacrine cells major role is inhibition!!!!**
- **Cells with medium-sized dendritic tree: acetylcholine (4-6%) orientation-selectivity detection of movement "starburst" cells: phylogenetically conserved cells**

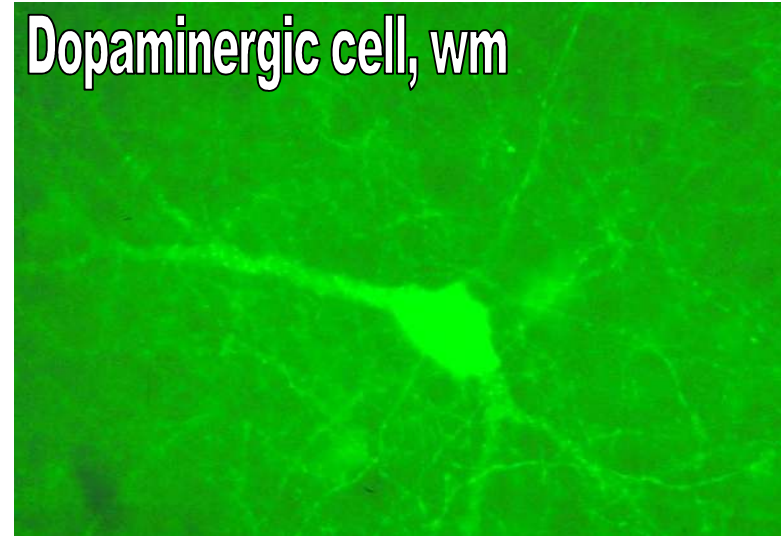
Neurochemical code system!



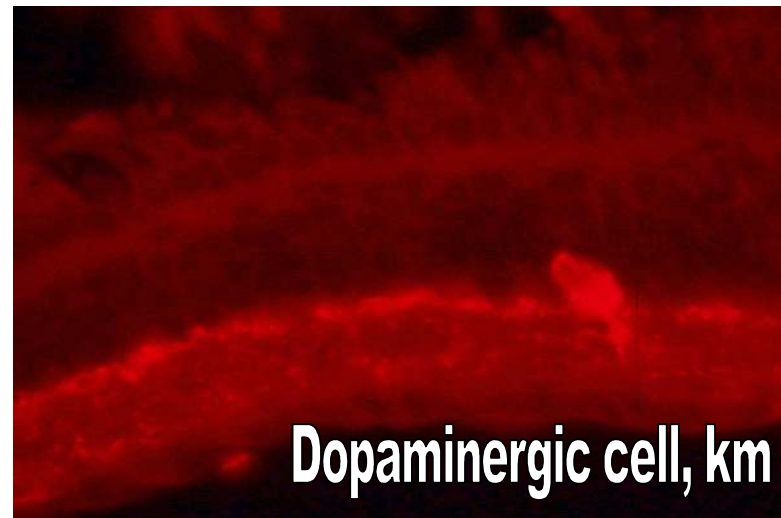
Neurochemistry of amacrine cells II.

- **Monoamines: DA, 5-HT**
- **Peptidergic cells: SP, NPY, CCK; most cases these peptide are present as co-transmitter with GABA or glycine**
- **Usually they are uni- or bistratified cells**
- **Their functions: neuromodulation, eg. light adaption**

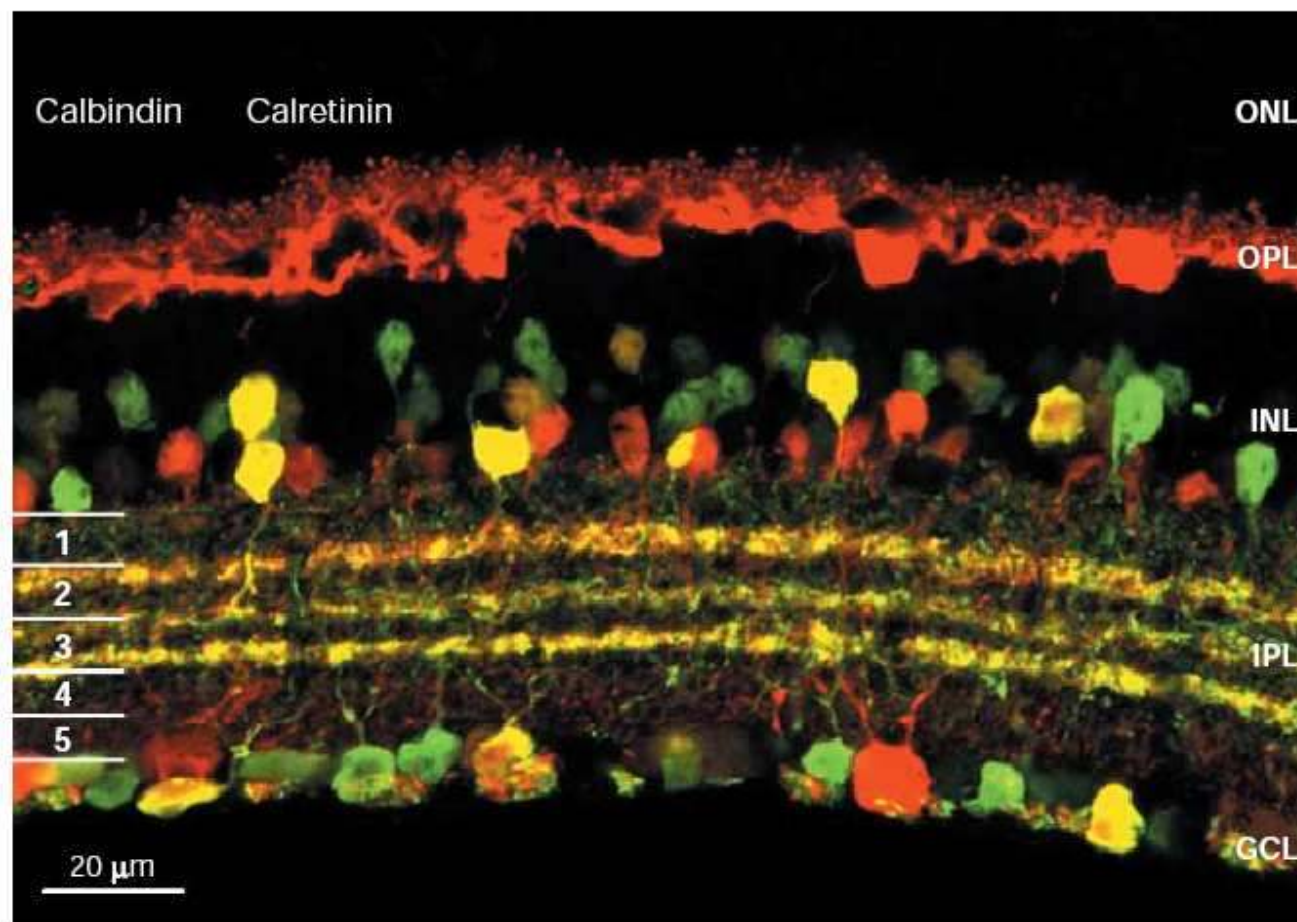
Dopaminergic cell, wm



Dopaminergic cell, km

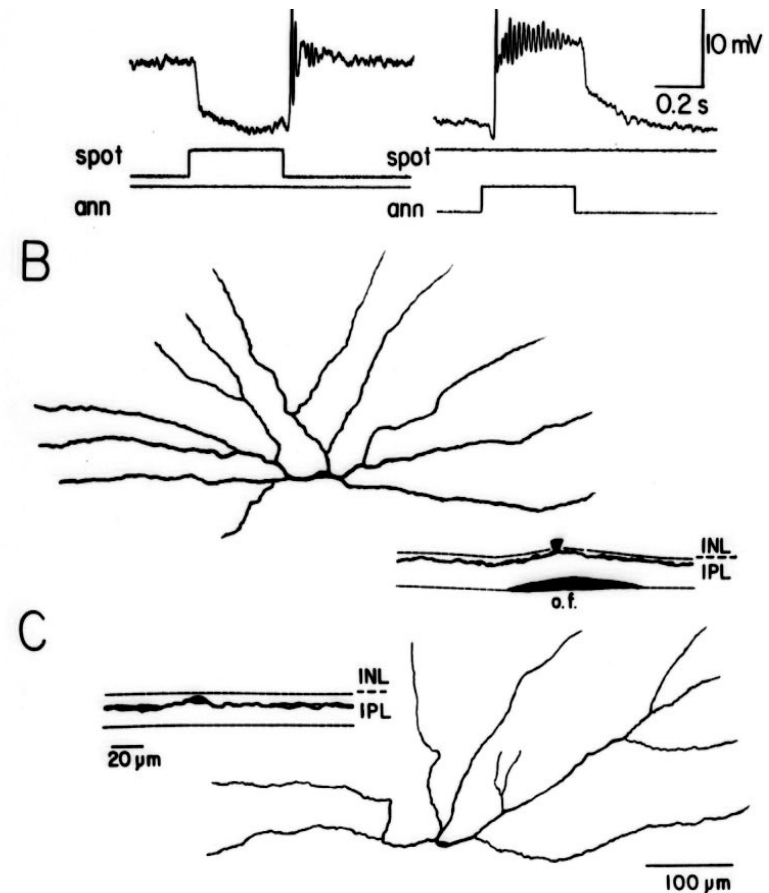


Neurochemistry of amacrine cells III.: Calcium binding proteins

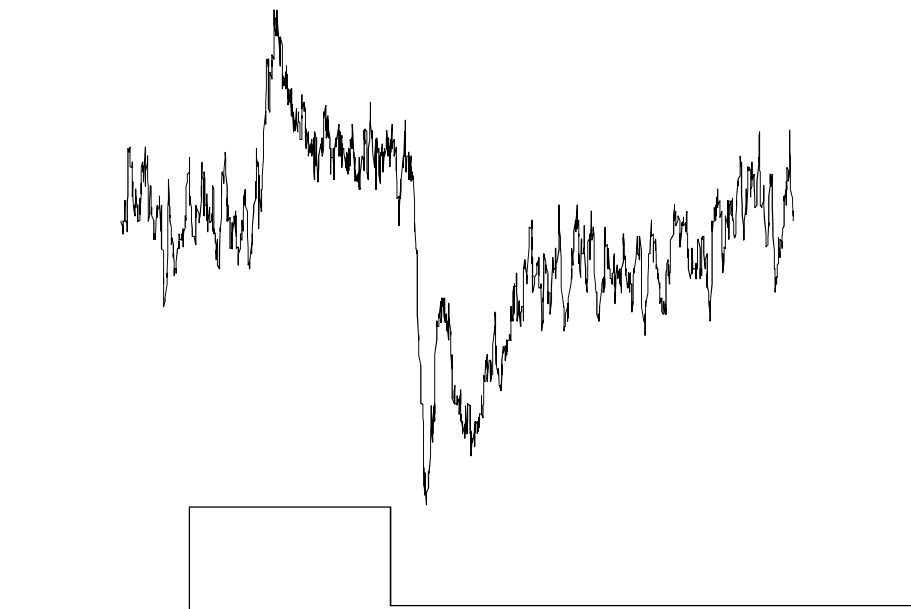
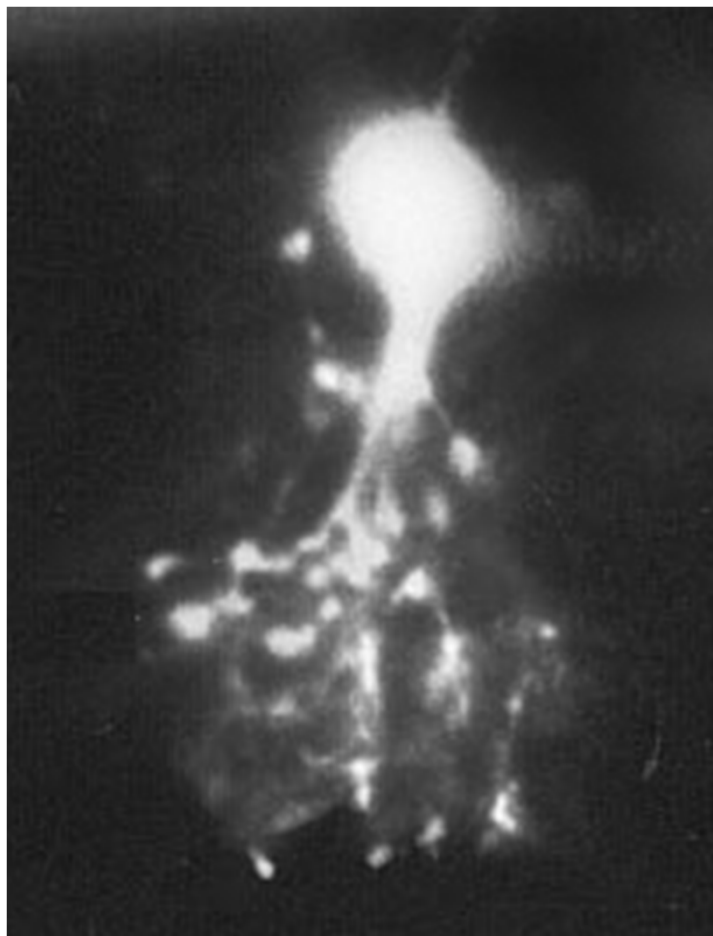


Physiology of amacrine cells

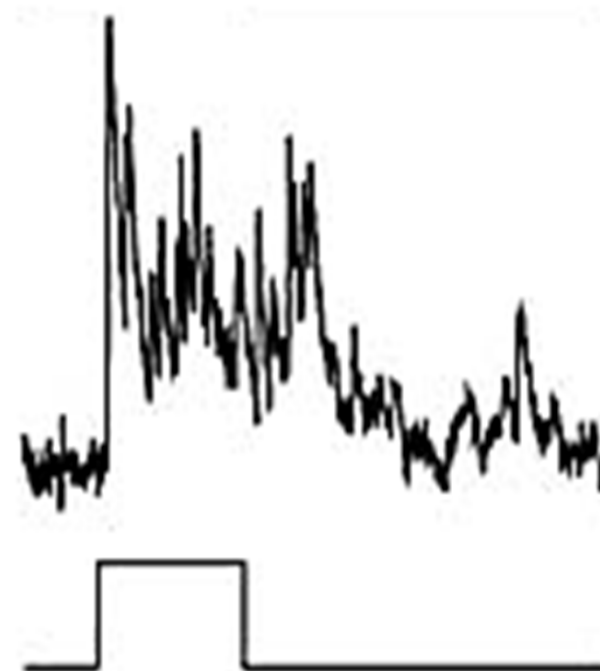
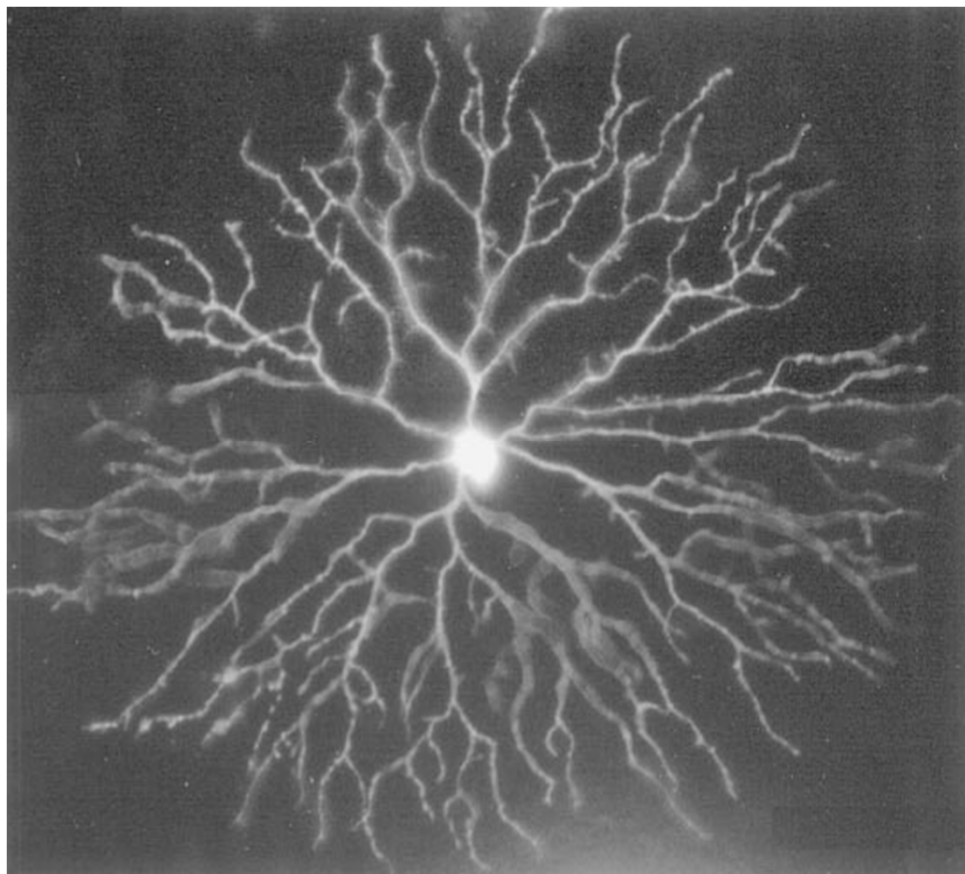
- ***Sustained and transient On, Off and On-Off***
- ***Sublaminar distribution of the dendrites is in overlap with the axonal ramifications of the bipolar cells and the dendritic tree of the ganglion cells.***
- ***Overlap of the morphological and physiological segregation***
- ***Orientation selectivity***



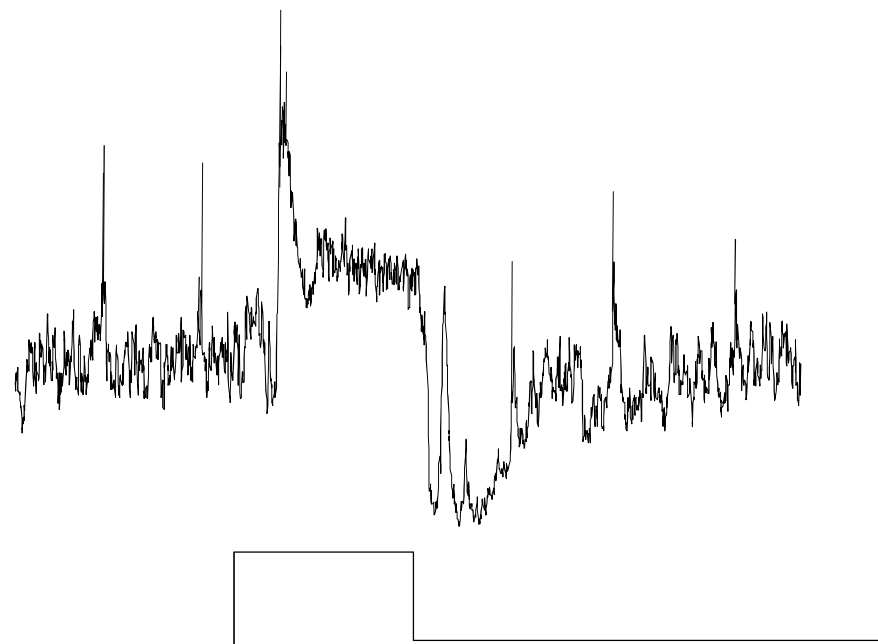
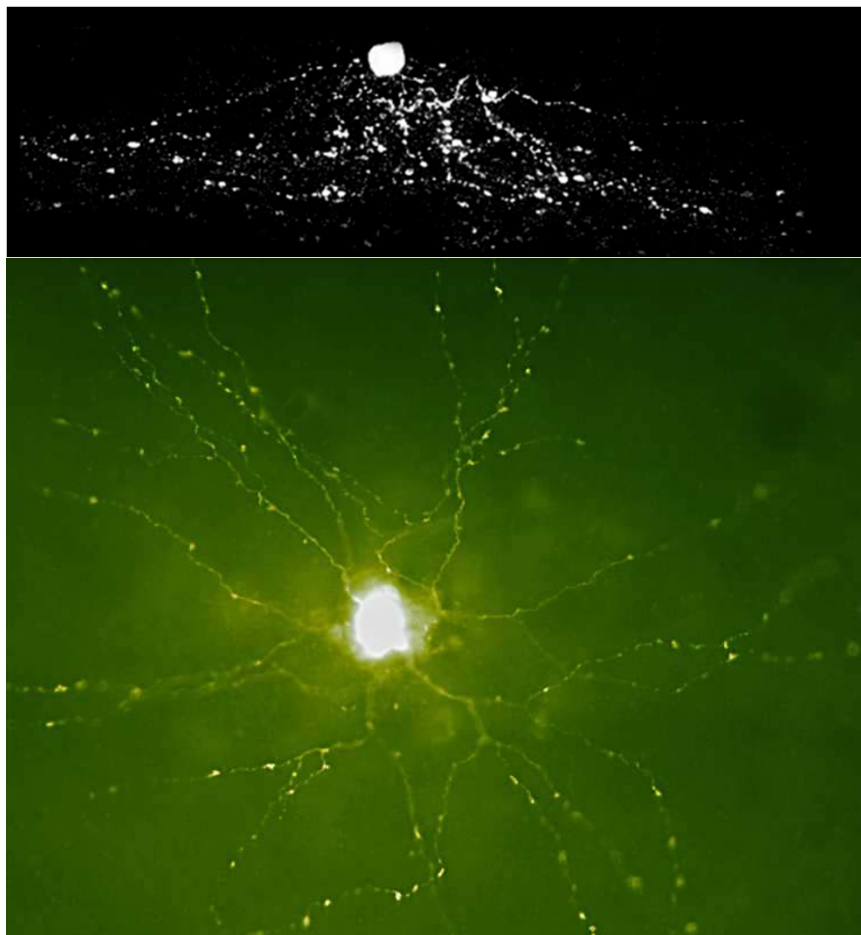
Amacrine cells I.



Amacrine cells II.



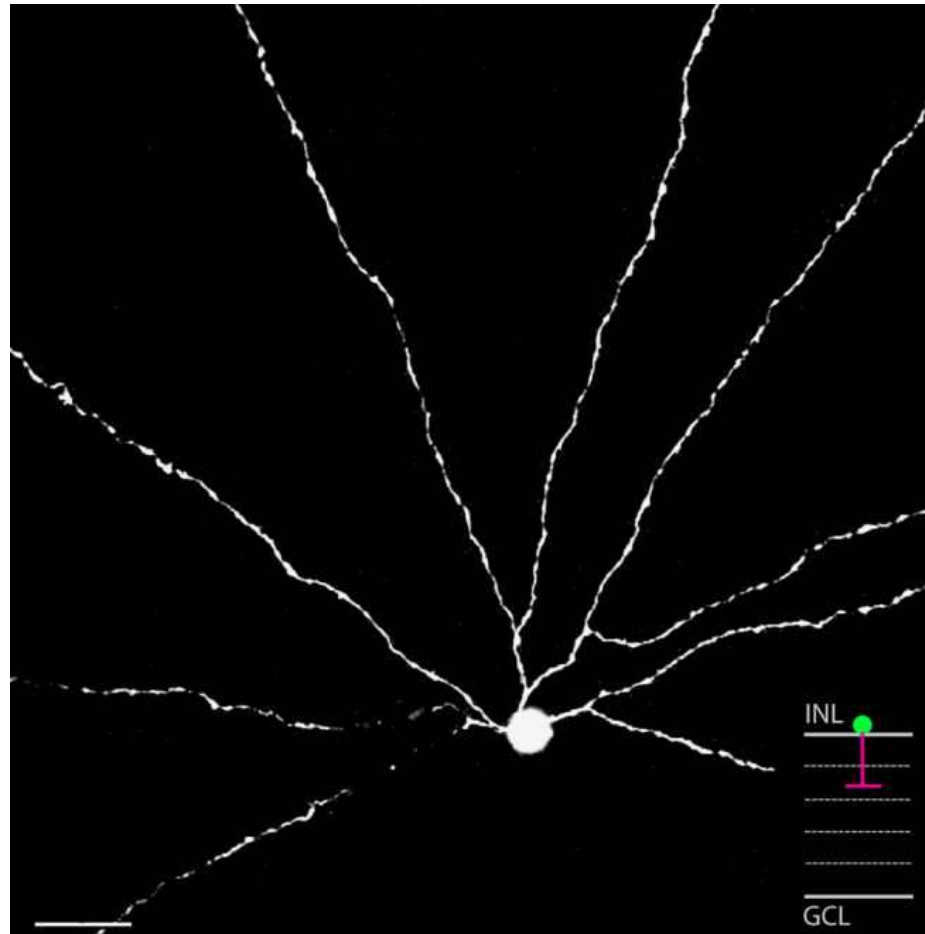
Amacrine cells III.



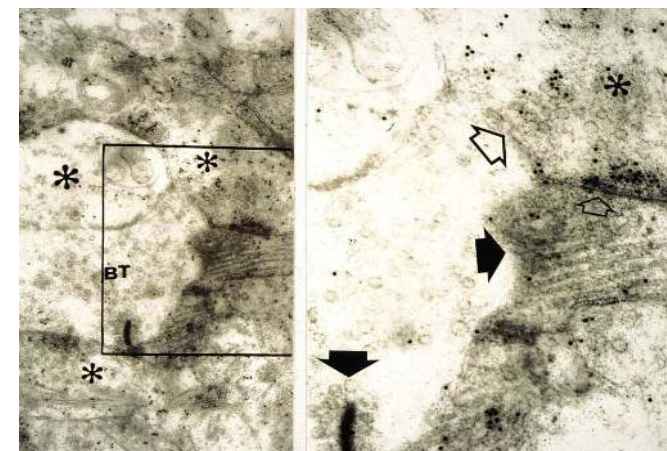
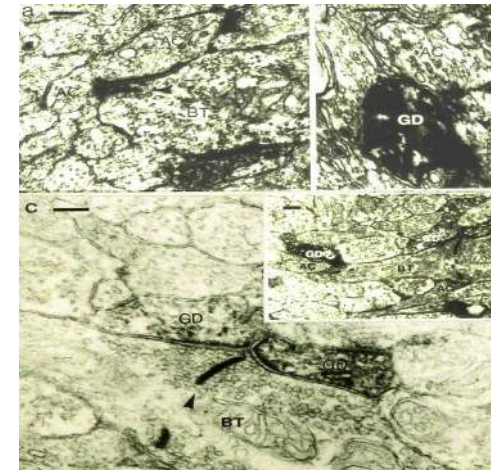
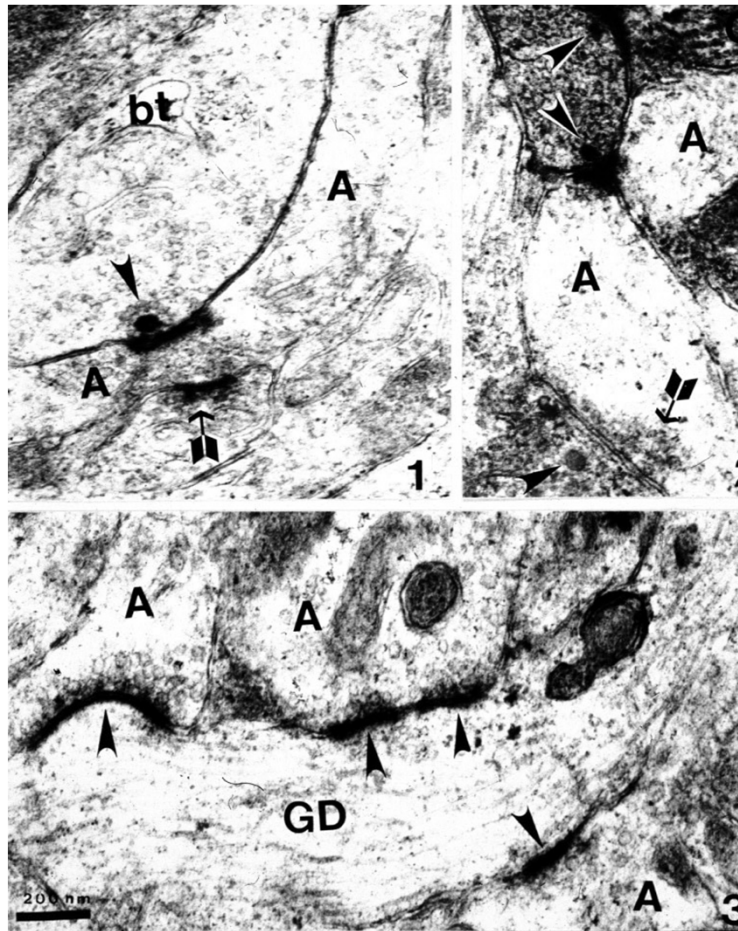
Amacrine cells IV.



Amacrine cells V.

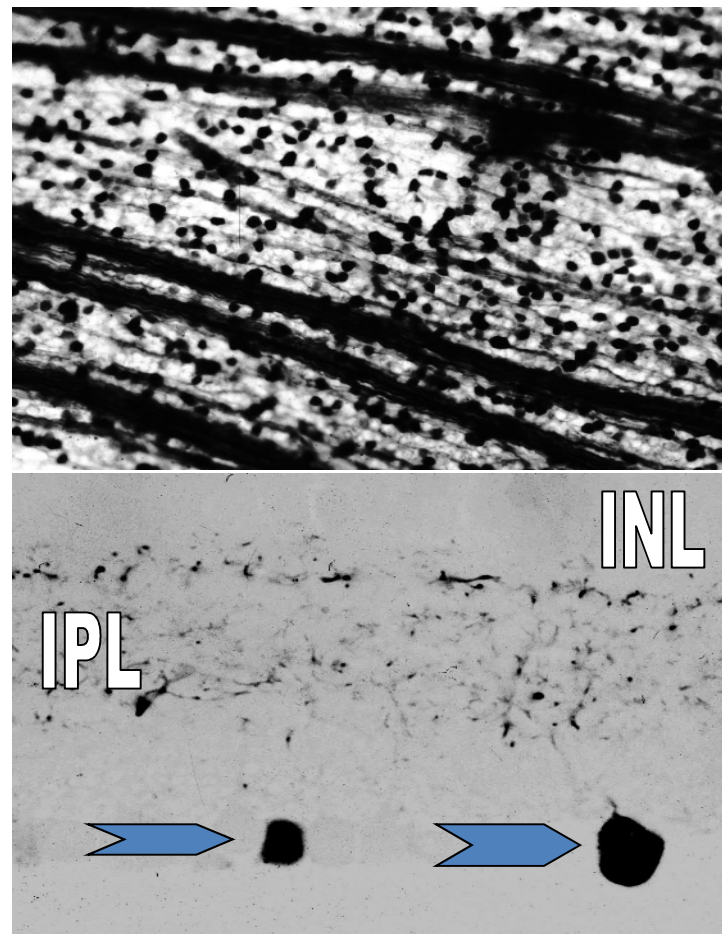


Synapses of the inner plexiform layer



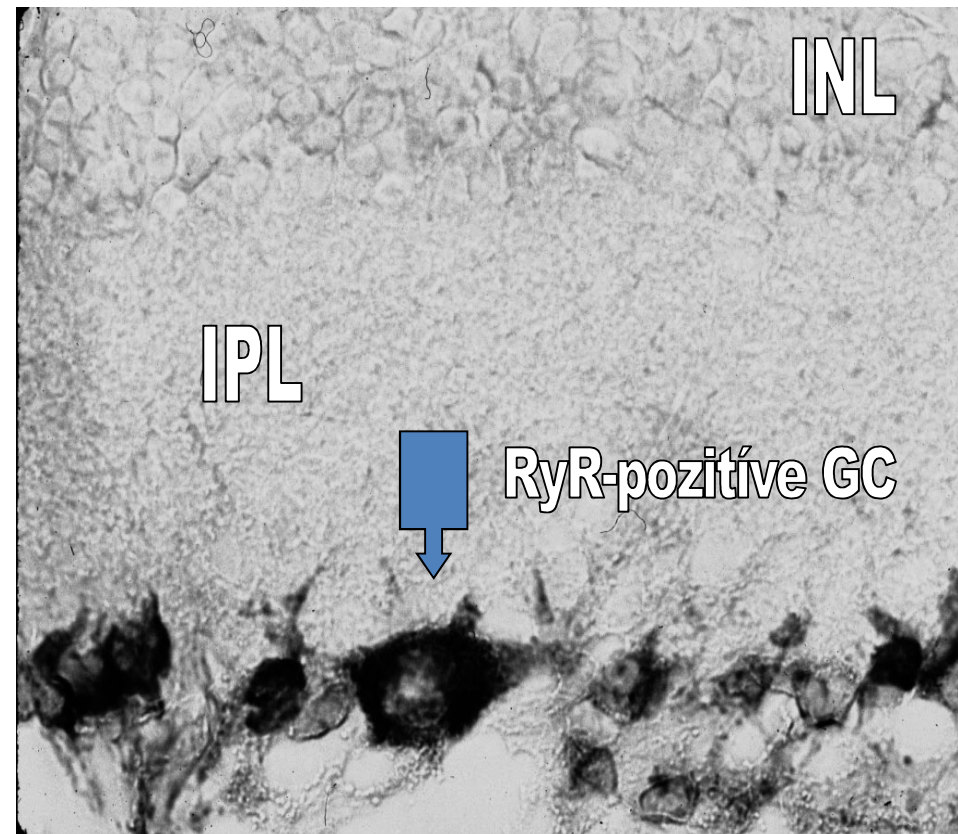
Microanatomy of ganglion cells

- *Mass filling, HRP injection in the eye*
- *Mozaics of cells*
- *Dendritic segregation of On and Off cells*
- *On-Off cells are present frequently, especially in lower vertebrates*

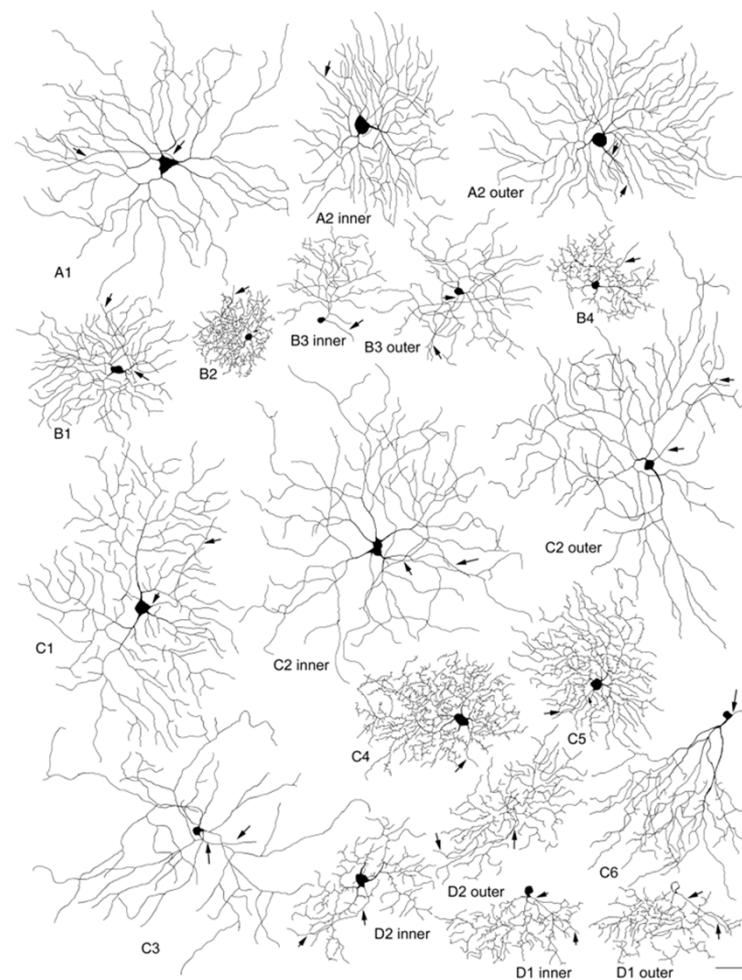
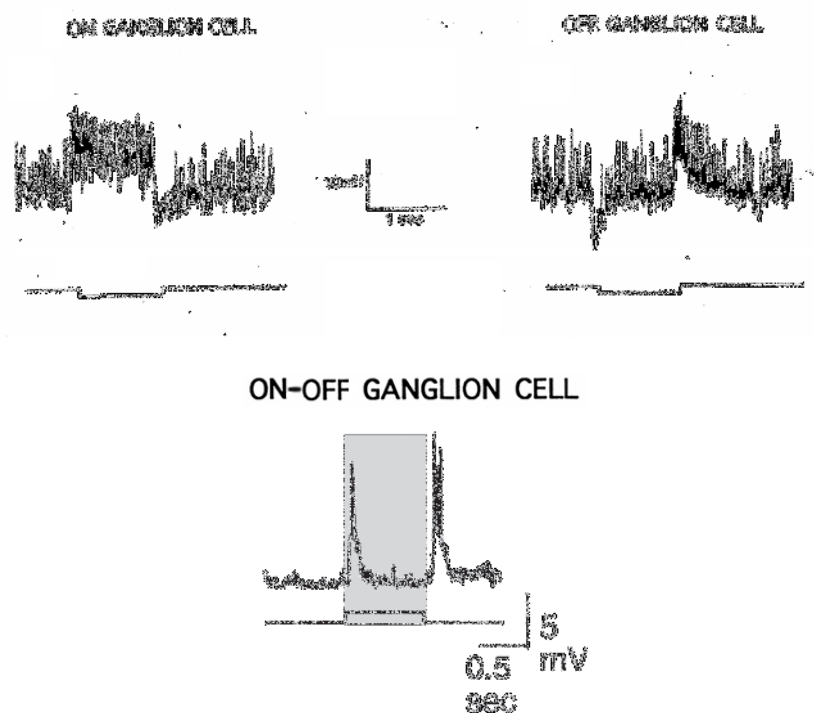


Neurochemistry of ganglion cells

- **Neurofilament proteins**
- **MAPs**
- **On the receiving side:
ionotropic and metabotropic
glutamate receptors (AMPA,
NMDA)**
- **IP3 and RyR systems**
- **Calciumbinding proteins**
- **Neurotransmitter: glutamic acid,
certain cells contain neuropeptides
(SP, NPY, PACAP): target-specificity!**



Physiology of ganglion cells I.

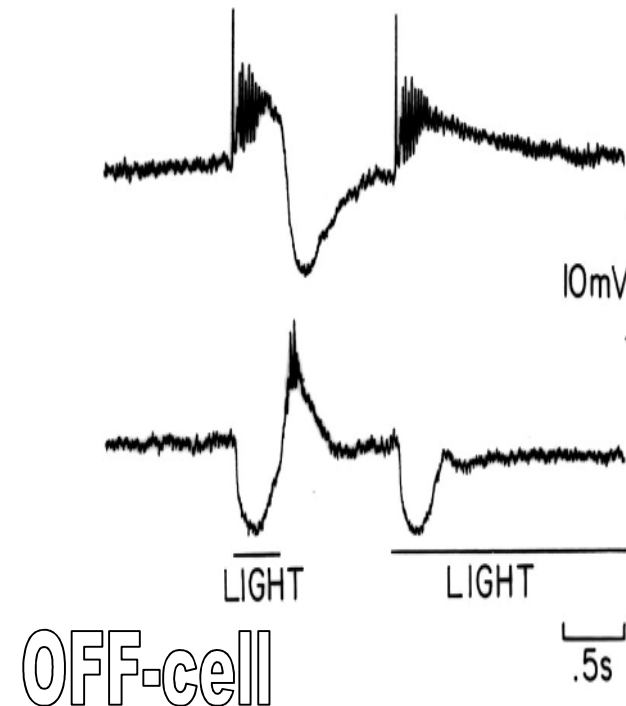


Sun et al. 2002

Microphysiology of ganglion cells II.

- **Generation of spikes**
- **Saturation, long-lasting after potentials**
- **Plateau phase, oscillations**
- **X, Y and W cells – anatomy can be brought in correspondence with electrophysiology characteristics**
- **Mosaics of ganglion cells, convergence!**

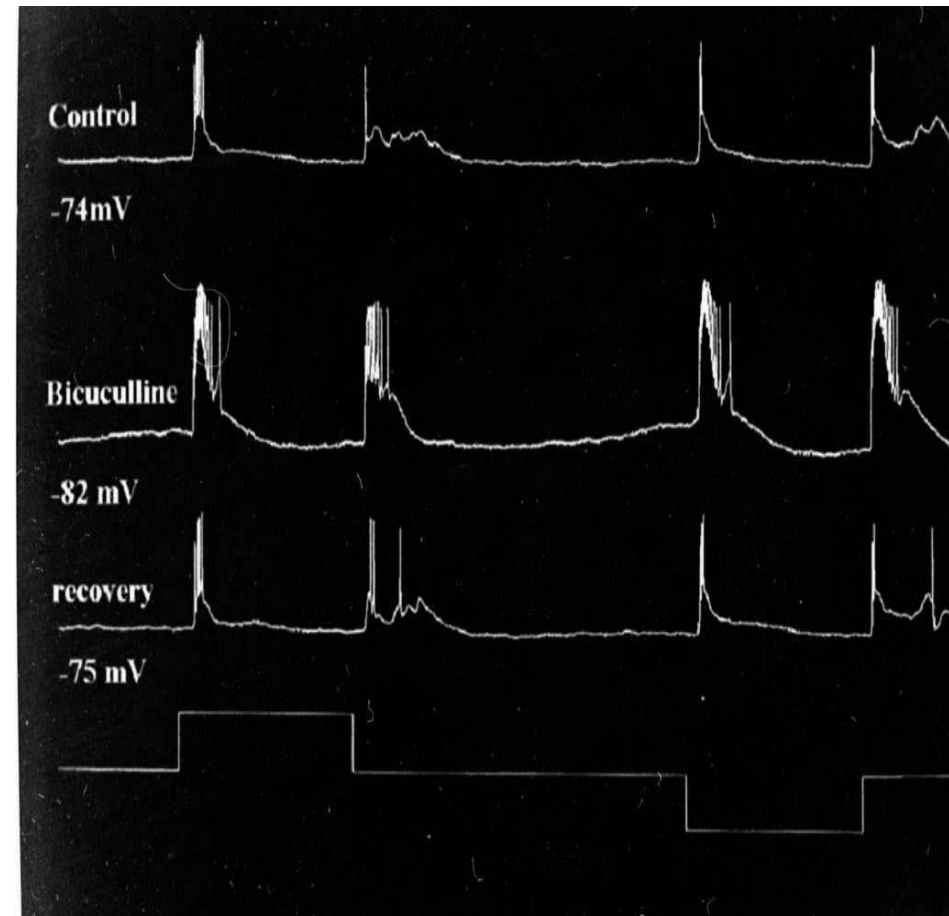
ON-cell



OFF-cell

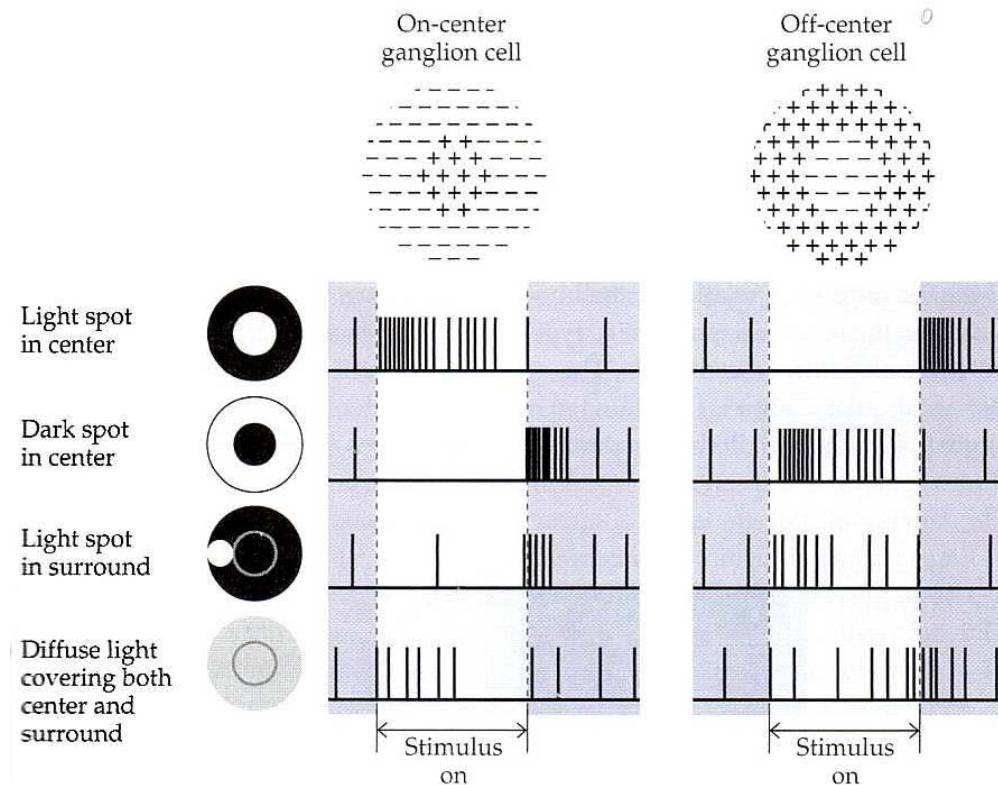
Microphysiology of ganglion cells III.

- *Tranzient ganglion cells can exhibit both ON and OFF characteristics*
- *Ganglion cells are under GABAergic inhibition. Inhibition is mediated through GABA_A receptors.*



Centre-surround organization

- ***Dendritic field, receptive field***
- ***Lateral inhibition***
- ***Horizontal cells, GABA***
- ***Amacrine cells, GABA and glycine***
- ***On-centrum, off-centrum***

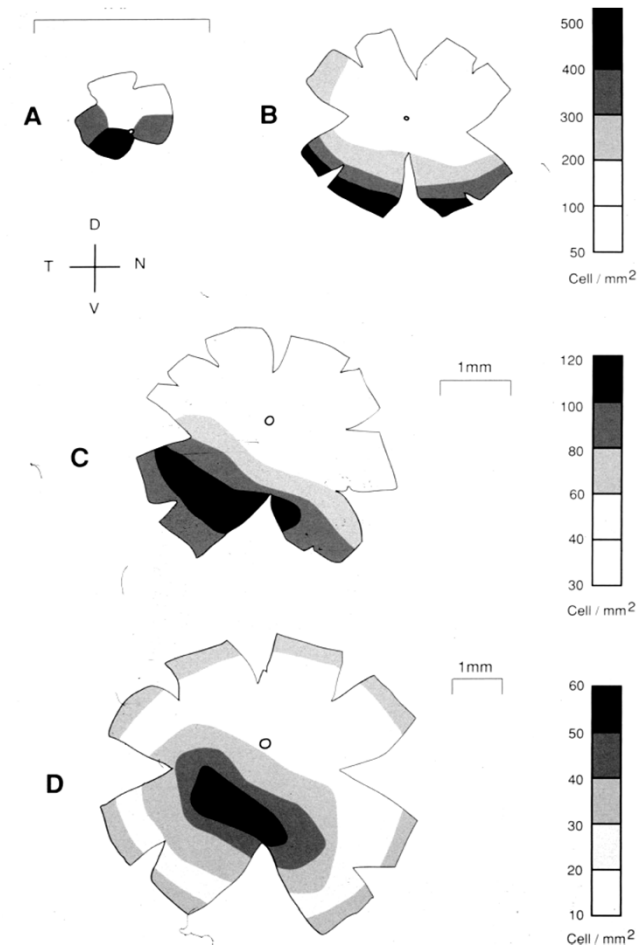


Communication with higher order visual centres



Mozaic of developing retina

- ***Development of central specialization begins already at early stage of ontogenesis.***
- ***The extent of specialization may vary from animal to animal depending on the territory they occupy***



A special mozaic of ganglion cells

- **Elephant: Perpendicular and horizontal specializations**
- **Horizontal is present to observe continuously the trunk at the highest resolution**
- **Primates: central fovea**
 - there are no rods at this site
 - bipolar cell-ganglion cell connection is in 1:1

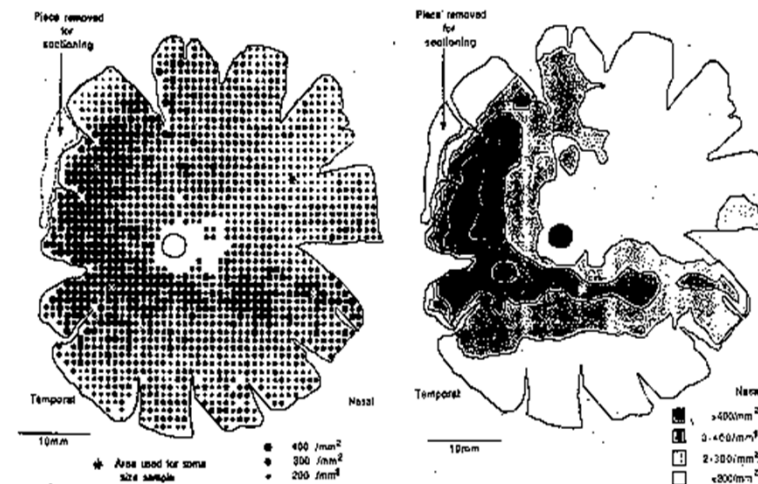
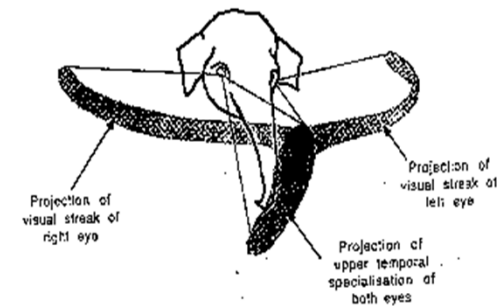
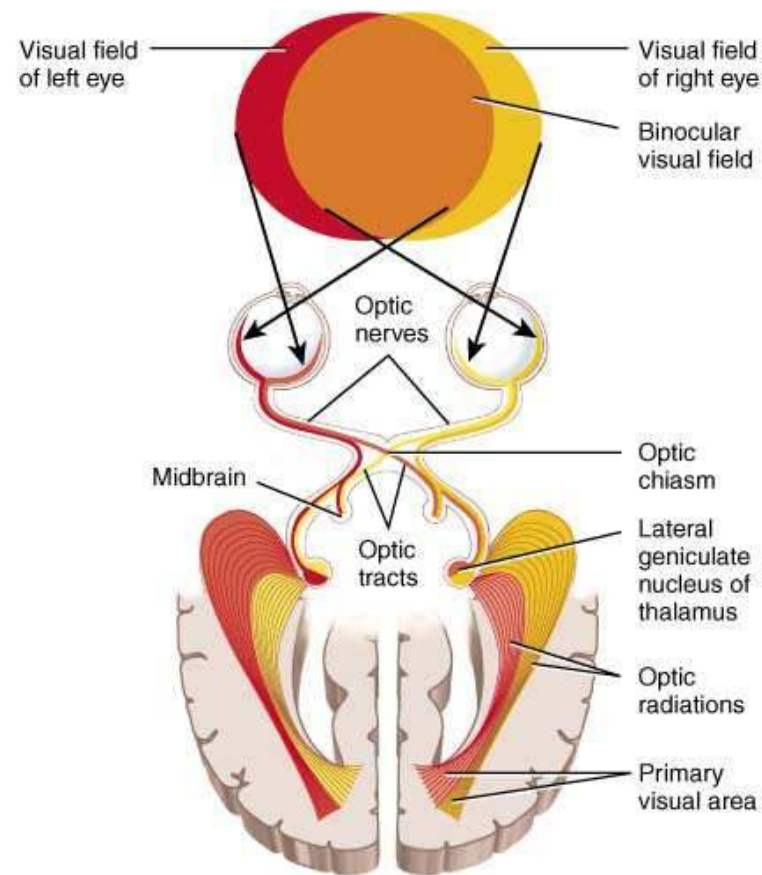


Fig. 7. Maps of the distribution of ganglion cells in the retina. Each position on the retina at which ganglion cell density was sampled is represented by a filled symbol whose size is proportional to density. The areas from which the cell samples used in figures 4 and 5 were taken are indicated with asterisks. Also indicated is the segment of retina taken for sectioning. The dotted lines are isodensity lines calculated by a computer-based paradigm.



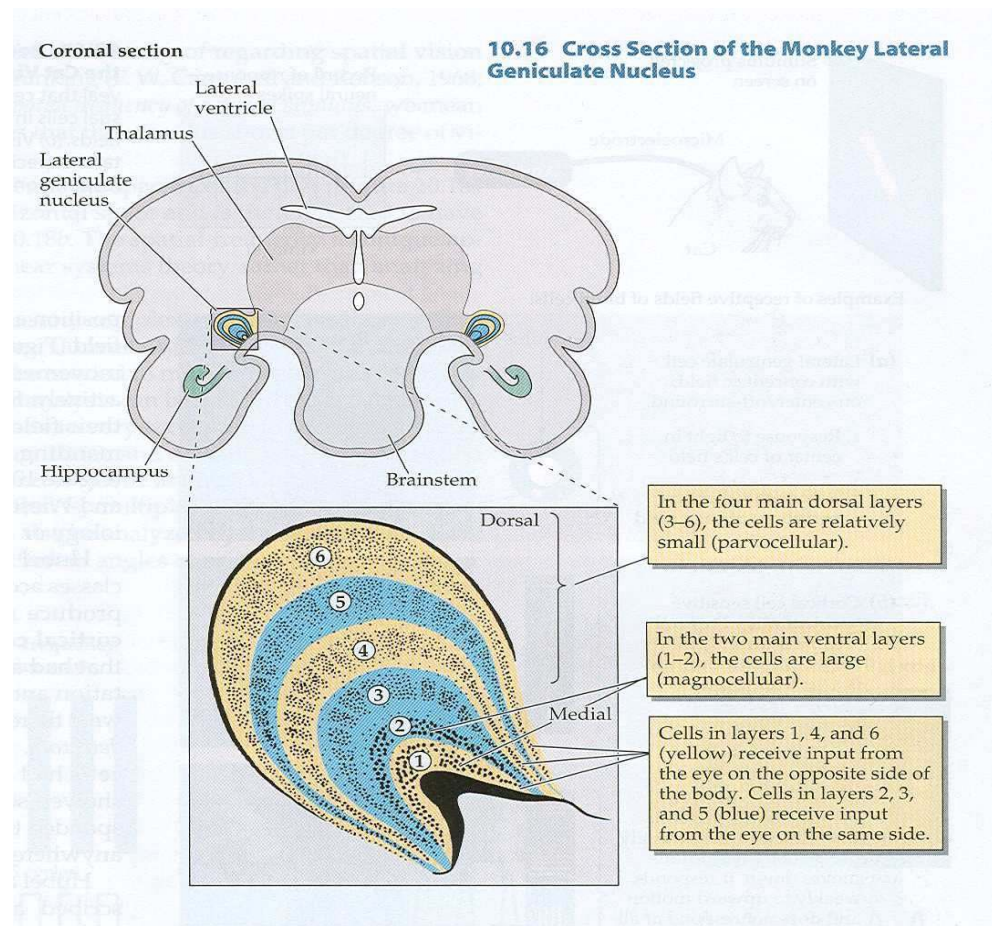
Central mechanisms of vision



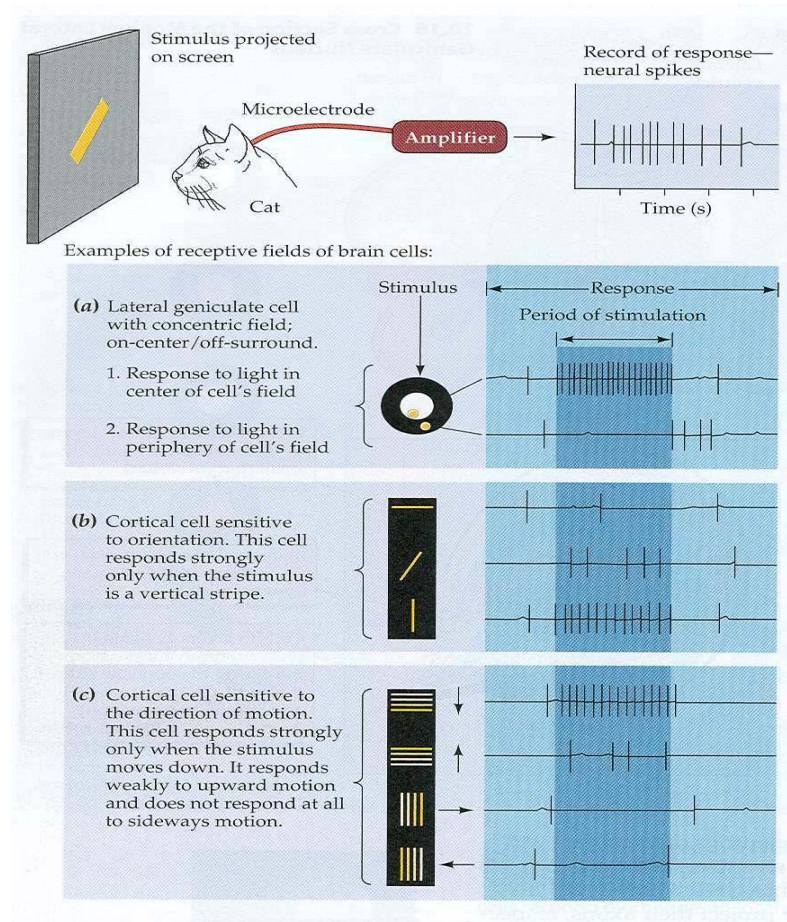
(b) Superior view of transverse section through eyeballs and brain

Adapted from Seeley et al., *Anatomy and Physiology*, Fourth Edition, Figure 15.22, p. 480 (New York: WCB McGraw-Hill, 1998). ©The McGraw-Hills Companies.
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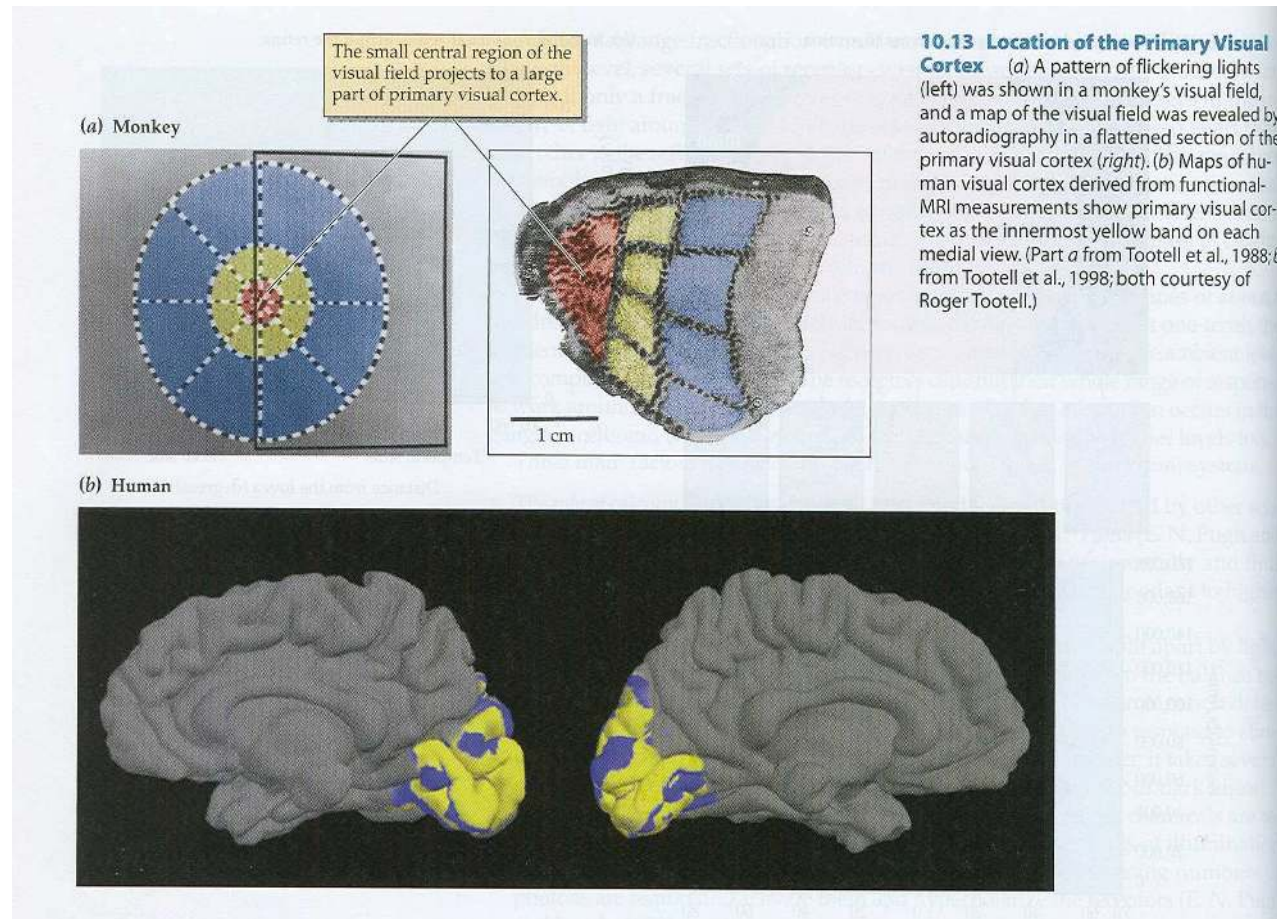
The lateral geniculate body (CGL, LGN)



Receptive fields of CGL and V1 cells



Retinal projection to the visual cortex



Thank you for your attention

