Formation of Vision in the Outer Retina

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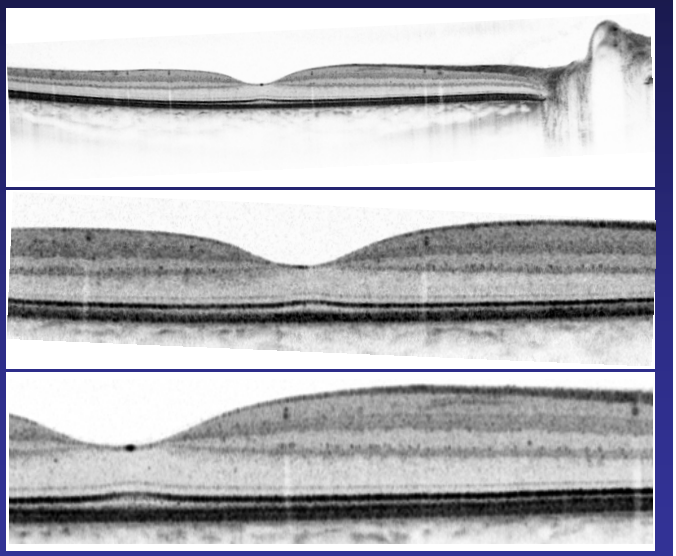
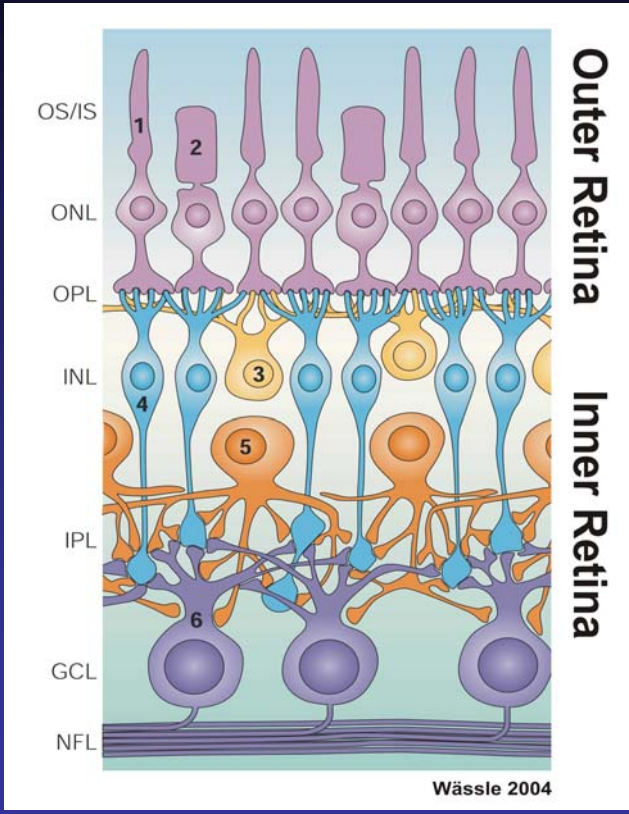
Position of the retina within the eye

OCT in vivo images of the retinal layers





Cell types of the retina:

1: Rod photoreceptors

2: Cone photoreceptors

3: Horizontal cells

4: Bipolar cells

5: Amacrine cells

6: Ganglion cells

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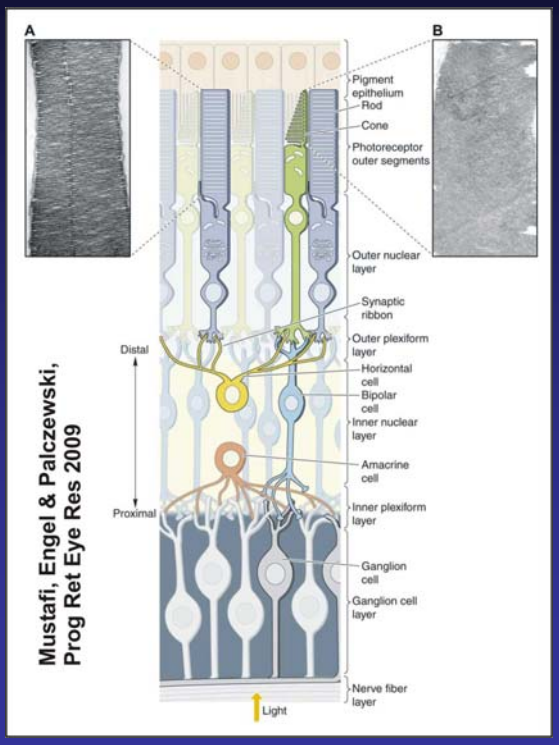
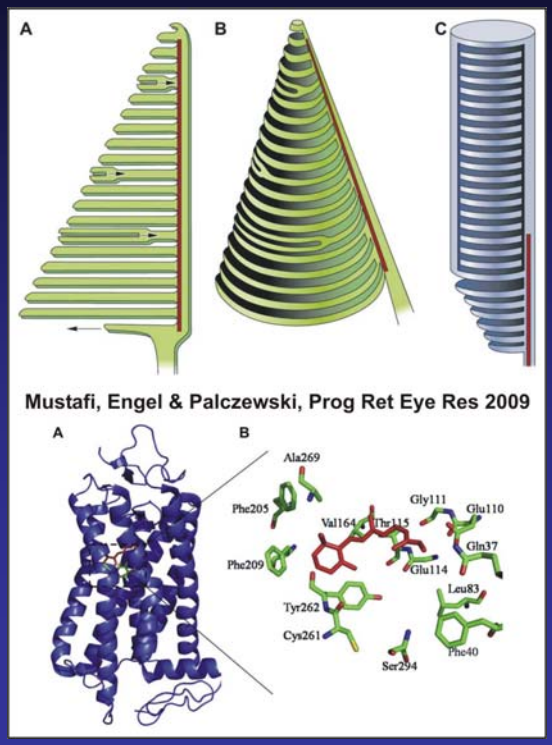
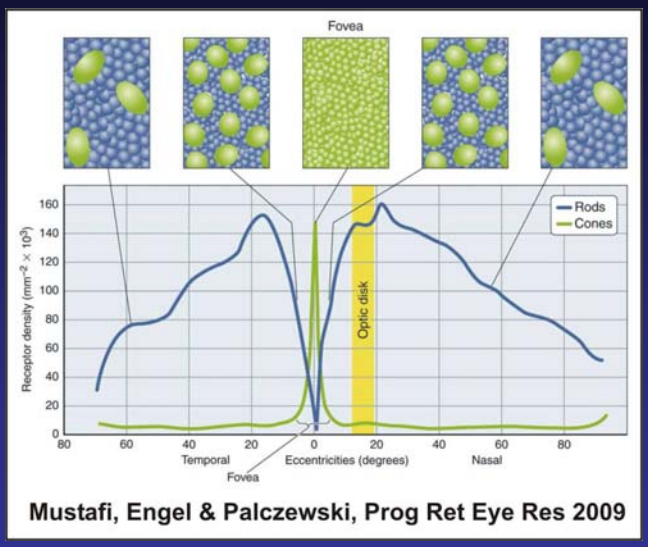
The photoreceptors (rods & cones)



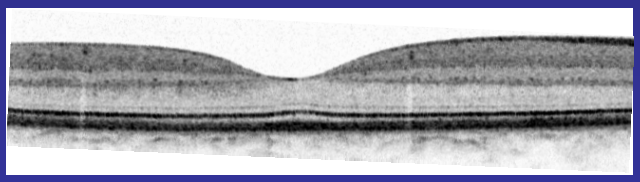
Photoreceptor outer segments



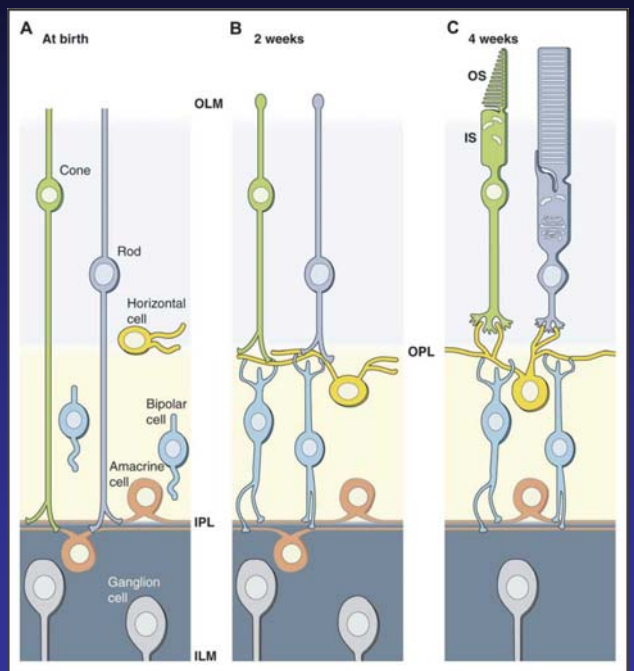
Photoreceptor distribution



Mustafi, Engel & Palczewski, Prog Ret Eye Res 2009



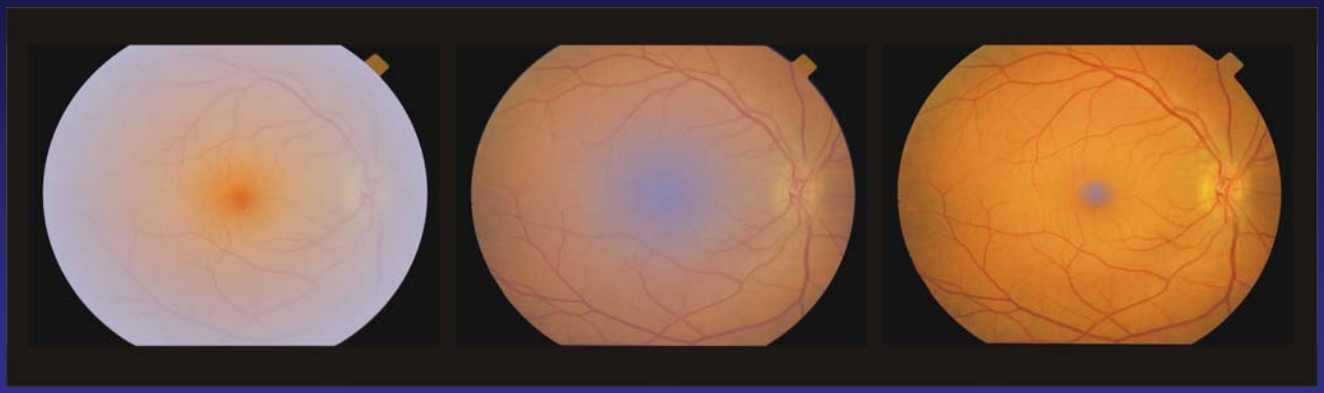
Photoreceptor system development



Mustafi, Engel & Palczewski, Prog Ret Eye Res 2009

Human hereditary retinal degenerations: Problem zones

A B C



Rods

- Night vision problems

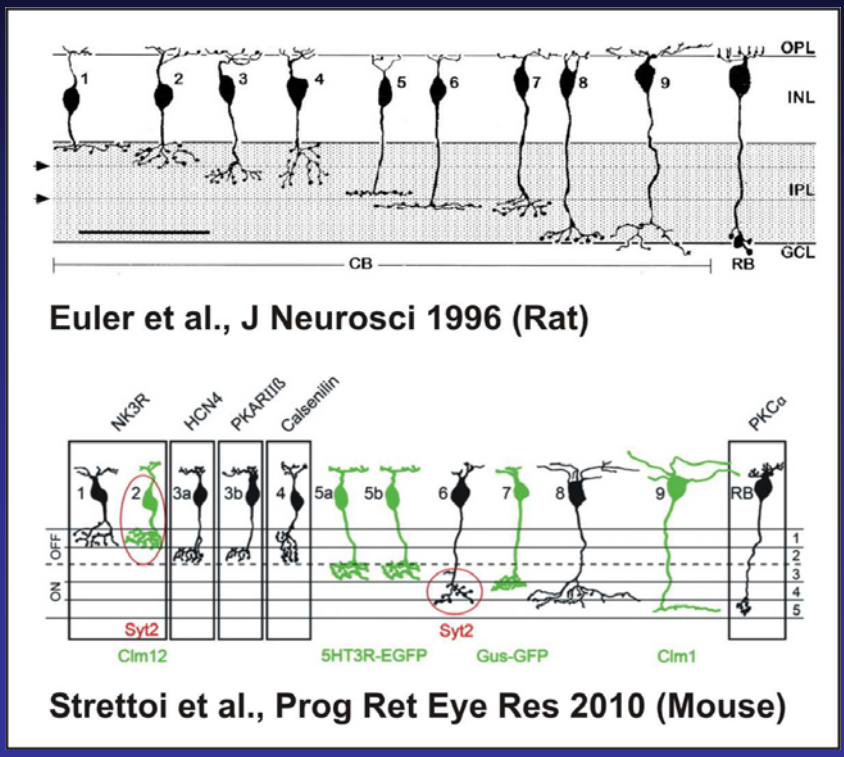
Cones

- Enhanced glare sensitivity
- Visual field loss
- Color vision problems

Macula/Fovea

- Reduced visual acuity

The next neuron: Bipolar cells



Euler et al., J Neurosci 1996 (Rat)

Strettoi et al., Prog Ret Eye Res 2010 (Mouse)

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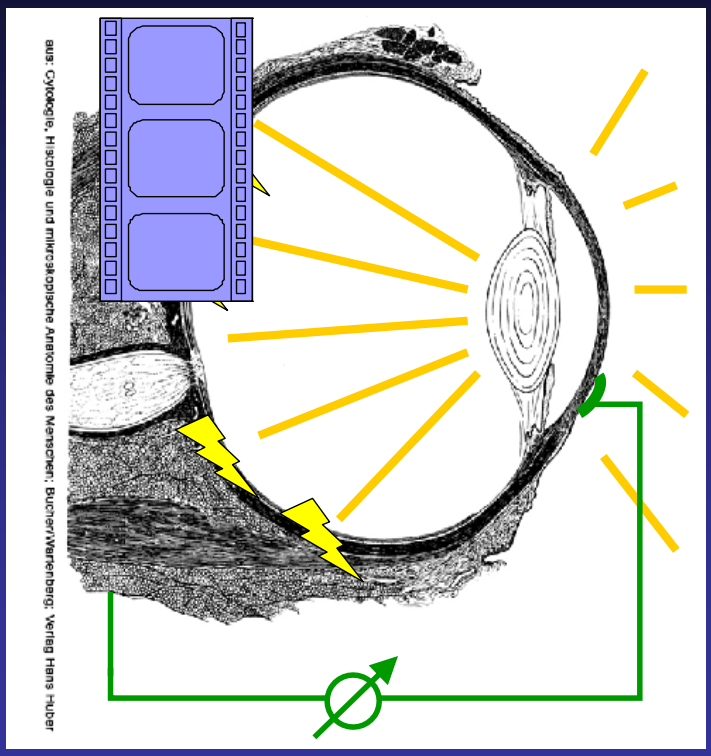
Diagnostic techniques:

Electroretinography (ERG)

Measurement of retinal function (ERG)



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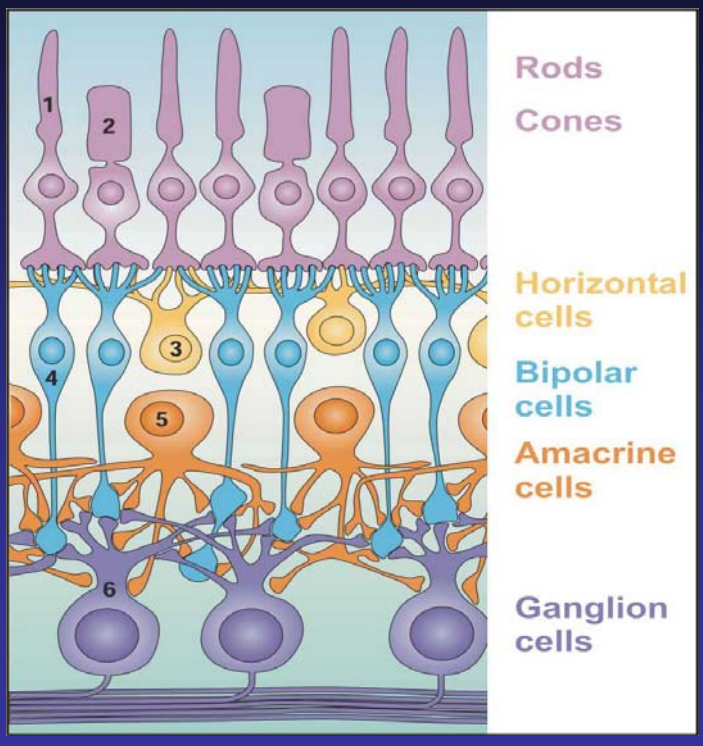
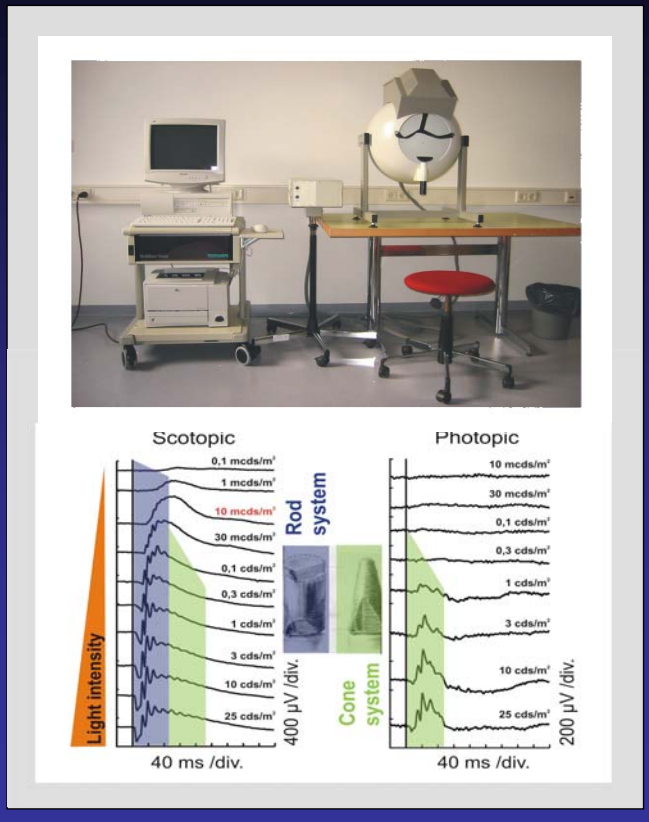
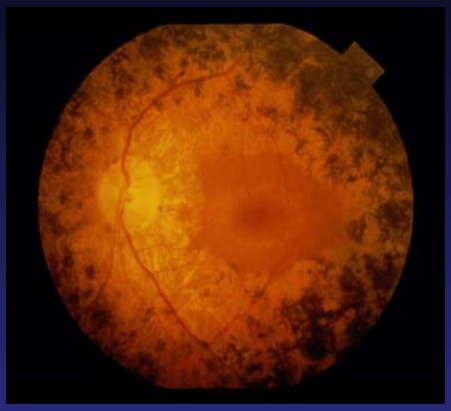
Measurement of retinal function (ERG)



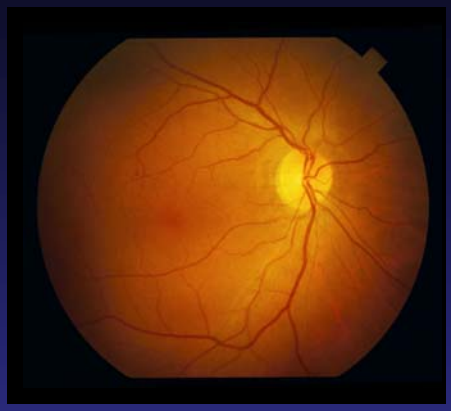
modified from Wässle 2004



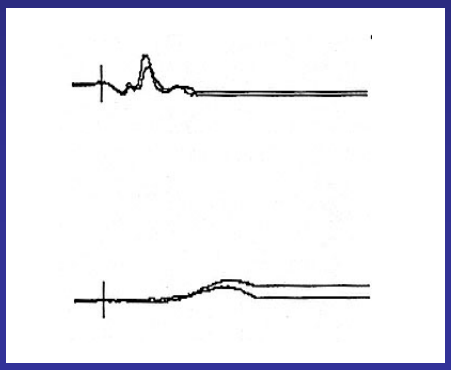


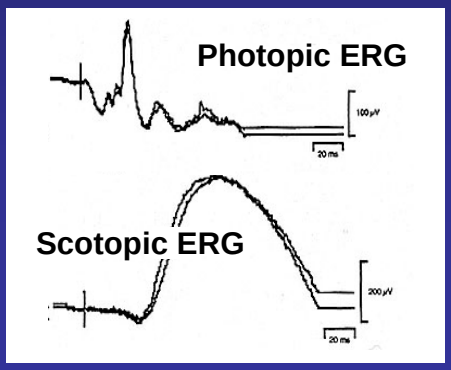
Retinitis pigmentosa (RP)

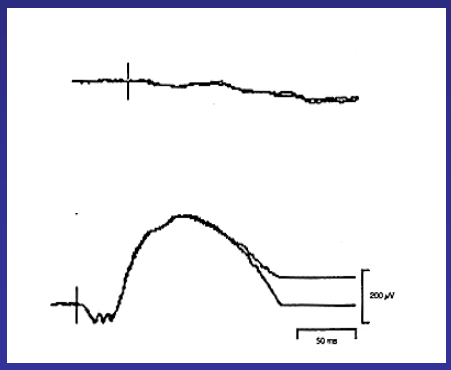
Normal subject



Cone dystrophy (CD)







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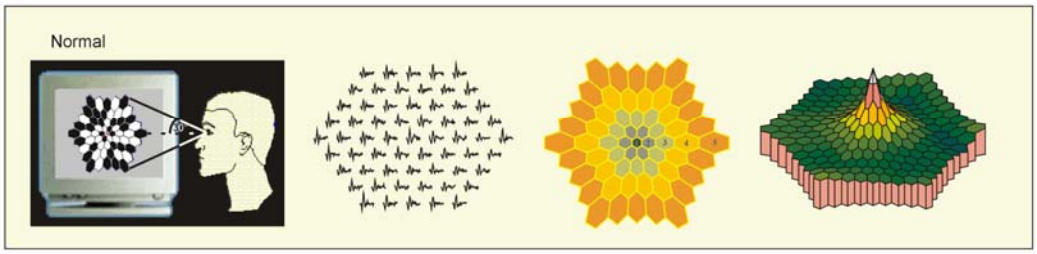

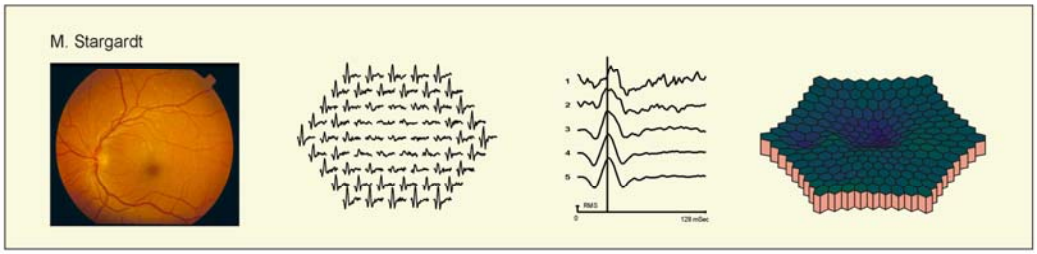

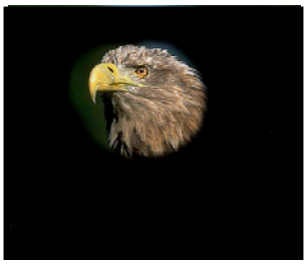

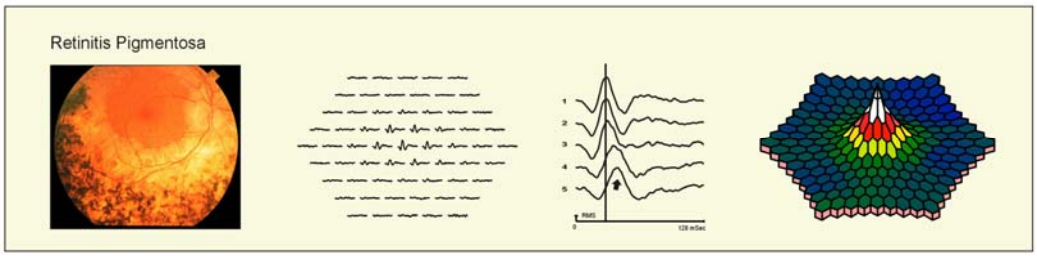

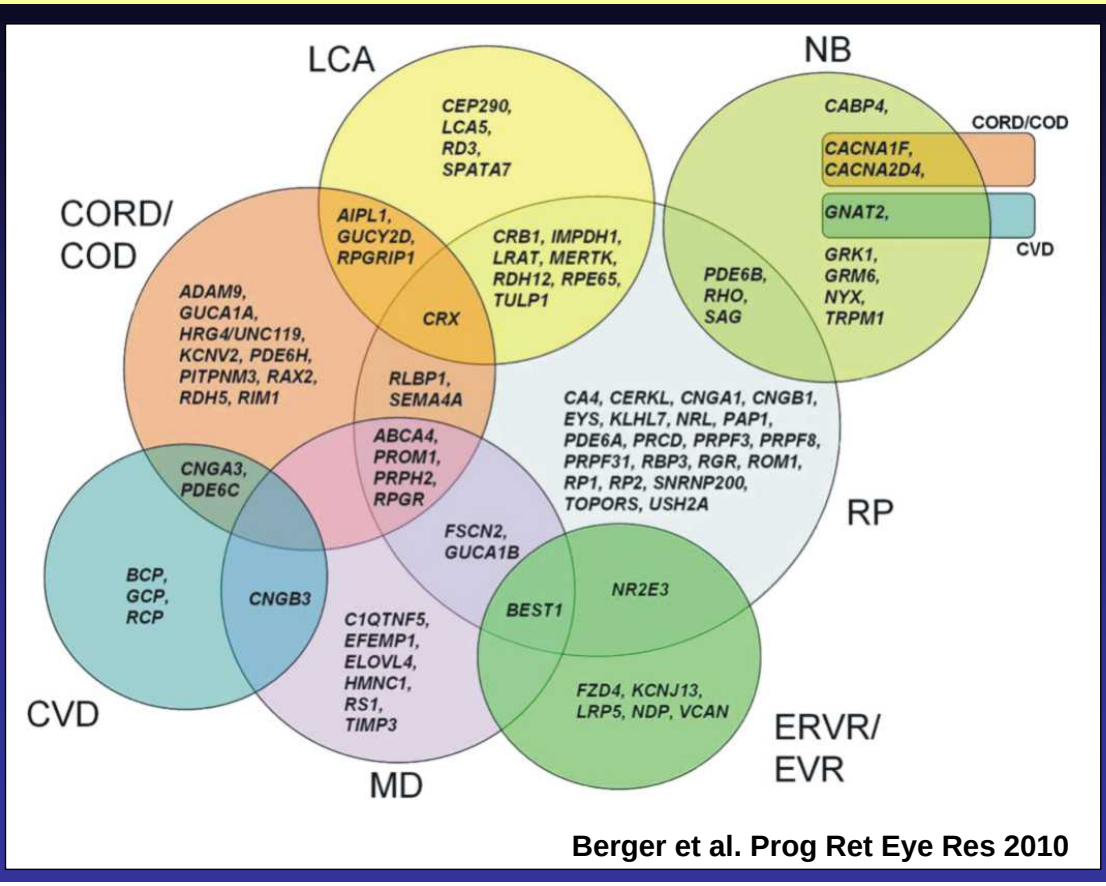

Berger et al. Prog Ret Eye Res 2010

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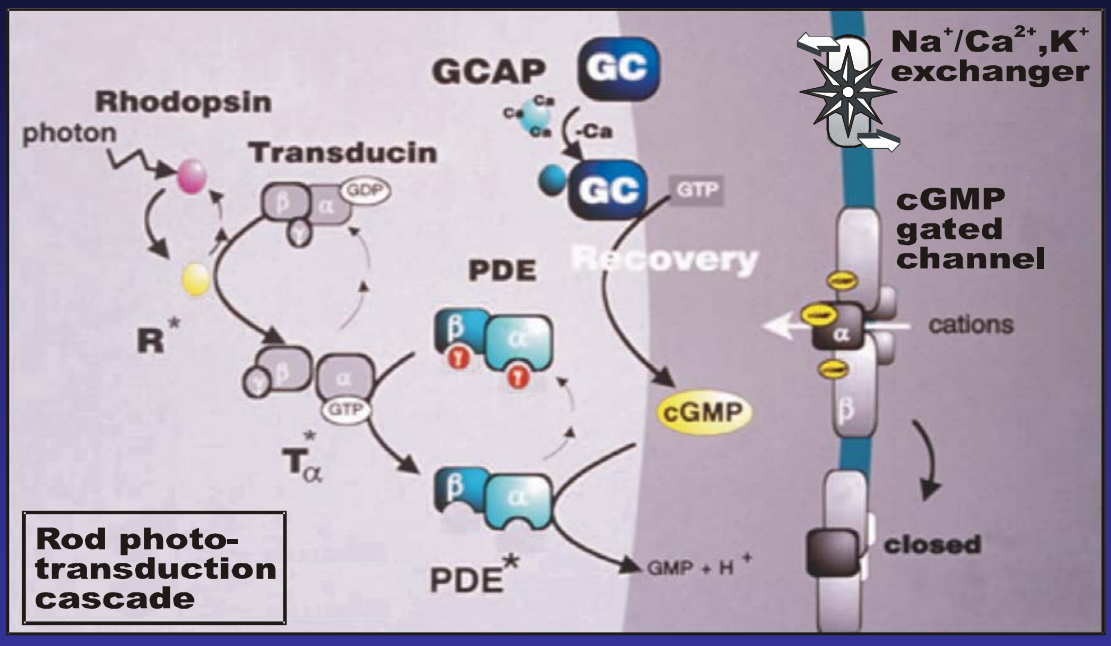
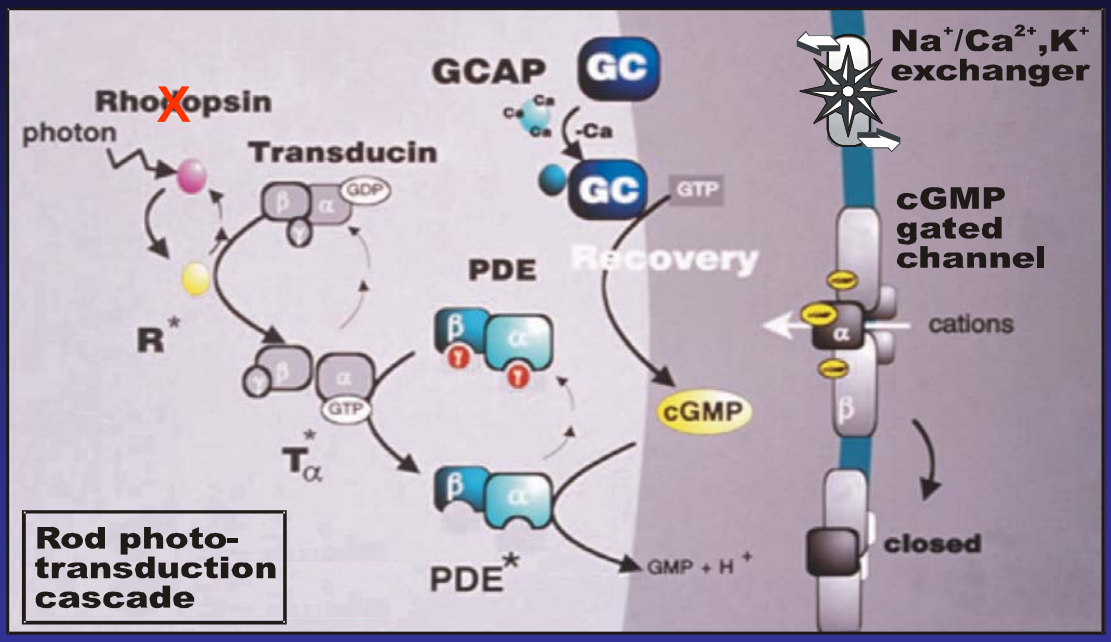
The phototransduction cascade in rods



rho$^{-/-}$: knock-out of the rod opsin

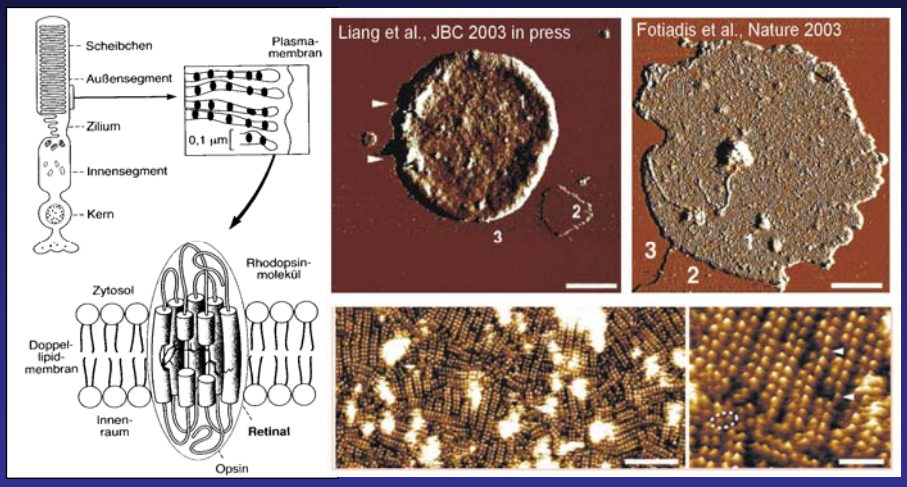


⇒ rod photoreceptor function loss

rho-/-

causing
a recessive form of
retinitis pigmentosa

Lack of opsin in rods



rho-/-

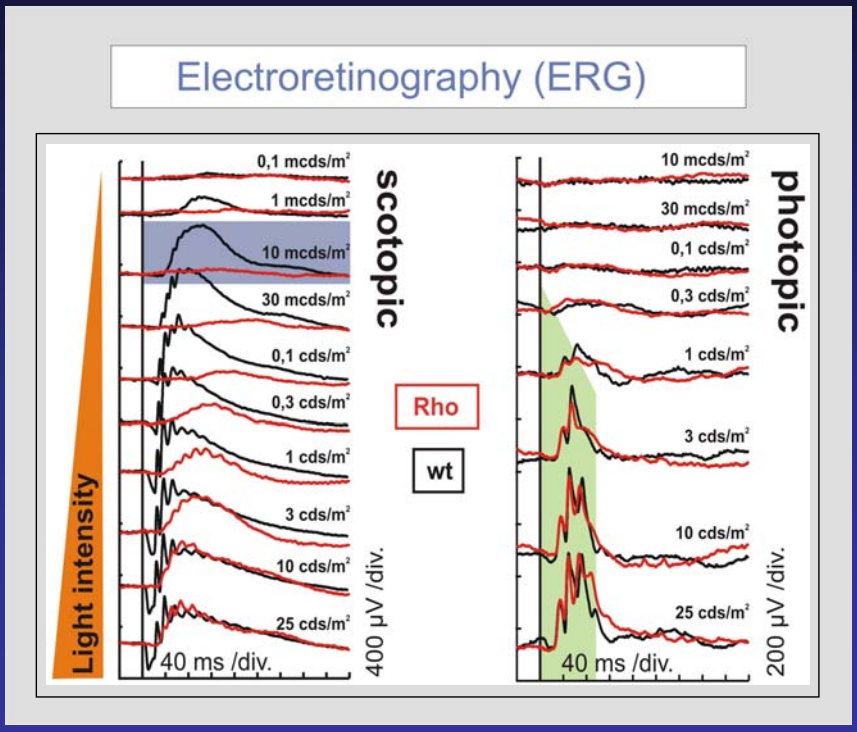
causing
a recessive form of
retinitis pigmentosa

ERG:

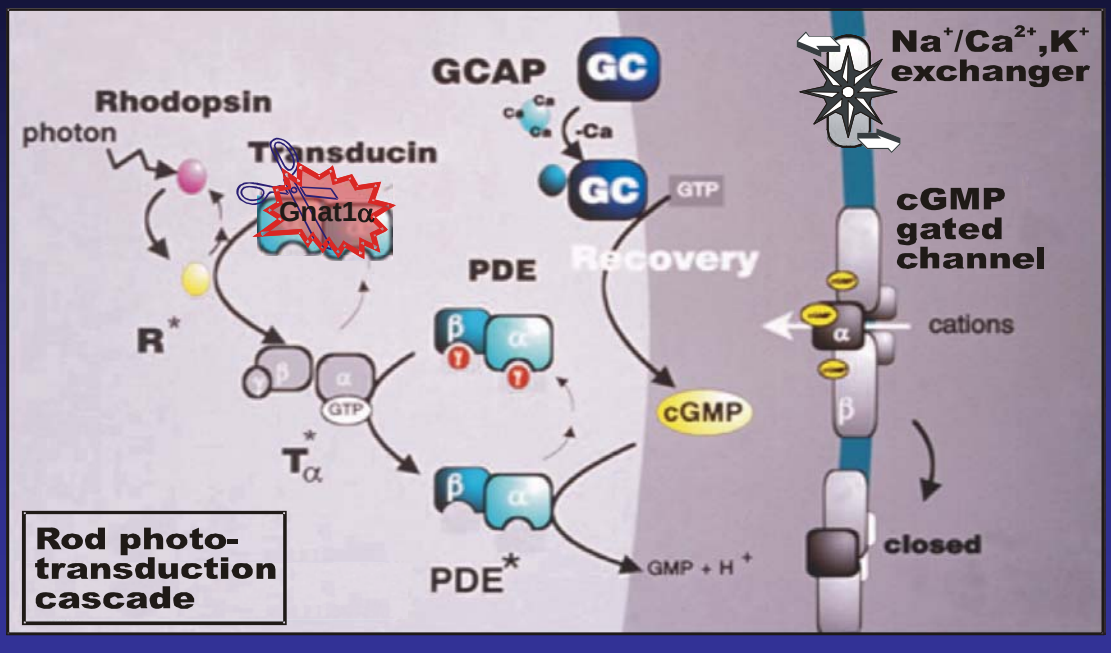
no rod function

initially normal cone system function

Lack of opsin in rods

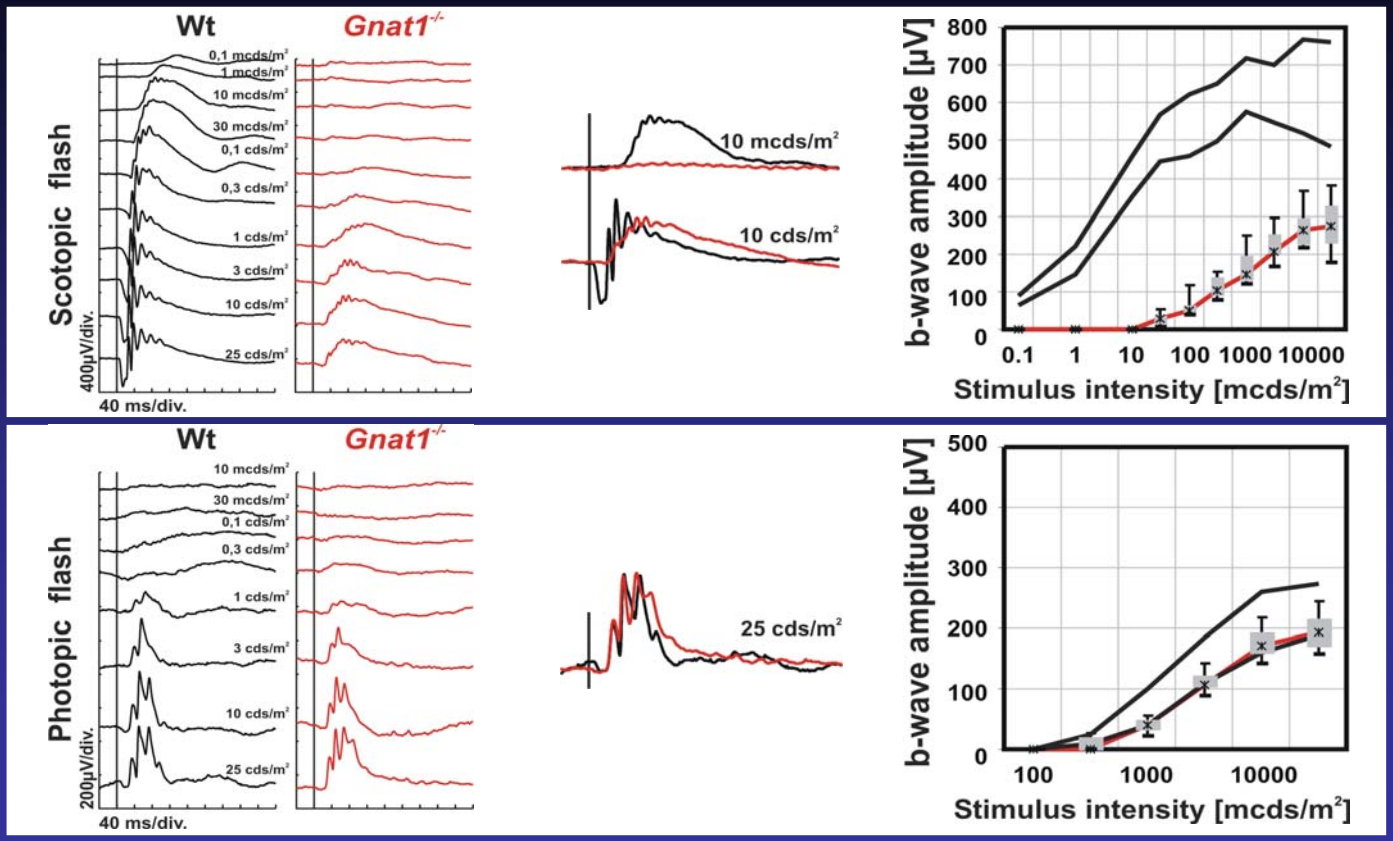


Gnat1$\alpha^{-/-}$: knock-out of the rod transducin α-subunit

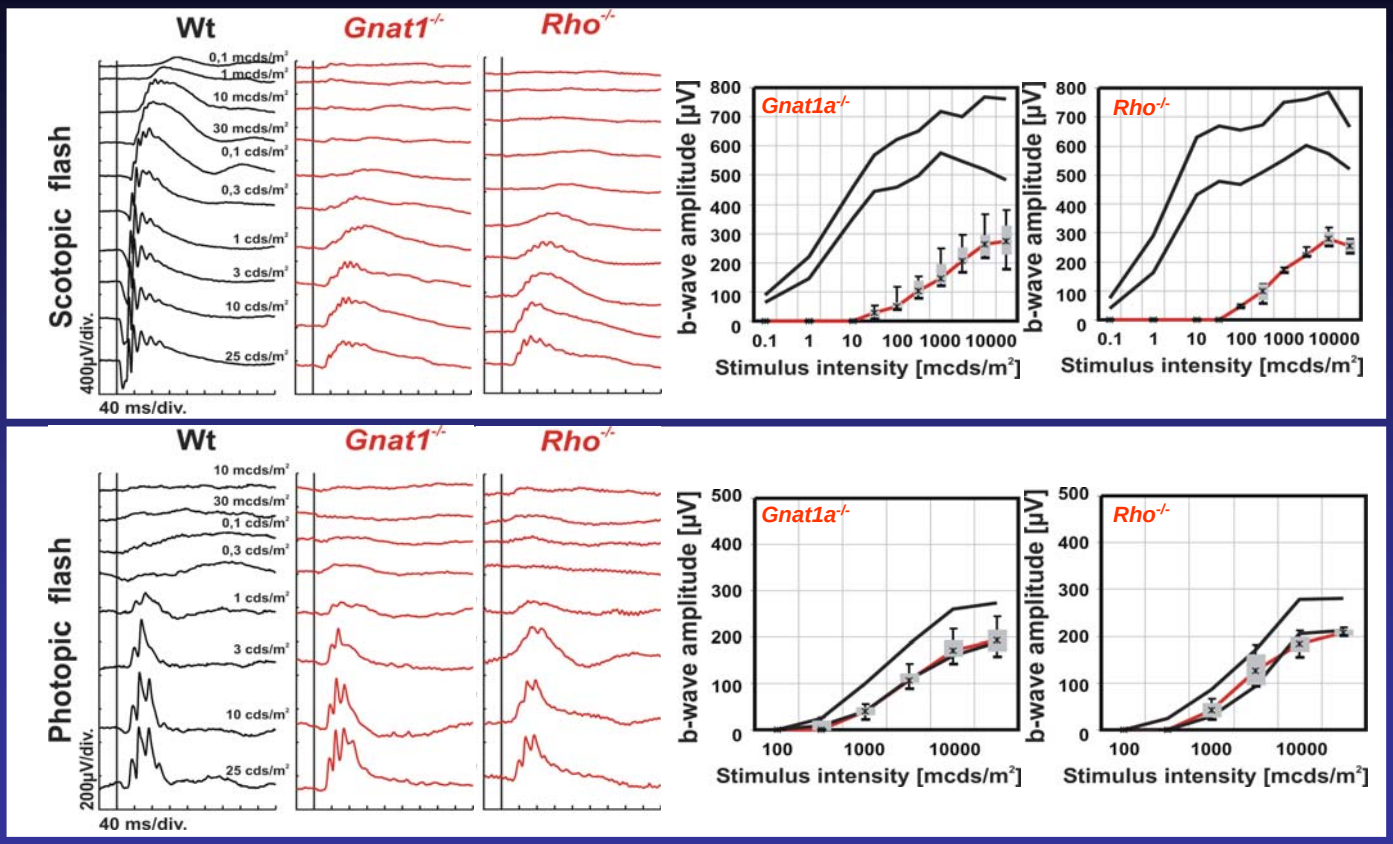


⇒ rod photoreceptor function loss

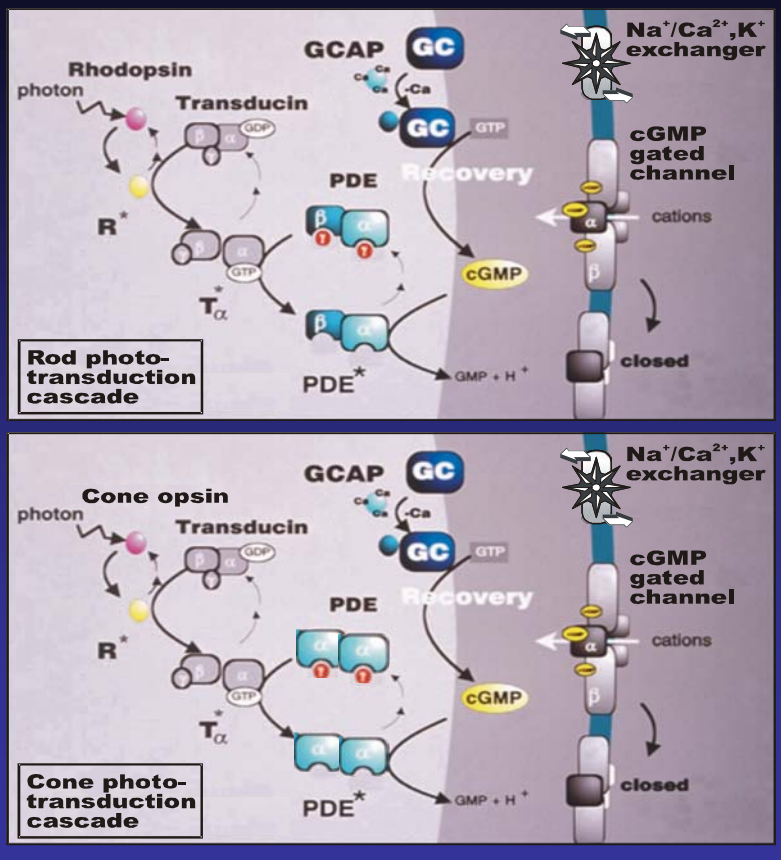
ERG in *Gnat1*$\alpha^{-/-}$ mice – scotopic and photopic flash



ERG in *Gnat1*$\alpha^{-/-}$ mice – Comparison to *Rho*$^{-/-}$



Phototransduction cascade: Rods vs. cones



Rod photoreceptor:

- rod opsin
- PDE: α-β-catalytic subunits
- Cng1 channel (3α, 1β)

Cone photoreceptor:

- cone opsins
- PDE: 2 α´-catalytic subunits
- Cng3 channel (2α, 2β)

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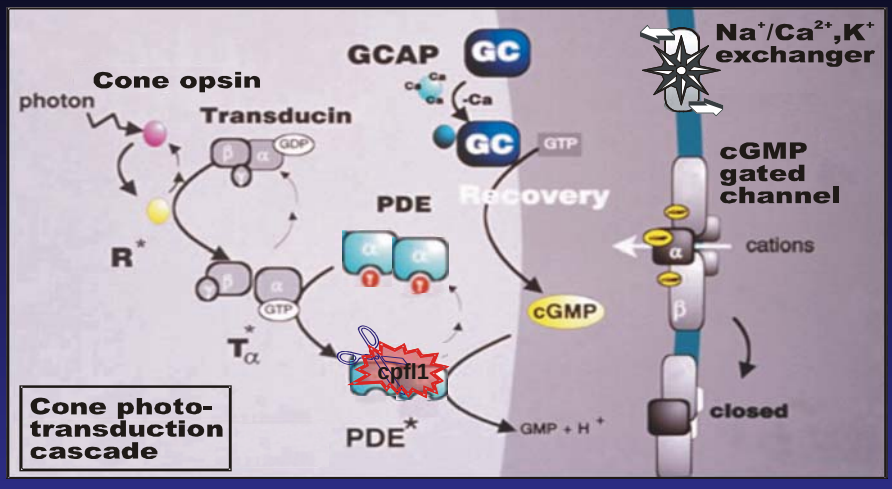
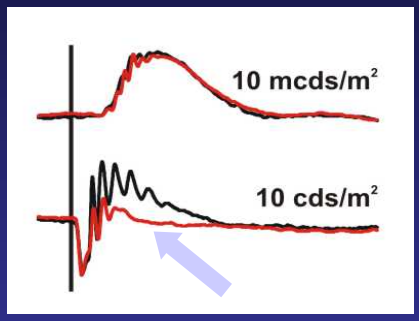
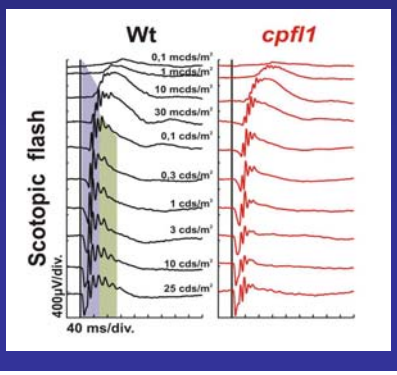
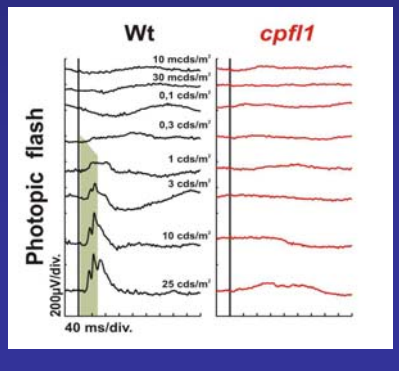
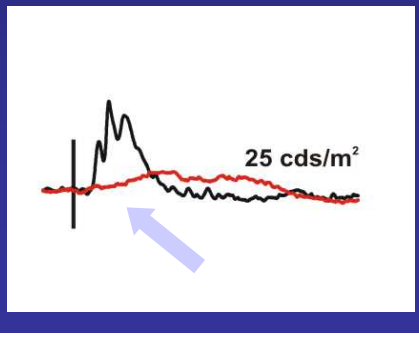


cpfl1:
Dysfunction of the PDE-α´ subunit in cone outer segments

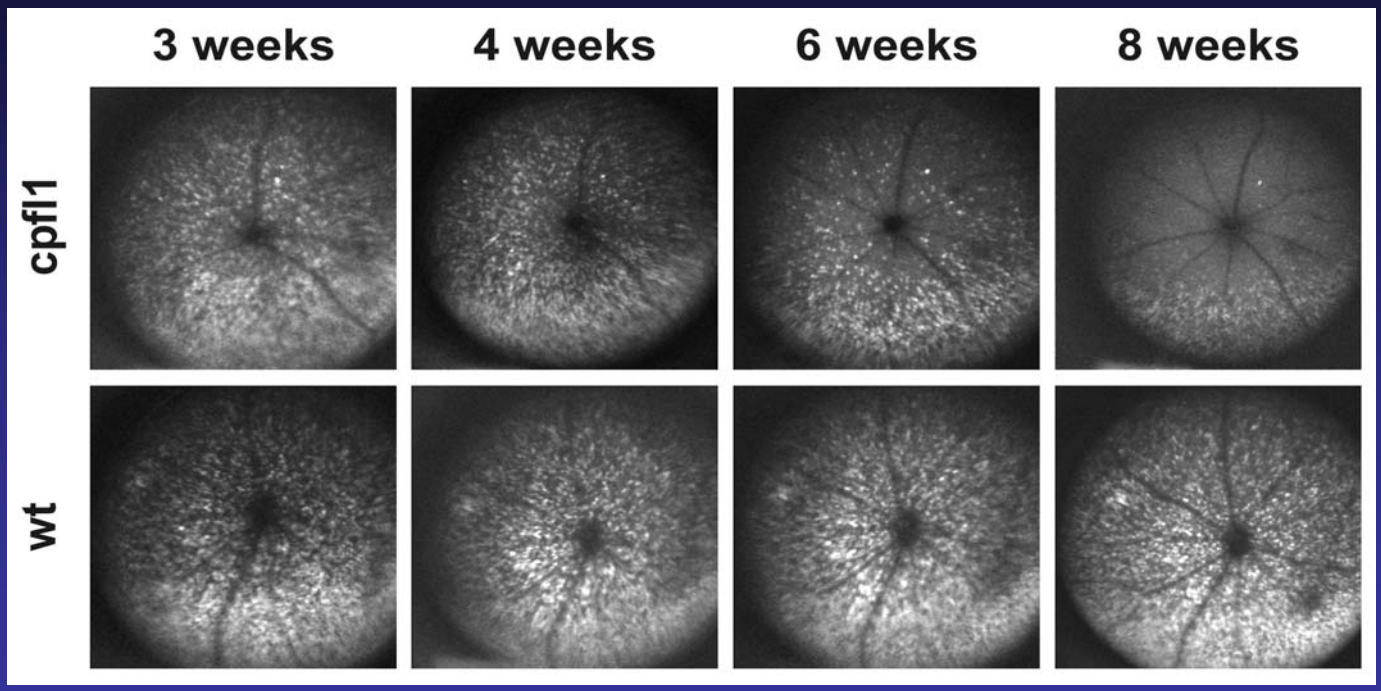








Course of cone degeneration revealed by cross-breeding with RG-GFP transgenics



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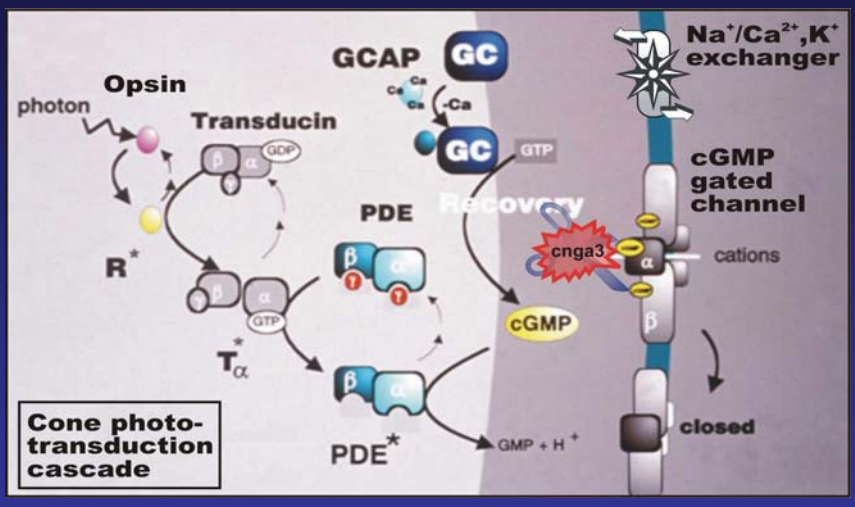
Cnga3-/-

causing achromatopsia (total colorblindness)

Lack of cGMP-gated channels in cones



Cnga3-/-

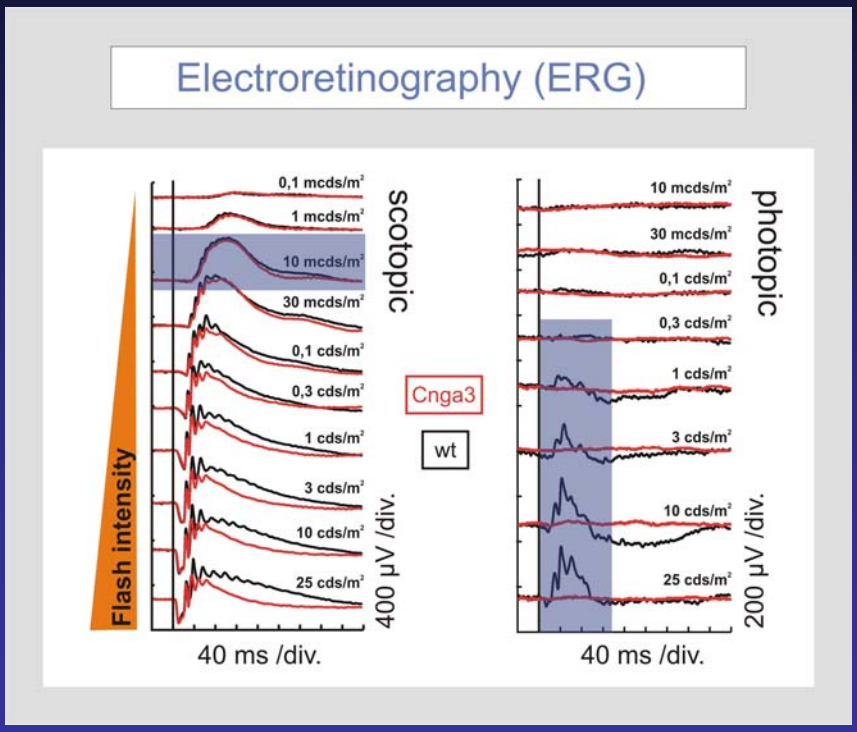
causing achromatopsia (total colorblindness)

ERG:

normal rod system

no cone function

Lack of cGMP-gated channels in cones



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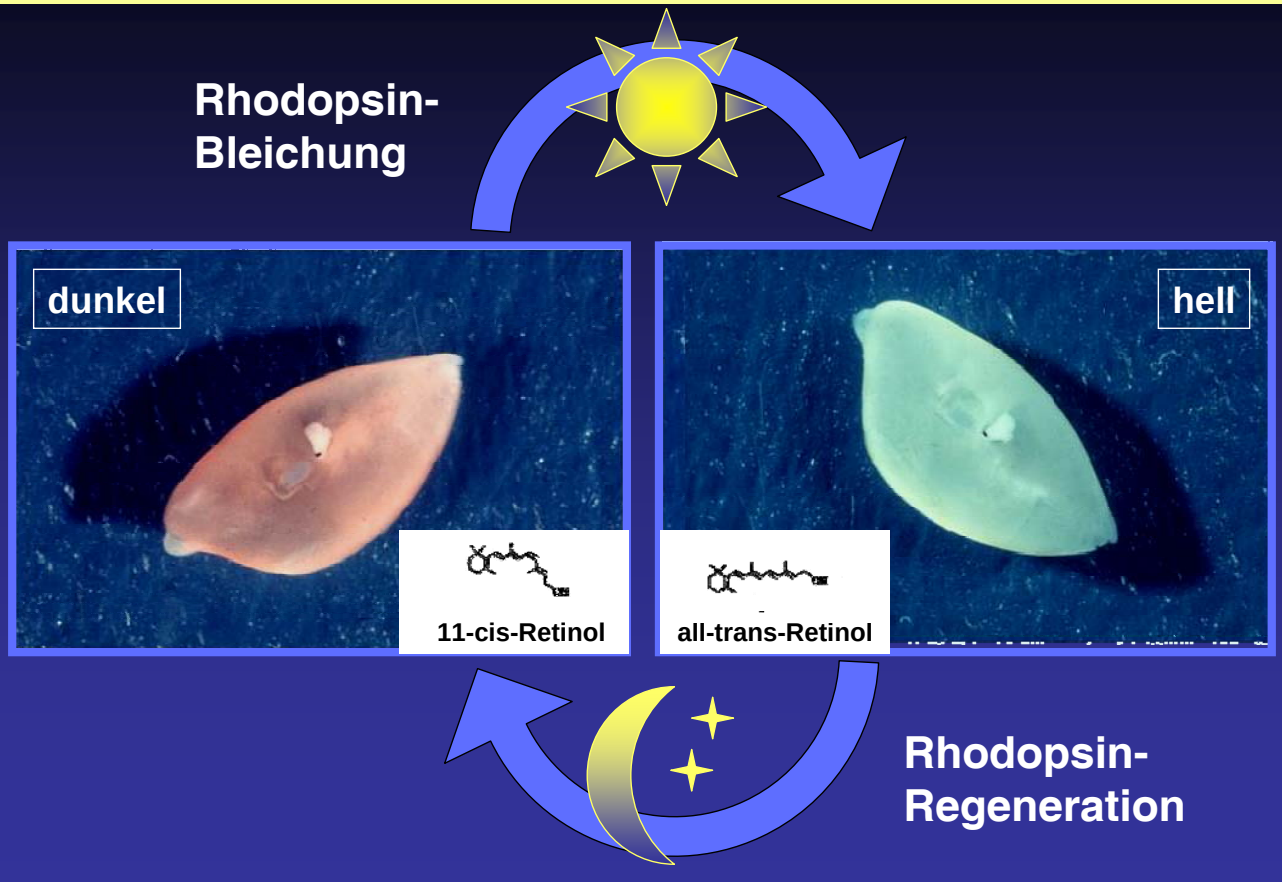
The role of Vitamin A for vision



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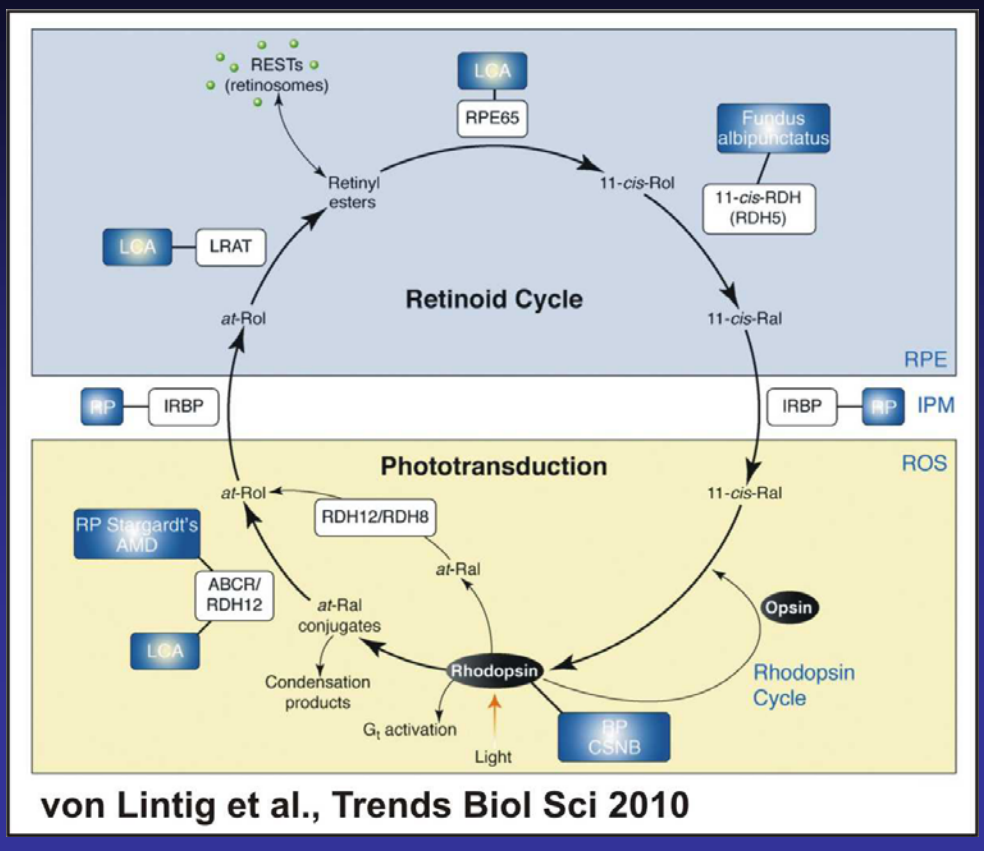
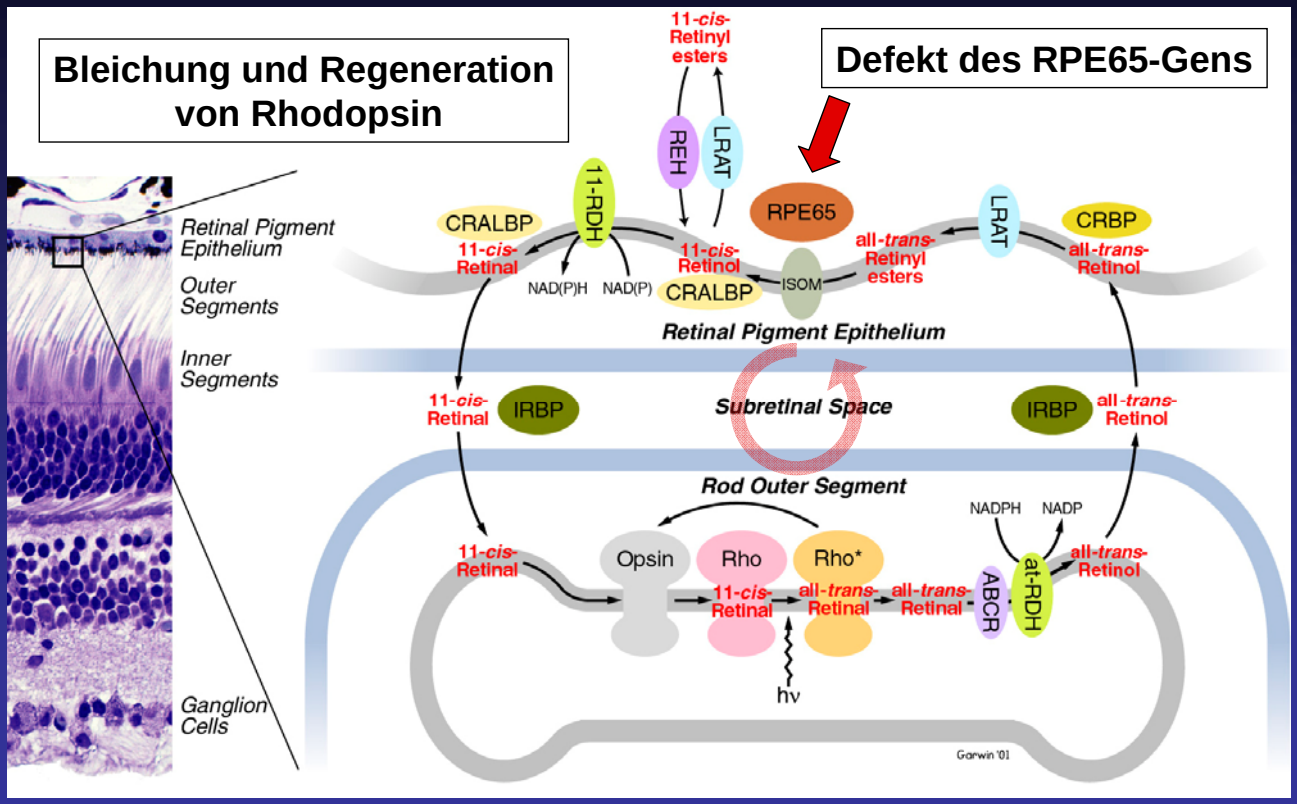


Bleichung und Regeneration von Rhodopsin

Defekt des RPE65-Gens



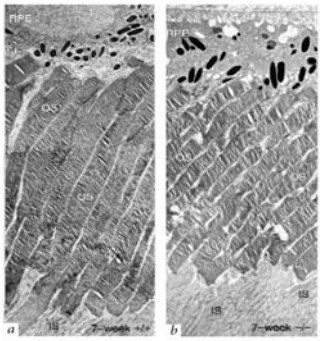
Pathophysiology of LCA due to RPE65$^{-/-}$ deficiency

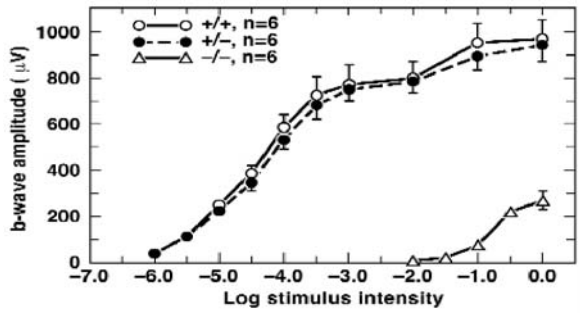
article

Rpe65 is necessary for production of 11-*cis*-vitamin A in the retinal visual cycle

T. Michael Redmond[1], Shirley Yu[1], Eric Lee[2], Dean Bok[3], Duco Hamasaki[4], Ning Chen[5], Patrice Goletz[5], Jian-Xing Ma[5], Rosalie K. Crouch[5] & Karl Pfeifer[2]

Mutation of *RPE65* can cause severe blindness from birth or early childhood, and RPE65 protein is associated with retinal pigment epithelium (RPE) vitamin A metabolism. Here, we show that *Rpe65*-deficient mice exhibit changes in retinal physiology and biochemistry. Outer segment discs of rod photoreceptors in *Rpe65*$^{-/-}$ mice are disorganized compared with those of *Rpe65*$^{+/+}$ and *Rpe65*$^{+/-}$ mice. Rod function, as measured by electroretinography, is abolished in *Rpe65*$^{-/-}$ mice, although cone function remains. *Rpe65*$^{-/-}$ mice lack rhodopsin, but not opsin apoprotein. Furthermore, all-*trans*-retinyl esters over-accumulate in the RPE of *Rpe65*$^{-/-}$ mice, whereas 11-*cis*-retinyl esters are absent. Disruption of the RPE-based metabolism of all-*trans*-retinyl esters to 11-*cis*-retinal thus appears to underlie the *Rpe65*$^{-/-}$ phenotype, although cone pigment regeneration may be dependent on a separate pathway.



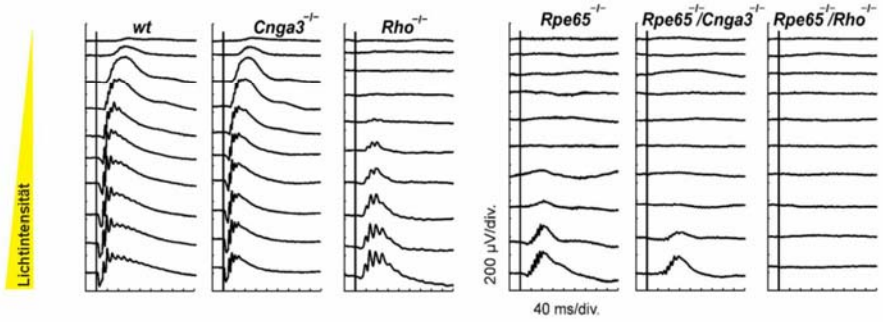


letter

New views on RPE65 deficiency: the rod system is the source of vision in a mouse model of Leber congenital amaurosis

Mathias W. Seeliger[1,*], Christian Grimm[2], Fredrik Ståhlberg[1,3], Christoph Friedburg[1], Gesine Jaissle[1], Eberhart Zrenner[1], Hao Guo[1], Charlotte E. Remé[2], Peter Humphries[4], Franz Hofmann[5], Martin Biel[6], Robert N. Fariss[7], T. Michael Redmond[8] & Andreas Wenzel[2,*]

Published online: 20 August 2001, DOI: 10.1038/ng712



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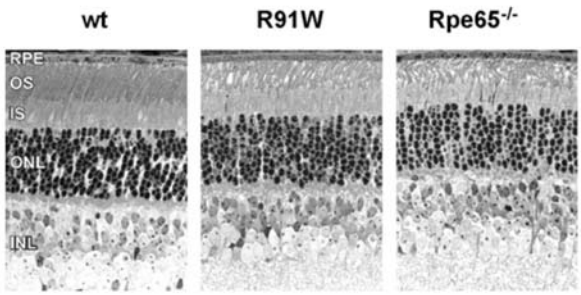
Retinal vitamin A deficiency: RPE65 R91W mutant mouse characteristics



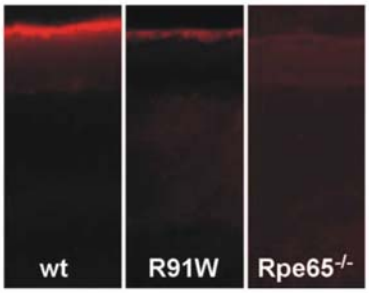
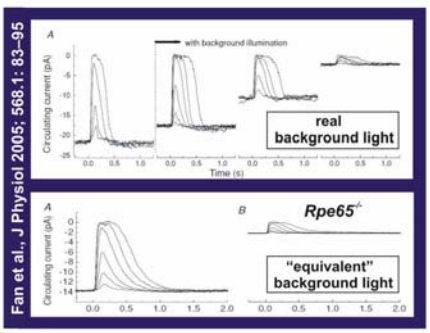


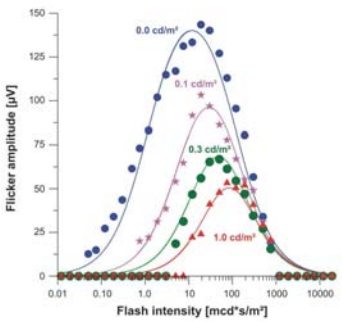
Table 1. Retinoid analysis

	Age	11-*cis*-retinal	Retinyl ester
Wild-type	4	380.2 ± 60.1	30.6 ± 5.6
	8	336.1 ± 21.8	39.2 ± 5.0
	12	336.7 ± 32.4	34.9 ± 4.6
	24	373.6 ± 75.5	106.2 ± 27.2
R91W	4	24.0 ± 3.0	420.7 ± 34.5
	8	15.4 ± 0.2	651.9 ± 127.4
	12	13.5 ± 0.2	1542.7 ± 271.8
	24	9.4 ± 8.2	2186.1 ± 160.1
	40	18.2 ± 4.8	2107.9 ± 138.9
Rpe65$^{-/-}$	4	n.d.	271.4 ± 22.8
	8	n.d.	474.9 ± 49.1
	12	n.d.	805.9 ± 57.5
	24	n.d.	1160.6 ± 529.0
	40	n.d.	2622.9 ± 531.3

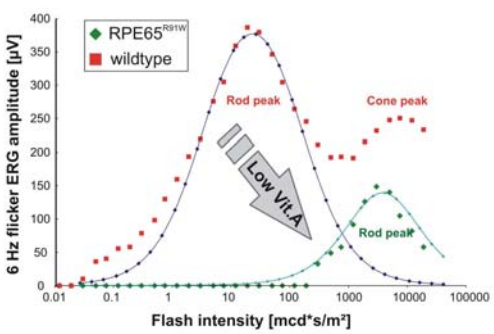
All values are given in pmol/eye ± SD ($n = 3$). Age in weeks, as indicated. n.d., not detectable.

The equivalent light effect on the rod ERG



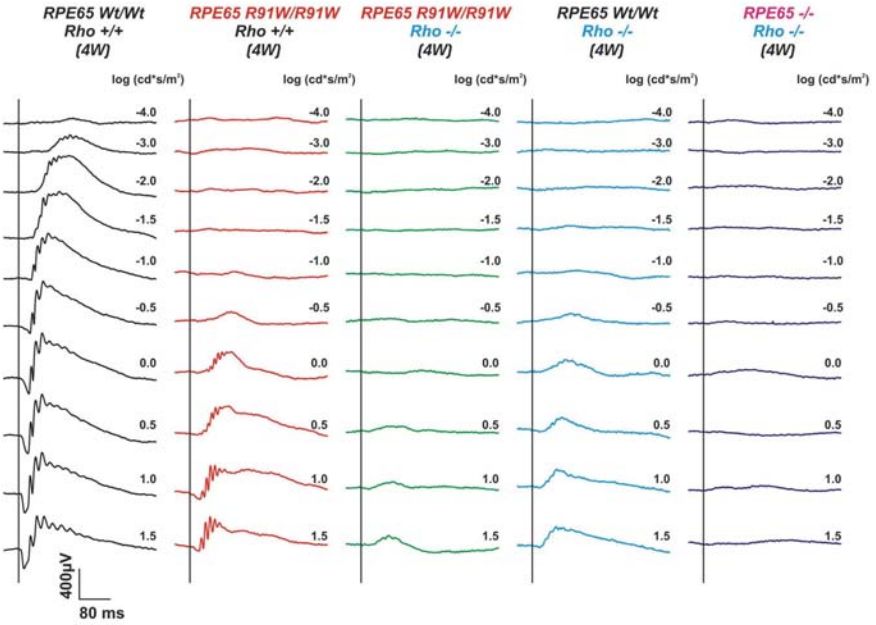


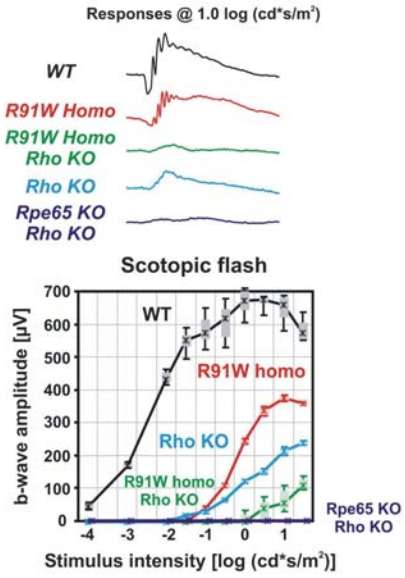
Summary of effects in R91W mutants



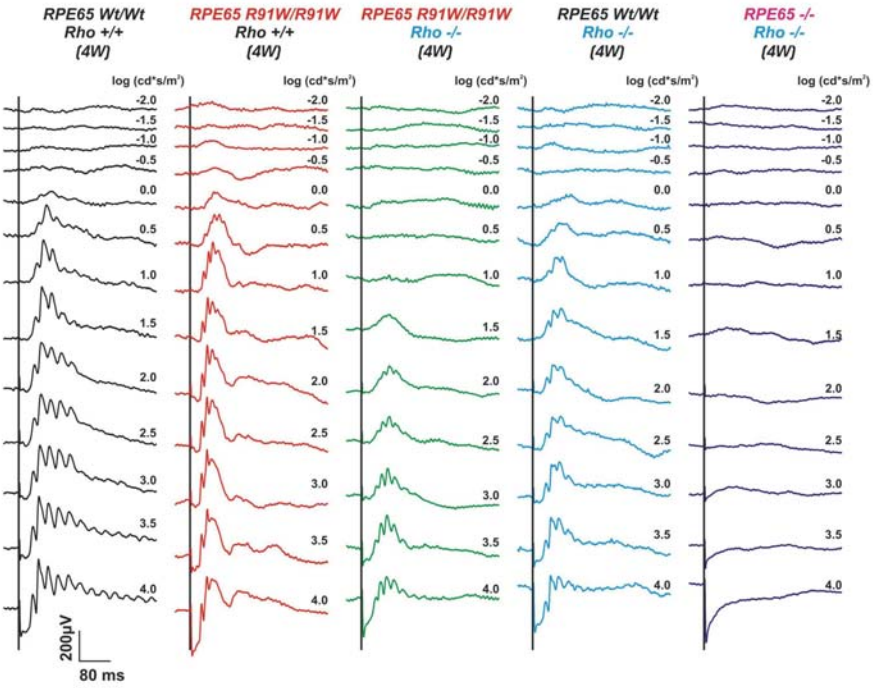
Electroretinography (ERG) in RPE65 R91W mutant mice

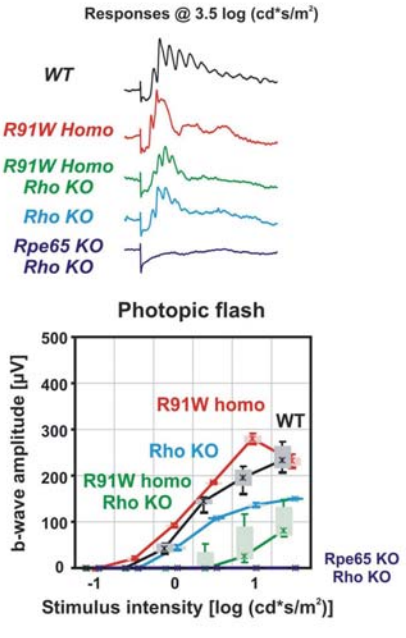
Scotopic flash ERG intensity series





Photopic flash ERG intensity series

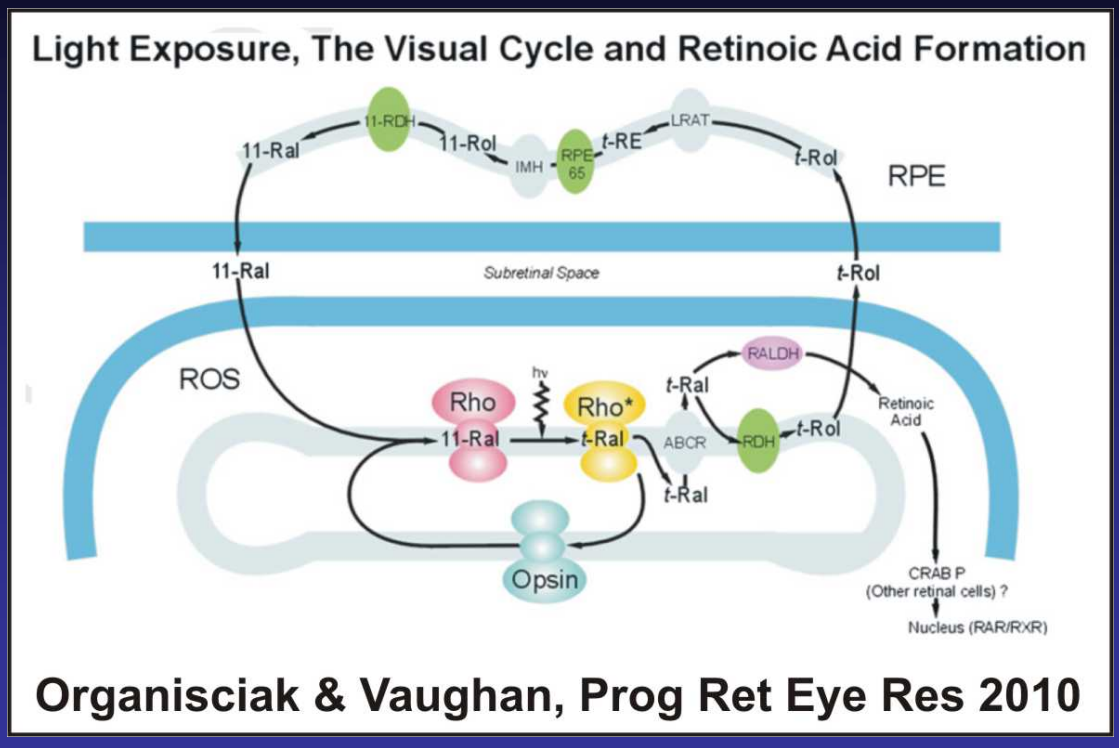




Too much light:

Light damage

Formation of vision in the outer retina May 17, 2010



Formation of vision in the outer retina

May 17, 2010

OCT

Non-invasive testing of retinal morphology

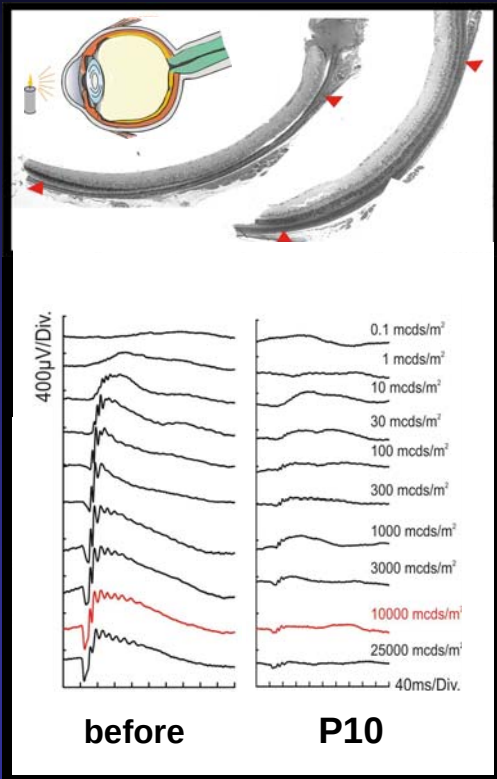
Histology-equivalent images realistic

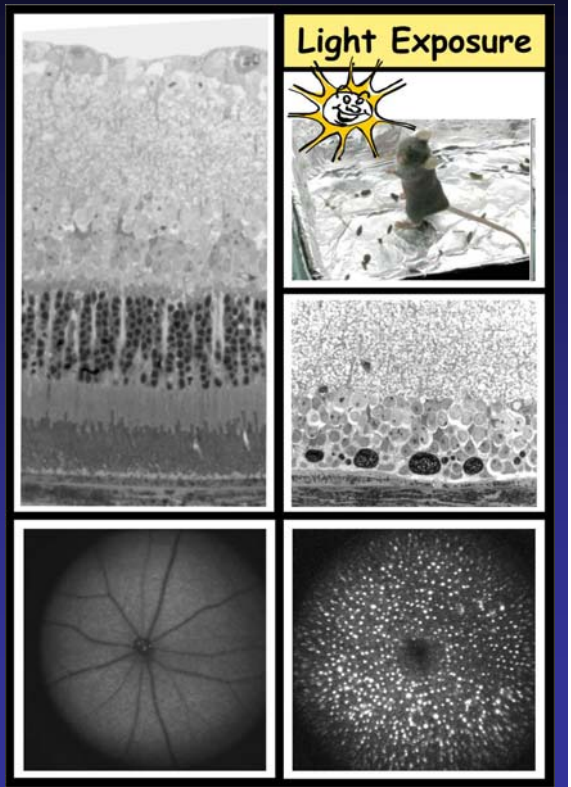
Allows sequential tests of the same individuals

Example:

Light damage model

Effects on ERG, SLO and histology





Formation of vision in the outer retina

May 17, 2010

OCT

Non-invasive testing of retinal morphology

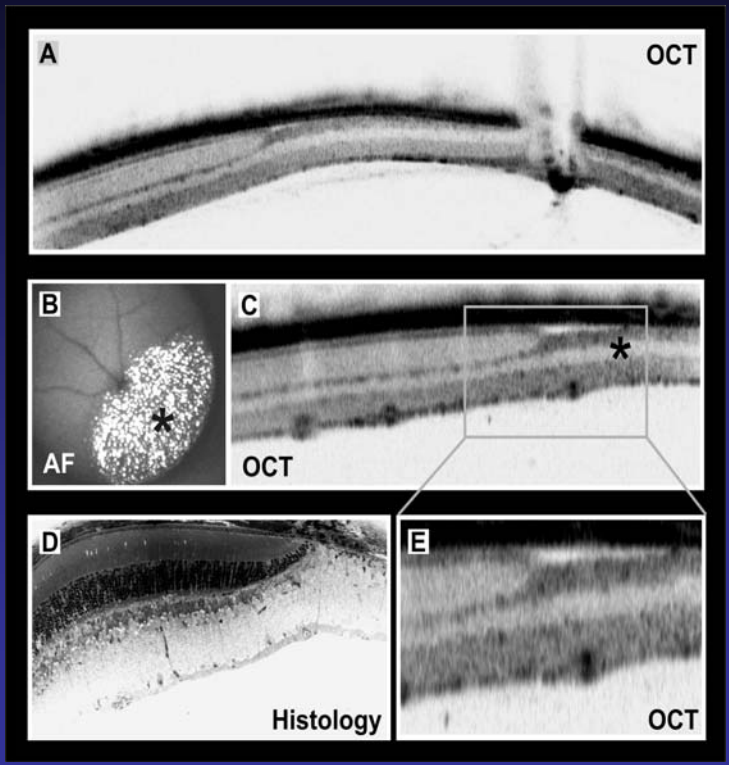
Histology-equivalent images realistic

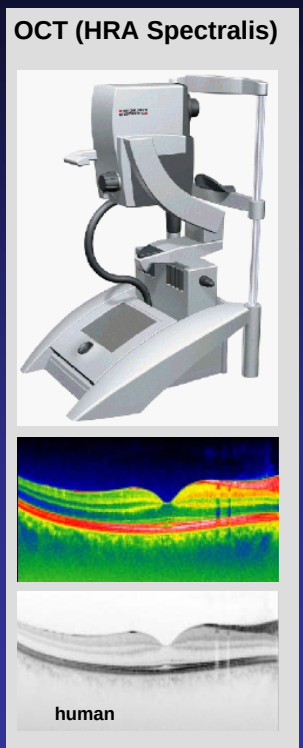
Allows sequential tests of the same individuals

Example:

Light damage

Comparison of OCT with SLO & histology at 1 wk post exposure

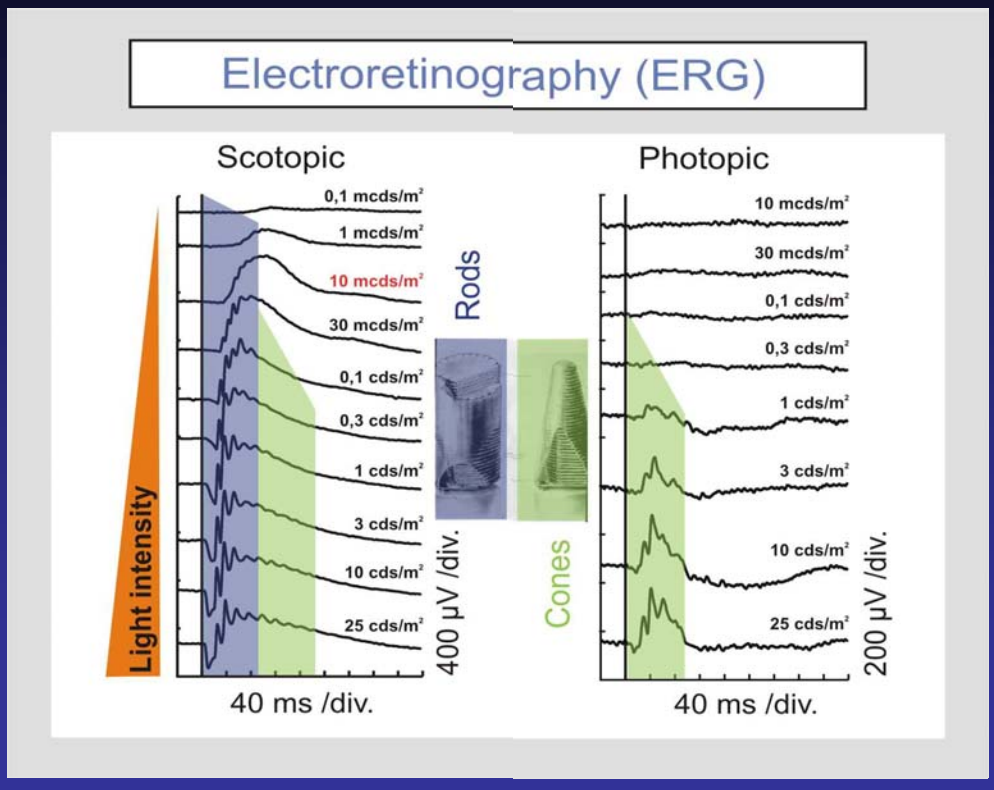




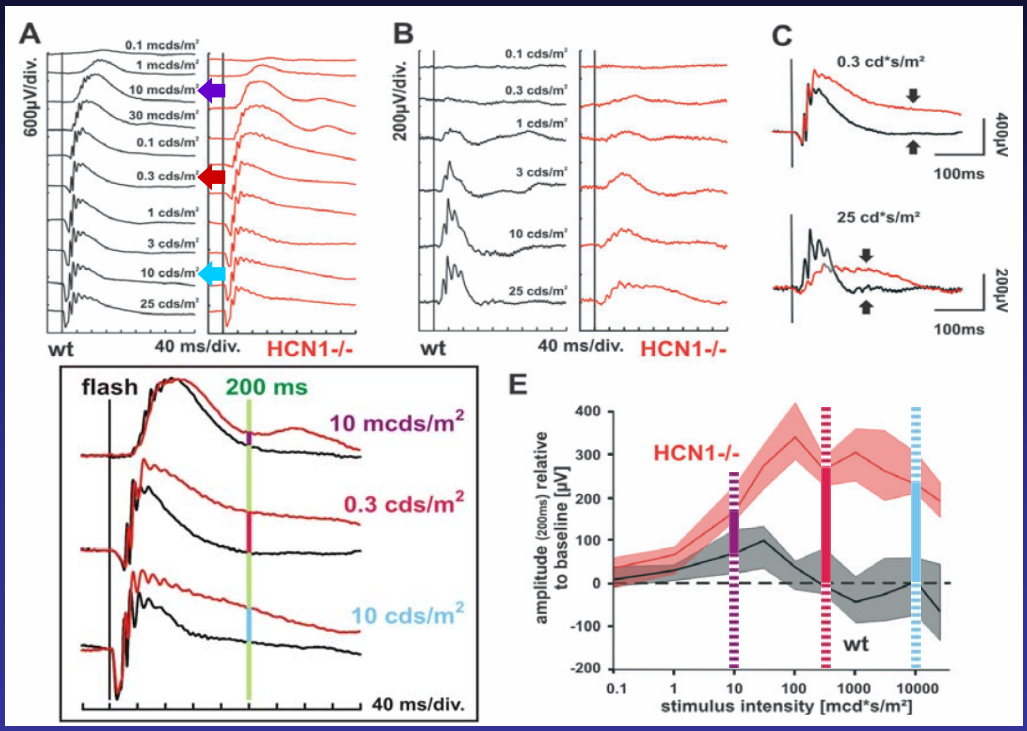
Models helping to understand retinal function:

HCN1 channel mutants

Formation of vision in the outer retina May 17, 2010



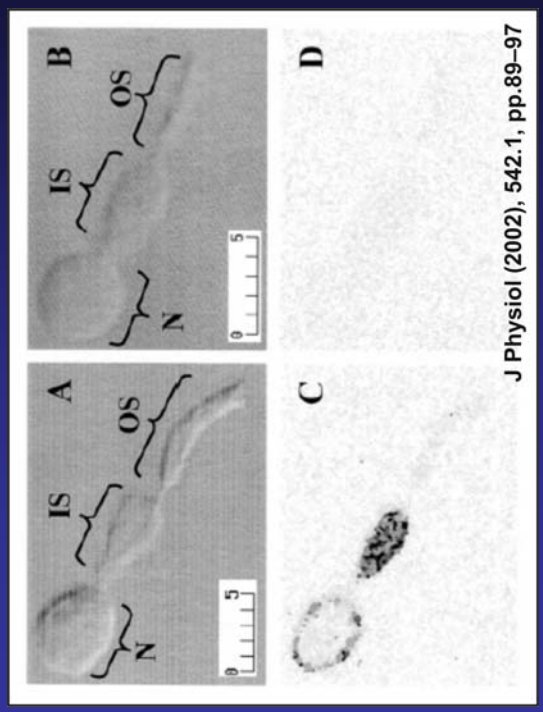
ERG in *Hcn1*$^{-/-}$ mice

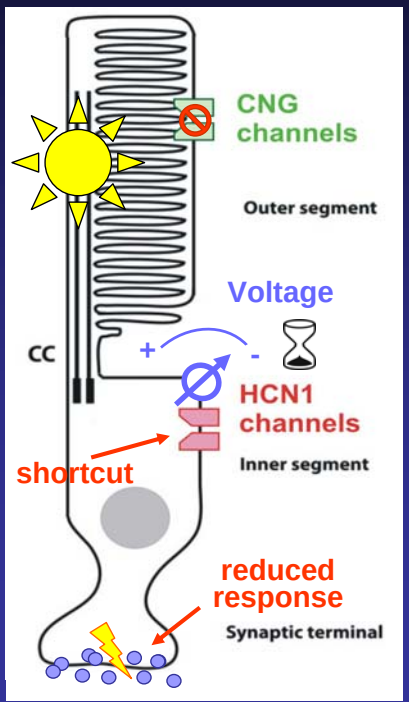


Knop et al., *Eur J Neurosci* 2008

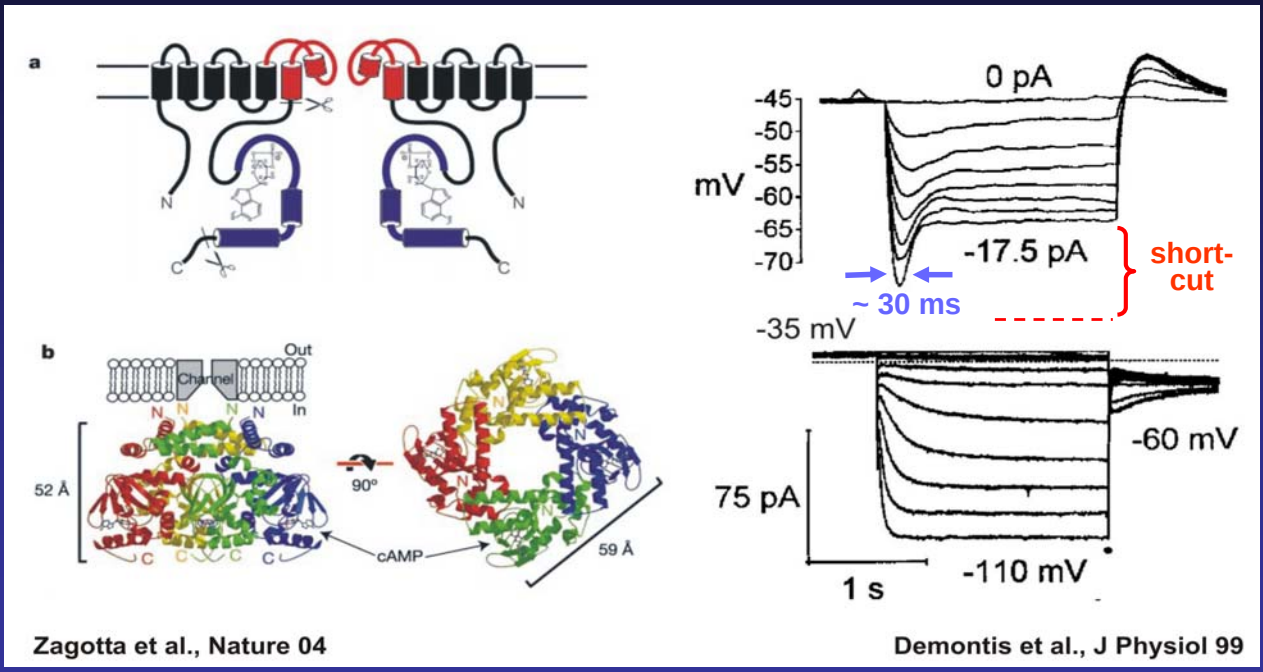
Formation of vision in the outer retina May 17, 2010

Mechanism of HCN1 channel activity in normal retina





Structure and function of HCN channels



Zagotta et al., Nature 04

Demontis et al., J Physiol 99

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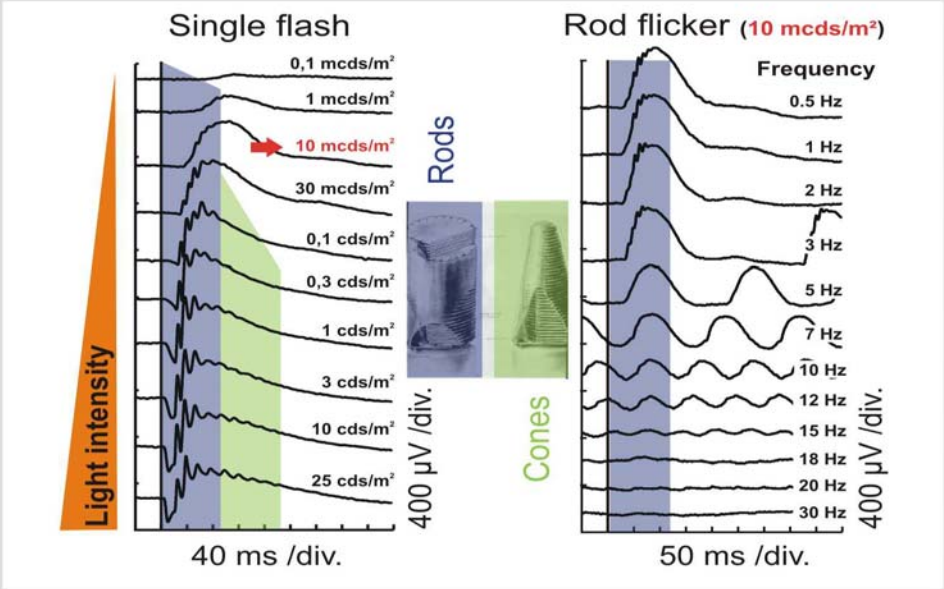
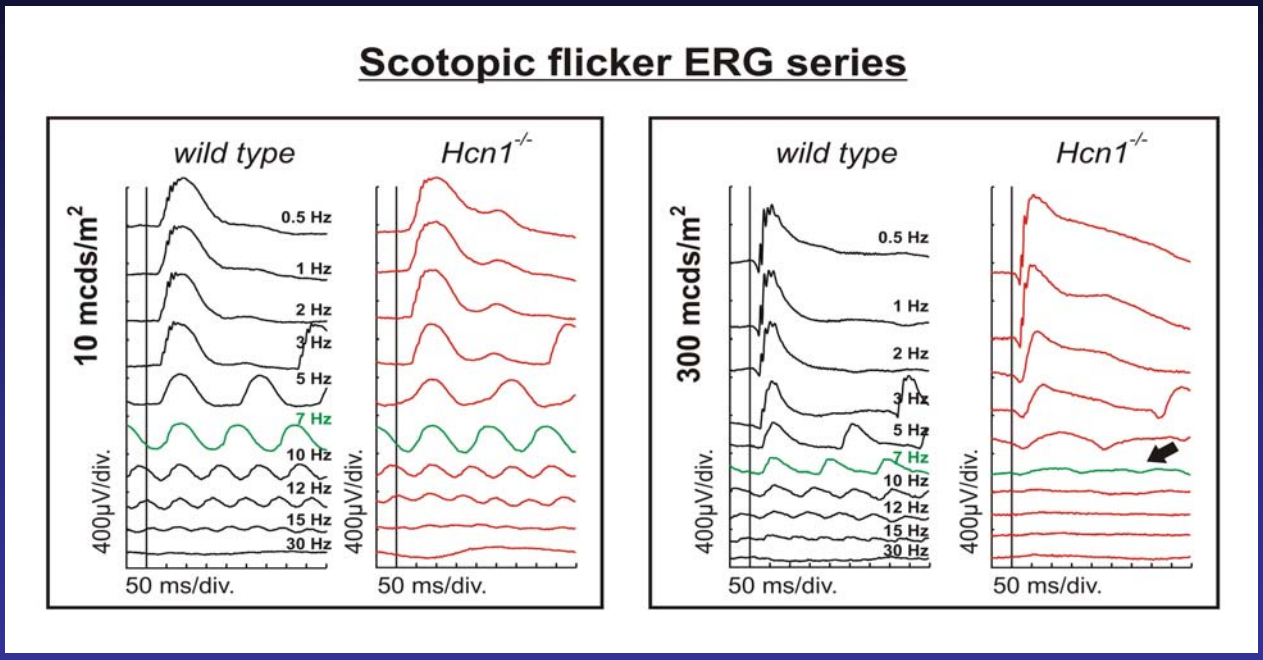
Scotopic electroretinography (ERG)





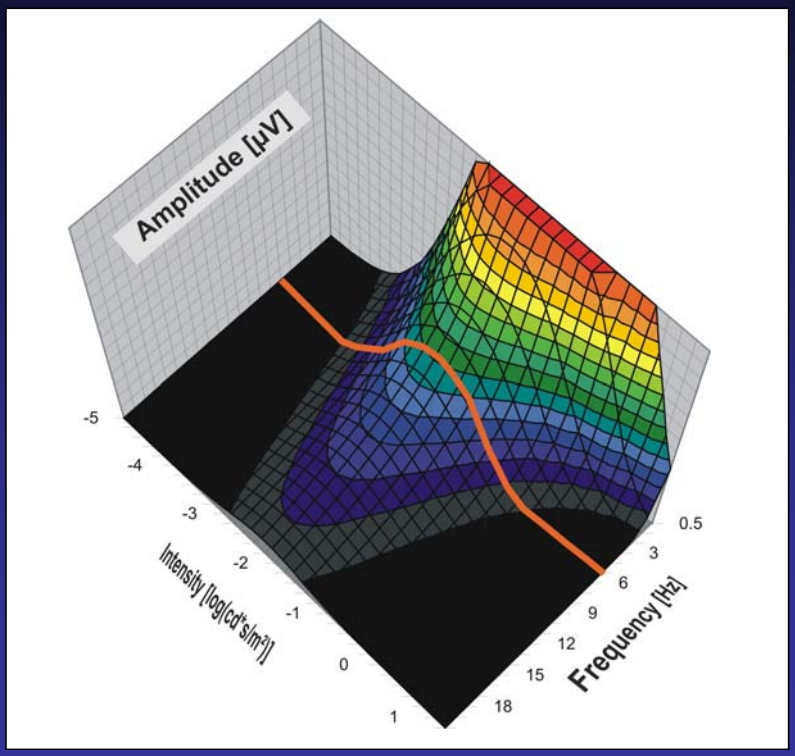
The flicker fusion frequency is lowered above HCN1 threshold.

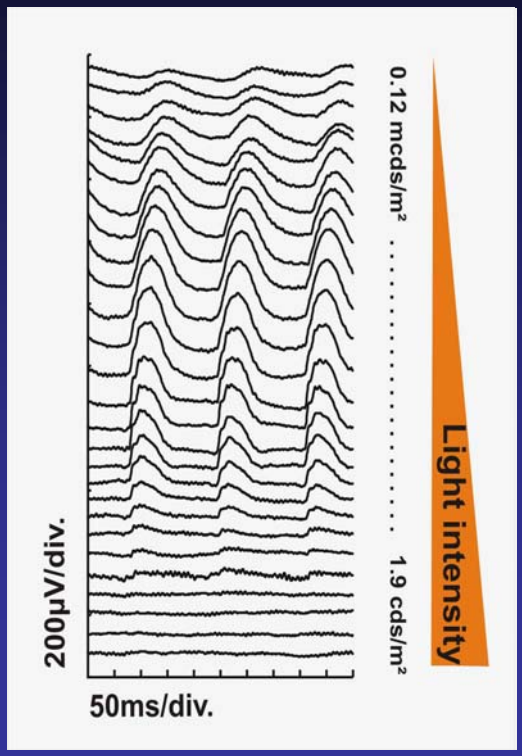
Formation of vision in the outer retina May 17, 2010

Models helping to understand retinal function:

Modelling ERG signals

Rod flicker ERG





April 29, 2008

Rod flicker ERG