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## Needs in omega 3 and ocular pathologies

Lionel Brétillon

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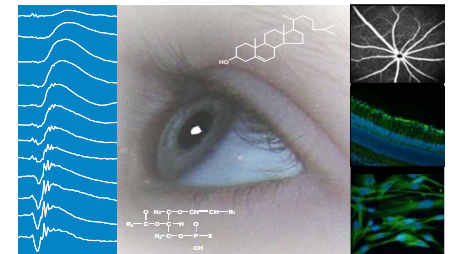
# Needs in omega-3 and ocular pathologies

Lionel BRETILLON, PhD

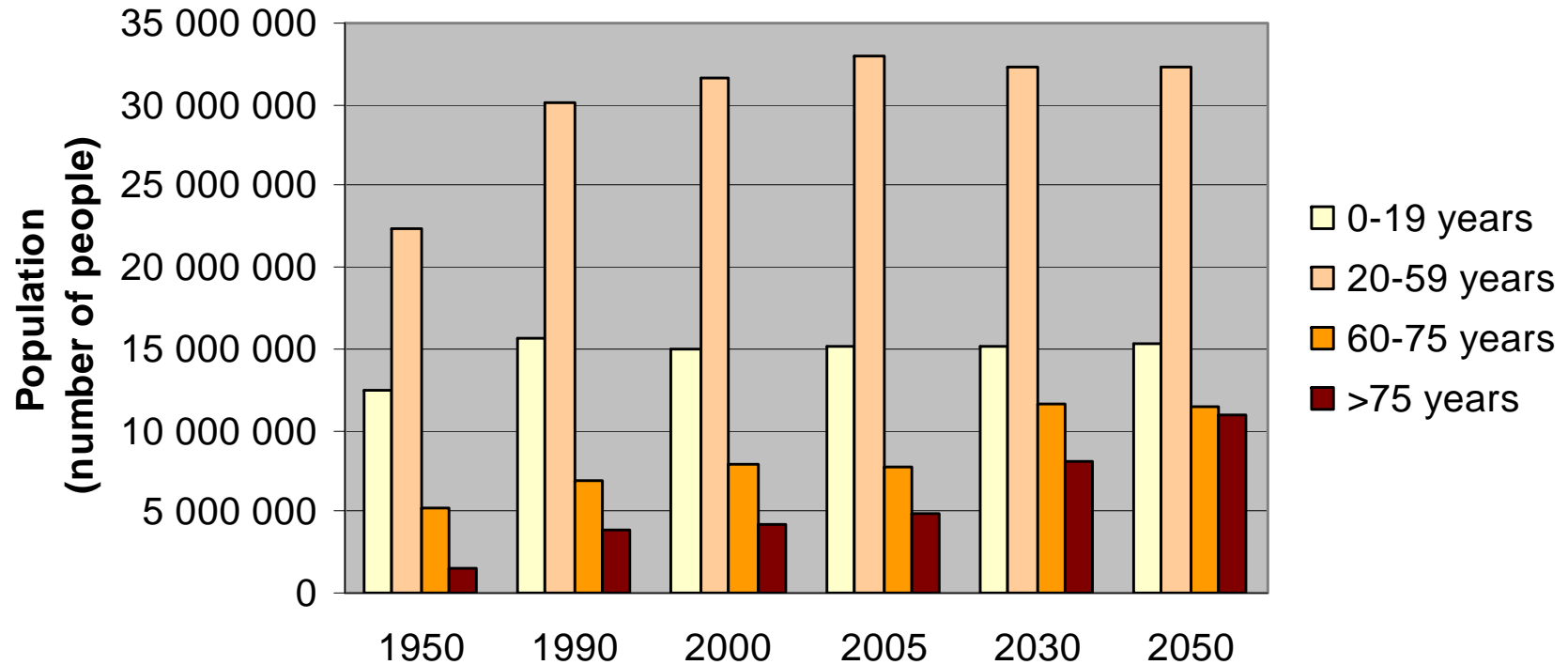
Eye & Nutrition Research Group

Dijon

FRANCE



# Aging: a socio-economic issue in the future

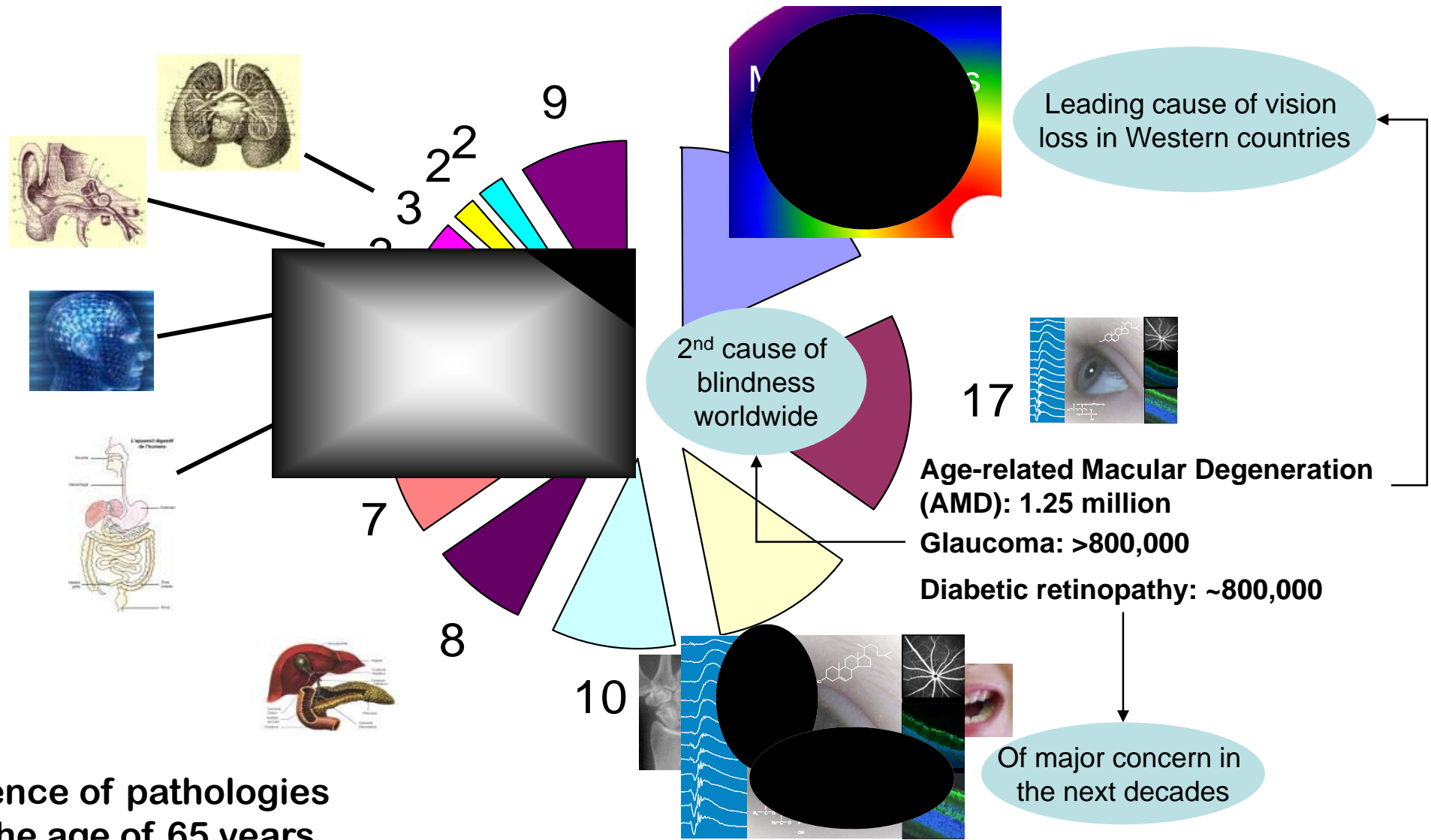


Population 2050 vs 2000

- >60 years: x2
- >75 years: x3
- >85 years: x5

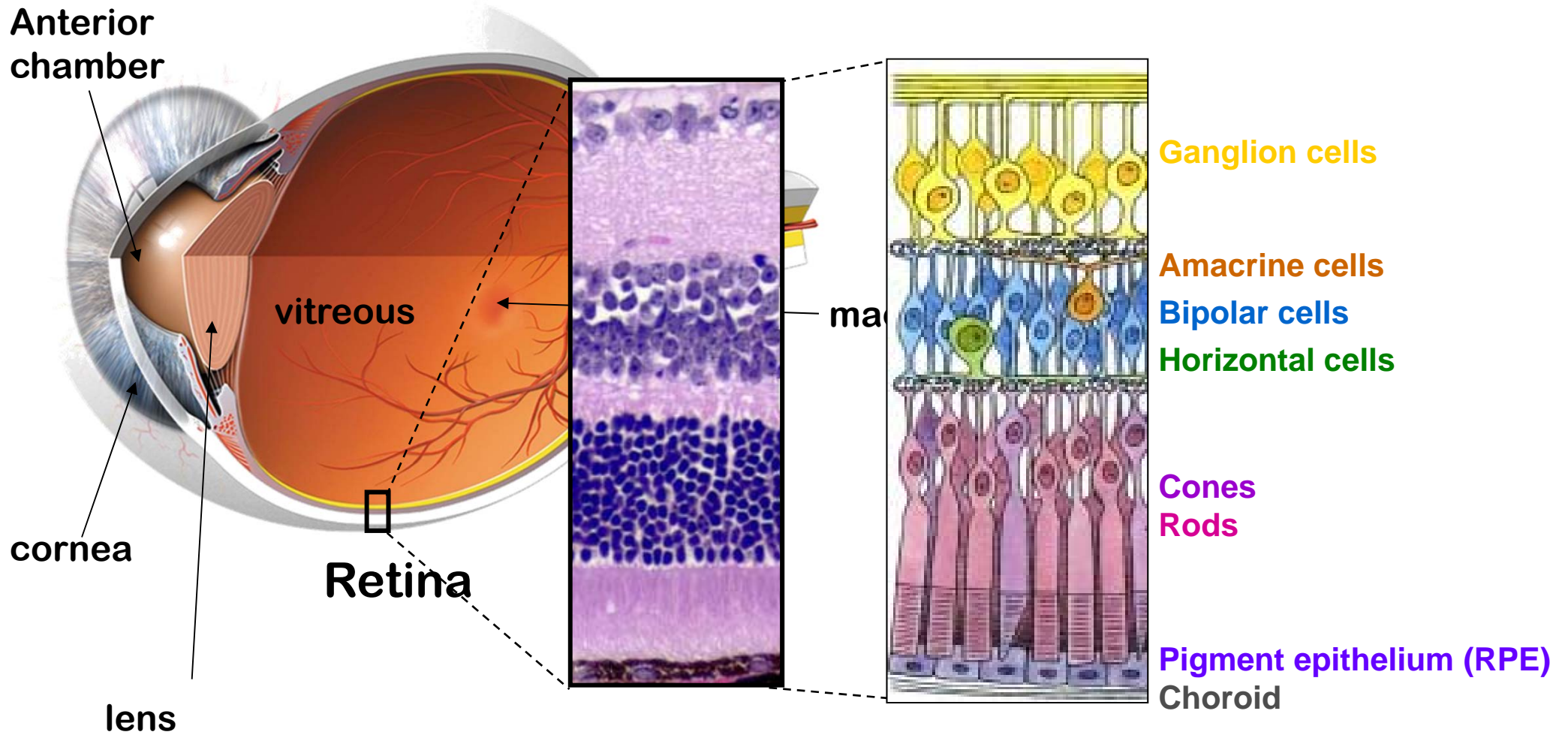
in France

# The neurosensory retina: a sensitive target of aging



Prevalence of pathologies after the age of 65 years

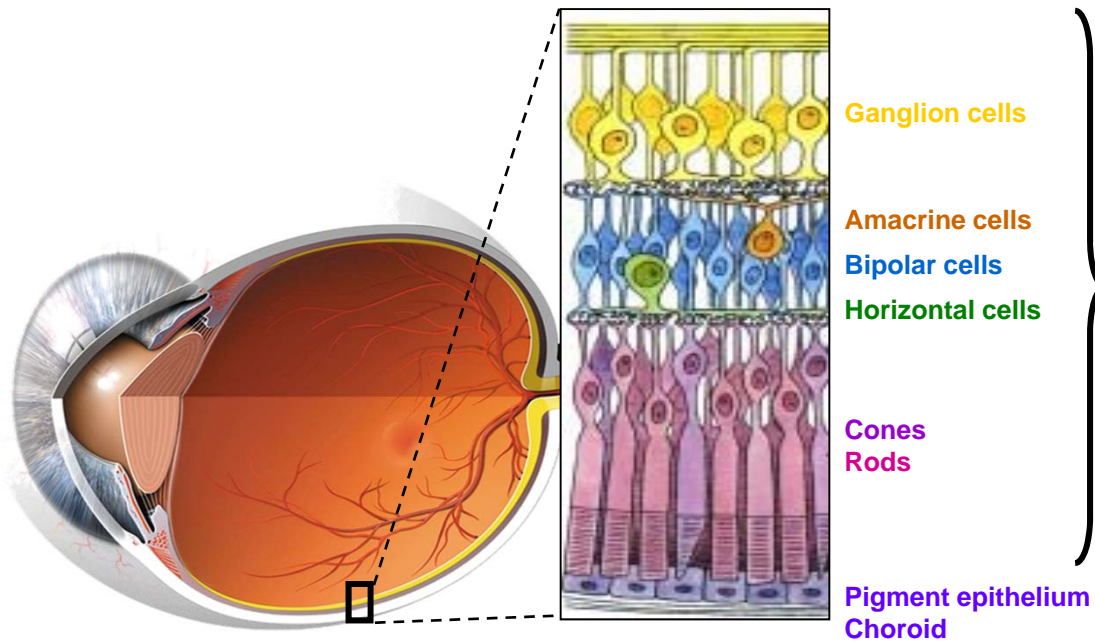
# Structural organization of the retina



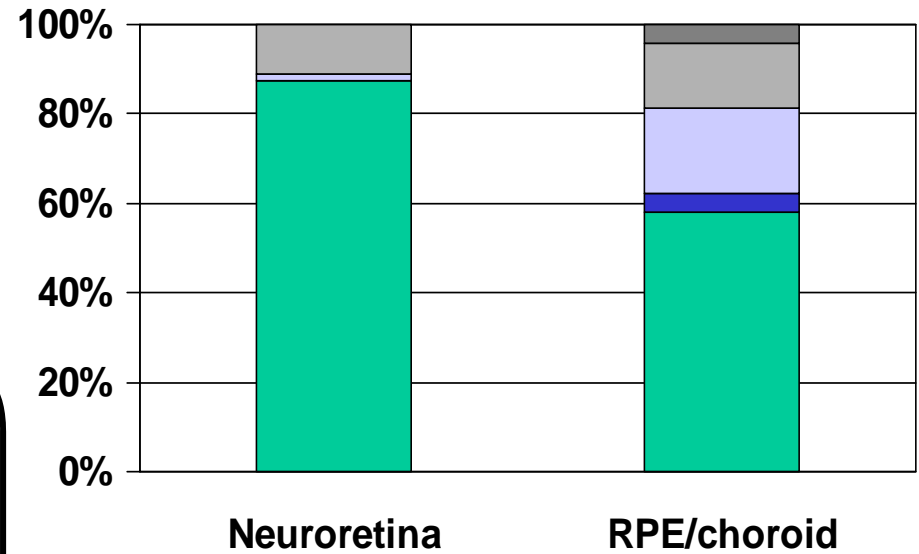
# Lipids in the retina

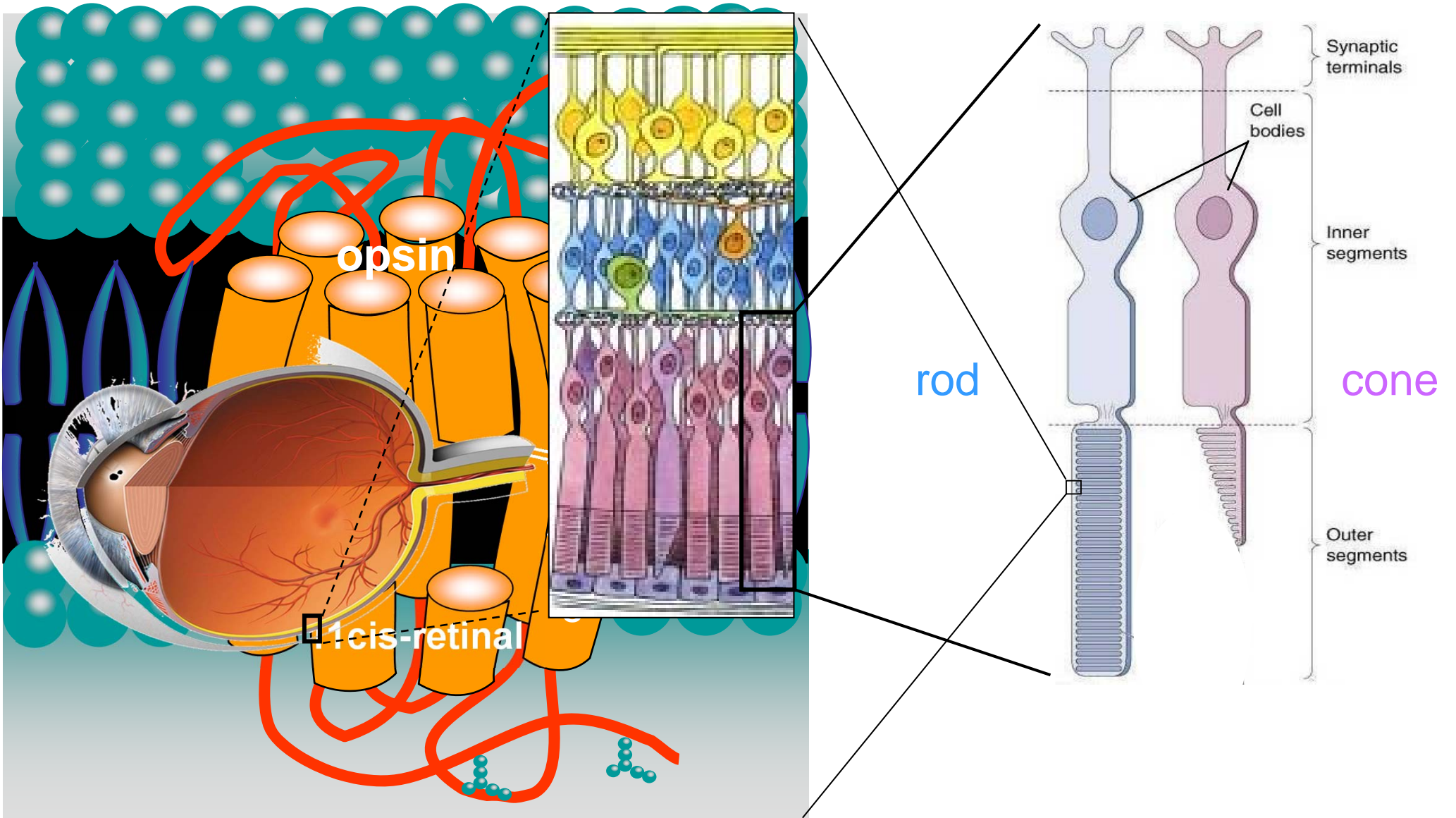


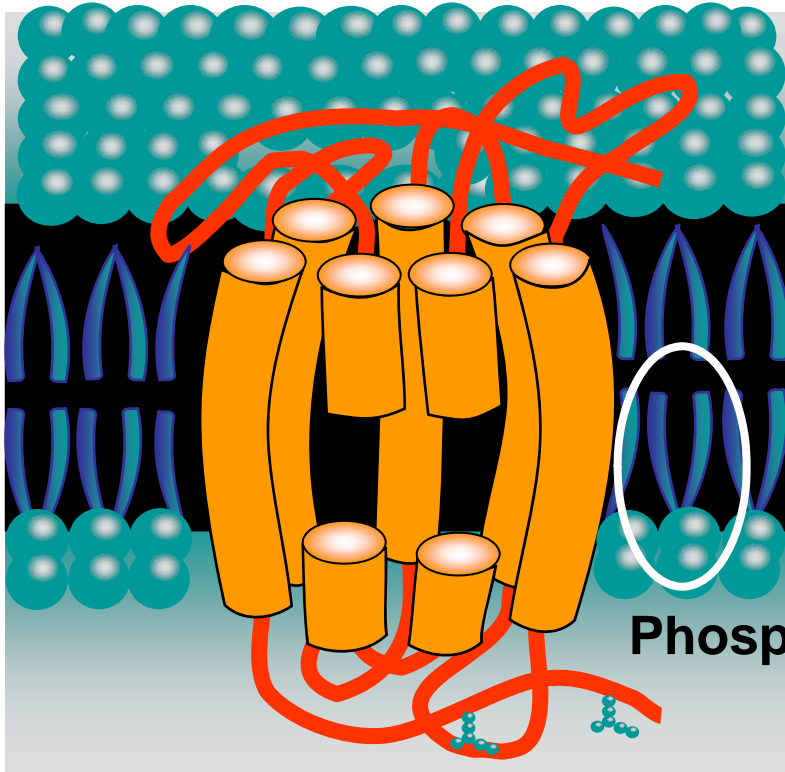
Lipids: 25% of dry matter



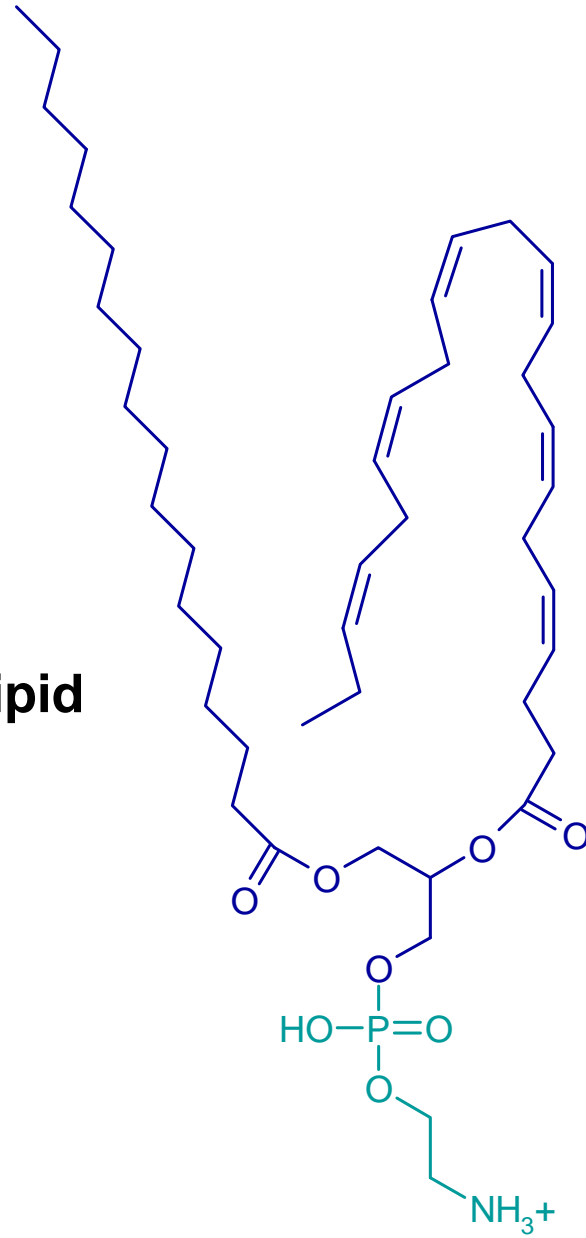
- Phospholipids
- Triglycerides
- Cholesteryl esters
- Cholesterol
- Free fatty acids





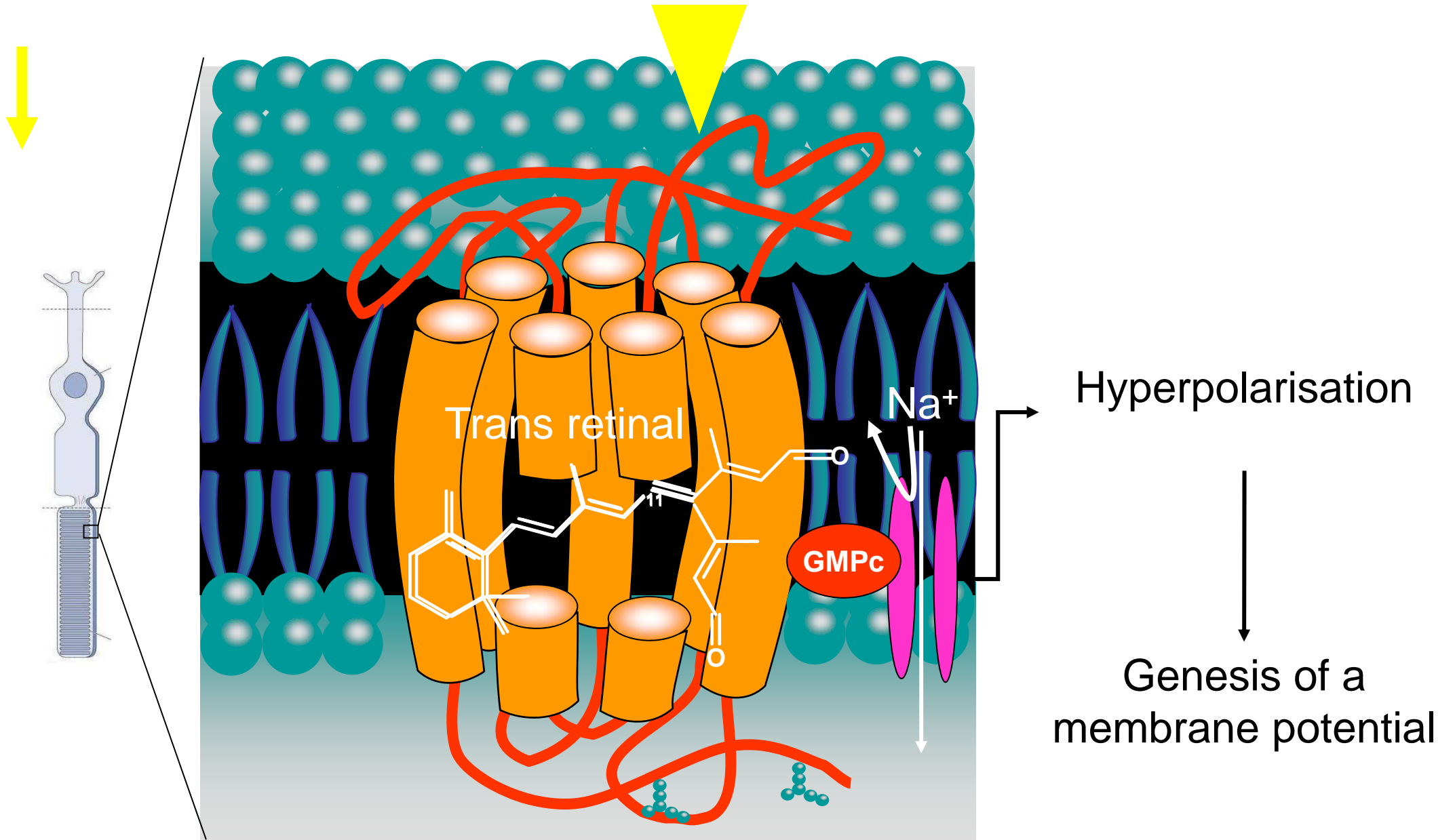


Phospholipid

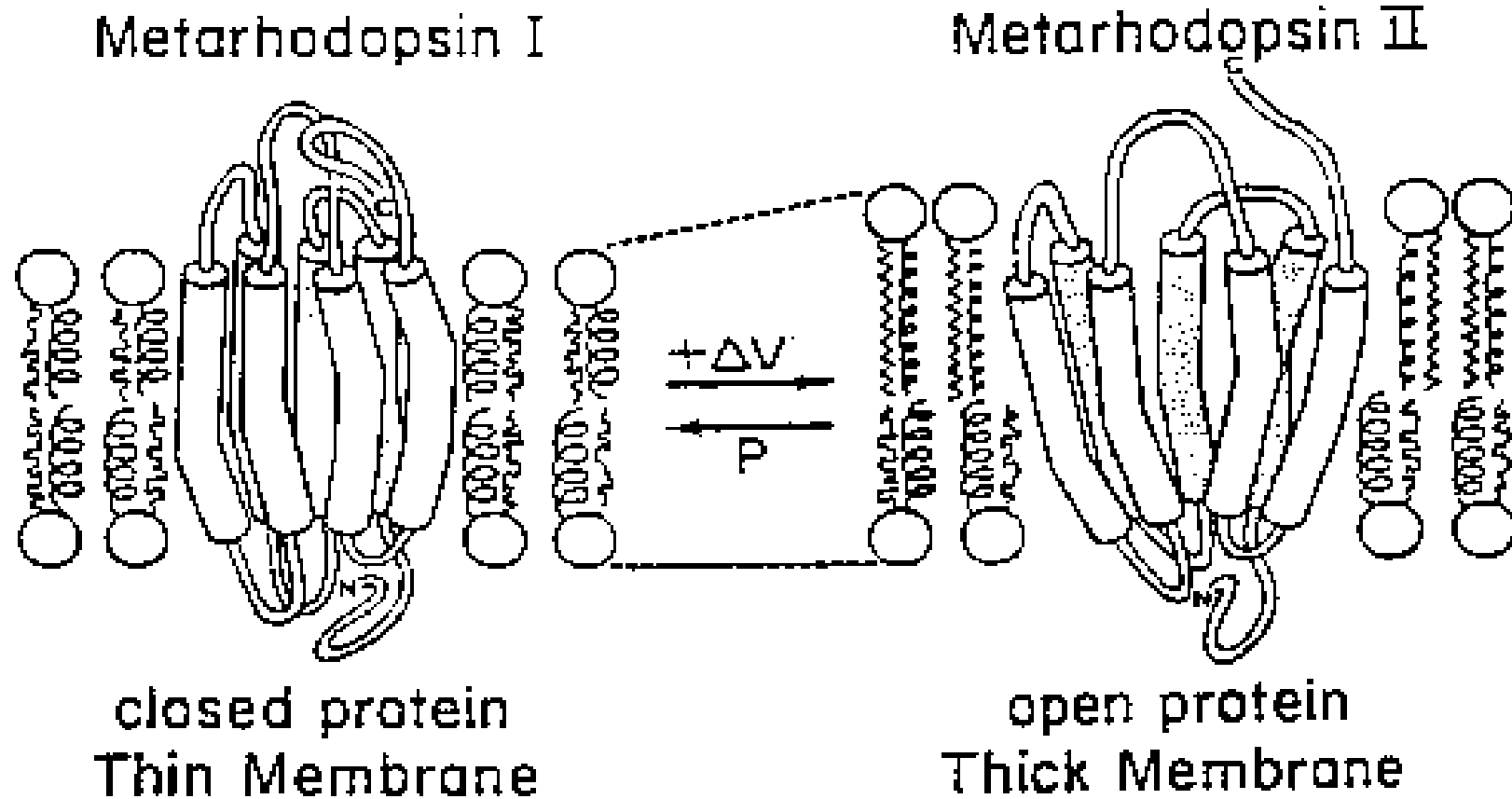


DHA  
C22:6n-3

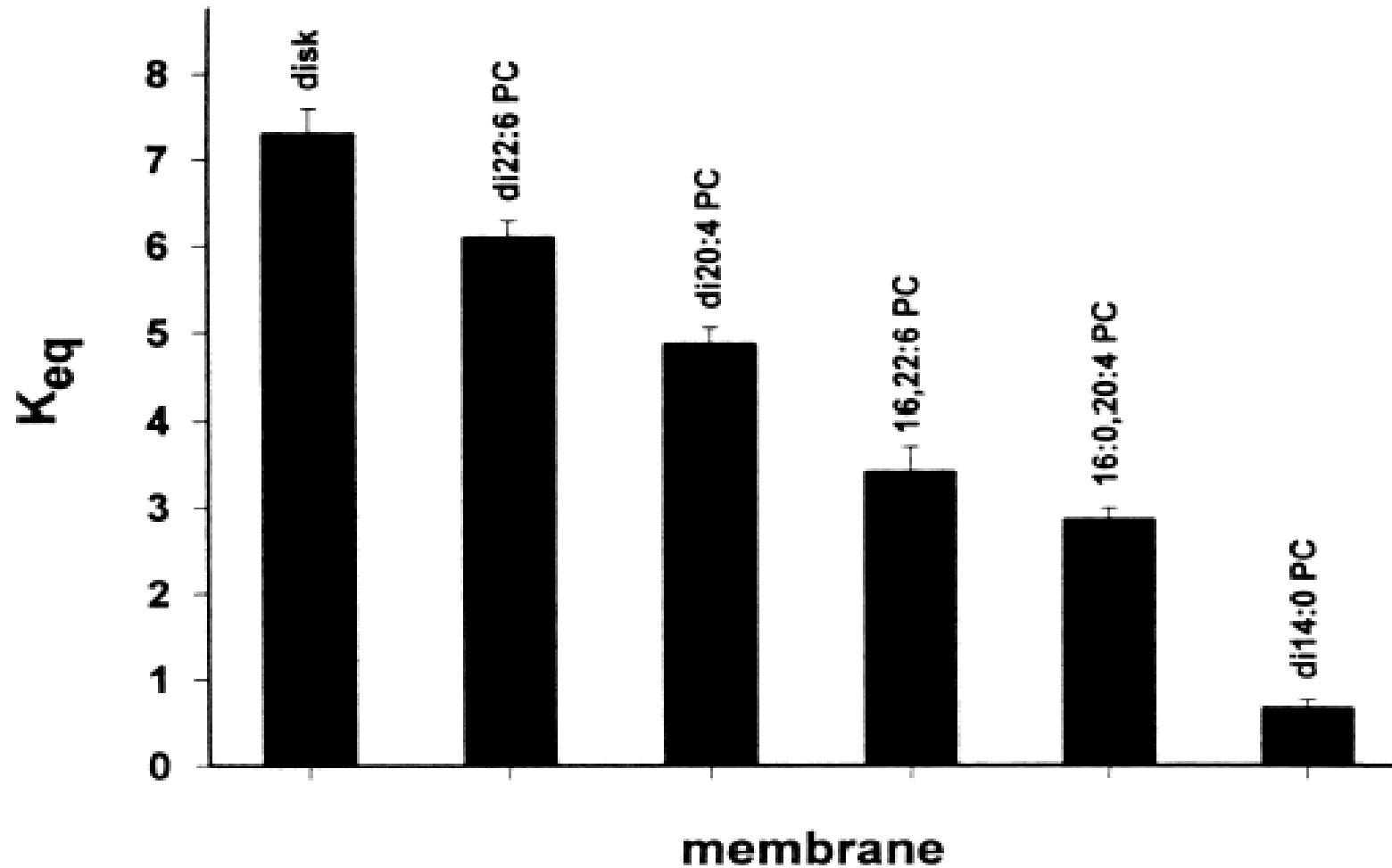
25-30% in the rat  
15-20% in humans



# The efficacy of the transduction pathway is dependent to the activation of rhodopsin



## DHA is crucial in rhodopsin activation



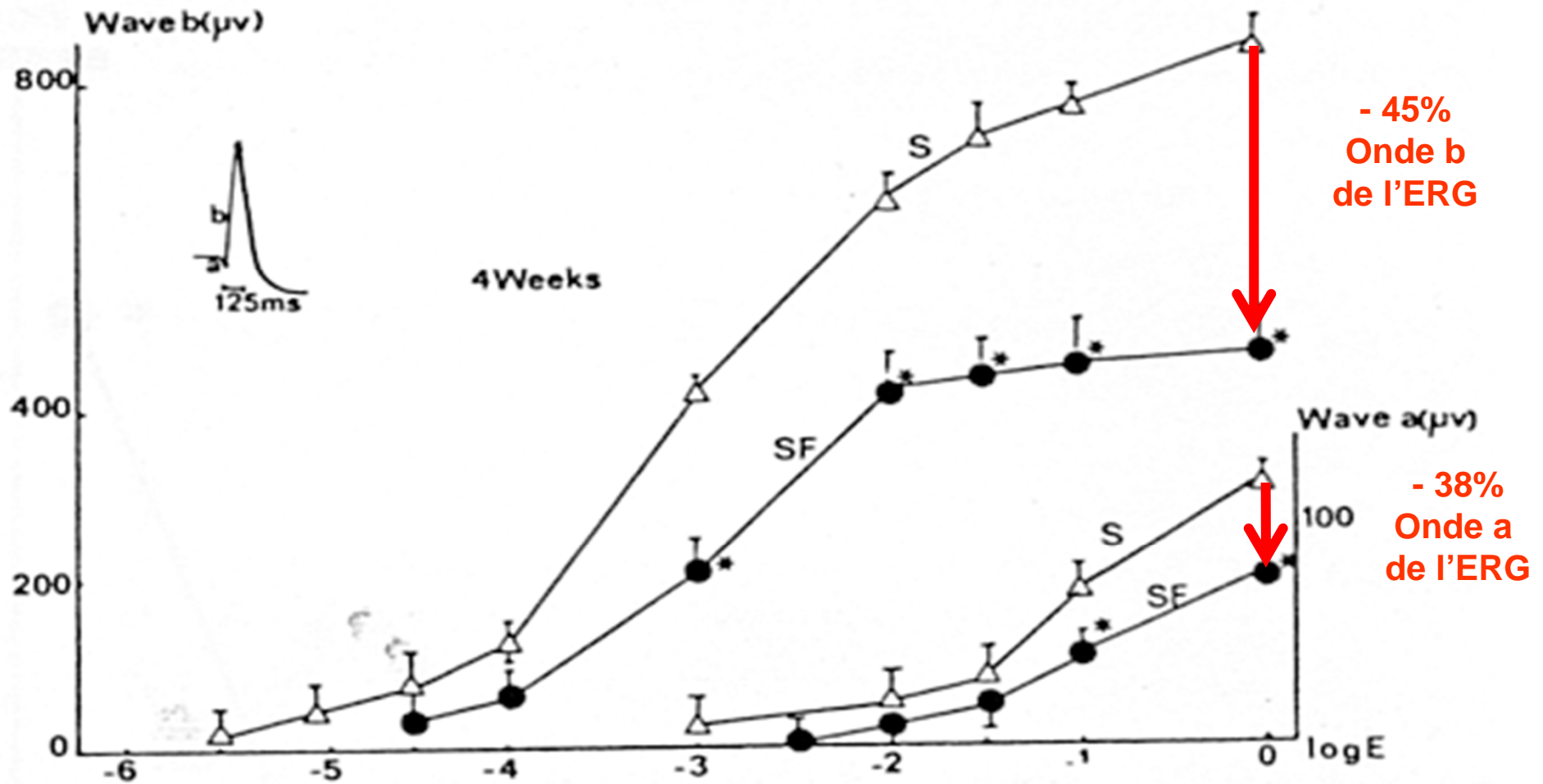
# Chronic dietary deficiency in omega 3 impairs retinal function

- 1976 Lamptey & Walker, *J Nutr*
- 1989 Bourre et al, *J Nutr*
- 1993 Yehuda et al, *Proc Natl Acad Sci USA*
- 1999 Wainwright et al, *J Nutr*
- 1999 Scheaff Greiner et al, *Lipids*
- 2001 Moriguchi et al, *J Lipid Res*
- 2004 Niu et al, *J Biol Chem*
- 2007 Connor et al, *Nat Med*



Low DHA in the retina is associated with reduced retinal function

# DHA deficient rats showed reduced electroretinographic response



Bourre et al, J Nutr 1989

# Where does DHA come from?

Plants



Oleic acid  
18:1n-9

$\Delta 12$



Linoleic acid  
18:2n-6

$\Delta 15$



$\alpha$ -linolenic acid  
18:3n-3

$\Delta 6$

Animals

But poor efficacy of the conversion pathway (<1-2%)



20:3n-6 (dGLA)

20:4n-3

$\Delta 5$

20:4n-6 (AA)

20:5n-3 (EPA)

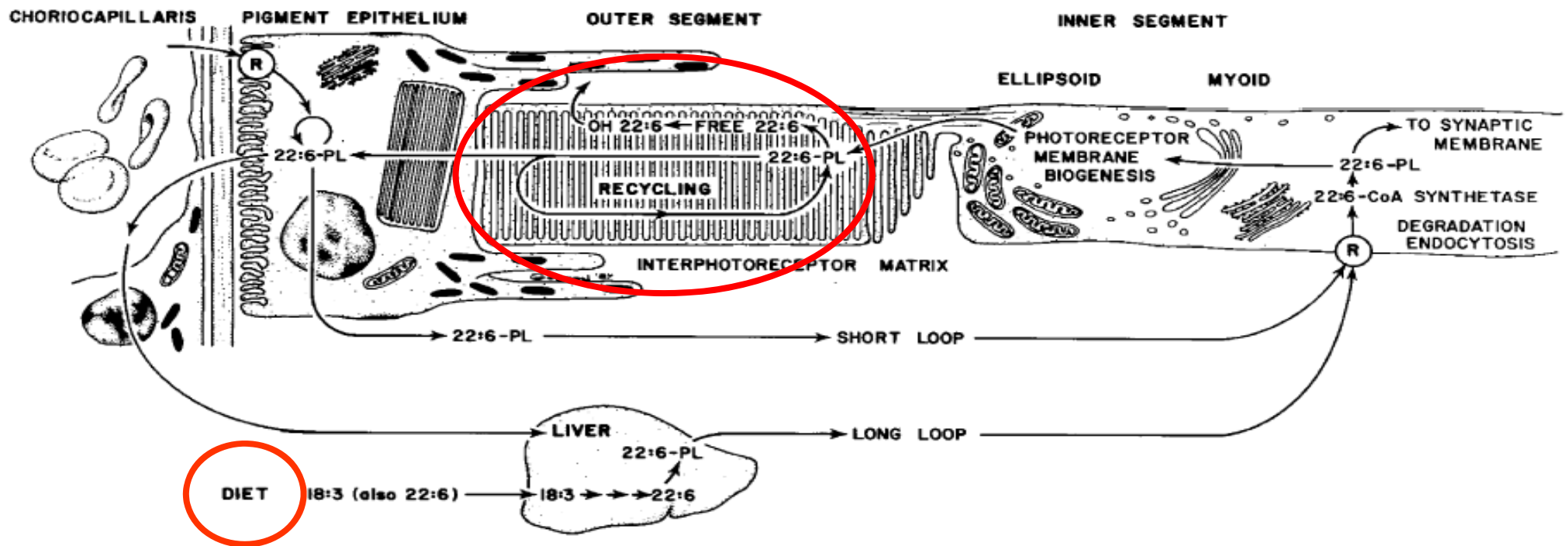
22:5n-6

22:6n-3 (DHA)

Desaturation

Elongation

# A balance between diet and endogenous recycling



Bazan NG, in: *Inherited and environmentally induced retinal degenerations*, LaVail MM, Anderson RE, Hollyfield JG eds 1989

# Would adipose tissue DHA correlate with retinal levels?

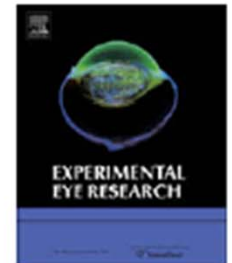
Experimental Eye Research 87 (2008) 521–528



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journal homepage: [www.elsevier.com/locate/yexer](http://www.elsevier.com/locate/yexer)



Lipid and fatty acid profile of the retina, retinal pigment epithelium/choroid, and the lacrimal gland, and associations with adipose tissue fatty acids in human subjects

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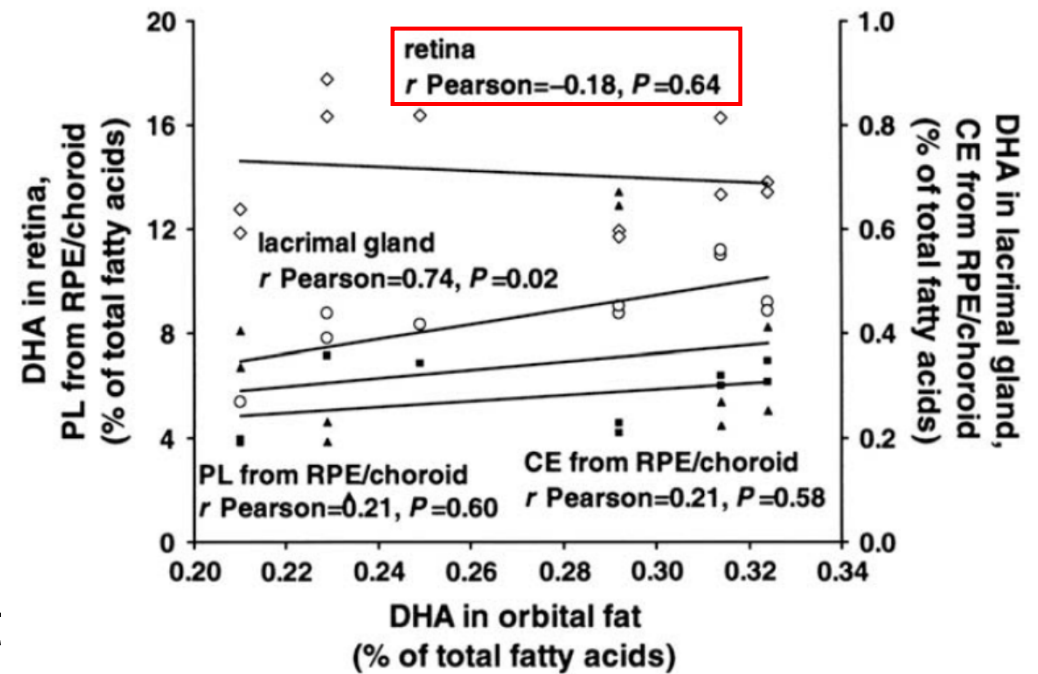
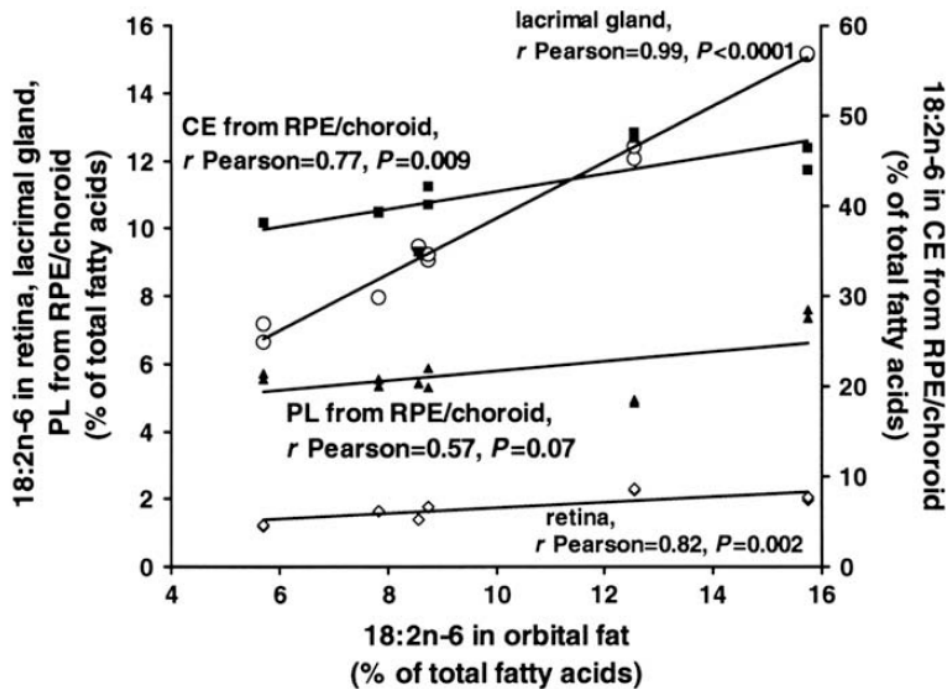
<sup>b</sup>Department of Ophthalmology, Biology, Imaging, and Engineering of Corneal Grafts, Faculty of Medicine, Saint Etienne, France

<sup>c</sup>Eye and Nutrition Research Group, UMR1129 FLAVIC, University of Burgundy, Dijon, France

<sup>d</sup>Department of Ophthalmology, University Hospital, Dijon, France

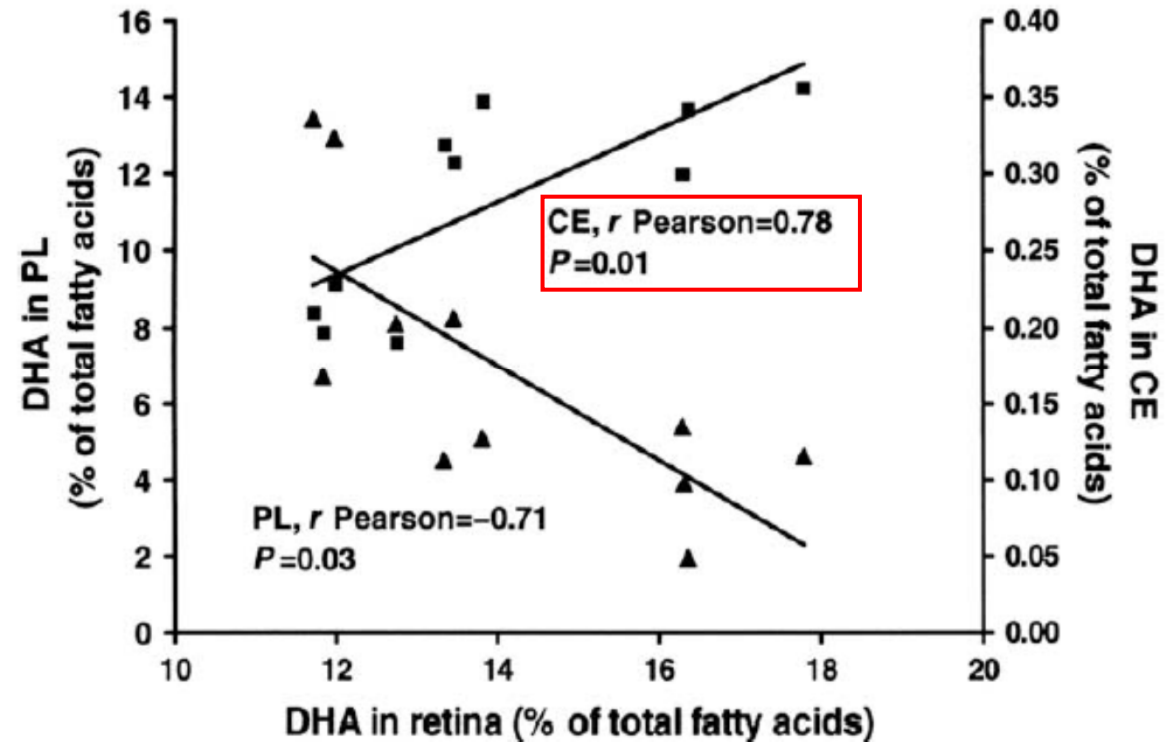
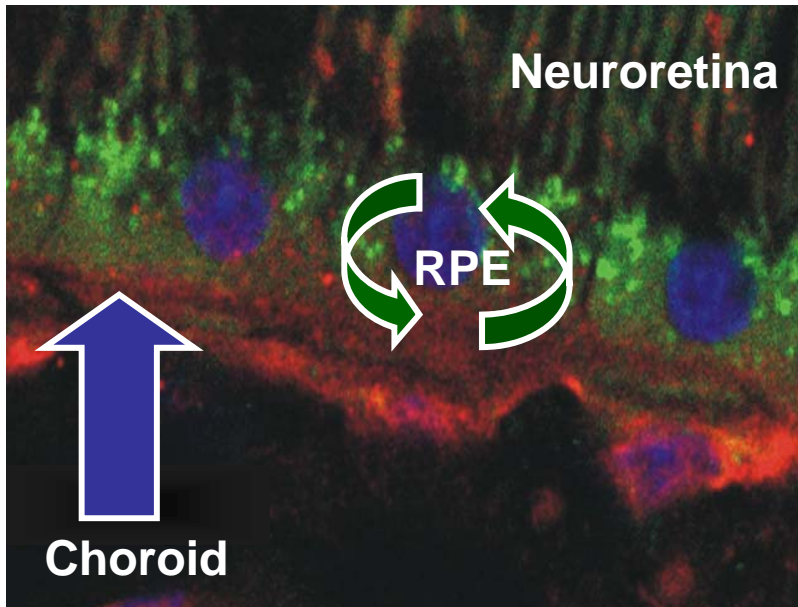


# DHA in adipose tissue is not associated with DHA in the retina

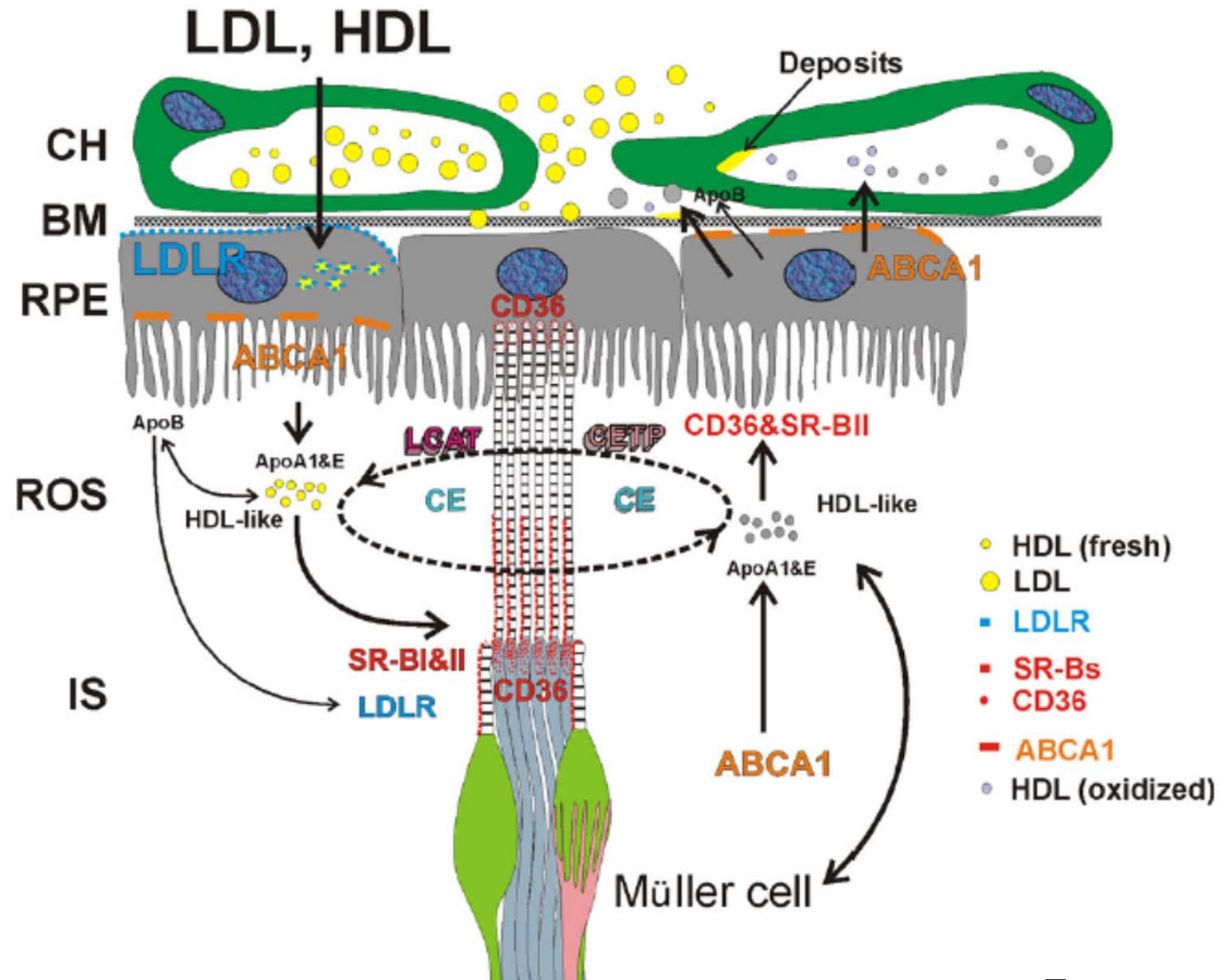


Circulating DHA (to some extent dietary) poorly participates to the retinal levels

# Despite cholesteryl esters in the RPE would be carriers of DHA and dietary fatty acids entering the retina

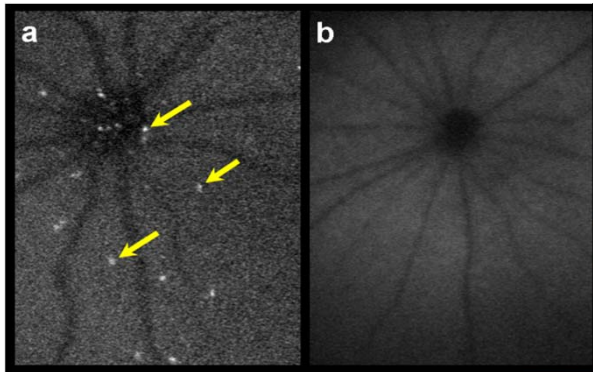


# Intraretinal lipid metabolism

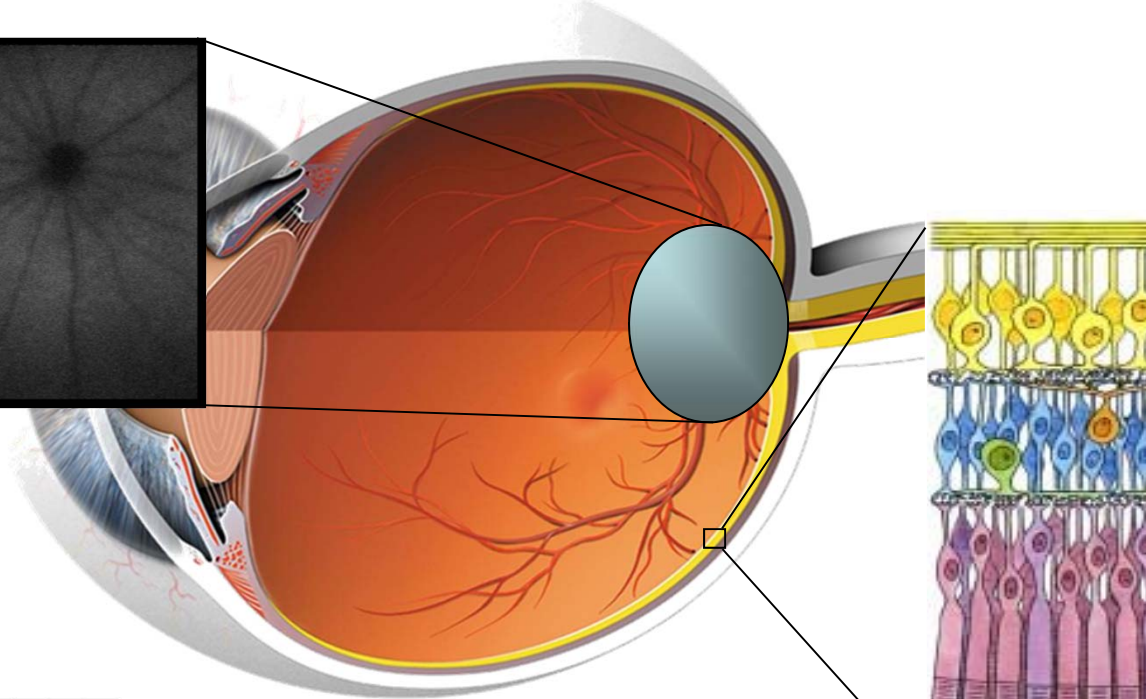


# Abrogating LDLR expression mimicks aging of the retina

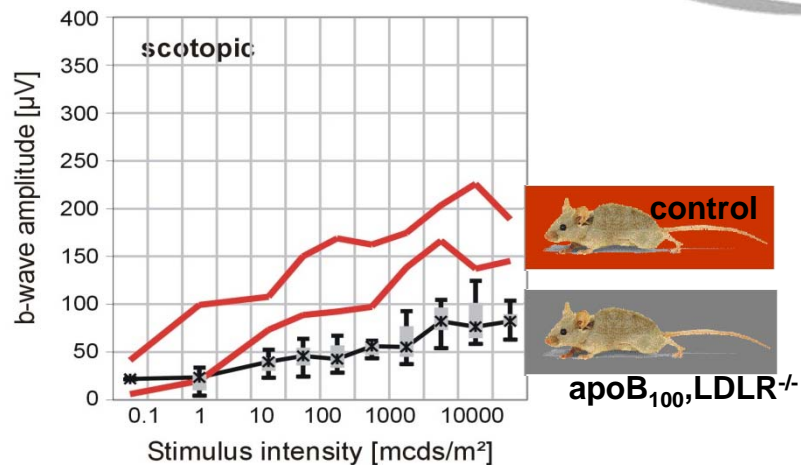
Accumulation of lipids (incl. cholesterol)



Fundus  
(cSLO 488nm)



Labelling of cholesteryl esters  
(filipin, 350/420nm)



Reduced retinal functionality

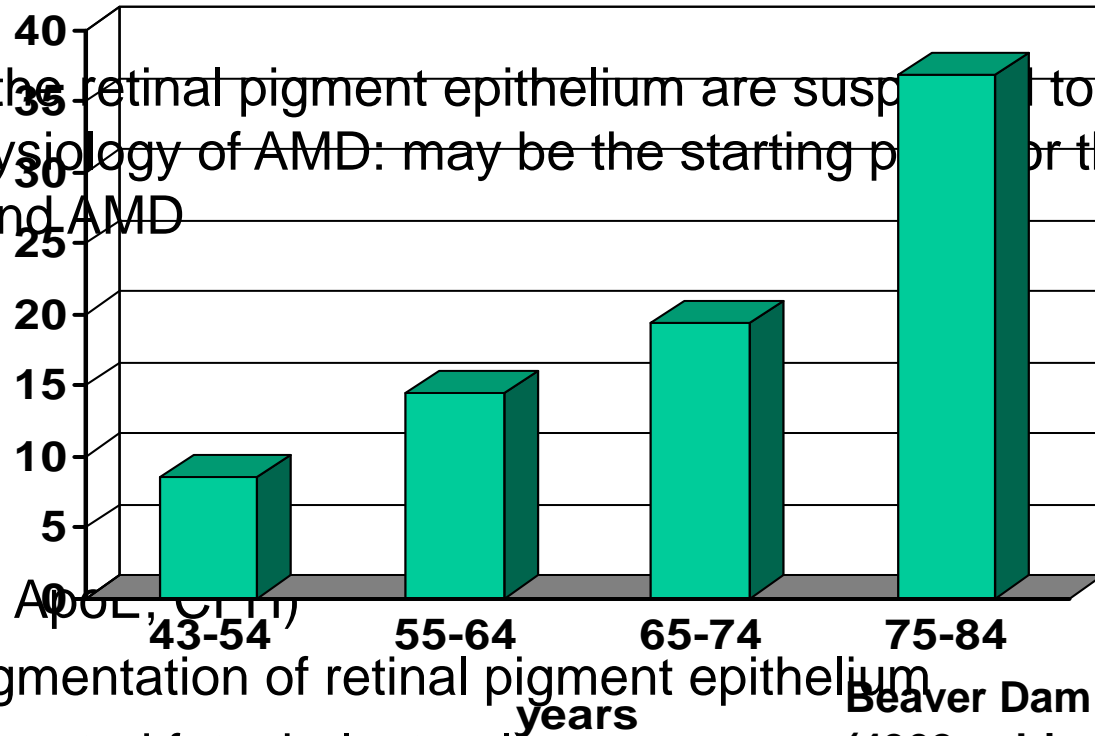
# $\omega$ 3 fatty acids and Age-related Macular Degeneration (AMD)

- The leading cause of visual loss in Western countries

- Dysregulations of the retinal pigment epithelium are suspected to play a major role in the pathophysiology of AMD: may be the starting point for the development of maculopathies and AMD

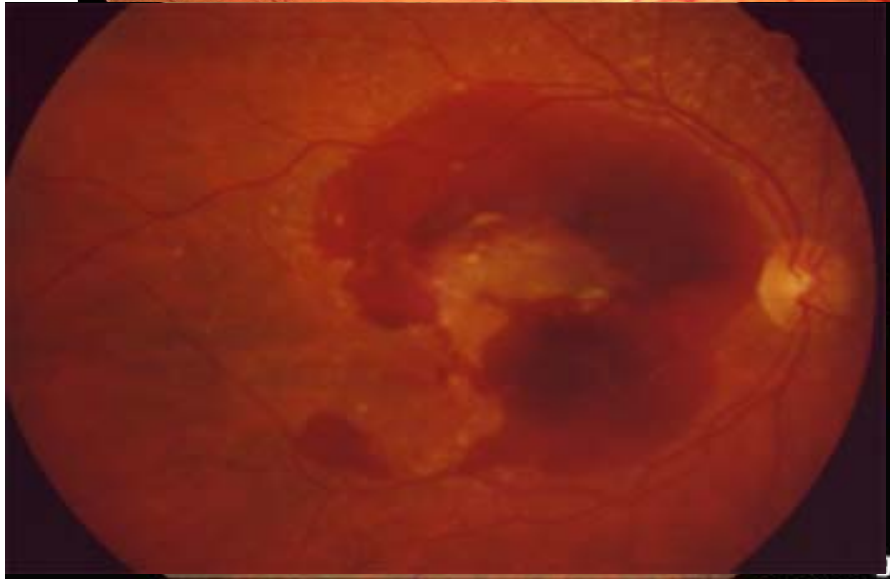
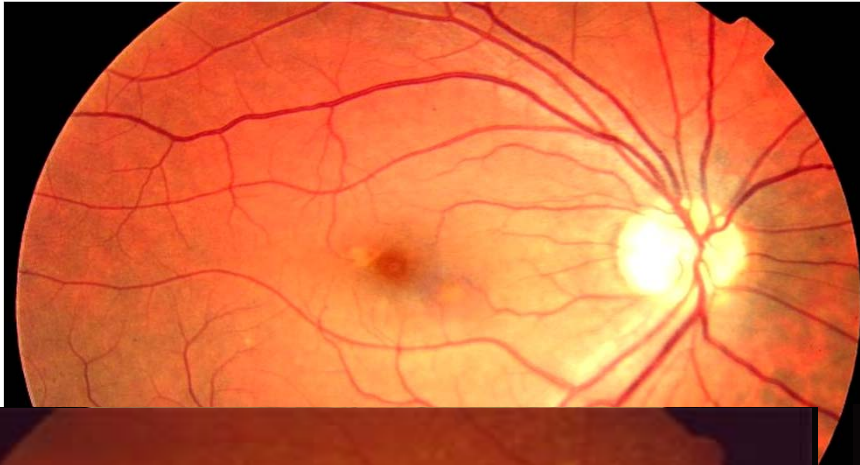
- Risk factors:

- age
- smoking habits
- genetics (ABCA4, APOE, C11orf90)
- light, abnormal pigmentation of retinal pigment epithelium
- dietary habits (saturated fat, cholesterol)



Beaver Dam Study  
(4962 subjects, USA)

# Grading AMD: from maculopathy to severe forms



Geographic Atrophy

- Pigment abnormalities affecting 1 eye or both
- Geographic atrophy
- Neovascularization

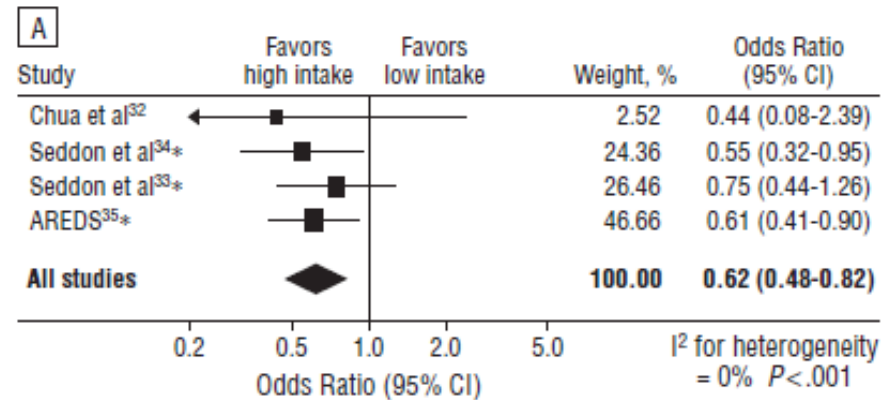
} 4 grades: from maculopathy to AMD

# Fish intake, $\omega$ 3 fatty acids and AMD

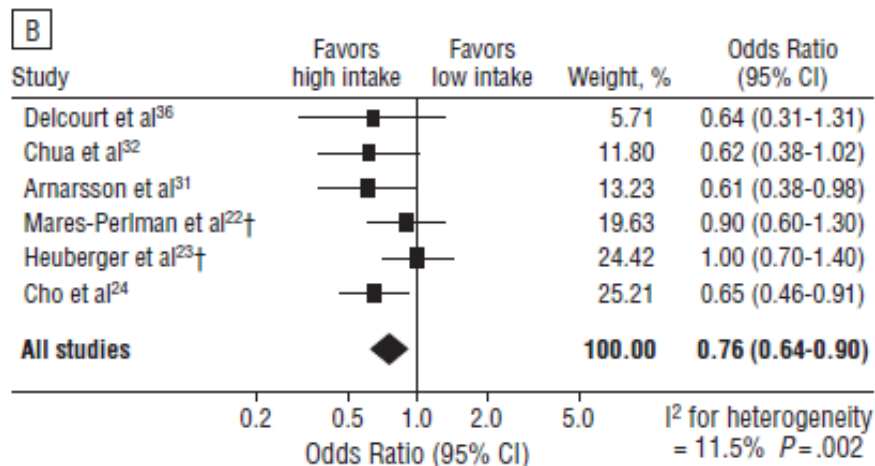
## Meta-analysis from 7 databases

(88,974 people including 3204 AMD)

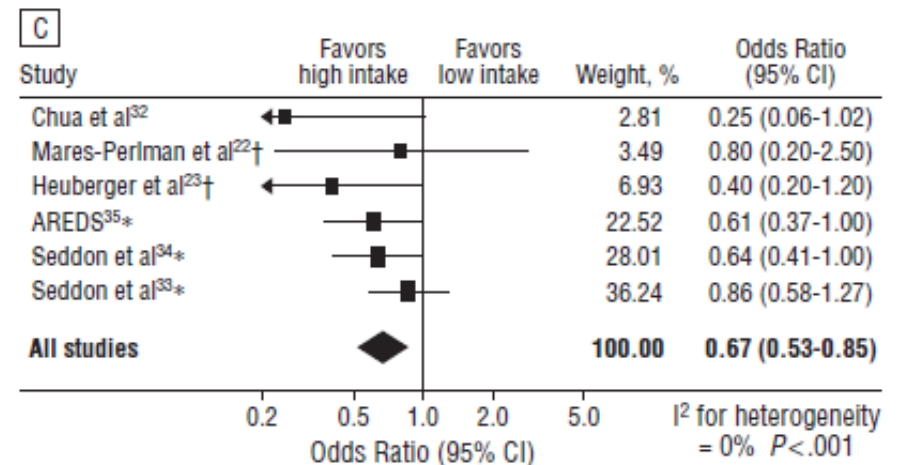
$\omega$ 3 and late AMD



Fish intake and early AMD



Fish intake and late AMD



# Protection from AMD is associated above 2 servings of fish per week

**Table 2. Odds Ratios for AMD According to Fish Intake**

	<1 Serving/wk	1 Serving/wk	≥2 Servings/wk	<i>P</i> Trend
Cases/controls, No.	74/131	75/144	73/184	
Median intake (servings per day)	0.080	0.18	0.36	
Adjusted OR*	1.0	0.97	0.68	.07
Multivariate OR1 (95% CI)†	1.0	0.94 (0.64-1.38)	0.63 (0.41-0.97)	.03
Multivariate OR2 (95% CI)‡	1.0	1.0 (0.67-1.48)	0.64 (0.41-1.00)	.04

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.

\*Adjusted for age (60-69, 70-79, and 80+ years), log calories (continuous), and protein intake (quartiles).

†Adjusted for education (≥high school vs <high school); smoking (current/past/never in the multivariate fish models); age (60-69, 70-79, and 80+ years); body mass index, calculated as weight in kilograms divided by the square of height in meters (<25, 25-29.9, and 30+); systolic blood pressure; cardiovascular disease; log calories (continuous); protein intake (quartile); log calorie-adjusted beta-carotene intake (continuous); alcohol intake (continuous); and physical activity (continuous, times per week vigorous).

‡Adjusted for variables in model 1 plus total intake of zinc, vitamin C, and vitamin E (log scale for all 3).

## ...primarily in patients with low intake in linoleic acid

**Table 4. Odds Ratios for AMD by Quartile of Omega-3 Intake, Linoleic Acid Intake, and Omega-3 Intake Within Strata of Linoleic Acid Intake**

Fatty Acid Intake	Quartile of Omega-3 Intake				P Trend
	1	2	3	4	
Omega-3 intake					
Cases/controls, No.	64/102	61/120	49/114	48/123	
Median intake, g	0.06	0.12	0.20	0.35	
Adjusted OR*	1.0	0.82	0.62	0.60	.02
Multivariate OR1 (95% CI)†	1.0	0.79 (0.52-1.21)	0.60 (0.36-0.97)	0.56 (0.33-0.94)	.01
Multivariate OR2 (95% CI)‡	1.0	0.80 (0.53-1.21)	0.60 (0.36-0.99)	0.55 (0.32-0.95)	.02
Linoleic acid intake					
Cases/controls, No.	43/127	60/110	65/107	54/115	
Median intake, g	7.12	10.45	13.34	18.46	
Adjusted OR*	1.0	1.72	1.81	1.37	.42
Multivariate OR1 (95% CI)†	1.0	1.89 (1.15-3.11)	2.07 (1.17-3.63)	1.56 (0.79-3.08)	.26
Multivariate OR2 (95% CI)‡	1.0	1.85 (1.12-3.08)	1.99 (1.12-3.54)	1.46 (0.72-2.96)	.32
Linoleic acid intake, quartiles 1 and 2 ( $\leq 11.79$ g)					
Cases/controls, No.	41/66	35/65	17/54	10/52	
Median intake of omega-3, g	0.06	0.12	0.20	0.35	
Adjusted OR*	1.0	0.79	0.90	0.92	.001
Multivariate OR1 (95% CI)†	1.0	0.97 (0.54-1.76)	0.48 (0.22-1.04)	0.30 (0.12-0.74)	.002
Multivariate OR2 (95% CI)‡	1.0	0.94 (0.52-1.72)	0.39 (0.18-0.88)	0.23 (0.09-0.57)	<.001
Linoleic acid intake, quartiles 3 and 4 ( $\geq 11.80$ g)					
Cases/controls, No.	23/36	26/55	32/60	38/71	
Median intake of omega-3, g	0.06	0.12	0.20	0.36	
Adjusted OR*	1.0	0.79	0.90	0.92	.98
Multivariate OR1 (95% CI)†	1.0	0.74 (0.37-1.47)	0.82 (0.40-1.69)	0.85 (0.41-1.77)	.93
Multivariate OR2 (95% CI)‡	1.0	0.73 (0.35-1.55)	0.84 (0.37-1.89)	1.07 (0.46-2.50)	.66

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.

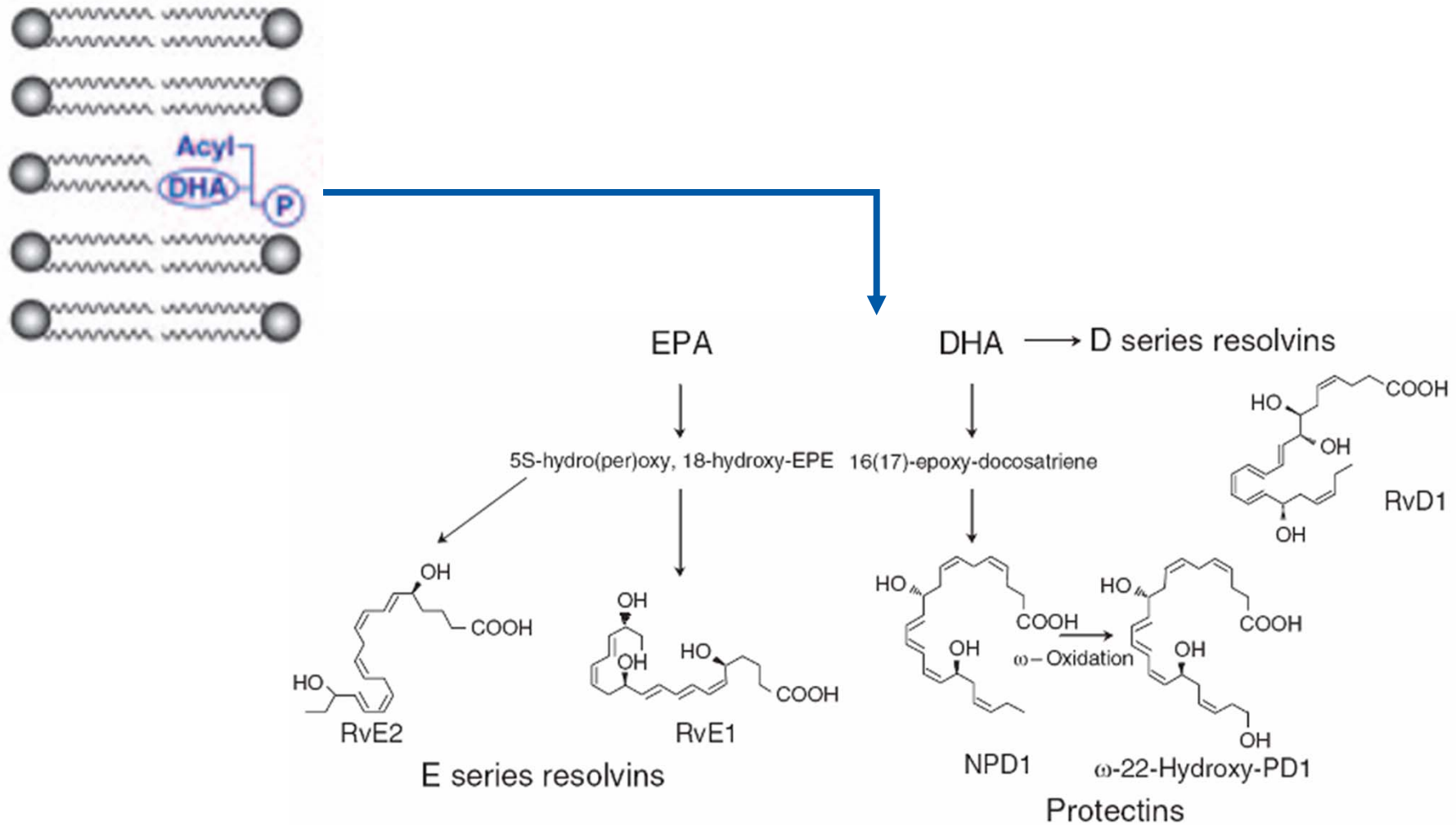
\*Adjusted for log calories (continuous) and protein intake (quartile).

†Adjusted for education ( $\geq$ high school vs  $<$ high school); smoking (current/past/never); age (60-69, 70-79, and 80+ years); body mass index, calculated as weight in kilograms divided by the square of height in meters ( $<25$ , 25-29.9, and 30+); systolic blood pressure; cardiovascular disease; log calories (continuous); protein intake (quartile); log calorie-adjusted beta-carotene intake (continuous); alcohol intake (continuous); and physical activity (continuous, times per week vigorous).

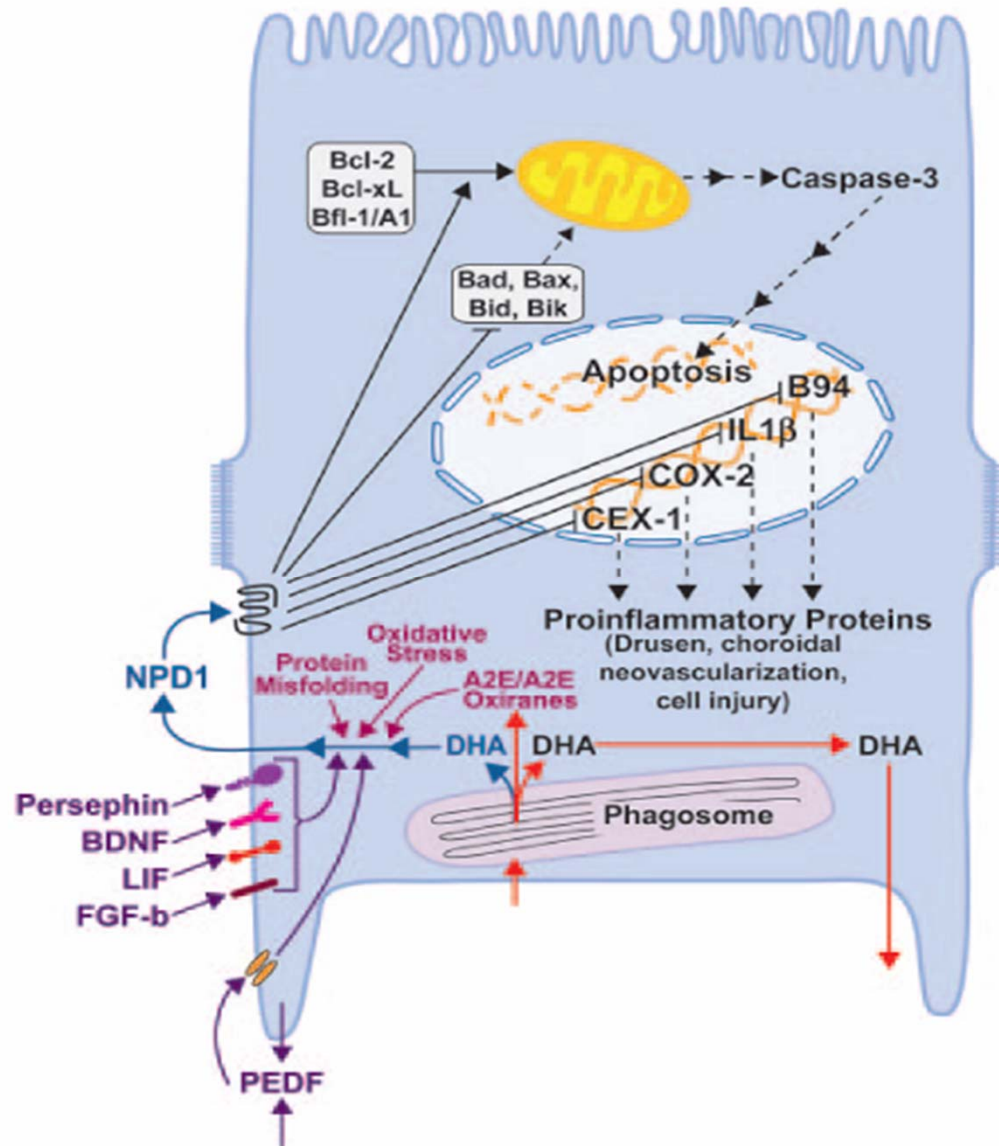
‡Adjusted for variables in model 1 plus total intake of zinc, vitamin C, and vitamin E (log scale for all 3).

**Seddon et al., Arch Ophthalmol 2007**

# Mechanism: $\omega$ 3 fatty acids may be converted into active metabolites in the RPE



# NPD1 exhibits protective properties against angiogenesis, apoptosis, inflammation



## Conclusion

- Lipids are essential components of the retina,  $\omega$ 3 key actors of its function
- Intraretinal lipid metabolism limits the influence of circulating (dietary) lipids to retinal profile in fatty acids
- Dietary lipids may participate to the prevention of retinal aging and AMD: not only by means of supplementations with  $\omega$ 3, but also via ameliorating the ratio between dietary linoleic acid and  $\omega$ 3
- The mechanisms of this prevention remains uncertain, but may involve intraretinal metabolism of fatty acids (active metabolites)