Needs in omega 3 and ocular pathologies

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Needs in omega-3 and ocular pathologies

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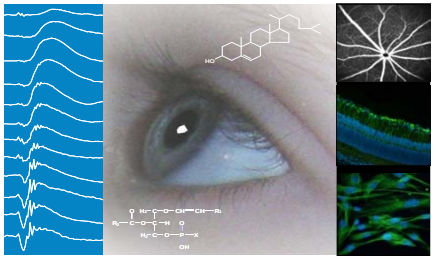
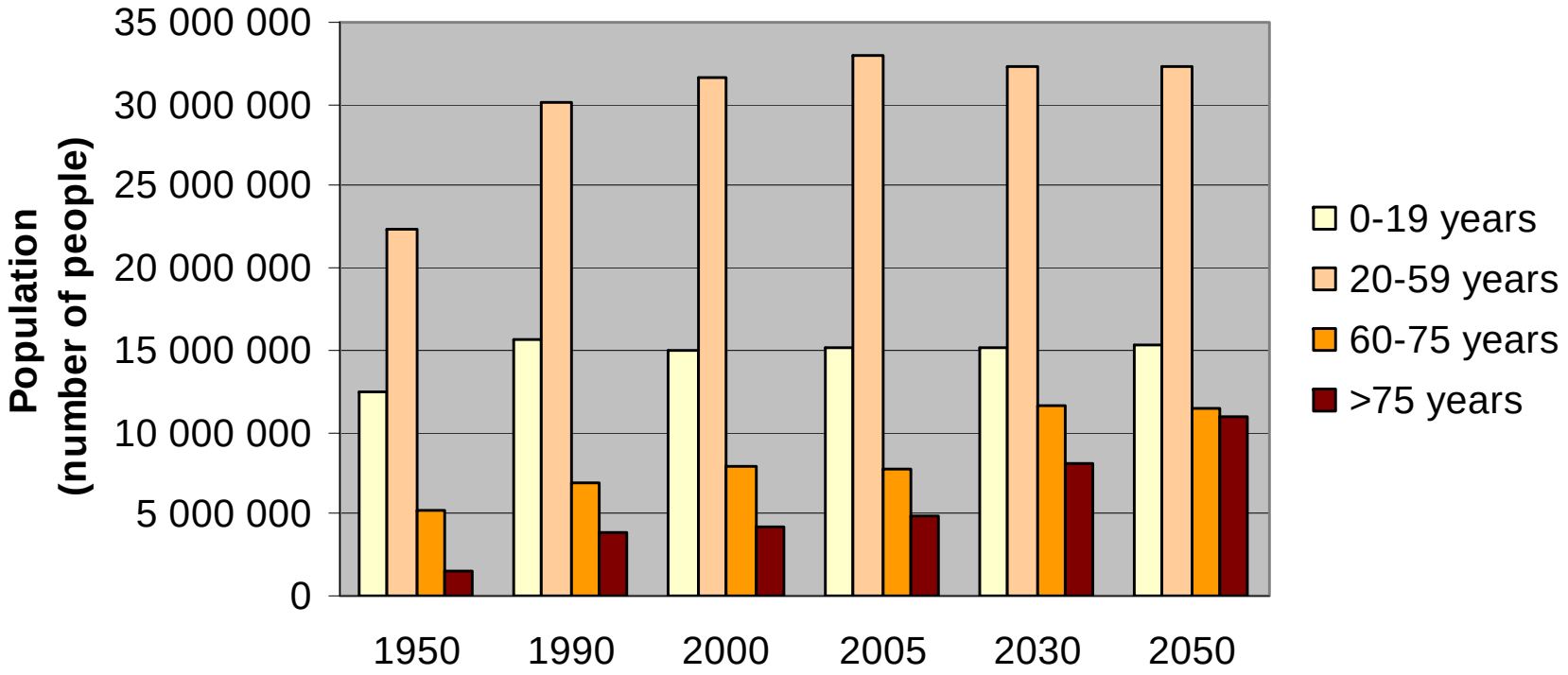


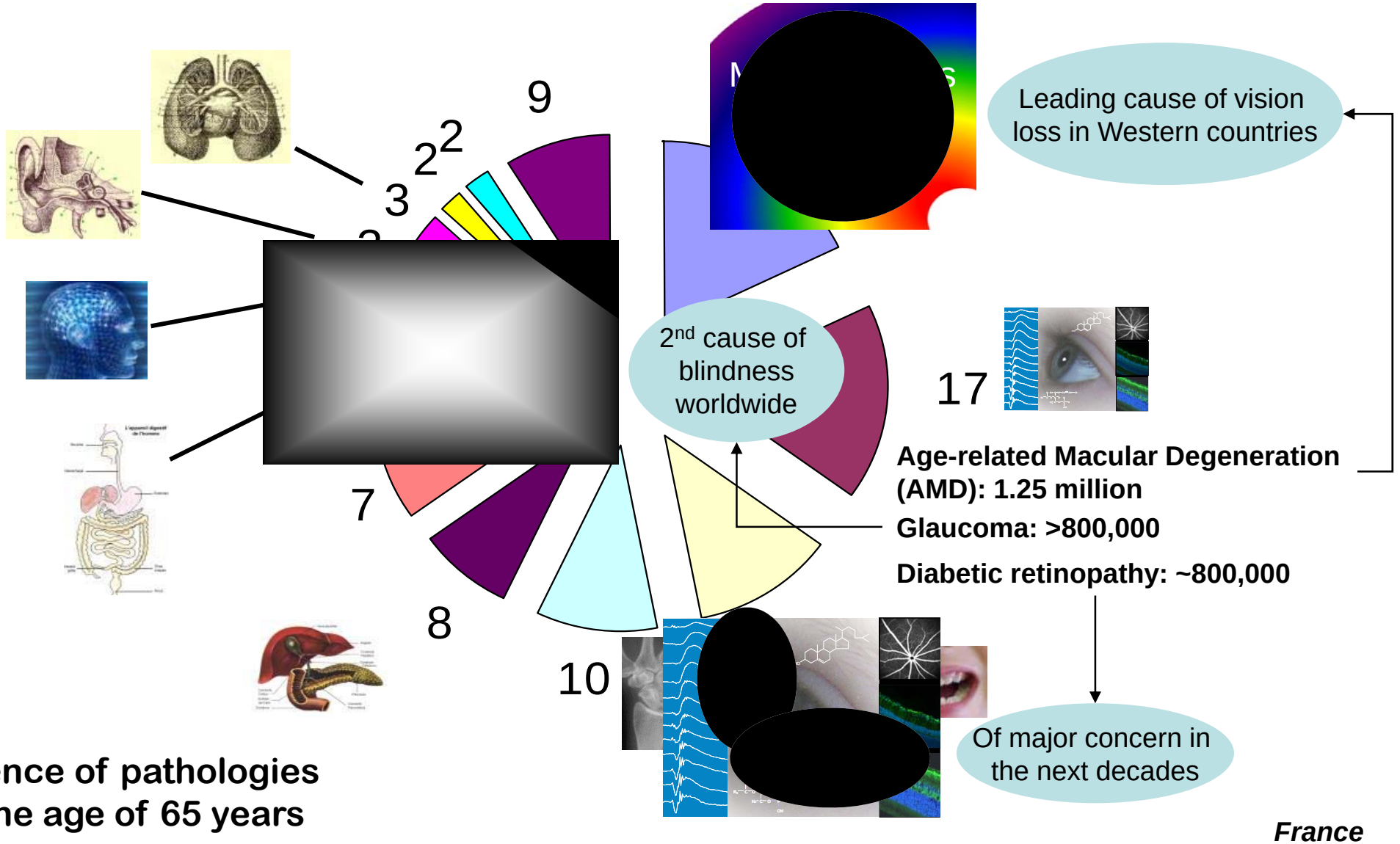
Aging: a socio-economic issue in the future



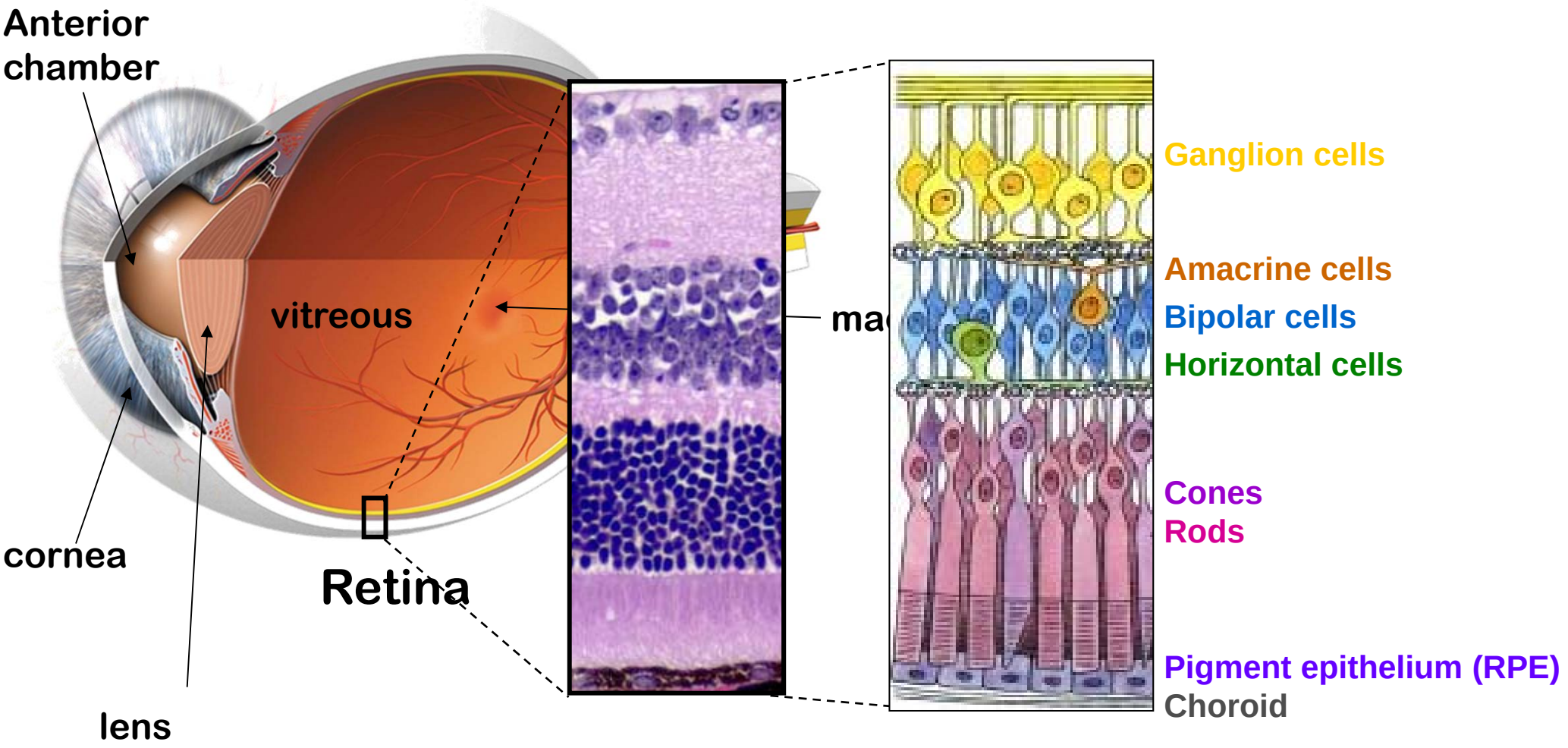
Population 2050 vs 2000 >60 years: ×2
>75 years: ×3
>85 years: ×5

in France

The neurosensory retina: a sensitive target of aging

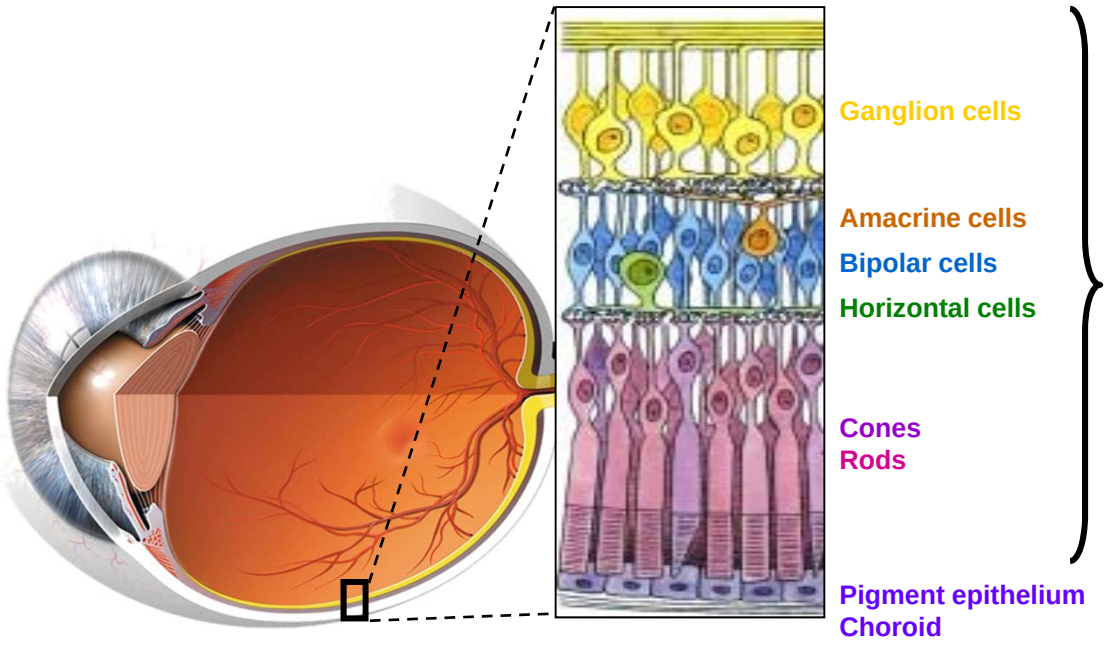


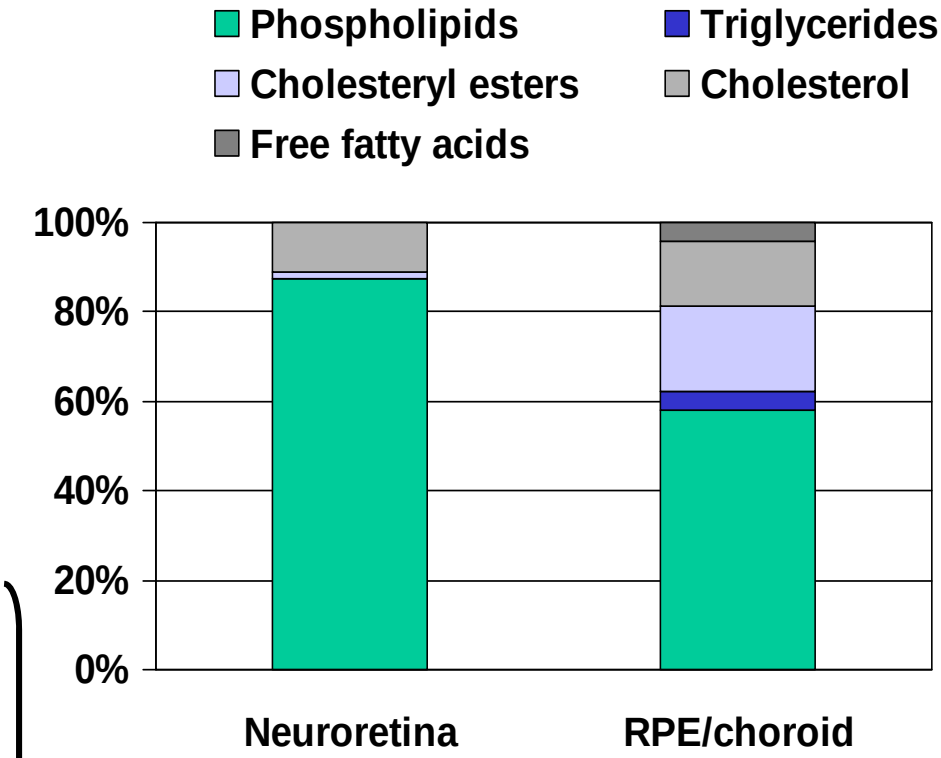
Structural organization of the retina



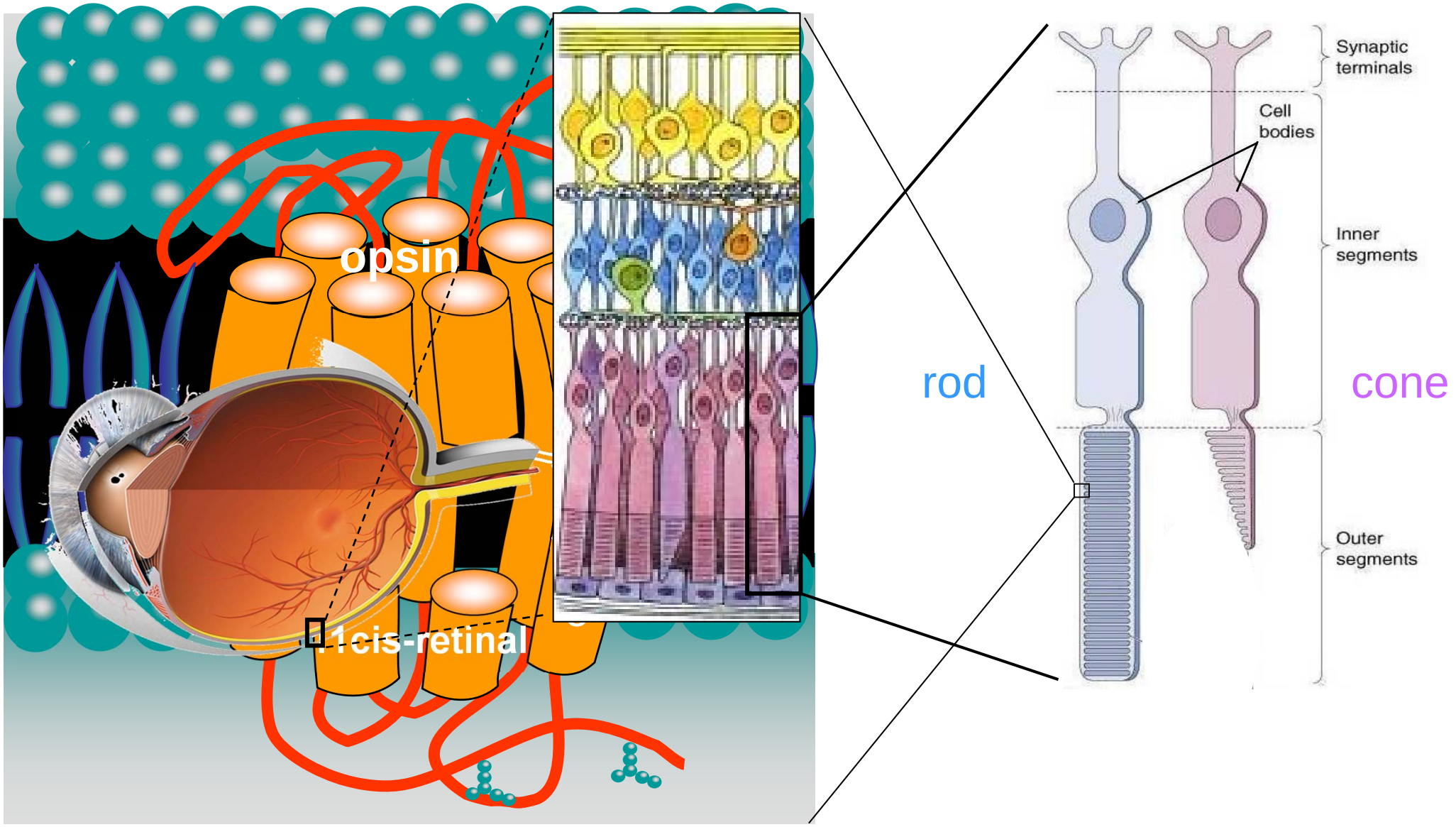
Lipids in the retina

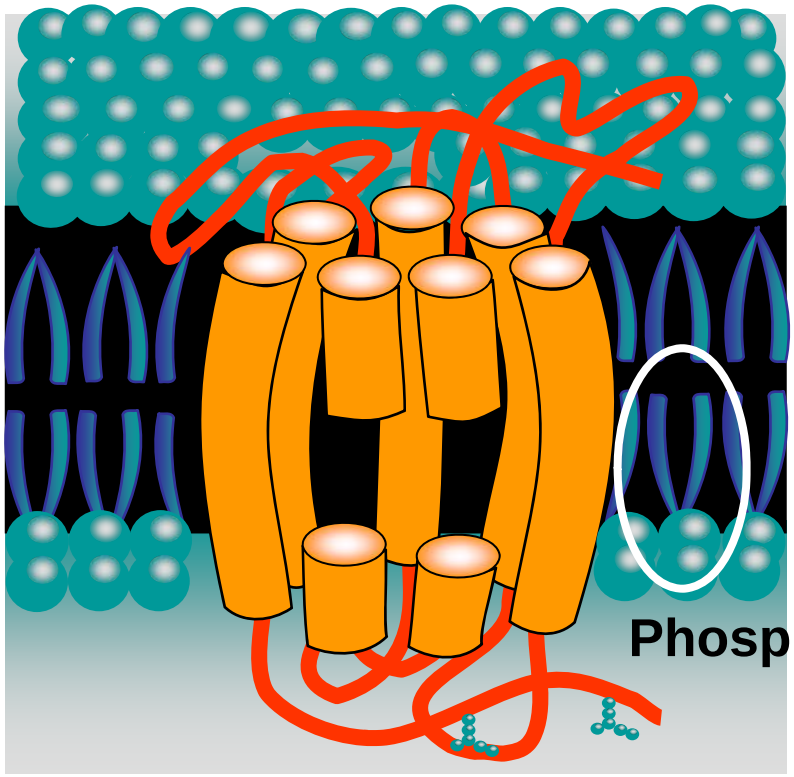
Lipids: 25% of dry matter



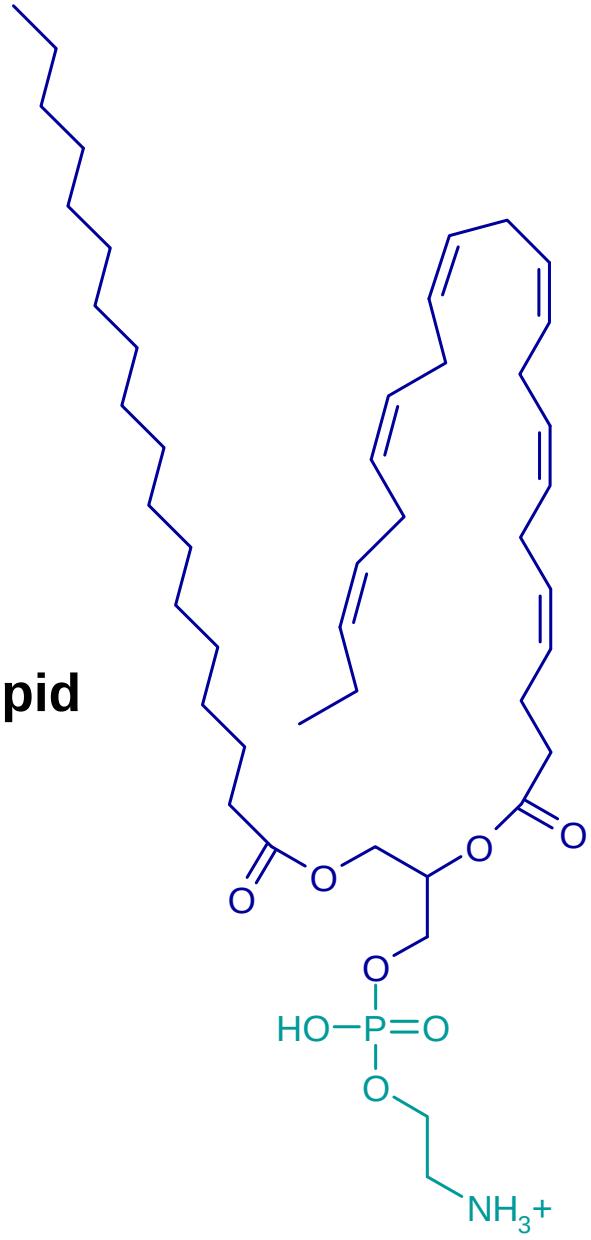


Bretillon et al., Exp Eye Res 2008


opsin
11cis-retinal
rod
cone
Synaptic terminals
Cell bodies
Inner segments
Outer segments



Phospholipid

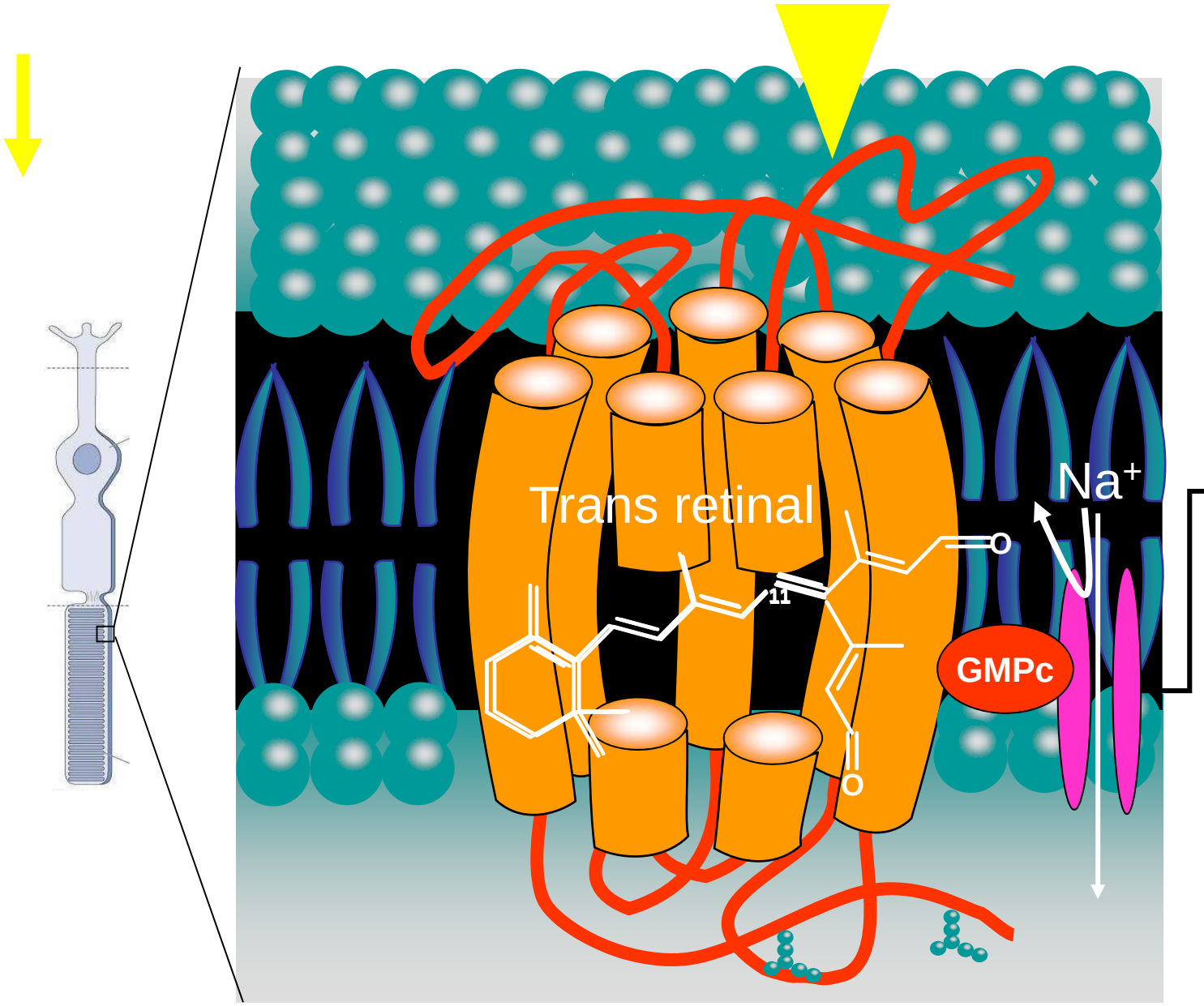


DHA

C22:6n-3

25-30% in the rat

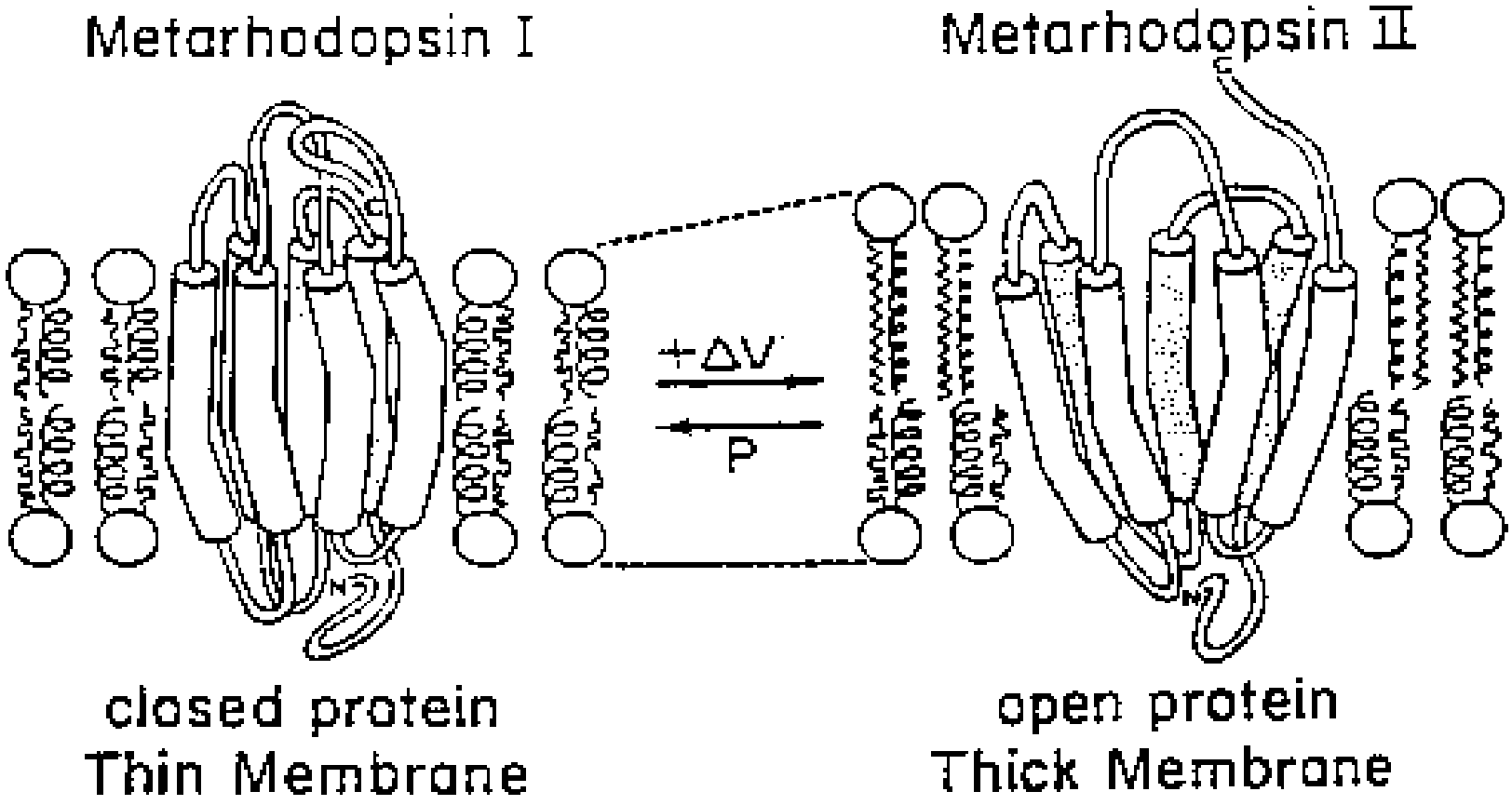
15-20% in humans



Hyperpolarisation

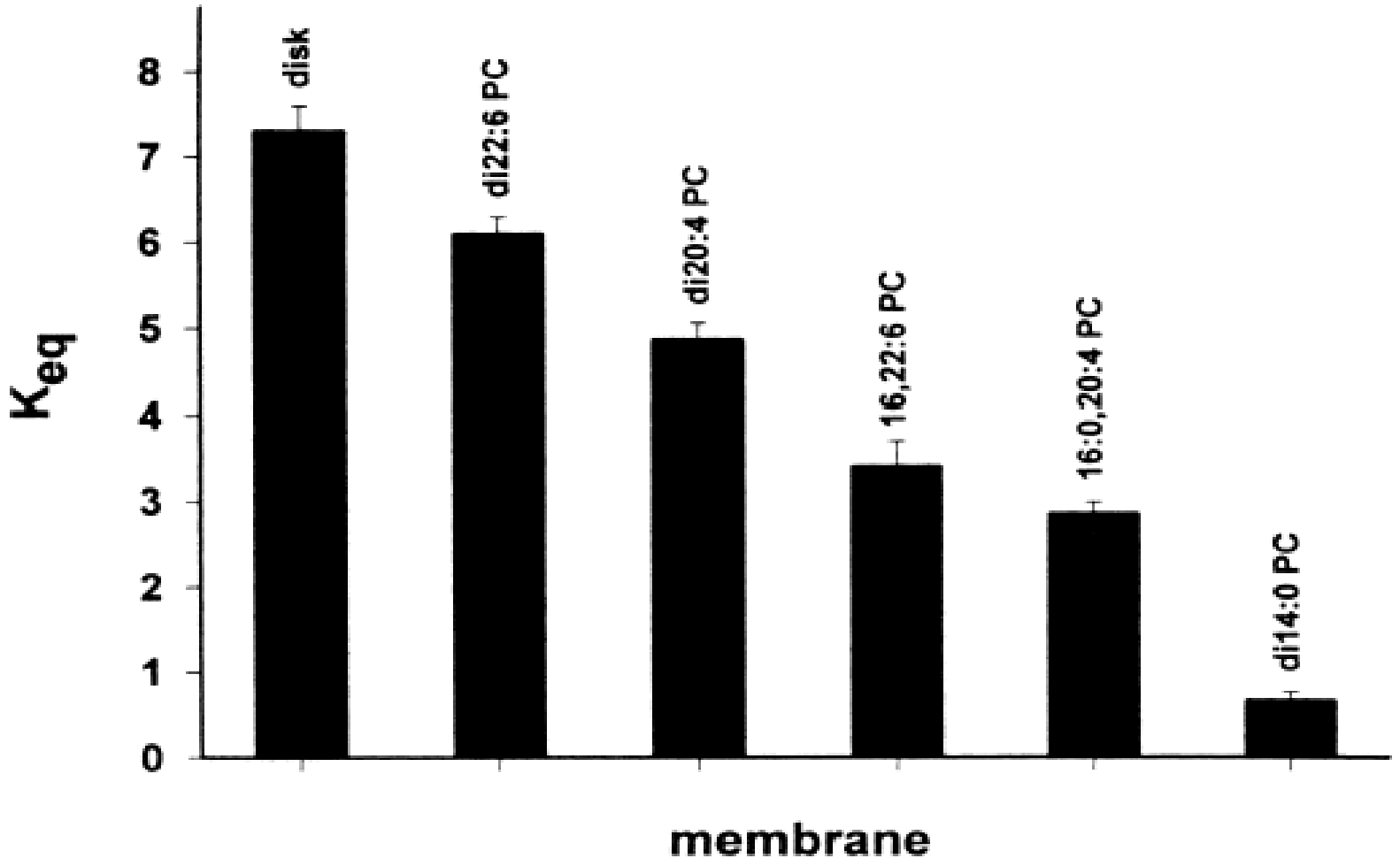
Genesis of a membrane potential

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



Dratz & Holte, J Nutr 1993

DHA is crucial in rhodopsin activation



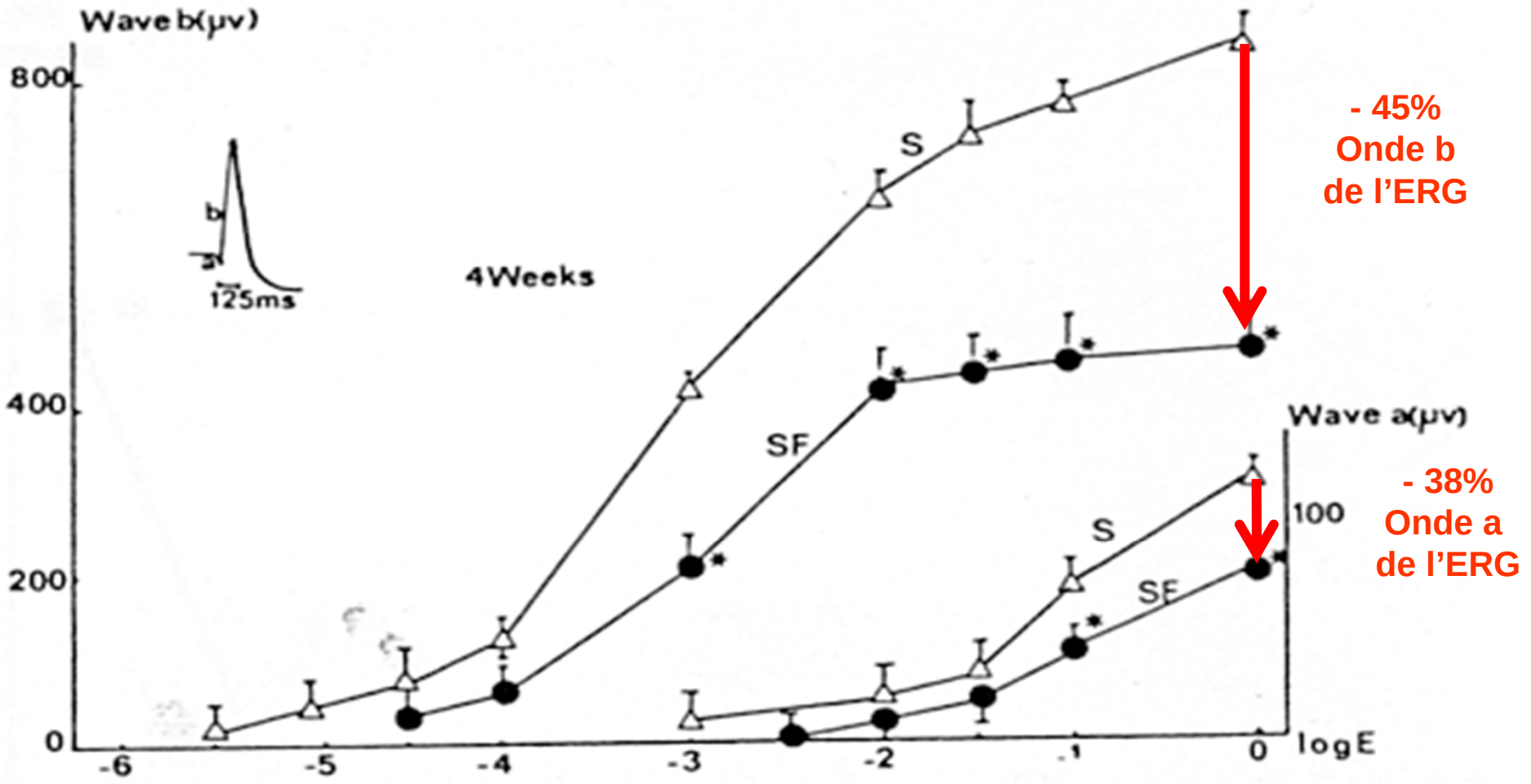
Litman & Mitchell, Lipids 1996

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

Δ12

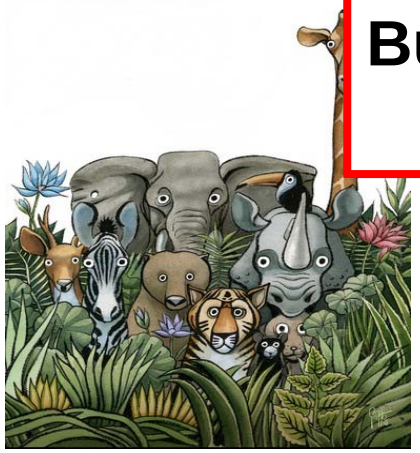
Linoleic acid
18:2n-6

Δ15

α-linolenic acid
18:3n-3

Δ6

Animals



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

20:3n-6 (dGLA)

Δ5

20:4n-6 (AA)

22:5n-6

20:4n-3

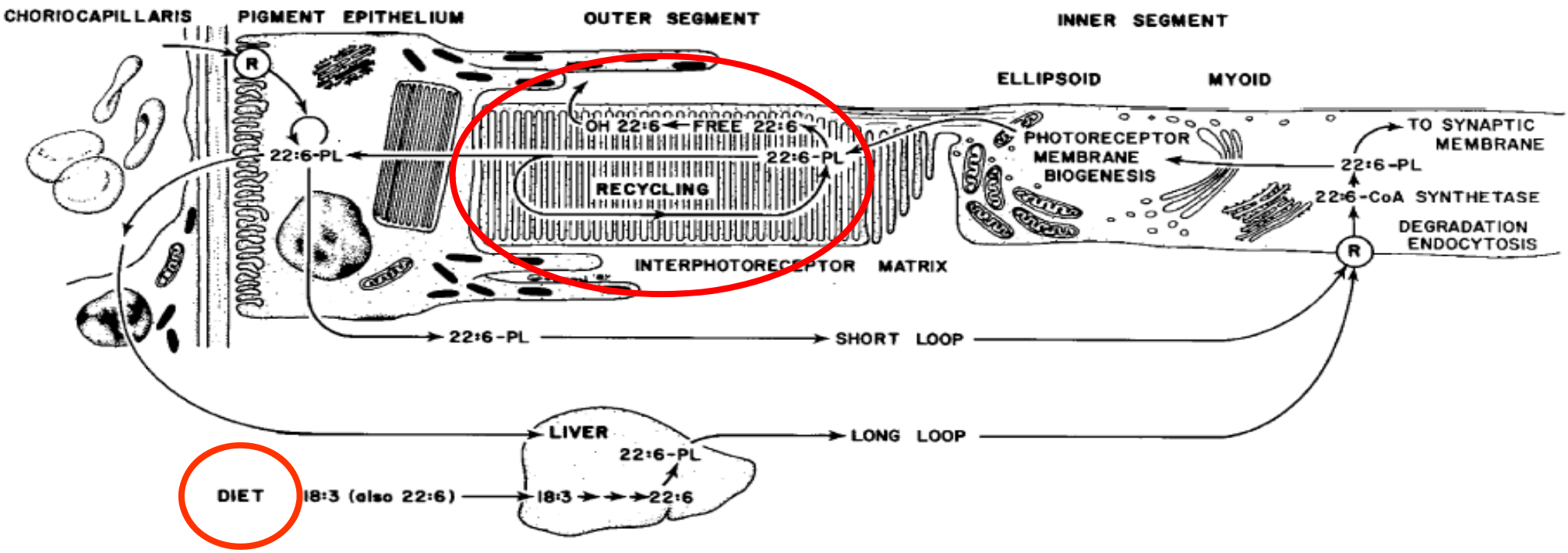
20:5n-3 (EPA)

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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Experimental Eye Research

journal homepage: 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

Lionel Bretillon [a,*], Gilles Thuret [b], Stéphane Grégoire [a], Niyazi Acar [a], Corinne Joffre [a], Alain M. Bron [c,d], Philippe Gain [b], Catherine P. Creuzot-Garcher [c,d]

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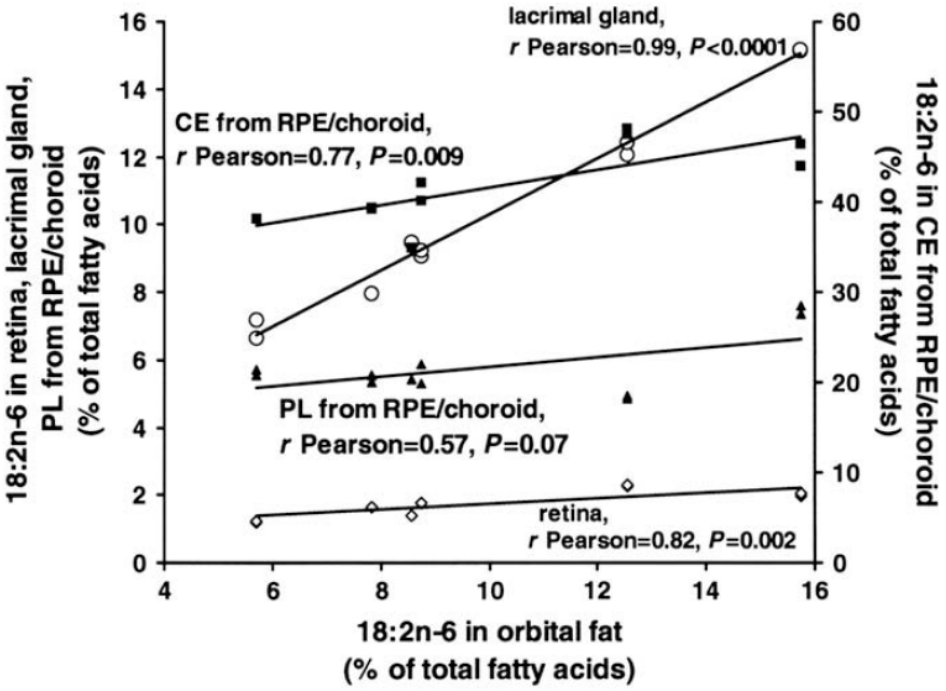
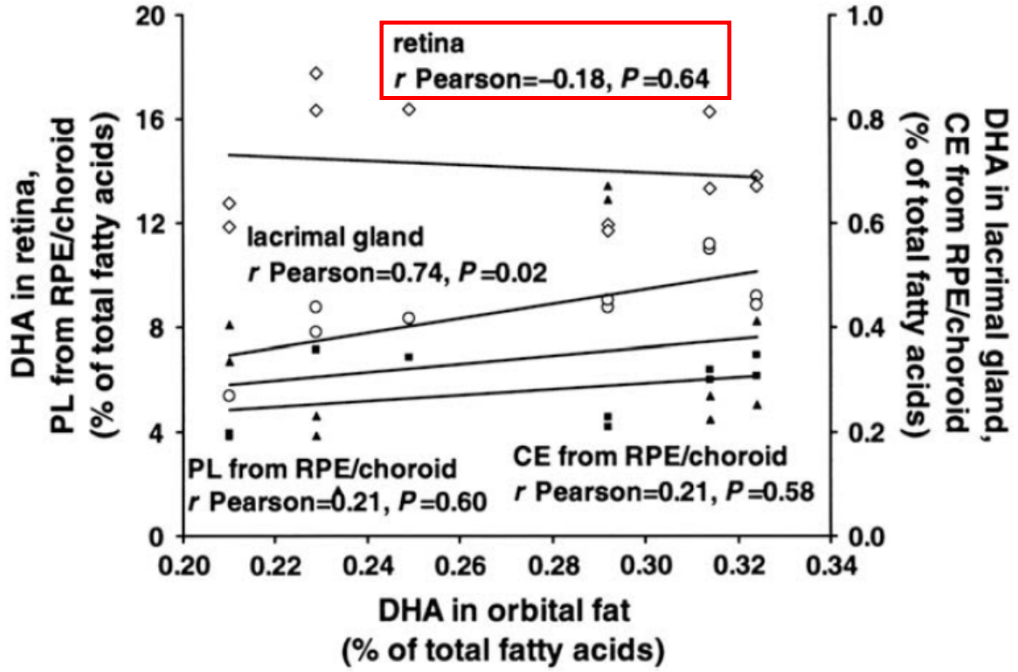
[d] Department of Ophthalmology, University Hospital, Dijon, France

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

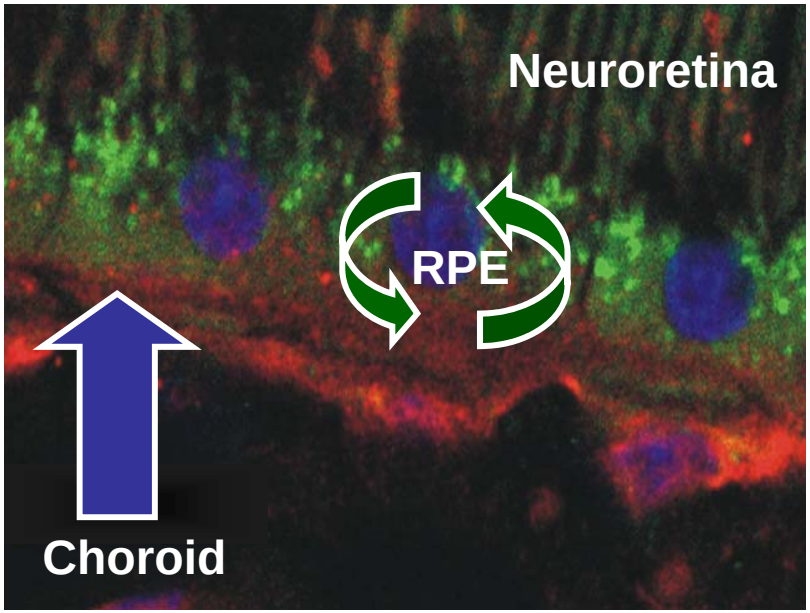


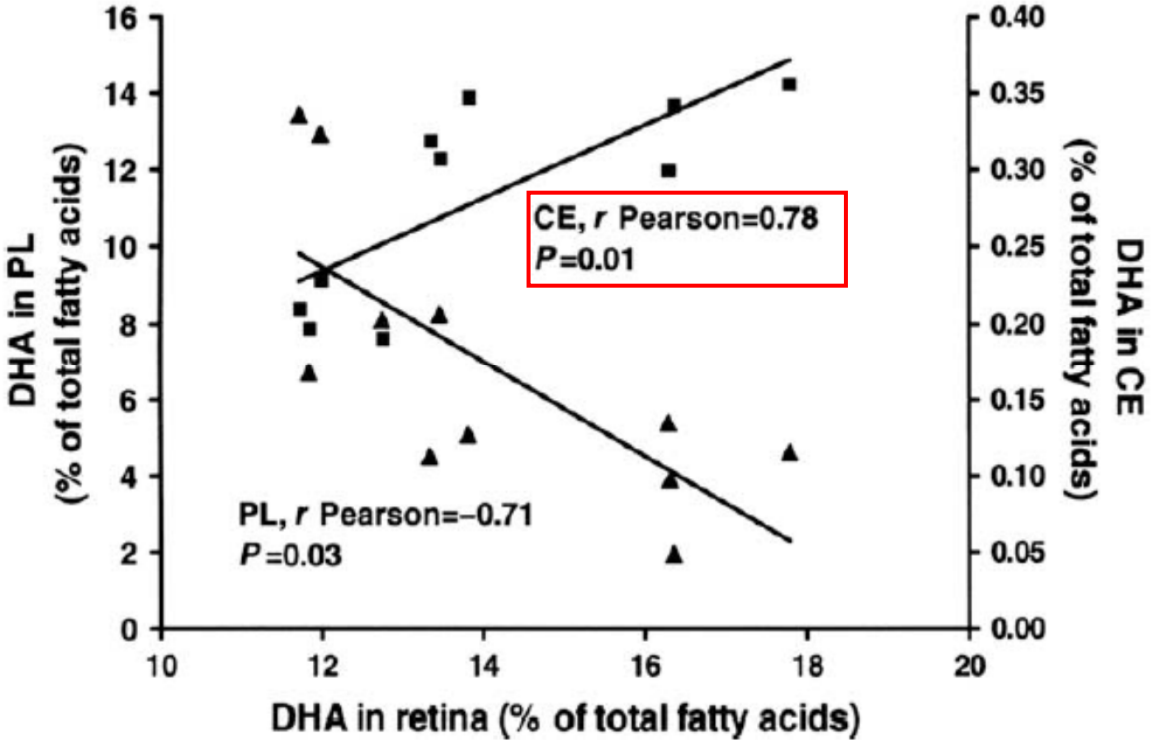


Circulating DHA (to some extent dietary) poorly participates to the retinal levels

Bretillon et al., Exp Eye Res 2008

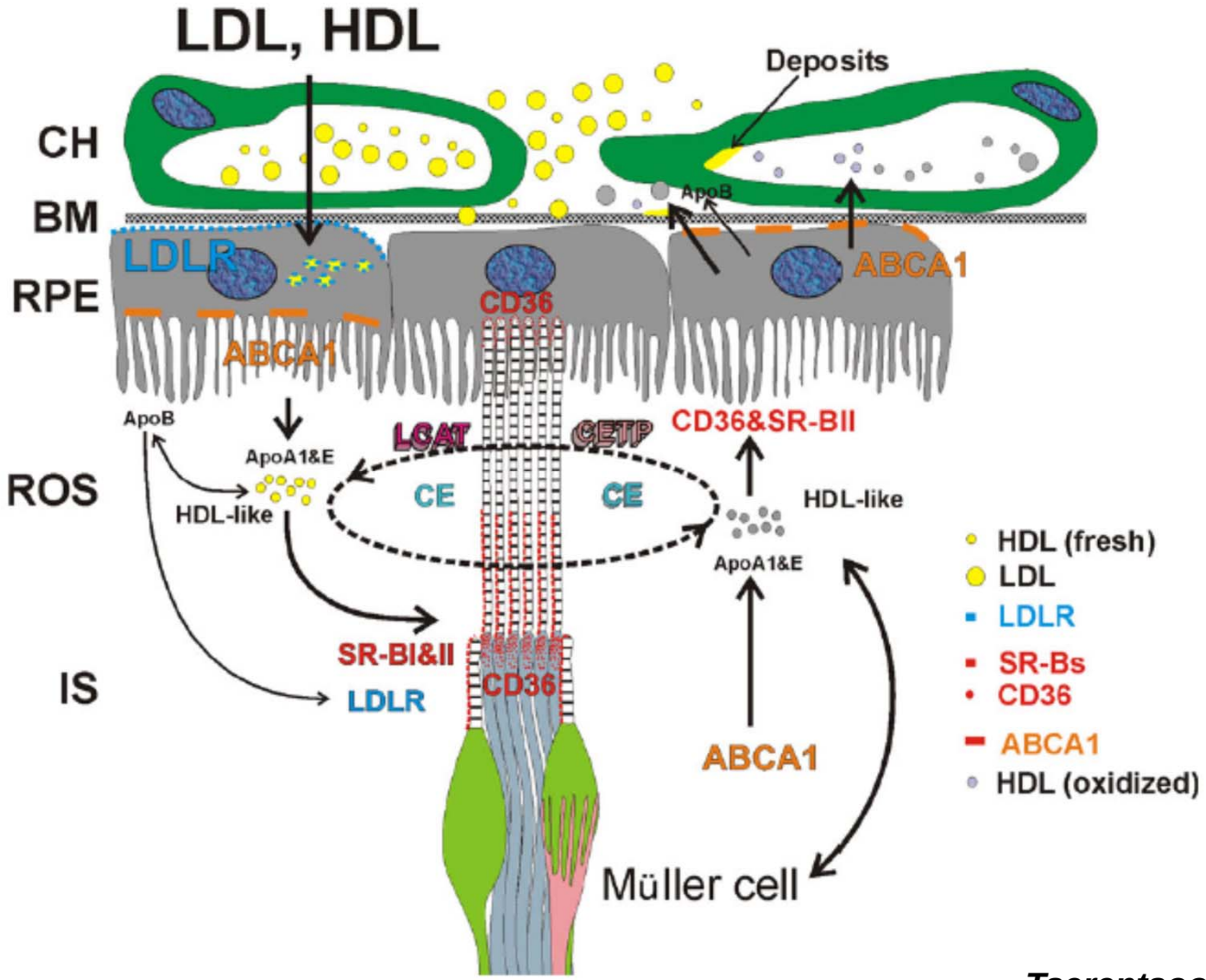
Despite cholesteryl esters in the RPE would be carriers of DHA and dietary fatty acids entering the retina





Bretillon et al. Exp Eye Res, 2008

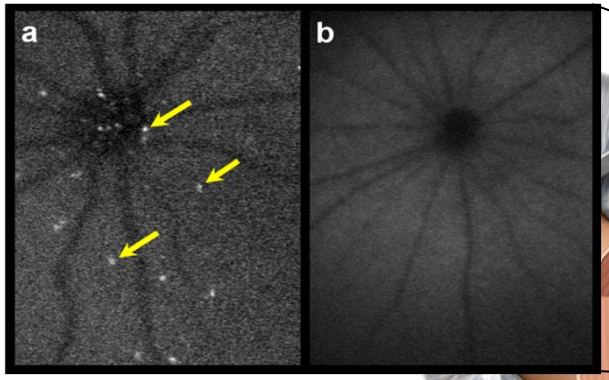
Intraretinal lipid metabolism



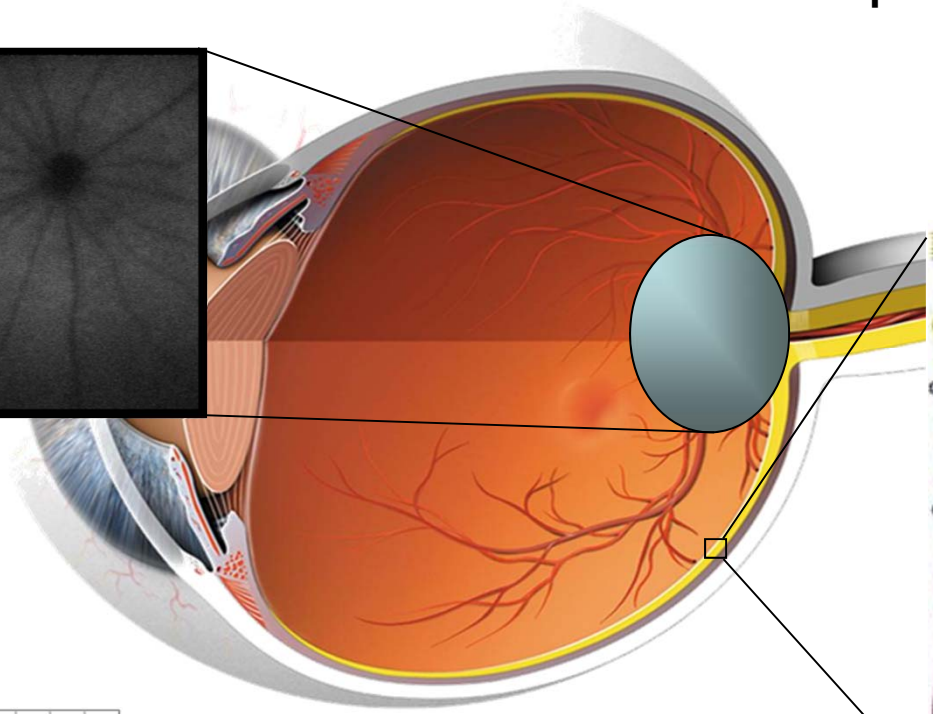
Tserentsoodol et al., Mol Vis 2006

Abrogating LDLR expression mimicks aging of the retina

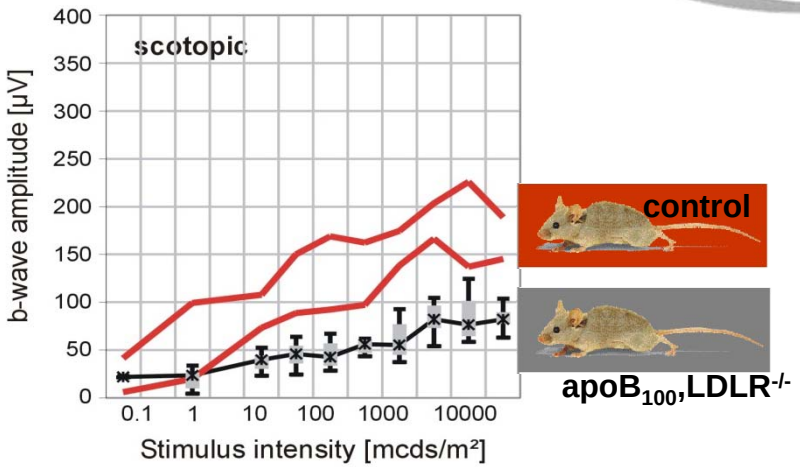
Accumulation of lipids (incl. cholesterol)



Fundus
(cSLO 488nm)



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



Reduced retinal functionality

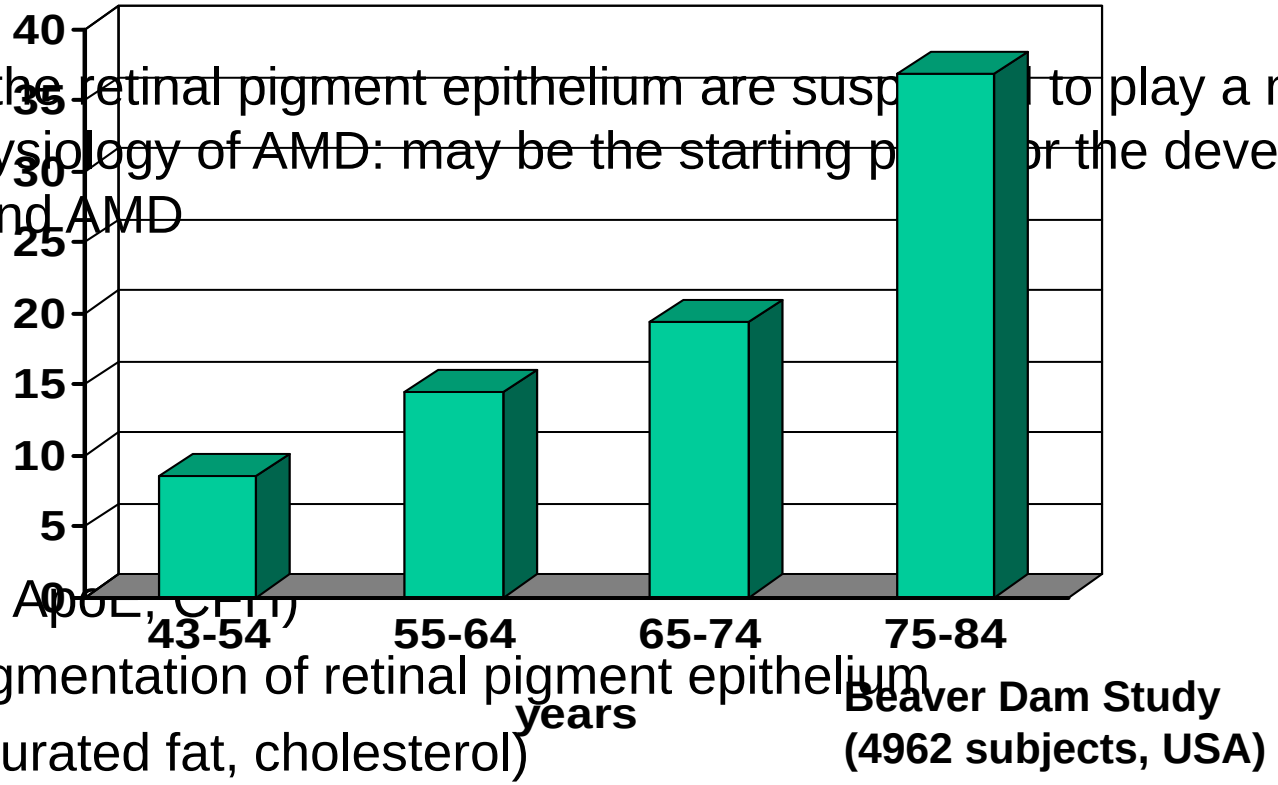
Bretillon *et al., Invest Ophthalmol Vis Sci 2008*

ω3 fatty acids and Age-related Macular Degeneration (AMD)

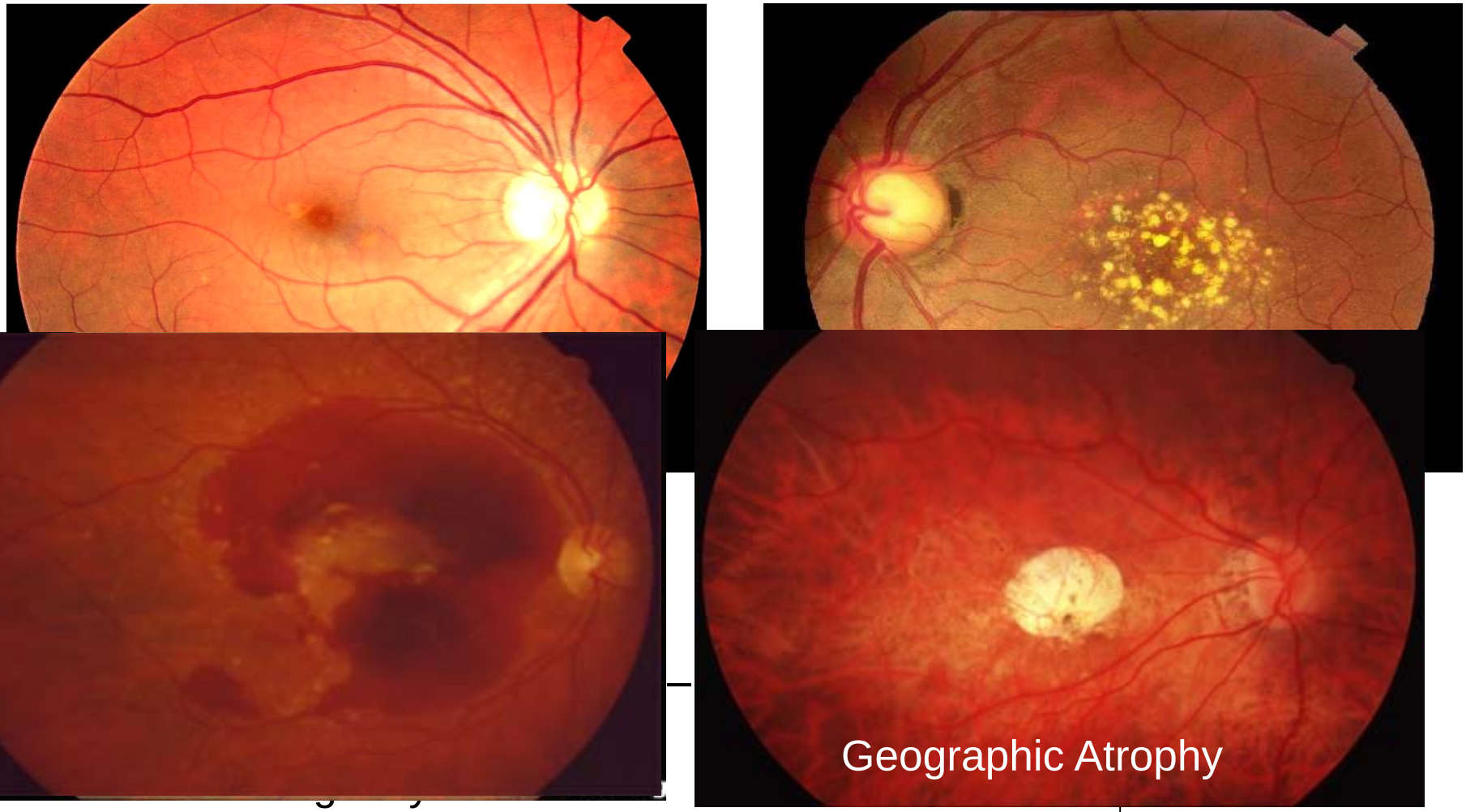
- The leading cause of visual loss in Western countries

- 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, CFH)
  - light, abnormal pigmentation of retinal pigment epithelium
  - dietary habits (saturated fat, cholesterol)



Grading AMD: from maculopathy to severe forms



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

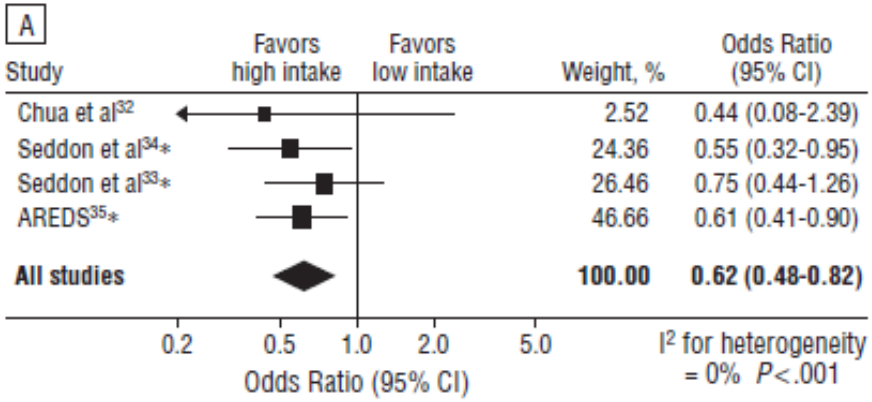
4 grades: from maculopathy to AMD

Fish intake, ω3 fatty acids and AMD

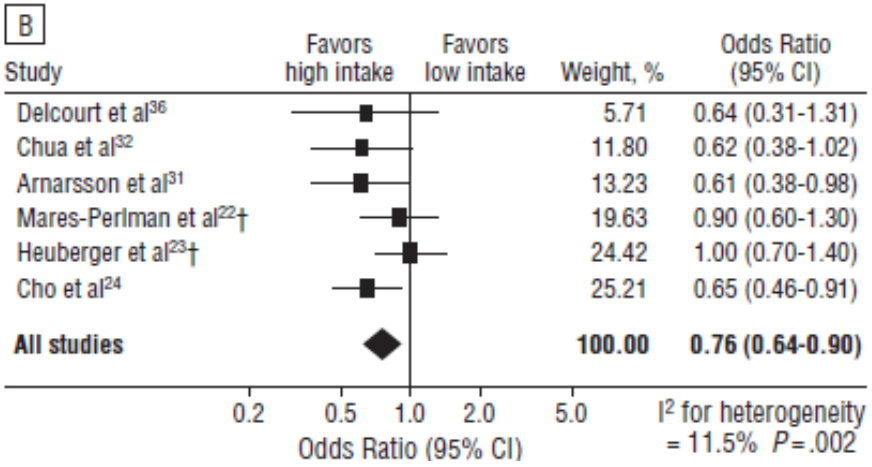
Meta-analysis from 7 databases

(88,974 people including 3204 AMD)

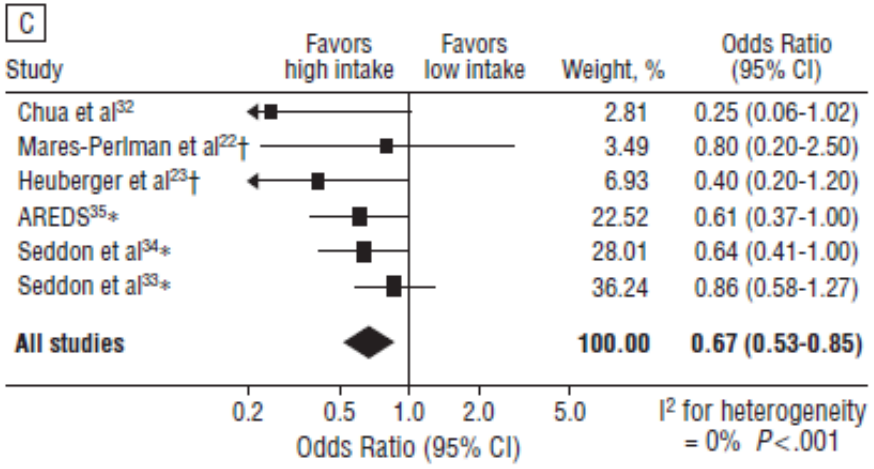
ω3 and late AMD



Fish intake and early AMD



Fish intake and late AMD



Chong et al., Arch Ophthalmol 2008

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	*P* 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).

Seddon et al., Arch Ophthalmol 2007

…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 1	2	3	4	*P* Trend
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 (≤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 (≥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.

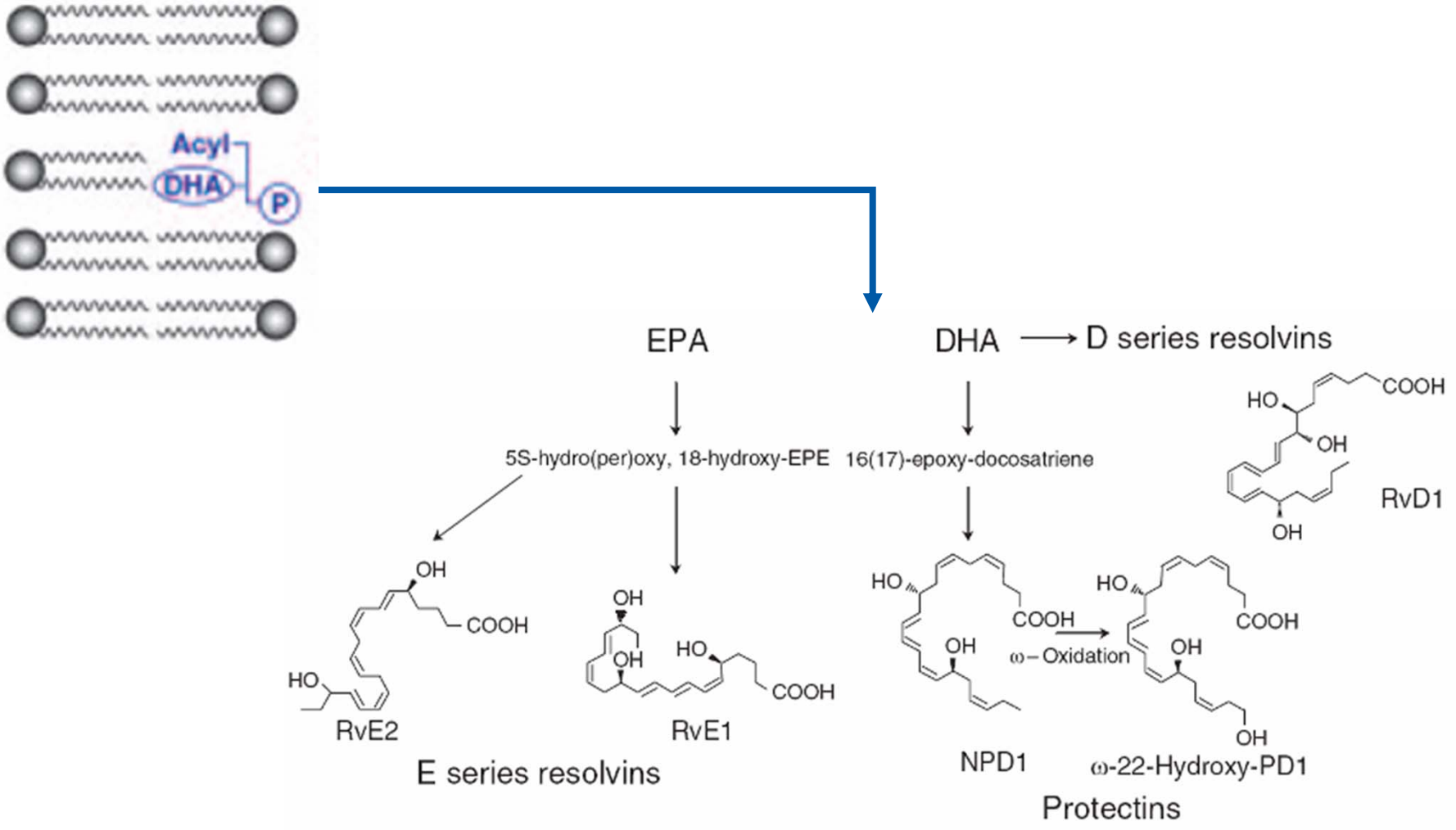
*Adjusted for log calories (continuous) and protein intake (quartile).

†Adjusted for education (≥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).

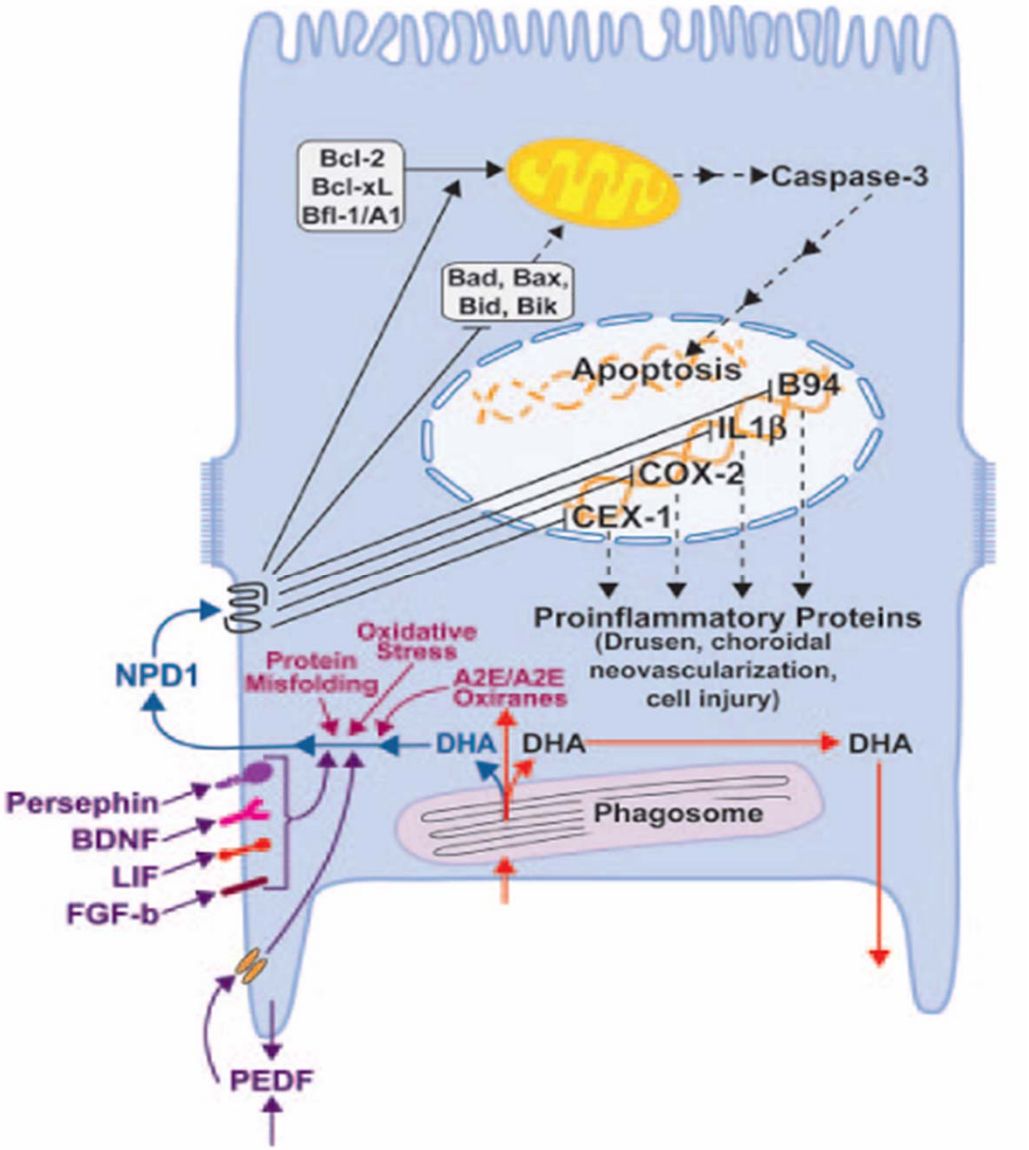
‡Adjusted for variables in model 1 plus total intake of zinc, vitamin C, and vitamin E (log scale for all 3).

Seddon et al., Arch Ophthalmol 2007

Mechanism: ω3 fatty acids may be converted into active metabolites in the RPE



NPD1 exhibits protective properties against angiogenesis, apoptosis, inflammation



Bazan, Invest Ophthalmol Vis Sci 2007

Conclusion

- Lipids are essential components of the retina, ω3 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 ω3, but also via ameliorating the ratio between dietary linoleic acid and ω3
- The mechanisms of this prevention remains uncertain, but may involve intraretinal metabolism of fatty acids (active metabolites)