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: ×2
>75 years: ×3
>85 years: ×5

in France
The neurosensory retina: a sensitive target of aging

Prevalence of pathologies after the age of 65 years

- Diabetic retinopathy: ~800,000
- Age-related Macular Degeneration (AMD): 1.25 million
- Glaucoma: >800,000
- Diabetic retinopathy: ~800,000

Leading cause of vision loss in Western countries

France

Of major concern in the next decades
Structural organization of the retina

- Anterior chamber
- Cornea
- Lens
- Vitreous
- Retina

Layers of the retina:
- Ganglion cells
- Amacrine cells
- Bipolar cells
- Horizontal cells
- Cones
- Rods
- Pigment epithelium (RPE)
- Choroid
Lipids in the retina

Lipids: 25% of dry matter

Bretillon et al., Exp Eye Res 2008
opsin

11cis-retinal
DHA
C22:6n-3

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

Phospholipid
Genesis of a membrane potential

Hyperpolarisation

Genesos of a membrane potential
The efficacy of the transduction pathway is dependent to the activation of rhodopsin.

Metarhodopsin I

Metarhodopsin II

closed protein Thin Membrane

open protein Thick Membrane

Drats & 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*
- 2007 Connor et al, *Nat Med*

Low DHA in the retina is associated with reduced retinal function
DHA deficient rats showed reduced electroretinographic response

- 45% Onde b de l’ERG
- 38% Onde a de l’ERG

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 dGLA (20:3n-6) → Δ5 AA (20:4n-6) → Δ5 EPA (20:5n-3) → Δ5 DHA (20:6n-3)

Animals:
- Linoleic acid (18:2n-6) → Δ12 α-linolenic acid (18:3n-3) → Δ5 EPA (20:5n-3) → Δ5 DHA (20:6n-3)

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

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?

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\textsuperscript{a, *}, Gilles Thuret\textsuperscript{b}, Stéphane Grégoire\textsuperscript{a}, Niyazi Acar\textsuperscript{a}, Corinne Joffre\textsuperscript{a}, Alain M. Bron\textsuperscript{c,d}, Philippe Gain\textsuperscript{b}, Catherine P. Creuzot-Garcher\textsuperscript{c,d}

\textsuperscript{a}Eye and Nutrition Research Group, UMR1129 FLAVIC, INRA, 17 rue Sully, BP 86510, F21065 Dijon cedex, France
\textsuperscript{b}Department of Ophthalmology, Biology, Imaging, and Engineering of Corneal Grafts, Faculty of Medicine, Saint Etienne, France
\textsuperscript{c}Eye and Nutrition Research Group, UMR1129 FLAVIC, University of Burgundy, Dijon, France
\textsuperscript{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.

Intraretinal lipid metabolism

Tserentsoodol et al., Mol Vis 2006
Abrogating LDLR expression mimics aging of the retina

Accumulation of lipids (incl. cholesterol)

Fundus (cSLO 488nm)

Reduced retinal functionality

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

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)

![Prevalence of AMD in Beaver Dam Study](beaver_dam Study_4962_subjects_usa)
Grading AMD: from maculopathy to severe forms

Criteria:
- Drusen
  - Size: <63µm – 63-125µm – >125µm
  - Total area
    - Affecting 1 eye or both
- Pigment abnormalities affecting 1 eye or both
- Geographic atrophy
- Neovascularization

4 grades: from maculopathy to AMD

Hemorrhagy
- Foveal neovascularization
- Exsudate

Geographic Atrophy

- 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors high intake</th>
<th>Favors low intake</th>
<th>Weight, %</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chua et al[32]</td>
<td></td>
<td></td>
<td></td>
<td>2.52 0.44 (0.08-2.39)</td>
</tr>
<tr>
<td>Seddon et al[34]</td>
<td></td>
<td></td>
<td></td>
<td>24.36 0.55 (0.32-0.95)</td>
</tr>
<tr>
<td>Seddon et al[35]</td>
<td></td>
<td></td>
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<td>26.46 0.75 (0.44-1.28)</td>
</tr>
<tr>
<td>AREDS[36]</td>
<td></td>
<td></td>
<td></td>
<td>46.66 0.61 (0.41-0.90)</td>
</tr>
<tr>
<td><strong>All studies</strong></td>
<td></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>0.62 (0.48-0.82)</strong></td>
</tr>
</tbody>
</table>

#### ω3 and early AMD

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors high intake</th>
<th>Favors low intake</th>
<th>Weight, %</th>
<th>Odds Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Detcourt et al[37]</td>
<td></td>
<td></td>
<td>5.71</td>
<td>0.64 (0.31-1.31)</td>
</tr>
<tr>
<td>Chua et al[32]</td>
<td></td>
<td></td>
<td>11.80</td>
<td>0.62 (0.38-1.02)</td>
</tr>
<tr>
<td>Arrarsson et al[38]</td>
<td></td>
<td></td>
<td>13.23</td>
<td>0.61 (0.38-0.98)</td>
</tr>
<tr>
<td>Mares-Pelman et al[39]</td>
<td></td>
<td></td>
<td>19.63</td>
<td>0.90 (0.60-1.30)</td>
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<tr>
<td>Heuberger et al[40]</td>
<td></td>
<td></td>
<td>24.42</td>
<td>1.00 (0.70-1.40)</td>
</tr>
<tr>
<td>Cho et al[41]</td>
<td></td>
<td></td>
<td>25.21</td>
<td>0.65 (0.46-0.91)</td>
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<tr>
<td><strong>All studies</strong></td>
<td></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>0.75 (0.64-0.90)</strong></td>
</tr>
</tbody>
</table>

#### Fish intake and late AMD

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors high intake</th>
<th>Favors low intake</th>
<th>Weight, %</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chua et al[32]</td>
<td></td>
<td></td>
<td></td>
<td>2.81 0.25 (0.06-1.02)</td>
</tr>
<tr>
<td>Mares-Pelman et al[42]</td>
<td></td>
<td></td>
<td></td>
<td>3.49 0.80 (0.20-2.50)</td>
</tr>
<tr>
<td>Heuberger et al[43]</td>
<td></td>
<td></td>
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<td>6.93 0.40 (0.20-1.20)</td>
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<tr>
<td>AREDS[36]</td>
<td></td>
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<td>22.52 0.61 (0.37-1.00)</td>
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<tr>
<td>Seddon et al[44]</td>
<td></td>
<td></td>
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<td>28.01 0.64 (0.41-1.00)</td>
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<td>Seddon et al[45]</td>
<td></td>
<td></td>
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<td>36.24 0.86 (0.58-1.27)</td>
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<tr>
<td><strong>All studies</strong></td>
<td></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>0.67 (0.53-0.85)</strong></td>
</tr>
</tbody>
</table>

*Chong et al., Arch Ophthalmol 2008*
Protection from AMD is associated above 2 servings of fish per week

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

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>
<thead>
<tr>
<th>Fatty Acid Intake</th>
<th>Quartile of Omega-3 Intake</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Omega-3 intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls, No.</td>
<td>64/102</td>
<td>61/120</td>
</tr>
<tr>
<td>Median intake, g</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>1.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Multivariate OR1 (95% CI)†</td>
<td>1.0</td>
<td>0.79 (0.52-1.21)</td>
</tr>
<tr>
<td>Multivariate OR2 (95% CI)‡</td>
<td>1.0</td>
<td>0.80 (0.53-1.21)</td>
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<tr>
<td>Linoleic acid intake</td>
<td></td>
<td></td>
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<tr>
<td>Cases/controls, No.</td>
<td>43/127</td>
<td>60/110</td>
</tr>
<tr>
<td>Median intake, g</td>
<td>7.12</td>
<td>10.45</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>1.0</td>
<td>1.72</td>
</tr>
<tr>
<td>Multivariate OR1 (95% CI)†</td>
<td>1.0</td>
<td>1.89 (1.15-3.11)</td>
</tr>
<tr>
<td>Multivariate OR2 (95% CI)‡</td>
<td>1.0</td>
<td>1.85 (1.12-3.08)</td>
</tr>
<tr>
<td>Linoleic acid intake, quartiles 1 and 2 (≤11.79 g)</td>
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<td></td>
</tr>
<tr>
<td>Cases/controls, No.</td>
<td>41/66</td>
<td>35/65</td>
</tr>
<tr>
<td>Median intake of omega-3, g</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>1.0</td>
<td>0.79</td>
</tr>
<tr>
<td>Multivariate OR1 (95% CI)†</td>
<td>1.0</td>
<td>0.97 (0.54-1.76)</td>
</tr>
<tr>
<td>Multivariate OR2 (95% CI)‡</td>
<td>1.0</td>
<td>0.94 (0.52-1.72)</td>
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<tr>
<td>Linoleic acid intake, quartiles 3 and 4 (&gt;11.80 g)</td>
<td></td>
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</tr>
<tr>
<td>Cases/controls, No.</td>
<td>23/36</td>
<td>26/55</td>
</tr>
<tr>
<td>Median intake of omega-3, g</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>1.0</td>
<td>0.79</td>
</tr>
<tr>
<td>Multivariate OR1 (95% CI)†</td>
<td>1.0</td>
<td>0.74 (0.37-1.47)</td>
</tr>
<tr>
<td>Multivariate OR2 (95% CI)‡</td>
<td>1.0</td>
<td>0.73 (0.35-1.55)</td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.
*Adjusted for log calories (continuous) and protein intake (quartile).
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‡Adjusted for variables in model 1 plus total intake of zinc, vitamin C, and vitamin E (log scale for all 3).
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, 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)