DHA: keeping our synapses sparking brightly as we age

At the Food Matters Live conference, Excel, London.

Wednesday 22nd November 2017

Dr Rob Winwood CSci FIFST-DSM Nutritional Products
Omega-3’s and Omega-6’s

- Omega-3’s are a broad group of fatty acids in which the first double bond exists at the third carbon.

- Omega-6’s are a broad group of fatty acids in which the first double bond exists at the sixth carbon.
LCP Dietary Sources

**Omega-6 FAs**
- LA (18:2) Linoleic acid
- ARA (20:4) Arachidonic Acid

**Omega-3 FAs**
- ALA (18:3) Alpha-linolenic acid
- EPA (20:5) Eicosapentaenoic Acid
- DHA (22:6) Docosahexaenoic Acid

Dietary Sources:
- Maize (corn) oil
- Cottonseed oil
- Safflower oil
- Soybean oil
- Eggs
- Meat
- Milk
- Fungal Oil from Mortierella Alpina
- Linseed (flax) oil
- Rape seed oil
- Fish oil
- Fish/Fish Oil Fortified foods
- Algal oil
- Fungal Oil from Mortierella Alpina

* Brenna et al 2009, ISSFAL Position Statement No. 5
**Carnielli et al 2007; Pawlosky et al., 2006
Marine Omega 3’s

Science shows their role for:-

- GOOD CARDIOVASCULAR HEALTH
- DEVELOPMENT OF THE NERVOUS SYSTEM AND MAINTENANCE OF BRAIN HEALTH
- VISUAL DEVELOPMENT AND MAINTENANCE OF EYE HEALTH
- EMERGING EVIDENCE THEY MAY REDUCE INFLAMMATION
Where do we get our Marine LC PUFA’s?

Marine microbes are primary source of PUFAs

Fish accumulate LC PUFAs

Fish are main source of LC PUFAs in diet

Bulk oils

LC PUFA genes in plants, fungi, and animals

Supplements

Enriched food products
Omega-3 Fatty Acids Are Not The Same

The distinct health benefits of Omega-3s:

- Cognitive development & function
- Visual development & function
- Inflammation
- Cardiovascular function

- Supports EFA status

DHA  EPA  ALA
Long-chain Fatty Acid Biosynthesis

Omega-6


Omega-3


Δ6-desaturase

Δ5-desaturase

Elongase

Peroxisomal oxidation

E-resolvins

D-resolvins

IMPORTANT TO ‘RE-BALANCE’

Hunter/Gatherer  Agriculture

1900 initial industrialized food system = complete imbalance

1970 completely industrialized food system

3 6

Ω  Ω
ESTIMATED AVERAGE DAILY INTAKES
EPA and DHA

Zone of Consensus for Nutritional Intake Recommendations

- American Heart Association
- British Nutrition Foundation
- Institute of Medicine of the National Academies
- ISSFAL
- Heart Foundation

mg/day

- Bulgaria
- China
- Romania
- Hungary
- Columbia
- Brazil
- Argentina
- Poland
- South Africa
- Czech Republic
- Germany
- Ireland
- Italy
- Switzerland
- UK
- USA
- Greece
- Australia
- Israel
- Russia
- France
- Denmark
- Sweden
- Chile
- UAE
- Canada
- New Zealand
- Jamaica
- Spain
- Portugal
- Korea
- Finland
- Norway
- Malaysia
- Japan
- Iceland
**Disclaimer: Not for purposes of claims**
Overview of mechanisms by which marine omega 3’s can influence cell function (adapted from Calder. P., 2014 Eur J Lipid Technol 116(10) )

- Marine Omega 3 Fatty Acid Exposure
- Receptors and Sensors
  - Raft Assembly
  - “Fluidity”
  - Membrane Composition
    - Substrate for eicosanoids, resolvins, maresins, Neuroprotectin D1 etc
- Intracellular and Extracellular signals
- Cell response
LCPUFA content in various tissues

What is DHA?

- Long chain omega-3 polyunsaturated fatty acid
- Important component of cell membranes
- *Found in all tissues;* most abundant in neural, retinal and CV conducting tissue
- Facilitates synaptic transmission
- Supports myelination
- Ultimately influences the speed at which information is acquired and processed
**EU authorized Health claims applicable to cognitive health***

<table>
<thead>
<tr>
<th>Vitamin C</th>
<th>Contributes to normal psychological functions. (source of = 15% RDA min).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B1</td>
<td>Contributes to normal psychological functions. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Vitamin B2</td>
<td>Contributes to the maintenance of the normal function of the nervous system. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Contributes to normal psychological functions. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Contributes to normal neurological and psychological functions. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Biotin</td>
<td>Contributes to normal psychological functions. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Contributes to normal psychological functions. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Niacin</td>
<td>Contributes to normal psychological functions. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Pantothenic Acid</td>
<td>Contributes to normal mental performance. Contributes to normal synthesis and metabolism of steroid hormones, vitamin D and some neurotransmitters. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>DHA</td>
<td>Contributes to the maintenance of normal brain function. (250 mg)</td>
</tr>
<tr>
<td>Iron</td>
<td>Contributes to normal cognitive function. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Zinc</td>
<td>Contributes to normal cognitive function. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Iodine</td>
<td>Contributes to normal cognitive and neurological functions (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Contributes to normal psychological functions. (source of = 15% RDA min).</td>
</tr>
<tr>
<td>Potassium</td>
<td>Contributes to normal neurological function. (source = 15% RDA min).</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Helps to increase alertness Helps to improve concentration (min 75mg per serving)</td>
</tr>
</tbody>
</table>

*Based on EFSA positive opinions*
Professor Michael Crawford receives the prestigious Rising Sun Medal - November 2015

Nutrients 2011, 3, 529-554; doi:10.3390/nu3050529

Review

Docosahexaenoic Acid (DHA): An Ancient Nutrient for the Modern Human Brain

Joanne Bradbury

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How do we think DHA works

- The omega 3 family are flexible. DHA has 6 double bonds which makes it the most flexible of all - able to adopt an indeterminately high number of conformations.
- DHA in the cell membrane lipids keeps the cell wall flexible, fluid and permeable.
- Ions can more easily cross the membrane and the specialised proteins in the membranes have to work harder to maintain the ionic gradients - which are key to driving the myriad of reactions within the cell. As a result, nerve impulses, signal reception and muscle contraction are sped up!
- The molecular movement of DHA will speed up many processes catalysed by membrane proteins (Hulbert, J. Exp. Biol. 2003, 206 p 2308).
- DHA is a precursor of the molecule Neuroprotectin D1 (NPD1).
DHA Distribution in the Brain

- DHA represents 10 to 15% of brain total fatty acids
  - DHA represents 97% of brain omega-3 fatty acids,
- DHA preferentially represented in cell membranes:
  - **DHA**
    - frontal cortex
      1. executive function
      2. working memory
        - sustained attention,
        - problem solving
    - hippocampus
      3. spatial learning
      4. declarative memory formation
        (ability to recall facts and events)
Role of DHA in Brain Structure and Function

**Structural Role**
- Modulates function of signal transduction molecules, G-protein coupled receptors (e.g. rhodopsin)
- Integrated into brain phospholipids

**Functional Roles**
- Converted to anti-inflammatory **docosanoids** (e.g. Neuroprotectins, Resolvins, Endocannabinoids & Anandamide)
- Participates in signaling via modulating G Protein Coupled Receptors (GPCR)
- Neuronal differentiation
- Synaptogenesis
- Apoptosis (Kim et al., JBC)
- Modulates Ion Channels: Na+ transport (Kang & Leaf)
How does DHA work in the brain

- Facilitates electrical transmission between neurons
- Source of essential brain messenger and anti-inflammatory molecules (e.g. resolvins, neuroprotectin D1)

Current theories:

- The “almost infinite” possible conformations of DHA produces constant movement that is imparted to neural membranes
- The DHA molecule transmits electrons along its length and acts a semi-conductor (Crawford, 2008)
- Preserves telomere length of DNA (Farzaneh-Far, JAMA 2010)
- Reduces effects of free-radical damage in frontal cortex cells of the brain.
DHA supports brain cell growth

Cerebral cortex neurons exposed to DHA in cell culture extend branches and make connections much like they do during memory and developmental processes. (Unpublished Martek data, details available on request)
Cell wall membrane bilayer

From www.agen.ufl.edu

From www.aber.acc.uk/gwydd-cym/graffeg/biolgell/mosaig.eng.jpg
Proposed Neuroprotective Properties of DHA

Omega-3 fatty acids and traumatic neurological injury: from neuroprotection to neuroplasticity?

Adina T. Michael-Titus and John V. Priestley

Centre for Neuroscience and Trauma, Blizzard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AT, UK
The impact of DHA supplementation in supporting cognitive health
Europe’s population will get older
The Dementia Explosion

• Globally there were 46.8 million cases of dementia in 2015 (World Alzheimer report) at a cost of US$ 818 Billion.

• The incidence is estimated to rise to 74.7 million globally in 2030 at a cost of US$ 2 trillion.

• By 2050 the number of cases anticipated to rise by 68% on the 2015 figure with much of this increase taking place in low and middle income countries.

• In 2015, 9.6 million Europeans were living with dementia ca 1 in 50 of the population. The prevalence rises to 44% in the over 90s.

(OECD 2016, Health at a Glance)
DHA and the Aging Brain

- Brain DHA is dependent on dietary intake
- Low brain and blood DHA status is associated with Alzheimer’s Disease \cite{Begin2010}
- Higher DHA dietary intake is associated with significantly reduced risk of AD \cite{Begin2010}
- Spatial memory tasks are dependent on DHA in rats
- DHA oxylipin derivatives (NPD1) are neuroprotective
- Transgenic animal models show DHA reduces beta amyloid plaques and neurofibrillar phosphorylated tau in the brain

**Goal:** Evaluate the effects of DHA on cognitive outcomes in healthy elderly (\(\geq 55\) yrs.) with a mild memory complaint (Martek-sponsored study)

**Trial Design**

- Randomized, double-blind, placebo-controlled, parallel, multi-centre
- Oral Dose: 900 mg/day DHA or placebo (corn/soy) for 6 months.
- 465 subjects with subjective memory complaint
- 1\(^{o}\) Endpoint: cognitive test of memory, attention & learning (Cantab™): Paired Associate Learning test (PAL)
- 2\(^{o}\) Endpoints: cognitive tests of executive function, Daily Living skills, visual acuity, plasma phospholipid fatty acid levels, safety and tolerability

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*The MIDAS Study*

MIDAS Study - Results

Compared to normative data on CANTAB PAL, results show a 7 year improvement with DHA versus 3.6 year improvement with placebo. A net 3.4 year improvement.
Alzheimer’s Disease

- The most common form of dementia
- A progressive, degenerative, ultimately fatal brain-wasting disease. The symptoms are:
  - Memory loss
  - Disturbed mood
  - Psychosis
  - Depression
  - Loss of linguistic articulation
- The main risk factors are age and genetics, but an imbalance of protective factors are also important
- There is no pharmaceutical treatment to halt progression of the condition despite 244 clinical trials to date (Lipids and the Brain Conference, 2017)
The pathological hallmarks of Alzheimer’s are brain lesions consisting of the extracellular accumulation of β-amyloid protein as amyloid plaques, and intracellular accumulation of hyperphosphorylated protein Tau in the form of neurofibrillary tangles.

These hallmarks can be seen in human brains many years before any symptoms of cognitive decline are apparent.

DHA is lost in the AD brain due to oxidations to F4 Neuroprostanes. Klosinski LP Ebiomedicine 2015, 2(12):1880-1904.
Could the Mediterranean diet offer protection from the onset of AD?

- The Mediterranean diet typically is associated with lower energy density and lower glycaemic index. It is also rich in marine omega 3 fatty acids, B, C and E vitamins, carotenoids and polyphenols.

- Observational studies (including 3C study in France) show that high adherence to a Mediterranean diet is associated with slower cognitive decline. However the possible confounding effect of a more healthy lifestyle must also be considered.

- The ApoE4 allele has a major effect.

- DHA and EPA intake was positively associated adherence to the Mediterranean diet, whilst intake of Omega 6 PUFA’s was negatively associated. There was no association with land derived Omega 3 fatty acid ALA. (Barberger-Gateau et al, 2011, OCL 18:4:224-7.)
Randomised clinical trials of omega 3 fatty acids interventions in MCI and AD patients

<table>
<thead>
<tr>
<th>Source by Study Condition</th>
<th>Mean Age, y</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcomes</th>
<th>No. of Participants</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>76</td>
<td>2 g/d of DHA vs placebo</td>
<td>18 mo</td>
<td>Cognitive tests</td>
<td>384</td>
<td>No overall effect</td>
</tr>
<tr>
<td>Quinn et al,¹³ 2010</td>
<td>73</td>
<td>1.7 g/d of DHA and 0.6 g/d of EPA vs placebo</td>
<td>12 mo</td>
<td>Cognitive tests</td>
<td>204</td>
<td>No overall effect</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>70</td>
<td>1800 mg/d of EPA-DHA and 400 mg/d of EPA-DHA vs placebo</td>
<td>6 mo</td>
<td>Cognitive tests</td>
<td>302</td>
<td>No overall effect</td>
</tr>
<tr>
<td>van de Rest et al,¹⁵ 2008</td>
<td>75</td>
<td>1080 mg/d of EPA and 720 mg/d of DHA vs placebo</td>
<td>24 mo</td>
<td>Cognitive tests</td>
<td>30</td>
<td>No overall effect. Among participants with MMSE score &gt; 27, improved cognition scores</td>
</tr>
<tr>
<td>Chiu et al,¹⁶ 2008</td>
<td>65</td>
<td>430 mg/d of DHA and 150 mg/d of EPA vs placebo</td>
<td>12 mo</td>
<td>Cognitive tests</td>
<td>36</td>
<td>Improved short-term and working memory</td>
</tr>
<tr>
<td>Lee et al,¹⁷ 2013</td>
<td>74</td>
<td>EPA (1.67 g/d EPA + 0.16 g/d DHA), DHA (1.55 g/d of DHA + 0.40 g/d of EPA) or linoleic acid (2.2 g/d)</td>
<td>6 mo</td>
<td>GDS and cognitive tests</td>
<td>54</td>
<td>Verbal fluency improved in the DHA group</td>
</tr>
</tbody>
</table>

From Yassine H, JAMA Neurology 2017
**NIH Trial - Algal DHA for the Treatment of Alzheimer’s Disease**  
(Quinn J et al, JAMA 2011; 304(17): 1903-1911)

Hypothesis: DHA supplementation will slow the rate of cognitive decline in patients with mild-to-moderate Alzheimer’s Disease (AD) by a combination of antioxidant, anti-amyloid, and neuroprotectant effects.

**Trial Design**

- Randomized, double-blind, placebo-controlled, parallel, multi-center study
- Doses: 2,000 mg DHA/day vs. placebo
- Study treatment: 18 months
- Sample size: 400 patients
- Sites: 50 (U.S.) coordinated by ADCS
- Study Timeline: Start: Jan 1, 2007   Complete: 2009
- Primary Endpoint: changes in Cognitive measures: ADAS-Cog and CDR-SOB
- Secondary Endpoints: biomarkers, fatty acid levels, MRI, safety measures
Pre-specified sub-group analyses: ADAS result in ApoE4 positive and negative
(Quinn J et al, JAMA 2011; 304(17): 1903-1911)

E4 positive  
n=135 DHA; n= 94 placebo

E4 negative  
n=91 DHA; n=67 placebo

*p not corrected for multiple comparisons
Mechanisms linking ApoE4 status with DHA delivery brain before neurodegeneration

From Yassine H, JAMA Neurology 2017
Summary and Final Thoughts

• DHA is an important structural component of the central nervous system and brain

• DHA has an important role in enabling the transmission of chemical messengers across nerve synapses.

• DHA metabolites can have potent anti-neuroinflammatory properties

• DHA shows some promise in arresting some forms of memory loss seen in mild cognitive decline (Mohajeri et al, Nutrition 2015; 31:261-275).

• DHA transport to the brain is highly dependant on ApoE4

• Intervention trials with DHA on Alzheimer's patients, classified by ApoE status in the prodromal state (i.e. before any neurodegeneration) remain to be done.

• Once AD patients are in a state of cognitive decline, DHA intervention is unlikely to have any benefit. The same is true of other pharmacological interventions to date.
Acknowledgements

• Professor Michael Crawford of Imperial College London - the “father” of DHA neuroscience
• Also to Captain Joe Hibbeln, Nicholas Bazan, Stephen Cunnane, Richard Bazinet and the many other scientists referenced in this presentation.
• And to my DSM colleagues: Norm Salem, Karin Yurko-Mauro, Hasan Mohajeri and Sheila Gautier.
Thank you! Grazie Mille! Bedankt! Merci! Danke! Spasebo! Tak! Gracias!

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