

Lipids & Brain 2: a symposium on lipids and brain health

Marleen Nys and Ignace Debruyne

Participants at the Omega-3 Summit in Bruges, Belgium (March 3–4, 2011) concluded that “brain and heart disorders resulting from long-chain omega-3 (LC omega-3) deficiency (both EPA and DHA) are the biggest challenges to the future of humanity.” (See *inform* 22:314–315, 2011.)

The Lipids & Brain 2—Journées Chevreul 2011 symposium addressed the brain-related challenge during a three-day conference held March 28–30 in Paris, France. This meeting of the minds was organized by the French Society for the Study of Lipids (SFEL, formerly AFECG) and attended by about 200 professionals. Thirty-five presentations by leading scientists highlighted a growing body of evidence that lipids are key to preventing the pandemic of mental and neurodegenerative diseases that threatens public health worldwide. Here are some conference highlights.

Neurodevelopment

Next to adipose tissue, the brain is the organ with highest lipid level. Lipids constitute 50–60% of the brain's dry weight. Of these lipids, 15–20% are long-chain (LC) polyunsaturated fatty acids (PUFA), primarily docosahexaenoic acid (DHA). DHA is concentrated in the brain's cellular membranes and plays a major role in signaling. The efficiency of DHA uptake in the brain depends on its bioavailability and form. According to M. Linder (France), phospholipids in the brain have three to five times more DHA than triglycerides do; phospholipid accumulation in the brain is also two to three times higher.

Lipids are essential for proper neuronal development related to brain and brain functions. Expectant mothers have a greatly increased need for LC-omega-3 fatty acids, as their fetuses need DHA for optimal brain and visual system development. DHA uptake also impacts fetal growth as well as behavior, metabolic, and immune system development. The DHA needs of the developing child are highest during the last months of pregnancy and during lactation. Recent human studies show that a high supply of linoleic acid (LA) negatively affects DHA uptake (R. Gibson and M. Makrides, Australia; B. Strandvik, Sweden; S. Osendarp, the Netherlands; G. Mathieu and B. Delplanque, France; C.E. Childs, UK).

S.C. Dyall (UK) discussed the potential of omega-3 fatty acids during neurogenesis in the hippocampus, dentate gyrus, and in individual neurons. At seven weeks' time, new neurons migrate to the sub-granula zone, leading to differentiation and dendrite development. In adults, the loss of neurons from aging can be partly offset by adequate DHA levels in the brain. This should positively improve memory, mood, and inflammation level.

Signaling mechanisms and omega-3-metabolism in the brain

DHA is intensively used and recycled in the brain (average daily uptake is 3.8 mg), with an average turnover of 42 days. The



eicosapentaenoic acid (EPA) level remains relatively low due to rapid removal through β -oxidation. Changes in the brain's lipid metabolism are at the origin of neurological pathologies such as Alzheimer's disease (AD) and bipolar disorder. A better understanding of the role of fatty acids in the brain could provide new therapeutic opportunities (R.P. Bazinet, Canada).

LC-PUFA are essential for proper signaling and for promoting so-called survival pathways (neurons with extended age), neurotrophic mechanisms (neurogenesis and synaptogenesis), and downregulation of neuro-inflammation. DHA depletion inhibits neurite growth, downregulates synaptic proteins in the hippocampus, and induces cell death in the hippocampus. Sufficient DHA (and its metabolites) provides for regeneration and long-term support of memory and learning. Ideally, high-DHA and phospholipid levels come together with a lower arachidonic acid (AA) level, a high omega-3 and low omega-6 metabolism (K. Hee-Yong, NIH, USA).

S.C. Cunnan (Canada) opened the conference asking whether DHA can sufficiently protect the aging brain from illnesses such as AD. The “World Alzheimer's Report 2009” states that AD will come to dominate as a disease, particularly in developing countries where facilities to deal with it are not readily available. Cunnan discussed DHA homeostasis (the relations between food and plasma DHA) and the needs, levels, and changes in the elderly and in AD patients. Reduced glucose uptake in the brain, an early metabolic problem in AD, is strongly associated with DHA levels. Unraveling this problem might lead to a solution for AD.

LC-omega-3s also influence the endo-cannabinoid signaling system (CR), playing a key role in the control of synaptic function and metabolism. This influences brain function and stress response, as well as the risk of metabolic syndrome and obesity. Stress and fasting will increase the pressure on CR, leading to hyperphagia. Omega-3 supplementation reduces the effect, allowing better stress tolerance and metabolic regulation. PUFA nutrition also influences CNTF (a cytokine controlling neural differentiation of astrocytes)

and hypothalamic control of energy homeostasis (V. di Marzo, Italy, and C.M. Vacher, France).

M. Taouis (France) indicated that central defects in insulin and leptin signaling not only precede obesity and diabetes development by changing energy homeostasis but also affect the central nervous system. Both signaling systems play a role in the phosphorylation of the tau protein associated with AD, and resistance to insulin and leptin increases the risk of developing AD: Both obese and AD patients have a reduced level of these hormones in their cerebrospinal fluid.

S.I. Rapoport (USA) discussed PET (positron emission tomography) scan imaging of DHA absorption and incorporation in the brain: mechanism, neurotransmitter functions, effect of gene mutations, receptors, and signaling pathways. B.K. Puri (UK) presented an advanced *in vivo* MRI imaging method that directly measures phospholipid molecules in brain cell membranes.

Depression and schizophrenia

Several epidemiological studies indicate that a high omega-6/omega-3 ratio increases the risk of depression. EPA is primarily responsible for the antidepressant effect. A large French study showed efficacy of EPA in treating major depression but found it had no effect on co-morbid anxiety disorder. The results of the “Nurses’ Health Study” show that risk of depression also goes down with a higher alpha linolenic acid (ALA) intake and a lower LA intake (M. Lucas, USA; F. Lesperance, France; J. Martin, UK).

The following hypothesis is also quite exciting: K^+ -channels (TREK-1) play a role in the resistance to depression—an inhibitor could therefore act as an antidepressant. Spadin, a peptide derived from sortilin (NTSR3), inhibits K^+ -channels. Animal studies confirm the potential antidepressant activity of spadin, which might therefore be the first-identified natural antidepressant peptide.

Studies of schizophrenia have investigated whether there is a relation between psychotic episodes and omega-3 blood levels. Disorders may be linked to redox and PUFA synthesis disorders, with low LC-omega-3 status leading to more negative symptoms and higher mortality and morbidity (H. Bentsen and D. Solberg, Norway).

According to L.E. Rhodes, UK, seven out of 10 epilepsy patients in a research study may have benefited from EPA supplementation, without any side effects. A larger study with higher doses is needed to confirm the effect. Animal studies have revealed the anticonvulsive effect of a magnesium and ALA combination that probably plays a preventive role against neurodegeneration (N. Pages, France).

Neuroprotection

LC-omega-3s are also essential for neuroprotection. Stroke is the third-highest cause of death, yet there are few preventions or treatments: 25% of patients die within one month of a stroke; another 50% remains severely disabled.

AD is the leading cause of dementia, which destroys neurons and synapses, memory, and thinking. Epidemiological studies suggest that poor nutritional status is a major cause of stroke and AD, with insufficient DHA and phospholipids as main indicators. The prevailing omega-3 deficiency in the Western population is primarily caused by the typical Western diet, that is, this could be a major reason for the large number of people suffering from neurodegenerative diseases.

The 2011 Chevrel Medal was awarded to Nicolas Bazan (USA) for his work on the role of DHA in the prevention of stroke, AD, and retinal degeneration. Bazan studied the apoptosis mechanisms in neurodegeneration and found that a metabolite of DHA, neuroprotectin 1 (NPD1), promptly formed during oxidative stress and ischemia. NPD1 regulates neuro-inflammatory signaling pathways and apoptosis mechanisms. It can switch down the pro-inflammatory gene cascade, and it can promote cell integrity. It protects against neuronal damage, downregulates the formation of amyloid- β ($A\beta$), and protects against $A\beta$ toxicity. NPD1 also appears to be drastically reduced in AD, and it protects the retinal epithelium from oxidative stress.

DHA biosynthesis in the liver is associated with cognition. Defects in DHA synthesis correlate with lower DHA-phospholipids in the brain and cognitive decline in AD (G. Astarita, USA). Cholesterol metabolism in the brain strongly influences neuronal plasticity, learning, and memory. At birth, the brain contains about 20% of the total cholesterol available, but this decreases with age. Increase in cholesterol turnover

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was shown to improve memory function in AD animal models. It can be influenced by dietary factors (M. Mulder, the Netherlands).

I. Denis (France) argued that an LC-omega-3 deficit can accelerate the functional loss of astro/glial cells, which may compromise the protective effect of astrocytes during aging. N. Blondeau (France) sought and found an effective therapy for stroke prevention using ALA. ALA affects both the neurovascular unit and the temporal mechanisms in stroke. ALA also protects neurons from glutamate excitotoxicity, and provides for vasodilation in arteries, thus improving cerebral blood flow, triggering neuronal plasticity, promoting neurogenesis, synaptogenesis, and increasing the expression of neurotrophic factors (which by itself improves recovery from stroke). Preconditioning with ALA may reduce brain damage, as was shown in animal tests.

The neuroprotective effect of LC-omega-3s is also valid for several traumas of the brain, spinal cord, and peripheral lesions—in both the acute and long-term phases. EPA and DHA provide increased neuronal and glial survival, reduce the neuro-inflammation, and protect neurites after paraplegia. LC-omega-3s also activate a broad range of repair pathways (A. T. Michael-Titus, UK).

Over age 65, eye pathologies (17%) are the second-most common ailment after heart disease (18%). Age-related macular degeneration (AMD) is the leading cause of blindness in later life, exceeding glaucoma and other retinopathies. The retina is one of the tissues with the highest level of PUFA, mainly phospholipids with DHA and 10–20% cholesterol esters. Phosphatidylcholine and DHA are essential for proper functioning of rods and cones in the retina. DHA deficiency is associated with poor retinal function. Dysregulation of the pigment of the retina is probably the first step in the development of AMD. Mutations in the elongase enzymes, which can extend fatty acid chains, have been described as a cause of juvenile macular degeneration and other eye pathologies. DHA plays a key role in metabolic pathways and mechanisms of eye protection against inflammation, apoptosis, and angiogenesis. Adequate supply of good dietary lipids (DHA + EPA + γ -linolenic acid) prevents aging of the retina and protects against AMD (L. Bretillon and O. Berdeaux, France).

Nutrition is essential

Epidemiological studies indicate that poor nutritional status is a major cause of degenerative diseases. Main indicators are insufficient levels of DHA and phospholipids (the main constituents of neural and synaptic membranes) and of B vitamins, which stimulate neurite development, as well as vitamins E and C. The synergy of these nutrients is essential for regeneration: A well-designed multinutrient supply will improve membrane and receptor function, as well as the processing of amyloid precursor protein, which results in reduced formation of amyloid- β plaques (Souvenir II LipiDiDietstudy; J. Sijben, the Netherlands).

(Neural) omega-3 fatty acids have strong immuno-modulating properties and reduce the neuro-inflammation that may arise with age. High levels of LC omega-3s directly improve well-being and cognition, as well as mood and functioning (S. Layé, France). Many studies have shown that a Mediterranean diet rich in omega-3s offers excellent protection against cognitive decline and other degenerative diseases (P. Barberger-Gateau, France).

C. Samieri (France) received the “Thesis Award” for her work on the role of diet on the aging brain, more specifically the role of fatty acids. Samieri analyzed several epidemiological studies and found the following relations:

- Fish, fruit, and vegetable consumption improves cognitive and psychological health;

- Mediterranean diet goes with slower cognitive decline;
- Increased plasma EPA levels come with a lower risk of dementia and a lower deterioration of memory in depressed people or in carriers of apolipoprotein E gene mutations (DHA only in the latter);
- A high omega-6/omega-3 ratio indicates increased risk, especially in people suffering from depression.

To conclude the conference, P. Guesnet (France) summarized as follows: PUFA = polyunsaturated fatty acids = LC-omega-3s. Whether these come directly from food (as DHA or EPA), or through food conversion (starting from ALA) isn't critical, so long as supply is sufficient. However, it has to be kept in mind that ALA conversion to EPA and DHA is inefficient especially at the high omega-6 levels found in a typical Western diet.

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