

# Nutrition in Brain Development and Aging: Role of Essential Fatty Acids

Ricardo Uauy, MD, PhD, and Alan D. Dangour, PhD

*The essential fatty acids (EFAs), particularly the n-3 long-chain polyunsaturated fatty acids (LCPs), are important for brain development during both the fetal and postnatal period. They are also increasingly seen to be of value in limiting the cognitive decline during aging. EFA deficiency was first shown over 75 years ago, but the more subtle effects of the n-3 fatty acids in terms of skin changes, a poor response to linoleic acid supplementation, abnormal visual function, and peripheral neuropathy were only discovered later. Both n-3 and n-6 LCPs play important roles in neuronal growth, development of synaptic processing of neural cell interaction, and expression of genes regulating cell differentiation and growth. The fetus and placenta are dependent on maternal EFA supply for their growth and development, with docosahexaenomic acid (DHA)-supplemented infants showing significantly greater mental and psychomotor development scores (breast-fed children do even better). Dietary DHA is needed for the optimum functional maturation of the retina and visual cortex, with visual acuity and mental development seemingly improved by extra DHA. Aging is also associated with decreased brain levels of DHA: fish consumption is associated with decreased risk of dementia and Alzheimer's disease, and the reported daily use of fish-oil supplements has been linked to improved cognitive function scores, but confirmation of these effects is needed.*

Key words: aging, brain development, essential fatty acids

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Drs. Uauy and Dangour are with the Nutrition and Public Health Intervention Research Unit, London School of Hygiene & Tropical Medicine (LSHTM), London, United Kingdom; Dr. Uauy is also with the Public Health Nutrition Division, Instituto Nutrición y Tecnología de Alimentos (INTA), Universidad de Chile, Santiago, Chile.

Please address all correspondence to: Professor Ricardo Uauy, Nutrition and Public Health Intervention Research Unit, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT; Phone: 44-20-7958-8126; Fax: 44-20-7958-8133; E-mail: ricardo.uauy@lshtm.ac.uk.

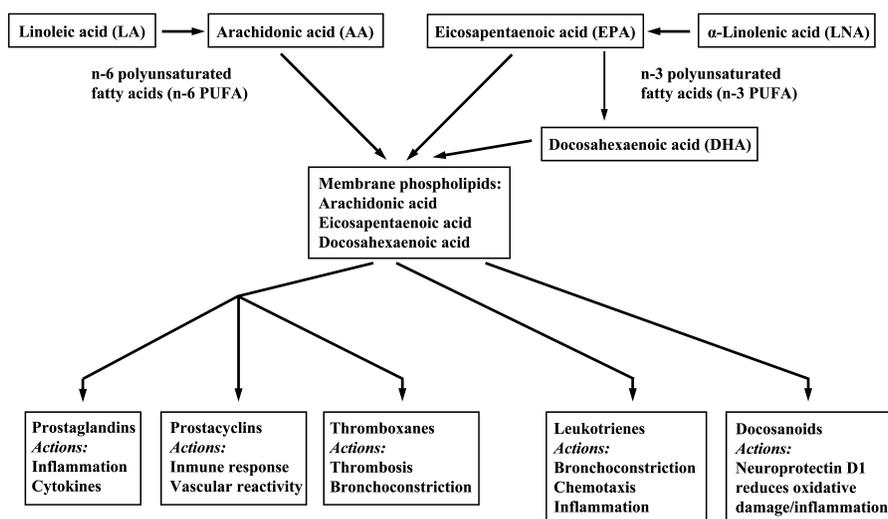
## INTRODUCTION

Numerous studies over the past 40 years have evaluated the impact of nutrition in early life on central nervous system development. These studies have clearly demonstrated that reductions in energy and/or essential nutrient supply during the first stages of life have profound effects on somatic growth, and on the structural and functional development of the brain.

The timing and nature of the nutritional insult affects brain development in different ways. For example, cell number as measured by DNA content is affected by intrauterine and early postnatal malnutrition, while synaptic connectivity can be affected if malnutrition occurs between birth and 3 years of age.<sup>1</sup> Similarly, variations in the supply of dietary precursors may determine neurotransmitter levels (serotonin, norepinephrine, dopamine, and acetylcholine), while variation in the supply of essential and nonessential lipids may affect the structural composition of the brain and of myelin sheaths.<sup>2</sup> It has also become clear that brain somatic growth may proceed normally in the face of certain nutritional insults (such as those caused by iron and taurine), but that brain structure and function are significantly altered if specific essential nutrients are lacking during development.

Taking this into consideration, it is perhaps not surprising that emerging evidence also suggests that nutritional status is associated with brain health in older age. At this last stage in the life course, it again appears that dietary sufficiency of micronutrients, including essential fatty acids (EFAs), may be key to ensuring good cognitive function.

We review the role of EFAs in the human brain during development and aging, the biochemical and molecular basis for their effect on neural development, the evidence of the effect of n-3 fatty acids on human brain development during growth of preterm and term infants, and the role of n-3 fatty acids in preventing cognitive decline during aging. Finally, we examine the challenge of promoting and preserving brain function throughout the life course. Figure 1 shows the overall



**Figure 1.** The metabolic processing and effects of n-6 and n-3 metabolism.

scheme of n-6 and n-3 essential fatty acid processing and some of their metabolites' functions.

## ROLE OF ESSENTIAL FATTY ACIDS

As early as 1929, researchers acknowledged that specific components of fat may be necessary for the proper growth and development of animals and possibly humans.<sup>3</sup> By the 1960s, the essentiality of certain fatty acids previously thought to be of marginal nutritional importance in humans was proposed when clinical signs of what are now known to be classic symptoms of EFA deficiency (e.g., dryness and thickening of the skin and growth faltering) became apparent in infants fed skim milk-based formulas and in those given lipid-free parenteral nutrition.<sup>4</sup> In a clinical and biochemical study of 428 infants fed cow's milk-based formulations with different types of fat, Hansen et al.<sup>4</sup> firmly established the essentiality of one such fatty acid, the n-6 fatty acid linoleic acid, in normal infant nutrition. Deficiency of n-3 fatty acids resulted in more subtle clinical symptoms such as skin changes unresponsive to linoleic acid supplementation, abnormal visual function, and peripheral neuropathy.<sup>5,6</sup>

Notable here are the effects of n-3 deficiency on the nervous system, which suggest that n-3 fatty acids may be key to its adequate development and functioning. This notion is further supported by the high concentrations of n-3 long-chain polyunsaturated fatty acids (n-3 LCPs) such as docosahexaenoic acid (DHA) in the cerebral cortex and the retina, a brain-derived neuronal network specialized for photo-signal transduction and processing.<sup>7,8</sup> Indeed, the dry weight of the human brain is predominantly lipid, with 22% of the cerebral cortex and 24% of white matter consisting of phospholipids. Brain

proteins are fixed by the genetic code, but the fatty acid composition of brain phospholipids can be modified by diet. Studies in animals and humans have established that dietary deficiency of n-3 fatty acids, or of linoleic acid in combination with linolenic acid, results in decreases in brain phospholipid arachidonic acid and DHA, with concomitant increases in brain n-9 and n-7 mono-(MUFAs) and polyunsaturated fatty acids (PUFAs).<sup>9-12</sup> In response to n-3 fatty acid deficiency, cells have decreased DHA levels and increased levels of n-6 docosapentaenoic acid, the most unsaturated product of n-6 fatty acid metabolism.

EFA's play a crucial structural role in brain tissue, especially in cell membranes, and the functional implications associated with diet-induced compositional changes have been much researched.<sup>13-15</sup> The function of membranes has been demonstrated to be modulated by their fatty acid composition, which can result in altered membrane fluidity, volume, and packing; changed lipid phase properties; and modification of membrane lipid-protein interactions within specific microdomains.<sup>13-17</sup>

During development, the changes in neural membrane composition of the greatest potential significance are those related to physical properties and membrane excitability. Diet-induced changes affecting these two factors have been demonstrated in animal and human neural cell lines.<sup>18,19</sup> Deficiency of n-3 fatty acids can modify membrane proteins' ability to bind ligands and activate enzymes, and alter receptor activity, antigenic recognition, signal transduction, and lateral mobility within the lipid bilayer.<sup>20-22</sup> The increased excitability of n-3-sufficient membranes has been demonstrated by studies showing that the formation of excited pyrene dimers in human retinal cells, which result from the collision of two pyrene monomers, is increased by DHA

supplementation of the culture media.<sup>23</sup> Moreover, this phenomenon was associated with enhanced choline transport into retinal cells. Membrane lipid composition also plays a crucial role in determining the electrical properties of cultured neuronal cells, possibly by altering the number of active Na<sup>+</sup> channels.<sup>24-26</sup>

Both n-3 and n-6 LCPs play important roles in neuronal growth and also affect the development of synaptic processes for neural cell interaction. For example, arachidonic acid, which is present in growth cones and synaptosomes,<sup>25</sup> is preferentially released from membrane phospholipids by the action of endogenous phospholipase A2, and participates in signal transduction events that regulate cone growth and activity, leading ultimately to the conversion of growth cones to mature synaptic endings.<sup>27</sup> Similarly, DHA, which is a major component of the membranes at the synaptic site, influences the membrane microenvironment and thereby modulates neurotransmitter uptake and release.<sup>19</sup> Arachidonic acid and DHA also act together by activating the transcription of genes responsible for lipid-binding proteins to affect the process of interaction between nerve cells during development. Specific fatty acid-binding proteins are crucial in the signaling pathway of the response of glial cells to neurons, and DHA binding regulates this activity.<sup>28</sup>

There is a growing body of evidence demonstrating that LCPs can affect the expression of genes that regulate cell differentiation and growth, and may thereby have a profound and long-lasting impact on human health. Indeed, via this mechanism, early diet may influence the structural development of organs, as well as the formation of neurologic and sensory functions. The provision of DHA to incubated rat retinal neurons has been demonstrated to be associated with increased rod outer segment growth and the presence of higher concentrations of rhodopsin.<sup>29</sup> In a study on human fetal retinal explants treated with DHA or oleic acid (an n-9 MUFA), 14% of all retinal genes studied were overexpressed when retinal explants were exposed to DHA at physiologic concentrations, while less than 1% were overexpressed when exposed to oleic acid. Transcripts displaying changes in abundance encoded for proteins involved in a variety of biological functions, including neurogenesis and neuronal function, while housekeeping genes were minimally affected.<sup>30</sup> Similarly, transcripts for ion channels involved in retinal synaptogenesis, such as the N-methyl-D-aspartate (NMDA)- and gamma amino butyric acid (GABA)-activated Ca<sup>2+</sup> channels, are highly expressed in retinal explants treated with DHA.<sup>31,32</sup> Ca<sup>2+</sup> influx through these channels increases the intracellular Ca<sup>2+</sup> concentration in specific cells,<sup>33</sup> which appears to trigger cellular responses that contribute to the establishment of neuronal connections. These results support the idea that

the effects of DHA on gene expression contribute to the development and maturation of the human retina.

The fetus and placenta are entirely dependent on maternal EFA supply for their growth and development. While the third trimester of pregnancy is the crucial period for fat deposition in the human fetus, key phospholipids in placental vessels and uterine vasculature require maternal EFA supply for eicosanoid formation from the moment of conception.<sup>34,35</sup> There is a progressive enrichment in the concentration of arachidonic acid and DHA in circulating lipids in the fetus during the third trimester,<sup>36</sup> and a significant increase in arachidonic acid and DHA content of fetal brain tissue has been observed during the last trimester of gestation and initial postnatal months,<sup>37</sup> times when the demands for vascular (and especially neural) growth are greatest.<sup>36</sup> A total of 600 g of EFA are transferred from mother to fetus during a full-term gestation, and most of the n-3 fatty acids that enter the fetal circulation are accrued from the mother even if maternal n-3 concentrations are low.

#### **EFFECT OF n-3 LCPs IN THE DEVELOPING BRAIN AND RETINA**

Preterm infants, who may not receive sufficient lipids during their third trimester of pregnancy, are often considered particularly vulnerable to EFA deficiency. Numerous studies have therefore investigated the effect of supplementation of preterm infants with LCPs on their plasma and tissue composition, as well as on measures of their visual and cognitive function. These studies have been reviewed previously.<sup>38</sup> The largest study of preterm infants included 427 subjects fed either a control formula or one of two different LCP-supplemented formulas containing DHA and different sources of arachidonic acid (one contained egg phospholipids and the other fungal oil).<sup>39</sup> The level of DHA was 0.25% of total fat in preterm formulas and 0.15% in the follow-up formula; both LCP-supplemented formulas contained 0.4% arachidonic acid. Significant differences were found in sweep visual evoked potential at 6 months, favoring the LCP-supplemented formula groups over the control formula group. No differences were found in a behavioral test of visual acuity (Teller cards), Fagan habituation, or MacArthur vocabulary tests. For infants below 1250 g at birth, an advantage in the Bayley Scales of Infant Development score in the LCP-supplemented group was observed at 12 months.<sup>39</sup>

A very recent study of preterm infants compared the effect of LCP supplementation of formula milk with arachidonic acid from fungal oils and DHA from either fish (n = 130) or algal (n = 112) sources with control unsupplemented milk (n = 199) on various measures of development.<sup>40</sup> The DHA-supplemented infants had sig-

nificantly greater scores than the infants fed the control formula in the mental and psychomotor development indices of the Bayley Scales at 18 months after term. However, all values stayed significantly below those of the reference sample of 105 term breast-fed infants.<sup>40</sup> Longer-term follow-up of these infants or those from other studies has not been reported.

Full-term infants also appear to be dependent on dietary DHA for optimal functional maturation of the retina and visual cortex,<sup>41-59</sup> and this finding has led to considerable debate over whether healthy full-term infants require LCPs in formula. Several studies have investigated the effect of LCP supplementation on term infants, although these studies are hard to design because they are often confounded by artificial feeding by the mother.

Gibson et al.<sup>54</sup> supplemented 52 mothers (postpartum) to produce breast milk with DHA concentrations ranging from 0.1% to 1.7% of total fatty acid, and found that there was an association between breast milk DHA and the plasma and erythrocyte phospholipid DHA content of the infants. Interestingly, this relationship was found to be saturable, in that there was no further increase in infant blood DHA content if breast milk DHA increased above 0.8% of total fatty acids. Infant visual evoked potential acuity was not found to be related to DHA; however, developmental quotient at 12 weeks but not at 24 months was significantly, if weakly, correlated to breast milk DHA.<sup>54</sup>

A smaller, single-center study assessed the behavior of two groups of term infants fed either a combined DHA- and arachidonic acid-supplemented formula (n = 21) or a control formula (n = 23) from birth to 4 months. The trial demonstrated that the results of habituation tests at 4 months<sup>59</sup> and means-end problem-solving at 10 months<sup>41</sup> were enhanced in the LCP-supplemented children. These findings are important, as higher problem-solving scores in infancy are related to higher IQ scores in childhood,<sup>56</sup> but may be limited in their extrinsic validity because of the small sample size and rather homogenous population.

More persistent benefits of DHA supplementation on visual acuity<sup>60</sup> and mental development<sup>44</sup> have been demonstrated in a trial involving 108 term infants, 79 of whom were exclusively formula fed (the randomized group), and 29 of whom were exclusively breast-fed. The formula was provided for the first 17 weeks of life, and the LCP-supplemented formula contained 0.35% DHA with or without 0.72% arachidonic acid derived from algal oil sources, while the control formula contained sufficient  $\alpha$ -linolenic acid but no LCPs. The exclusively breast-fed group and the supplemented groups receiving either DHA or DHA + arachidonic acid, had significantly better visual evoked potential acuity than the

control group. However, the differences were only significant at periods of rapid changes in development of acuity, the first 20 weeks and after 35 weeks of age, and not at about 6 months of age when acuity development reaches a plateau.<sup>60</sup> Fifty-six of the formula-fed children were followed up at 18 months and assessed for mental development,<sup>44</sup> and this was the first time more long-term effects on mental development from LCP supplementation had been reported. Despite the small sample size, a significant 7-point normalized difference between LCP-supplemented and non-supplemented children was detected in the mental development index of the BSID-II. Significant correlations between blood DHA levels with measures of visual acuity during the first year of life and mental development at 18 months were also noted.<sup>44</sup> Similar results of the beneficial effect of DHA and arachidonic acid supplementation on visual evoked potential acuity at 52 weeks was very recently reported by the same researchers in a trial among 103 term infants.<sup>61</sup>

However, a larger trial of 447 healthy full-term infants (138 breast-fed; 309 formula-fed infants) did not find a benefit of LCP supplementation.<sup>62</sup> The formula-fed infants were randomized to receive LCP-supplemented milk (n = 154) and the controls received non-supplemented milk (n = 155) for at least the first 6 weeks of life. The infants were followed up for 18 months, and no effect of LCP supplementation was noted on cognitive function, motor development, infection, atopy, or formula tolerance. The interpretation of this data is limited, as the two formulas differed in several fatty acids, not just LCPs. Furthermore, the expected higher intelligence quotient of breast-fed infants was not found in this study, and no biochemical evaluation of the effect of dietary LCP supplementation on infant EFA status was included.<sup>62</sup>

Results from a recent trial in Norway suggest that supplementation of the mother with a relatively large quantity of n-3 LCPs during pregnancy and for 4 months postpartum may have important benefits for children.<sup>63</sup> Children born to mothers who received cod liver oil during pregnancy and lactation (n = 48) scored 4 points higher on the mental processing composite of the Kaufman Assessment Battery for Children at 4 years of age than children whose mothers received the control (corn oil; n = 36). Moreover, the mental processing scores of the children at 4 years of age correlated significantly with maternal intake of n-3 LCPs during pregnancy. Indeed, in a multiple regression model, maternal intake of DHA during pregnancy was the only variable significantly related to mental processing scores at 4 years of age.<sup>63</sup>

No longer-term follow-up of term infants has been reported, although some results should be forthcoming in the near future. A review of studies of this kind highlighted several reasons for the lack of a consistent pattern

of results, including differences in the level, nature, and duration of supplementation, the use of tools that are insufficiently sensitive to measure small changes in performance, and the complexities caused by the longevity and reversibility of diet-induced changes in developmental outcomes.<sup>64</sup>

Notwithstanding the limitations, several potential mechanisms by which early dietary EFA supply may affect visual and brain maturation and long-term function can be outlined that provide strong evidence for the plausibility of these effects. The potential role of DHA as a modulator of membrane properties can be supported by the *in vitro* studies of membrane fluidity and transport in neural cells modified in their membrane fatty acids. The role of DHA in amplifying the photo-transduction cascade is supported by the electrophysiological findings in animals and humans. Decreased retinal rod cell threshold means that less light is required to trigger a response, and a higher maximum amplitude means that more signal is being transmitted to the visual pathway. Moreover, the discovery of EFA effects on gene expression of neural tissues and the observed biochemical differences in phosphorylated microtubular-associated proteins in neurons from the visual cortex of light-deprived cats during early development provide a mechanism for the classical observations by Hubel and Wiesel.<sup>65,66</sup>

#### EFFECT OF n-3 LCPS IN THE AGING BRAIN AND RETINA

At the opposite end of the life course, in old age, the LCP concentrations of brain tissues appear to decrease. Early studies demonstrated that the proportion of PUFAs in total phospholipids from the frontal brain cortex is reduced with increasing age, and aging has been shown to be associated with decreased levels of DHA in rat<sup>67,68</sup> and human brains.<sup>69</sup> It has been suggested that these changes in lipid composition are associated with changes in function of the central nervous system,<sup>70</sup> a proposal that is supported by animal studies demonstrating that

feeding rats a low-DHA diet for one or more generations is associated with clear deficits in cognitive function.<sup>71-73</sup>

The underlying cause of these changes in n-3 LCP concentrations in the aging brain is largely unknown. Clearly, there is a role for dietary intake throughout life in determining lipid composition, with high consumption of n-6 linoleic acid potentially reducing the synthesis of longer-chain n-3 PUFAs, while the consumption of diets containing 20 or 22 carbon PUFAs might increase n-3 LCP concentrations. Alternatively, impaired  $\Delta 6$ - and  $\Delta 5$ -desaturase activity, resulting in the formation of gamma linolenic acid from linoleic acid, and arachidonic acid from gamma linoleic acid, respectively, may affect brain lipid composition.<sup>74,75</sup> Indeed, the desaturase capacity of the liver and brain have been shown to be decreased in aging rats.<sup>75-77</sup> A third possibility is that age-related defects in antioxidant systems increase lipid peroxidation and thereby decrease concentrations of LCPs. Such a hypothesis would be consistent with reports suggesting that in the hippocampus, aging is associated with increased production of reactive oxygen species, enhanced lipid peroxidation, and decreased concentrations of the antioxidant vitamin E.<sup>78</sup>

Unlike infancy, for which there is a large body of research on the effects of n-3 LCP supplementation on cognitive health and development, the data in older age are scarce. Observational data suggest that increased fatty fish and n-3 LCP consumption is associated with reduced risk of impaired cognitive function.<sup>79</sup> Similarly, prospective studies have demonstrated that increased fish consumption is associated with decreased risk of dementia<sup>80,81</sup> and Alzheimer's disease<sup>82</sup> among older people. Recently, the reported daily use of fish-oil supplements has been demonstrated to be associated with improved scores in measures of cognitive function at age 64 years, even after correcting for childhood cognitive ability<sup>83</sup> (Tables 1 and 2). This latter study also demonstrated that the level of total n-3 LCPS, and specifically of DHA, in erythrocytes was significantly associated with cognitive ability in older age.<sup>83</sup>

**Table 1.** Mean (SD) Erythrocyte Membrane Fatty Acid Content among Fish Oil Supplement Users and Non-Users. Groups Were 64 Years of Age and Matched for Gender and Childhood Intelligence Quotient (IQ)

Fatty Acid	Fish Oil User (n = 60)	Non-Fish Oil User (n = 60)	P*
	<i>% Total</i>		
Total n-3 PUFAs†	9.00 (1.5)	7.8 (1.3)	<0.001
Eicosapentaenoic acid	1.1 (0.6)	0.8 (0.3)	<0.001
Docosahexaenoic acid	5.4 (1.2)	4.6 (1.0)	<0.001
Total n-6 PUFAs	22.2 (2.1)	23.0 (1.4)	<0.02
Arachidonic acid	10.0 (1.4)	10.9 (1.9)	<0.005

\*Tested by ANOVA after log transformation.

†Polyunsaturated fatty acids.

**Table 2.** Pearson's Correlations Between Cognitive Test Scores and Log-Transformed Erythrocyte Membrane Fatty Acid Content ( $N = 120$ ) (Modified from Whalley LJ, Fox HC, Wahle KW, Starr JM, Deary IJ. Cognitive aging, childhood intelligence, and the use of food supplements: possible involvement of n-3 fatty acids. *Am J Clin Nutr.* 2004;80:1650–1657.)

Cognitive Test	Total n-3 PUFAs*		EPAs†		DHA‡	
	Coefficient	<i>P</i>	Coefficient	<i>P</i>	Coefficient	<i>P</i>
IQ at age 11 years	0.211	<0.05	0.256	<0.01	0.196	<0.05
IQ at age 64 years	0.211	<0.05	0.198	<0.05	0.206	<0.05
Block design subtest	0.213	NS	0.179	NS	0.229	NS
Digit symbol subtest	0.181	<0.05	0.162	NS	0.226	<0.05
Uses of objects test	−0.070	NS	−0.048	NS	0.048	<0.05
Raven's Progressive Matrices	0.195	<0.05	0.184	<0.05	0.140	NS

\*Polyunsaturated fatty acids.

†Eicosapentaenoic acid.

‡Docosahexaenoic acid.

Analysis of erythrocyte membrane composition was also conducted in the Etude du Vieillissement Artériel (EVA) study,<sup>84</sup> which demonstrated that cognitive decline over a 4-year follow-up period was positively related to the level of stearic acid (a saturated fatty acid) in these membranes. Total n-3 PUFAs and DHA concentrations were inversely associated with cognitive decline.<sup>84</sup>

The actions of n-3 LCPs in enhancing vascular health may well provide the mechanisms for the potential beneficial effect of these EFAs on cognitive health. This hypothesized link may prove relevant, since the results of the Rotterdam Scan Study have suggested that vascular health is crucial for the maintenance of cognitive function.<sup>85,86</sup> In this context, n-3 LCPs are known to inhibit hepatic triglyceride synthesis and, by modifying eicosanoid function, cause vascular relaxation, a diminished inflammatory process, and decreased platelet aggregation.<sup>87</sup>

Recently, some new protective actions of DHA have been discovered that may well be directly related to its effects in maintaining cognitive health in older age. In a mouse model of ischemic stroke, a bioactive docosanoid derived from DHA was found to inhibit two of the major causes of post-stroke neuronal injury, lipid peroxidation and leukocyte infiltration.<sup>88</sup> This novel docosanoid, 10-17S-docosatriene, recently named neuroprotectin D1,<sup>89</sup> appears to potently down-regulate pro-inflammatory gene expression in cultured neuronal cells.<sup>88</sup> DHA is also known to protect in vitro-cultured hippocampal neurons from apoptosis (programmed cell death),<sup>90</sup> potentially via the ability of neuroprotectin D1 to counteract oxidative-stress-triggered DNA damage, as well as to up-regulate anti-apoptotic and down-regulate pro-apoptotic protein expression.<sup>89</sup>

In a recent study investigating the effects of DHA supply on a mouse model of Alzheimer's disease

(Tg2576),<sup>91</sup> dietary DHA deficiency was shown to induce a decline in DHA content of the frontal cortex. This decline was associated with an increase in the ratio of fractin to actin, and accumulation of fragmented actin (fractin), which was associated with decreased concentrations of key proteins responsible for postsynaptic processing (specifically drebrin and synapsin). The accumulation of fractin was significantly associated with the loss of dendritic spine formation. DHA deficiency also resulted in increased oxidative damage and a very large reduction in the level of the p85-alpha subunit of phosphatidylinositol kinase in the mouse cortex and in its mRNA transcript. This latter finding is potentially very relevant, as certain actions of phosphatidylinositol kinase are neuroprotective, and deficiency of this enzyme may therefore result in postsynaptic pathology. DHA deficiency appeared to bring about decreased postsynaptic processing rather than neuronal loss in the hippocampus, and this resulted in poorer short-term memory and learning capacity. Subsequent supplementation of these mice with DHA and increased n-3 LCP content of the brain protected them from the adverse biochemical effects of deficiency and resulted in improved cognitive performance.<sup>91</sup>

## CONCLUSION: PROMOTING AND PRESERVING MENTAL DEVELOPMENT

The challenge for nutritionists now is to integrate existing scientific knowledge and further advance applied research on effective ways to attain and maintain optimal brain function throughout the life course.

Optimal brain development in early life, starting at or most likely before conception, should include the provision of key micronutrients including folate, retinol, iodine, iron, zinc, and copper, all of which are necessary to support neurogenesis during embryonic and fetal de-

velopment. In infancy and childhood, preventing iodine, iron, and zinc deficiency while avoiding exposure to neurotoxic elements such as lead and other heavy metals is key in achieving full potential cognitive capacity and unnecessary loss of mental capacity.

We now know that micronutrient sufficiency and quality of the lipid supply play key roles in brain development. Loss of intellectual function linked to iodine deficiency remains the most frequent preventable cause of mental retardation globally. Finally, addressing age-related declines in neural function is key to preserving the autonomy and well-being of older people. Age-related cognitive decline is by now among the main causes of lost disability-adjusted life years in people older than 65 years of age.

The authors are currently conducting an evaluation of the effect of n-3 LCs on the prevention of cognitive decline (the OPAL study), and a cost-effectiveness study on the role of nutrition and physical activity in preserving functional status, muscle strength, and host defenses in older people (the CENEX-Chile study). We must define cost-effective interventions for promoting optimal mental development, preserving function during adult life, and preventing cognitive loss in older people. Otherwise, we will continue to pay the human, social, and economic costs of our insufficient action.

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