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Fatty Acids and Neurodevelopment

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ABSTRACT

Knowledge of the importance of docosahexaenoic acid (DHA), arachidonic acid (AA), and long-chain polyunsaturated fatty acids (LCPUFAs) in neurodevelopment was originally obtained from animal studies. These fatty acids are rapidly accreted in brain during the first postnatal year in animal and human infants, and they are found in high concentrations in breast milk. Reports of enhanced intellectual development in breast-fed children, and reports linking LCPUFA deficiency with neurodevelopmental disorders have stressed the physiological importance of DHA in visual and neural systems. In addition to high concentrations of fatty acids in breast milk, they are also present in fish and algae oil and have recently been added to infant formulas. Esterified poplyunsaturated fatty acids act in cellular membranes, in signal transduction, in neurotransmission, and in the formation of lipid rafts. Nonesterified polyunsaturated fatty acids can modulate gene expression and ion channel activities, thus becoming neuroprotective agents. The conversion of linoleic acid and α-linolenic acid into ARA and DHA have led to randomized clinical trials that have studied whether infant formulas supplemented with DHA or both DHA and ARA would enhance visual and cognitive development. This review gives an overview of fatty acids and neurodevelopment, focusing on the findings from these studies. ***JPGN 47:S7–S9, 2008.*** **Key Words:** Long-chain polyunsaturated fatty acids—Maternal supplement—Neurodevelopment—Preterm—Term infants. © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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Arachidonic acid (AA) (20:4n-6) and docosahexaenoic acid (DHA) (22:6n-3) are the major long-chain polyunsaturated fatty acids (LCPUFAs) in the membranes of brain cells. DHA, the most abundant, is found in high concentrations in aminophospholipids of synaptosome cell membranes. AA and DHA are an integral part of the cerebral cortex. Diau et al (1) reported that in 4-week-old baboons, more than 13% of the total body stores of DHA and AA are found in the brain, in motor-coordination regions, and more abundantly in the gray matter. The ratio of n-3 and n-6 long chain fatty acids in the diet is critical because the 2 families compete for same enzymatic pathway and convert into biologically active eicosanoids.

REQUIREMENTS DURING PREGNANCY AND CHILDHOOD

The LCPUFAs are important during pregnancy and infancy (1) and are essential for the development of the fetal brain and retina (2). Fatty acids are of specific significance during fetal life, when processes like brain development and organogenesis take place during a limited time interval. Fatty acid analysis of total lipids from fetal brain tissues have shown that during the last trimester of pregnancy, the quantitative accretion of total n-3 and n-6 fatty acids increases progressively as gestation progresses. For fetal liver tissue, a linear increase has been observed, indicating a high fetal demand for these fatty acids during intrauterine development (3).

EFFECT OF ESSENTIAL FATTY ACIDS ON THE CENTRAL NERVOUS SYSTEM

Esterified polyunsaturated fatty acids (PUFAs) integrated into the cellular membrane with phospholipids act within the membrane in signal transduction, neurotransmission, and formation of lipid rafts. Nonesterified PUFAs can modulate gene expression, ion channel activities, and become neuroprotective agents (4). A detailed transcriptome analysis by Kitajka et al (5) showed that different genes in diverse brain regions are affected by PUFA supplementation in experimental rats. Also, in their nonesterified form, PUFAs can bind to the ligand

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domain of nuclear receptors such as retinoid X receptor (6), which play key roles during development, such as neurogenesis, neuron differentiation, and plasticity (4). As a neurotrophic factor, DHA is able to increase neurite length and the number of ramifications in cultured murine neurons from hippocampus (7) and cortex (8). Finally, neuron survival seems to be influenced by DHA (8).

FATTY ACIDS AND NEURODEVELOPMENTAL DISORDERS

Clinical manifestations such as attention-deficit/hyperactivity disorder, dyspraxia, dyslexia, and autism may be associated with abnormalities of enzymes involved in phospholipid metabolism. Such symptoms may be relieved after dietary supplementation with LCPUFAs (9). Deficiency of DHA or eicosapentaenoic acid (EPA) (20:5n-3) is related to neuronal arborization deficits and synaptic pathological changes, including serotonin and mesocorticolimbic dopamine neurotransmission, and in some cases may limit the regulation of the limbic system by the frontal cortex. These occur because of lower dopamine release, lower expression of vesicular monoamine transporter 2, lower D2 receptors in the frontal cortex and higher in the nucleus accumbens, and higher immunoreactivity of tyrosine 3-monooxygenase in the ventral tegmental area (10). This may lead to neurocognitive deficits, anxiety, aggression, and depression (11,12). Schizophrenia may be related to membrane defects, specifically myelin-related dysfunction, characterized by increased turnover of phospholipids and decreased incorporation of AA and other PUFAs in membranes (13).

EFFECTS OF FATTY ACID SUPPLEMENTATION IN THE PRE- AND POSTNATAL PERIOD

Several randomized trials have found a specific benefit of LCPUFA supplementation during pregnancy (14–16), the postnatal period, and infancy for the development of visual acuity and cognition (17–19) (Table 1), whereas other studies are inconclusive (20,21). Some of these discrepancies may be due to methodological differences in these studies. A Cochrane Database System Review of LCPUFA in term infants concluded that there is little evidence that supplementation confers a benefit for vision, but minor effects were suggested by some studies. A beneficial effect on information processing is possible, but larger studies over longer periods are required to conclude that LCPUFA supplementation provides a benefit when compared with standard formula. Finally, those results do not suggest that LCPUFA supplements influence the growth of term infants (20). A review

TABLE 1. *Effects of supplementation of fatty acids during pregnancy and postnatal period*

Study design	Supplement and period	Test or quantify variable	Effect	Reference
Fatty acid supplementation in pregnant women				
RCT	DHA and EPA or olive oil, 20 wk of gestation until delivery	Breast milk fatty acid composition and Griffith developmental scores	Increased n-3 LCPUFA in breast milk; EPA and DHA positively associated with Griffith developmental scores at 1 y	Dunstan et al (14)
Double-blind RCT	PUFA (fish oil) or olive oil, 1 wk after delivery, followed up until 4 mo	Infant visual acuity (swept visual evoked potential)	Maternal supplementation influenced visual maturation	Lauritzen et al (15)
Double-blind RCT	DHA, EPA, linoleic acid, α-linolenic acid, or placebo, 18 wk of pregnancy until 3 mo after delivery	Cognitive function and Intelligence testing (Kaufman Assessment Battery for Children)	Maternal supplementation significantly improved children's mental processing scores at 4 y	Helland et al (16)
Fatty acid supplementation in infants with formula				
Double-blind, RCT	DHA, DHA plus AA-supplemented infant formula, at 4 y of age	Visual acuity, Wechsler Preschool and Revised Primary Scale of Intelligence	DHA and AA supplementation supported visual acuity and IQ maturation	Birch et al (17)
Double-blind RCT	DHA (algal oil), AA (fungal oil), DHA (fish oil), AA (fungal oil), and placebo, infants followed up to 118 wk	Growth, tolerance, adverse events, and Bayley development scores	DHA- and AA- supplemented formulas resulted in enhanced growth and provided better developmental outcomes	Clandinin et al (18)
Double-blind RCT	Preterm infants: PUFA-supplemented formula (fish oil) or control, 9 mo after term	Bayley Mental Index and Psychomotor Index	No significant differences between groups overall; in boys, supplement was significant for growth and neurodevelopment at 18 mo after term	Fewtrell et al (19)

RCT = Randomized controlled trial.

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in preterm infants concluded that no long-term benefits were demonstrated for infants receiving formula supplemented with LCPUFA, but no evidence was found that supplementation impairs the growth of infants (21). However, Fewtrell et al (19) reported that LCPUFA supplementation in preterm boys was associated with higher mental Bayley scores and a significantly greater weight and length gain.

CONCLUSIONS

The effect of dietary LCPUFA on fatty acid status; immune function; and visual, cognitive, and motor functions has been evaluated in preterm and term infants. The plasma and red blood cell fatty acid status of infants fed formulas supplemented with both n-3 and n-6 LCPUFAs was closer to the status of breast-fed infants than to that of infants fed formulas containing no LCPUFAs. Adding n-3 LCPUFA to preterm infant formulas led to initial findings of beneficial effects on visual acuity. Few data are available on cognitive function, but some reports suggest better cognitive development in comparison with infants receiving no LCPUFA.

Term infants need an exogenous supply of AA and DHA to achieve similar accretion of fatty acids in plasma and red blood cells similar to that in breast-fed infants. In long-term studies, feeding more than 0.2% DHA and 0.3% AA improved the status of these fatty acids for many weeks after supplementation, enabling DHA and AA status more similar to that of infants fed human milk (22). However, although the evidence for the potential benefits of fatty acid supplementation is promising, it is not yet conclusive. Further studies are needed to fully explain the effects of fatty acids during pregnancy and lactation, dose-response relations, and the potential differences between subgroups. The relative effects of PUFA supplementation on neurodevelopmental outcome depend on the dosage, source, and gestational period when used. The differences in results of previous studies could possibly be explained by the different methodological designs of the studies.

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