

Long-Chain Polyunsaturated Fatty Acids Influence the Immune System of Infants¹⁻³

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Abstract

Several events occur during the first months of life that allow the immune system to become competent and functional. The aim of this article is to review the rationale and evidence of an influence of (n-3) long-chain PUFA (LCPUFA) on the immune system of infants. The (n-3) LCPUFA exert their immunomodulatory activities at different levels. The (n-3) LCPUFA metabolites induce eicosanoid production, alter gene expression, and modify lipid raft composition, altering T-cell signaling; all contribute to immunological functional changes. However, the roles of these mechanisms and the types of T or other immunological cells involved remain unclear at present. Moreover, the effect of (n-3) LCPUFA on the immune system of infants may vary according to dose, time of exposure, and profile of the immune system (T-helper, Th1/Th2). Most of the interventional studies in infancy have been performed for the prevention of allergy. They all confirmed influence on T-cell function and cytokine profiles, but clinically beneficial effects are more conflicting. Supplementation of the maternal diet in pregnancy or early childhood with (n-3) LCPUFA is potentially a noninvasive intervention strategy to prevent the development of allergy, infection, and possibly other immune-mediated diseases. However, any long-term in vivo effects on (n-3) LCPUFA early in life for immunomodulatory defense in infants and later on immune status and health remain to be assessed. J. Nutr. 138: 1807S–1812S, 2008.

Introduction

The immune system exists to protect the host against pathogenic organisms and also to ensure tolerance to “self,” to food and other environmental components, and to commensal bacteria. It is now recognized that regulation of tolerance and active immune responses is critical to health, and failure to regulate these responses can lead to recurrent infections, inflammatory diseases, and allergic reactions. Fetal and neonatal periods are key periods for immunological adaptation, and many of the allergic and inflammatory diseases of adults are thought to originate during these crucial periods. The education of the immune system in early life is thought to be critical in minimizing the occurrence of these immune-based disorders (1). Intervention with (n-3) long-chain PUFA (LCPUFA)⁴ in the neonatal and/or in utero period

may alter cytokine profiles (2) and possibly disease outcome in later infancy and adult life. The (n-3) LCPUFA have indeed been shown to influence the immune system via different mechanisms, which have recently been better described and understood.

Development of immune system in early life

Maturation of the immune system during pregnancy and early infancy has been extensively described in an article in this supplement. Components of both the innate and acquired immune systems are present in the newborn but at reduced amounts/numbers and at reduced activities. The newborn can be considered as immunocompetent but immunologically naïve (3). Several events occur during the first months of life that allow the immune system to become both competent and functional. The development of tolerance is the result of active immune mechanisms, and both development and maintenance of tolerance are lifelong processes that start very early in life, even prenatally. If the neonatal immune system is not able to down-regulate the preexisting T-helper-2 (Th2) dominance effectively, then an allergic phenotype may develop (4).

Metabolism of (n-3) LCPUFA

The 2 essential fatty acids, linoleic [C18:(2n-6)] and α -linolenic acid [C18:(3n-3)], can be elongated and desaturated in animal cells forming the (n-6) and (n-3) families of PUFA. The major endproduct of the (n-6) pathway is arachidonic acid (AA), whereas the major endproducts of the (n-3) pathway are eicosapentaenoic acid (EPA) and docosapentaenoic acid. In

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⁴ Abbreviations used: AA, arachidonic acid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ICAM, intercellular adhesion molecule; LCPUFA, long-chain PUFA; NF- κ B, nuclear factor κ B; PG, prostaglandin; Th, T-helper; VCAM-1, vascular cell adhesion molecule-1.

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infants, maternal milk contains lipids that have a high proportion of the long-chain (n-3) PUFA; EPA and docosahexaenoic acid (DHA) are the chief sources of these fatty acids. Dietary (n-3) PUFA can significantly alter the fatty acid composition of membrane phospholipids by decreasing AA and increasing EPA. These changes in fatty acid composition are consistent with the overall suppression of eicosanoids associated with systemic inflammatory response syndrome and shift to the less biologically active 3-series prostaglandins (PG) and 5-series leukotrienes (LT) (Fig. 1) (5). In addition to proinflammatory effects, PGE₂ exerts effect on the Th1/Th2 balance. It decreases the production of the Th1-type cytokines interferon (IFN γ) and interleukin-2 (IL-2), enhances the production of Th2-type cytokines IL-4 and IL-5, and promotes IgE synthesis by B cells (6,7).

In addition to (n-3) LCPUFA modulation of eicosanoids, a novel group of mediators termed E-series resolvins formed from EPA by cyclooxygenase (COX)-2 have been shown in cell culture and animal models to be antiinflammatory (8,9).

The (n-6) PUFA are essential in relation to a thymus/thymocyte accretion of AA in early development, and there is a high requirement of lymphoid and other cells of the immune system for AA and linoleic acid to form membrane phospholipids. Low (n-6) PUFA intakes enhance, whereas high intakes decrease, certain immune functions. AA metabolites can limit or regulate cellular immune reactions and can induce deviation toward a Th2-like immune response (10).

The (n-3) LCPUFA also induce direct alteration of gene expression through modification of transcription factor activity such as nuclear factor- κ B (NF- κ B). NF- κ B plays a role in inducing a range of inflammatory genes including COX-2, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, tumor necrosis factor- α (TNF α), IL-1 β , inducible nitric oxide synthase (iNOS), acute-phase protein, in response to inflammatory stimuli. The (n-3) LCPUFA decrease the activity of NF- κ B via inhibition of I κ B, the inhibitory subunit of NF- κ B. The (n-3) LCPUFA are natural ligands of nuclear receptors such as peroxisome proliferator-activated receptors PPAR- α and - γ . PPAR are ligand-activated transcription factors present in a variety of cell types including

inflammatory cells (11). The (n-3) LCPUFA have also been shown to influence the expression of adhesion molecules (ICAM-1, VCAM-1, and E-selectin). Adhesion molecules direct the leukocyte-endothelium interactions, transendothelial migration of leukocytes, and leukocyte trafficking in general (5).

(n-3) LCPUFA and T-cell function

Several mechanisms by which (n-3) LCPUFA can affect T cells have been identified (Table 1) (6,12–15). As mentioned above, (n-3) LCPUFA in membrane compete with AA as substrates for cyclooxygenase and lipoxygenase enzymes (Fig. 1). The (n-3) LCPUFA decrease production of AA-derived eicosanoids such as PGE₂. PGE₂ is immunosuppressive at high concentration, and a low concentration is required for normal T-cell function. PGE₂ regulates cellular immune responses through distinct receptors on different immune cell populations: some receptors directly inhibit T-cell proliferation, whereas others regulate antigen-presenting cell functions (15).

The (n-3) LCPUFA bind with PPAR- γ , which has been shown to be involved in regulation of immune and inflammatory responses (16). Other nuclear factors, such as liver X receptor and retinoid X receptor (which forms a heterodimer with several nuclear receptors, i.e., PPAR- γ), could also be involved in mediating the action of (n-3) LCPUFA on the immune system.

Incorporation of (n-3) LCPUFA into membrane phospholipids modulates membrane structure and function. Indeed, incorporation of EPA and DHA into lymphocyte membranes alters their fluidity and is associated with the effects of these fatty acids on T-cell proliferation. Lipid rafts are crucial for T-cell activation, as are fences and pickets and protein-protein interactions that take part in the formation of the immunological synapse as a highly organized structure at the T-cell contact site to the antigen-presenting cell (17). (n-3) LCPUFA treatment alters lipid rafts in altering the protein composition of the inner membrane lipid leaflet and inhibits T-cell responses (17,18).

Both in vitro and animal-feeding studies have reported that the (n-3) LCPUFA inhibit T-cell proliferation, production of IL-2 and IFN γ , and surface expression of CD25 (12). Human studies provide more conflicting results, suggesting that the actions of (n-3) LCPUFA may differ according to the situation or age of the patients, Th1/Th2 balance, dose of fatty acids, and experimental conditions (19).

(n-3) LCPUFA and immune function of infants

A few studies have suggested that early intervention with (n-3) LCPUFA may influence immune functioning and may affect the cytokine phenotype during development. Some of these studies demonstrated that early exposure to (n-3) LCPUFA during the fetal and neonatal period has a prolonged impact on Th1/Th2 immune responses and T-cell cytokine profiles (2,3). Maternal fish oil supplementation during the first 4 mo of lactation resulted in an increased production of lipopolysaccharide-induced IFN γ on stimulation in 2.5-y-old children, whereas IL-10 production was similar to that of the olive oil group. The IFN γ /IL-10 ratio was 2-fold higher in the fish oil group and was positively correlated with EPA/DHA in erythrocytes at 4 mo (2). Adding DHA plus AA to a standard infant formula for healthy infants increased the proportion of antigen-mature (CD45RO⁺) CD4⁺ cells, improved IL-10 production, and reduced IL-2 production to levels not different from those of human milk-fed infants (20). Healthy term infants at age 2 wk receiving the same formula supplemented with ARA and DHA produced less TNF α (unstimulated) and had a higher amount of CD3⁺CD44⁺ cells before stimulation with phytohemagglutinin and higher CD11c⁺

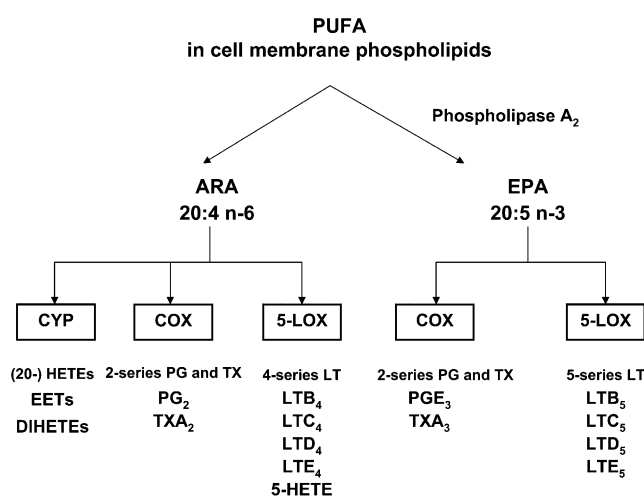


FIGURE 1 Synthesis of eicosanoids from ARA and EPA released from cell membranes. Abbreviations: CYP, cytochrome P-450; thromboxane, TX; hydroxyeicosatetraenoic acids, HETEs; epoxyeicosatetraenoic acids, EETs; dihydroeicosatetraenoic acids, DiHETEs; 5-LOX, 5-lipoxygenase; prostaglandin, PG; leukotrienes, LT.

TABLE 1 Primary mechanisms by which (n-3) LCPUFA influence immunological responses¹

Biological properties of (n-3) LCPUFA	Mediator	Mechanism	Immunological cells involved	Effect
Membrane constituent	TCR clusters within lipid rafts on contact with an antigen-presenting cell	Modification of lipid rafts and caveolae structure	Th1 (Th2)	Inhibits T-cell response
Competition between (n-6) and (n-3) LCPUFA for the production of eicosanoids	Cyclooxygenase Lipoxygenase	Decreases PGE ₂ Decreases LTB ₄ Increases 3-series prostaglandins Increases 5-series leukotrienes	Lymphocytes Monocytes, macrophages NK Leukocytes	Lymphocyte proliferation NK-cell activity Production of Th1 cytokines (IL-2, IFN γ) MHC II expression and production of TNF α , IL-1 and IL-6 by monocyte and macrophage IgE production leukocyte activation, chemotaxis and degranulation
Direct action on gene expression	NF κ B (ligand of TLR4) PPAR γ (natural ligand)	Inhibits expression of adhesion molecules (ICAM-1, VCAM-1, and E-selectin) Inhibits expression of inflammatory genes (COX-2, IL-1 α , TNF α , 5-LOX...)	Endothelial cell T and B cells Monocyte, macrophage	Reduces adherence to human blood monocytes Upregulates genes of fatty acid oxidation and thermogenesis Inhibits proliferation of human T cells Decreases I κ B phosphorylation Decreases endotoxin activation of NF- κ B Reduces production of inflammatory eicosanoids by immune cells

¹ TCR, T-cell receptor; LTB₄, leukotriene; MHC, major histocompatibility complex; TLR4, toll-like receptor; IL, interleukin; I κ B, inhibitor of NF κ B.

cells poststimulation (21). Compared with formula-fed controls, the infants receiving LCPUFA had an immune cell distribution (higher percentage CD3⁺CD44⁺ and CD4⁺CD28⁺ cells) and cytokine profile (lower production of TNF α poststimulation) that did not differ from breast-fed infants (21).

It has also been shown in vitro that (n-3) LCPUFA modulate apoptosis of monocytes, which are major effector cells of the innate immune system, from cord blood with a dose-dependent effect. The influence of LCPUFA on neonatal monocyte-cell survival suggests another mechanism whereby LCPUFA may modulate the immune response (22). All these results demonstrate that early diet influences both the presence of specific cell types and function of infant blood immune cells.

However, because some classes of fatty acid possess immunosuppressive properties, the issue of impairment of host resistance to infection and therefore undesirable effects of LCPUFA has been subject to controversy (13,23). Studies conducted in animals, investigating the influence of dietary fatty acids on host survival and/or pathogen clearance in animals challenged with a live infectious agent, are inconclusive, some showing that (n-3) PUFA improve host defense (24,25) and others showing impairment (26). However most of the studies demonstrated that (n-3) PUFA induce modulation of the inflammatory response that can influence the response to a bacterial challenge (27).

(n-3) LCPUFA and allergy in infants

The increased prevalence of atopic disease observed in Western countries during the last decades parallels the profound changes in the type of fat consumed (9). Intake of saturated fatty acids decreased, but (n-6) PUFA, mainly linoleic acid, increased. Several epidemiological studies support the hypothesis of the link between increased intake of the (n-6) PUFA linoleic acid and increased prevalence of allergic disease (28–31).

Observational studies. Low levels of (n-3) LCPUFA in breast milk were associated with increased risk of infant atopy (32). Two-year-old children breast-fed for the first 4 mo of life by

mothers with a high intake of (n-3) LCPUFA had a significantly higher production of IFN γ on stimulation of whole blood compared with a control group with low maternal (n-3) LCPUFA intake during lactation (2). In a case-control study, children born to mothers with a history of asthma had an odds ratio of asthma of 0.20 (95% CI = 0.06–0.65) when mothers ate oily fish at least monthly during pregnancy compared with no consumption (33). Maternal oily fish consumption during pregnancy did not benefit children of nonasthmatic mothers in this study (33). Other studies did not show that fetal exposure to (n-6) and (n-3) fatty acids was an important determinant of early childhood wheezing and atopic disease in the general population, also suggesting that benefit should be limited to a selected population at high risk of allergy (34). A recent study (35) examined fatty acids in serum cholesteryl esters in relation to asthma and lung function in children. Although there was a strong positive association between AA levels and current asthma and a negative association with forced expiratory volume, levels of EPA were not related to asthma and impaired lung function (35). In another study performed in 308 Korean children ages 4–6 y, it was found that red blood cell EPA plus DHA were lower in children with atopy than controls, whereas ARA was greater (36).

Intervention trials.

Treatment. A number of trials of dietary supplementation with (n-3) LCPUFA in patients with asthma have been performed, mainly in adults. Their results were largely disappointing, showing no consistent effect on both clinical and functional respiratory parameters (37–39). Very few studies have been performed in children (40). The effects of dietary supplementation with fish oil for 10 mo in children with bronchial asthma were investigated in a randomized controlled study (41). Asthma symptom scores decreased, and responsiveness to acetylcholine decreased, in the fish oil group but not in the control group plasma, whereas EPA levels increased significantly only in the fish oil group (41). The Childhood Asthma Prevention Study included 6-mo-old infants at risk of developing asthma to receive

either EPA plus DHA or placebo. Although no effect of fish oil was observed at 3 y of age on prevalence of asthma, wheeze, and atopic dermatitis, some beneficial effects on wheeze at 1.5 y of age (42) and cough at 3 y of age were observed (42,43). Moreover, no effect of fish oil was observed on the prevalence of asthma, wheezing, eczema, or atopy at the age of 5 y (44).

Prevention. Because allergies appear to be determined early in life or even antenatally, (n-3) LCPUFA intervention should be more prevalent early in life for the prevention of allergic disease rather than for the treatment of allergy manifesting later in life (45). Several recent studies seem to support this hypothesis. Breast milk of atopic mothers supplemented during pregnancy with dietary fish oil contains higher levels of (n-3) LCPUFA and lower (n-6) LCPUFA than that of controls (46). In this study, the (n-3) PUFA concentration of breast milk on d 3 postpartum was positively associated with IgA, IL-10, and IL-6 and soluble CD14 levels (47). In these children, IL-13 (a predictor of allergic disease) was detected in 64% of cord plasma samples in the placebo group and in 45% of samples in the fish oil group (48), and percentages of CD34⁺ cell numbers (that are hematopoietic progenitors altered in infants at risk of atopy) were higher after (n-3) PUFA treatment than placebo (49). In this study, although no difference was observed for food allergy, asthma, chronic cough, and angiodema, infants in the fish oil group were one-third as likely to have a positive skin prick test to egg at 1 y of age and less severe atopic dermatitis compared with the placebo group (50).

(n-3) LCPUFA and infection in infants

Today there are very few studies assessing intervention with (n-3) PUFA in infection in childhood (51,52). From experimental and adult studies, there is, however, a strong rationale to investigate the effect of (n-3) PUFA in the treatment and/or the prevention of infections (i.e., intensive care unit, prematurity, cystic fibrosis) (22).

Excessive or inappropriate inflammation and immunosuppression are components of the response to surgery, trauma, injury, and infection in some individuals, and these responses can lead to sepsis and septic shock. Hyperinflammation is characterized by the production of inflammatory cytokines, AA-derived eicosanoids, and other inflammatory mediators, whereas the immunosuppression is characterized by impairment of antigen presentation and of Th lymphocyte type-1 responses. The (n-3) LCPUFA should indeed be helpful in such situations (53).

A large number of clinical trials have been performed in adult patients postsurgery and with severe sepsis (54). These studies using parenteral or enteral nutrition products have showed that (n-3) LCPUFA may influence leukocyte function and plasma lipids in critical care patients, i.e., suppression of proinflammatory cytokines by mononuclear leukocytes (54). These studies report beneficial outcomes including a decreased number and severity of infectious complications, decreased need for mechanical ventilation, decreased time in the intensive care unit and/or total hospital stay (55), even a reduction of mortality (56,57).

In a large but open and nonrandomized study of 1342 non-breast-fed infants receiving either a formula containing DHA plus ARA and a control formula, it was shown that there was a higher incidence of bronchiolitis in controls than in the DHA-plus ARA-supplemented group at 5, 7, and 9 mo (51). The incidence of all other respiratory illnesses measured was similar among the study groups with the exception of a significantly higher occurrence of rhinitis at 1 mo of age for the control group compared with the DHA plus ARA group (6.7 vs. 3.0%, $P = 0.05$) and a higher incidence of upper airway infection in the

control group than in the DHA plus ARA group at 1 mo (12.1 vs. 6.6%, $P = 0.05$) and 12 mo (24.2 vs. 16.2%, $P = 0.01$). No significant differences were observed regarding the incidence of pharyngitis, otitis, or conjunctivitis (51). The administration of DHA during the acute phase of sepsis protected the nutritional status of neonates (52). Indeed, the DHA group presented increases in body mass and fat mass, whereas infants in the placebo group did not show an increase in any body composition components after 14 d of follow-up. In this study, no difference in outcome (mortality, mechanical ventilation) and/or severity of the sepsis (C-reactive protein, platelets) could be demonstrated (52).

Unanswered questions, perspectives

There are strong data from experimental studies showing that (n-3) LCPUFA alter immune cell function and could influence the immune system of infants. The (n-3) LCPUFA may influence the number and/or activity of certain subpopulations of cells, which could affect subsequent maturation and polarization of the immune system. Their application during infancy should be for prevention of infection and allergy. However, the mechanisms involved are complex because several modes of action have been described (reduction of synthesis of some types of eicosanoids, modification of gene expression, and modification of the signaling process). Effects on the immune system may also vary according to age and polarization, Th1/Th2 immune status, dose of (n-3) LCPUFA, and type of T cells. Effects of (n-3) LCPUFA on naturally or adaptative T_{reg} cells comprise a promising but largely unexplored area of research (58). Supplementation of the maternal diet in pregnancy or early childhood with (n-3) PUFA may provide a noninvasive intervention with significant potential to prevent the development of allergic and possibly other immune-mediated diseases. However, long-term *in vivo* effects of (n-3) LCPUFA early in life on immunodefense of infants and later immune status and health remain to be assessed.

Other articles in this supplement include references (59–68).

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