

Fatty acids and atopic disease

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The link between fatty acids and atopic disease

The key link between fatty acids and atopic diseases is that a number of the mediators which play a role in these diseases are synthesized from arachidonic acid (20:4n-6). This fatty acid is consumed in relatively low quantities in the human diet (<300 mg per day) yet in many inflammatory and immune cells it constitutes more than 20% of the fatty acids present in the membrane phospholipids. Thus, much of the arachidonic acid found in cells is synthesized (most probably in the liver) from linoleic acid (18:2n-6), a major component of vegetable oils and products made from them; a typical Western diet provides approximately 10–15 g of linoleic acid per day. Once consumed, linoleic acid is metabolised by the enzyme Δ^6 -desaturase to γ -linolenic acid (GLA; 18:3n-6), then to dihomo- γ -linolenic acid (DGLA; 20:3n-6) and then to arachidonic acid (Fig. 1).

Arachidonic acid in inflammatory cell membranes can be mobilized by various phospholipase enzymes, most notably phospholipase A_2 , and the free arachidonic acid can subsequently act as a substrate for cyclooxygenase (COX), forming prostaglandins (PG) and related compounds, or for one of the lipoxygenase (LOX) enzymes (Fig. 1). There are at least 16 different 2-series PG and these are formed in a cell-specific manner. For example, monocytes and macrophages produce large amounts of PGE_2 and PGF_2 , neutrophils produce moderate amounts of PGE_2 and mast cells produce PGD_2 . The last is a bronchoconstrictor and is produced by lung mast cells during asthmatic attacks. Synthesis of PG,

including PGD_2 , is prevented by inhibitors of COX such as aspirin and other non-steroidal anti-inflammatory drugs. Despite this, these drugs exacerbate asthmatic bronchoconstriction, indicating that mediators other than PG are involved.

The LOX enzymes have different tissue distributions with 5-LOX being found mainly in mast cells, monocytes, macrophages and granulocytes and 12- and 15-LOX being found mainly in epithelial cells. Metabolism of arachidonic acid by the 5-LOX pathway gives rise to hydroxy and hydroperoxy derivatives (5-HETE and 5-HPETE, respectively), and the 4-series leukotrienes (LT), LTA_4 , B_4 , C_4 , D_4 and E_4 (Fig. 1). The latter three compounds, also known as the sulphidopeptide LTs and as “slow reacting substance”, are produced by the cells that mediate pulmonary inflammation in asthma such as mast cells and are believed to be the major mediators of asthmatic bronchoconstriction. These compounds increase post capillary permeability, are potent stimulators of airway smooth muscle cells, and mediate vasoconstriction and mucus secretion (1). 4-series LTs have been detected in the blood, bronchoalveolar lavage fluid and urine of asthmatics (2). The principal 5-LOX product of human eosinophils and mast cells is LTC_4 (3, 4), which appears to act in asthma through amplification of local processes and through the induction of other cells to produce LTA_4 and 5-HETE (5). Because of the central role of 4-series LTs in asthma and other diseases (6), there is great interest in developing pharmacological agents which inhibit the release of arachidonic acid

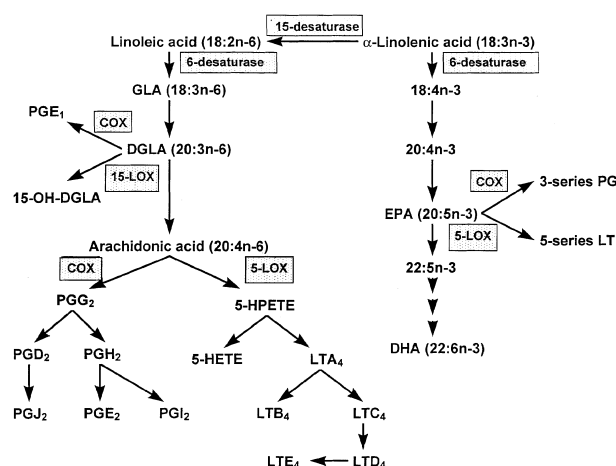


Fig. 1. Metabolism of n-6 and n-3 PUFA. Only selected enzymes and arachidonic acid-derived mediators are shown; note that Δ^{15} -desaturase is found in plants only. Metabolism of arachidonic acid by 12- and 15-LOX is not shown.

from inflammatory cell membranes, or inhibit 5-LOX, or act as LT receptor antagonists. The possible reason why aspirin exacerbates asthma is that inhibition of COX diverts arachidonic acid towards LT synthesis.

Although its action as a precursor to LT has highlighted the significance of arachidonic acid in the aetiology of asthma, a second link with this fatty acid has been made. This is because PGE₂, the principal COX product of arachidonic acid metabolism by monocytes and macrophages, regulates the activities of macrophages and lymphocytes. Of particular relevance in the context of allergic disease is the ability of PGE₂ to inhibit the production of the Th-1 type cytokines interleukin-2 (IL-2) and interferon- γ (IFN- γ) without affecting the production of the Th-2 type cytokines IL-4 and IL-5 (7, 8), and to stimulate B-cells to produce IgE (9, 10). These observations suggest that PGE₂ regulates the development of the allergic disease.

Changes in consumption of certain fatty acids have occurred over the last 40 years: a link with increased incidence of atopic disease?

Linoleic acid consumption has increased dramatically in developed countries since the mid-1960's, largely as a result of decreased use of butter and lard and increased use of margarine and vegetable oils. In the United Kingdom the contribution of linoleic acid to dietary fatty acid intake increased from about 8% to 16% between 1960 and 1990 (11). This period of increased intake of linoleic acid coincides with the period over which the incidence of childhood allergy has increased (12–14). Furthermore, marked differences in the prevalence in asthma and allergic

rhinitis and in the concentrations of specific IgE in the circulation between children in the former East and West Germany (15–18) are in accordance with differences in butter and margarine consumption in the two regions (19). Likewise, the marked differences in the prevalence of bronchial asthma, allergic rhinitis and atopic dermatitis among children in different regions of Finland are linked with the levels of linoleic acid in plasma cholesterol esters, an indicator of dietary linoleic acid intake (20–22); the area with lowest linoleic acid intake had the lowest prevalence of all three diseases.

On the basis of such observations there has been speculation that increased vegetable oil (and hence linoleic acid) consumption results in increased cellular arachidonic acid levels, so increasing the capacity to produce PGE₂, which in turn alters the balance of Th-1 and Th-2 cytokines, enhancing IgE production and encouraging the development of asthma and other allergic diseases (23, 24).

Abnormalities in fatty acid composition in atopic disease: a basis for supplementation with specific fatty acids?

The notion that elevated arachidonic acid levels are associated with allergic disease is opposed by the frequently reported abnormalities in fatty acid composition of blood, cells and milk from atopic mothers and/or their offspring. Lowered proportions of GLA, DGLA and/or arachidonic acids have been observed in (i) plasma, epidermal and erythrocyte phospholipids, and adipose tissue of patients with atopic dermatitis, (ii) umbilical cord blood lipids of new-born infants with increased cord blood IgE levels, (iii) cord blood T-cells and mononuclear cells of new-born infants "at risk" of atopy, (iv) breast milk and colostrum of mothers with a history of atopic dermatitis, and (v) breast milk of mothers of infants with atopic dermatitis (25–38; see also 39). Recent studies have found a lowered proportion of arachidonic acid in serum phospholipids of allergic children who had a positive skin prick test (40) and an association between the fatty acid composition of maternal serum and the development of allergic disease in children in the first 6 years of life (41). One study suggests that the fatty acid composition of cord blood may even be predictive of later development of atopic disease (35). These observations have been taken to suggest that a deficiency in Δ^6 -desaturase plays a role in these diseases. Such a deficiency would result in an imbalance between different members of the n-6 PUFA family and between the n-6 and the alternative n-3 PUFA

families. Melnik & Plewig (39) speculate that PGE₂ plays a role in thymic T-cell development and in controlling T-cell activity and that this regulation is diminished in atopics, due to a decreased availability of arachidonic acid. Furthermore, and in contrast to other workers (9, 10), they show that exogenously-added PGE₁ and PGE₂ suppress IgE synthesis by cultured mononuclear cells from the blood of atopic individuals (42).

There are also abnormalities in the proportions of the long chain n-3 PUFAs in atopic disease. For example, the proportions of eicosapentaenoic (EPA; 20:5n-3), docosapentaenoic (22:5n-3) and docosahexaenoic (DHA; 22:6n-3) acids were lower in umbilical cord serum phospholipids from allergic compared with non-allergic mothers (43) and the proportions of DHA and total n-3 PUFA were lower in serum phospholipids from 12–15-year-olds with asthma and/or atopic dermatitis compared with age-matched, non-atopic controls (40). These abnormalities most likely arise through the putative Δ^6 -desaturase inefficiency, since the consumption of long chain n-3 PUFA is low in most Western populations (<300 mg/day) and these fatty acids are therefore formed from their precursor (α -linolenic acid; 18:3n-3) using the same enzymes which are responsible for the metabolism of linoleic acid (Fig. 1). Thus, a case has been made for increasing the consumption of these fatty acids by patients with allergic diseases (23, 24). The chief dietary sources of these fatty acids are oily fish (tuna, salmon, mackerel, herring, etc.), and fish oil (FO), either in liquid form (e.g. cod liver oil) or in capsules; most preparations of the latter contain 20–40% EPA plus DHA. There is some epidemiological evidence to support a protective role of long chain n-3 PUFA in allergic disease. Asthma is uncommon in Greenland Eskimos who have a high intake of fish and marine mammal oils (44), while data from the 1st and 2nd National Health and Nutrition Surveys in the USA found that dietary fish intake was positively associated with forced expiratory volume for 1 second (FEV₁) (45) and protected against wheezing (46), respectively. Australian schoolchildren who included oily fish in their diet had a lower likelihood of having asthma (odds ratio 0.26) than children who did not consume oily fish (47). The biochemical basis for a protective effect of n-3 PUFA in allergic disease is outlined below. These observations make a compelling argument for trials of FO in asthma and related diseases. A number of such trials have been performed and are summarized below.

Supplementation with n-6 PUFA in atopic disease

Biochemical and immunological basis

Since a block or inefficiency in Δ^6 -desaturase activity is suspected, one way to overcome this would be to provide increased amounts of the substrate (i.e. linoleic acid) or to provide the product (i.e. GLA). The main sources of GLA are evening primrose oil (EPO), which contains 5–10% GLA, and borage oil, which contains up to 25% GLA. Elongation of GLA to DGLA is unimpaired in allergic disease but it is possible that the conversion of DGLA to arachidonic acid is inefficient. Thus, when GLA is provided orally, the content of DGLA in cells and tissues is increased. The significance of this is that DGLA is a substrate for COX, giving rise to the 1-series PG (e.g. PGE₁) as well as for 15-LOX, giving rise not to inflammatory LT but to 15-hydroxy-DGLA (48). This may be particularly important in the skin, where the 15-hydroxy-DGLA, a known inhibitor of 5- and 12-LOX (49), is synthesized following EPO administration (50). Thus, DGLA should have anti-inflammatory actions due to its capacity to reduce synthesis of arachidonic acid-derived mediators.

DGLA also decreases lymphocyte responsiveness (51–55) and suppresses the production of interleukin-2 (IL-2) (56) and IL-1 β and tumour necrosis factor- α (57) by cultured lymphocytes and monocytes, respectively. These might be important effects upon the signalling between, and the activities of, cells involved in allergic disease.

Results of supplementation studies

Several early studies obtained effective treatment of atopic dermatitis with linoleic acid-rich oils but doses up to 60 g linoleic acid per day were used (see 58 for references); doses <10 g per day were ineffective. Horrobin (58) suggests that the effectiveness of high, but not low, doses of linoleic acid might be because formation of metabolites via Δ^6 -desaturase may have been forced, thereby suggesting that provision of the product of this reaction (i.e. GLA) should be effective.

The earliest study of EPO in atopic dermatitis patients showed modest beneficial effects (59), and a follow-up study reported using 2, 4 or 6 g EPO daily found a dose-dependent clinical improvement in such patients (60). Several other studies report significant clinical improvement in atopic dermatitis patients given 2.4–4 g EPO per day for several weeks (61–66), including reduced use (by up to 66%) of medication (61). In a more recent study, 16 weeks' EPO treatment of children with atopic dermatitis, some of whom also had

asthma, significantly improved eczema symptoms but had no effect on asthma symptoms (67). EPO also reduced the elevated blood noradrenaline and adrenaline concentrations in patients with atopic dermatitis (68). Many of these studies also report a "normalization" of the fatty acid composition of various tissues sampled (e.g. blood, skin, neutrophils) with EPO treatment. A meta-analysis of the placebo-controlled studies of EPO in atopic dermatitis has been published and shows significant effects with respect to certain symptoms, particularly itching (69).

Supplementation with fish oil in atopic disease

Biochemical and immunological basis

When FO is provided in the diet, EPA and DHA replace arachidonic acid in the membranes of various cells including monocytes, macrophages, neutrophils and other granulocytes, lymphocytes and presumably mast and epithelial cells and in tissues such as the lung and skin. This has the effect of decreasing the supply of substrate for the synthesis of 2-series PG, 4-series LT and other eicosanoids. In addition, EPA and DHA inhibit the metabolism of arachidonic acid, amplifying the effect of their incorporation. Since 4-series LT are key mediators involved in the pathology of asthma (see above) these are potentially important effects, which might result in clinical benefit. Many studies in animals and humans have shown that dietary FO results in decreased *ex vivo* production of PGE₂ and 4-series LT by various cell types (see 70, 71 for references). An FO-induced reduction in *ex vivo* LTB₄ production by neutrophils from asthmatic patients has been demonstrated (72). As well as decreasing production of arachidonic acid-derived mediators, EPA is a substrate for COX and 5-LOX, giving rise to an alternative set of mediators, the 3-series PG and the 5-series LT. FO consumption has been shown to increase the production of 5-series LT by rodent (73–75) and human (76, 77) cells. In addition, circulating (78) and urinary (77, 79) concentrations of 5-series LT are enhanced after FO feeding, indicating that these changes in LT metabolism occur *in vivo*. The significance of this is that the 5-series LT have different biological activities and potencies than the 4-series analogues. Thus LTB₅ is 10–100-fold less potent as a neutrophil chemoattractant than LTB₄. Broughton et al. (79) suggest that 5-series LT might be beneficial in asthma because they are unable to elicit an asthmatic response and/or because they block 4-series LT binding to their receptors. Thus, supplementation of the diet with FO causes a

decrease in production of active arachidonic acid-derived mediators and enhances the production of less active EPA-derived mediators. Dietary FO also has a number of other effects that might be beneficial in allergic diseases. These include:

- reduced chemotaxis of monocytes, neutrophils and eosinophils towards various agents (80–83);
- decreased production of platelet activating factor (84);
- decreased production of the pro-inflammatory cytokines tumour necrosis factor- α , IL-1, IL-6 and IL-2 (81, 85–87);
- decreased adhesion molecule expression (88), resulting in decreased adhesion of leukocytes to endothelial cells (89);
- decreased lymphocyte responsiveness (see 70 for references).

Results of supplementation studies

FO has been used to treat skin disease for many years. Fox in 1877 (90) wrote "if eczema be present, cod liver oil should be given freely" and that for severe itching "no remedy is so good as cod liver oil". Despite this enthusiasm, several studies published in the 1930s showed no benefit of cod liver oil in atopic dermatitis (see 58 for references). More recently, however, Bjorneboe et al. (91) found significant improvements in itching, scaling and patient's assessment in patients with atopic dermatitis given 10 g FO per day (approximately 1.8 g EPA per day) for 12 weeks.

Early studies of FO supplementation in asthma reveal limited clinical impact (72, 92) despite significant biochemical changes (e.g. reduced 4-series LT production). Some recent studies echo these findings. For example, Hodge et al. (93) found that, although n-3 PUFA intervention in asthmatic children aged 8–12 years increased plasma n-3 PUFA content and decreased *ex vivo* tumour necrosis factor- α production, there was no significant change in day and night symptoms, peak flow rates or medication use. Similarly, 3.2 g EPA per day for 6 months did not alter bronchial reactivity, peak expiratory flow, nocturnal cough and wheeze, daytime wheeze, nasal symptoms, or use of medication in pollen-sensitive asthmatics, compared with an olive oil placebo (94).

In contrast, some studies have shown significant clinical improvements at least in some patient groups and suggest that this type of approach may be useful in conjunction with other drug- and diet-based therapies. Dry & Vincent (95) reported that 9 months' intervention with n-3 PUFA increased FEV₁ in 12 asthmatic patients. Masuev reported less frequent severe attacks of asphyxia, reduced

drug doses and a significant reduction in the response to allergen challenge in asthmatic patients given n-3 PUFA compared with a placebo group (96). Attenuation of the late allergic response with n-3 PUFA supplementation of asthmatics was also reported (97). Likewise, consumption of 3 g EPA plus DHA per day for 30 days significantly improved bronchial responsiveness to ultrasonically nebulized distilled water: the maximum fall in FEV₁ was decreased (–11% vs. –28% before n-3 PUFA treatment) and the maximum increase airway resistance was reduced (37% vs. 265% before treatment) (98). In a very detailed study by Broughton et al. (79), 26 carefully selected atopic asthmatics consumed “low” and “high” dose FO for 4 weeks; the actual amount of FO each patient consumed was calculated according to their regular n-6 PUFA intake such that the n-6:n-3 PUFA ratio was 10:1 (low FO) or 2:1 (high FO). At baseline and after each treatment period (i.e. with low and then high FO), forced vital capacity (FVC), FEV₁, peak expiratory flow (PEF) and forced expiratory flow 25–75% (FEF_{25–75}) were measured in response to increasing doses of methacholine. With low n-3 PUFA ingestion, methacholine-induced respiratory distress increased. In contrast, high n-3 PUFA ingestion resulted in an improved response in more than 40% of subjects; all measures of respiratory function were improved in this group of patients who also showed markedly elevated appearance of the EPA-derived 5-series LT in their urine. In this group of patients the dose of methacholine required to cause a 20% reduction in FVC, FEV₁, PEF and FEF_{25–75} could not be calculated because of lack in significant respiratory reduction. However, some patients did not respond to the high n-3 PUFA intake, which in some cases worsened respiratory function. This study suggests that there are subjects who respond positively to FO intervention and subjects whose response is worsened by such intervention.

Why have trials been disappointing?

Clearly, then, there are studies which show beneficial interventions with long chain n-6 or n-3 PUFA. In contrast, there are a number of studies which show lack of benefit. The study of Broughton et al. (79) highlights the variation in possible responsiveness to such intervention and suggests caution. Despite a lack of positive clinical outcomes in many studies, there are consistent changes in biochemical markers (e.g. blood and cell fatty acid composition, 4-series LT production), which suggest good compliance. One reason why the clinical improvements are less dramatic

than the observed biochemical alterations may be that the intervention is effectively too late; the key time for such intervention might be during the early stages of the disease, perhaps during the sensitisation phase. To date there are no published studies of the influence of dietary fatty acids upon the development of atopic diseases. This is clearly an important area for future research if we are to understand more fully the link between dietary fatty acids and atopic diseases and if we are to design nutritionally-based approaches for protection against and therapy of such diseases.

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