Omega-3 Fatty Acids and Airway Hyperresponsiveness in Asthma

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ABSTRACT

Despite the progress that has been made in the treatment of asthma, the prevalence and burden of this disease has continued to increase. Exercise is a powerful trigger of asthma symptoms and reversible airflow obstruction and may result in the avoidance of physical activity by patients with asthma, resulting in detrimental consequences to their health. Approximately 90% of patients with asthma are hyperresponsive to exercise and experience exercise-induced bronchoconstriction (EIB). While pharmacologic treatment of asthma is usually highly effective, medications often have significant side-effects or exhibit tachyphylaxis. Alternative therapies for treatment (complementary medicine) that reduce the dose requirements of pharmacologic interventions would be beneficial, and could potentially reduce the public health burden of this disease. There is accumulating evidence that dietary modification has potential to influence the severity of asthma and reduce the prevalence and incidence of this condition. A possible contributing factor to the increased incidence of asthma in Western societies may be the consumption of a proinflammatory diet. In the typical Western diet, 20- to 25-fold more ω-6 polyunsaturated fatty acids (PUFA) than ω-3 PUFA are consumed, which causes the release of proinflammatory arachidonic acid metabolites (leukotrienes and prostanoids). This review analyzes the existing literature on ω-3 PUFA supplementation as a potential modifier of airway hyperresponsiveness in asthma and includes studies concerning the efficacy of ω-3 PUFA supplementation in EIB. While clinical data evaluating the effect of ω-3 PUFA supplementation in asthma has been equivocal, it has recently been shown that pharmaceutical-grade fish oil (ω-3 PUFA) supplementation reduces airway hyperresponsiveness after exercise, medication use, and proinflammatory mediator generation in nonatopic elite athletes with EIB. These findings are provocative and suggest that dietary ω-3 PUFA supplementation may be a viable treatment modality and/or adjunct therapy in airway hyperresponsiveness. Further studies are needed to confirm these results and understand their mechanism of action.

INTRODUCTION

Asthma is a significant worldwide health problem, with high and increasing incidence in many countries (Burney et al., 1990); morbidity—reflected in hospital admission rates (Halfon and Newacheck, 1986), use of medical services, drug use, and trends in mortality rates are substantial (Anderson, 1989; Klaukka et al., 1991). The incidence of asthma varies by region and by age, but the global burden of asthma can be approximated from measured prevalence (reflecting incidence, duration, persistence, and recurrence of disease). Approximately 20.3 million Americans (6.3 million children) had asthma in 2001; 73.4 per 1000 population (American Lung Association, 2003), while it is esti-
estimated that approximately 300 million people in the world currently have asthma (Masoli et al., 2004). Despite the progress that has been made in the treatment of asthma, it remains a major illness in terms of morbidity, suffering, and cost (National Heart, Lung and Blood Institute, 2002).

Asthma is a chronic inflammatory disorder of the airways and causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough (Barbato et al., 2003). Long-term airway remodeling is characteristic of asthma and may be associated with an increase in airway hyperresponsiveness to a variety of stimuli (Barbato et al., 2003). While pharmacological medications have proven highly effective as medications in relief of symptoms and have facilitated the management of asthma, prolonged use of some medications may result in reduced efficacy or tachyphylaxis (Bisgaard, 2000; Hancox et al., 2002). Therefore, complementary and alternative medicine (CAM) approaches that focus on manipulation of dietary factors in obstructive lung disease are of real interest because they could potentially reduce the dose requirements of pharmacologic medications (Baker and Ayres, 2000; Denny et al., 2003; Devereux and Seaton, 2001; Fogarty and Britton, 2000; Hackman et al., 1996; McKeever and Britton, 2004; Mickleborough and Gotshall, 2003; Picado et al., 2001; Romieu and Trenga, 2001; Smit, 2001; Smit et al., 1999), and reduce the public health burden of this disease.

The purpose of this review is to critically examine the existing information regarding the relationship between \( \omega-3 \) polyunsaturated fatty acids (PUFA) supplementation and airway hyperresponsiveness in asthma, and in particular to address the question as to whether supplementing the diet with \( \omega-3 \) PUFA represents a viable alternative or complementary treatment for asthma. For this review, the keywords \( \omega-3 \) PUFA, \( \omega-6 \) PUFA, and fish oils were coupled with keywords asthma, exercise-induced asthma, exercise-induced bronchoconstriction and airway hyperresponsiveness for a MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and SPORTDiscus search.

**\( \omega-3 \) FATTY ACIDS AND ASTHMA**

Over the past three decades there has been considerable interest in the therapeutic potential of \( \omega-3 \) PUFA for various inflammatory conditions such as rheumatoid arthritis, inflammatory bowel diseases, and asthma. \( \omega-3 \) PUFA, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in fish oils, compete with arachidonic acid (AA) as substrates for the formation of eicosanoids, such as leukotrienes (LTs) and prostaglandins (PGs) (Lee et al., 1985). Arachidonic acid-derived eicosanoids are proinflammatory, while EPA-derived eicosanoids are more immunonueral. Moreover, \( \omega-3 \) PUFA appear to have additional anti-inflammatory effects mediated through direct action on neutrophil and monocyte production of inflammatory mediators (e.g., cytokines) and chemotactic responses (Endres et al., 1989; Lee et al., 1985).

In the typical Western diet, 20- to 25-fold more \( \omega-6 \) PUFA than \( \omega-3 \) PUFA are consumed (Gadek et al., 1999). This predominance of \( \omega-6 \) PUFA is because of the abundance of dietary linoleic acid (18:2\( \omega-6 \)), which is present in high concentrations in soy, corn, safflower, and sunflower oils. By contrast, there is a low intake of the \( \omega-3 \) homologue of linoleic acid, \( \alpha \)-linolenic acid (18:3\( \omega-3 \)), which is present in leafy green vegetables and in flaxseed and canola oils. Once ingested, the 18-carbon fatty acids are desaturated and elongated to 20-carbon \( \omega-6 \) PUFA. Linoleic acid is converted to AA and \( \alpha \)-linolenic acid is converted to EPA (20:5\( \omega-3 \)) (Fig. 1). Compared to linoleic acid there is little dietary intake of AA and EPA, which are present in meat and fish, respectively. Linoleic acid and \( \alpha \)-linolenic are necessary for a complete diet and cannot be synthesized in vertebrates; therefore, they are essential fatty acids. As a consequence, the relative dietary amounts of \( \omega-6 \) and \( \omega-3 \) PUFA are determinants of the relative cellular amounts of linoleic acid and \( \alpha \)-linolenic acid.

There has been increased emphasis on the beneficial effects for cardiovascular health of replacing lard and dairy fats rich in saturated fatty acids. This has led to increased consumption of vegetable oils rich in \( \omega-6 \) PUFA and a si-
multaneous decrease in consumption of oily fish and leafy vegetables, the major sources of ω-3 PUFA. This dietary shift is characterized by a decrease in consumption of saturated fats and an increase in ω-6 PUFA (Kelley, 2001). The anti-inflammatory properties of ω-3 PUFA such as EPA and DHA and generally proinflammatory properties of dietary ω-6 PUFA (Broughton et al., 1997; Okamoto et al., 2000a), such as linoleic acid, suggest that these dietary trends may have predisposed some individuals to inflammatory disorders, including asthma.

**Epidemiologic and cross-sectional studies**

The notion that consumption of dietary fatty acids can influence the development and activity of an inflammatory disease such as asthma is attractive in view of the complex metabolic role that fatty acids play in cell metabolism and structure. During the period of increasing asthma prevalence in England and Wales, dietary consumption of fatty acids also changed, with a marked increase in the intake of ω-6 PUFA and a decrease in saturated fatty acids (Black and Sharpe, 1997). Support for the hypothesis that fat intake may be important is available from a case-control study showing an association of higher fat intake with adult onset wheeze in Scotland (Bodner et al., 1999), and a cohort study from Malmo in which men with asthma had a higher intake of dietary fat (Strom et al., 1996). Haby and colleagues (2001) assessed the prevalence of asthma and risk factors for asthma in Australian preschool children and found that a high level of PUFA (high ω-6, low ω-3) was associated with increased risk of recent asthma. Hodge et al. (1996) found an inverse relationship between weekly oily fish intake over the course of 12 months and the prevalence of asthma in 574 schoolchildren in a cross-sectional study. These studies suggest that consumption of oily fish is associated with a reduced risk of asthma in childhood. Patal and coworkers (2002) demonstrated an association between consumption of oily fish and symptomatic wheeze in individuals with and without physician diagnosed asthma. Takemura et al. (2002) assessed the relationship between dietary fish intake and the prevalence of asthma among a Japanese childhood population and their results indicated that the frequency of fish intake was positively related to the prevalence of asthma. Nafstad and coworkers (2003) evaluated the relationship between the introduction of a fish diet during the first year of life and the risk of developing asthma and allergic rhinitis in a prospective 4-year cohort study of 2531 Norwegian children. This group of researchers found that the introduction of a fish diet was negatively associated with the risk of developing allergic rhinitis and asthma. Additionally, Oddy and colleagues (2004) recently investigated whether childhood asthma was associated with the ratio of ω-6 to ω-3 fatty acids in the diet (ω-6:ω-3) using a cross-sectional study design. They found evidence for the promotion of a diet with increased ω-3 PUFA (fresh or oily fish at least once per week, whole-grain cereals, raw sunflower and flaxseeds, and canola oil) and reduced ω-6 PUFA (margarines, vegetable oils, processed foods) to protect children against symptoms of asthma. Woods and colleagues (2004), in a community-based cross-sectional study, sought to determine whether plasma levels of ω-3 PUFA, as a measure of dietary intake, was protective against asthma and atopy in young adults. These authors did not find any evidence to suggest that ω-3 PUFA are associated with a reduced risk of asthma or atopy. Interestingly, their results suggest that the ω-6 PUFA γ-linolenic acid has the strongest association with asthma. Because this was a cross-sectional study, the authors were unable to establish a cause-and-effect relationship for the fatty acid/asthma associations found. Recently Broadfield and coworkers (2004) conducted a case-control study of dietary and erythrocyte membrane fatty acids in asthma and found that a higher erythrocyte membrane level of linoleic acid, an ω-6 PUFA, was associated with a decreased risk of asthma.

**Interventional studies**

Considering the role of LTs, PGs, and cell–cytokine interactions in airway inflammation, remodeling, and hyper-reactivity in asthma, the potential therapeutic effect of a diet rich in fish oil has been examined repeatedly. However, clinical data on the effect of fish oil supplementation in asthma has been equivocal. While no clinical improvement in asthmatic symptoms has been observed in some interventional studies (Arm et al., 1988; Hodge et al., 1998; Kirsch et al., 1988; Stenius-Aarniala et al., 1989; Thien et al., 1993), other studies have demonstrated an improvement in asthmatic status after ω-3 PUFA supplementation (Arm et al., 1989; Broughton et al., 1997; Dry and Vincent, 1991; Emelyanov et al., 2002; Nagakura et al., 2000; Okamoto et al., 2000a; Okamoto et al., 2000b; Villani et al., 1998). Early short-term trials (8 weeks) of up to 4 g/d of EPA in patients with severe asthma showed no clinical benefit, despite demonstrating profound suppression of neutrophil chemotaxis and LT mediator production (Kirsch et al., 1988). Six weeks of 3 g/d of EPA had a deleterious effect on patients with aspirin-intolerant asthma (Picado et al., 1988), consistent with the known aspirin-like effect of cyclooxygenase inhibition by EPA. Further studies in patients with milder asthma with 3.2 g/d for 10 weeks showed no benefit in either clinical symptoms or bronchial hyperresponsiveness (Arm et al., 1988), despite demonstrating attenuation of allergen-induced late-phase bronchoconstriction induced in the laboratory (Arm et al., 1989). A more prolonged trial for 6 months with 3.2 g/d of EPA also showed no clinical benefit in patients with pollen-induced asthma and seasonal hay fever (Thien et al., 1993). In addition, Stenius-Aarniala and coworkers (1989) demonstrated no clinical benefit of 10 weeks of fish oil supplementation in relatively stable patients with asthma. However, their method of assessing lung
function is open to question because each subject used a peak flow meter at home under no supervision. Recently Surette et al. (2003) showed no change in baseline pulmonary function occurred in a population of atopic asthmatics, even though daily consumption of dietary γ-linolenic acid (GLA) and EPA-inhibited LT biosynthesis. However, asthma severity and reliance on medication were not assessed. McDonald et al. (1990) provided 2.7 g of EPA and 1.8 g of DHA for 10 weeks to 15 nonsmoking patients with asthma and found no change in peak expiratory flow rate after fish oil supplementation.

In contrast, Dry and Vincent (1991) have shown positive results using a small placebo-controlled trial of low-dose EPA (1 g/d) for 12 months in 12 adults with asthma; after 9 months a small but significant improvement of 23% was found in forced expiratory volume in 1 second (FEV1). However, no details were given of concurrent medication use or confirmation of compliance by leukocyte membrane phospholipid analysis. Hodge et al. (1998) demonstrated that dietary supplementation with ω-3 PUFA over 6 months increased plasma levels of these fatty acids and reduced stimulated tumor necrosis factor (TNF-α) and circulating eosinophils, with a concurrent improvement in peak expiratory flow and reduced medication use in children with asthma (Hodge et al., 1998). Nagakura and colleagues (2000) showed that dietary supplementation with fish oil (84 mg of EPA and 36 mg of DHA per day) over 10 months decreased asthma scores and reduced acetylcholine threshold levels during an acetylcholine inhalation test in children with bronchial asthma. Okamoto et al. (2000a, 2000b) observed suppression of leukotriene B4 (LTB4) and LTC4 generation by leukocytes and improvement in respiratory function following 4 weeks of perilla seed oil (ω-3 PUFA)-rich supplementation in subjects with asthma. Payan and coworkers (1986) found that high doses, compared to low doses, of EPA ethyl ester taken daily for 8 weeks increased LTβ3 generation, and reduced AA, LTβ4, and prostaglandin E2 (PGE2) generation by polymorphonuclear (PMN) and mononuclear leukocytes in patients with asthma. These authors did not report pulmonary function scores, medication use or asthma symptom scores. Villani et al. (1998) observed a significant improvement in FEV1 with a concomitant reduction in airway resistance after only 30 days of supplementation with 3 g/d of ω-3 PUFA in 7 atopic patients. Massuev (1997a) observed significant attenuation of the late allergic response in 13 patients with asthma supplemented for 2 weeks with ω-3 PUFA, and in another study showed that ω-3 PUFA supplementation resulted in a significant decline of the late allergic response and reduced drug doses in 27 patients with asthma (Massuev, 1997b). Provocative tests with allergen after 10 weeks of either ω-3 PUFA or placebo showed a significant decline in the late allergic response and suppression of inflammatory mediators (50% reduction in the capacity of PMN to produce LTB4) in the treatment group (Arm et al., 1989). Broughton et al. (1997) demonstrated that supplementing the diet with 3.3 g/d of EPA and DHA daily in 27 subjects with asthma ameliorated methacholine-induced respiratory distress, which may be predicted by LT metabolism. Emelyanov and colleagues (2002) recently showed a decrease in daytime wheeze, concentration of exhaled hydrogen peroxide (a marker of airway inflammation), and an increase in morning peak expiratory flow rate in 46 atopic patients with asthma receiving a lipid extract of New Zealand green-lipped mussel, rich in ω-3 PUFA, for 8 weeks compared to placebo (olive oil).

A number of salient points may be made regarding the conflicting results between studies assessing the efficacy of fish oil (ω-3 PUFA) supplementation on airway hyper-responsiveness in asthma: (1) the dosage (1 to 4 g/d) and duration (3 weeks to 12 months) of fish oil supplementation varied greatly among studies; (2) the heterogeneity of asthmatic patients between studies was not accounted for; (3) patients with asthma do not always have highly reproducible responses to bronchial challenge testing (methacholine/histamine); particularly when assessment of peak expiratory flow rate is the solitary measurement (Anonymous, 1995; Crapo et al., 2000); (4) not all supplementation studies used the same grade or standard of fish oil. Pharmaceutical-grade fish oil has only recently become available and enables the experimental evaluation of the specific mechanism of ω-3 PUFA action without the confounding variables of impurity. In addition, pharmaceutical-grade fish oil has a higher percentage of total long-chain ω-3 PUFA than lower-grade fish oil; and (5) in only one study (Hodge et al., 1998), was dietary manipulation performed as part of the treatment phase. It is noteworthy that this study demonstrated a significant improvement in peak expiratory flow and a reduction in asthma medication use on the ω-3 PUFA diet (canola-oil and canola based margarines and salad dressings), while a decrement in resting peak expiratory flow and increased medication use was observed on the ω-6 PUFA diet (sunflower oil and sunflower oil-based margarines and salad dressings). Interestingly, Woods et al. (2003) in the Cochrane Database of Systematic Reviews, assessing the efficacy of fish oil for asthma in adults and children, identified 22 studies for possible inclusion; however, the authors only included 9 studies. Reasons for noninclusion were (1) not a randomized controlled trial (4 studies); (2) not using marine fatty acids in asthma (3 studies); (3) no outcome measures reported (3 studies); and (4) an inadequate intervention period (1 study). None of the studies reported asthma exacerbations, health status (quality of life) or hospital admissions. These authors stressed that further studies should address these issues. Woods et al. (2003) concluded that they were unable to determine the effect of fish oil supplementation in asthma or answer the question whether increasing dietary marine ω-3 PUFA by increased fish intake results in improved asthma control.
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ω-3 FATTY ACIDS AND EXERCISE-INDUCED BRONCHOCONSTRICTION

Exercise is a powerful trigger of asthma symptoms and may result in patients with asthma avoiding physical activity, resulting in detrimental consequences to their physical and social well-being. Approximately 90% of patients with asthma and a high prevalence of nonatopic elite athletes are hyperresponsive to exercise and experience exercise-induced bronchoconstriction (EIB) (Rundell and Jenkinson, 2002). A characteristic evident in individuals with EIB is a marked decrease in exercise capacity and breathlessness upon exertion. Individuals who demonstrate EIB often have asthma; however, significant numbers of healthy individuals without asthma also demonstrate EIB and these individuals are often referred to as having solitary EIB.

To date only one study has evaluated the effect of fish oil (ω-3 PUFA) supplementation on the airway response to exercise in patients with asthma (Arm et al., 1988). After 10 weeks of daily supplementation with 3.2 g of EPA and 2.2 g of DHA, subjects underwent a histamine challenge, exercise challenge, and blood neutrophil studies. Although there was a significant increase in ω-3 PUFA neutrophil content and a 50% inhibition of total LTB synthesis (LTB4 and LTB5), there was no detectable change in the clinical outcome (e.g., histamine response, exercise response, specific conductance of the airway or symptom scores).

Recently, Mickleborough and colleagues (2003) demonstrated that 3 weeks of fish oil supplementation reduces the severity of EIB and resulted in a significant suppression of several proinflammatory mediators in nonatopic elite athletes who exhibited “asthma-like symptoms” after exercise (Mickleborough et al., 2003). The airway response to exercise was used to assess changes in nonspecific bronchial responsiveness during dietary supplementation with ω-3 PUFA. The exercise challenge test consisted of running to volitional exhaustion on a treadmill while breathing compressed dry air. The fish oil supplement had no effect on baseline pulmonary function in EIB (n = 10) and control subjects (n = 10) or after exercise in control subjects. However, in the group of athletes who had a history of exercise-induced narrowing, the fish oil supplement reduced the decrease in FEV1 at 15 minutes postexercise by almost 80% (Fig. 2) in conjunction with a greater than 20% reduction in bronchodilator use. In addition, the increase in tissue phospholipid ω-3 PUFA concentration in EIB subjects was coincident with a significant suppression of the proinflammatory eicosanoids LTE4, PGD2 urinary metabolite 9α, 11β-PGF2 and LTB4 and proinflammatory cytokines interleukin (IL)-1β and TNF-α.

The divergent findings between the studies by Mickleborough et al. (2003) and of Arm and colleagues (Arm et al., 1988) are difficult to reconcile, especially because the study by Arm et al. had a longer duration supplementation period with an identical fish oil dosage. The negative findings observed by Arm et al. (1988) may be the result of methodological and statistical limitations of their study. These authors exercised a cohort of mild asthmatics at low exercise intensity (80% predicted maximal oxygen consumption for 8 minutes at ambient temperature and humidity). It is generally accepted that inhaling cold–dry air at high ventilation rates initiates EIB. Rundell and coworkers (2000) have shown that out of 23 subjects who tested positive for EIB in cold–dry air, 18 (78%) subjects tested negative in ambient conditions (21°C and 50% relative humidity). This suggests that the exercise protocol performed in ambient conditions in the study by Arm et al. (1988) may have been less sensitive to identifying changes in airway hyperresponsiveness after exercise caused by inadequate environmental stress. In addition, an assessment of the numbers used in the airway response to exercise in the study by Arm and coworkers (1988) (5 subjects receiving placebo and 6 subjects receiving fish oil supplementation) suggests insufficient patients to detect a statistical difference and avoid a Type I error.

MECHANISM OF ACTION

Although the impact of ω-3 PUFA on lipid mediator generation has been greatly clarified, the understanding of subcellular effects is still limited. ω-3 PUFA affects biophysical characteristics of cellular membranes by alteration of the membrane phospholipid composition and may modify the function of membrane-linked enzyme systems and signal transduction pathways. Many of the anti-inflammatory ef-
Effects of ω-3 PUFA appear to be exerted at the level of altered gene expression and have been demonstrated only a limited number of times in vitro, and thus the extent of these effects in vivo is not yet clear. Mounting evidence now suggests that fatty acids are not only the precursors of eicosanoids and other lipid mediators, but also can modulate signaling molecules and transcription factors such as nuclear factor-kappaB (NF-κB) (Hwang, 2000; Jump, 2002; Liu et al., 2001). Since macrophages of induced sputum and bronchial epithelial cells from stable asthmatics exhibit increased NF-κB activity compared with cells from healthy individuals (Hart et al., 1998), it has been suggested that NF-κB plays a pivotal role in the pathogenesis of asthma (Bureau et al., 2000; Gagliardo et al., 2003; Hart et al., 1998, 2000; Zhao et al., 2001). Recently, Lee and coworkers (2001, 2003) demonstrated that activation of general proinflammatory pathways, such as NF-κB and cyclooxygenase-2 (COX-2) expression by saturated fatty acids and inhibition of this induction by ω-3 PUFA, are mediated through a common signaling pathway derived from toll-like receptor 4 (Tlr-4). If activation of Tlr-4 is modulated by ω-3 PUFA, then signaling pathways downstream, such as proinflammatory transcription factor NF-κB, and consequent cellular responses (e.g., inducible nitric oxide, proinflammatory cytokines, TNF-α, IL-1β, and eicosanoids [prostanoids and LTs]) should also be modulated by ω-3 PUFA (Lee et al., 2001, 2003) (Fig. 3). Indeed, It has been demonstrated that proinflammatory cytokine inhibition in murine macrophages by ω-3 PUFA is mediated, in part, through inactivation of NF-κB (Lo et al., 1999; Novak et al., 2003) and inhibition of COX-2 and PGE2 expression in blood monocytes with a Tlr-4 agonist (Lee et al., 2003). Therefore, because Tlr-4 conveys signals as a part of innate immunity from the endotoxin receptor (CD14) on the surface of macrophages to the inner cell, a downregulation of nuclear factor-kappaB (NF)–κB formation of cytoplasmic NF-κB begins with stimulation of specific receptor families at the cell surface (e.g., Tlr-4). This activation promotes the activation of NF-κB, which is rapidly translocated to the nucleus where the NF-κB binds to specific promoter regions of various genes encoding proinflammatory cytokines, enzymes, chemokines, adhesion molecules, and receptors. The cytokines (tumor necrosis factor [TNF]–α and interleukin (IL)–1β are both activated and amplified by NF-κB. Potential sites of ω-3 polyunsaturated fatty acids (PUFA) inhibition are shown. iNOS, inducible nitric oxide; mRNA, messenger RNA; COX-2, cyclooxygenase-2; 5-LO, 5-lipoxygenase.

A potentially beneficial anti-inflammatory effect of ω-3 PUFA. Supplementing the diet with ω-3 PUFA has been shown to reduce AA concentrations in neutrophils and neutrophil chemotaxis, reduce LT generation (Lee et al., 1985; Payan et al., 1986) and reduce airway late response to allergen exposure (Arm et al., 1989). These data are consistent with the proposed pathway by which dietary intake of ω-3 PUFA modulates lung disease. ω-3-PUFA therefore seems to interfere with early inflammatory signal transduction processes and is thus capable of blunting hyper-inflammation. Elucidating the mechanism of this modulation could help us to understand how dietary ω-3 PUFA achieve their specific effects on airway hyperresponsiveness.

CONCLUSION

In view of the clinical consequences, these findings point toward prophylactic and acute therapeutic effects in inflammatory diseases, which seem to be attainable by simple rearrangement of nutritional components. Additionally, because individuals with asthma with hyperresponsive airways produce increased quantities of LTs compared to healthy individuals, dietary interventions that decrease the capacity to synthesize these and other proinflammatory me-
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