



Review

Combinations of distinct long-chain polyunsaturated fatty acid species for improved dietary treatment against allergic bronchial asthma



Christopher Beermann Ph.D.^{a,*}, Sandy Neumann M.Sc.^a, Daniela Fußbroich M.Sc.^a, Stefan Zielen M.D.^b, Ralf Schubert Ph.D.^b

^aFood Technology, Department of Biotechnology, University of Applied Sciences, Fulda, Germany

^bPediatric Pulmonology and Allergology, Children's Hospital I, Goethe-University, Frankfurt/Main, Germany

ARTICLE INFO

Article history:

Received 2 March 2016

Accepted 11 April 2016

Keywords:

Arachidonic acid

Allergic disease

Eicosapentaenoic acid

Fat metabolism

Inflammation

Pulmonology

ABSTRACT

Allergic bronchial asthma is a chronic inflammatory disease of the airways with an increasing incidence in Western societies. Exposure to allergens provokes recurrent attacks of breathlessness, airway hyperreactivity, wheezing, and coughing. For the early phase and milder forms of allergic asthma, dietary supplementation with long-chain polyunsaturated fatty acids (LCPUFA), predominantly fish oil-associated eicosapentaenoic (C20:5 ω -3) and docosahexaenoic acid (C22:6 ω -3), and distinct crop oil-derived fatty acids might provide a sustainable treatment strategy, as discussed in several studies. In addition to immune-controlling prostaglandins, leukotrienes, and thromboxanes, specialized proresolving mediators, such as lipoxins, resolvins, protectins, and maresins, are metabolized from different LCPUFA, which actively resolve inflammation. The aim of this review was to discuss the possible synergistic effects of ω -3 and ω -6 LCPUFA combinations concerning rebuilding fatty acid homeostasis in cellular membranes, modifying eicosanoid metabolic pathways, controlling inflammatory processes by focusing on resolving inflammation in the bronchoalveolar system on the cellular level, and helping to control clinical symptoms in bronchial asthma.

© 2016 Elsevier Inc. All rights reserved.

Introduction

Bronchial asthma is a chronic inflammatory disease of the airways, with an increasing incidence in Western societies [1]. To date, several asthma treatment concepts, like bronchodilating beta-2 receptor agonists, leukotriene (LT) receptor antagonists, anti-inflammatory glucocorticoids, and monoclonal anti-immunoglobulin (Ig)E are available, which are associated with total resistance or receptor-desensitizing caused loss of effectiveness with long-term therapy [2,3]. As a possible therapeutically supportive or even an alternative treatment concept, ω -3 and ω -6 long-chain polyunsaturated fatty acids (LCPUFA), especially eicosapentaenoic acid (EPA; C20:5 ω -3), docosahexaenoic acid (DHA; C22:6 ω -3), and dihomo- γ -linolenic acid (DGLA; C20:3 ω -6), have been suggested by many studies to

possess immunomodulatory effects in acute or chronic pneumonia [4–6].

Since the late 1970s, studies have promoted the immunomodulatory potential of marine ω -3 PUFA. Since then, the controversial discussion on the truth of the health promoting effects of EPA and DHA has continued [7]. Currently, fish, plants, algae, and fungi containing LCPUFA, as well as modern oil processes for refining dietary oils, have enabled the creation of complex oil blends with specific LCPUFA profiles. Several distinct species of ω -3 and ω -6 LCPUFA have been shown to have wide beneficial effects in the control of inflammatory processes [7–11].

The resolution phase of inflammation is a strongly regulated, energetic, and complex program that fails in asthma and therefore becomes a key point of intervention [4]. This review investigates the possible synergistic combinations of ω -3 and ω -6 LCPUFA species in allergic bronchial asthma, focusing on resolving inflammation by metabolically associated specialized proresolving mediators (SPM).

* Corresponding author. Tel.: +49 661 964 9506; fax: +49 661 964 0505.

E-mail address: Christopher.beermann@lt.hs-fulda.de (C. Beermann).

LCPUFA connects fat metabolism with immune reactions in asthma

Asthma is defined as a chronic inflammatory disease characterized by chronic inflammation and remodeling of airways, reversible airflow limitation, eosinophil and leukocyte tissue infiltration, and airway hyperactivity [12]. Furthermore, asthma is associated with hyperresponsiveness (e.g., triggered by allergens and/or enhanced by low temperatures and exercise) [13]. Figure 1 shows the immunologic processes in asthma related to ω -3 and ω -6 fatty acids and their derivatives. The allergic response is generally mediated by a T-helper cell type-2 immune response characterized by the secretion of interleukin (IL)-4, IL-5, IL-9, and IL-13, which promote eosinophilic inflammation and IgE production by plasma cells. In the early phase of the asthmatic response, allergen recognition by specific IgE on mast cells triggers the release of mediators (i.e., histamine and LCPUFA-derived lipid-mediatory eicosanoids) [14]. In asthma, eicosanoids derived from arachidonic acid (AA), such as the cysteinyl leukotrienes, induce bronchospasm, edema, and mucous hypersecretion [15]. Additionally, these mediators released during the early phase of an immune response also gradually initiate and support a late-phase asthmatic response configured around T-helper cell type-2 cells and eosinophils [16].

Generally, linoleic acid (LA; C18:2 ω -6) and α -linolenic acid (ALA; C18:3 ω -3) are essential fatty acids and precursors of LCPUFA, such as EPA, DHA, or AA [17]. They are synthesized through a series of elongation and desaturation steps within the same enzymatic metabolic pathway [18,19]. LCPUFA integrated into the cell membrane phospholipids of immune cells are released by phospholipase A₂ in response to appropriate

triggers and are transformed by specific lipoxygenases (LOX) and cyclooxygenases (COX) into hormone-like immune regulatory eicosanoids, which are involved in the pathogenesis of asthma [7,20].

There is evidence that airway inflammation and airway hyper-responsiveness are influenced by the ratio of ω -6 to ω -3 LCPUFA in tissues and cells [21,22]. One study showed that decreased inflammation could be partially due to reduced ω -6 PUFA-derived lipid mediator formation as a result of competitive inhibition or downregulation of COX or LOX [21]. The LCPUFA profiles of cell and organelle membranes strongly influence its functions and numerous cellular processes such as cell survival and death [20,23]. Several studies have clearly demonstrated that dietary LCPUFA supplementation can affect the fatty acid composition of these membranes [24,25]. Thus, the already reported association between asthma and dietary LCPUFA intake is reasonable [26–28]. Concerning the immune response, T-cell function is modulated by this directly through effects on cell signaling and gene transcription [29]. Again, ω -3 and ω -6 LCPUFA are ligands and/or modulators for the nuclear factor (NF)- κ B and peroxisome proliferator-activated receptors (PPAR), which control various genes of immune response regulation, whereas especially ω -3 LCPUFA downregulate proinflammatory genes [20]. Taking this into consideration, it might be possible to precisely ameliorate or even resolve the inflammation by dietary interventions with preformed LCPUFA. Based on this knowledge of the associated disease-specific immunologic mechanisms, the dietary rebuilding of LCPUFA homeostasis has been shown to improve asthma control, lung function, and inflammatory markers in children with asthma [30,31].

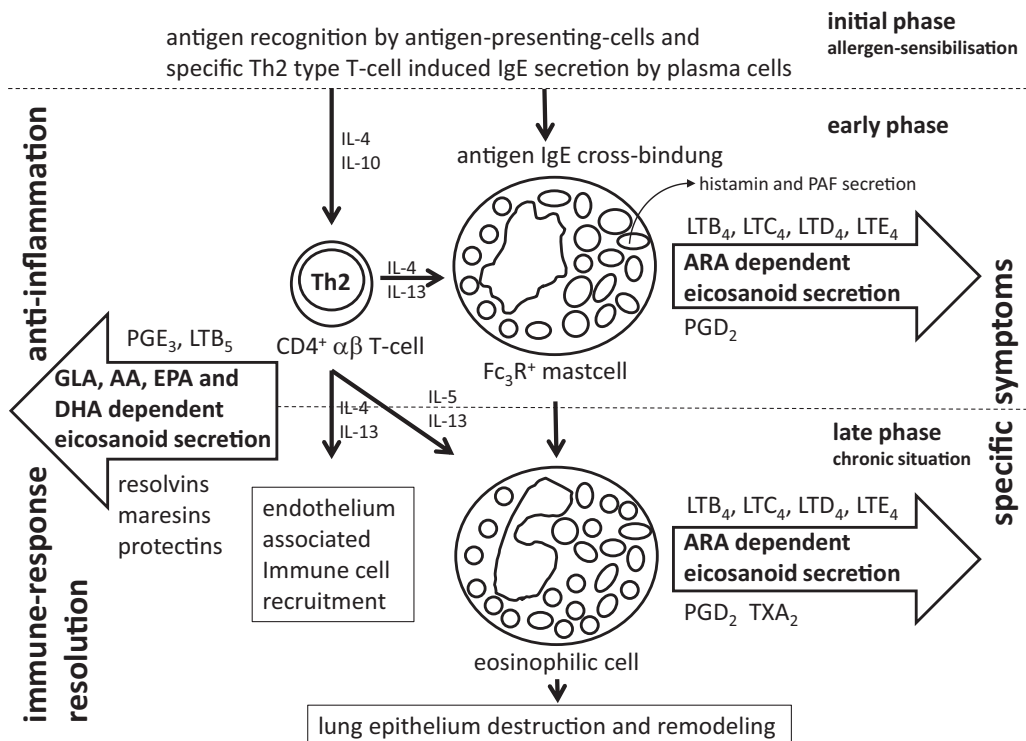


Fig. 1. The developmental process of allergic asthma and the regulatory function of LCPUFA-derived eicosanoids. AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ -linolenic acid; LCPUFA, long-chain polyunsaturated fatty acid; Ig, immunoglobulin; IL, interleukin; LT, leukotriene; PAF, platelet-activating factor; PG, prostaglandin; Th, T helper; TX, thromboxane.

Effects of particular LCPUFA in asthma

To date, many studies have investigated the influence of particular LCPUFA species and their synthesized eicosanoids on inflammation in terms of asthma incidence [32–39].

α-Linolenic acid

A major plant-based essential fatty acid occurring in flaxseed oil, beans, and walnuts, ALA has to be obtained through nutrition [40,41]. The main effects of ALA result from its biochemical conversion into EPA and DHA [35]. However, the metabolic conversion efficiency in humans is poor and limited by Δ -6 desaturase (rate-limiting enzyme). Additionally, most absorbed ALA undergoes β -oxidation [17,37]. Nevertheless, dietary ALA supplementation leads to several effects on IL secretion and transcription factor synthesis. On the intercellular signaling level, it has been found that ALA suppresses the production of proinflammatory tumor necrosis factor- α , IL-6, and IL-8 [42,43]. One study demonstrated that ALA downregulates the activation of NF- κ B, which is a central transcription factor in the immune response [44]. Moreover, high intake of ALA was previously associated with a decreased risk for allergic sensitization and allergic rhinitis [35], leading to lower exhaled nitrogen monoxide (NO) and thereby a reduced probability of non-controlled asthma [44]. Interestingly, a diet rich in ALA leads to increased levels of EPA, but not DHA, in erythrocytes, platelets, leukocytes, and plasma phospholipids [45]. Consequently, the synthesis and release of DHA-associated anti-inflammatory and inflammatory-resolving eicosanoids is not affected by ALA supplementation, which argues in favor of combined supplementation of ALA and DHA.

Stearidonic acid

Generally, seafood, seaweed, and some specific plant seed oils contain stearidonic acid (SDA; C18:4 ω -3). Seed oils from borage and echium are the most prominent SDA source commercially available [46,47]. SDA-rich oils can be an alternative to fish and encapsulated fish oil supplements and are appropriate for vegetarians [48]. Along the metabolic pathway of LCPUFA, SDA is directly formed from ALA by the action of Δ -6-desaturase [47]. After conversion, the intermediate SDA is rapidly converted to EPA by elongation and a further desaturation step [46]. One study found that supplemented SDA could modify the ω -3 fatty acid index more efficiently than ALA [46,47]. In vivo, SDA conversion to EPA is four- to fivefold more efficient than ALA [49].

It has been observed that daily ingestion of SDA increased EPA and docosapentaenoic acid (DPA; C22:5 ω -3) concentrations in erythrocyte and plasma phospholipids. In comparison, dietary ALA supplementation at the same dose (0.75 g/d) did not [48]. Results from one study found that mice fed a diet containing SDA had lower whole blood tumor necrosis factor- α levels [50]. Furthermore, SDA has been described as a potent biologically active surrogate for EPA because of its anti-inflammatory characteristics [46,47]. Beside the inhibitory effect of SDA on 5-LOX and epoxide hydrolase, the competitive inhibition of AA metabolism is similar to EPA and the most important attribute of SDA [51].

EPA and DHA

Sea fish oil is a major source of EPA and DHA [8,18]. A few studies have shown that EPA blocks the desaturation of DGLA to form AA [52,53], and EPA-derived eicosanoids antagonize the

action of the eicosanoids (prostaglandin [PG]-2-series, thromboxane [TX]-2-series, and LT-4-series) derived from AA [11]. EPA-derived PG inhibits TXB₂-mediated platelet aggregation, produced from AA, and promotes vasodilation [20]. Furthermore, LTB₅ derived from EPA obstructs the AA-dependent biosynthesis of the highly proinflammatory LTB₄ [20]. LTB₄ is also a lipid mediator derived from AA and induces the activation and adhesion of leukocytes in lung tissue [54]. Considering asthma, several studies have shown that DHA in particular is able to reduce eosinophilic infiltration, decrease leukocyte accumulation in the lung, and improve lung function [21,55,56]. In vitro studies have illustrated that DHA decreases the expression of proinflammatory cytokines and cell adhesion molecules to an even greater extent than EPA [57]. In mice, the expression of proinflammatory cytokines was significantly increased with DHA supplementation, but not with EPA [58,59]. These confusing results might reflect the differences between in vitro and in vivo disease models in relation to LCPUFA.

The anti-inflammatory properties of these two fatty acids are due to inhibiting COX activity and decreasing eicosanoid synthesis from AA [9,11,60]. Moreover, EPA and DHA suppress IgE production and thereby reduce airway inflammation and bronchoconstriction in asthma [35], leading to reduced cytokine expression and reduced NF- κ B DNA-binding proinflammatory activities. Thus, it is believed that EPA is a more potent NF- κ B inhibitor than DHA [60,61]. However, in an in vitro study DHA more effectively induced an anti-inflammatory profile in bacterial lipopolysaccharide-stimulated human macrophages compared to EPA [62]. In human monocytes, it has been demonstrated that EPA and DHA block NF- κ B activity directly through decreased degradation of the inhibitory subunit of NF- κ B, which might reduce inflammation in asthma [63]. Furthermore, PPAR are able to bind ω -3 PUFA and their eicosanoids, which activates these receptor and thus modulates the inflammatory response [64]. The activation of PPAR inhibits the expression of proinflammatory genes, such as cytokines; negatively regulates the transcription of inflammatory response genes by antagonizing NF- κ B and T-cell signaling pathways; and stimulates the catabolism of proinflammatory eicosanoids [20,65].

EPA and DHA are direct precursors of resolvins (E- and D-series), protectins, and maresins, which are SPM and play a significant role in the downregulation of inflammation in bronchial asthma [11,66]. SPM act as agonists at specific receptors of neutrophils, macrophages, and lymphocytes and decrease the synthesis of proinflammatory cytokines, chemokines, and lipid mediators. Moreover, SPM inhibit neutrophilic cell migration but increase macrophage phagocytosis of apoptotic neutrophils [4,8,67]. Furthermore, these molecules reduce airway hyper-responsiveness and mucus production [4,8]. Taken together, these results point to a broad role of ω -3 fatty acids in the resolution of inflammation.

γ-Linolenic acid and DGLA

Although the research focus is preliminary on ω -3 LCPUFA, ω -6 LCPUFA such as γ -linolenic acid (GLA; C18:3 ω -6) and DGLA possess anti-inflammatory potential [5,68]. The anti-inflammatory characteristics of GLA may be due to its molecular structural isomerism to ALA [17]. GLA is present in trace amounts in green leafy vegetables and nuts, but it is mostly generated by a desaturation step from LA [17,69]. In contrast, DGLA cannot be derived directly from the diet; rather, it is formed by elongation from GLA [17]. Due to the rapid

transformation of GLA to DGLA in inflammatory cells, GLA competes with AA for the metabolic enzyme reactions to form eicosanoids [70]. Generally, dietary intake of GLA results in the accumulation of DGLA in plasma lipids and cells [71]. One study indicated that the DGLA level in peripheral blood mononuclear cells was significantly higher after 12 wk of GLA supplementation in healthy individuals compared with baseline and that GLA consumption decreases lymphocyte proliferation [5]. Studies with fish cell cultures revealed that DGLA competitively depresses the production of eicosanoids from AA [72]. Additionally, DGLA is a precursor of the anti-inflammatory eicosanoid PGE₁ [35], and in human mononuclear leukocytes, DGLA is metabolized to 15-hydroxyeicosatetraenoic acid, which is an effective inhibitor of LTB₄ formation from AA [68].

Arachidonic acid

The precursor of proinflammatory eicosanoids, such as PG, TX, and LT, is AA [7,11]. It can be ingested via nutrition, but it is also synthesized from the essential fatty acid LA [60]. Regarding asthma, AA is a double-edged sword with pro- and anti-inflammatory regulatory potential. The lipid mediator lipoxin (LX)A₄ is generated from AA in a multistep enzymatic process. Its transcellular biosynthesis occurs in the lung during cell–cell interactions and is potentially vulnerable to oxidative stress [73,74].

Severe asthma leads to increased airway oxidative stress; therefore, the activity of soluble epoxide hydrolase is high and LX levels have been found to be decreased in human cells in vitro and in rodent lung in vivo [73]. Consequently, in uncontrolled asthma, LXA₄ levels were strongly decreased; thus, endogenous LXA₄ cannot resolve airway inflammation and never acts in an anti-inflammatory manner by inhibiting neutrophil and eosinophil migration, transendothelial and transepithelial migration, and the generation of superoxide anions [73,75].

Although AA-derived PGE₂ possesses proinflammatory properties, the respiratory tract seems to be the only system in which this eicosanoid PGE₂ is helpful to asthmatic patients by exerting bronchoprotective effects [11]. Hereby, PGE₂ inhibits 5-LOX, leading to decreased production of the 4-series LT [11]. Nevertheless, the main products of AA are proinflammatory PG, LT, and TX [7]. Results from one study indicated that children with asthma have significantly higher LTB₄ concentrations in the small airways or alveolar fraction than controls [76]. Considering this, for asthma treatment, it might be worthwhile to reduce the metabolic AA pool. SDA competes with DGLA for the Δ -5 desaturase and might be a tool to decrease the formation of AA (Fig. 1).

The effectiveness of combinations of different LCPUFA species in asthma treatment

A few studies have examined the effect of supplementation with LCPUFA blends, which might lead to a synergistically pro-resolution effect in inflammatory diseases, especially in asthma.

One study found that diets enriched with either DHA or EPA never improved asthma, whereas combinations of both fatty acid species help to reduce asthma symptoms in mice [58], substantiating the conflicting evidence on applying only a single ω -3 LCPUFA for the prevention and treatment of allergic diseases, including asthma [56,77–81]. Moreover, another study showed that high intake of ALA in humans is associated with lower exhaled NO, thus reducing the probability of non-controlled asthma [44]. Interestingly, a higher dietary intake of ALA in

combination with EPA and DHA reduced the odds of non-controlled asthma [35]. It has been demonstrated that not only does increased ingestion of GLA result in the accumulation of DGLA in plasma lipids and cells, but also that GLA in combination with SDA increased the ratio of EPA in some lipid fractions in humans. Furthermore, the combination had the tendency to increase the DGLA content of blood cells without a subsequent increase in the AA content [71]. In one study, patients with mild asthma received supplementation with diverse doses of borage and echium seed oil combinations that contained SDA (0.25–1.75 g), ALA (0.57–4.02 g), and GLA (consistent dose of 1.5 g) for 3 wk. The supplementation led to an increased plasma concentration of SDA, GLA, DGLA, and EPA as well as its elongation product DPA. This increase in DPA rate never altered DHA plasma concentrations, possibly due to the poor enzymatic EPA/DPA to DHA bioconversion rate. As a functional consequence, asthma-relevant AA-associated cysteinyl leukotriene generation in stimulated basophils was attenuated by >50% and in stimulated neutrophils by >35% [70].

Taking this into consideration, including the particular effects of distinct LCPUFA on inflammatory and resolution processes, it might be possible that GLA, ALA, SDA, EPA, and DHA exert a synergistic beneficial effect on bronchial asthma. Figure 2 demonstrates these interactions after treatment with distinct ω -3 and ω -6 fatty acids and the consequences of AA synthesis and its derived eicosanoid metabolism at a glance. GLA supplementation, together with ALA and SDA, synergistically lead to EPA synthesis as well as the accumulation of DGLA. Furthermore, treatment with SDA increases the amount of DPA, which can be metabolized into DHA. It has been observed that the combination of SDA and GLA is useful in treatment of inflammatory disease [51]. Within this metabolic model, additional dietetic supplementation of EPA and DHA might be supportive to increase the anti-inflammatory ω -3 eicosanoid pool, such as PG (3-series), TX (3-series), LT (5-series), resolvins (E- and D-series), as well as protectins and maresins. Consequently, supplementation with these fatty acids at best decreases (or at least maintains) the AA-dependent proinflammatory eicosanoid pool. Accumulations of intermediates within the pathways of ω -3 and ω -6 LCPUFA lead to different feedback inhibitions. PGE₂ derived from AA inhibits the conversion from LA to GLA, LA leads to a decreased EPA pool by inhibiting metabolism from ALA to EPA, and EPA blocks the enzyme Δ -5 desaturase by the conversion of eicosatetraenoic acid into EPA [48,82].

These data lead to the assumption that a disease-specific combination of LCPUFA might have beneficial synergistic effects, which might be based on different substrate-product competitions of the desaturase, elongase, and oxygenase systems of the eicosanoid metabolic pathway. Further animal and clinical studies investigating immunologic parameters and lung function must outline whether combined application of ALA, GLA, SDA, EPA, and DHA can synergistically enhance their anti-asthmatic effect.

Conclusion

In conclusion, ω -3 ALA, SDA, EPA, or DHA influence several immunologic parameters connected to the asthmatic situation and clinical aspects (i.e., lung function and inflammatory markers). However, the anti-inflammatory effects of some ω -6 LCPUFA, such as DGLA and GLA, are not negligible. AA is a double-edged sword with pro- and anti-inflammatory aspects, although asthma-enhancing properties dominate. Combinations of complex oil blends with distinct ω -3 and ω -6 LCPUFA species

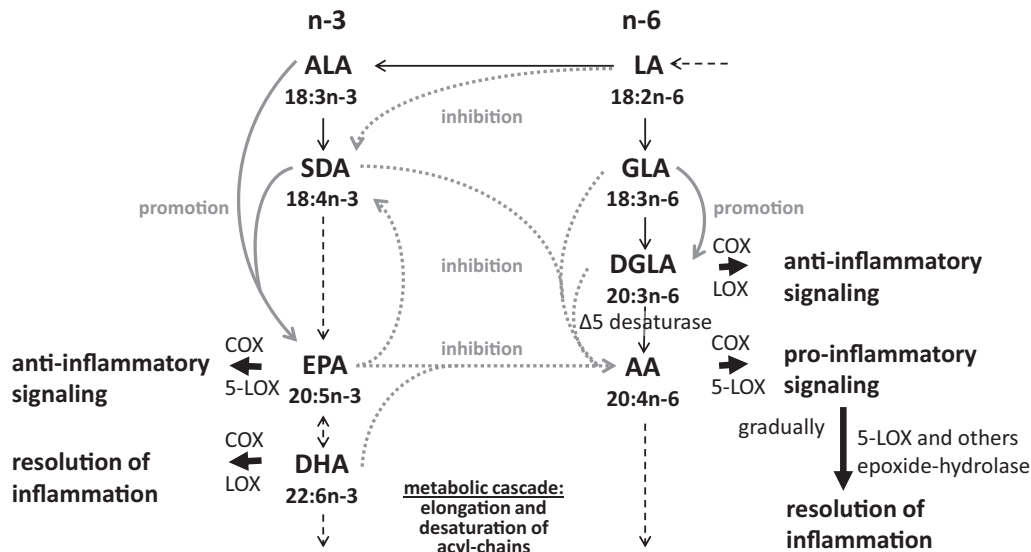


Fig. 2. Interactions between distinct ω -3 and ω -6 fatty acids within the metabolic LCPUFA pathway with consequences on AA-derived eicosanoid metabolism. Supplementation with SDA, EPA, DHA, and GLA can affect AA metabolism. In detail, GLA competes with AA for phospholipase A2 and COX. DGLA, which is synthesized from GLA and a 15-hydroxyl derivative of DGLA, blocks the transformation of AA into leukotrienes. Furthermore, SDA can block 5-LOX and epoxide hydrolase and hinder AA-derived eicosanoid generation. EPA is able to inhibit Δ -5 desaturase and thus the conversion from DGLA to AA. Additionally, EPA and DHA decrease the AA eicosanoid pool by interfering with the desaturase, elongase, and oxygenase system of the AA-associated eicosanoid metabolic pathway. AA, arachidonic acid; ALA, α -linolenic acid; COX, cyclooxygenase; DGLA, dihomogamma-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; LA, linolenic acid; LOX, lipoxygenase; LCPUFA, long-chain polyunsaturated fatty acid; SDA, stearidonic acid.

may direct the eicosanoid pathway into an anti-inflammatory direction, especially an early stage in mild asthma. These molecules may effectively reduce inflammation in the bronchoalveolar system on the cellular level and help to control the clinical symptoms of bronchial asthma. New approaches are needed to investigate this opportunity.

References

- Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869–77.
- Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184–90.
- Durham A, Adcock IM, Tliba O. Steroid resistance in severe asthma: current mechanisms and future treatment. *Curr Pharm Des* 2011;17:674–84.
- Duvall MG, Levy BD. DHA- and EPA-derived resolvins, protectins, and maresins in airway inflammation. *Eur J Pharmacol*; 2015. <http://dx.doi.org/10.1016/j.ejphar.2015.11.001> [Epub ahead of print].
- Thies F, Nebe-von-Caron G, Powell JR, Yaqoob P, Newsholme EA, Calder PC. Dietary supplementation with gamma-linolenic acid or fish oil decreases T lymphocyte proliferation in healthy older humans. *J Nutr* 2001;131:1918–27.
- Levy BD, Serhan CN. Resolution of acute inflammation in the lung. *Annu Rev Physiol* 2014;76:467–92.
- Wendell SG, Baffi C, Holguin F. Fatty acids, inflammation, and asthma. *J Allergy Clin Immunol* 2014;133:1255–64.
- Miyata J, Arita M. Role of omega-3 fatty acids and their metabolites in asthma and allergic diseases. *Allergol Int* 2015;64:27–34.
- Gogus U, Smith C. n-3 Omega fatty acids: a review of current knowledge. *Int J Food Sci Technol* 2010;45:417–36.
- Calder PC. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. *Biochim Biophys Acta* 2014;1851:469–84.
- Giudetti AM, Cagnazzo R. Beneficial effects of n-3 PUFA on chronic airway inflammatory diseases. *Prostaglandins Other Lipid Mediat* 2012;99:57–67.
- Holgate ST. Innate and adaptive immune responses in asthma. *Nat Med* 2012;18:673–83.
- Boulet L. Physiopathology of airway hyperresponsiveness. *Curr Allergy Asthma Rep* 2003;3:166–71.
- Holgate ST. Pathogenesis of asthma. *Clin Exp Allergy* 2008;38:872–97.
- Yonetomi Y, Sekioka T, Kadode M, Kitamine T, Kamiya A, Matsumura N, et al. Leukotriene C4 induces bronchoconstriction and airway vascular hyperpermeability via the cysteinyl leukotriene receptor 2 in S-hexyl glutathione-treated guinea pigs. *Eur J Pharmacol* 2015;754:98–104.
- Holt PG, Sly PD. Th2 cytokines in the asthma late-phase response. *Lancet* 2007;370:1396–8.
- Kim K, Nam YA, Kim HS, Hayes AW, Lee B. alpha-Linolenic acid: nutraceutical, pharmacological and toxicological evaluation. *Food Chem Toxicol* 2014;70:163–78.
- Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol* 2013;75:645–62.
- Hageman HJ, Hooyenga P, Diersen-Schade DA, Scalabrini DM, Wichers HJ, Birch EE. The impact of dietary long-chain polyunsaturated fatty acids on respiratory illness in infants and children. *Curr Allergy Asthma Rep* 2012;12:564–73.
- Schmitz G, Ecker J. The opposing effects of n-3 and n-6 fatty acids. *Prog Lipid Res* 2008;47:147–55.
- Bilal S, Haworth O, Wu L, Weylandt KH, Levy BD, Kang JX. Fat-1 transgenic mice with elevated omega-3 fatty acids are protected from allergic airway responses. *Biochim Biophys Acta* 2011;1812:1164–9.
- Miedema I, Feskens EJ, Heederik D, Kromhout D. Dietary determinants of long-term incidence of chronic nonspecific lung diseases. The Zutphen study. *Am J Epidemiol* 1993;138:37–45.
- Antony B, Vanni S, Shindou H, Ferreira T. From zero to six double bonds: phospholipid unsaturation and organelle function. *Trends Cell Biol* 2015;25:427–36.
- Lee TH, Hoover RL, Williams JD, Sperling RI, Ravalese J, Spur BW, et al. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *N Engl J Med* 1985;312:1217–24.
- Healy DA, Wallace FA, Miles EA, Calder PC, Newsholme P. Effect of low-to-moderate amounts of dietary fish oil on neutrophil lipid composition and function. *Lipids* 2000;35:763–8.
- Miyake Y, Sasaki S, Arakawa M, Tanaka K, Murakami K, Ohya Y. Fatty acid intake and asthma symptoms in Japanese children: the Ryukyus Child Health Study. *Clin Exp Allergy* 2008;38:1644–50.
- Oddy WH, de Klerk NH, Kendall GE, Mihrshahi S, Peat JK. Ratio of omega-6 to omega-3 fatty acids and childhood asthma. *J Asthma* 2004;41:319–26.
- Woods RK, Raven JM, Walters EH, Abramson MJ, Thien FC. Fatty acid levels and risk of asthma in young adults. *Thorax* 2004;59:105–10.
- Allan K, Devereux G. Diet and asthma: nutrition implications from prevention to treatment. *J Am Diet Assoc* 2011;111:258–68.
- Bilal MA, Baset AA, Bassiouny M, Kasrawi MA, Attia M. Omega-3 fatty acids, vitamin C and Zn supplementation in asthmatic children: a randomized self-controlled study. *Acta Paediatr* 2009;98:737–42.
- Lundström SL, Yang J, Brannan JD, Haeggström JZ, Hammock BD, Nair P, et al. Lipid mediator serum profiles in asthmatics significantly shift

- following dietary supplementation with omega-3 fatty acids. *Mol Nutr Food Res* 2013;57:1378–89.
- [32] Kitz R, Rose MA, Schubert R, Beermann C, Kaufmann A, Böhles HJ, et al. Omega-3 polyunsaturated fatty acids and bronchial inflammation in grass pollen allergy after allergen challenge. *Respir Med* 2010;104:1793–8.
 - [33] McKeever TM, Lewis SA, Cassano PA, Ocke M, Burney P, Britton J, et al. The relation between dietary intake of individual fatty acids, FEV1 and respiratory disease in Dutch adults. *Thorax* 2008;63:208–14.
 - [34] Kompauer I, Demmelmair H, Koletzko B, Bolte G, Linseisen J, Heinrich J. Association of fatty acids in serum phospholipids with lung function and bronchial hyperresponsiveness in adults. *Eur J Epidemiol* 2008;23:175–90.
 - [35] Barros R, Moreira A, Fonseca J, Delgado L, Castel-Branco MG, Hahtela T, et al. Dietary intake of α -linolenic acid and low ratio of n-6:n-3 PUFA are associated with decreased exhaled NO and improved asthma control. *Br J Nutr* 2011;106:441–50.
 - [36] Nakamura K, Wada K, Sahashi Y, Tamai Y, Tsuji M, Watanabe K, et al. Associations of intake of antioxidant vitamins and fatty acids with asthma in pre-school children. *Public Health Nutr* 2013;16:2040–5.
 - [37] Bolte G, Kompauer I, Fobker M, Cullen P, Keil U, Mutius E, et al. Fatty acids in serum cholesteryl esters in relation to asthma and lung function in children. *Clin Exp Allergy* 2006;36:293–302.
 - [38] Li J, Xun P, Zamora D, Sood A, Liu K, Daviglius M, et al. Intakes of long-chain omega-3 PUFAs and fish in relation to incidence of asthma among American young adults: the CARDIA study. *Am J Clin Nutr* 2013;97:173–8.
 - [39] Schubert R, Kitz R, Beermann C, Rose MA, Lieb A, Sommerer PC, et al. Effect of ω -3 polyunsaturated fatty acids in asthma after low-dose allergen challenge. *Int Arch Allergy Immunol* 2009;148:321–9.
 - [40] Barcelo-Coblijn G, Murphy EJ, Othman R, Moghadasian MH, Kashour T, Friel JK. Flaxseed oil and fish-oil capsule consumption alters human red blood cell n-3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n-3 fatty acid. *Am J Clin Nutr* 2008;88:801–9.
 - [41] Ayerza R Jr, Coates W. Effect of dietary alpha-linolenic fatty acid derived from chia when fed as ground seed, whole seed and oil on lipid content and fatty acid composition of rat plasma. *Ann Nutr Metab* 2007;51:27–34.
 - [42] Xie N, Zhang W, Li J, Liang H, Zhou H, Duan W, et al. α -Linolenic acid intake attenuates myocardial ischemia/reperfusion injury through anti-inflammatory and anti-oxidative stress effects in diabetic but not normal rats. *Arch Med Res* 2011;42:171–81.
 - [43] de Batlle J, Sauleda J, Balcells E, Gómez FP, Méndez M, Rodríguez E, et al. Association between Q3 and Q6 fatty acid intakes and serum inflammatory markers in COPD. *J Nutr Biochem* 2012;23:817–21.
 - [44] Hassan A, Ibrahim A, Mbodji K, Coeffier M, Ziegler F, Bounoure F, et al. An alpha-linolenic acid-rich formula reduces oxidative stress and inflammation by regulating NF-kappaB in rats with TNBS-induced colitis. *J Nutr* 2010;140:1714–21.
 - [45] Burdge GC, Calder PC. Conversion of alpha-linolenic acid to longer-chain polyunsaturated fatty acids in human adults. *Reprod Nutr Dev* 2005;45:581–97.
 - [46] Whelan J. Dietary stearidonic acid is a long chain polyunsaturated fatty acid with potential health benefits. *J Nutr* 2009;139:5–10.
 - [47] Whelan J, Gouffon J, Zhao Y. Effects of dietary stearidonic acid on biomarkers of lipid metabolism. *J Nutr* 2012;142:6305–45.
 - [48] James MJ, Ursin VM, Cleland LG. Metabolism of stearidonic acid in human subjects: comparison with the metabolism of other n-3 fatty acids. *Am J Clin Nutr* 2003;77:1140–5.
 - [49] de Lorgeril M, Salen P. Alpha-linolenic acid and coronary heart disease. *Nutr Metab Cardiovasc Dis* 2004;14:162–9.
 - [50] Ishihara K, Komatsu W, Saito H, Shinohara K. Comparison of the effects of dietary α -linolenic, stearidonic, and eicosapentaenoic acids on production of inflammatory mediators in mice. *Lipids* 2002;37:481–6.
 - [51] Guichardant M, Trautler H, Spielmann D, Sprecher H, Finot P. Stearidonic acid, an inhibitor of the 5-lipoxygenase pathway. A comparison with timnodonic and dihomogammalinolenic acid. *Lipids* 1993;28:321–4.
 - [52] Barham JB, Edens MB, Fonteh AN, Johnson MM, Easter L, Chilton FH. Addition of eicosapentaenoic acid to gamma-linolenic acid-supplemented diets prevents serum arachidonic acid accumulation in humans. *J Nutr* 2000;130:1925–31.
 - [53] Surette ME, Koumenis IL, Edens MB, Trampusch KM, Chilton FH. Inhibition of leukotriene synthesis, pharmacokinetics, and tolerability of a novel dietary fatty acid formulation in healthy adult subjects. *Clin Ther* 2003;25:948–71.
 - [54] Goldklang MP, Perez-Zoghbi JF, Trischler J, Nkyimbeng T, Zakharov SI, Shiomi T, et al. Treatment of experimental asthma using a single small molecule with anti-inflammatory and BK channel-activating properties. *FASEB J* 2013;27:4975–86.
 - [55] Aoki H, Hisada T, Ishizuka T, Utsugi M, Ono A, Koga Y, et al. Protective effect of resolvin E1 on the development of asthmatic airway inflammation. *Biochem Biophys Res Commun* 2010;400:128–33.
 - [56] Yokoyama A, Hamazaki T, Ohshita A, Kohno N, Sakai K, Zhao GD, et al. Effect of aerosolized docosahexaenoic acid in a mouse model of atopic asthma. *Int Arch Allergy Immunol* 2000;123:327–32.
 - [57] de Caterina R, Liao JK, Libby P. Fatty acid modulation of endothelial activation. *Am J Clin Nutr* 2000;71:213S–23S.
 - [58] Schuster GU, Bratt JM, Jiang X, Pedersen TL, Grapov D, Adkins Y, et al. Dietary long-chain omega-3 fatty acids do not diminish eosinophilic pulmonary inflammation in mice. *Am J Respir Cell Mol Biol* 2014;50:626–36.
 - [59] Schubert R, Kitz R, Beermann C, Rose MA, Baer PC, Zielen S, et al. Influence of low-dose polyunsaturated fatty acids supplementation on the inflammatory response of healthy adults. *Nutrition* 2007;23:724–30.
 - [60] Yates CM, Calder PC, Ed Rainger G. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. *Pharmacol Ther* 2014;141:272–82.
 - [61] Galli C, Calder PC. Effects of fat and fatty acid intake on inflammatory and immune responses: a critical review. *Ann Nutr Metab* 2009;55:123–39.
 - [62] Weldon SM, Mullen AC, Loscher CE, Hurley LA, Roche HM. Docosahexaenoic acid induces an anti-inflammatory profile in lipopolysaccharide-stimulated human THP-1 macrophages more effectively than eicosapentaenoic acid. *J Nutr Biochem* 2007;18:250–8.
 - [63] Novak TE, Babcock TA, Jho DH, Helton WS, Espot NJ. NF-kappa B inhibition by omega -3 fatty acids modulates LPS-stimulated macrophage TNF- α transcription. *Am J Physiol* 2003;284:L84–9.
 - [64] Georgiadi A, Kersten S. Mechanisms of gene regulation by fatty acids. *Adv Nutr* 2012;3:127–34.
 - [65] Delerive P, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors in inflammation control. *J Endocrinol* 2001;169:453–9.
 - [66] Swanson D, Block R, Mousa SA. Omega-3 fatty acids EPA and DHA: health benefits throughout life. *Adv Nutr* 2012;3:1–7.
 - [67] Basil MC, Levy BD. Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. *Nat Rev Immunol* 2016;16:51–67.
 - [68] Iversen L, Fogh K, Kragballe K. Effect of dihomogammalinolenic acid and its 15-lipoxygenase metabolite on eicosanoid metabolism by human mononuclear leukocytes in vitro: selective inhibition of the 5-lipoxygenase pathway. *Arch Dermatol Res* 1992;284:222–6.
 - [69] Kapoor R, Huang Y. Gamma linolenic acid: an antiinflammatory omega-6 fatty acid. *Curr Pharm Biotechnol* 2006;7:531–4.
 - [70] Arm JP, Boyce JA, Wang L, Chhay H, Zahid M, Patil V, et al. Impact of botanical oils on polyunsaturated fatty acid metabolism and leukotriene generation in mild asthmatics. *Lipids Health Dis* 2013;12:141.
 - [71] Miles EA, Banerjee T, Calder PC. The influence of different combinations of gamma-linolenic, stearidonic and eicosapentaenoic acids on the fatty acid composition of blood lipids and mononuclear cells in human volunteers. *Prostaglandins Leukot Essent Fatty Acids* 2004;70:529–38.
 - [72] Bell JG, Tocher DR, Sargent JR. Effect of supplementation with 20:3, 20:4 and 20:5 on the production of prostaglandins E and F of the 1-, 2- and 3-series in turbot brain astroglial cells in primary culture. *Biochim Biophys Acta* 1994;1211:335–42.
 - [73] Ono E, Dutilleul S, Kazani S, Wechsler ME, Yang J, Hammock BD, et al. Lipoxin generation is related to soluble epoxide hydrolase activity in severe asthma. *Am J Respir Crit Care Med* 2014;190:886–97.
 - [74] Eickmeier O, Hilberath JN, Zielen S, Haworth O. Die Rolle neuer “pro-resolving” Lipidmediatoren bei entzündlichen Lungenerkrankungen [Pro-resolving lipid mediators in inflammatory lung diseases]. *Pneumologie* 2011;65:149–58.
 - [75] Trischler J, Müller C, Könnitzer S, Prell E, Korten I, Unverzagt S, et al. Elevated exhaled leukotriene B₄ in the small airway compartment in children with asthma. *Ann Allergy Asthma Immunol* 2015;114:111–6.
 - [76] Klemens CM, Berman DR, Mozurkewich EL. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: a systematic review. *BJOG* 2011;118:916–25.
 - [77] Raviv S, Smith LJ. Diet and asthma. *Curr Opin Pulm Med* 2010;16:71–6.
 - [78] Reisman J, Schachter HM, Dales RE, Tran K, Kourad K, Barnes D, et al. Treating asthma with omega-3 fatty acids: where is the evidence? A systematic review. *BMC Complement Altern Med* 2006;6:26.
 - [79] Stephensen CB. Fish oil and inflammatory disease: is asthma the next target for n-3 fatty acid supplements? *Nutr Rev* 2004;62:486–9.
 - [80] Mukherjee PK, Marcheselli VL, Serhan CN, Bazan NG. Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. *Proc Natl Acad Sci U S A* 2004;101:8491–6.
 - [81] Smink W, Gerrits WJ, Gloaguen M, Ruiter A, van Baal J. Linoleic and alpha-linolenic acid as precursor and inhibitor for the synthesis of long-chain polyunsaturated fatty acids in liver and brain of growing pigs. *Animal* 2012;6:262–70.
 - [82] Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, et al. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. *Circulation* 2005;111:157–64.