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Dietary n-3 long chain polyunsaturated fatty acids in allergy prevention and asthma treatment

Linette E.M. Willemsen

Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands

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ABSTRACT

The rise in non-communicable diseases, such as allergies, in westernized countries links to changes in lifestyle and diet. N-3 long chain polyunsaturated fatty acids (LCPUFA) present in marine oils facilitate a favorable milieu for immune maturation and may contribute to allergy prevention. N-3 LCPUFA can suppress innate and adaptive immune activation and induce epigenetic changes. Murine studies convincingly show protective effects of fish oil, a source of n-3 LCPUFA, in food allergy and asthma models. Observational studies in human indicate that high dietary intake of n-3 LCPUFA and low intake of n-6 PUFA may protect against the development of allergic disease early in life. High n-6 PUFA intake is also associated with an increased asthma risk while n-3 LCPUFA may be protective and reduce symptoms. The quality of the marine oil used has impact on efficacy of allergy prevention and several observations link in particular n-3 LCPUFA DHA to allergy suppression. Randomized controlled trials indicate that optimal timing, duration and dosage of n-3 LC-PUFA is required to exert an allergy protective effect. Supplementation during early pregnancy and lactation has shown promising results regarding allergy prevention. However these findings should be confirmed in a larger cohort. Although clinical trials in asthma patients reveal no consistent clinical benefits of n-3 LCPUFA supplementation on lung function, it can suppress airway inflammation. Future food-pharma approaches may reveal whether adjunct therapy with dietary n-3 LCPUFA can improve allergy prevention or immunotherapy via support of allergen specific oral tolerance induction or contribute to the efficacy of drug therapy for asthma patients.

1. Dietary fatty acids and allergic disease

Over the last decades the prevalence of allergic disease has steadily been rising and recent figures indicate that in the western world 10–25% of people are affected with allergic diseases ranging from food allergy, atopic dermatitis/ eczema, allergic rhinitis, hay fever to asthma (Levy et al., 2007; Platts-Mills, 2015). In early life food allergy and atopic dermatitis are the first occurring allergic diseases, peaking at one year of age. 2-8% Of young infants and 5% of adults are affected with food allergy (Sanchez-Garcia et al., 2015; Sicherer and Sampson 2014), while the prevalence of asthma reaches 5% in western countries (Barros et al., 2015). In the majority of cases children out grow food allergy by the age of three to five years however later in life allergic rhinitis and asthma can develop as a consequence of the atopic constitution (Malmberg et al., 2010; Alduraywish et al., 2015). Changing environmental conditions such as urbanization, sedentary lifestyle and dietary alterations have been suggested to impair immune maturation and increase immunological disorders such as allergic diseases, fitting in the category of non-communicable diseases (Prescott, 2013; Haahtela et al., 2015; Dunstan and Prescott, 2005; Schroder et al., 2015). Increased fat, sugar and salt intake and reduced fiber and antioxidant intake have been suggested to contribute to allergic sensitization and/or severity of allergic symptoms (Nagel et al., 2010; Ellwood et al., 2013; Barros et al., 2015; Trak-Fellermeier et al., 2004) and fish, fruit and vegetable intake have been associated with allergy protection (Barros et al., 2015; Magnusson et al., 2013; Shaheen et al., 2001; Lumia et al., 2011; Woods et al., 2003; Calvani et al., 2006). Besides the increase in quantity also

Abbreviations: AA, arachidonic acid; ALA, alpha linolenic acid; aOR, adjusted odds ratio; aRR, adjusted risk ratio; BLG, beta-lactoglobulin; CCL, chemokine ligand; cysLT, cysteinyl leukotrienes; DC, dendritic cell; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; eNO, exhaled nitric oxide; FA, Fatty Acids; FADS, Fatty Acid Desaturase; FEV_1, Forced Expiratory Volume; HR, Hazard Ratio; LA, linoleic acid; LCPUFA, long chain poly unsaturated fatty acids; LPS, lipopolysaccharide; MLN, mesenteric lymph nodes; OVA, ovalbumin; PA, palmitic acid; PBMC, peripheral blood mononuclear cells; SFA, saturates fatty acids; SPT, skin prick test; Treg, regulatory T cell; T_H, T helper cell; Tr1, type 1 regulatory T cell

E-mail address: L.E.M.Willemsen@uu.nl

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the quality of dietary fat has changed over the decades. N-6 polyunsaturated fatty acid (PUFA) linoleic acid (LA; 18:2, n-6) is increasingly consumed since it is abundantly present in vegetable oils such as sunflower, corn, and soybean oil which are present in margarine, while the increased consumption of meat enhances arachidonic acid intake (AA; 20:4, n-6). In female increased intake of saturated fatty acid (SFA) and mono-unsaturated FA for example has been associated with increased risk of allergic sensitization while an increasing intake of PUFA over SFA was associated with protection (Trak-Fellermeier et al., 2004). However in the same study cohort increasing intake of n-6 PUFA over n-3 PUFA enhanced the risk of developing atopic eczema in females and the same was shown for an increasing intake of n-6 LA over n-3 alpha-linolenic acid (ALA; 18:3, n-3) (Trak-Fellermeier et al., 2004). LA and ALA are essential FA that need to be acquired via the diet and can slowly be converted in biologically active long chain poly-unsaturated fatty acid (LCPUFA), AA or eicosapentaenoic acid (EPA; C20:5 n-3) and docosahexaenoic acid (DHA; C22:6 n-3). Intake of n-3 LCPUFA EPA and DHA, which are present in fatty fish (such as salmon, herring, mackerel and tuna), algae, krill and marine oils, is traditionally low in westernized countries. ALA from vegetable sources only allows for 0.1-10% of the n-3 LCPUFA pool depending on the conversion rate which is determined in part by polymorphisms in the fatty acid desaturase (FADS) gene (Lattka et al., 2012). Similar applies for n-6 LCPUFA AA derived from LA (Koletzko et al., 2014; Lattka et al., 2012). In the cell membrane n-6 and n-3 PUFA compete for incorporation into phospholipids. n-3 LCPUFA will replace AA resulting in altered FA composition of the cell membrane and an altered pattern of eicosanoid and resolvin production (Calder, 2015). Intake of n-3 LCPUFA during pregnancy or postnatally, has often been suggested to be beneficial for the cognitive and visual outcome of the infants and although randomized controlled trial outcomes currently are inconclusive the data are encouraging (Koletzko et al., 2014; De Giuseppeet al., 2014). The European Food Safety Authority advises 100–200 mg DHA during pregnancy and 100 mg DHA/day for young infants, with the addition of 140 mg/day AA during the first 6 months of life, and 250 mg EPA plus DHA/day after two years of age (WHO, 2010). Also the Nutrition Academy for the Asian population advices a minimum intake of 200 mg DHA per day (can be achieved by eating two portions of fatty fish per week) during pregnancy while higher amounts (600–800 mg DHA/day) are preferable to prevent preterm birth (Koletzko et al., 2014). Also during breast-feeding women are advised to acquire at least 200 mg DHA per day to allow for 0.3% DHA in the FA pool of human milk and the supply of 100 mg DHA should be provided during infancy (Koletzko et al., 2014). Beyond their function in neurological development and vision n-3 LCPUFA may affect allergy development (De Giuseppeet al., 2014). It has been suggested that the FA composition and n-3 over n-6 LCPUFA ratio of breast milk influence the susceptibility of the infant to develop allergic disease (Friedman and Zeiger, 2005; Wijga et al., 2006). Indeed some studies indicate that marine oil, such as fish oil, intake during pregnancy and lactation, may positively affect allergy development in the offspring, which may apply in particular for those having low endogenous n-3 LCPUFA precursor conversion rates (Koletzko et al., 2014). This review aims at describing the known effects of n-3 versus n-6 PUFA on sensitization and allergy development with a focus on food allergy and asthma.

2. Allergy and effects of PUFA on innate, adaptive and effector immune cells

In IgE mediated allergic disease a T helper cell (T_H) 2 polarized adaptive immune response towards otherwise tolerized proteins (allergens) occurs. Allergens from for example food can induce food allergy and airborne allergens such as present in birch pollen or house dust mite (HDM) can induce allergic asthma. In general it is thought that AA derived eicosanoids such as prostaglandin (PGE)-2 contribute to allergic sensitization since PGE_2 contributes to a T_H2 polarized immune response and is responsible for IgE isotype switching in B-cells (McIlroy et al., 2006; Fedyk and Phipps, 1996; Kay et al., 2013; Roper et al., 1990; Roper et al., 1995). In addition, depending on its concentration PGE_2 can dampen or enhance the allergic effector response (Church et al., 2012; Safholm et al., 2015). Antigen presenting cells (APC) like dendritic cells (DC) present the allergens to T-cells which polarize into T_H2 effector cells instead of being deleted, rendering anergic or develop into regulatory T-cells (Treg). These T_H2 cells drive B-cell isotype switching and maturation into allergen specific IgE-producing plasma cells. Allergen specific IgE binds the FcεRI on mast cells and basophils (sensitization). Allergic symptoms occur upon allergen challenge which crosslinks membrane-bound IgE resulting in effector cell degranulation and mediator release like histamine, PGD_2 and cytokines which cause the allergic symptoms. T_H2 biased immune responses can be restored via the installation of allergen specific Treg ($CD4^+CD25^{high}FoxP3^+$, Tr1 or T_H3 cells) that produce suppressive cytokines like IL-10 and/or TGF-β or T_H1 cells that produce IFN-γ which counteracts T_H2 activation and survival.

2.1. Effect of PUFA on DC-T-cell interaction

Tolerogenic DC can instruct T-cell anergy or Treg, while activated DC can induce effector T-cell responses. Inflammatory mediators like lipopolysaccharide (LPS) activate DC which induce maturation resulting in increased expression of major histocompatibility complex II, costimulatory molecules and T-cell polarizing cytokine release. Draper et al. studied the effects of EPA and DHA on LPS induced murine bone marrow derived DC maturation and showed EPA and DHA (25μM added during differentiation and maturation) to suppress MHCII and costimulatory molecule expression and T_H1 driving IL-12p70 release while increasing IL-10 secretion by DC (Draper et al., 2011). EPA and DHA suppressed nuclear factor κB (NF-κB) activation in these cells. By contrast, LA did not suppress DC maturation (Draper et al., 2014). In human monocyte derived DC (moDC) EPA as well as AA (20μM) were found to suppress basal expression of costimulatory molecules on DC when added during differentiation and/or maturation. These remained reduced upon LPS induced maturation while IL-12p40 and TNFα were reduced in a dose dependent manner (Zeyda et al., 2005). Palmitic (PA) and oleic (OA) acid had no effect. EPA and AA exposed DC also suppressed T-cell proliferation in a mixed lymphocyte reaction (Zeyda et al., 2005). EPA and AA did not reduce activation of NF-κB or MAPK signaling cascades in this study and cyclooxygenase and lipoxygenase inhibitors did not interfere with their effect either (Zeyda et al., 2005). Although in these studies both n-3 LCPUFA EPA as well as n-6 LCPUFA AA inhibited LPS induced DC activation, a dietary intervention study with fish oil in healthy volunteers showed that supplementation of 0.3–2.0 g fish oil (EPA: DHA, 2:1) per day for four weeks lowered basal and/or LPS induced TNFα and IL-6 release by peripheral blood mononuclear cells (PBMC) (Trebble et al., 2003). Also in a study in elderly humans, consuming oil rich in ALA (2 g), GLA (720 mg), AA (680 mg), DHA (720 mg) or fish oil (1 g EPA and DHA) for four weeks, only in the GLA and fish oil groups PBMC proliferation was reduced, however no effects on IFN-γ production were shown (Thies et al., 2001). In a study by Kew et al. in human volunteers receiving a daily diet enriched with either 9.5 g ALA or 1.7 g EPA and DHA for a period of 6 months LPS induced TNFα, IL-1β, IL-6 or IL-10 release by PBMC remained unaltered (Kew et al., 2003). However *in vitro* exposure of human PBMC shows LCPUFA