Immunology Letters 206 (2019) 54–58

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Does a carrot a day keep the allergy away?

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ARTICLE INFO

Keywords:
Vitamin A
Retinoic acid
Lipocalin
Allergy
Asthma
Immunomodulation

ABSTRACT

Vitamin A is an important micronutrient, from plants diet taken up as carotenoids, from animal food sources as retinol. Its active metabolite retinoic acid (RA) binds to nuclear hormone receptors, thereby regulating gene transcription programs in various cells. Adequate nutritional intake of vitamin A is essential for pre- and postnatal development, eyesight and reproduction, and it contributes to the maintenance and regulation of the immune system. Recent molecular studies indicate that lipocalins play an important role in the bioavailability of RA and its immune modulation against Th2 responses. There is emerging evidence that supply with vitamin A determines the susceptibility to allergic diseases: significantly reduced serum vitamin A levels are commonly observed in allergic patients compared to healthy controls. In line, findings from nutritional and clinical trials suggest that sufficient vitamin A supplementation in pregnancy prevents the development of allergic diseases in the offspring, and helps in controlling symptoms in adult asthmatics. Overall, retinoids have a key role in regulating immune homeostasis on mucosal surfaces because they are able to interfere with inflammatory signalling pathways. In this mini-review we will concentrate on the current knowledge about the influence of dietary and supplementary vitamin A on allergic diseases in humans from infancy to adulthood.

1. Introduction

Vitamin A is an important factor in human nutrition derived from plants (e. g. carrots, red peppers, lettuce) as carotenoids or from animal-derived food sources (e. g. fish, milk, eggs) as retinol. Both ß-carotene and retinol are converted into active retinoic acid (RA) via a multistep enzymatic process mainly in the liver [1]. In the target tissue the two isoforms of RA, all-trans-RA and 9-cis-RA, bind to nuclear receptors to regulate gene transcription programs in various cells including cells of the immune system [2]. Thus, the active vitamin A metabolite RA promotes the maturation of innate immune cells, regulates the differentiation of adaptive immune cells, and enables the regeneration of epithelial barriers damaged by infection [3]. Vitamin A has been long known to prevent child mortality and recommendations for vitamin A supplementation by WHO date back to the seventies (Table 1) [4]. At the same time evidence emerged that dietary factors such as vitamin A seem to be related to chronic diseases [5]. The broad impact of vitamin A on the immune system and the immunomodulatory role of RA imply that the development of allergic diseases could be influenced by this important micronutrient as well [6,7].

In this mini-review we will focus on vitamin A as a dietary factor or as supplementation and its effects on allergic diseases (atopic dermatitis, allergic rhinitis, allergic asthma) in humans from infancy to adulthood.

2. Serum vitamin A in health and allergic disease

Earlier observations showed significantly lower levels of serum vitamin A in asthmatics in comparison to healthy controls, and this was observed in asthmatic children [8] as well as in asthmatic adults [9]. In both studies, levels of the precursor form ß-carotene displayed no differences between the healthy and the diseased groups [8,9]. Similar results were reported in meta-analysis investigations conducted by Allen et al and Nurmatov et al [10,11]. More recent studies gave conflicting results. In a nested case-control study in a Finnish birth cohort, no strong associations between serum carotenoid concentrations and asthma risk up to five years of age could be found [12]. A more recent case-control study in Chinese children with stable asthma reported significantly decreased serum vitamin A (and serum vitamin D) levels in asthmatics showing a positive correlation of serum vitamin A to

Abbreviations: AD, atopic dermatitis; FEV, forced expiratory volume; GSDMB, gasdermin B; GST, glutathione S-transferase; Ig, Immunoglobulin; IL, Interleukin; NF, nuclear factor; RA, retinoic acid; RCT, randomized control trial; VAS, vitamin A supplementation; WHO, World Health Organization

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https://doi.org/10.1016/j.imlet.2018.10.009
Received 5 September 2018; Received in revised form 9 October 2018; Accepted 15 October 2018
Available online 16 October 2018

Table 1
Timeline of vitamin A synthesis, recommendation as a supplement for health benefit and its correlation to chronic disease and health outcomes.

Timeline		References
1910–1950	Isolation and synthesis of vitamin A	[60]
1970–2000	Diet and supplements related to chronic diseases	[5]
1976	WHO guideline: vitamin A prevents child mortality and disease	[4]
1997	WHO guideline on vitamin A supplements	[61]
2000 - ongoing	Nutrition studies and clinical trials on supplements and specific diet patterns	[21-26, 29-30, 33-34, 41-43]
2011	WHO guidelines: vitamin A supplementation in pregnancy, neonates and children	[27,62]
2016–2018	WHO guidelines: fortification of maize/corn flour and rice with vitamin A	[63,64]

pulmonary function and good quality of life [13]. Apart from allergic asthma also in atopic dermatitis vitamin A status seems to play an important role [14]. A case-control study in a cohort of Indian children revealed significantly reduced serum and skin retinol levels in comparison to healthy controls [15].

It is beyond dispute that vitamin A and its active metabolite RA are crucial for development and differentiation of airways. Disruption in RA signaling or deficiency in vitamin A could lead to altered lung function and disease such as asthma [16]. Vitamin A is also an important nutrient in the human diet and as an antioxidant [17] dampens oxidative stress and inflammation, two central factors in the clinical manifestation of asthma and allergic diseases in general [14,18]. On the other hand, inflammatory processes are known to negatively influence the vitamin A balance and reduced serum retinol concentrations could, in fact, originate from ongoing inflammation while falsely attributed to insufficient nutritional intake [19]. Nevertheless, the amount and the time of exposure to vitamin A and carotenoids especially via maternal intake could have a major influence on the development of allergic diseases in the offspring (Fig. 1) [20].

Fig. 1. Vitamin A and its role in health and allergic disease. Vitamin A, taken up via the diet or as a supplement especially during pregnancy could prevent the development of allergic diseases in children and is able to confer immune tolerance towards allergenic molecules such as from cow's milk (©Anastasia Anisenko, ©PhotoSG, ©ksena32, ©Lenid&AnnaDedukh, ©pololia, ©taborsky, ©by-studio - Fotolia.com).

3. Vitamin A as a dietary and supplementary component

3.1. Maternal intake of vitamin A

A placebo-controlled vitamin A/retinol supplementation trial comprising pregnant women in rural Nepal revealed that vitamin A supply did not affect the asthma prevalence in the offspring [21]. Likewise, a Finish study correlated the amount of carotenoids consumed by pregnant women to the risk of rhinitis or asthma in offspring, with no positive association [22]. Around the same time, two contradictory studies reported a lower risk for wheezing and eczema in the offspring of mothers with high dietary carotenoid intake during pregnancy implying contradictory evidence [23,24]. More recent evidence comes from a large prospective cohort of Danish mothers and children [25]. The authors correlated nutritional vitamin intake (diet and supplements) during pregnancy with asthma and allergic rhinitis outcome in the children. The results for vitamin A showed a modestly decreased risk of child allergic rhinitis during the first seven years of life. The asthma risk was decreased for high maternal doses specifically of ß-carotene implying that besides quantity the quality of vitamin A seems to play a role [25]. A recent Norwegian mother and child cohort study even showed that excessive intake of vitamin A (more than 2.5 times of the recommended dosage) during pregnancy increased the risk for asthma development in the children at school-age [26] (Table 1).

Taken together, these studies demonstrate the difficulties of analysing and correlating dietary vitamin intake with allergic diseases, including biases on the self-reported intake of nutrients and outcome measurements as well as confounding by covariates. Additionally, specific supplementation in a vitamin A deficient study population could differently affect the development of the respiratory and immune system in the next generation than in a population with sufficient vitamin A levels [16,25].

3.2. Neonatal vitamin A supplementation

Neonatal vitamin A supplementation (VAS) is recommended by the World Health Organization for young children that live in areas of vitamin A deficiency to prevent child morbidity and mortality (Table 1) [27]. The supplementation is often linked with vaccination campaigns (e.g. polio, measles, BCG) [28]. In a double-blind placebo-controlled VAS follow-up study no significant effect on the risk of atopy was described. The study limitations were a small sample size and a low prevalence of atopy in the study population in Guinea-Bissau [29]. A larger randomized controlled trial conducted in the same area two years later revealed that in the VAS group the risk for atopy and wheezing was increased but only in girls [30]. This observation may also relate to the overall higher allergy prevalence in the female gender during and after puberty [31,32]. Thus, the results suggest that for neonatal health support vitamin A supplementation in regions with deficiency seems adequate.

3.3. Dietary vitamin A in children

In a cross-sectional study of Korean children allergic rhinitis was correlated with high-fat and low-carbohydrate diets, but no significant effect of dietary vitamin A intake could be found [33]. In another Korean cross-sectional study the authors reported an increased risk of childhood asthma in school children in correlation with low dietary vitamin A intake and environmental tobacco smoke, the latter likely corroborating their antioxidant capacity [34]. Additional analysis of glutathione S-transferase (GST) enzyme polymorphism revealed that affected children carried the GSTP1 genotype AA, which has been associated with a higher asthma risk in children and adults [35,36]. The results from the Korean Cohort for Childhood Origin of Asthma and Allergic Disease study showed that high prenatal maternal vitamin A intake was associated with a reduced risk of respiratory tract infections in infants with certain genotypes of CD14 and of gasdermin B (GSDMB) [37]. GSDMB represents a prime candidate asthma gene on chromosme17q12-21 asthma locus and the 17q genotype effects on asthma risk seem to be modified by early-life exposure [38]. Therefore, antioxidant intake already in the prenatal phase may positively influence genetic polymorphisms in immunity-related genes.

Such studies on dietary vitamin A intake point out that measurable co-factors and genetic polymorphisms related to allergic diseases should not be neglected, but we emphasize that the design (e.g. cross-sectional or case-control) of epidemiological studies only provide correlative evidence, but are not suited to ultimately determine causal correlations between factors.

3.4. Non-dietary vitamin A supplementation in children

Reports on vitamin A interventions in children that use other application routes than the dietary are scarce. There is one report from a small randomized cross-over study in asthmatic children receiving vitamin A as an aerosol via metered-dose inhalation [39]. The authors found no beneficial effect on asthma symptoms in the vitamin A treated children but rather worsening of post beta-agonist FEV1, implying that aerosolized vitamin A application should not be advised in general for disorders of the respiratory tract.

3.5. Vitamin A supplementation via special diets in adults

Dietary vitamin A supplementation in adults as a single component is rather unusual. Dietary measures almost always include other antioxidants, vitamins, and trace elements [40]. Conclusions on positive effects of dietary vitamin A intake alone on an already established allergic disease seem therefore rather difficult. Some studies have analyzed the effect of a Mediterranean Diet, which is rich in fruits and vegetables and should include relevant amounts of carotenoids [11], especially on chronic airway inflammation and the control of asthmatic symptoms. In this respect, improvement of clinical asthma outcomes and fewer exacerbations in adults with allergic asthma were recently reported [41]. Supplementation with anti-oxidants seemed to be less effective in improving asthma outcome [41]. Similarly, a high intake of raw vegetables was significantly correlated with good asthma control in a Japanese study including over 400 asthmatic patients [42]. One of the few supplementation studies in adult allergic asthmatic patients was able to show that a combination of vitamins A, B6, C, trace elements and fish oil led to a significant increase of asthma control and health-related quality-of-life scores [43]. Thus, a diet with a high proportion of fruits and vegetables rich in anti-oxidants such as carotenoids but also flavonoids [44], showing anti-inflammatory effects in animal asthma models [45], could be beneficial in asthmatic adults and helpful in symptom control (Fig. 1).

4. Mechanisms underlying the immunomodulatory effect of vitamin A

In vitro studies utilizing human immune cells or cell lines were used to investigate the influence of carotenoids in relation to inflammatory signalling pathways. Studies in human epithelial cell lines demonstrated that carotenoids were able to interfere with the nuclear factor-kB pathway resulting in decreased DNA-binding activity and in inhibition of inflammatory cytokines such as IL-8 [46]. Cellular studies have their limitations with respect to investigated cell types, physiological carotenoid concentrations, and cellular uptake, making it difficult to translate these results into complex in vivo settings. Nevertheless, human intervention studies involving vitamin A rich food demonstrated reduced NF-kB expression and IL-6 production in peripheral lymphocytes [46,47]. This regulatory influence on the transcription factor NF-kB could be of importance in allergic diseases such as asthma because NF-kB signalling plays a major role in regulating cytokine activity in airway pathology [48]. Thus, the advances of antioxidant treatments including vitamin and food supplementation in asthma therapy are gaining attention together with investigations on the antioxidant properties of current asthma medications (e.g. corticosteroids, leukotriene receptor antagonists) [49].

In atopic dermatitis patients, retinoid synthesis and signalling were dysregulated in tissue biopsies even in non-affected skin areas [50]. The proliferation and degranulation of isolated human skin-derived mast cells were affected by the vitamin A metabolite RA [51].

RA-primed human dendritic cells were able to induce IL10-producing regulatory T-cells, indicating that retinoid signalling pathways are of importance to maintain tolerance on mucosal surfaces [52,53]. Carotenoids and RA may via the diet contribute to gut immune homeostasis by directly regulating IgA production, which in turn could prevent the development of dysbiosis of the gut microbiota [54]. In accordance, there seems to exist an inverse association between IgA levels and incidence of allergic airway diseases [55]. Thus, diet seems to be one of the most important factors influencing gut microbiome. On the contrary, impaired microbiome diversity of the gut - but also of the lung - could enhance the prevalence of allergic diseases [56].

5. Vitamin A and molecular allergens

Lipocalins are small globular proteins that fulfill innate immune defense and carrier functions in animals [57]. They have an intramolecular pocket allowing them via hydrophobic interaction to bind and transport small lipids, odorant molecules, or – vitamin A metabolites. The cow`s milk protein beta-lactoglobulin (BLG) is a prototypic lipocalin, secreted by the cows into the milk. Besides its defensive function in the cow, BLG may act as an allergen for humans and in 2–3% of infants lead to milk-allergic symptoms [58]. RA directly influences the immunogenicity of certain allergenic molecules belonging to the protein family of lipocalins. Our recent studies have shown that binding of RA to the intramolecular pocket of BLG led to a suppression of allergenic immune response in human peripheral lymphocytes [59]. These data suggest that the loading of milk BLG is decisive for subsequent immune tolerance versus allergic responses in the consumer (Fig. 1). Defatting of milk during industrial processing or insufficient dietary vitamin A/RA supply in cows feed could cause deficient loading of vitamin A into the BLG pocket. This mechanism might be responsible for turning a harmless nutritional milk protein into an allergen.

6. Conclusions

Vitamin A and its metabolite RA are important factors to maintain immune homeostasis and to prevent hypersensitivity to harmless antigens. Still, the results of epidemiological studies on dietary/supplementary vitamin A and its effect on allergic diseases are conflicting. The picture that emerges is that vitamin A exposure early in life - via maternal intake and during childhood - may rather prevent the development of allergic diseases in childhood by positively manipulating immune responses. The optimal timing and dosage of vitamin A still need further investigations and multiple adverse environmental factors, especially smoking or other oxidative processes, can interfere with vitamin A mediated immune protection [16]. Additionally, there is an unmet need for more mechanistic studies on the cellular targets of retinoid pathways [19]. In adults with an established allergic disease the substitution of vitamin A, or provided via a healthy mixed diet, likely supports the management of allergic symptoms. Vitamin A contents in cow`s milk may be affected by animal feed or milk processing, therefore its fortification should be taken into consideration to prevent milk allergy. Based on the current data, in the authors´ view vitamin A supplementation could be an interesting strategy to prevent the increasing incidence of allergic diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This work was supported by grant SFB F4606-B28 of the Austrian Science Fund FWF.

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