

Potential Role of Antioxidant Food Supplements, Preservatives and Colorants in the Pathogenesis of Allergy and Asthma

Daniela Zaknun^a Sebastian Schroecksadel^b Katharina Kurz^c Dietmar Fuchs^b

^aDivision of Nutrition and Lipid Metabolism Disorders, Department of Pediatrics, University Hospital of Vienna, Vienna, and ^bDivision of Biological Chemistry, Biocenter and ^cClinical Immunology and Infectious Diseases, Department of Internal Medicine, Innsbruck Medical University, Innsbruck, Austria

Key Words

Allergy • Asthma • Immunomodulation • Antioxidants • Food preservatives • Food colorants

Abstract

A significant increase in the incidence of allergy and asthma has been observed during the past decades. The background of this phenomenon has not been well explained, but changes in lifestyle and habits are heavily discussed as contributing factors. Among these is a too clean environment, which may predispose individuals to increased sensitivity to allergic responses. Also the increase in dietary supplements including preservatives and colorants may contribute to this. In vitro, we and others have shown in freshly isolated human peripheral blood mononuclear cells that antioxidant compounds like vitamins C and E as well as food preservatives and colorants exert significant suppressive effects on the Th1 immune activation cascade. The effects observed may be based on the interaction of antioxidant compounds with proinflammatory cascades involving important signal transduction elements such as nuclear factor- κ B. Although only obtained in vitro, these results show an anti-inflammatory property of compounds which could shift the

Th1-Th2-type immune balance towards Th2-type immunity. This review article discusses the potential role of increased use of antioxidant food supplements as well as preservatives and colorants in the increase in allergy and asthma in the Western world.

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Introduction

The term ‘allergy’ was first introduced by the Viennese pediatrician Clemens von Pirquet [1] in 1906 and was defined as ‘a reaction of the body to foreign substances’ [1]. Pirquet was the first to recognize that the human immune response can become harmful when hypersensitized to certain antigens. Common allergic reactions include hives, hay fever, asthma, food allergies or reactions to the venom of stinging insects. Thereby, allergic asthma is characterized by variable and recurring symptoms including wheezing, coughing, tightness of chest and shortness of breath as well as reversible bronchospasm and airway obstruction. Severe allergies to environmental and/or dietary allergens may result in life-threatening reactions such as anaphylactic shock and, potentially, death.

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1018–2438/12/1572–0113\$38.00/0

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Correspondence to: Dr. Dietmar Fuchs
Division of Biological Chemistry, Biocenter
Innsbruck Medical University, Fritz Pregl Strasse 3
AT–6020 Innsbruck (Austria)
Tel. +43 512 507 3519, E-Mail dietmar.fuchs@i-med.ac.at

Allergic diseases and atopy have increased significantly around the world over the past 2–3 decades, especially in children, but also in adults [2, 3]. In industrial nations, a steady rise in sensitization has been observed since the 1920s, with a strong increase in the 1990s. Up to 11% of the US population suffer from allergic rhinitis, 3% from asthma and 6% from food allergies [4, 5]. Similar data are reported from the UK and Europe. In developing countries, diseases caused by allergies are predominantly found in the big cities; however, they remain less dominant than in Western countries. Although there is strong evidence for a genetic predisposition [6], the strongest risk factors for development of hypersensitivity may comprise several additional causes such as change in lifestyle, atmospheric pollution, diesel fumes, maternal smoking and others [7–9]. Epidemiologic data enforce the hygiene hypothesis [10, 11] suggesting that individuals growing up in an environment which is too sterile are not enough exposed to pathogens in order to keep Th1-type immunity busy, so Th2-type immunity may occur [12–14]. Several researchers found that migrants from developing countries to the industrial world developed accelerated allergic symptoms in their new environment. Extensive use of antibacterials or antiseptics during early infancy and childhood has been linked to an increasing incidence of asthma and other allergic diseases [12, 13, 15, 16].

Finally, in industrial countries a significant change in modern lifestyle has been taking place in the last decade, and this may have contributed to changes in allergy and asthma epidemics. Smaller family structures, nutritional habits, shorter duration of breast feeding, artificial food preservation and supplementation of selected nutrients and, last but not least, less need for physical activity are referred to as reasons for the allergy epidemic [17]. There is no doubt that such immense changes in overall lifestyle have a significant impact on the epidemiology and probably also activity of diseases. It may influence, for instance, the transition from acute infections to chronic diseases such as cancer or also atopy [18].

The use of food additives like preservatives or colorants has been suspected to play a role in the rise of allergic disorders for decades [19, 20]. There is evidence for a temporal association, but there has never been final proof of a cause-effect relationship. However, more recent data are coming up from in vitro studies, indicating that the chemical structure of these compounds could indeed modulate the interaction between Th1- and Th2-type immunity, and probably has contributed to the overwhelming preponderance of Th2-type responses in recent decades.

Immunopathogenesis of Allergy

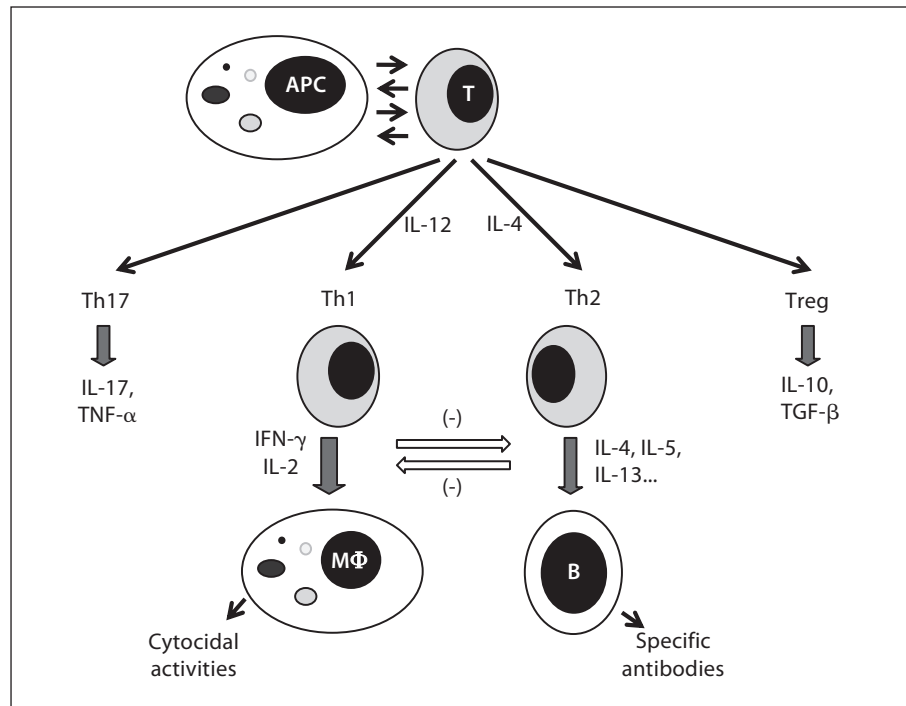
The pathophysiology of atopic diseases is strongly associated with immunophysiological imbalances within the Th cell system. Current theory favors the notion that a lack of triggers for Th1-type immune response – such as exposure to infections, endotoxins or even dirt – in childhood results in a preponderance of Th2-type immune responses, causing atopy at the end [7, 10, 21].

The human immune system comprises a complex network of cells and mediators providing sufficient defense against invading antigens such as pathogens and malignant transformation. Immune responses rely on specific effector cells such as Th1- and Th2-type T cells, macrophages and B cells, and are regulated by cytokines released upon activation [21, 22]. In the process of immune responses against intracellular pathogens like viruses, Th1 cells are activated and release specific Th1-type cytokines such as interleukin-2 (IL-2) and interferon- γ (IFN- γ). As opposed to this, cytokines released by Th2-type cells including IL-4, -5, -6 and -13 induce B cells to produce immunoglobulin E (IgE). IgE is the main immunoglobulin responsible for histamine release from mast cells and in allergic responses. There is strong evidence for a cross-regulatory interplay between Th1- and Th2-type immune responses as they downregulate each other when activated [21–23] (fig. 1).

Allergic responses are biphasic, an acute response occurring immediately after exposure to an allergen, and late-phase reactions representing delayed symptoms of immune response resulting in tissue damage. In the early stages, large amounts of IgE are produced by B cells upon stimulation of the Th2-type cytokine IL-4. Secreted IgE circulates in the blood and eventually binds to high-affinity IgE receptor (Fc ϵ RI), and activation of effector cells occurs due to cross-linking of IgE molecules on the surface of mast cells and basophils, releasing histamine, the main inductor of allergic reactions [24]. At this stage, sensitization to a specific antigen is recorded in cells. In case of repeated contact, allergens can bind to the IgE molecule on the surface of mast cells. Activated effector cells undergo degranulation, releasing histamine and other mediators causing vasodilatation, mucous secretion, nerve stimulation and muscle contraction; both system-wide and localized symptoms may occur. The late-phase response, seen 2–24 h after the acute reaction, is caused by the release of mediators from eosinophils and is still dependent on the activity of Th2 cells.

Accordingly, it has been proposed that pro- and prebiotics, or microbe-derived immunoregulatory vaccines,

Fig. 1. Simplified scheme of T cell activation and differentiation involving antigen-presenting cells (APC) and naive T cells (T) as well as cross-regulatory interplay between Th1-type and Th2-type immunity. Different CD4+ T cell (Th) populations develop from activated naive T cells: Th1-type (cellular) immune response involves Th1 cells and Th1-type cytokines IL-12 and IL-2 and IFN- γ , which slow down Th2-type (humoral) immunity via suppression of Th2 cells and Th2-type cytokines such as IL-4, -5 and -13, and vice versa. APC can also induce Th17-type cells producing IL-17 and tumor necrosis factor- α (TNF- α) as well as regulatory T cells (Treg) releasing anti-inflammatory cytokines IL-10 and transforming growth factor- β (TGF- β). M Φ = Macrophages.



might become valuable to prevent allergic disease [25]. However, airway inflammation in asthma is characterized not only by activation of Th2 cells, Th2-type cytokines, IgE production and eosinophilia. Although the hygiene hypothesis appears to be rather old-fashioned and several other T cell-dependent functions and pathways have more recently come into focus [26], the underlying concept still seems relevant. Th17 cells [27], the cytokines IL-17 and IL-9 as well as regulatory CD4+CD25+ T cells (Treg) have more and more been recognized as also being of greater relevance to the pathogenesis of allergy and asthma [28]. IL-17-producing T cells have recently been classified as a new effector T cell subset termed Th17, which is distinct from the Th1 and Th2 subsets. CD4+ Th17 cells constitute a third effector arm of Th cells, complementing the Th1 and Th2 lineages [29] (fig. 1). Th17 cells are part of the adaptive immune response mounted against fungal and bacterial infections, and they may also contribute to autoimmune diseases; for instance, Th17 cells promote neutrophil recruitment via IL-17 for clearance of bacteria and fungi [30]. Th17 cells also play an important role in allergic inflammation, and sensitization to allergens primes Th2 and Th17 cell responses that promote airway neutrophilia and acute airway hyperresponsiveness [26]. Th17 cells also exacerbate Th2 cell-mediated eosinophilic airway inflammation [31]. Several re-

cent studies suggest that IL-9 is also involved in the development of allergic inflammation. IL-9 is detected in biopsies from patients with asthma and localizes to CD4+ T cells, but mast cells and eosinophils are sources of IL-9 as well [32].

Treg cells generally dampen inflammatory reactions, their suppressive function being directed against adaptive and innate immune responses [33]. Downregulatory cytokines such as transforming growth factor- β and IL-10 may be involved in the suppressive effects of Treg cells, and the suppressive function of Treg is reversed by Toll-like receptor activation of dendritic cells, resulting in restoration of proliferation in cocultures of naive T cells and Treg [34]. Oral tolerance to dietary antigens was found to be associated with the development of Treg cells, with Foxp3, CTLA-4 and IL-10 being suppressive molecules [35, 36]. There is evidence that the numbers and function of Treg may be deficient in patients with atopic allergic disease [28].

Reactive Oxygen Species

Oxidation is a chemical reaction that transfers electron(s) from one substance to another; the oxidizing agent becomes chemically reduced by taking away the

electron(s) from its reaction partner, which itself is oxidized. Although such reduction/oxidation (redox) reactions are crucial for life, they can also become damaging [37]. Reactive oxygen species (ROS) are defined as strongly oxidizing chemicals such as hydrogen peroxide (H_2O_2), ions like hypochlorite (OCl^-) and the most reactive radicals hydroxyl radical ($OH^\bullet$) and superoxide anion (O_2^-). In vivo, ROS are formed as a by-product of cellular respiration in mitochondria. During an immune response, ROS are important products synthesized and released by immunocompetent cells like neutrophils and/or macrophages as part of their microbicidal and tumoricidal armament. In this process, the cytokine IFN- γ – which is preferentially released upon stimulation of Th1-type cells – is probably the most potent stimulus for the formation of ROS within the oxidative burst response [38, 39]. Apart from their primary role, ROS not only lead to the destruction of cellular components such as DNA, proteins and lipids. They additionally trigger redox-sensitive intracellular signal transduction cascades, e.g. nuclear factor- κB (NF- κB), a central element in perpetuating inflammatory responses [40, 41]. In the chronically activated Th1-type immune response, depletion of antioxidants takes place, and the continuous and overwhelming production of ROS causes the development of oxidative stress.

There are numerous studies in process in order to extrapolate whether ROS may trigger specific disease conditions including aging, and how the immune system might be involved in the pathophysiology. Oxidative stress is thought to contribute to the development of a wide range of diseases including cardiovascular and neurodegenerative diseases [42, 43]. Early cell death by ROS is also discussed for several pathologies which are associated with a chronically activated immune system, such as human immunodeficiency virus infection and acquired immunodeficiency syndrome, and also malignant tumors and autoimmune pathologies like rheumatoid arthritis. The role of oxidative stress in cardiovascular diseases seems to be rather well understood [44], where low-density lipoprotein oxidation appears to trigger the process of atherogenesis, but ROS are also regarded as playing a major role in the normal aging process [45].

To counteract the harmful effects of ROS, cells have a variety of defense strategies, among which are several small molecules that function as antioxidants as well as two major enzymes, namely catalase and superoxide dismutase, which are induced to biochemically neutralize ROS [46–48]. The risk of developing diseases is considered to increase when ROS are only insufficiently neu-

tralized due to overwhelming production. As a consequence, antioxidant supplements like vitamins are increasingly used, and a variety of products is put on the market. Nowadays, pharmacy shelves and modern gastronomy are filled with antioxidant supplements that people take in the hope of warding off the damaging effects of ROS, and especially of aging [45]. Therefore, the global market for antioxidants – driven almost solely by hopes for beneficial antiaging effects – reached a total amount of EUR 2.4 billion in 2007, although the disease-preventing capacity of antioxidants is very controversially discussed in the literature.

Antioxidants and Disease

An antioxidant is a chemically reducing compound which slows down or prevents an oxidation process. Thereby, to some degree, it is capable of protecting other compounds from being oxidized. Antioxidants also terminate oxidative chain reactions by removing free radical intermediates [48]. Antioxidants may be synthesized in the body or obtained from the diet since many normal food compounds are antioxidants, which are especially abundant in fruits and vegetables such as bananas, cranberries, apples, dates, red grapes, potatoes, tomatoes, as well as in soft drinks such as coffee, cacao and tea. In recent years, glutathione, ascorbic acid (vitamin C), carotenes (vitamin A), melatonin, tocopherols and tocotrienols (vitamin E) have been under intense investigation in regard to their capacity of antioxidant and free radical neutralization [49]. Originally, research on antioxidants focused on their use in preventing oxidation of unsaturated fats, which is the cause of rancidity [50]. However, it was the identification of vitamins C, E and A as antioxidants that led to the realization of the importance of antioxidants for the biochemistry of living organisms [51]. Today, physicochemical approaches such as the oxygen radical absorbance capacity (ORAC) assay [52] are widely in use to quantify the specific radical-scavenging capacity of such compounds and foods.

The most renowned antioxidants nowadays are: vitamins C, E and A; carotenoids like lutein and zeaxanthin; ubiquinol (coenzyme Q); polyphenols like flavonoids, and the stilbene resveratrol. Many of them are contained in so-called ‘healthy’ food, preferentially fruits and vegetables, and in beverages such as red and white wines, cacao and teas, and they are considered to be the key compounds in improving health and preventing disease [53], although a clear demonstration of any beneficial effects

of these compounds is not yet available, especially when used as dietary supplements [54]. Apart from these natural products, dietary supplements such as food preservatives and colorants as well as supplemented vitamins are probably the antioxidant compounds which humans are most widely exposed to during their life. Food preservatives like sodium sulfite and benzoate, but also colorants like curcumin from curcuma or betalain from beet root, are documented to be strong antioxidants [55–57].

Natural antioxidants, and also secondary plant compounds like phytoestrogens, are usually considered to be beneficial to humans by preventing oxidative stress and damage induced by ROS, and to be of crucial importance to the prevention and delay of, for instance, cardiovascular disease. Accordingly, Mediterranean food, which is rich in fruits and vegetables, has been observed to be associated with a lower incidence of cardiovascular diseases. An association between prehypertension and oxidative stress markers both systolic and diastolic blood pressures were shown to inversely correlate with total antioxidant capacity, and positively with oxidized low-density lipoprotein [58]. Likewise, in patients who underwent coronary angiography, inverse associations were observed between serum concentrations of the immune activation marker neopterin and several antioxidant compounds [59]. Consequently, one could speculate that supplementary intake of antioxidants should be able to protect the endothelium from ROS, and that a diet rich in fruits and vegetables, i.e. rich in antioxidants, may promote health and reduce the effects of aging by cancelling out the cell-damaging effects of free radicals.

Redox Regulation of Immune Response

The Th1-type cytokine IFN- γ is probably the most powerful trigger for antimicrobial and antitumor defense, including a high output of ROS [38]. ROS are directed at destroying cellular structures, and consequently inhibiting the growth and proliferation of malignant cells and microbial organisms by their oxidizing property, which degrades vital cellular structures like lipids and proteins. In addition, ROS trigger redox-sensitive intracellular signal transduction pathways [41], which further accelerate the production of proinflammatory cytokines and ROS in an autocrine manner. The deleterious effects of the oxidation reactions by ROS can be monitored in the serum or plasma of patients by measurements of malondialdehyde concentrations, one of the most frequently used indicators of lipid peroxidation [60] or iso-

propane 8, a peroxidation product of arachidonic acid [61]. The opposite strategy is measurement of the decline in antioxidant compounds as an indicator of oxidative stress conditions [59]. The monitoring of Th1-type immune response by soluble factors is hampered by the fact that specific cytokines like IFN- γ are short-lived, and their determination is almost impossible in circulation. In vitro measurement is biased by the fact that T cells activated in vivo are usually less responsive to secondary stimulation after having isolated them from patients [62]. Instead, Th1-type immune response can be assessed by monitoring enzymatic pathways that are induced by IFN- γ , such as neopterin formation and tryptophan degradation. The key enzymes of both pathways, GTP cyclohydrolase I (EC 3.5.4.16) [63] and indoleamine 2,3-dioxygenase (IDO; EC 1.13.11.52) [64], are strongly induced by IFN- γ , and neopterin and tryptophan metabolites are stable analytes that can be easily measured in vitro or in vivo to detect and monitor Th1-type immune response [63–65]. Production of neopterin and degradation of tryptophan are closely associated with the oxidative burst response of these cells, and thus with the formation of ROS [66]. Likewise, a close association was observed in stimulated myelomonocytic THP-1 cells between the expression of NF- κ B, the production of neopterin and the degradation of tryptophan, as is indicated by an increased kynurenine-to-tryptophan ratio, an index of IDO activity [67] (fig. 2).

Increased concentrations of neopterin and an increased kynurenine-to-tryptophan ratio are common in the blood of patients suffering from conditions like virus infections, autoimmune syndromes, malignant diseases and neurodegeneration, as well as cardiovascular disease [63, 64]. They correlate with the extent and activity of diseases and are strong predictors of outcome; an inverse correlation has been observed between higher neopterin concentrations and diminished antioxidant vitamins and compounds [59, 68].

Cross-Regulation of Th1- and Th2-Type Immune Responses

Th1-type immune response is accompanied by the formation of ROS, which results in specific cellular cytotoxicity and forward regulation of Th1-type immunity, whereas Th2-type (humoral) immune response is characterized by the formation of specific antibodies (immunoglobulins), and Th2-type cytokines induce hyperproduction of IgE. Antioxidant compounds suppress Th1-

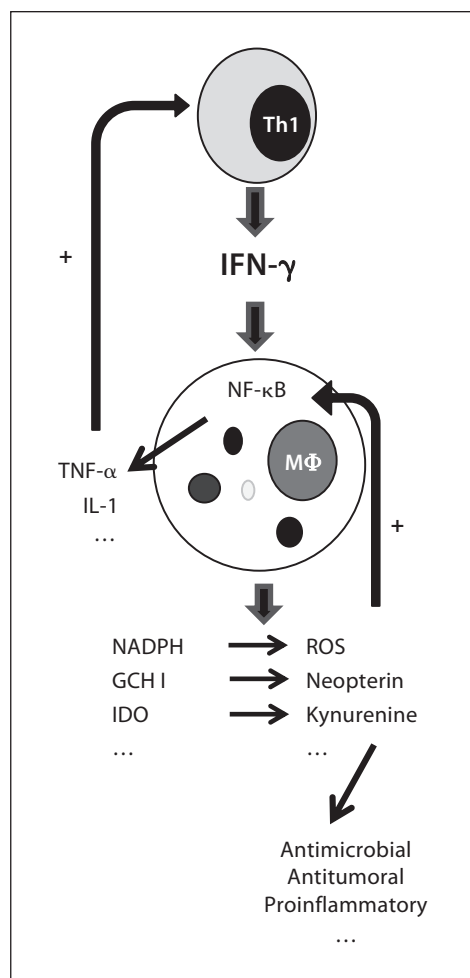


Fig. 2. Simplified scheme of a Th1-type (cellular) immune response involving activation of Th1-type cells (Th1) and macrophages (MΦ), production of specific cytokines like IFN-γ and the effector mechanism aimed at suppressing the growth of pathogens or malignant cells. The production of ROS like H₂O₂ and/or radicals OH[•] and O₂[•] by NADPH oxidase (NADPH), and of proinflammatory molecules like neopterin by GTP cyclohydrolase I (GCH I) and kynurenine by IDO, contributes to an autocrine loop of the inflammatory activation cascade involving the central signal transduction element NF-κB, which on the one hand is triggered by ROS and on the other hand accelerates the production of proinflammatory cytokines.

type responses and Th1-type cytokine production. As a consequence of the suppressed Th1-type immunity and due to the cross-regulatory interaction between Th1-type and Th2-type immune responses [21, 22], Th2-type cytokines are upregulated and the development of asthma and allergic diseases is favored [69]. Overall, one can summarize that oxidants and antioxidants are able to modulate the immune response [70–72]. Upon exposure

to an allergen, Th2-type cytokines like IL-4, -10 and -13 are predominantly produced. This strengthens the Th2-type immune response whenever it is triggered by an allergen, so that under antioxidant-loaded conditions, allergens appear to become stronger sensitizers and the allergic response becomes stronger as compared to the condition without extra antioxidants. Thus, according to the hygiene hypothesis, one may conclude that in an environment with too many antioxidants, the frequency and intensity of allergy and asthma increase in a similar way as is assumed for an environment that is too clean (fig. 3).

This conclusion is based on several *in vitro* studies which demonstrated that a variety of antioxidant compounds including vitamins C and E, as well as plant extracts and several common beverages with known antioxidative and anti-inflammatory properties, suppress the stimulation of peripheral blood mononuclear cells (PBMC), and this is reflected by a significant decline in neopterin production and tryptophan degradation in cells stimulated by mitogens [71, 72] (table 1). The effects of antioxidant compounds were comparable to those observed earlier when effects of the Th2-type cytokine IL-4 or allergic mediators like histamine were investigated on stimulated PBMC and monocytic THP-1 cells [65, 73], and they were also evident when the expression of NF-κB was monitored [55]. Overall, a close relationship was demonstrated between the stimulated expression of NF-κB and the production of neopterin and degradation of tryptophan [67], and compounds like phenols, flavonoids and ascorbic acid exert a suppressive influence as chemical antioxidants and may detoxify ROS. Moreover, by reducing effects mediated by IFN-γ, they also reduce the intracellular pathways which accelerate the formation of ROS.

Thus, various antioxidant compounds have been demonstrated to suppress features of the Th1-type immune response. Among these agents there are not only vitamins, antioxidant phytochemicals, plant extracts and beverages, but also food preservatives like sodium sulfite, benzoate and sorbate as well as colorants like curcumin and beet root extract that are active in this way [71]. Moreover, in addition to slowing down the pathways related to Th1-type immunity in PBMC [74], vitamins C and E were also observed to induce the production of the Th2-type cytokine IL-4 and of IL-10 in a dendritic cell coculture system [75], and it was shown that the T cells expressed FoxP3 and, besides being anergic, might have acquired Treg properties. Likewise, the antioxidant compound astaxanthin was found to suppress IFN-γ produc-

Table 1. Compounds and extracts shown to suppress Th1-type immune response in human PBMC stimulated by the mitogen phytohemagglutinin

Class of compounds	Test substance
Antioxidants	Ascorbic acid, resveratrol, α -tocopherol
Beverages	Beer, black tea, cacao, green tea, grape juice, wine (red, white)
Drugs	Aspirin, atorvastatin, cannabidiol, salicylic acid, tetrahydrocannabinol
Food preservatives	Propionic acid, sodium benzoate, sodium sulfite, sorbic acid
Food colorants	Beet root extract, curcumin

Adapted from Schroecksnadel et al. [70] and Jenny et al. [71].

tion in a Th1 cell clone with a parallel increase in the number of antibody-secreting cells [76], and in a rat model with *Salmonella enteritis*, dietary fish oil was found to suppress IFN- γ production [77]. The cyclooxygenase inhibitors acetylsalicylic acid (aspirin) and salicylic acid were observed to downmodulate neopterin production and tryptophan degradation in stimulated PBMC [78], and also this effect is most likely due to their antioxidant and radical scavenging properties rather than due to cyclooxygenase inhibition [79–82]. Overall, there is a large overlap between the findings from our PBMC assay and the results obtained when suppression of NF- κ B was tested for [55] or when the ORAC assay was applied [52]. Most of the compounds and extracts which efficiently suppress NF- κ B translocation have been revealed to be strong antioxidants by the ORAC assay and have also been able to significantly suppress the activation of IDO and the production of neopterin and IFN- γ in mitogen-stimulated human PBMC. It seems that most if not all the abovementioned compounds had been claimed to play a role in allergy development in the past, and often under very different mechanistic considerations, but it seems that they share the property of inhibiting Th1-type immune responses, and their antioxidant nature plays an important role as well.

In vivo Correlates

In addition to the classic allergy-triggering factors, the adjuvant role of environmental factors like supplements in food or cosmetics gains increasing importance in allergy induction. For instance, experience with atopic eczema patients showed that pseudoallergic mechanisms caused by additive-rich food or other environmental agents have become increasingly relevant as causal fac-

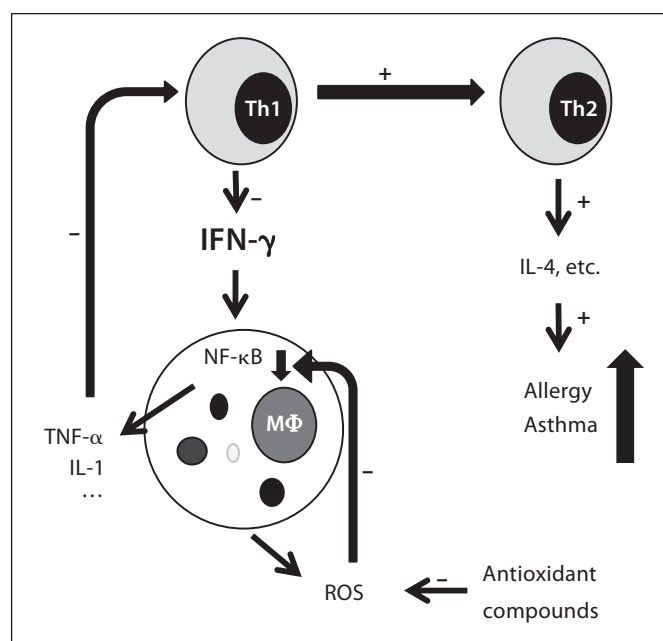


Fig. 3. Antioxidants interfere with the cross-regulatory interplay between Th1- and Th2-type immune responses. Antioxidants neutralize ROS by suppression of NF- κ B and interrupt the auto-crine loop of Th1-type cytokines. As a consequence, Th2-type immunity becomes overwhelming and the risk of allergic responses and their intensity increase. MΦ = Monocyte/macrophage.

tors [83]. Especially in early infancy, food allergy can be related to the development of future asthma, which can be IgE mediated or not, and besides foods, some additives and preservatives were found to be triggers for asthma in certain people [84]. Asthma may develop in about 5% of individuals who suffer from food allergy, and current asthma may be triggered by foods in 6–8% of children and 2% of adults [85]. However, even though sulfite al-

lergy, for instance, is becoming more common, and is often recognized after exposure to cosmetics leading to contact dermatitis, its relevance is still questioned [85].

There are also only anecdotal reports that nutrition rich in antioxidants may increase susceptibility to allergic reactions and asthma; the increased frequency of allergic reactions against citric fruit allergens, for instance, is well documented, showing that antioxidants could be responsible for specific allergic reactions in certain individuals [86, 87]. This conclusion is further strengthened by the fact that cooking of such foods is able to prevent allergic responses as antioxidant compounds and vitamins are destroyed. A higher intake of β -carotene was also reported to be associated with a higher prevalence of rhinitis [88] and hay fever [89]. Reported side effects of food preservatives like sodium sulfite and benzoate comprise the possibility of allergic reactions. Finally, also aspirin – widely used for the treatment of inflammatory disorders mainly because of its inhibitory effects on cyclooxygenases I and II – is well known to occasionally induce asthma in patients [90].

In healthy individuals, a significant inverse association was observed between concentrations of neopterin, a marker of Th1-type immunity, and IgE levels, an indicator of Th2-type immunity [91]. And there is also evidence from patients with allergy and asthma that disturbed Th2- over Th1-type immunity is reflected in an abnormal tryptophan metabolism: patients with allergic asthma and rhinitis present with higher tryptophan concentrations, and this is particularly true out of season [92–95]. Moreover, patients with the highest tryptophan levels did not respond to pollen extract therapy [94]. Interestingly, the behavior of IDO activity in patients with pollen allergy was different from that observed in allergy against *Aspergillus* when IDO and tryptophan metabolites were discussed to be potent regulators capable of taming innate and adaptive pathogenic inflammatory host responses [96]. In this way, IDO upregulates Treg via tryptophan catabolism, and is thereby able to suppress T cell responses [96]. In this effect, 3-hydroxyanthranilic acid seems to play a major role [97]; 3-hydroxyanthranilic acid is a catabolite of tryptophan, which accumulates in the supernatants of PBMC when IDO is activated [98]. Thus, one can speculate that the suppression of IDO will also impact the Th17/Treg balance when the accumulation of tryptophan catabolites is diminished. However, one has to keep in mind that experimental settings may differ considerably from the situation in patients where repeated rather than single exposure to allergens has to be considered.

Notably, some of the changes in lifestyle which are heavily discussed as enhancing allergy risks – such as atmospheric pollution, diesel fumes and smoking as well as obesity [7–9] – are well in line with the potential pathogenetic role for antioxidants. In fact, diesel and gasoline fumes and smog contain incompletely burned/oxidized organic compounds which are of an antioxidative rather than oxidative nature. Apart from exposure to potent carcinogens, smoking is associated with inhalation of carbon monoxide, which is well established as the gaseous product of anti-inflammatory enzyme heme oxygenase [99]. Finally, inactivity and insufficient physical activity are the most important contributors to the development of obesity, and physical exercise is well known to be associated with burning (i.e. oxidizing) fat and carbohydrates and also with reducing the antioxidant pool. From this point of view, physical exercise should be able to improve symptoms in patients suffering from allergy when the antioxidant pool becomes diminished. In agreement with this, physical exercise has been proven to be beneficial to children with asthma, even though it has already been demonstrated that antioxidant supplements counteract at least some of the effects of sports in humans [100].

Antioxidants Are a Two-Edged Sword

The conclusion that a higher intake of antioxidants might promote the development of allergic disease is certainly contrary to the prevailing antioxidant paradigm [88]. Earlier studies showed that frequent consumption of fruit and raw vegetables reduced the risk of asthmatic symptoms like wheezing [101]. Also, naturally occurring polyphenolic antioxidants were described to modulate IgE-mediated mast cell activation [102]. In contrast, ROS were suggested to enhance allergic inflammation [103]. At first glance, such observations contradict our conclusions, and obviously, the strict balance between Th1- and Th2-type immune responses is too simplistic [21, 25, 104]. However, results on the effect of antioxidant compounds on Th17 or Treg cells, for instance, are still scarce, although the stilbene resveratrol was found to exert a suppressive effect on Treg cells in mice [105], and the observation has been made that Treg cells activate multiple strategies for interfering with the extracellular redox environment during T cell activation, affecting dendritic cells as well. Treg cells obviously use various strategies for extracellular redox remodeling, diminishing glutathione synthesis and consuming cysteine [106].

It must be considered that the composition of fruits and vegetables is rather complex – the effects of many of their components on the human organism are not yet clear in detail – and that the ultimate biologic activity of a given food depends on a large number of variables including food processing, preparation methods and interactions between compounds [56, 107, 108]. Moreover, it seems that high-dose supplementation with extra vitamins or preservatives and colorants is of higher relevance as, in most cases, the human organism can handle naturally occurring concentrations of food compounds rather well. Especially the large-scale introduction of antioxidant compounds as food preservatives and colorants could play a major role. The clinical effects caused by sulfite additives as preservatives and antioxidants have recently been reviewed [109], and after enteral or parenteral exposure to foods and drinks containing such additives, symptoms were reported to range from skin reactions like dermatitis and urticaria to abdominal pain, diarrhea and even life-threatening anaphylactic and asthmatic reactions. Preservatives do not necessarily serve as allergens, rather they may increase the likelihood of a Th2-type allergic response when an individual is exposed to a potent allergen at the same time. When the *in vitro* findings hold true for *in vivo* conditions, the excessive use of food preservatives may increase allergy risks via the modulation of cytokine profiles towards a Th2-type pattern. It is interesting to note that the large-scale introduction of antioxidant food preservatives like sulfites matches the increase in allergy epidemics in the Western world well. Certainly, the use of antimicrobially active food preservatives simply has reduced the exposure of humans to microbes, which – according to the hygiene hypothesis – may contribute to the higher risk of allergy development [10]. But in addition to that, antioxidant food additives have the potential to interfere with immunoregulatory events and to direct the cytokine environment towards Th2-type immune responses.

Antioxidant compounds are well capable of neutralizing ROS, which represents an important aspect of the proinflammatory cascade and Th1-type immunity. From this point of view, dietary supplementation with antioxidants can be beneficial in reducing the side effects the inflammatory response may have with regard to the autocrine production of proinflammatory cytokines. As a consequence, the development and progression of proinflammatory conditions such as cardiovascular and neurodegenerative disorders, but also of malignant tumors, can probably be reduced by healthy food or antioxidant food supplements [110]. One possible side effect of anti-

oxidants is a dampening of the antimicrobial and antitumoral effects of Th1-type immune responses, although the clinical relevance of this effect is still unclear [111]. A second potential risk is the shift from Th1-type towards Th2-type immunity when too many antioxidants are ingested. The price which may have to be paid is an increase in allergy and asthma, as is the case with many things where – according to William Shakespeare – ‘too much of a good thing’ may do harm. There is no doubt that natural antioxidant compounds and vitamins are essentially good. However, only during clinical conditions which go along with chronic Th1-type immune activation, ROS production and thus depletion of antioxidant pools can an increased intake of antioxidants in the form of food supplements be recommended. A well-functioning human organism does not require extra antioxidants. Regular intake of natural products within the framework of a balanced diet, along with adequate physical exercise and sports, is capable of keeping us healthy. To avoid the development of oxidative stress and inflammation, a slight shift towards food rich in antioxidant compounds and vitamins can be recommended. By this strategy, overdosing on antioxidants can be avoided. However, nowadays, when antioxidant supplements are added to almost all kinds of food, it is not easy to avoid overexposure, especially to food preservatives and colorants as well as to high-dose vitamin supplements to beverages.

Conclusion

Th2-type immune response and allergy development can be enhanced in an environment marked by an excess of antioxidant compounds. In susceptible individuals, the frequency and intensity of allergic responses to environmental and/or dietary allergens may increase in an environment rich in antioxidants. Extending our previously published hypothesis [69], it appears that especially antioxidants added in high doses as preservatives and colorants may play a major role. Because the intestinal immune system may play the most important role in the development of an allergic response to food allergens, and the gut is a major site for Treg cell induction [112], it is important to conclude that concentrations of food compounds can reach high enough levels, especially in the gut, to modulate cytokine profiles which are able to favor and strengthen an allergic response. Changes in lifestyle, an increase in atmospheric pollution, diesel fumes and maternal smoking, among other things, may additionally contribute to this. However, there is still

room for a role of antioxidant food additives in allergy and asthma epidemics, even when well-designed epidemiologic surveys thus far have been unable to substantiate this association. In addition, allergy development in early childhood may differ considerably from that in adulthood [113].

The situation is complicated even more by the fact that food additives do not serve as allergens themselves but only support the allergic response to common allergens. Epidemiologic studies addressing this aspect are not easy to conduct anymore in the Western world because it has already become very laborious to find food without add-

ed antioxidants that could be used in a representative control group. Furthermore, epidemiologic studies are hampered by the fact that self-reporting of allergic responses usually does not match findings after a challenge very well; in a recent study in young adults, approximately one quarter of the individuals reported food hypersensitivity, which could only be confirmed in less than 2%, however [114]. In any case, epidemiologic studies alone are not sufficient as they can only show associations, not causality. Thus, so far, any role that antioxidant food additives may have in shifting the immune response to allergy is still merely deduced from in vitro investigations.

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