

EDITORIAL

Clinical & Experimental Allergy

Antioxidant intake and allergic disease

This editorial discusses the findings of the paper in this issue by H. Rosenlund et al. [14], pp 1491–1500.

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The background of the increased allergy and asthma incidences during the past decades is still not well explained. Certainly, there is strong evidence for genetic predisposition, but changes in lifestyle and habits are strongly discussed to contribute. Risk factors for development of hypersensitivity may comprise atmospheric pollution, diesel fumes, maternal smoking *et cetera* [1], but the strongest epidemiological data still enforce the hygiene hypothesis [2]: A too-clean environment may predispose individuals to an increased sensitivity to allergic Th2-type immune responses when individuals growing up in a too-sterile environment are not exposed enough to pathogens to challenge Th1-type immunity [3, 4]. Along these lines, extensive antibacterial or antiseptic use during the early infancy and childhood has been linked to an increasing incidence of asthma and other allergic diseases [4–7]. This view is further supported by the observation that migrants from developing countries to the industrial world developed accelerated allergic symptoms in their new environment [3]. The increase of dietary supplements like preservatives and colourants, many of which with antioxidant properties, can also play a role [8]. It is quite obvious that the antibiotic effect of food preservatives also further reduces the exposure of humans to pathogens and thus increases the hygiene effect. Still, there is no final proof and the available epidemiological, molecular and immunological data can only suggest that there are associations between antioxidants and asthma and probably also to atopic dermatitis and allergic responses [9].

Immunosurveillance plays a major role to defend the integrity of the human organism. Thereby, immunocompetent cells like lymphocytes and monocytes detect foreign cell-surface structures, and in case of, e.g. intracellular infection or malignant cell transformation, they orchestrate a defence response dedicated to destroy abnormal cells and tissues. Within this response, cells communicate via cytokines and among the biochemical pathways utilized for the destruction of cells, the production of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-) and hydroxyl radical ($OH\cdot$) plays a major role as it was discovered already more than three decades ago [10]. However, ROS production is part of normal cell physiology and takes place especially in mitochondria. To establish a stable redox equilibrium in cells, endogenous antioxidant defence systems are established, which include potent detoxifying enzyme systems like superoxide dismutase (SOD) and catalase. In addition, dietary antioxidants are important to protect host cells from oxidative damage.

During the cellular immune response, Th1-type cytokine interferon- γ (IFN- γ) is one of the most important stimulators of ROS production by NADPH oxidase [11] and of other specific enzymes such as inducible nitric oxide synthase (iNOS) and indoleamine 2,3-dioxygenase (IDO), which are devoted to interfere with proliferation of pathogens or target cells either by oxidation and/or nitration of vital cellular components or by deprivation of essential nutrients such as tryptophan by IDO. Accordingly, when huge amounts of IFN- γ are released during Th1-type immune response, ROS production is elicited and antioxidant pools may become wiped out. Then, oxidative stress is developing, which also accelerates the Th1-type immune response in an autocrine way when redox-sensitive signal transduction elements such as nuclear factor- κ B (NF- κ B) are triggered and, in a vicious cycle, super-induce the formation of pro-inflammatory cytokines such as tumour necrosis factor- α (TNF- α). Thereby, the continued immune activation will increase the inflammatory process, which may also initiate a chronic inflammatory

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disease such as atherosclerosis, neurodegeneration or even cancer. During these clinical conditions, antioxidant systems seem required to protect host cells from ROS-induced damage.

Because of their chemical nature, antioxidants are able to neutralize ROS and thus also dampen the pro-inflammatory Th1-type cytokine cascades [8, 12] and related symptomatology. This is well in line with historical considerations of grandma that 'one needs to take in extra vitamins while one is sick'. This is most probably also the reason why we are educated to take in food rich in vitamins such as fruit and vegetables, which in some studies were found to improve the health condition of humans [13]. However, with time, this conclusion became more and more nebulous when food industry began to add extra vitamins to our daily dietary products, but not considering that also too much of an essentially good thing may turn to bad. In fact, today most fruit juice preparations and other beverages on the market contain high-dose supplements of vitamins, preferentially vitamins A, B and C, although their natural content is already high. Moreover, during recent decades, the addition of preservatives and colourants to food has become more and more popular, most of the added compounds like vitamin C and sodium sulphite being strong antioxidants. Consequently, individuals can become overloaded with dietary antioxidants, which may not only hinder the antimicrobial oxidation strategy of the immune system and thus delay the clearance of infections but also may promote development of diseases when redox-sensitive signal transduction cascades are influenced in the organism. Particularly in the gut, the concentrations of these compounds can reach easily high enough concentrations to influence cell metabolism and modulate cytokine profiles able to favour and strengthen an allergic response. Notably, the intestinal immune system plays the most important role in the development of an allergic response against food allergens, e.g. the gut is a major site for induction of Treg cells. [13].

In vitro, we and others have shown in freshly isolated human peripheral blood mononuclear cells [8] and dendritic cells [12] that not only antioxidant compounds like vitamins C and E but also food preservatives like sodium sulphite or benzoate and colourants like beetroot or curcumin exert significant suppressive effects on IFN- γ production and on the Th1 immune activation cascade. The effects observed may be based on the interaction of antioxidants with pro-inflammatory cytokine cascades that involve important signal transduction elements such as NF- κ B [8]. Although only *in vitro*, results show an anti-inflammatory property of compounds which can shift the Th1–Th2-type immune balance towards Th2-type immunity. There is a potential risk that too much intake of dietary antioxidants

could precipitate allergic responses in sensitized individuals. Thus, especially the increased use of antioxidant food supplements as well as preservatives and colourants could contribute to the increase of allergy and asthma in the Western world [1]. Thereby, antioxidants do not serve as allergens themselves; they only strengthen the immune response once an allergen is met. This prediction would also be well in line with the impression that allergens became stronger throughout decades. However, the chemical structure of allergens has not necessarily changed, rather the intensity how immunocompetent cells are handling these target structures has changed.

Most observational studies report potentially beneficial associations between dietary antioxidants and allergic outcomes, but a small minority report potentially adverse associations [9]. On the basis of a very large-sized database, Rosenlund et al. report a significant inverse association between intake of β -carotene during the past year and current rhinitis [14], whereas vitamin C and α -tocopherol intake was not found to be associated with specific diagnoses like rhinitis, asthma, eczema or atopic sensitization. In their study, a sub-analysis was performed in which 237 of 2470 children (9.6%) had been excluded from statistical analyses because they reported allergic symptoms related to fruits or vegetables, among them citrus fruit, fresh carrot and tomato. After their exclusion, the association between intake of β -carotene and rhinitis got lost, but a new association appeared between higher intake of α -tocopherol and a greater frequency of asthma and atopic sensitization became significant [14]. Thus, there are two probably contradictory findings that β -carotene has some protective effect on rhinitis, whereas α -tocopherol may support the development of asthma and atopic sensitization. Moreover, earlier results in adults showed a higher intake of β -carotene to be associated with a higher prevalence of rhinitis and hay fever [15].

In general, the frequency of allergies was rather high in children when allergy to fruits and vegetable were considered [14]. This result adds perfectly to the existing confusion in the available literature whether antioxidants may have a protective or promoting effect on allergy development [9]. Overall, it is rather disappointing that the large enough and at-first-glance well-designed study by Rosenlund et al. is unable to reveal more clear-cut results, and one may be forced to conclude that the role of dietary antioxidants on allergy and asthma epidemiology in children is less important than thought previously. However, there still can be contributing factors which were not addressed in the analysis by Rosenlund et al., e.g. any possible involvement of antioxidant compounds contained in spices, food supplements (antioxidant vitamins) and/or preservatives (e.g. sulphites) was neglected despite the fact

that there are considerable data in the literature about their potential role in allergy and asthma development. Especially in urban areas, the exposure to antioxidant food supplements cannot easily be avoided. Future studies should give special attention to that aspect particularly when e.g. fruits and vegetable are associated with higher risk of allergy, which should include not only rhinitis but also gastrointestinal complaints. The same is true for diet rich in fish or white bread, when nowadays flour is supplemented with ascorbic acid to protect it from oxidation – approximately 1.5 g/100 kg of vitamin C are added to wheat flour and 10 g/100 kg to bread and this supplementation does not even need to be declared. When studies are undertaken in adults, thereby including alcoholic beverages, it will be important to consider the antioxidant content of alcoholic beverages (no one really drinks pure alcohol), and also what about the role of histamine content in alcoholic beverages or in cheese? Once one accepts that overexposure to antioxidant compounds may increase risks, various other aspects in allergy and asthma epidemiology can be better understood, e.g. smoking may

increase the risks because antioxidant and Th1-inhibitory compound carbon monoxide (CO) accumulates in the blood of smokers. Also, air pollution is often due to insufficiently burned wood, benzene or gas upon which several compounds of more antioxidant than oxidant character are set free.

In conclusion, there are data in the literature which suggest that abnormally high intake of antioxidants may precipitate a kind of 'antioxidative stress', which could play a role in allergy development. Oxidative stress can be counteracted by higher intake of antioxidant vitamins and compounds, but there is less of a strategy to overcome 'antioxidative stress'. It seems that only physical exercise is a convenient way to reach this goal. Likewise, cooking of foods destroys antioxidant compounds and vitamins and is known to reduce or prevent allergic responses.

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