

Does Sensitization to Foods in Adults Occur Always in the Gut?

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Abstract

It is widely accepted that, under normal conditions, the contact between allergens and the immune system via the gut results in immune tolerance. Thus, it is rather surprising that normal adults may become sensitized to foods that they have consumed a number of times without any consequence. However, the medical literature is crowded with reports suggesting that sensitization to food allergens may occur outside the intestinal tract in many instances. The present article reviews and discusses current data suggesting, either directly or indirectly, a possible initiation of food allergy in the respiratory tract or in the skin in the light of recent findings about mechanisms of tolerance and sensitization.

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Introduction

Despite the barrier function of the gastrointestinal mucosa, in normal adults about 2% of immunologically active food proteins are absorbed and systemically distributed [1, 2]. Nonetheless, under normal conditions,

this does not produce harmful consequences because the contact between allergens and the immune system via the gut results in immune tolerance. In fact, the intestinal mucosa is characterized by a down-regulatory microenvironment whose role is to ensure that active immune responses are not elicited against dietary proteins. Recent studies have identified several mechanisms that are possibly involved in the development and maintenance of oral tolerance; these include clonal anergy of T cells, mucosal IgA, and specialized Treg cells [these concepts are extensively reviewed in 2–4].

What Might Prompt Food Sensitization to Occur Outside the Gut?

There is growing evidence that, in genetically predisposed individuals, sensitization to foods is more likely if the gastrointestinal tract is by-passed and the contact between allergens and the immune system occurs via another route.

The high prevalence of food allergy (in most cases to milk and egg) that characterizes young children has been associated to the immaturity both of the gut barrier and of the immune system [1]. In effect, although a proportion of food allergic children retain their sensitivity up to adulthood, the large majority of them outgrow their disease during childhood. However, in children there is a close association between food allergies and eczema [5], and in young patients with atopic dermatitis the use of

peanut oil-based ointments has been associated with a significantly increased prevalence of peanut allergy [6]. Based on these observations a 'dual-allergen exposure hypothesis' has been developed suggesting that exposure through the skin leads to sensitization, whereas ingestion results in the induction of oral tolerance [5]. In effect, recent studies have shown that the filaggrin gene defect eventually results in a facilitated penetration of environmental allergens through the skin, which increases the risk of allergic sensitization [7, 8]. In animal models, epicutaneous exposure to ovalbumin is able to induce egg allergy [9], and similar results have been obtained by the epicutaneous exposure to completely different food allergens, namely peanut and cashew nut [10, 11], suggesting that the sensitization process, albeit allergen-specific, follows a common pathway irrespectively from the sensitizing food.

Some studies suggest that the age of exposure may be relevant in the development of tolerance to foods, as feeding with a related dose of ovalbumin in neonate or adult mice results in sensitization and tolerance, respectively [12]. However, other data suggest that in infancy the early consumption of foods such as peanut, fish or wheat may lead to a decreased risk of allergy or eczema [13–16]; these observations have been very recently confirmed in children up to 4 years of age with a familial history of allergic disorders [17].

In adults, food allergy is comparatively less common than in children, although some surveys carried out in different areas suggest a prevalence ranging between 1.5% and 2% of the general population [18–21]. However, the most frequent food allergies in adults are the result of the cross-reactivity between pollen allergens, which act as primary sensitizers, and homologous proteins in plant-derived foods, which act as elicitors of symptoms [20, 22, 23]. In contrast, in the case of primary food allergies the reason why an adult becomes allergic to a food that has been ingested thousands of times before without any problem remains unknown. Some studies support the idea that the respiratory tract may be involved as well in inducing de novo food allergy [24].

A prerequisite to hypothesize that sensitization to foods may occur outside the gut is the presence of food allergen particles in different normal environments. In effect, food allergen particles can be measured in the environment [25], and sensitization to a variety of foods could occur through environmental exposure [26]. For instance, very recently, household peanut consumption was found to be a risk factor for peanut allergy in children [27].

Evidence for Adult Extra-Intestinal Sensitization to Food Allergens

Secondary Allergies to Plant-Derived Food

Several allergies to plant-derived foods are a consequence of sensitization to non-food airborne allergens.

Pollen-Food Allergy Syndrome and Mugwort-Celery-Spice Syndrome

These food allergies are obviously the result of a primary sensitization to seasonal airborne allergens, including the major birch pollen allergen, Bet v 1, the plant pan-allergen profilin, and a so far uncharacterized allergen in mugwort pollen. These types of food allergy will not be reviewed in detail here.

Latex-Fruit Allergy Syndrome

A large proportion of natural rubber latex-allergic subjects develop food allergy to a series of plant-derived foods such as chestnut, banana, avocado, kiwi, papaya and peach. In young patients with spina bifida, latex sensitization has been frequently observed following multiple surgeries, probably as the result of repeated parenteral exposure to NRL allergens. In these patients a direct correlation between NRL sensitization and number of surgical treatments has been observed [28]. In contrast, in healthcare workers, which are the other main group at high risk for latex allergy (and probably represent the largest part of the latex-allergic population) sensitization may occur transdermally [29, 30] or via the respiratory tract [31]. An epidemiological study carried out in France demonstrated a very high percentage of food allergy in latex-sensitive health care workers [32].

In fact, latex sensitization has dramatically decreased since the use of cornstarch powder as lubricant for latex gloves was abolished [33].

Primary Allergies to Plant-Derived Foods

There are a number of reported cases in which primary sensitization to plant foods does not seem to have occurred in the digestive tract. These will be reviewed in the following paragraphs.

Allergy to Lipid Transfer Proteins

Lipid transfer proteins are by far the most frequent cause of type 1 food allergy in adults living in Mediterranean countries [20, 23] but are very rare in Northern

Europe [23]. Also offending fruits differ between geographical areas, peach being the most frequent sensitizers in Italy and Spain and wine or hazelnut causing the rare cases observed in the North. The reasons for this strange distribution are still unclear, but some published data provide clues that point to a possible transdermal or respiratory sensitization to this protein.

LTP is particularly abundant in peach fuzz [34], which is in turn particularly abundant in freshly picked peaches. Most fuzz is removed during the washing and brushing procedures that precede packaging and sale in supermarkets or export in foreign countries. Interestingly, many workers employed in picking and handling peaches in the area of Ferrara (a commune of northern Italy) have to wear gloves during the working hours in order to avoid the occurrence of contact urticaria induced by these fruits [A. Martinelli, Consorzio Italiano Vivaisti, Ferrara; pers. commun.] but the same workers never report similar problems handling nectarines, apples, pears, plums or cherries. In a Spanish cohort of peach-allergic subjects, contact urticaria was the second more frequent symptom after oral allergy syndrome and occurred in 68% of subjects; notably in 14% of patients contact urticaria was the only symptom of peach allergy [35]. In another study, contact urticaria was the only symptom present in one third of subjects allergic to asparagus LTP [36], and a woman got sensitized to LTP following prolonged occupational contact to massive amounts of spelt [37].

In other instances sensitization to LTP seems to involve the airways. Lombardero and co-workers suggested that in some patients primary sensitization occurs against Art v 3, a LTP present in mugwort pollen [38], although others concluded that such sensitization follows peach sensitization [39]. Sensitization via the inhalation of Pru p 3 derived from peach leaves has been suggested to precede the clinical expression induced by the allergen via the oral route [40]. A woman employed in a fruit and vegetable wholesale store developed rhinitis and asthma in the workplace well before becoming allergic to fruits [41]. Another LTP-allergic patient experienced several episodes of asthma when she was near a mulberry tree, well before developing an anaphylactic reaction following the ingestion of a mulberry [42]. Finally, LTP seems involved in respiratory allergy produced by rice inhalation [43], and wheat LTP has been associated with baker's asthma [44]. Very interestingly, in a recent Spanish survey LTP sensitization was much more frequent in areas characterized by extensive crops of orchard trees [45]. Thus, the different concentrations of orchard trees in Southern and

Northern Europe might be a key factor for the epidemiological differences observed.

Allergy to Seeds and Nuts

Sunflower Seeds. Bird fanciers who breed parrots seem at risk for developing sunflower seed allergy. Sunflower seeds are always present in commercial birdseed products for parrots, and allergic reactions frequently occur upon the first ingestion of the seeds [46]. Interestingly, in several cases respiratory symptoms upon exposure to seed particles preceded by months the first allergy reaction upon ingestion [47–49].

Sesame Seeds. These seem able to sensitize via the respiratory tract in the baking industry [50]. Further, severe reactions upon the first known exposure to the food have been reported in adolescents [51].

Poppy Seeds. Inhalation of poppy seeds was found to induce erythema, angioedema, dyspnea, and conjunctivitis in an adolescent [52].

Pine Nuts. Severe pine nut allergy either following ingestion, inhalation or skin testing was recently reported [53], and allergy upon first ingestion of pine nut well after the onset of contact urticaria was observed [54]. Finally, similar to sunflower seed allergy, pine nut allergy may occur in bird fanciers [55].

Almonds. In a 28-year-old man with a history of repeated episodes of almond- and pine-nut-induced anaphylaxis (whose relevant allergens were subsequently shown to cross-react), food allergy was preceded by years by almond-induced contact urticaria [56].

Peanut and Other Legumes

Allergic reactions to the first known exposure to peanut are very common in children [57–59]. Although such cases have been interpreted as secondary to sensitization in utero, through breastfeeding, or via an unknown route of exposure [60], recent studies found that the presence of the allergen in the environment may represent a more relevant risk factor for sensitization [27].

Inhalation of lupine flour may induce sensitization in exposed workers that subsequently develop asthma and food allergy [61].

In adults, soybean sensitization seems to occur via the respiratory tract not only for Gly m1, the inedible allergen of soybean hull involved in epidemic asthma breakdowns, but also for the food allergens of soy flour in exposed workers both in bakeries and food processing plants [62, 63].

Allergic symptoms have been observed in children exposed to boiling lentils [64] and also in adults exposed to

vapors of different boiling legumes, including pea, chickpea, bean, and lentil [65–67]. A case of contact urticaria from chickpea and of anaphylaxis following inhalation of vapors from cooking lentils has been reported as well [68].

Kiwi

In a cohort of kiwi-allergic children younger than 5 years, 73% of patients reacted upon their first known exposure to the fruit [69] suggesting that sensitization had occurred by an alternative route.

Spices

Garlic allergy upon ingestion may be preceded by the onset of contact urticaria [70]. In a case of allergy to dill the inhalation of foods prepared with dill was able to induce severe systemic symptoms [71].

Grains

Along with the obvious example of baker's asthma, which never develops into frank food allergy due to the heat-sensitivity of the relevant allergenic protein(s) (in effect, cases of frank food allergy after ingesting meals contaminated by uncooked wheat flour are reported [72]), there are several other examples of airborne sensitization to grains followed by food allergy. Similarly to sunflower seed, millet may cause severe food allergy in bird keepers, following sensitization by inhalation [73].

Buckwheat flour and buckwheat chaff-stuffed pillows have been shown to be able to sensitize via the respiratory tract [74, 75], and cases of either respiratory or skin symptoms upon contact with ground buckwheat have been reported [76]. Importantly, recent observations show that buckwheat airborne allergy may precede by years the onset of food allergy [77].

Finally, most cases of allergic reactions following the ingestion of foods containing barley proteins (e.g. beer) or maize occur in lipid transfer protein-sensitized subjects as a consequence of cross-reactivity with peach LTP (see above) [78, 79]. The same holds true for some allergic reactions induced by rice [80].

Fish and Seafood

Allergic reactions to airborne proteins from fish, crustaceans and mollusks seem all but uncommon both in exposed workers and in home environments, although food allergy by ingestion develops only when the relevant allergens are heat-stable [81–83]. Fish protein allergens

have been detected in the air samples of open-air fish markets [84], and anaphylaxis following exposure to rooms where fish was being fried has been documented [85]. Further, allergic reactions to airborne fish particles are not rare among fish allergic children, clearly suggesting that sensitizing particles are frequently present in home environments [86].

The cross-reactivity between house dust mite tropomyosin and homologous proteins in crustaceans and mollusks is well known and largely documented, and is probably one cause of shrimp sensitization observed in unexposed subjects [87]; anaphylaxis or asthma following the ingestion of snails [88] or mites [89] has been described as well and is also the consequence of primary mite respiratory allergy. In these cases the pepsin-resistance of allergens might also play a role in the severity of reactions [89]. Further, occupational asthma seems rather common among workers employed in crab-processing plants [90] where airborne allergens can be detected in the environment [91].

Egg

There is evidence that in the so-called 'egg-egg' syndrome which can be observed in bakery and confectionery workers [92], and in the 'bird-egg' syndrome which can be observed in bird fanciers as well as in workers exposed to chicken [93], airborne sensitization precedes the onset of the food allergy. Interestingly, in the latter syndrome one study confirmed the presence of airborne chicken serum albumin in the environment [94].

Milk

Milk allergy is extremely rare in adults [20]. Nonetheless, hypersensitivity reactions following inhalation of milk proteins have been reported [95, 96]; such reactions can be very severe and even lethal [97]. These cases show that milk allergen proteins can be airborne and, hence, are potentially able to induce sensitization via the respiratory tract. It is also theoretically possible that sensitization through the skin or lungs may generate a different IgE response to allergens. Although the sensitization route was not specifically investigated, Lam et al. found that the rare adults allergic to milk show IgE reactivity to casein, lacto-albumins and whey proteins without preference for one of the proteins in adults, whereas IgE to casein seems to be dominant in young children [98].

Meats

Although allergy to meats is very rare in adults, a case of occupational airborne allergy to pork followed by food allergy to pork and chicken has been reported [99].

What Stands against the Hypothesis of the Extra-Intestinal Sensitization to Food Allergens?

It is generally accepted that oral tolerance depends on the presence of several mechanisms that eventually lead to a down-regulated immune response to food proteins [2–4]. Such mechanisms are those possibly involved in children who outgrow their food allergies [100]. A breach in any of these mechanisms has been demonstrated to result in loss of oral tolerance to antigens in animal models; however, whether this is also the case in adult patients who develop de novo food allergy is as yet unproven [4].

The way tolerance develops might heavily influence the occurrence of food allergy via the respiratory tract. It is well known that high-dose oral tolerance is characterized by specific anergy, whereas low-dose tolerance depends on the active role played by allergen-specific Treg cells [4]. It is possible to hypothesize that in the latter situation oral tolerance is sometimes unstable and may depend on the dose and frequency of allergen exposure. Skin reactivity to commonly ingested foods is a relatively frequent phenomenon and the negative effect of elimination diets has been known for a long time [101]. The use of inappropriate diet regimens, particularly in children, might favor this situation [102]. Such model of tolerance resembles respiratory allergy [103, 104]. Multiple, unidentified, mechanisms seem involved in a complex interplay between different lymphocyte populations, and the detection of specific IgG₄ to allergen components might represent a useful marker to detect this condition. Interestingly, one study found that PBMC from peanut-allergic and peanut-tolerant subjects show qualitatively similar peanut-specific Th2 responses in the absence of any protective Th1 immunity, the difference between the two groups being only quantitative [105].

Thus, it is possible to hypothesize that in adults, food allergy occurs in four different situations, two of which support a relevant role of inhalation route and two stand against it.

(1) Absence of oral tolerance due to absent or minimal contact between allergen and gut mucosa, with respiratory sensitization to airborne allergen. The severity of food allergy depends on pepsin-stability of the allergen.

Table 1. Possible sensitization route outside the gut reported for different primary food allergens

Allergen	Possible sensitization route
Lipid transfer protein	transdermal, airborne
Sunflower seed	airborne
Sesame seed	airborne
Poppy seed	airborne
Pine nut	transdermal, airborne
Almond	transdermal
Peanut	transdermal ^a , airborne ^a
Lupine	airborne
Soybean	airborne
Other legumes	transdermal, airborne
Garlic	transdermal
Dill	airborne
Kiwi	unknown
Cereals	airborne
Buckwheat	transdermal, airborne
Fish and seafood	airborne, transdermal
Egg	airborne
Milk	airborne
Pork Meat	airborne
Anisakis	transdermal, airborne

^a Allergy upon first exposure has been reported but sensitization route is unknown.

(2) Low-dose oral tolerance with transdermal or respiratory sensitization. In this model, sensitization through the airways or the skin might unbalance the immune profile supporting tolerance, which is already unstable or minimal due to a specific genetic background or due to long intervals between ingestions of the relevant allergen. Allergic reactions upon first exposure to sunflower seed, millet, psyllum, peach, peanut, or anisakis [106] might represent good examples of such mechanism.

(3) High-dose oral tolerance is broken by airborne sensitization. Little data support this hypothesis. Anecdotal reports of the onset of food allergy in workers professionally exposed to poultry or bovine meats [92, 99] or to latex [32] were reported. Nonetheless, food allergy is uncommon in workers with occupational asthma to crustacean or fish proteins [107], although it sometimes occurs [106].

(4) Defect of oral tolerance with appearance of respiratory symptoms following inhalation of the same allergen [72].

Table 2. Possible ways of sensitization to food allergens and subsequent immunological events

Site of sensitization	Allergen resistant to		Food is ingested	Clinical symptoms	Examples
	pepsin	heat			
Airways	no	no	raw processed	OAS none	pollen-food allergy syndrome
	yes	no	raw processed	systemic none	latex-fruit allergy syndrome
	yes?	no	processed	none	baker's asthma, legumes, soybean, dill, crustaceans
	yes	yes	raw/processed	systemic	mugwort-celery-spice-syndrome
	yes	yes	processed	systemic	shrimp/snail allergy in mite allergy
	yes	yes	processed	systemic	sunflower allergy in bird fanciers buckwheat? poppy seed? egg? pork?
Skin or airways	yes	yes	raw/processed	OAS or systemic	fruits, vegetables, cereals (LTP)
	yes	yes	processed	systemic	peanut
Skin	yes	yes	processed	systemic	garlic, almond
animal model	yes	?	raw	systemic	peanut, ovalbumin, cashew

Conclusion

The data reported above show that allergic reactions are frequently experienced upon first exposure to a certain food. In the medical literature there is plenty of data suggesting that in adults (but probably in children as well) sensitization to food allergens may occur via the respiratory tract or through the skin (summary in table 1). It has been shown that respiratory symptoms upon inhalation and/or urticaria upon contact with foods may precede by years the onset of allergy upon ingestion, but in many cases no classical food allergy will develop due to the heat- and/or pepsin sensitivity of the relevant allergen proteins [for a review of these latter cases, see 24]; the different combinations of physical/chemical characteristics of food allergen, conditions of exposure, and clinical events are summarized in table 2.

Many of the examples cited above come from occupational environments; of course, allergen exposure in such environments is different, at least quantitatively, from everyday life exposure for the majority of the population. Nonetheless, the long-lasting exposure of a large number of individuals to high levels of potential allergens might represent an interesting model of sensitization reproducing on a large scale what happens only in few cases outside. Food-derived allergen particles in sufficient amounts

to elicit sensitization are likely to be present in several different environments, and it is possible that genetically predisposed subjects may mount their IgE-mediated responses to these proteins in the same way others become allergic to pollens or mites. If the level of food allergens in the environment is low, as is probably the case in most instances, clinically appreciable respiratory or skin allergy symptoms will not develop or may be so slight as to be overlooked; in other cases (e.g. workers in the food industry, bird fanciers) exposure to higher amounts of allergens causes appreciable respiratory or skin symptoms. Finally, although a systematic review of this aspect is out of scope of this paper, more and more data suggest that also in food-allergic adults oral tolerance may be restored, at least in part, by the oral administration of increasing doses of the offending allergen.

In conclusion, contact between allergens and the immune system via the digestive tract is generally associated with the induction of tolerance whereas epidermal or respiratory exposure can prevent it [24, 108]. The possibility that, at least in some cases, a story of food allergy in adults may start outside the gut cannot be ruled out.

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