The Concept of Oral Tolerance Induction to Foods

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Abstract

The conventional wisdom is that early exposure to allergenic food proteins during pregnancy, lactation, or infancy leads to food allergies, and that prevention strategies should therefore aim to eliminate allergenic food proteins during pregnancy, breastfeeding, and early childhood. Prolonged exclusive breastfeeding and delayed weaning onto solid foods is therefore seen as an effective public health policy to prevent allergies. However, there is little epidemiological data to support this belief. Intervventional studies on dietary elimination have failed to reduce IgE-mediated food allergies. Conversely, there is preclinical data and some clinical data to suggest that early cutaneous exposure to food protein through inflamed skin leads to allergic sensitization and that early oral exposure results in the induction of tolerance. New strategies to prevent food allergy in infants need to be put to test in randomized controlled interventional studies.

Despite increasing efforts to prevent food allergies in children, IgE-mediated food allergies are rising and now affect 4–7% of infants. At a global level, the World Health Organization’s (WHO) strategy to prevent food allergies is to promote exclusive breastfeeding during the first 6 months of the infant’s life and thus delay weaning onto solid foods [1]. In order to prevent specific food allergies, some countries recommend the avoidance of specific foods such as egg and peanut in atopic infants, and some national guidelines promote the avoidance of peanuts during pregnancy and lactation and in the first 3 years of childhood.

The evidence to support these guidelines is not entirely clear, and evidence for their efficacy is lacking. Studies of egg-allergic and peanut-allergic infants show that most affected cases react on first oral consumption of these foods, and therefore early oral exposure cannot explain the genesis of these
allergies. Two birth cohort studies have failed to find an association between the development of peanut allergy and consumption of peanuts during pregnancy, lactation and infancy [2, 3]. Prospective randomized controlled interventional studies that remove food allergens from the maternal diet during the 3rd trimester and during lactation, and from the infant's diet in the first 3 years of life have consistently failed to show a significant long-term reduction in IgE-mediated food allergies, although they do show a transient improvement in eczema [4]. Similarly, prolonged exclusive breastfeeding has not been shown to prevent IgE-mediated food allergies [3].

Peanut allergy has become increasingly prevalent: recent studies demonstrate that the prevalence of peanut allergy has doubled in 10 years and approximates 1.3–1.5% [5]. Peanuts are a frequent cause of anaphylaxis for which there is no established treatment except allergen avoidance. Children with peanut allergy additionally have to avoid tree nuts since up to 50% have allergies to individual tree nuts. It is perhaps surprising that studies eliminating food allergens during pregnancy, lactation and infancy have consistently failed to reduce IgE-mediated food allergy in children. Three explanations for this failure with respect to peanut allergy include the following. (a) Allergen reduction measures have been insufficient in previous studies and elimination from the diet was not sufficiently rigorous. (b) Sensitization to food allergens does not occur through oral exposure but may occur via other routes. Indeed, the application of topical preparations containing peanut oil on infants with eczema during the first 6 months of life was associated with a high risk of developing peanut allergy [3]. A recent study has shown that even after washing hands and tabletops after eating peanuts, peanut protein was detectable in significant amounts (10 to several 100 µg) on hands and table surfaces [6]. (c) The paradigm of allergen avoidance is flawed and early oral exposure may be required to prevent the development of allergy. Oral tolerance induction is well recognized in murine models and even in the human literature [7, 8].

Murine studies exist showing that allergic sensitization to antigen can occur on cutaneous exposure. One study showed that exposure of mice to milligram quantities of ovalbumen on abraded skin led to significant anti-OVA IgE responses and positive intradermal tests [9]. More recently, it has been shown that cutaneous sensitization on the abraded skin of mice led to significant IgE responses to peanut and T cell responses to peanut [10]. This occurred even with the application of arachis oil to the skin of mice (less than 6 µg/ml of peanut protein).

Animal models demonstrate that a high early dose of oral protein antigen is highly effective in inducing tolerance to the respective antigen, even in the case of subsequent administrations of antigen in the presence of potent immune adjuvants. A literature search on oral tolerance induction in animal models has revealed 33 publications over the last 35 years in which a single oral dose of antigen was sufficient to induce tolerance. The phenomenon has been demonstrated for different antigens in different experimental models.
The data is consistent, uniformly showing that a single dose of oral protein administration effectively causes immunological tolerance and prevents the expression of related clinical disease. Oral tolerance induction in animal models is most potent in its effects on delayed type I hypersensitivity responses; prevention of antibody responses through induction of oral tolerance is less consistent. However, numerous publications point to the fact that a single dose of food allergen in mice (β-lactoglobulin, ovalbumen, peanut) is particularly effective in preventing the development of subsequent IgE-mediated responses. A most recent study [11] showed that naive mice orally tolerized to β-lactoglobulin were unable to mount significant IgE responses after subsequent sensitization with β-lactoglobulin injected with alum (intraperitoneally). Similarly, there were no significant T cell responses to β-lactoglobulin in the pretolerized animals.

Later in 2004, Strid et al. [12] fed mice a single intragastric feed of defatted peanut flour at doses varying from 0.2 to 100 mg per mouse. Seven days after the feed, animals were immunized with 100 μg of peanut antigen emulsified with complete Freund's adjuvant. Three weeks later, animals were given a recall immunization with 100 μg antigen. Mice were assayed for T cell proliferation to peanut, cytokine production, delayed-type hypersensitivity responses and antibody responses. Tolerizing doses of 100 mg of peanut protein resulted in significant reduction in delayed-type hypersensitivity responses and inhibition of proliferative responses to peanut. Animals tolerized to 100 mg of peanut protein showed significantly reduced interferon-γ and IL-4 production. Specific IgE responses to peanut following sensitization were almost completely prevented by the single tolerizing dose. However, very low ‘tolerizing’ doses of peanut below 2 mg per animal resulted in enhanced delayed-type hypersensitivity responses, T cell proliferative responses, cytokine production and IgE production. Doses between 2 and 20 mg of peanut protein induced no difference in T and B cell responses compared to sham-tolerized animals. Tolerance to peanut was only achieved at doses of 100 mg per animal. Oral tolerance to peanut was shown to be antigen specific. Tolerizing doses of peanut did not promote tolerance to ovalbumen and vice versa.

In the atopic march during infancy, atopic dermatitis (AD) usually precedes the development of IgE-mediated food allergy. Indeed, more severe AD is associated with a higher risk of food allergies, and in some studies, food allergen-specific T cells have been isolated from the lesional skin in patients with AD [13]. More recently, it has been shown in a prospective birth cohort study that low-dose exposure to peanut in the form of arachis oil applied to inflamed skin is associated with an increased risk of developing peanut allergy. While the use of such oils is not widespread in all countries, it is worth noting that food allergens can be measured in the environment and cutaneous sensitization to a variety of foods could occur through environmental exposure [6].

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There is evidence that cutaneous exposure to nickel causes allergic sensitization while oral exposure to nickel results in tolerance. Numerous studies, both prospective and retrospective, show that early cutaneous exposure to jewelry, particularly through ear piercing, is a risk factor for the development of contact dermatitis to nickel. Three independent studies [14–16], including one prospective birth cohort study, show that the early application of orthodontic braces made of nickel strongly protects against the development of contact dermatitis to nickel (in one study there was an odds ratio of 0.07). Indeed, the level of nickel in both saliva and serum of individuals increases significantly after the insertion of fixed orthodontic appliances and this is thought to result in oral tolerance. Similarly, parents exposed to pancreatic extract by inhalation or contact develop IgE-mediated allergic reactions but not the patients who were exposed to the extract by oral route [17].

It has been observed however that in African and Asian countries where peanuts are consumed throughout pregnancy and early childhood, peanut allergy is rarely seen compared to western industrialized societies such as the UK and USA where peanut allergy is high despite peanut avoidance during pregnancy and infancy (table 1) [18–20]. Differential predisposition to atopy due to both genetic and environmental factors could explain these differences.

There are no studies that examine the potential of oral tolerance induction to foods in the human infant. There is one adult study showing that feeding keyhole limpet hemocyanin (KLH) results in immunological tolerance to KLH antigen [8]. One study that attempted to induce tolerance to a food allergen [21] was conducted in patients who already had established milk allergy. The result of this study was promising: 71% of highly allergic children were able to tolerate a daily intake of 200 ml of milk after treatment. However, this was an uncontrolled study and therefore the possibility that these children would have shown spontaneous resolutions cannot be discounted. A more recent controlled study [22] showed that sublingual exposure to hazelnut in allergic individuals raised their allergic reactivity threshold to hazelnut.

In summary, the long-held view that allergic sensitization to food occurs through oral exposure and prevention of food allergy is best accomplished

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**Table 1. Food allergies among allergy clinic patients**

<table>
<thead>
<tr>
<th>Country</th>
<th>Peanut allergy %</th>
<th>Dietary practice recommendations (infant peanut consumption)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (n = 191; Lack et al., 2004)</td>
<td>25</td>
<td>Avoidance</td>
</tr>
<tr>
<td>USA (n = 300) [18]</td>
<td>69</td>
<td>Avoidance</td>
</tr>
<tr>
<td>Israel (n = 992) [19]</td>
<td>2.1</td>
<td>High infant exposure</td>
</tr>
<tr>
<td>Philippines (n = 184) [20]</td>
<td>0</td>
<td>High infant exposure</td>
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through elimination diets is being challenged. It is proposed that allergic sensitization to food may occur through low-dose cutaneous sensitization and that early food protein exposure may induce oral tolerance and prevent the development of food allergies. The validity of these hypotheses will need to be tested in randomized controlled, interventional studies.

References

Discussion

Dr. Bergmann: In Germany, midwives visit mothers after delivery at home and help them with breastfeeding and the care of the newborn. Some recommend adding mother’s milk to the baby’s bath, even if the infant develops eczema. In my opinion, there is no study on the benefit of a breast milk bath for the prevention and treatment of eczema.

Dr. Lack: That is interesting. Certainly this is done with egg and in fact egg is used in shampoo. We have seen a few babies who presented with anaphylaxis to egg after the parents were advised to put egg white on their babies’ skin.

Dr. Nowak-Wegrzyn: Your observations have been well documented, but how early is early and would you comment on milk allergy? It is hard to imagine more high-dose exposure to a food allergen than with cow’s milk-based formula introduced on the first day of life but these children still develop allergy to cow’s milk. So at what age would you consider to start feeding peanut? I hope that your studies will be able to answer this question.

Dr. Lack: Babies 4–11 months of age and generally the majority of children in the UK have not developed peanut allergy at this stage. Our study will be stratified because there will be some who already have low levels of IgE to peanut but a negative skin prick test. One of the questions is how far can you modulate in the very primary sense, and in a secondary sense once the IgE is detectable. Is it too late to intervene once the biologic ball has started rolling and IgE is present? We should be able to answer that hopefully. Milk is puzzling and as you pointed out, very often babies can have milk many times before they develop symptoms of milk allergy, which is very different to egg and peanut allergy. I think there are problems in milk allergy, one of which is that historically most studies have not separated the different phenotypes of milk allergy; so there is a quick onset of IgE mediated milk allergy, then eczema, and gastrointestinal symptoms and many of the studies lump them all together. It may be that milk is only started in a very partial form in combination with breastfeeding and a higher dose is needed. Milk is a bit of a puzzle, as is fish because a lot of people with fish allergy have of course eaten fish many times before they develop fish allergy. It is interesting that the fish allergen Gad c 1 is present in very low concentrations as a constituent of fish protein compared to other foods. So it may be that tolerance requires exposure to high concentration of allergens.

Dr. Beyer: How do the data from the United States fit in because almost 90% of the children are given peanut butter very early on? Although the recommendation is to avoid it in high-risk children, it is given and eaten there, and there is a high prevalence of peanut allergy in the USA. So how do you fit all these confusing data together?

Dr. Lack: I am actually not sure that this is the case in the United States. People don’t always follow recommendations. In the United States 80–90% of children who react to peanuts do so on the first known exposure as in the rest of the world. Also it seems socially related. For example there is the WIC program in the United States where children from low socioeconomic groups are given nutritional supplementation and peanut butter earlier on. I have been told anecdotally that this group of
children had the least peanut allergy. So there might be other confounding factors related to the socioeconomic status. I don't think the evidence is strong that American babies in general are eating huge amounts of peanut protein in the first 4–10 months of life.

**Dr. Ruemmele:** You succeeded in focusing on one single pathology. I think that is important when speaking about allergy and atopy, otherwise there is a mixture of different pathophysiological mechanisms, which is always quite difficult to compare. Do you consider that the route of antigen administration, cutaneous versus GI, decides whether a child develops an allergic disease or not, or is this too simplistic? Comparing allergy to celiac disease, as an example of an immune-mediated disorder, in both diseases there are clearly identified antigens, a T cell-mediated immune response on the level of the intestinal mucosal barrier. However, the immune responses are completely different with varying Th profiles. So how is it that proteins of cow's milk or whey provoke a Th2 or Th2-oriented immune response whereas in celiacs an Th1 immune-mediated response to gliadin is observed?

**Dr. Lack:** Yes, hypothetically I do believe that it is likely that sensitization occurs to the skin rather than the GI tract. Yes it is a simplistic hypothesis but I prefer to deal with something that I can understand at least in terms of translating it into human behaviour. What I think is going on is that there are two routes of antigen presentation, one is the oral route and the other is environmental, be it cutaneous or respiratory. In southern or western Africa or Asia, where there is higher environmental exposure, the babies will have eczema which induces sensitization, but at the same time there are oral tolerance signals through the GI tract. If environmental exposure is allowed to continue and cause sensitization but the tolerogenic signals to the GI tract are removed, then there is a potential for disaster. Removing peanuts and other foods from developing countries could result in malnutrition because they are a major source of proteins in these countries. The disjunction in routes of presentation leads to an allergic or a tolerant outcome. Peanut allergy is a Th2-mediated disease, which is not the case with celiac disease. There are epidemiological studies suggesting that early introduction of wheat may work both ways. One line of evidence suggests that wheat predisposes to celiac and other data suggests that it may be protective. Interpreting these studies is difficult. Even if it is shown that a food which is introduced early in life causes symptoms, this does not mean that the introduction of the food is causing the primary disease; it may simply mean that the disease is already there and the earlier the food is introduced the earlier symptoms are seen. If you have any thoughts on how celiac disease arises I will be grateful to hear them.

**Dr. Ruemmele:** It is amazing to see two different responses to major antigens of whey characterizing celiac disease or whey allergy; perhaps the antigens are not the same. One is Th1 and the other is Th2 disease; one is autoimmune and the other systemic allergic atopic disease. So what makes the switch? I don’t have the answer but it is quite an interesting comparison.

**Dr. Wahn:** There was a time when I thought things were so easy and now they are so complicated; we are all getting confused. For clarification, when you showed this bell-shaped curve of environmental exposure you were implying that a lot of environmental exposure could be beneficial. Then you mentioned peanuts and said that the environmental exposure to peanuts is bad whereas oral exposure is potentially good. Is it just that things are totally different or are you still at the ascending part of the dose-response curve? Are you assuming that you will never reach the right side of the bell, or would you hypothesize that there is no bell with regard to peanut exposure?
**Dr. Lack:** Yes I think high-dose exposure or moderate- to high-dose exposure to peanut in the environment is problematic. I didn’t show the data but it is interesting that children with egg allergy as a group had much lower exposure and they were all clustered down at the bottom in terms of environmental exposure, except for a very small subgroup who was way out and who had even more environmental exposure than the peanut group. What is high and what is low of course becomes a relative concept. I think that very high-dose exposure in its own right may tolerize but again is it tolerizing through the skin or is it tolerizing because there is a very high amount of the allergen in the environment and it gets into the saliva?

**Dr. Wahn:** But what doses are you using in your ITN prospective trial?

**Dr. Lack:** We are mirroring the natural pattern of introduction in terms of frequency, amount of snacks, and total protein amount because there is also a safety issue here. So we are not introducing something that has never been done before. We are mirroring this on the basis of other population-feeding studies.

**Dr. Nowak-Wegrzyn:** Regarding what you said about the introduction of peanut butter in America, I think it mostly occurs after 8 months of age, which is pretty early but it is not that early. We actually see a high percentage of young children sensitized and allergic to peanut in the inner city population. The question is about Bamba snack that you will use in your study. Is the peanut in Bamba processed differently from peanut butter?

**Dr. Lack:** We are not just feeding this Israeli snack, we are feeding other snacks including peanut butter and in fact peanut soup. We looked carefully at the amounts of major peanut allergens in peanut butter and in peanut-containing snacks, and a variety of peanut butters in different countries. We found no important differences. There are minor differences in protein content but IgE binding on these peanut snacks is the same, and in fact they are all made of roasted peanut butter. I don’t think there really is an issue unless we get down to the variations in processing that Dr. Beyer was talking about that may affect hypoallergenic milk formulae. Sensitisation is not the same as allergy. It is very interesting that infants who are eating peanuts in high amounts may have moderate to high levels of specific IgE to peanut. This is another problem with studies; when we look for causality in large epidemiological studies, the production of IgE in a lot of these children is a normal tolerant phenomenon. We have to be very careful about distinguishing sensitization versus allergy.

**Dr. Chubarova:** How is it that children with eczema are recommended to apply an antigenic product on skin because there is a regular recommendation to avoid this? The theoretical question that I am especially interested in regards applying an antigen to a compromised skin barrier in children with eczema which can cause general sensitization and be realized at any locus. You are telling us that gastrointestinal allergy is not the main cause of the allergy. What about the risk?

**Dr. Lack:** There is no direct proof that these creams are causing peanut allergy. It would be unethical to randomize babies to receive these creams or not and I think very few parents would permit this. My advice is to avoid any topical preparation that contains a food protein that is known to be an allergen on eczematous skin. But another problem that we realize now is that these proteins are not just from these creams; they may be from the environment. Egg and milk and peanut are measurable in the environment; they are measurable in the air, on surfaces, hands and bed clothes, and we can’t do much about this. If the environment were totally hypoallergenic with no milk protein at all, and no peanut and no egg, these food allergies might not exist. Kiwi allergy only developed in the UK after we started importing kiwi. If total environmental exposure and all forms of exposure could be brought down to zero then everything might be alright, but this is not practically possible.
Dr. Chubarova: Why have you taken eczema as independent risk factor because in that case you apply antigen to a compromised barrier?

Dr. Lack: It is a risk factor that we found in our studies and others have found it as well. Hill and Hosking [1] in Melbourne have shown very nicely that the severity of eczema directly correlates with the number of foods to which the infant is allergic and the number of days topical steroids are required. This increases the risk of food allergy; it is a risk factor. It is part of the atopic phenotype but the eczema is not being driven by these food allergies because these children aren’t eating those foods.

Dr. Chubarova: That is exactly what I am saying, that the child has an allergic phenotype, maybe sensitization to some other antigen and then he gets another one. It is not surprising that he became sensitized to peanut. Everybody knows that when a child has an allergy to one antigen, the risk of allergy to other antigens increases.

Dr. Lack: That is true to a certain extent but not invariably so. Yes, there is an association between egg and peanut allergy; there is a much higher association between peanut, tree nut and sesame seed allergy; there is very little association between milk allergy and peanut allergy. Whether these differences can be explained by epitope spreading or common T cell epitopes, is not known. There are homologous sequences for some of the major allergens in peanuts and tree nuts and perhaps in sesame seeds. The acquisition of other food allergies may be related to structural similarities in a whole group of food proteins. It may also be that by tolerizing to one food there could be cross-tolerance to a group of structurally related foods. Just the way there is cross-sensitization between birch pollen and fruits, there may be cross-tolerance.

Dr. B. Koletzko: You deserve to be applauded for your intervention study. Are you taking into account whether some of these infants are still breastfed when peanut allergen is introduced? Swedish pediatricians claim that the risk for celiac disease is much lower when limited amounts of wheat protein are introduced while infants are still being breastfed, rather than introducing wheat protein after weaning. What is the practice in Israel? Is it possible that the introduction of peanut allergen during or after breastfeeding might affect the risk of developing an allergy to peanuts?

Dr. Lack: All geographical differences in PA might be explained on the basis of different breast-feeding patterns. Actually if that was the case, then it would be expected to have an influence in a nonallergen-specific way and a reduction in egg and milk allergy would be expected, but the levels of egg and milk allergy are very similar. There does not appear to be a difference in duration of breast-feeding in countries with very different prevalence of PA. It is interesting that the use of hypoallergenic formulae and soy formulae is also very similar in terms of the types introduced and the age at which they were introduced. Therefore we don’t think that that is going to have an important effect. Adam Fox looked at maternal consumption during breastfeeding and his data didn’t suggest that this was relevant.

Dr. Nowak-Wegrzyn: I want to go back to your comment on IgE sensitization to peanut in children with atopic dermatitis. Many children that we see with atopic eczema don’t have obvious acute reactions when they eat milk or egg on a regular basis. However, if milk or eggs are removed from the diet for 2 weeks and are then reintroduced under supervision (oral food challenge), then acute reactions can be seen. If there is complete tolerance to food, it doesn’t matter if it is eaten every day or once a year. I am curious whether these children with atopic dermatitis are truly permanently tolerant to peanut regardless of the frequency of peanut ingestion?

Dr. Lack: These infants are eating it very regularly and that is what is fascinating. At the moment the question is whether this is really allergy to peanut or is it low-affinity cross-reactive IgE to some other food? We are planning a study with Hugh Sampson as a collaborator, in which we will be able to look at IgE epitopes to peanut in sensitised and allergic children. We are also looking to see whether this is functional.
or nonfunctional IgE by purifying the IgE from the serum, adding the IgE to basophils and adding peanut antigen. One of the central questions in allergy is why sensitisation occurs in some children who remain asymptomatic despite exposure to allergen.

Reference