

Hypoallergenicity: A Principle for the Treatment of Food Allergy

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Abstract

Food allergy is a common disease with the treatment of choice being complete avoidance of the incriminated food. In cow's milk allergy a hypoallergenic milk substitute is necessary during infancy and childhood. Hypoallergenic formulas are produced through enzymatic hydrolysis of different sources such as bovine casein or whey followed by further processing such as heat treatment and/or ultrafiltration. According to the degree of protein hydrolysis the resulting products have been classified into 'extensively' or 'partially' hydrolyzed. Reduction of allergenicity should be assessed in vitro and in vivo. Hypoallergenic formulas might also be based on amino acid mixtures. These elementary diets can be considered as nonallergenic. Several novel therapies are currently being explored in food allergy. One of the most promising approaches is the immunotherapy with mutated proteins. For this approach, alteration of the IgE-binding sites through single amino acid substitution is performed resulting in reduced to complete loss of IgE binding. For the major peanut allergens such mutations were introduced into the cDNA sequences and successfully expressed as hypoallergenic recombinant proteins. In peanut-sensitized mice, the use of these modified proteins co-administered with adjuvant such as heat-killed *Escherichia coli* showed promising results for future therapeutic approaches.

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Introduction

Food allergy is a major public health issue. About 6–8% of children and 1–2% of adults are affected. The prevalence rate is even higher in patients with atopic dermatitis with around one third of these children having a clinically relevant food allergy [1]. Despite the enormous diversity of the human diet, few foods are responsible for the vast majority of food-allergic reactions. Cow's milk, hen's egg, soy, wheat, peanut, tree nuts, fish and crustaceans are the most commonly offending foods. The characterization of

these allergenic food proteins has increased dramatically within the last several years [2].

The majority of food-allergic reactions are IgE-mediated. Food proteins bind to the allergen-specific IgE molecules residing on mast cells and basophils and trigger the release of mediators, such as histamine, and an acute onset of symptoms occurs. Clinical reactions to these foods range from mild skin symptoms to life-threatening anaphylactic reactions.

The majority of children with food allergy will become tolerant later on in life. However, the natural course is different for each allergen. Most cow's milk-allergic patients will develop symptoms in the first year of life, but about 85% become clinically tolerant by their third year [3]. Hen's egg allergy appears to be more persistent with approximately half of the patients becoming tolerant in 3 years and up to two thirds of children in 5 years [4]. In contrast, peanut allergy tends to persist throughout adulthood; only about 20% of patients will lose their allergy [5, 6].

Today, the treatment of choice for food allergy is complete avoidance of the incriminated food. In the case of some food allergens there will be no nutritional problems; however, during infancy and childhood an alternative hypoallergenic milk substitute is necessary in children with cow's milk allergy. Moreover, a strict elimination diet is always difficult. Dietary failures occur frequently resulting sometimes in severe reactions. Therefore, new therapeutic approaches especially for the long-lasting peanut allergy are currently under development. One of these approaches is an immunotherapy with the mutated hypoallergenic proteins.

The following paragraphs will describe how hypoallergenicity can be used as a principle in the treatment of food allergy. First, current knowledge on the use of hypoallergenic formulas for the treatment of cow's milk allergy is described. Second, novel therapeutic approaches with mutated proteins are discussed.

Hypoallergenic Formulas for Cow's Milk Allergy

Cow's milk allergy is the most common cause of food allergy in the first years of life, affecting approximately 2–3% of children [7]. The majority of children outgrow their cow's milk allergy by 3–4 years of age [3]. Currently, the only treatment is strict avoidance; however, a hypoallergenic substitute is necessary at this young age.

Milk of another animal source such as goat or sheep cannot be recommended as a general substitute in cow's milk allergy. For example, many proteins in goat milk show a high similarity with cow's milk proteins resulting in a cross-reactivity of 92% [8]. Therefore, patients might react severely at first exposure. In contrast, cross-reactivity with mare's milk occurs only in about 4% [8]. Furthermore, soy formula may provide a safe and growth-promoting

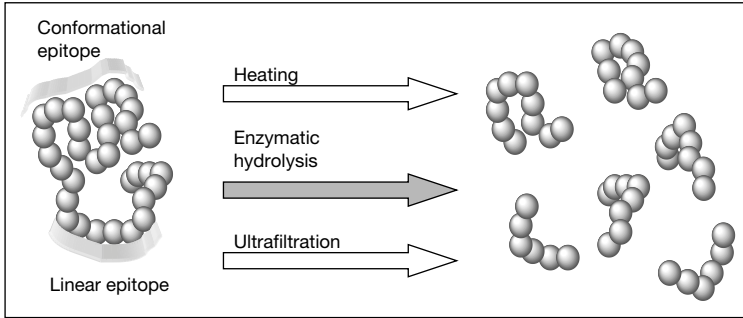


Fig. 1. Technologies to reduce the allergenicity of a protein. Hypoallergenic formulas are produced through enzymatic hydrolysis of different sources such as bovine casein, bovine whey or soy followed by further processing such as heat treatment and/or ultrafiltration.

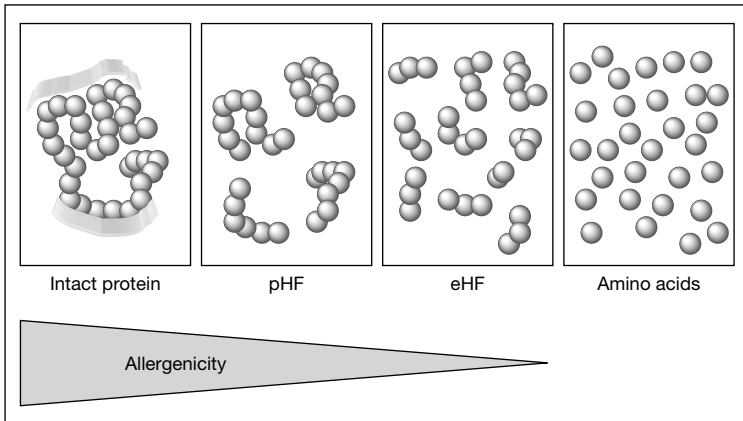


Fig. 2. Hypoallergenic formulas have been classified into ‘extensively’ (eHF) or ‘partially’ (pHF) hydrolyzed formulas according to the degree of protein hydrolysis. Hypoallergenic formulas might also be based on amino acid mixtures.

alternative for children with cow’s milk allergy [9]. However, soy is a potent allergen itself and sensitization resulting in allergic reactions might occur.

For many years hypoallergenic formulas have been used in cow’s milk allergy. As shown in figure 1 hypoallergenic formulas are produced through enzymatic hydrolysis of different sources such as bovine casein, bovine whey or soy followed by further processing such as heat treatment and/or ultrafiltration [10]. The resulting products have been classified into ‘extensively’ or ‘partially’ hydrolyzed formulas (fig. 2) according to the degree of protein

hydrolysis [11]. The degree of hydrolysis may be characterized by biochemical techniques, such as the spectrum of peptide molecular weights or the ratio of alpha amino nitrogen to total nitrogen [10]. Assuming the theory that the shorter the peptides the less allergenic the product, much work has been done to determine the molecular weight of residual peptides in the hydrolysates [12]. As a practical guideline for industry the appropriate cutoff for the absence of larger peptides has been determined to be approximately 1,500 Daltons [12].

Anaphylactic reactions have been reported not only for partially hydrolyzed formula but also for extensively hydrolyzed ones; therefore, reduction of allergenicity should be assessed *in vitro* and *in vivo* [13]. Residual allergenicity can be explained by the degree of hydrolysis. Peptides representing IgE-binding sites might still be present. In addition, higher-molecular-weight particles that might be allergenic can occur in hydrolyzed formula through aggregation of smaller peptides [14]. Moreover, contamination with native proteins during production of the hypoallergenic formula is possible.

Reduction of allergenicity of dietary products may be assessed *in vitro* using various immunological methods, such as IgE-binding test, inhibition assays or immunoelectrophoresis methods [10]. Especially hypoallergenic formulas used for treatment in cow's milk allergy should undergo clinical *in vivo* testing. Skin testing should be the first step followed by challenge tests [15]. Suitable hypoallergenic formulas should be tolerated by at least 90% of infants with documented cow's milk allergy with 95% of confidence in double-blind placebo-controlled food challenges. It is recommended that trials should be performed in two independent centers, and be divided into IgE- and non-IgE-mediated cases before statistical treatment [15]. For each type of allergy ≥ 28 patients should be included in each trial [15]. If 1 patient reacts, 46 subjects must be included and the remaining 45 must be without reactions. In order to ensure long-term tolerance a normal daily intake during a period of 3 months is recommendable. In addition, the nutritional value of the products has to be documented.

Hypoallergenic formulas might also be based on amino acid mixtures (fig. 2). These elementary diets can be considered as nonallergenic. They do not need any clinical testing provided the production is sufficiently controlled assuring no contamination [15]. The hypoallergenicity and the nutritional value of such elementary diets have been documented [16].

Specific Immunotherapy for Food Allergy with Mutated Proteins

Currently the only treatment for food allergy is strict avoidance of the offending food. In the past years much effort has been made to develop new treatment methods. Specific immunotherapy using injections is commonly used for the treatment of inhalant allergies. However, for food allergy it is

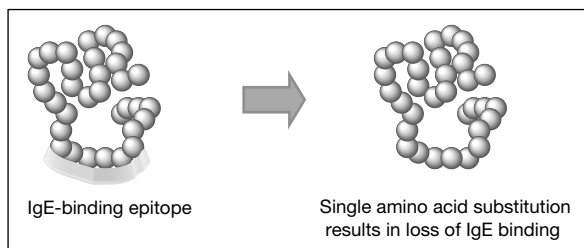


Fig. 3. IgE-binding sites have been identified for many food allergens. Mutation through single amino acid substitution at these binding sites resulted in reduced to complete loss of IgE-binding.

currently not recommended because of the allergic side effects of the therapy. A study by Oppenheimer et al. [17] showed that patients with peanut allergy tolerated an increased amount of peanuts following a rush immunotherapy but an unacceptable rate of adverse systemic reactions occurred.

As traditional immunotherapy has been largely impractical for the treatment of food allergies, several novel therapies are currently being explored [18, 19]. One of the most promising approaches is the immunotherapy with mutated proteins. Within the last couple of years food allergens have been better characterized [2, 20]. IgE-binding sites have been identified for many of these food allergens [21–26]. With this knowledge attempts to alter IgE antibody binding through alteration of the amino acid sequences of the IgE-binding sites have started (fig. 3). Mutation through single amino acid substitution resulted in reduced to complete loss of IgE binding [26–29]. For the major peanut allergens Ara h 1, Ara h 2 and Ara h 3 such mutations were introduced into the cDNA sequences and successfully expressed as hypoallergenic recombinant proteins [18]. Most importantly, mutation of the IgE-binding sites appears to leave the T cell response unaffected [30].

In peanut-sensitized mice, the use of these modified proteins showed some protection; however, alone it did not appear to be adequate for the treatment of peanut allergy [19]. However, using co-administration of modified peanut proteins and heat-killed *Listeria monocytogenes* as an adjuvant resulted in much better protection [19]. However, although modified proteins reduce the concern regarding activation of mast cells during immunotherapy, the safety of subcutaneous injections of heat-killed *L. monocytogenes* remains to be determined. Another promising approach appears to be the rectal administration of mutated proteins with heat-killed *Escherichia coli* as an adjuvant. This novel immunotherapeutic approach has the benefit that expensive purification of the engineered proteins generated in *E. coli* is not necessary because it is administered into an environment replete with *E. coli* [19].

Although animal studies using mutated hypoallergenic proteins seem to be very promising, studies in humans will be necessary to prove the effect.

Heterogeneity in IgE-binding sites and amino acids critical for IgE binding as shown for cow's milk proteins [29] might lead to problems that need to be addressed in the future.

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Discussion

Dr. Bojadzieva: I would like to ask if all these skin tests are valid for the first year of life, especially for the first 6 months of life? We know as pediatricians that sometimes cow's milk allergy can be only manifested with diarrhea, with other skin manifestations, and we also know that the immunologic reaction in the bowel is not the same as in the skin.

Dr. Beyer: In general it is possible to perform skin prick tests in children in the first year of life. However, age differences have to be taken into account [1]. In regard to gastrointestinal diseases, many of them are non-IgE-mediated. In these cases the skin prick test will not help you. Most important is the double-blind placebo-controlled food challenge test.

Dr. Sorensen: I was fascinated looking at the experiments with the mutated proteins that you discussed, but I am not sure really if you can say that you induce tolerance versus desensitization. Second, if you tolerize against the native protein, are you implying that you can use a mutated protein to then induce tolerance to the native protein?

Dr. Beyer: It is always a big discussion whether tolerance is induced. The aim is to use the modified proteins for specific immunotherapy to avoid immediate reactions. Whether tolerance can be induced has to be shown with future studies.

Dr. Sorensen: First of all I do not give allergy immunotherapy in general if I can avoid it. Second I think that the aim of immunotherapy is to induce tolerance, meaning that the time between the last deliberate allergen exposure of the individual and the challenge is long enough to exclude desensitization; that is then true tolerance.

Dr. Beyer: Common specific immunotherapy with aeroallergens is performed for about 3 years in which the individuals will gain tolerance that last for many years. This is what we aim for in food allergy with different approaches, e.g. therapy with mutated proteins or specific oral tolerance induction where children are fed with increasing amounts of food.

Dr. Sorensen: I think that tolerance has to be differentiated. Is it clinical tolerance or T cell tolerance? That was discussed earlier but you may have intense T cell reactivity and clinical tolerance.

Dr. Lack: You spoke very nicely about the different amounts of protein fractions in hypoallergenic formulae. But of course the main hypoallergenic formula is breast milk which the WHO recommends until 6 months and we recommend as pediatricians. We know that it can contain cow's milk proteins and other food proteins and cause symptoms. How important do you think those are, what sort of levels do you think they can be detected at and how careful should we be about controlling maternal diet in our treatment?

Dr. Beyer: I would distinguish two things, treatment and prevention. We never would recommend a partially hydrolyzed formula for a therapeutic approach in a cow's milk-allergic child but it might be a completely different story for prevention. The same with breastfeeding, we recommend breastfeeding for a time period of 4-6 months. We know that what the mother eats is normally also found in the breast milk, however, we do not recommend dietary restrictions.

Dr. Lack: I am actually talking about treatment, not prevention.

Dr. Beyer: In case an infant is fully breast-fed but diagnosed for example with clinical relevant hen's egg allergy an elimination diet for the mother would be recommended because enough protein might get to the child with the breast milk to induce symptoms.

Dr. Heine: You mentioned the double-blind, placebo-controlled food challenge as the 'gold standard' of diagnosing food allergy, but in clinical practice it is often unreliable, and you may end up with dubious results or false-positives. How do you get around this issue, how can you actually confirm 100% whether, for example, someone is intolerant to extensively hydrolyzed formula?

Dr. Beyer: I think there is no 100% certainty. At the moment the double-blind placebo-controlled food challenges are the best way to go in most cases. There might be false positive reactions, this is why we perform it placebo controlled.

Dr. Mason: Have you any experience in the use of transfer factor in cow's milk allergy or in food allergy? Is it useful in this situation as a transfer factor in aeroallergens?

Dr. Wahn: This is an old immunological story. I think it addresses my age group a little bit. It was an attempt to provide immunomodulation and it is really interesting to hear that younger scientists don't know this anymore. Twenty years ago you would not have had to explain this.

Dr. Mason: Many pediatricians use it to treat aeroallergies and I don't know if they are using it in gastrointestinal allergies.

Dr. Haschke: This might be a slightly provocative remark. We are discussing formulas which can be used in treatment but we must be clear that less than 10% of children have access to these formulas. There are countries where even if people could buy the formulas, they are not available due to regulatory issues but most people have no access whatsoever. Now fortunately most children born in so-called Third World and emerging countries are breastfed for even longer than 6 months, which minimizes the problem to a certain extent. Industry is challenged to look for cheaper sources of so-called hypoallergenic proteins. So far we only have soy formulas which to a certain extent might help, but unfortunately we have never gone into detailed research looking for other sources like rice protein, which is probably an alternative and affordable choice and could be cheaply fortified with amino acids. What might be alternative protein sources for such formulas?

Dr. Beyer: It is a very difficult question because you have to consider a lot of things in relation to nutrition. Can nutrition for the child be provided by the different

protein sources? It is really hard to do because the same clinical trials are needed to determine if the protein source is hypoallergenic.

Dr. S. Koletzko: You showed us this nice experiment changing only one amino acid in your proteins. Now does this happen in nature? In other words: if we talk about milk or egg, are they from the immunological point of view always the same or do we have spontaneous mutations between proteins from different cows and hens?

Dr. Beyer: Each of the proteins I just showed you has a lot of isoforms. Some of the isoforms are more allergenic than others. Comparing these different isoforms, it is interesting enough to see whether in nature there already are differences that account for less allergenicity. But it is very complex to do research this way because you would have to sequence all the different isoforms and this is very costly and time-consuming.

Dr. S. Koletzko: What does it mean from the clinical point of view? We perform a double-blind placebo-controlled egg challenge and no reaction occurs. We send the child home and it has a severe reaction to egg because there is a different protein in the egg?

Dr. Beyer: No, this is not the way. Normally the egg, as long it is from a hen, should behave the same whether it is eaten in Germany or in the United States. The same hen's egg protein has different isoforms that are more or less allergenic. Replacement of amino acid exists, but the content of the different isoforms are usually similar.

Dr. Kamenwa: You already answered my question because I was going to ask about alternatives in poor countries like mine because these formulas are actually very expensive for most of our population. My comment is on the prevalence of food allergies in the world. There are no data for Africa mainly due to little research if any in this area of food allergy in children. The prevalence is more or less the same. We have a lot of allergies to cow's milk protein, eggs and common weaning foods such as corn and bananas.

Dr. Beyer: I would be happy to include any data from other parts of the world because I think it is very important to know the main allergens. It is very interesting that cow's milk is a major allergen throughout the world.

Dr. Shaaban: Don't you think that there is a basis for genetics in food allergies? In Africa where I come from we consume a lot of peanuts and there is no prevalence of this allergy. You showed that there is some allergy to sesame seeds, and although we consume it we don't have this allergy. Have you ever thought about camel's milk? It is very expensive but very nutritious.

Dr. Beyer: Let's start with camel's milk first because this is a very interesting topic. In southern Germany, near Stuttgart, there is a camel farm. I talked to the farmers there because they see it as a source of hypoallergenic milk.

Dr. Shaaban: The cross-reactivity is not like goat's or sheep's milk?

Dr. Beyer: No, it is said that the cross-reactivity is more like mare's milk although I do not know studies about it so I have to be a bit cautious. However, we do not normally recommend such milk for children because we don't want to make them allergic to a new source. Regarding genetics and peanuts, you know that the genetic background is important. However, it is not everything. There must be other, e.g. environmental factors involved.

Dr. Balanag: As Dr. Haschke said earlier there are very limited alternatives if you don't have any other source of protein. You have given children less than 6 months of age soy-based milk. What is the importance of age as a risk factor?

Dr. Beyer: These of course are recommendations for Germany. We are a fortunate country that we have these products available on the market. This might be different of course in other countries. However, we know from a nutritional aspect that soy,

especially in the first 6 months, might not be as good as cow's milk based formula. But before I would give anything to a child in a country where nothing else is available, I might switch to a soy formula to see if the child will tolerate it. What do you think, Dr. Koletzko?

Dr. B. Koletzko: Allow me to refer you to the recent comment of the ESPGHAN Committee on Nutrition on the use of soy protein-based formula [2]. The Committee appreciates that soy-based formulae are far cheaper than therapeutic hydrolysate formulae, and therefore for economical reasons it may be a choice for families that cannot afford hydrolysates under circumstances where the health care system does not offer reimbursement. However, in our comment we clearly emphasize soy formulae are a secondary choice for a number of reasons, including nutritional considerations. The high phytate content found in many soy formulae has been showed to reduce the bioavailability of zinc, iron and iodine. Soy formulae tend to have 10–100 times higher aluminum intake than cow's milk formulae, raising concerns about long-term effects. Moreover, soy formulae contain very high levels of phytoestrogens, suppling amounts in the order of 6–12 mg/kg/day to a 4-month-old infant fed such formulae. This results in about 100–300 times higher phytoestrogen levels in the serum of infants fed soy formulae than in breastfed infants, and 50–150 times higher levels than found in infants fed cow's milk-based formulae. In rodents such high serum levels of phytoestrogens significantly reduce antibody responses. Moreover, a follow-up study by Strom et al. [3] reported that the use of antiasthmatic drugs was twice as high in adult women who had been fed soy formula as infants than those fed cow's milk formula. A study by Ford et al. [4] reported that feeding soy formula is associated with later autoimmune disease of the thyroid. All these data do not provide hard and conclusive evidence, but they raise sufficient concern to let it appear prudent not to use soy formula preferentially in young infants during the first months of life.

Dr. Beyer: But would you also then recommend it if nothing else is available, even in children younger than 6 months of age?

Dr. B. Koletzko: I certainly agree that soy-based infant formula is far better than feeding unmodified animal milks, and that the level of concern is highest in younger infants.

Dr. Nowak-Węgrzyn: I have a comment pertaining to Dr. Lack's question regarding breastfeeding and allergy. It is very important to emphasize that breast milk is the gold standard for infant nutrition. It has been shown to be protective in several forms of food allergy. For instance we have never seen a severe form of food allergy such as food protein-induced enterocolitis in children who are breastfed. However it is also well documented that breast milk contains foods that mothers eat. Peanut, egg and milk proteins in the breast milk are predigested and different (less allergenic) from those proteins in the foods that are fed directly to the infants. So the recommendation regarding a restricted diet for the mother has to be based on whether the child developed food allergy while being exclusively breastfed. If this is the case, the child most likely is reacting to the sequential epitopes. These children tend to have more severe and long-lasting food allergy, and therefore extreme avoidance is necessary.

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