

Animal models of food allergy

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Purpose of review

The focus of this review will be on recent animal models of food allergy. Animal models are being used to investigate underlying mechanisms of IgE-mediated disease and for prophylactic/intervention therapies to treat allergic disease.

Recent findings

Considerable advances have been made in the dosage and use of sensitization routes with and without adjuvant and determinations of the pathophysiology of food allergy in murine, dog and swine food allergy models. Continued research on the neuroendocrine and novel immunoregulatory peptides is also providing new insight into inflammatory regulation and immunity. With the advent of genetically modified food crops, animal models are becoming a central theme for prediction/assessment of allergenicity for novel proteins based upon known food allergens. Therapeutic strategies involving cytokine and allergen, DNA immunizations and the use of probiotics are receiving new interest.

Summary

Although murine models still predominate the literature with respect to animal models of food allergy, the atopic dog and neonatal swine model are contributing knowledge with respect to symptoms more closely related to human allergic responses. Continuing investigations into the mechanisms of IgE-mediated food allergy and therapeutic strategies are providing new insights into prevention and intervention therapies for food allergy.

Keywords

food allergy, animal models, allergenicity

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Abbreviation

SCF stem cell factor

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Introduction

Food allergy is a pattern of immune reactivity to the ingestion of natural food components resulting in IgE-mediated food allergy, which by nature routinely results in tolerance. To determine the immunoregulatory mechanism of clinically relevant gastrointestinal immediate hypersensitivity, to develop predictive roles for food and novel proteins in immune sensitization/allergic responses, and to offer therapeutic options for the treatment of food allergy, numerous animal models have been evaluated. Murine, swine and dog models have been used to assess routes of administration for sensitization as well as for the definition of the gastrointestinal allergic response. Each model contributes significant information with the most recent findings showing routes of administration, dosage and timing for sensitization to be relevant factors in obtaining a clinical response to oral challenge that mimics that of the human response. A critical role of epithelial and mast cells involved in immunoregulatory mechanisms has contributed significant information on gastrointestinal dysfunction attributed to IgE-mediated food allergy. The introduction of genetically modified foods resulted in an extensive series of investigations to determine the potential allergenicity of newly introduced proteins in animal models. Although there is no validated animal model to address protein allergenicity, strains of rats and mice with genetic backgrounds that predispose them to IgE-mediated food allergy are contributing to the knowledge of food protein-induced allergy. In the absence of acceptable treatments for food allergy, animal models, in particular rats and mice, are being used to determine prophylactic and therapeutic strategies to eliminate or reduce the allergic response.

The immunopathogenesis of food allergy may be driven by more than one immunological mechanism, including immediate hypersensitivity (manifestations mediated by IgE), delayed hypersensitivity (reactions associated with specific T lymphocytes), and inflammatory reactions caused by immune complexes. For a variety of reasons, there are very few mechanistic investigations in humans to determine the sensitization and allergic responses of IgE production to innocuous food proteins. Recently, the development of genetically modified crops as sources of human food raised the safety issue of gene products inserted into crop plants having the potential to cause allergic sensitization. In this review, animal models and methods being used to investigate the mechanisms to bypass the innate tendency to develop tolerance to ingested proteins and initiate food hypersensitivity, to

predict the allergenicity of novel proteins, and to treat food allergy by immunotherapeutic strategies to alleviate life-threatening reactions will be presented.

In several previous studies, the Brown Norway rat, atopic dog, and several strains of mice have been used to show antigen-specific IgG and IgE responses after the administration of food allergens. For these studies the reader is referred to articles by Knippels [1], Ermel and Frick [2], Dearman and Kimber [3], and Li and Sampson [4]. Many such studies set the foundation for the manuscripts that are the subject of this review. Studies directed more towards characterization and the mechanisms of food allergy will be presented in the following section.

Mechanistic studies

Food allergy, defined as the ability to induce specific IgE antibody of sufficient avidity/affinity to cause sensitization and upon re-exposure to induce an allergic response, will be highlighted in this section. Akiyama *et al.* [5•] administered ovalbumin in the absence of adjuvant by gavage or drinking water, followed by intraperitoneal challenge to assess active systemic anaphylaxis in Brown Norway rats and three strains of mice. The route of administration and age had a profound effect on sensitization in BALB/c mice. Daily gavage doses of 1 mg compared with 5 mg/ml ovalbumin via drinking water for 9 weeks produced a stronger ovalbumin-specific response; however, both sensitization protocols produced significant increases in serum histamine levels. Twenty-week-old mice exhibited pronounced serum titers of ovalbumin-IgG1 and IgE and serum histamine levels compared with 7-week or 1-year-old mice, with the serum histamine levels correlating mainly with the increase in ovalbumin-specific IgG1. Similar but more varied results were obtained in Japanese source strain of ASK mice. In B10A mice, serum histamine increases correlated mainly with increases of ovalbumin-specific IgE in 0.1 mg ovalbumin-gavaged mice compared with 1.0 mg gavaged mice. The oral administration of ovalbumin in the drinking water was unsuccessful. The authors concluded that low doses (0.004 mg/g body weight) by gavage primed the animals for systemic immune responses. Serum histamine was determined to be a good marker for acute systemic anaphylaxis (ASA), and both Brown Norway rats and the B10A strain of mice were suitable animal models for investigating IgE-mediated allergenicity.

The late-phase allergic reaction in horseradish peroxidase-sensitized and orally challenged Sprague–Dawley rats revealed abnormal jejunal mucosal pathophysiology and inflammation several days after the acute reaction [6•]. In the acute phase, rat mast cell protease and IgE serum antibody titers were elevated. Thirty minutes

after antigen challenge, mononuclear cells increased dramatically, and by 48 h the cell number had increased approximately 10-fold that of controls. Accompanying this cellular infiltration was a noticeably altered mucosa, with swelling of the villi, obvious edema, detachment of epithelial cells from the underlying tissue, and enhanced permeability for at least 72 h.

Physical symptoms, serum IgE, skin testing and histological assessment of the small intestine during peanut sensitization in the acute allergic phase of a swine food allergy model revealed similar denudation of the villi, edema of the submucosa, and vascular congestion [7].

In such studies, mast cells were proposed to be critical to the mucosal barrier dysfunction, and could result in the greater non-specific uptake of luminal antigens/microbial products with the potential to exacerbate inflammatory responses. Further evidence and mast cell activity that may regulate/modulate inflammatory conditions can be found in studies performed by Forsythe *et al.* [8] and Stenton *et al.* [9]. A neuroendocrine control of allergic reactions has also been under investigation by that group, and it may offer insight into the regulation and modulation of life-threatening anaphylactic reactions. Mathison *et al.* [10•] showed that a tripeptide (feG), a D-isomeric form of the salivary gland tripeptide (FEG), released from the submandibular gland, inhibits gastrointestinal motility in ovalbumin-sensitized hooded-Lister rats. feG offered the best protection when administered prophylactically, and could be used to prevent amplification and shorten the duration of intestinal anaphylactic reactions [11].

Naturally occurring allergic skin disease in dogs is similar to human atopic dermatitis, and IgE-dependent food-related atopic dermatitis is well documented in both humans and canines. In both humans and canines, primed effector cells distinguish atopic from non-atopic conditions. Moreover, stem cell factor (SCF) has been shown to enhance the human and canine mast cell degranulation response to the cross-linking of high-affinity receptors for IgE (FcεRI). Immunohistochemistry studies of skin biopsies from atopic and non-atopic dogs revealed an obvious difference in SCF that led the authors to suggest that higher levels of SCF production in the skin of atopic dogs was the cause of the hyperexcitability of skin mast cells [12]. Skin cell preparations from normal dogs showed significant spontaneous histamine release in the absence of IgE, suggesting that IgE occupation of the high-affinity receptor might lower spontaneous release. The role of SCF and mast cell hyperexcitability in this dog model is being used to address the question of whether there is an increased sensitivity to SCF or increased production

of SCF in canine atopic dermatitis. In a subsequent paper [13], canine atopic dermatitis was shown to be associated with more variability in circulating monocytes and lower numbers of monocytes expressing IgE than control dogs. A significant difference in this model and human reports is that total serum IgE concentrations did not correlate with cell-bound IgE.

Various reports suggest an immunomodulatory effect of milk proteins. An oral administration of a whey protein extract was shown to downregulate immune activation (spleen cell proliferation with transforming growth factor beta production and reduced MHC-1 expression) to orally administered ovalbumin in suckling rats [14•]. The authors speculated that growth factors present in whey milk could be a potential benefit for formula-fed infants in reducing the susceptibility to inappropriate activation to food allergens. Intestinal anaphylaxis as a criterion of allergic sensitization in a guinea pig model suggested that the allergenicity of milk may vary according to the proportion of constitutive proteins [15•]. Goats' milk, devoid of α_{s1} -casein, had a lower sensitizing capacity and anti- β -lactoglobulin IgG1, suggesting that the use of goats' milk in cows' milk allergy could be a result of goats' milk proteins high in genetic polymorphism. The authors suggested that β -lactoglobulin, which is resistant to gastric pepsin hydrolysis, might be facilitated in the absence of α -caseins, as caseins and β -lactoglobulins are tightly linked into casein micelles.

At the 11th International Congress of Mucosal Immunology, a series of abstracts were presented that merit comment. A low/high dose of ovalbumin or peanut sensitization was used to investigate the induction of sensitization or oral tolerance in BALB/c mice [16]. Tolerance, as measured by the suppression of both Th1 and Th2 responses to peanut, required a 50-fold higher oral dose than ovalbumin. Low doses of peanut in comparison with ovalbumin were more likely to induce sensitization. The group also demonstrated that cutaneous exposure (abraded skin) to peanut induced both local and systemic antigen T cell proliferation [17]. Furthermore, tolerogenic feeding was shown to be time dependent, with the induction of oral tolerance apparently evident within 6 days after cutaneous exposure; however oral tolerance was prevented 3 weeks after topical exposure. Teixeira *et al.* [18] showed that the CBA strain of mice given a novel protein in their diet, while presenting with an inflamed gastrointestinal tract, resulted in systemic sensitization and high IgE titers. A crossreactive mucosal immune response to different legumes was investigated in a mouse nasal challenge model [19]. In peanut-sensitized mice, serum analysis by enzyme-linked immunosorbent assay detected minimal crossreactive IgE; however, all legumes tested demonstrated proteins that bound IgE by immunoblot.

Sensitization with peanut did not cause clinical symptoms with lupine, soybean or pea proteins by nasal challenge.

Activation of the gastrointestinal-associated lymphoid tissue, as analysed by the cytokine production of mesenteric lymph nodes and Peyer's patch cell culture, was demonstrated by two different oral administrations of β -lactoglobulin [20]. C3H/HeJ mice freely receiving β -lactoglobulin during a 4-week exposure were tolerized (IFN- γ production), whereas those receiving β -lactoglobulin plus cholera toxin demonstrated a shift to a Th2 response (IL-4 production). Immunohistochemical analysis of BALB/c mice large intestine tissue after the repeated oral administration of ovalbumin induced allergic diarrhea with high levels of IL-12 [21]. Interestingly, the administration of anti-IL-12 reduced the levels of ovalbumin-specific IgE and reduced the disease condition, suggesting that an overexpression of IL-12 could be contributing to allergic diarrhea. Helminth-infected mice demonstrated a marked reduction of peanut-specific IgE and anaphylactic symptoms that correlated with reduced IL-13 production in mice sensitized to peanut [22]. The authors concluded that helminth infection protected against allergic disease by involving immunoregulatory mechanisms blocking allergen-specific IgE. Tissues in Ussing chambers from horseradish peroxidase-sensitized rats or mice revealed an increased expression of CD23 protein and the uptake of antigen on epithelial cells [23]. The removal of IgE or IL-4 in passively sensitized mice abolished antigen uptake, suggesting that IL-4-stimulated expression of CD23 on epithelial cells was responsible for the rapid uptake and immediate hypersensitivity responses in food allergy.

Prediction studies

Beginning in 1996 with the advent of bioengineered food crops, decision trees to evaluate safety issues regarding our food supply led to recommendations, i.e. decision trees to assess the potential allergenicity of novel (biotechnology derived) proteins were being developed. From the outset, the development of valid animal models to test the potential allergenicity of novel proteins was recommended. In this section, animal models being developed to assign safety strategies for the direct evaluation of the potential allergenicity of novel proteins will be presented. Reports from several conferences and workshops have been undertaken in recent years, and should soon be available to interested individuals. The results of a 2000 National Center for Food Safety and Technology/Institute of Life Sciences Institute/Health Environment Science Institute (NCFST/ILSI/HESI) symposium in Summit, Illinois 'Genetically engineered foods: assessing potential allergenicity' can be found electronically on

www.annalsnyas.org. [24•,25–28]. A workshop organized in 2001 by National Institute Environmental Health Sciences (NIEHS), in association with the National Institutes of Health, Environmental Protection Agency, and Food and Drug Administration, to assess progress specifically related to the design and evaluation of animal models to determine the allergenic potential of genetically modified foods in the rat, mouse, dog and in swine has also been summarized [29]. A workshop/panel discussion at the 2002 Society of Toxicology, held to address progress for assessing strategies, including animal models, for potential allergenicity, was summarized by Ladics *et al.* [30]. The reader is also alerted to a report of the Health Canada Workshop on 'Animal models to detect allergenicity to foods and GM products', which is also in the constructive phases for publication.

Standardized toxicity testing and the tools necessary for immune studies in the rat offer advantages to developing a good model to obtain further information for oral allergy research. Immunoblotting experiments with serum obtained from Brown Norway rats orally sensitized to hens' egg white and cows' milk revealed antibody recognition profiles similar to those identified using serum obtained from humans having the same food allergy [1]. The inclusion of this article is to acquaint the reader with the investigations and contributions of Drs Knippels and Penninks in their development of the Brown Norway rat model as a predictive model for assessing novel protein allergenicity. Oral sensitization in Brown Norway rats to various allergenic food proteins in the absence of adjuvant resulted in antigen-specific IgE, local and systemic immune responses, and decreased respiratory function and blood pressure [31]. Although further testing is required to validate this model, the Brown Norway rat model is a promising model for food allergy determinations. In another rat model, the relative safety of genetically modified to the non-genetically modified soybeans was investigated. Based upon the annual consumption of soybean as a food in Korea, Chang *et al.* [32] sensitized Sprague–Dawley rats to either 2 mg/kg (low dose) or 20 mg/kg (high dose) genetically modified soybean versus non-genetically modified soybean homogenates. The results of passive cutaneous tests and histamine release from mast cells from rats receiving either of the soybean homogenates were similar, i.e. both appeared to be non-allergenic, confirming earlier reports that glyphosate-tolerant soybeans were as safe as conventional soybeans. To address hazard identification and humoral immune responses to novel proteins, a murine model is being used to distinguish immunogenic properties of novel proteins. Immune responses, regardless of the route of administration, are being undertaken to distinguish allergenic responses

(IgG and IgE production) versus antigenic responses (IgG in the absence of IgE production). An assessment of the inherent sensitization potential of proteins for hazard identification has been conducted by Dearman *et al.* [3]. A systematic approach to the routes of exposure and immunological responses (IgE and IgG) induced in Brown Norway rats and BALB/c mice by peanut agglutinin, ovalbumin, and a crude potato protein extract was undertaken. Despite confirmed immunogenicity (IgG production) and allergenicity (IgE production) of the three proteins by parenteral injection, Brown Norway rats failed to mount an IgE response to the proteins using gavage exposure. Gavage exposure in BALB/c mice elicited both an IgG and IgE antibody response to proteins in a ranking order of known allergenic potency, from a low, moderate to high sensitization/allergic response profile. However, a much more robust response was provoked by intraperitoneal administration of the same proteins [33]. These results suggest that the inherent sensitizing potential of novel proteins could be evaluated as a function of IgE responses in mice. Using BALB/c mice, the group also assessed the protein stability in simulated gastric fluid (SGF) to that of the allergenicity of two protein preparations, ovalbumin and a purified potato extract (PPE) containing potato acid phosphatase activity [34•]. A differential ability of two proteins to provoke immune responses suggested that rapidly degraded protein, PPE, compared with a more stable protein, ovalbumin, could explain why orally ingested labile proteins fail to invoke antibody responses, whereas those that are not rapidly degraded in the stomach may reach mucosal immune systems in the small intestine. However, PPE, which was rapidly degraded in SGF, was able to elicit a substantial IgG antibody response when administered orally. This evidence suggested that the association between stability in SGF and antigenic/allergenic potential may not be solely a function of the survivability of proteins in the gastrointestinal tract, and that additional factors such as regional enzymatic processing by antigen processing cells are critical to allergic sensitization.

Therapeutic options

As there is no established therapy to treat or prevent food allergy, a number of investigations are being undertaken in animal models. In a mouse model of peanut anaphylaxis, mouse recombinant IL-12 was used prophylactically (administered at the time of peanut sensitization) or therapeutically (3 weeks after sensitization) for the treatment of peanut allergy [35•]. Both regimens were able to reduce anaphylactic symptoms, with marked reductions in plasma histamine levels compared with non-treated controls. Prophylactic treatment with rIL-12 completely blocked peanut-specific IgE production and reduced levels of anti-peanut IgE in therapeutic treated mice. A protective immune response

(increased levels of IFN- γ and a switch to a Th1 antibody response) was also identified. Although the IgG1/IgG2a ratio was reduced in treated groups, the results were caused by a marked reduction in IgG1 rather than an increase in IgG2a. The role of peanut-specific sIgA is also discussed, with speculation concerning the protective effect of this antibody in the peanut anaphylaxis model. Similar reduced symptomatic scores, IgE levels, suppression of peanut-specific T cell proliferation and Th2 cytokine production (IL-4, IL-5 and IL-13) was evident with a therapeutic herbal formula treatment by intragastric gavage [36•].

DNA immunizations have received considerable interest in treating and preventing food allergy in animal models. A primary Th1-type immune response was shown in mice treated with β -lactoglobulin-encoding plasmid (pBLG) compared with control animals receiving β -lactoglobulin or control plasmid [37]. The efficiency of the preventative effect was highly time dependent requiring a single intramuscular administration and a latent period of 21 days, leading to the inhibition of IgE and an increase in specific IgG2a to β -lactoglobulin. Alum was used as an adjuvant for the presentation of the β -lactoglobulin in its native structure, and an association of the immunostimulatory sequence of the plasmid DNA was proposed as a likely reason for the Th1 orientation of the immune response.

With the inverse relationship between atopy and infectious disease, species of *Lactobacillus* have received considerable interest as a probiotic therapy in preventing food allergy. Shida *et al.* [38•] developed a novel IgE response model, ovalbumin-T-cell Receptor Transgenic mice (OVA-TCR-Tg mice), to investigate the regulatory role of heat-killed *Lactobacillus* originally isolated from humans. The intraperitoneal administration of heat-killed *Lactobacillus* during the ovalbumin oral sensitization period led to increased IL-12 production and inhibited both IgG1 and IgE production, resulting in reduced systemic anaphylaxis. These investigations may contribute to the anti-allergic mechanisms of lactic acid bacteria in the treatment of food allergy.

Conclusion

Murine animal models predominate in the literature with regard to the topics of food allergy reviewed in this article. The prominence is principally related to the better characterized immunology, ease of handling, and lower cost to the investigator, permitting a greater degree of flexibility in protocol design. Strain difference, route of administration and expected clinical symptoms are still problematic, and are often not reproducible depending upon experimental designs and the food source or allergen. Results from high IgE-producing dogs and the similarity of natural food allergic immune responses in

both swine and canines to humans suggest that these higher animal species could be used to assess immunoregulatory mechanisms and the relative allergenicity of novel proteins. Animal models are increasingly being used to determine mechanisms to induce tolerance by way of prophylactic treatments as well as intervention or therapeutic options to reduce food allergy. In each report, significant information is made available that contributes to our knowledge of the immunopathogenesis of human food allergy.

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