

Hapten may play an important role in food allergen-related intestinal immune inflammation

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Abstract

There has been a significant increase in the prevalence of allergic diseases especially over the past 2 to 3 decades. However, the etiology and pathogenesis of food allergy are not fully understood. In recent years, with the huge increase in atopic disease, there has also been an increase in dietary hapten exposure. Allergic reactions to chemical haptens occur, in the overwhelming majority of cases, as an inflammatory reaction in the skin to direct contact with haptens. While reactions to haptens on other epithelial surfaces have only rarely been investigated; it is still not clear whether haptens can combine the food antigens and play a role in the induction of food allergen-related inflammation in the intestine. Further research is needed to reveal the underlying mechanism.

Keywords: Food allergy, dietary hapten, intestine, epithelial surfaces, inflammation, antigens.

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Introduction

It is estimated that 6~8% of the children, and 4% of the adult have immunoglobulin (Ig) E-mediated hypersensitivity to food Ag [1, 2]. The prevalence of food allergy has increased rapidly across the world in last few decades [3]. Research in the area of food allergy has advanced rapidly in recent years [4]. However, the etiology and pathogenesis of food allergy are not fully understood. Symptoms of food allergy vary from slightly abdominal discomfort to life-threatening anaphylactic shock reactions [3]. Food allergy reactions involve not only the intestinal tract, but other body systems as well, such as the skin [5], airway and cardiovascular system [6, 7]. The gastrointestinal tract has been described as the body's largest immunologic organ. A single epithelial layer lines the gastrointestinal tract and receives multiple daily exposures to a variety of proteins from foods and microorganisms [4]. Although antigen in the intestine exposures are complicated and frequent, the result of these exposures is tolerance or development of allergy when proteins do not luminal digested completely. There are several ways of encountering the immune system under

the epithelium. The dendritic cells under epithelial extend processes into the lumen and sample ingested antigen. M cells in Peyer's patches can take up particulate antigens and deliver them to dendritic cells [8]. Soluble antigens are thought to cross the epithelium through transcellular or paracellular routes directly leading to T cell or macrophage encounters. The timing of initial exposure to a food allergen also likely influences the development of tolerance. Oral antigen dose also seems important in determining which of two distinct effector mechanisms mediates the development of tolerance. In animal models, high doses of antigen lead to lymphocyte anergy or clonal deletion. [8]. Haptens are low molecular weight chemicals (usually less than 500 daltons), which are low reactive organic molecules that can bind to proteins and peptides, rendering them allergenic. Allergic reactions to chemical haptens occur, in the overwhelming majority of cases, as an inflammatory skin reaction to direct contact with the hapten. Reactions to haptens on other epithelial surfaces have rarely been described [9].

Intestinal sensitization is involved

in Th2 polarization

The key feature of food allergy is a Th2-predominant allergen-specific immune response, with the production of IgE antibodies specific for the food allergen. The T cells of T-helper (Th)2 phenotype are known to be involved in the development of allergic disease. Th1 cells release type 1 cytokines such as interferon (IFN)- γ , while the major cytokines secreted by Th2 cells are interleukin (IL)-4, IL-5, and IL-13. These cytokines play an important role in the production of antigen-specific IgE and in mucus secretion, muscle contractility, and eosinophilia [10]. Thus, the activation of Th2 cells is a critical step in the immune mechanisms of food allergy [11]. Yet it still remains unclear what are the initial steps of intestinal sensitization in human beings. The "hygiene hypothesis" postulates that limited exposure to bacterial and viral pathogens during early childhood results in an insufficient stimulation of T helper (Th)1 cells, which in turn cannot counterbalance the expansion of Th2 cells and results in a predisposition to allergy. While yielded conflicting results also raising the possibility that this model may be something of an over simplification [12,13]. Immunologic adjuvants are often included in vaccines to stimulate the immune system's response to the target antigens. Some studies showed that adjuvants such as pertussis toxins together with antigens [11, 14]. Cholera toxins, Freund's adjuvant, etc are necessary in developing allergic animal models. There is a causal relationship between the increasing environmental pollution and the fast increasing of allergic diseases. The exogenic and endogenic noxious agents contributing to the total environmental load are primarily acting through immunotoxic, sensitizing and neurotoxic mechanisms in animal experiments and in humans. Beside classic allergic-triggering factors, toxic environmental agents (formaldehyde, industrial and traffic smog, wood preservatives, microbial toxins, additive-rich food, nicotine, alcohol, pesticides, solvents, amalgam-heavy metals) are increasingly incriminated as causal factors for the complex symptomatology [15]. Studies showed that the intestinal mucosal barrier permeability is essential to prevent antigen uptake, while there are conflicting results concerning allergic diseases in inflammatory bowel diseases (IBDs), some studies suggest an increase of atopic diseases, whereas others have noted no difference from control populations [16].

Hapten exposure may influence the epitope and immunogenicity of the antigen

One explanation for the obviously increase in atopic disease in developed countries over the last 50 years has been the 'Hygiene Hypothesis'; a reduced exposure to pathogenic microorganisms. Hapten exposure via other surfaces such as the skin and airways might also be important in promoting atopic disease. the 'Hapten-Atopy Hypothesis' was put forward that oral and cutaneous exposure to chemicals generally and to haptens in particular, may have also contributed to the increased

prevalence of atopic disease [17]. Consistent with this hypothesis it is apparent that over 40 years, with the huge increase in atopic diseases, there has also been an increase in dietary hapten exposure through processed food, formula milk and oral antibiotic and drug uses. Local lymph node activation and increased total serum IgE levels are suggested to be predictive parameters of airway hypersensitivity caused by low molecular weight (LMW) chemicals. Studies [18] showed that increased total serum IgE after topical sensitization is associated with immediate-type specific airway reactivity after inhalation challenge in BN rats and thus may be a valuable parameter in testing for respiratory sensitization potential of LMW compounds. Other studies compared rates of atopic dermatitis between patients with allergic contact dermatitis arising out of individual fragrance chemicals with known oral/cutaneous exposure against exclusively cutaneous exposure. Their results showed that patients allergic to individual fragrances with dietary exposure have reduced rates of atopic dermatitis. This may indicate that patients with atopic dermatitis have heightened oral tolerance to dietary haptens, in contrast to the known close association of atopic dermatitis with food-protein allergy. Interactions with foreign proteins/haptens in the gastrointestinal (GI) tract have a tolerogenic influence on interaction elsewhere such as in the skin [19]. So they speculate that hapten exposure through the GI tract in the form of formula milk, antibiotics and food additives, through the skin in the form of skin care products and through respiratory tract in the form of airborne chemicals, will be potential to hamper any epithelial tolerance mechanisms to self-proteins and peptides, which may predispose to atopy/protein allergy while at the same time the haptens may induce self-tolerance [20].

TNBS as a representative hapten was adopted in the animal model inducing contact dermatitis and colitis

Trinitrobenzene sulfonic acid (TNBS) is a chemical hapten that binds to tissue proteins and is capable of stimulating cell-mediated immunity [21]. As a strong experimental sensitizer, TNBS was used in vitro in induction of allergic contact dermatitis [22], TNBS is a classical skin contactant which can induce delayed hypersensitivity reactions when applied to the skin because it hapteneates body proteins with trinitrophenyl (TNP) groups and renders such self-protein immunogenic to the immune system. While, when TNBS is introduced into the colon of susceptible mice via intra-rectal instillation, it induces T cell-mediated immune response in the colonic mucosa, in this case leading to a massive mucosal inflammation characterized by the dense infiltration of T cells and macrophages throughout the entire wall of the large bowel, TNBS-colitis is regarded as Th1 T cell-mediated inflammation [23, 24, 25]. Another study showed [26] that intratracheal (IT) inoculation of 2,4,6-trinitrobenzene sulfonic acid (TNBS) led to maximal ear swelling 24 hr

after challenge on the ear with 2,4,6-trinitrochlorobenzene (TNCB) in carrier. This response was specific for immunizing hapten. The possibility was speculated that the alveolar macrophages in the lung possess a similar capability for antigen presentation of hapten in the induction of allergic contact dermatitis as does the Langerhans cell. While it is still not clear whether TNBS as a representative hapten can combine the food proteins and play an important role in the inducing of food allergy, further research is needed to reveal the underlying mechanism.

Hapten may associate with the pathogenesis of food allergy

The intact protein antigens absorption into the intestinal tissue is regarded to be a prerequisite in the development of intestinal sensitization. Most food allergens are water soluble glycoproteins with molecular weight from 10-75 kD and stable proteins that are resistant to the intestinal digestive effects, and may be absorbed in a relatively intact form to be able to trigger an immune response [27]. Examples are ovalbumin (OVA) and milk casein protein. As a model food antigen, OVA is widely used in the development of food allergy in animal models [28, 29, 30]. Chemical haptens, in contrast with food proteins, are low molecular weight (usually <500 D) and have the ability to bind with proteins or peptides, rendering them antigenicity [9]. With the increases of atopic diseases, Dietary hapten exposure has distinctly increased in different ways, such as processed food, oral antibiotic, formula milk and drug use. Contact dermatitis to chemical haptens may occur when direct contact with the haptens [31, 32], while there are rarely studies about the reactions to haptens on other epithelial surfaces being reported. Cutaneous hapten exposure may also be important in the development of atopic dermatitis, one possible mechanism by which haptens interfere with protein tolerance is through their known ability to covalently bind to peptides and proteins and thus alter their immunogenic profiles [33, 34]. Thus, this modifications may cause atopic diseases, and most of the data are from experimental studies on contact allergy. If haptens do bind to skin proteins, then it may possibly be expected that these chemicals would also bind similarly to food proteins. It is still unknown about how hapten exposure on different epithelial surfaces such as the intestine, and the role of hapten in the pathogenesis of food allergy. Further experimental studies about the effect of hapten on oral tolerance to food proteins are needed.

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