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Oral tolerance and its relation to food hypersensitivities

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The gastrointestinal tract is the largest immunologic organ in the body. It is constantly bombarded by a myriad of dietary proteins. Despite the extent of protein exposure, very few patients have food allergies because of development of oral tolerance to these antigens. Once proteins contact the intestinal surface, they are sampled by different cells and, depending on their characteristics, result in different responses. Antigens might be taken up by Microfold cells overlying Peyer's patches, dendritic cells, or epithelial cells. Different cells of the immune system participate in oral tolerance induction, with regulatory T cells being the most important. Several factors can influence tolerance induction. Some are antigen related, and others are inherent to the host. Disturbances at different steps in the path to oral tolerance have been described in food hypersensitivity. In this review we provide an overview of oral tolerance and cite data related to food hypersensitivity wherever evidence is available. (J Allergy Clin Immunol 2005;115:3-12.)

Key words: *Oral tolerance, food allergy, food hypersensitivity, mucosal immunity, antigen uptake, intestine*

Abbreviations used
APC: Antigen-presenting cell
DC: Dendritic cell
M cells: Microfold cells
PP: Peyer's patch

The gastrointestinal tract is the largest immunologic organ in the body. It is lined by a single layer of epithelium. Underneath this epithelial layer are abundant numbers of lymphocytes interspersed in a loose connective tissue stroma. The surface epithelium is directly exposed to the external environment, the lumen, which is bombarded daily by a myriad of bacteria and dietary proteins. Despite the large extent of dietary antigenic exposure, only a small percentage of individuals have food allergy. This is due to development of oral tolerance to dietary proteins. Oral tolerance, as characterized by Chase[1] in 1946, refers to a state of active inhibition of immune responses to an antigen by means of prior exposure to that antigen through the oral route (Fig 1).

The journey for a dietary protein antigen involves multiple steps before T cells can respond to it and cause either tolerance or food hypersensitivity. After undergoing modification in the lumen, the antigen is in contact with specific antigen-presenting cells (APCs) with distinct activation requirements, which then help to activate regulatory T cells, resulting in the net suppression of an immune response. It is postulated that a breakdown in oral tolerance mechanisms or a failure of induction of oral tolerance results in food hypersensitivity. In this article we provide an overview of protein processing and uptake in the gut, the different mechanisms of oral tolerance to that protein, and finally the factors that influence oral tolerance. Throughout the review, we will provide data related to food hypersensitivity wherever evidence is available.

ANTIGEN PROCESSING AND UPTAKE IN THE GUT

Proteins are essential for nutritional homeostasis. A normal healthy adult requires approximately 0.75 g/kg/d of protein to maintain positive nitrogen balance and to provide essential amino acids.[2] It is estimated that the average North American daily diet provides 70 to 100 g of protein. These proteins are assimilated in an efficient manner after the action of gastric, pancreatic, and small intestinal brush border proteases, resulting in a reduction of the majority of dietary proteins to a mixture of free

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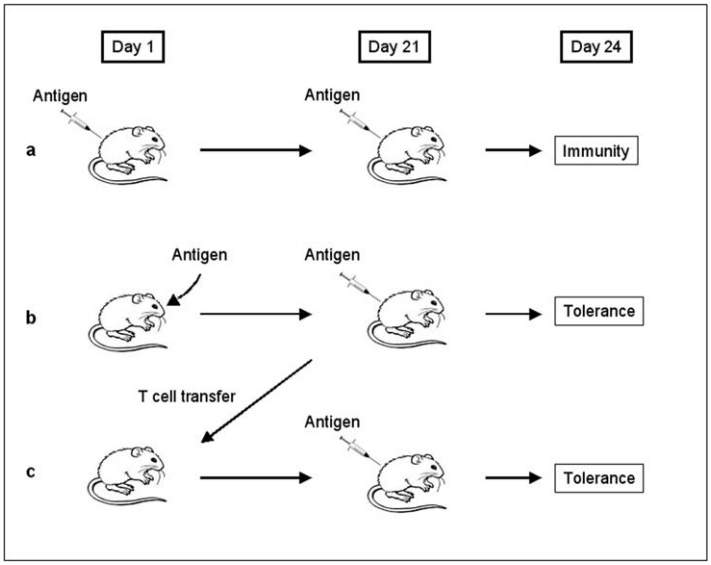

FIG 1. Induction of oral tolerance. **a**, When mice are immunized subcutaneously and then boosted subcutaneously with an antigen, strong *in vitro* cell-mediated and antibody responses to the antigen occur. **b**, When mice are first fed the antigen orally and then immunized subcutaneously, *in vitro* immune responses to the antigen are greatly reduced. **c**, When T cells from mice that were fed antigen are transferred to naive mice, subcutaneous immunization of these naive mice results in reduced *in vitro* immune responses as well. This shows that oral feeding of an antigen can induce a T cell–mediated active inhibitory immune response.

amino acids, dipeptides, and tripeptides, which are absorbed by intestinal epithelial cells.[3] Products of proteolysis, as well as intact proteins that escape digestion, can also be sampled by distinct immune cells, resulting in a state of immunologic tolerance through different mechanisms.

Antigen processing in the lumen

Ingested dietary proteins are subject to degradation and destruction of their conformational epitopes by gastric acidity and luminal digestive enzymes, resulting, in many cases, in the destruction of immunogenic epitopes (immunologic ignorance) to the protein. In animal models a disturbance in these factors has been shown to lead to food hypersensitivity rather than tolerance or ignorance.

To address gastric acidity, Untersmayr et al[4] examined the effect of antacids on food allergy induction in a murine model of gastrointestinal hypersensitivity to caviar proteins. Groups of mice fed caviar extract in combination with different types of antacids had significant levels of caviar-specific IgE antibodies and demonstrated positive immediate-type skin reactivity to the protein subsequent to immunization with the extract. Furthermore, T-cell reactivity to caviar was shown to be increased in stimulated spleen cell cultures. These responses were not seen in the group fed the extract without antacids, pointing toward a potential role of acidity in the prevention of allergies and possibly promoting tolerance.

The importance of digestive enzymes was demonstrated in an elegant experiment by Michael,[5] who observed that a peptic digest of BSA was tolerogenic when administered orally or directly injected into the ileum of mice. In contrast, untreated BSA was tolerogenic when administered orally but immunogenic after direct ileal administration. To address both acidity and digestive enzyme effects, Barone et al[6] were able to demonstrate interruption of already established tolerance to egg protein, ovalbumin, by protecting it from digestion through encapsulation in water-soluble, low-pH-resistant acrylic microspheres. This technique likely protects the protein from both acid and enzymatic digestion but might also alter its site of entry into the host. Hogan et al[7] were able to successfully use this technique to create a murine model of ovalbumin-induced eosinophilic gastrointestinal allergy.

Other luminal factors affecting proteins in the lumen include gastrointestinal peristalsis and the protective mucus layer that lines the intestinal epithelium and prevents some proteins from contacting the epithelium.

Those dietary proteins that escape luminal digestion and processing subsequently contact the epithelium, beneath which is both an organized and disorganized mucosal immune system, to generate a wide range of immunologic responses. Peyer's patches (PPs) sit underneath Microfold cells (M cells), dendritic cells (DCs), antigen-presenting macrophages, T cells bearing receptors for MHC class I– and II–mediated antigen presentation, and other cytokine-producing cells. Protein antigens can be taken up by different cell types, depending on their specific properties (Fig 2). The site of entry for these proteins might also dictate the nature of the immune response to these antigens.

Sites of antigen sampling in the gut

PPs. PPs are organized lymphoid structures distributed in the small intestine and rectum. They consist of a germinal center comprised of B lymphocytes surrounded