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The role of protein digestibility and antacids on food allergy outcomes

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Abstract

Digestion assays with simulated gastric fluid have been introduced for characterization of food proteins to imitate the effect of stomach proteolysis on dietary compounds *in vitro*. By using these tests, dietary proteins can be categorized as digestion-resistant class 1 (true allergens triggering direct oral sensitization) or as labile class 2 allergens (nonsensitizing elicitors). Thus the results of these digestion assays mirror situations of intact gastric proteolysis. Alterations in the gastric milieu are frequently experienced during a lifetime either physiologically in the very young and the elderly or as a result of gastrointestinal pathologies. Additionally, acid-suppression medications are frequently used for treatment of dyspeptic disorders. By increasing the gastric pH, they interfere substantially with the digestive function of the stomach, leading to persistence of labile food protein during gastric transit. Indeed, both murine and human studies reveal that antiulcer medication increases the risk of food allergy induction. Gastric digestion substantially decreases the potential of food proteins to bind IgE, which increases the threshold dose of allergens required to elicit symptoms in patients with food allergy. Thus antiulcer agents impeding gastric protein digestion have a major effect on the sensitization and effector phase of food allergy.

Keywords

Food allergy; gastric digestion; acid-suppression medication; digestion assay; simulated gastric fluid

Despite being considered a pleasure by most persons, food intake might also represent a health hazard in situations of altered metabolism or if food proteins are recognized as potentially harmful by the immune system. This failure of oral tolerance leading to hyperimmune reactions toward food compounds is termed *food allergy*¹ and is considered to be a major health concern in Western society. Even though population studies indicate that more than 20% of all patients believe themselves to be allergic to food,² the true prevalence of this disorder ranges between 3% and 4% in the general population.^{3,4} The number of affected patients peaks in children younger than 3 years,⁵ and an increasing prevalence of peanut sensitization has been shown.^{6,7}

Not only the rising number of food-allergic patients but also the severity of food-induced adverse reactions accounts for the importance of this disorder. On intake of the offending food, susceptible persons report a large variety of symptoms, ranging from mild local

reactions at the first contact sites (oral allergy syndrome) to life-threatening systemic reactions, such as asthma or anaphylactic shock.⁸⁻¹² Interestingly, food allergy accounts for up to 50% of all anaphylactic episodes resulting in hospitalization and represents the major cause for these hazardous reactions.¹³⁻¹⁵ Therefore it is obvious that greater knowledge of the underlying mechanisms and characteristics of food allergens is crucial for a better understanding of this disease.

FOOD ANTIGEN ABSORPTION: A DELICATE BALANCE BETWEEN ORAL TOLERANCE AND INDUCTION OF IMMUNE RESPONSES

During human evolution, a sophisticated safety system developed to simultaneously allow immune defense against pathogens and avoidance of hypersensitivity reactions against harmless substances, such as food. The mucosal barrier, consisting of intestinal epithelial cells joined together by apical and basolateral tight junctions and mucus produced by specialized epithelial cells, such as goblet cells, prevents antigen penetration.¹⁶ Additionally, immunologic mechanisms, including immune exclusion accomplished by mucosal secretory IgA antibodies, and downregulatory mechanisms contribute to oral tolerance.¹⁷ T-cell anergy, clonal deletion, and T regulatory cell induction are induced under normal conditions by orally ingested food proteins.^{18,19} Here the amount of the administered food antigen plays a decisive role. Relatively low antigen dosage preferentially induces active suppression by regulatory T cells, whereas higher antigen amounts seem to be associated with clonal T-cell anergy or deletion.^{20,21} Also, intestinal epithelial cells play a decisive role in tolerance induction. They were shown to express MHC class II on their surfaces and might function as antigen-presenting cells.²² These cells do not express costimulatory molecules and therefore induce anergy in T cells responding to the presented antigen.²³

Despite the barrier and control function of the gastrointestinal mucosa, immunologically active food proteins can be absorbed and systemically distributed. At the beginning of the 20th century, the topic of food absorption through the gastrointestinal tract was addressed in pioneer studies. Through passive sensitization with sera derived from patients with fish allergy, the absorption of immunologically active proteins after a meal of fish was proved for the first time in healthy individuals.^{24,25} Part of these proteins might enter the circulation through the oral mucosa, representing the first contact site of food proteins with immune cells of the oropharynx. Recently, the absorption of peanut proteins into the circulation through the buccal mucosa was reported,²⁶ which has been indicated also for fish proteins.²⁷ In the latter study, the time kinetics of protein absorption revealed the presence of the maximal amount of fish proteins in the circulation 1 or 2 hours after the fish meal, correlating with the average gastric transit time determined for drug compounds.²⁸

Regarding the amount of absorbed, intact food proteins, it was shown that between 0.1 and 3 ng of β -lactalbumin per milliliter of serum could be detected in the circulation 30 minutes to 3 hours after consumption of 1.2 L of cow's milk.²⁹ Up to 10 ng of ovalbumin per milliliter of serum was found in the circulation 2 to 3 hours after protein ingestion.³⁰ The quantity of proteins entering the circulation in an intact form through the intestinal mucosa might be increased under certain disease conditions, such as untreated celiac disease,³¹ or in the perinatal period because of an immature barrier function of the intestinal tract.³²

Nevertheless, the majority of ingested food proteins are exposed to the denaturing environment and to digestive enzymes on their travel through the gastrointestinal tract.

PHYSIOLOGIC DIGESTION OF DIETARY PROTEINS

After a relatively quick passage through the esophagus, proteins contained in the macerated food bolus enter the gastric lumen. Here the stomach is distended by the entering food, resulting in increased gastrin secretion. Absorbed from the blood stream, gastrin triggers hydrochloric acid production in the parietal cells and, to a lesser extent, digestive enzyme secretion by the chief cells of the gastric glands.³³ In the stomach the chyme is not only exposed to hydrochloric acid, mucins, and inorganic salts but also to different pepsins, the major gastric proteases.³⁴ These proteinases are produced and secreted into the gastric lumen as inactive proenzymes, called zymogens or pepsinogens.³⁵ At low pH levels, the acidic amino acid (AA) residues in the active enzyme moieties undergo protonation. The electrostatic interactions between the N-terminal prosegment and the active pepsin are disrupted, which initiates a conformational change in both the prosegment and the active enzyme portion. Thus the removal of the prosegment results in conversion into the enzymatically active form of pepsin.^{36,37} Only then is the substrate-binding cleft with the 2 active-site aspartates accessible for binding to protein chains, and protein cleavage can take place (Fig 1). Whereas at a pH of greater than 5.0, limited pepsin is activated, the rate of active enzyme increases with decreasing gastric pH.^{38,39} An acidic milieu is required for the proteolytic activity of pepsins, with an activity optimum between pH 1.8 and 3.2.⁴⁰ Pepsins have a broad specificity against large molecular peptides, preferentially cleaving proteins at phenylalanine, tyrosine, and leucine residues.^{41,42}

Subsequently, the remaining peptones and polypeptides present in the chyme are released into the small intestine. Here they are exposed to a variety of proteases and peptidases produced and secreted by the pancreas, such as trypsin, chymotrypsin, or carboxypeptidases, or to brush border peptidase of the intestinal mucosa. Requiring an alkaline pH level, these enzymes catalyze further digestion into single AAs or small peptides of up to 3 AAs in length, which are actively taken up by enterocytes and serve as nutrients for the human body.^{43,45} This extensive digestion renders small compounds of less than a size of 8 AAs, which are non-reactive with any structure responsible for antigen recognition and presentation and are therefore immunologically ignored.⁴⁶

CLASSIFICATION OF FOOD ALLERGENS

Only dietary proteins large enough to elicit immune responses are potential food allergens. It has been hypothesized previously that protein epitopes recognized by IgE antibodies are of conformational nature,^{47,48} which we recently confirmed for the IgE-binding site of the major fish allergen parvalbumin,⁴⁹ as well as for other allergens.⁵⁰⁻⁵² However, on chronic allergen exposure, such as in milk allergy, linear epitopes might become important in later stages of the disease.⁵³ Additionally, polyvalence has been identified as a general characteristic of allergens that enable cross-linking processes,⁵⁴ which has also been discussed for food proteins.⁵⁵

For classification purposes, food allergens have been divided in 2 classes based on their potential to trigger specific IgE antibody formation. The complete or class 1 allergens not only cross-link IgE but are also the primary source of sensitization. These allergens are described as resistant to the denaturing conditions of food processing or of enzymatic digestion in the gastrointestinal transit, thereby enabling direct oral sensitization.⁵⁶ Prominent examples for these class 1 allergens are β -lactoglobulin in cow's milk and stable peanut proteins.^{57,58} In contrast, the class 2 or incomplete food allergens are postulated to lack sensitizing capacity. These proteins have the potential to elicit symptoms only after primary sensitization with cross-reactive inhalative allergens and were therefore termed *nonsensitizing elicitors*.⁵⁹ Prominent examples are protein homologues of Bet v 1, the major

birch pollen allergen, which are present in fruits and vegetables, such as apple, pear, apricot, and cherry. Their susceptibility to peptic digestion has been demonstrated^{60,61} and might explain why most often local but not systemic symptoms are triggered on ingestion of Bet v 1 homologues. Only stabilization of a Bet v 1 epitope in a mimotope configuration rendered a successful oral sensitization.⁶⁰

PREDICTING THE ALLERGENIC POTENTIAL OF FOOD PROTEINS BY USING DIGESTION ASSAYS

Based on current knowledge on the relation of gastrointestinal digestion, food allergy, and dietary allergens, digestion experiments have been introduced for assessing the allergenic capacity of novel food proteins. In 1996, Astwood et al⁶² reported in a cutting-edge study that digestion experiments in simulated gastric fluid (SGF) ideally distinguish between potentially allergenic and nonallergenic food proteins. Their work was triggered by reports on common characteristics of food allergens⁶³ and the emerging need to predict the allergenic potential of novel dietary compounds. The growing number of genetically modified plants entering the market was a challenge for regulatory authorities to ensure consumer safety,⁶⁴ as indeed potent allergens had previously been transferred into transgenic food.⁶⁵ Therefore the methodology of testing food for its resistance to pepsin digestion was incorporated in a decision tree protocol that was elaborated in a joint Food and Agriculture Organization/World Health Organization expert meeting in 2001, which was approved by the US Food and Drug Administration in 2004.^{66,67} Testing proteins for resistance to SGF exposure has since become a tool extensively applied in food allergy research to gain novel insights into food allergen biology. Peanut allergens were discovered to contain large, digestion-stable, allergenic fragments⁵⁸ or to form aggregates that act as potent triggers of allergic reactions.⁶⁸ Moreover, a multiphase model of gastrointestinal digestion has been developed to analyze emulsification effects and the effect of food phospholipid content on dietary protein digestibility.^{69,70}

It has become evident that some potent allergens are not stable in SGF, as previously expected.⁷¹⁻⁷³ Even though the outcome of these digestion assays might depend on the applied protein to pepsin ratio,⁷⁴ digestion experiments with the basal gastric pepsin concentration for SGF or even pharmaceutical enzyme tablets revealed the quick digestibility of potent allergens, such as milk, fish, and hazelnut, by gastric enzymes.^{27,75-79} Thus these allergens do not show features previously postulated for true class 1 allergens; however, they might still contain peptide fragments recognizable by allergen-specific T cells.⁸⁰

PHYSIOLOGICALLY AND PATHOLOGICALLY ALTERED GASTRIC DIGESTION CAPACITY

Interestingly, gastric digestion assays only simulate situations in which both the production of digestive enzymes and the acid-secretion capacity of the stomach are intact. It is noteworthy that the secretory capacity of the stomach changes physiologically throughout a lifetime, influencing gastric protein digestion. Early studies indicated that in newborns the intragastric pH ranges from 6.0 to 8.0,^{81,82} which is followed by a burst of acid secretion leading to adult gastric pH levels (pH 1.0-3.0) 24 to 48 hours after birth. After these first days of life, the gastric acid production remains low during the next months, and adult pH levels in the stomach are not reached until the average age of 2 years.⁸³⁻⁸⁷ It is well established that gastric acid secretion decreases with age, resulting in low gastric acidity in more than 50% of all patients aged 60 years and older.⁸⁸ It has been reported that low gastric

acid output is associated with pathologies like atrophic gastritis, celiac disease, diabetes mellitus, rheumatoid arthritis, and Sjögren syndrome.^{89,91}

On the other hand, increase of the gastric pH is the therapeutic goal in patients with dyspepsia, such as gastritis, ulcer, erosions, and reflux symptoms. Approximately 25% to 54% of the adult population in Western countries is affected by dyspeptic disorders per year.⁹²⁻⁹⁵ Even though most of them take medication without specialist consultation and adequate diagnosis, dyspeptic symptoms account for up to 5% of all consultations to general practitioners.⁹⁶⁻⁹⁸ Moreover, gastroesophageal reflux (ie, the presence of gastric fluid proximal to the stomach) is one of the most prevalent problems affecting the gastrointestinal tract in infancy,⁹⁹ being today treated with long-term acid suppression by proton pump inhibitors (PPIs) or H₂-receptor blockers.^{100,102}

ACID SUPPRESSION MEDICATION: WORLDWIDE PRESCRIPTION HABITS, MECHANISMS OF ACTION, AND POSSIBLE SIDE EFFECTS

From their broad application in clinics, it is not surprising that antiulcer agents are among the top-selling drugs worldwide. The use of antiulcer medication is rapidly increasing in Western countries and comprises up to 10% of the national medical budget.^{103,106} In 1996, 2% of the English health authority budget was spent on acid-suppression drugs, with 80% of the costs being caused by repeated prescriptions without further medical consultation.^{107,109} Despite clear evidence-based guidelines, approximately 60% of acid-suppressive therapy is started inappropriately during hospitalization.^{110,112} Between 1997 and 2001, antiulcer medication use increased from 9.6% to 15.9% in a Taiwanese cohort, being highest in patients 60 years and older (with a prevalence of 25.9%) in 2001.¹¹³ Reflecting the worldwide situation, the sales volume of PPIs has almost doubled in some European countries between 2000 and 2005.^{114,115}

Despite large differences in mechanisms of action between the currently available drug subclasses of antacids, sucralfate, H₂-receptor blockers, and PPIs (Table I), all these pharmaceuticals effectively suppress gastric acidity and therefore substantially increase intraluminal pH levels.^{116,118} Five days of PPI intake was shown to increase the gastric pH to an average pH of 5.0.¹¹⁹

Even though long-term use of this medication is generally accepted as safe for infants, adolescents, and adult patients, including pregnant women,^{120,123} it is important to note that antiulcer agents interfere with the protective function of gastric acidity against bacterial overgrowth, both in the stomach and the gut.^{124,126} Gastric pH increase has been discussed to be associated with pneumonia development in ventilated intensive care patients,¹²⁷ as well as with an increased risk for community-acquired pneumonia.¹²⁸ Persistent hypergastrinemia induced by long-term gastric acid suppression has been suggested as a risk factor for gastric carcinogenesis.¹²⁹ In the early 1980s, the first correlation between allergic and dyspeptic disorders was reported, even though only the observed drug allergy was interpreted in association with the multipharmaceutical treatment, whereas the food-induced adverse reactions were attributed to genetic and alimentary factors.¹³⁰ Researchers later reported high IgE levels and food-specific IgE in the gastrointestinal mucosa in patients with peptic ulcers.^{131,133} IgE against *Helicobacter pylori* and antacids has been reported in clinical practice, in which acid reduction combined with antibiotics is standard treatment.^{134,136} This might be due to the fact that aluminum compounds found in antacids are potent adjuvants.^{137,138} However, none of these studies addressed the question of whether interference with protein digestion by gastric acid suppression because of antiulcer drug intake could have an effect on food allergies.

INTERFERENCE WITH GASTRIC DIGESTIVE CAPACITY REPRESENTS A RISK FACTOR FOR FOOD-INDUCED ALLERGIC REACTIONS

When gastric digestion experiments with digestion-labile food allergens, such as fish, milk, or hazelnut, were performed with SGF pH at 5.0, these allergens remained stable, even for 2 hours.^{27, 77-79} Titration experiments revealed that the enzymatic capacity of pepsin contained in SGF was completely eliminated when the pH was increased to 2.75 in the case of codfish and to 3.0 for milk proteins.^{77, 78} Additionally, RAST inhibition experiments showed the IgE-binding capacity of fish allergens to be reduced up to 10,000-fold, accompanied by a loss of their histamine-releasing capacity after SGF digestion.⁷⁸

These *in vitro* data point toward a strong effect of digestive proteolysis on IgE-binding capacity. *In vivo* studies in BALB/c mice demonstrated for the first time the association between antiulcer drug intake and food allergy induction. Concomitant administration of digestion-labile food allergens, such as caviar, hazelnut, or parvalbumin, and acid-suppression drugs, such as sucralfate, H₂-receptor blockers, or PPIs, induced allergen-specific IgE antibodies and positive mucosal and skin reactivities.^{76, 79} These mice also had a pronounced infiltration of eosinophils into the gastric mucosa.¹³⁹

Interestingly, the effect of the gastric digestive system on acquiring tolerance toward orally administered dietary proteins was suggested based on murine experiments carried out 20 years ago.¹⁴⁰ Encapsulation of dietary proteins, preventing degradation during gastrointestinal transit, has been used for oral allergy induction in murine models of food allergy¹⁴¹ and was reported to eliminate previously established oral tolerance.¹⁴² The correlation of food allergy induction with gastric acid suppression was found to be not dependent on age, with a major effect for aged individuals,¹⁴³ as well as with a T_H2-biasing potential in the off-spring induced by gastric acid neutralization during pregnancy.¹⁴⁴

The effect of these murine findings was confirmed in a human cohort study of 152 gastroenterologic patients with dyspeptic disorders. After a 3-month course of medication with either H₂-receptor blockers or PPIs, a boost or *de novo* IgE formation toward regular constituents of the daily diet was observed in 25% of the followed up patients. Sensitization in these patients could be confirmed by positive skin test results 5 months after discontinuation of antiacid treatment.⁷⁷ In a group of patients who had hazelnut-specific IgE antibodies during the 3-month antiulcer medication therapy, hazelnut allergy could be diagnosed by means of positive double-blind, placebo-controlled, food challenges.⁷⁹ Almost 12% of all patients had formed IgE antibodies toward those food allergens that would have been previously interpreted as nonsensitizing elicitors.⁷⁷

Clinically important, the interference with gastric digestion capacity might also influence allergic responses in already sensitized patients, in whom IgE is already bound to the effector cells of allergy. Decreased skin reactivity to melon extract after different time points of *in vitro* digestion in a patient with grass pollen and melon allergy showed that gastric digestion substantially decreased the allergenic capacity of these cross-reactive food proteins (Fig 2). Skin testing in patients with fish allergy with SGF-predigested or SGF-undigested codfish allergens showed a significant digestion time-dependent reduction of induced wheal reaction. Moreover, double-blind, placebo-controlled, food challenges in these patients with fish allergy resulted in a 10- to 30-fold higher tolerated allergen dose if the fish proteins were previously subjected to *in vitro* gastric digestion.²⁷

SAFETY ISSUES AND CLINICAL IMPLICATIONS FOR ALLERGIC AND NONALLERGIC CONSUMERS

The data reviewed here suggest that the immunologic or clinical outcome after the consumption of a digestion-sensitive dietary protein depends to a certain degree on the gastric digestive capacity. If the food protein is exposed to gastric enzymes during transit, protein cleavage takes place, inducing either oral tolerance or immune ignorance toward the ingested food protein. However, if proteins persist during the gastric transit because of impaired digestion, such as during acid-suppression treatment, IgE-mediated food allergy can be induced. Gastric digestion might also influence the extent of reactivity in already sensitized patients. Physiologic gastric proteolysis substantially decreases the allergenic capacity of ingested food proteins, whereas severe allergic reactions at much lower amounts of ingested food proteins could occur if digestion is impaired (Fig 3).

The reviewed data indicate that the current concept of food allergen classification into class 1 (true food allergen) and class 2 (labile food proteins) is misleading and thus should be reconsidered. We suggest introducing the concept of allergen persistence in food allergen terminology. Serious implications for patients' and consumers' safety might be envisaged (Table II). It should be taken into consideration that currently applied safety tests for novel dietary compounds do not account for situations of impaired digestive capacity.^{145,146} Thus these protocols should be reconsidered to ensure consumers' safety and to prevent novel sensitizations. Additionally, antiulcer treatment might substantially alter the reactivity in patients with food allergy, such that previously diagnosed threshold levels and estimated no-observed-adverse-effect levels¹⁴⁷ might not be valid. Strict food allergen labeling, independent of content level, might be the only legislative tool to ensure comprehensive patient safety.¹⁴⁸ Most importantly, the interference of antiulcer treatment with the important gate-keeping function of the stomach should be recognized in daily clinical practice, and patients should be advised to limit medication intake to the prescription time period. Dietary recommendations (eg, light meals) during antiulcer therapies combined with repeated allergologic diagnosis of patients on long-term acid-suppression therapy could prevent novel sensitizations or food-induced adverse reactions in sensitized individuals.

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Activity Objectives

1. To review the influence of gastric digestion on food protein allergenicity.
2. To discuss the implications of impaired gastric digestion on the development of food allergy.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: Eva Untersmayr and Erika Jensen-Jarolim have no significant relationships to disclose.

What do we know?

- The ability of a food protein to keep gastrointestinal digestion structurally intact increases its potential to be an allergen.
- Classification of food proteins with digestion stability as a criterion does not provide sufficient information for safety aspects.
- Impairment of gastrointestinal digestion (eg, with antiulcer medication) represents a risk factor for food allergy induction.
- Impairment of digestion decreases the threshold dose of food allergens needed to elicit symptoms in sensitized individuals.

What is still unknown?

- The exact site of food protein absorption and of food allergy induction in the gastrointestinal tract remains unknown.
- Common characteristics of food allergens need to be defined.
- The amount of undigested dietary proteins that has to persist gastrointestinal digestion to induce food allergy is unknown.

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Abbreviations used

AA	Amino acid
PPI	Proton pump inhibitor
SGF	Simulated gastric fluid

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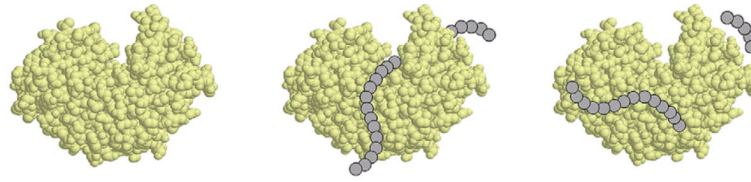


FIG 1. Physiologic gastric protein digestion by pepsin. After activation of pepsin, the substrate-binding cleft is accessible for proteins, and protein cleavage into peptides takes place. The figure was created with the program Protein Explorer 2.411 Beta (available at: <http://proteinexplorer.org>) by using the structural information of porcine pepsin provided with the Research Collaboratory for Structural Bioinformatics Protein Data Bank accession number 5PEP.

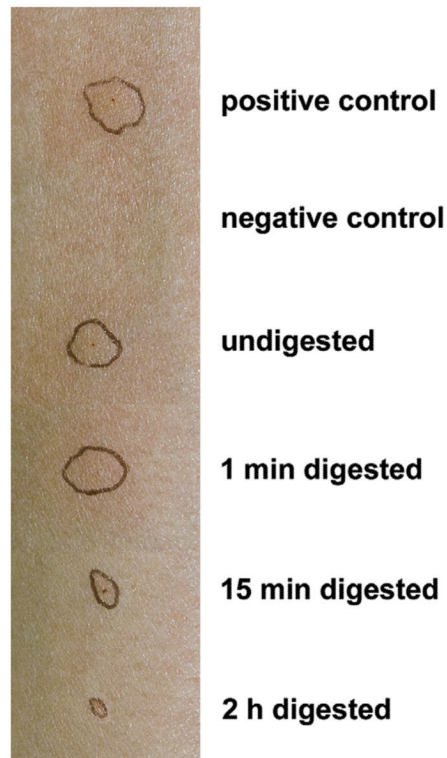
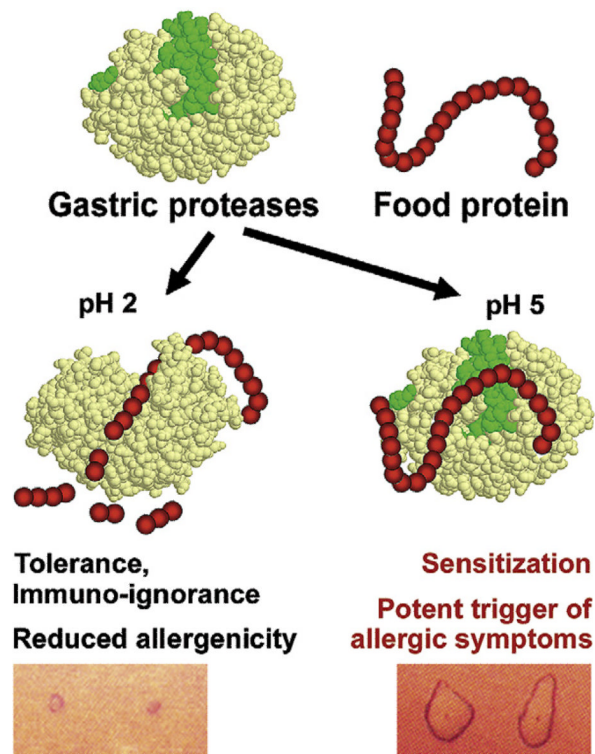


FIG 2. Reduced allergenicity of melon allergens after incubation with gastric enzymes. After subjection to SGF, melon allergens induce a smaller wheal reaction in a patient with melon allergy compared with the undigested extract. The alteration of skin reactivity was dependent on the incubation time with the proteolytic enzymes.

**FIG 3.**

The gate-keeping function of the stomach in the sensitization and effector phase of food allergy. The fate of a dietary protein depends on the gastric digestive function mainly accomplished by the gastric protease pepsin. If the protein structure is destroyed because of proteolysis, oral tolerance or immune ignorance and a reduced allergenic potential might be the result. However, when gastric digestion is impaired (eg, under hypoacidic gastric conditions), digestion-labile proteins might trigger oral sensitization or severe allergic symptoms in a previously sensitized individual. The figure was created with the structural information provided from Research Collaboratory for Structural Bioinformatics Protein Data Bank accession numbers 3PSG and 5PEP.

TABLE I

Drug action mechanisms of acid-suppression medication

Active substance	Mechanism of gastric acid suppression
Antacids	Slight bases neutralizing gastric acid
Sucralfate	Aluminum compound acquiring a strong negative charge on aluminum release, binds to positive charges in its environment
H2-receptor blocker	Antagonist for the stimulating effect of histamine through its H2-receptor on the basolateral surface of parietal cells
PPI	Potent, irreversible blocker of the acid pump function (H ⁺ , K ⁺ , ATPase) on parietal cells

TABLE II**Key concepts and safety implications**

Regulatory authorities might consider a re-evaluation of currently applied safety tests for novel (eg, genetically modified) food compounds.
Patients should be advised that threshold levels might vary in situations of altered protein digestion. This problem also affects current efforts to define no-observed-adverse-effect levels for food allergens.
Dietary recommendations and repeated allergologic testing of long-term acid-suppressed patients could prevent unexpected allergic reactions on food ingestion.